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

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 inhibitors, 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 fluorescein dye and scans with oral contrast are not nephrotoxic.
ACUTE KIDNEY INJURY (AKI)
AKI leads to progression to ESRD, especially if CKD pre-exists.
# Hospital Mortality Associated with Changes in SrCr

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

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

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)

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

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

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 $\Rightarrow$ 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\(^1\)

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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

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)
Stamp et al. 2011

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

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)
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?

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

Mean change in SrCr (p<0.05)$^1$

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

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)

Shingles

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

Antivirals recommended in:

- Ophthalmic zoster
- Disseminated zoster (IV acyclovir if CNS involvement)
- Immunocompromised 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 immunocompetent 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

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.:

• 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 but neurotoxicity is listed as a side effect in it’s monograph
• Is famciclovir less neurotoxic than acyclovir/valacyclovir??

## Renal Adjusted Dosing

### Famciclovir:

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>500 mg q8h</td>
</tr>
<tr>
<td>40 to 59</td>
<td>500 mg q12h</td>
</tr>
<tr>
<td>20 to 39</td>
<td>500 mg q24h</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>250 mg q24h</td>
</tr>
<tr>
<td>HD</td>
<td>250 mg qHD</td>
</tr>
</tbody>
</table>

500 mg = $1.83

### Valacyclovir:

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 30</td>
<td>1 g q8h</td>
</tr>
<tr>
<td>15 to 30</td>
<td>1 g q12h</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>1 g q24h</td>
</tr>
</tbody>
</table>

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

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.

Colonoscopy Preparations

AVOID ➔ Oral phosphate containing bowel preparations when eGFR < 60 ml/min/1.73 m²

• 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 (PO₄³⁻) or 36 cans of Coca Cola

2. Lerma EV. Chapter 37. Chronic Tubulointerstitial Nephritis. In: Lerma EV, Berns JS, Nissenson AR. eds. CURRENT Diagnosis & Tr
Acute Phosphate Nephropathy

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

2 presentation patterns of AKI with NaPO₄ colon prep:

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

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

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]