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Medications and CKD

The CKD Symposium For Primary Care Providers

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No conflicts of interest

Learning Objectives

Review answers to common prescribing questions for:

1. Gout
2. Urinary tract infections
3. Shingles
4. Colonoscopy preparation
5. Avoiding acute kidney injury

To find this document:
Google search ➔ BCPRA common prescribing questions

COMMON PRESCRIBING QUESTIONS FOR PATIENTS WITH CHRONIC KIDNEY DISEASE NOT ON DIALYSIS

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Your patient has chronic kidney disease (CKD). Listed below are some of the most common prescribing questions for patients with CKD. These recommendations are only a guide. If you have a patient specific question, please contact your patient's nephrologist or care team.

1. **Gout**
   a. Acute treatment:
   AVOID: NSAID's (including COX-2 selective drugs).
   SUGGEST: colchicine 0.6-1.2mg at onset of attack, then 0.6mg po BID OR Prednisone 15-50 mg po daily x 3 -5 days.
   b. Uric Acid lowering (suggest if > 2 episodes of gout/year)
   Allopurinol (with dose adjusted based on eGFR)

2. **Urinary tract infections**
   AVOID: Nitrofurantoin (lower efficacy and increased toxicity in CKD)
   SUGGEST: All other oral antibiotics generally ok. Ensure they are dosed for renal function as required.
   - **NOTE:**
     i. Trimethoprim/Sulfamethoxazole and Ciprofloxacin may transiently increase creatinine. This does not indicate renal toxicity and should reverse when the course of antibiotics are over.
     ii. Most antibiotics require dose adjustment. However, macrolides, clindamycin, cloxacillin and metronidazole do not require adjustment if eGFR > 15 mL/min.

3. **Pain**
   AVOID: NSAID's (including COX-2 selective drugs)
   SUGGEST: Acetaminophen, tramadol (reduce dose if eGFR <30 mL/min), topical preparations (ex. diclofenac emugel)

4. **Shingles**
   - All antivirals (acyclovir, valacyclovir, famciclovir) require dose adjustment in CKD. Significant neurologic toxicity can occur if dose not adjusted.
   - If gabapentin or pregabalin are being used for analgesia, these also require dose adjustment.
   - If opiates are indicated, agents such as hydromorphone or fentanyl are preferred as the metabolites are less neurotoxic than those of other agents. No dosage adjustments are required in CKD.

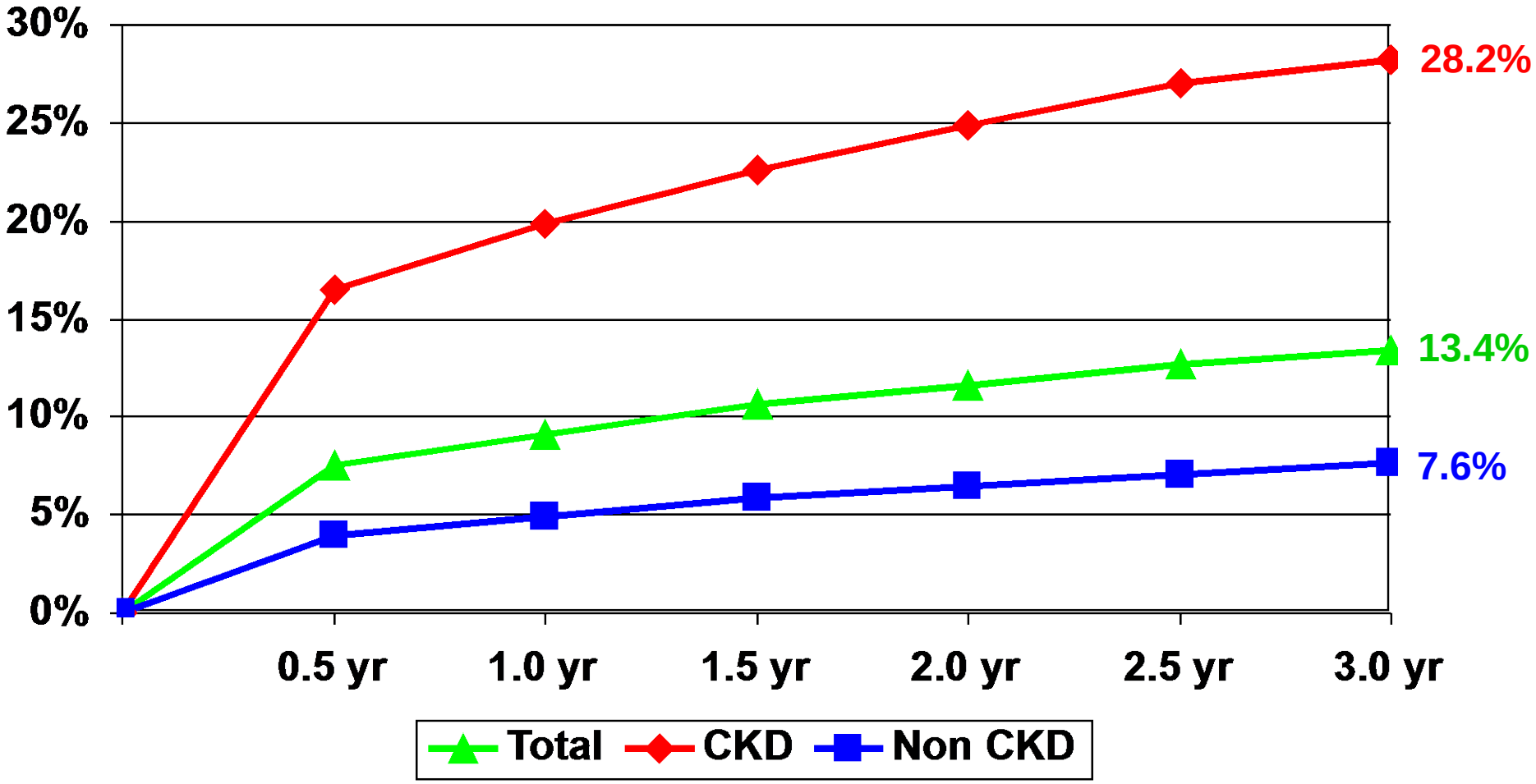
5. **How do I help my patient avoid acute kidney injury (AKI)?**
   Counsel your patient to hold their ACE inhibitors, Angiotensin receptor blockers (ARB's), diuretics and metformin if they are ever suffering from an illness that causes them to be dehydrated. Please see bcrenalagency.ca/node/1338 for a helpful patient teaching tool.

6. **My patient needs to go for a colonoscopy, what preparations are safe?**
   AVOID: Oral phosphate containing bowel preparations.
   USE: PEG-3350 solutions without electrolytes.

7. **My patient needs to go for an angiogram or a CT with contrast.**
   SUGGEST:
   i. Health care provider (or patient) encouraged to contact nephrologist or kidney clinic.
   ii. Ask patient to HOLD ACE inhibitor, ARB, diuretic and metformin the day before the test.
   iii. Check creatinine 3-7 days post procedure and then restart the medications that were on hold.
   - **NOTE:**
     i. Eye exams with fluroscein dye and scans with oral contrast are not nephrotoxic.

ACUTE KIDNEY INJURY (AKI)

AKI leads to progression to ESRD, especially if CKD pre-exists



Courtesy of Dr. Adeera Levin MD, FRCPC

Hospital Mortality Associated with Changes in SrCr

Criterion (mg/dL)	Criterion (umol/L)	Unadjusted Odds Ratio (95% CI)	Age- & Sex-Adjusted OR	Multivariable OR*
⇑SCr ≥ 0.3	**⇑SCr ≥ 26.5**	6.9 (5.2-9.0)	6.6 (5.0-8.7)	4.1 (3.1-5.5)
⇑SCr ≥ 0.5	⇑SCr ≥ 44	11.1 (8.7-14.2)	10.6 (8.3-13.6)	6.5 (5.0-8.5)
⇑SCr ≥ 1.0	⇑SCr ≥ 88	19.9 (15.1-26.1)	19.0 (14.4-25.0)	9.7 (7.1-13.2)
⇑SCr ≥ 2.0	⇑SCr ≥ 177	36.4 (24.3-54.6)	37.7 (25.0-56.9)	16.4 (10.3-26.0)

*Adjusted for age, sex, disease severity, admission diagnosis, CKD

Chertow et al. 2005. "AKI, mortality, length of stay and costs in hospitalized patients." *JASN;* 16(11):3365-70

Stage-based Management of AKI

Nephrotoxic drugs account for a portion of AKI in 20 to 30% of patients

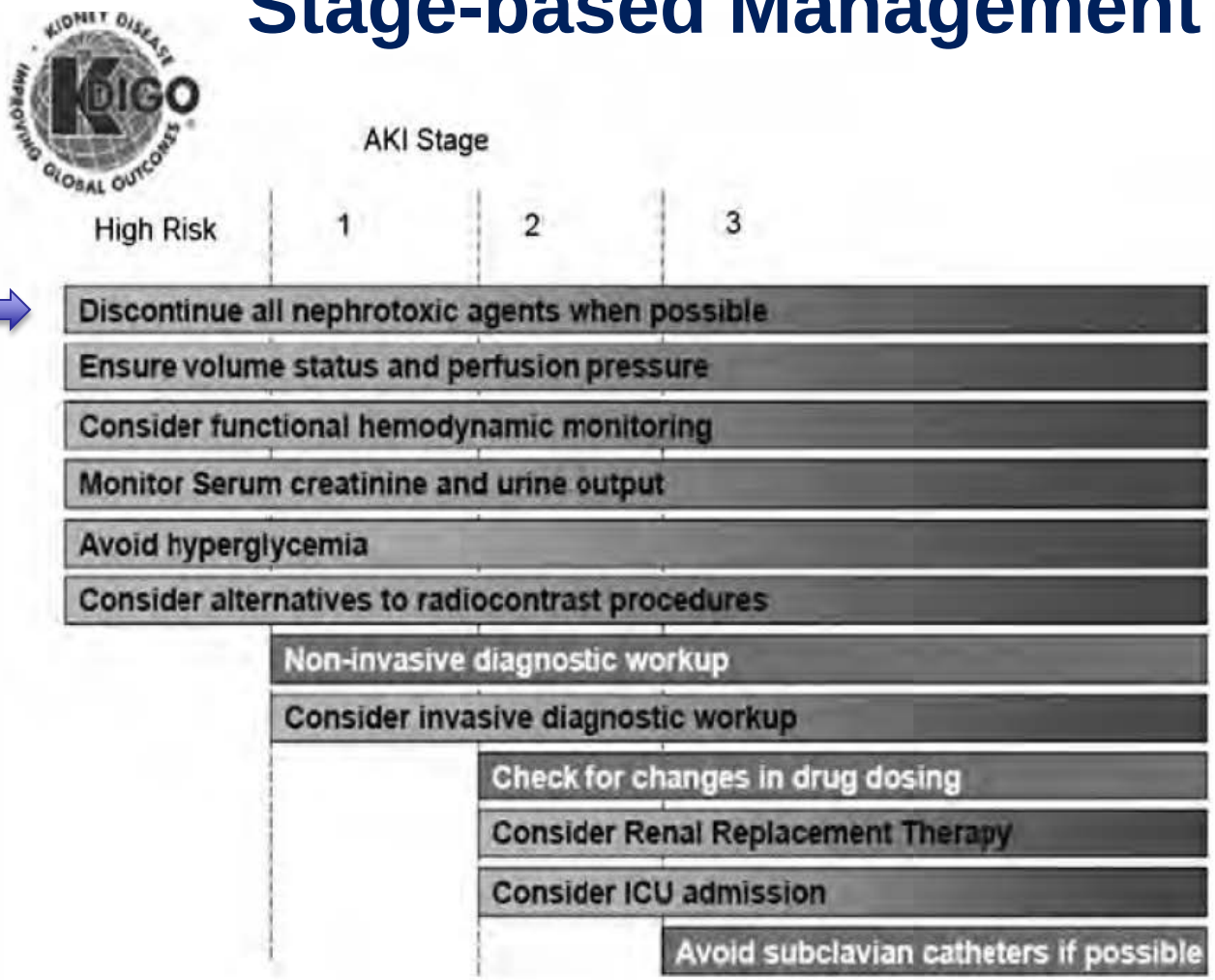


Figure 4 | Stage-based management of AKI. Shading of boxes indicates priority of action—solid shading indicates actions that are equally appropriate at all stages whereas graded shading indicates increasing priority as intensity increases. AKI, acute kidney injury; ICU, intensive-care unit.

ACE-I, ARBS AND METFORMIN

ACE-I and ARBs

Renal protective effects:

1. Reduces intra-glomerular pressure
2. Increases selectivity of the filtering membrane, thereby diminishing exposure of the mesangium to proteins
3. Intrarenal reduction in angiotensin II (growth factor) may attenuate mesangial cell growth and matrix production

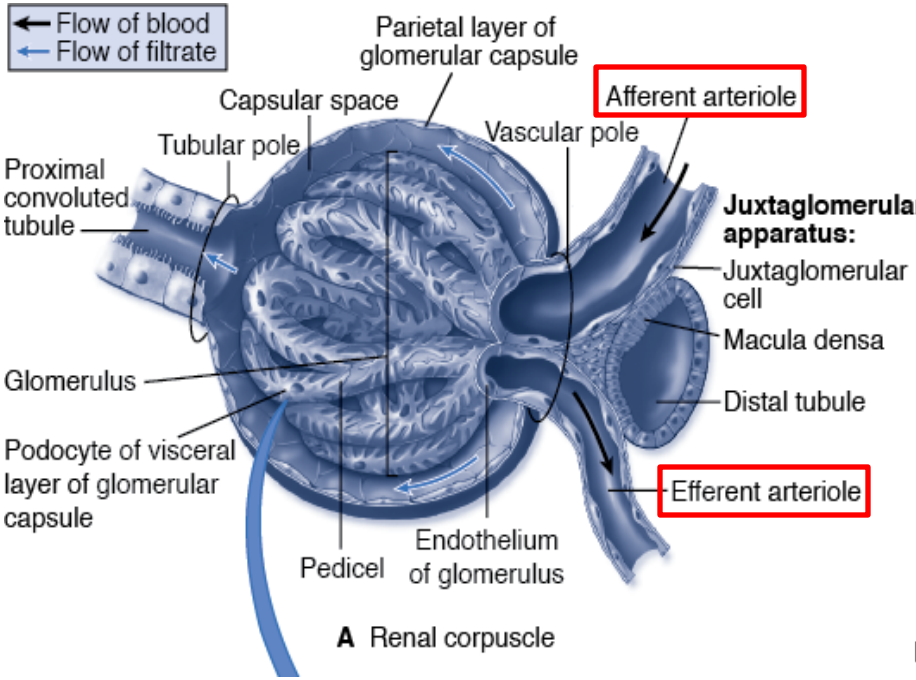
Beneficial in DM patients and in CKD patients with albuminuria (> 30 mg/day)

1. Hilal-Dandan R. Chapter 26. Renin and Angiotensin. In: Brunton LL, Chabner BA, Knollmann BC. eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e.* New York, NY: McGraw-Hill; 2011

ACE-I and ARBs

Mechanism of AKI:

- Blocks angiotensin II, therefore will vasodilate the efferent artery resulting in decreased intra-glomerular pressure



Risks:

- When renal perfusion pressure is low
- Heart failure, volume depletion (e.g. diarrhea, diuretics)
- Bilateral renal artery stenosis

1. Naughton CA. Drug-induced nephrotoxicity. *Am Fam Physician*. 2008;78(6):743–750.
2. Eaton DC, Pooler JP. Chapter 1. Renal Functions, Basic Processes, and Anatomy. In: Eaton DC, Pooler JP, eds. *Vander's Renal Physiology*. 8th ed. New York: McGraw-Hill; 2013. http://www.accessmedicine.com/content.aspx?aID=57340001. Accessed September 4, 2013.
3. Hilal-Dandan R. Chapter 26. Renin and Angiotensin. In: Brunton LL, Chabner BA, Knollmann BC. eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e.* New York, NY: McGraw-Hill; 2011

ACE-I and ARBs

AKI prevention tips (in addition to general rules):

- Check SrCr 1 to 2 weeks after initiation, then repeat in 2 to 4 weeks
  - Accept a 20 to 30% rise in SrCr within 2 months of initiation
- Advise patients to hold their ACE-I/ARB if they are sick and cannot drink their normal amount of fluid

PATIENT TEACHING TOOL

Medication Changes When You Are Sick

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If you have a bad flu or other illness which causes you to vomit or have diarrhea AND you cannot eat or drink normally, you may become dehydrated (dry). Dehydration can affect your kidney function and blood pressure.

If you are vomiting or have diarrhea or feel very sick:
- Try to drink fluids. It is best to drink fluids that do not have caffeine.

If you are so sick that you cannot drink your normal amount of fluids:
- Stop taking the medications listed below until you are able to start drinking fluids again.
- **Contact your doctor or nurse if you have to stop taking your medications for more than 2 days.**

- ☐ ACE inhibitor: _____
- ☐ Angiotensin receptor blocker: _____
- ☐ Anti-inflammatory: _____
- ☐ Metformin
- ☐ Water pill: _____
- ☐ _____

Contact Phone Number:

_____

Patients most likely to benefit from receiving this teaching sheet include those who:
- Experience episodes of vomiting or diarrhea
- Are planning to go travelling
- Have had acute kidney injury and/or were recently hospitalized.

This brochure can be downloaded from the BC Renal Agency website: **bcrenalagency.ca**.

This brochure is based on a similar pamphlet developed by the KCC team at St Paul's Hospital, with appreciation.

1. Naughton CA. Drug-induced nephrotoxicity. *Am Fam Physician*. 2008;78(6):743–750.
2. http://www.bcrenalagency.ca/sites/default/files/documents/files/BC%20Kidney%20Care%20Guideline-Medication_Changes_when_you_are_sick.pdf

Metformin

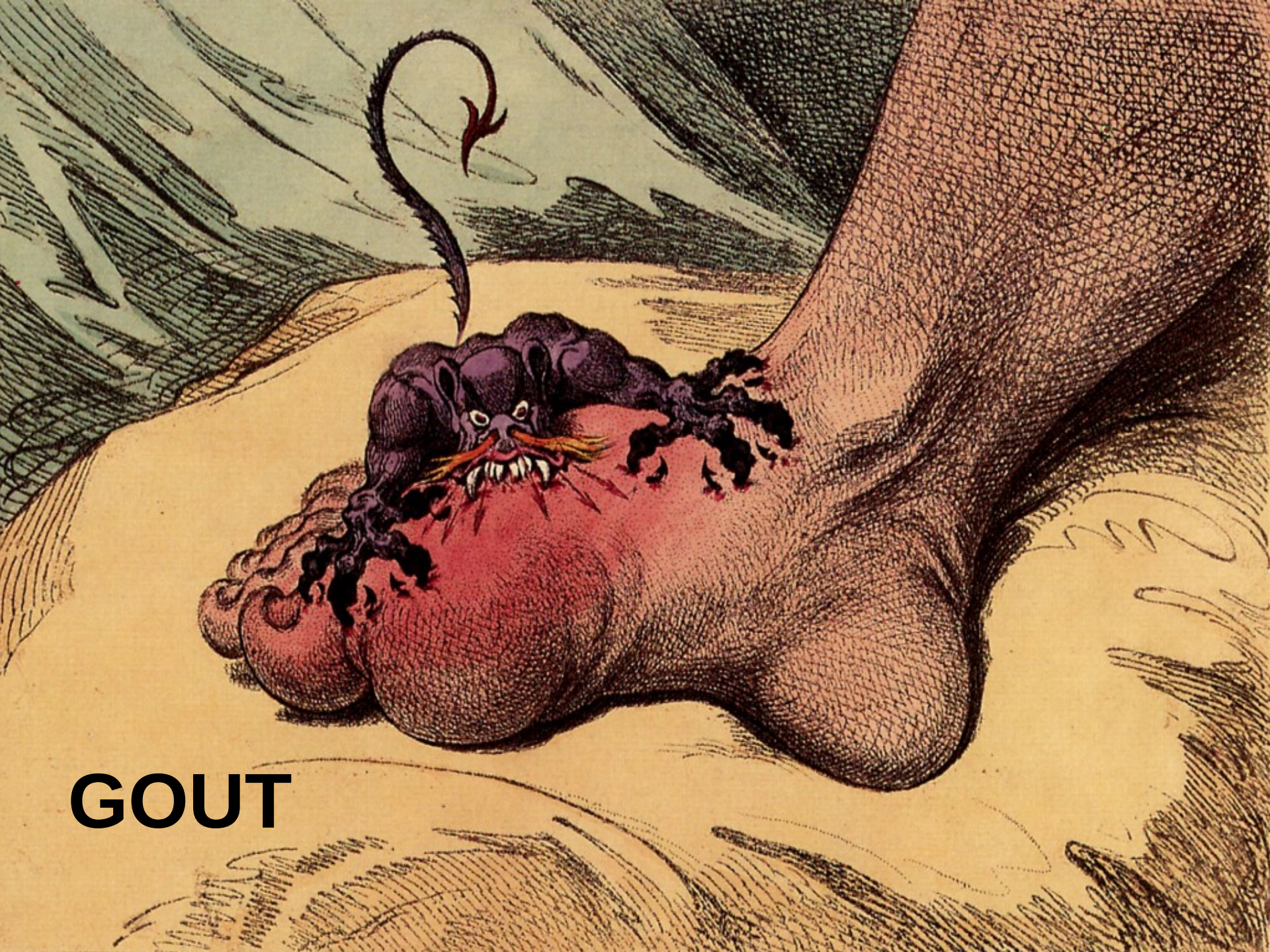
Lactic Acidosis Risk with Metformin use in DM II:[1]

- 4.3 vs. 5.4 cases per 100,000 patient years (metformin vs. no metformin)
- Conclusion ➔ metformin does not cause lactic acidosis in study populations
  - Study populations did not include patients with CHF, hepatic failure, **renal failure**, hypoxic states (shock, sepsis)

Lactic Acidosis Mechanism with CKD:[2]

- Metformin produces lactic acid as part of how it works
  - Converts glucose to lactate in the splanchnic bed of the small intestine
  - Decreases hepatic gluconeogenesis from lactate, pyruvate and alanine
- When GFR deteriorates, not only is **lactate excretion impaired** but metformin rises above the therapeutic range and **blocks hepatic uptake of lactate** provoking lactic acidosis without an increase in lactate production[1]

1. Salpeter et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes meilltus. *Cochrane 2010*
2. Masharani U. Chapter 27. Diabetes Mellitus & Hypoglycemia. In: Papadakis MA, McPhee SJ, Rabow MW. eds. *CURRENT MED DIAG TREATMENT. 2014*


GOUT

NSAIDs

Mechanism of AKI:

- Anti-prostaglandin activity will vasoconstrict the afferent artery

AKI prevention tips:

1. Use alternate analgesia, especially in patients with CKD stage 3 or greater (eGFR < 60 ml/min) or in patients with ↓ intravascular volume

★ *COX-2 inhibitors are not a better choice as the renal vasodilatory prostaglandins (E2 & I2) are produced by COX-2*

Alternative analgesia for gout:

- Colchicine or prednisone
- Uric acid lowering (e.g. allopurinol) suggested if > 2 gout attacks per year

1. Naughton CA. Drug-induced nephrotoxicity. *Am Fam Physician*. 2008;78(6):743–750.

Allopurinol – Treat to Target

Strategy in CKD patients:

- Target serum uric acid (SUA) levels < 360 umol/L
- May need doses above proposed CrCl based guidelines

Monitor for allopurinol hypersensitivity syndrome:

- Typically occurs 2 to 8 weeks after initiation
- Needs 3 of the following characteristics (including extracutaneous organ involvement):
  - Major skin manifestation, fever, multi-organ involvement (e.g. liver), lymphadenopathy, hematological abnormalities (e.g. eosinophilia)

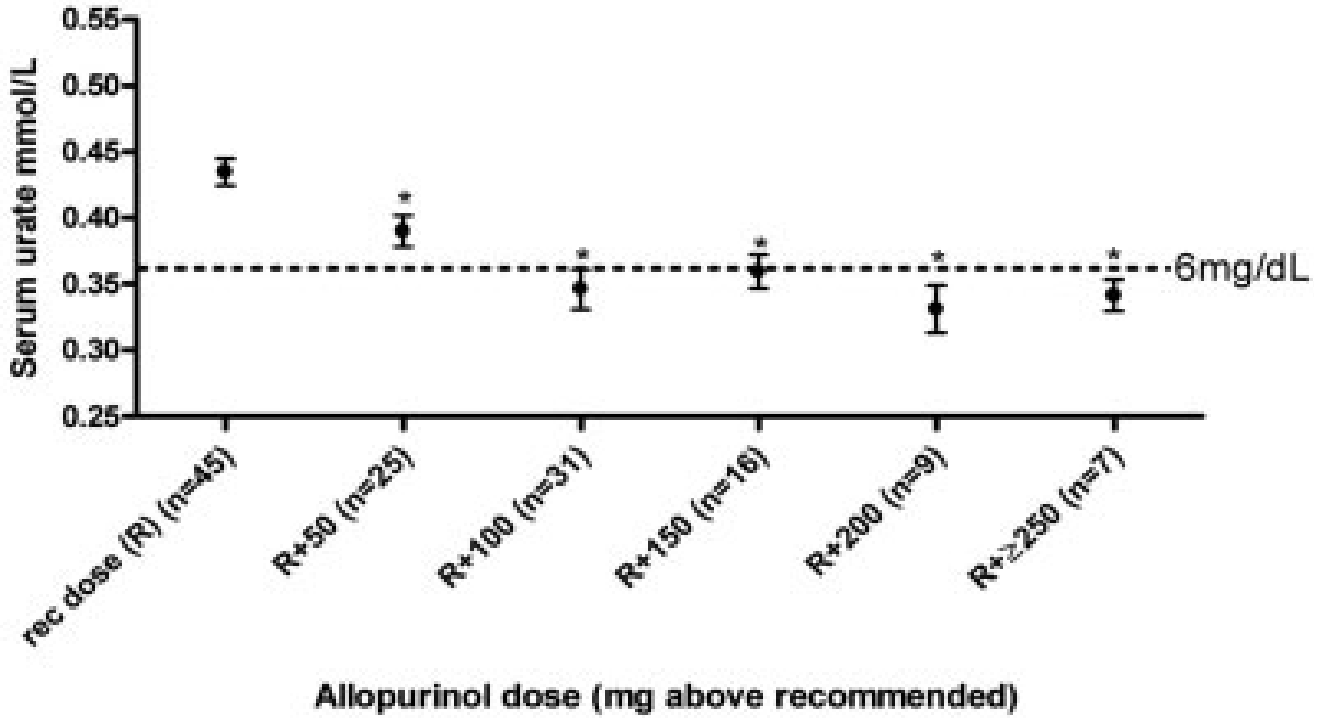
1. Stamp et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. *Arth Rheum* 2011;63(2)
2. Canadian Expert Drug Advisory Committee. Febuxostat CEDAC final recommendation. *CADTH* 2011

Stamp et al. 2011

Design	Prospective, open-label cohort study
P	Uncontrolled gout while on stable doses of allopurinol
I	45 patients had allopurinol dose increased by 50 to 100 mg monthly until SUA < 360 umol/L
C	38 patients continued the same CrCl based allopurinol dose since SUA < 360 umol/L
O	1º: % of patients obtaining SUA < 360 umol/L 2º: adverse drug reactions
L	12 months

1. Stamp et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. *Arth Rheum* 2011;63(2)

Stamp et al. 2011



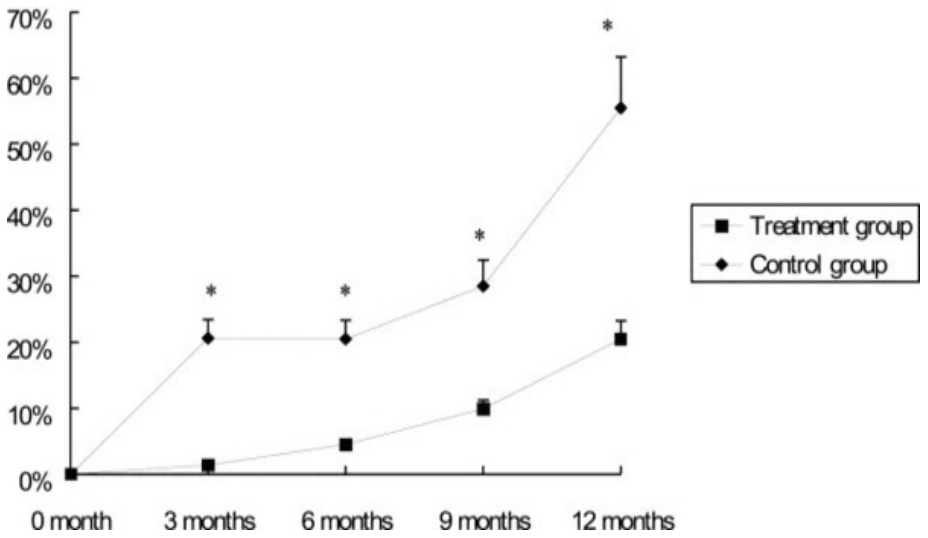
- 89% of patients in the intervention group achieved a SUA < 360 umol/L
- The median allopurinol dose was 450 mg/day
- There were no major ADEs with increasing allopurinol above CrCl based dosing

Allopurinol – Slows Renal Disease?

Mean change in SrCr ($p<0.05$)[1]

Requires further research!

- High uric acid induces HTN
- Uric acid is pro-inflammatory
- Uric acid increases glomerular hydrostatic pressure by stimulating smooth muscle proliferation of the afferent



- N = 52
- Allopurinol dose titrated to keep uric acid within normal range

1. Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis 2006;47:51-9.

Febuxostat

- Like allopurinol, it is a xanthine oxidase inhibitor but with a different chemical structure (option in allopurinol sensitivity)

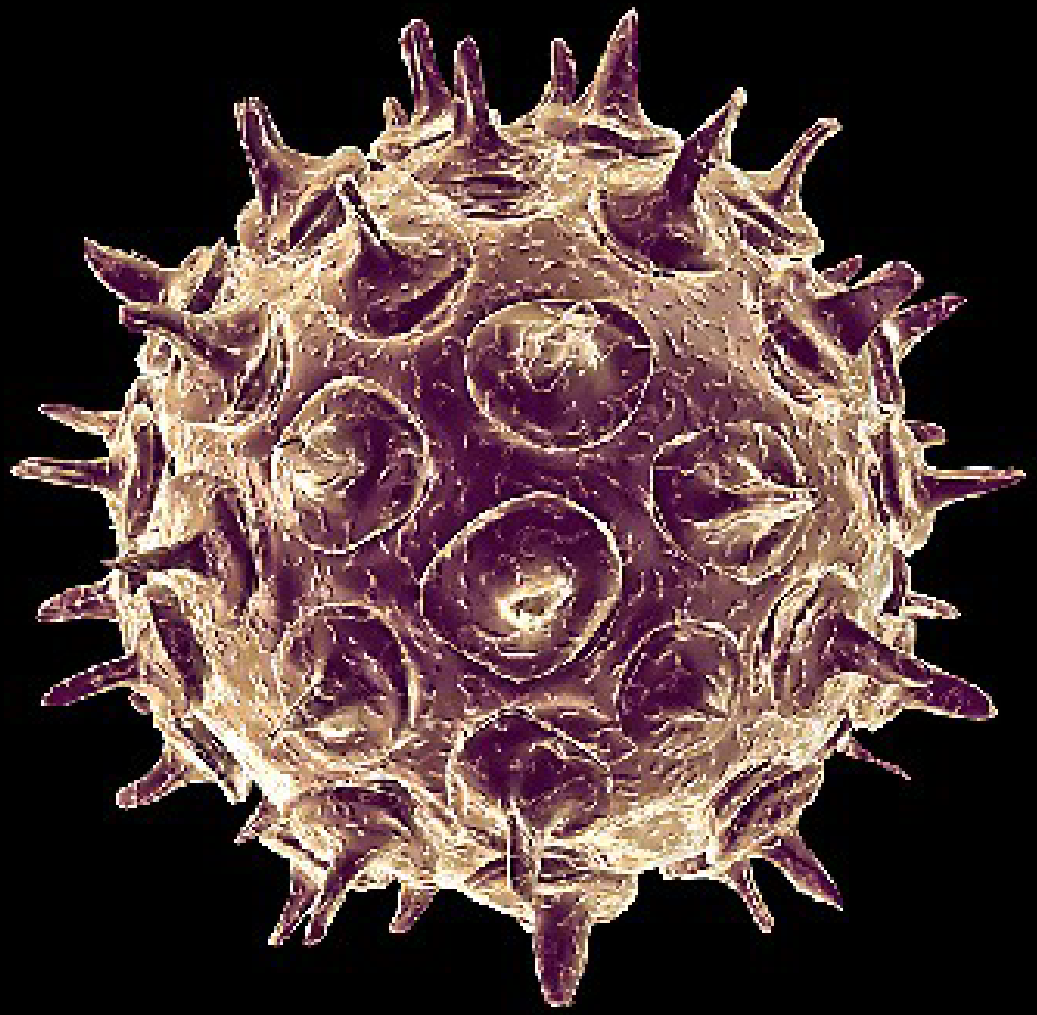
Phase III studies:

- More effective than allopurinol 300 mg (fixed dose unfair?) in lowering SUA but similar QoL (including pain) and ADEs

Other points to consider:

- Does not require renal dosage adjustment
- There is no long-term safety data in CKD patients
- Febuxostat 80 mg ($1.59) vs. allopurinol 300 mg ($0.77)

1. Canadian Expert Drug Advisory Committee. Febuxostat CEDAC final recommendation. CADTH 2011



SHINGLES

Shingles

The average family MD with a base population of 2,000 will see 4 to 8 new cases per year

Antivirals recommended in:

- Opthalmic zoster
- Disseminated zoster (IV acyclovir if CNS involvement)
- Immunocomprimised patients
- Immunocompetent patients presenting within 72 hours of rash onset
  - Age ≥ 50 years old, moderate or severe pain, moderate or severe rash, nontruncal involvement

In an immunocomptetent patient, antivirals will reduce lesions by 1 to 2 days and post herpetic neuralgia from a median of 100 days to 40 to 60 days

1. Dynamed. "Zoster: ESCO:2013. Accessed Nov 20, 2013

Neurotoxicity

Typically appears within 24 to 72 hours of treatment and resolves within 2 to 7 days after treatment is discontinued

In a review article published in 2009 by Asahi et al.:[1]

- There were 20 case reports of acyclovir or valacyclovir neurotoxicity published between 1998 and 2009
- 85% of the patients had chronic kidney disease (65% were on dialysis). The rest of the patients developed AKI prior to symptoms
- 57.1% of patients clearly received excessive doses

There is only 1 case report of neurotoxicity with famciclovir in PubMed[2] but neurotoxicity is listed as a side effect in it's monograph[3]

- Is famciclovir less neurotoxic than acyclovir/valacyclovir??

1. Asahi et al. Valacyclovir neurotoxicity: clinical experience and review of the literature. *Eur J Neuro*. 2009;16(4):457-460
2. Gates et al. Confusion and bradykinesia associated with famciiclovir therapy for herpes zoster. *AJHP* 1996; 53(12): 1454-1456
3. Novartis. Famciiclovir Monograph. April 2013. http://www.pharma.us.novartis.com/product/pi/pdf/Famvir.pdf

Renal Adjusted Dosing

Famciclovir:

CrCl (ml/min)	Dose
> 60	500 mg q8h
40 to 59	500 mg q12h
20 to 39	500 mg q24h
< 20	250 mg q24h
HD	250 mg qHD

500 mg = $1.83

Valacyclvoir:

CrCl (ml/min)	Dose
> 30	1 g q8h
15 to 30	1 g q12h
< 15	1 g q24h

1 g = $1.83

URINARY TRACT INFECTIONS

Nitrofurantoin

Does it work in patients with CKD?

- Avoid when CrCl < 60 ml/min
  - Based on small pharmacokinetic studies demonstrating inadequate urinary concentrations when CrCl < 60 ml/min[1,2]

- Retrospective studies have found nitrofurantoin to result in a **clinical cure** with CrCl 30 to 50 ml/min[1]
  - However, **pulmonary reactions** leading to hospitalizations increased (HR 4.1, 95% CI 1.31-13.09) in the 90 days after the start of nitrofurantoin

1. Eur J Clin Pharmacol. 2013 Sep;69(9):1701-7
2. AHFS 2013, Nictrofurantoin Monograph

Antibiotics

Ciprofloxacin:[1]

- ~ 1% of patients will experience a transient rise in SrCr and BUN
- Crystalluria is rare (2 in 63,000) if urine pH < 6.8 (normal)

Trimethoprim/Sulfamethoxazole:[2]

- Trimethoprim causes reversible competitive inhibition of the tubular secretion of creatinine
- Average SrCr can increase by 15 to 35% in 3 days

Tetracyclines (except doxycycline):[3]

- Has an antianabolic effect (inhibits incorporation of aminoacids into proteins), which can worsen uremia.

1. Guo X, Nzerue C. How to prevent, recognize, and treat drug-induced nephrotoxicity. *Cleve Clin J Med*. 2002;69(4):289–290, 293–294, 296–297
2. Ntyre et al Ther Drug Monit. 1987 Jun;9(2):161-5
3. Olsen et al. Complications of tetracyclines. *J Pediatrics.1966;20(5)*


COLONOSCOPY PREP

Colonoscopy Preparations

AVOID ➔ Oral phosphate containing bowel preparations when eGFR < 60 ml/min/1.73 m^2

- 5 mL of oral sodium phosphate has:
  - 2.4 g of sodium phosphate monohydrate
  - 0.9 g of dibasic sodium phosphate heptahydrate

- Equivalent to ~ 2 g of phosphate (PO_4^{3-}) or 36 cans of Coca Cola

1. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116988.htm
2. Lerma EV. Chapter 37. Chronic Tubulointerstitial Nephritis. In: Lerma EV, Berns JS, Nissenson AR. eds. *CURRENT Diagnosis & Tr*
3. British Society of Gastroenterology *Consensus Guidelines For the Prescription and Administration of Oral Bowel Cleansing Agents; http://www.rcr.ac.uk/docs/radiology/pdf/Oral_Bowel_Cleansing_Guidelines.pdf*

Acute Phosphate Nephropathy

- Newly described entity with incidence rate of 1 to 4%

2 presentation patterns of AKI with $NaPO_4$ colon prep:

Factor	Early symptomatic	Late insidious
Timing of onset after bowel preparation	<24 h	Days to months
Symptoms	Lethargy, confusion, seizure, and tetany	Asymptomatic or nonspecific
Serum phosphorus and calcium levels	Hyperphosphatemia and hypocalcemia	Normal, unless measured within 3 days of bowel preparation
Phosphate load	Excessive	Standard
Pathology	Unknown	Nephrocalcinosis
Treatment options	Intravenous fluid, oral phosphate binder, intravenous calcium gluconate, and/or hemodialysis	None
Outcomes	Recovery, chronic kidney disease, or death	Chronic kidney disease

1. Lien, Is Bowel Preparation Prior to Colonoscopy Risk Business for the Kidney? *Nature.* 2008;(4)11

Bowel Agents to Use

1. Polyethylene glycol preparations preferred in CKD patients who can tolerate the volume (2 to 4 L)
2. Sodium picosulfate/citric acid/magnesium oxide (Pico-Salax®, Purg-Odan®, Picoflo®) reserved for patients who cannot tolerate the volume of polyethylene glycol
   - Magnesium can accumulate in CKD 4 and 5

1. British Society of Gastroenterology *Consensus Guidelines For the Prescription and Administration of Oral Bowel Cleansing Agents; http://www.rcr.ac.uk/docs/radiology/pdf/Oral_Bowel_Cleansing_Guidelines.pdf*

QUESTIONS?

USEFUL RESOURCES:

- BCPRA Common Prescribing Questions for Patients with CKD http://www.bcrenalagency.ca
- KDIGO Guidelines www.kidgo.org
- Dialyze IHD http://www.dialyzeihd.com/
- QxMD – Read and Calculate apps http://www.qxmd.com