MEDICATION USE IN PATIENTS WITH KIDNEY DISEASE

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I have no actual conflict of interest in relation to this program
Objectives

- Recognize risk factors for drug-related adverse events in patients with CKD
- Identify ways how drugs could lead to adverse events in patients with CKD
- Identify medications and medication classes associated with acute and chronic kidney damage
- Recognize commonly used drugs that require dose adjustment or use with caution in patients with CKD
How are we going to spend the next hour!

- Drug-Related adverse safety events in CKD

- Drug Induced Kidney Damage
  - Direct kidney injury
  - Dosing error
  - Drug-drug interaction
How often? And Who’s at risk?

- Occurs in ~50% of patients with estimated GFR (eGFR) <60 ml/min
- **Risk factors**
  - Non-white
  - Older age
  - ACEi/ ARB use
  - Diabetes
  - More advanced CKD

## Rate of adverse drug events in ambulatory patients with CKD

<table>
<thead>
<tr>
<th></th>
<th>N=267</th>
<th>Rate (per 100 patients)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PATIENT REPORTED</strong></td>
<td></td>
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<tr>
<td>Hypoglycemia</td>
<td></td>
<td>57.6</td>
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<tr>
<td>Falling/ severe dizziness</td>
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<td>23.1</td>
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<tr>
<td>Nausea, vomiting ± diarrhea</td>
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<td>21.1</td>
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<tr>
<td>Hyperkalemia</td>
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<td>18.1</td>
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<tr>
<td>Confusion</td>
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<td>16.9</td>
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<tr>
<td><strong>DETECTED AT STUDY VISIT</strong></td>
<td></td>
<td></td>
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<tr>
<td>Hypoglycemia</td>
<td></td>
<td>8.3</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td></td>
<td>8.3</td>
</tr>
<tr>
<td>Bradycardia</td>
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<td>6.4</td>
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</tbody>
</table>

*Adjusted for sociodemographics, comorbid conditions, GFR, and number of medications

Rate of adverse drug events in in-patients with CKD

- High rate of both ADEs (10.0 per 100 admissions) and potential ADEs (55.3 per 100 admissions)
- 5% were life-threatening
- Most potential ADEs were preventable, almost none were intercepted.
- Patients with elevated serum creatinine concentrations who experienced an ADE had, on average, a more than 5-day excess length of stay when compared with hospitalized patients with elevated serum creatinine concentrations who did not have an ADE.
CKD and medication safety

- Anemia
- Drug dosing
- Transfusion
- Diagnostics
- Edema
- Poor literacy
- ‘Toxic’ meds
- Multiple meds
- Hypoglycemia
- Cognitive impairment
- Comorbidities

Chronic kidney disease

Poor disease recognition

Lapses in patient safety

Fink et al. KI 2009;76:1123–1125
CKD progression: biology versus “iatrogenesis”? 

Baseline rate of decline in GFR 

Fink, et al, AJKD, 2009
CKD progression: biology versus “iatrogenesis”?

Fink, et al, AJKD, 2009
Modes of Drug-Related Adverse Events in CKD

- Drug-Related adverse safety events in CKD
- Drug Induced Kidney Damage
  - Direct kidney injury
  - Dosing error
  - Drug-drug interaction
### PRERENAL
- NSAIDs
- ACEIs
- ARBs
- Cyclosporin & Tacrolimus

### INTRARENAL
- Contrast media
- AGs
- Cisplatin & carboplatin
- Amphotericin B
- Lithium
- Cyclosporin

### POSTRENAL
- Sulfonamides
- Methotrexate
- Acyclovir
- Oral Phosphate
Hemodynamically Mediated kidney failure (Prerenal)

- NSAID
- ACEI & ARB
- Cyclosporine & Tacrolimus
NSAIDs- ACEI & ARB

1. ACE inhibitor dilates the efferent arteriole, and reduces GFR

2. Diuretics reduce plasma volume and GFR

3. NSAIDs constrict blood flow into the glomerulus via the afferent arteriole and reduce GFR
NSAIDs

• Injure kidneys directly
  – Induce acute kidney injury (AKI) from “pre-renal” or ATN
  – Interstitial nephritis
  – Nephrotic syndrome

• Decrease kidney potassium excretion → hyperkalemia

• Decrease sodium excretion → HTN, edema

• Prevention Use therapies other than NAIDs when appropriate
ACEIs & ARB

- Prevention
  - Initiate therapy with low doses and gradually titrate upward.
  - Monitor kidney function and SCr
  - Avoid use of concomitant diuretics
A 48-year-old man is admitted to the ICU after an acute MI.

Hx: type 2 DM, HTN, and tobacco use.

Drugs: Metformin 500 mg 2X, lisinopril 20 mg/day, nicotine patch, and naproxen 500 mg/day.

Lab: BUN 20 mg/dL, SCr 2.1 mg/dL (1mg/dL 24 hours before). He has been anuric for 6 hours. His current BP is 110/70 mm Hg. He has edema and pulmonary congestion.
Question

• Which medication is best to discontinue at this time?
  • A. Lisinopril.
  • B. Naproxen.
  • C. Metformin and lisinopril.
  • D. Metformin, naproxen, and lisinopril
Hemodynamically Mediated kidney failure (Prerenal)

- NSAID
- ACEI & ARB
- Cyclosporine & Tacrolimus
Cyclosporin & Tacrolimus

- 7-21% CKD in transplant patients
- ↑ Vasoconstriction of afferent arterioles through ↑ activity of thromboxane A2, endothelin, sympathetic nervous system
- ↓ activity of vasodilators (nitric oxide, prostacyclin)
- Can occur within days of starting therapy
- **Risk factors:**
  - High dose
  - Kidney graft rejection
  - Hypotension
  - Infection
  - Concomitant nephrotoxins
Cyclosporin & Tacrolimus

• **Prevention**
  
  – Monitor serum cyclosporine and tacrolimus concentrations closely.
  
  – Use lower doses in combination with other nonnephrotoxic immunosuppressants (e.g., steroids, mycophenolate mofetil).
  
  – Calcium channel blockers to antagonize the vasoconstrictor effects
Prerenal

Intrarenal

Postrenal

NSAIDs – ACEIs-ARBs - Cyclosporin & Tacrolimus

Contrast media
AGs
Cisplatin & carboplatin
Amphotericin B
Lithium
Cyclosporin

Sulfonamides
Methotrexate
Acyclovir
Oral Phosphate
ATN (Intrarenal)

- Radiographic contrast media
- Aminoglycosides
- Cisplatin and carboplatin
- Amphotericin B
Iodinated Contrast

- Risk factors
  - CKD (esp. eGFR <30 ml/min/1.73m$^2$)
  - Diabetes, CHF, gout
  - Age>75 years
  - Race: Non white
  - Anemia (Hct<39% men, <36% women)
  - Dehydration
  - Concurrent use of NSAIDs or RAAS-antagonists and metformin
  - High osmolality agents, large or repeated doses

- Pathogenesis
  - Direct tubular toxicity
  - Renal ischemia (osmotic diuresis)
Iodinated Contrast

- Minimize risk of AKI
  - Use low or iso-osmolar agents at lowest doses possible
  - Consider d/c NSAIDS, diuretics or RAAS-antagonists and metformin prior and shortly after procedure
  - Optimize volume status: 0.9% saline 1 ml/kg /hour for 3-12 hours before and after the procedure or 100 ml/hr, 6-12 hours before and 4 to 12 hours after
  - Acetylcysteine has not been shown to be a consistent benefit
  - Check Scr 48-96 hrs post-procedure
  - Avoid repeated contrast load within days

Case Presentation

- A 67-year-old man is referred for intermittent chest pain. He has a medical history significant for stage 3 CKD, type 2 DM, HTN.
- Drug: enalapril, hydrochlorothiazide, and pioglitazone.
- Lab: SCr 1.8 mg/dL, glucose 189 mg/dL, hemoglobin 12 g/dL, and Hct 36%. The plan is to undergo elective cardiac catheterization. Which of the following best characterizes the risk factors for developing contrast-induced nephropathy in this patient?
  - A. CKD, and DM
  - B. CKD, DM, anemia and enalapril
  - C. DM, anemia, and age
  - D. DM
Questions 2

• Which approach is the best choice for hydration?
  • A. 0.45% NaCl.
  • B. 0.9% NaCl
  • C. 5% dextrose/0.45% NaCl.
  • D. Oral hydration with water
Question 3

After the administration of radiocontrast, when is it optimal for reevaluation of renal function to assess for possible contrast associated nephropathy?

A. 6 hours  
B. 24 hours  
C. 2 days  
D. 7 days
Aminoglycosides

• Risk factors
  – Large total cumulative dose, prolonged therapy, trough concentration > 2 mg/L
  – Concurrent use of other nephrotoxins (cyclosporine, amphotericin B, and diuretics)
  – Preexisting kidney disease/damage, increased age, dehydration, and K/Mg deficiencies

• Pathogenesis
  – proximal tubular damage leading to obstruction of the lumen
  – Cationic charge of drug leads to binding to tubular epithelial cells
Aminoglycosides

• **Minimize risk of AKI**
  – Avoid in high-risk patients
  – Maintain adequate hydration
  – Limit the total cumulative aminoglycoside dose
  – Avoid other nephrotoxins.
  – Use extended-interval (once daily) dosing; need to monitor these and other high-risk patients closely
Cisplatin & Carboplatin

- **Pathogenesis:** Direct tubular toxins
- **Presentation**
  - SCr peaks 10–12 days after starting therapy
  - Renal Mg wasting is common along with hypo K+, and hypo Ca++
- **Risk factors:**
  - N# of courses
  - Age,
  - Dehydration,
  - Concurrent nephrotoxins
- **Prevention**
  - Avoid concurrent nephrotoxins.
  - Aggressive intravenous hydration: 1–4 L within 24 hours of high-dose cisplatin or carboplatin
Amphotericin B

• Pathogenesis
  – Direct proximal and distal tubular toxicity electrolyte wasting (especially K+, Na+, and Mg2+) and distal tubular acidosis
  – Arterial vasoconstriction $\downarrow$ in kidney blood flow $\downarrow$, GFR, $\uparrow$SCr increases

• Prevention
  – Avoid other nephrotoxins (especially cyclosporine), and limit the total cumulative dose.
  – IV hydration with at least 1 L/day of 0.9% NS before each dose
  – Use a liposomal product in high-risk patients.
Prerenal

Intrarenal

Postrenal

NSAIDs –ACEIs-ARBs- Cyclosporin & Tacrolimus

Contrast media

AGs

Cisplatin & carboplatin

Amphotericin B

Lithium

Cyclosporin

Sulfonamides

Methotrexate

Acyclovir

Oral Phosphate
Postrenal (Obstructive) Nephropathy

- Intratubular precipitation of tissue degradation products or precipitation of drugs or their metabolites
- Results in rapid decline in kidney function with resultant oliguric or anuric kidney failure
- **Tissue degradation products**
  - Uric acid
  - Myoglobin
- **Drug precipitation**
  - Sulfonamides
  - Methotrexate
  - Acyclovir
Case presentation

70 yo woman with HTN, DM, CKD. 3 mo ago - Scr 1.2 mg/dl, eGFR 42 ml/min/1.73m², CO₂ 23 mEq/l, urine albumin to creatinine ratio (ACR) 320 mg/g.

She is fatigued. Severely constipated with ↓ oral intake, but now with loose stools after OTC laxatives, but not dizzy.

Meds: Losartan/HCTZ, metformin.

BP 136/70 mmHg (~ baseline 140/80 ). Scr 4.0 mg/dl, CO₂ 21 mEq/l.

You call her for to go to the ER and ask about OTC NSAIDs.

What do you think happened?

A. Progression of CKD
B. Too much RAAS blockade with too low target blood pressure
C. Metformin induced AKI
D. Phosphate containing laxatives
Sodium Phosphate Bowel Preparations

- 1/14/14 - FDA Blackbox warning for oral or rectal sodium phosphate products do not to take more than one dose/24 hours

- The predominant electrolyte disturbances were hyperphosphatemia, hypocalcemia, and hypernatremia

- Risk Factors
  - Older age,
  - Impaired kidney function
  - Pre-renal state/physiology
  - Decreased GI motility
  - ACEi, ARB or NSAID use
Oral Sodium Phosphate Preparations

- Hyperphosphatemia + volume depletion

- Acute Phosphate Nephropathy
  - Ca-phosphate deposits in tubules & interstitium
  - Leads to AKI/CKD within days to months

Modes of Drug-Related Adverse Events in CKD

- Direct kidney injury
- Dosing error
- Drug-drug interaction
Pharmacokinetic changes
Absorption

• Oral absorption can be decreased.
  – Nausea and vomiting
  – Increased gastric pH (uremia)
  – Edema
  – Physical binding of drugs to phosphate binders
• Loading doses usually do not need to be adjusted
• Normal doses are maintained with the extended drug formulation, but the dosing interval is lengthened to allow time for drug elimination before re-dosing
Pharmacokinetic changes
Distribution

- Changes in concentrations in highly water-soluble drugs occur as extracellular fluid status changes.
- Acidic and neutral protein-bound drugs are displaced by toxin buildup.
- Conformational changes of the plasma protein–binding site.
- Phenytoin. The “normal” free fraction of phenytoin is 10%. Free fraction can be as high as 25%–30% in patients with ESKD and hypoalbuminemia.
- Dosage adjustment of phenytoin not needed, just a different approach to evaluating concentrations.
Drug Elimination in CKD

• Adjustments usually needed when >25-30% of active drug/metabolite eliminated renally:
  – Azithromycin 5-12%
  – Moxifloxacin 15-21%
  – Pioglitazone (Actos) 15-30%
  – Ciprofloxacin 30-57%
  – Amoxicillin 50-70%
  – Digoxin 57-80%
Case Presentation

74 yo W woman Scr of 1.9 mg/dl, eGFR 34 ml/min/min/1.73m² has dysuria, urgency. Urinalysis reveals 3+ leukocyte esterase.

Which antibiotic will be the best for efficacy, but will also need to be dose adjusted for CKD?

A. Cephalexin
B. Ciprofloxacin
C. Nitrofurantoin
D. All of the above
Antimicrobial Agents & CKD

• Most require renal dose adjustments
  – Common exceptions: Ceftriaxone, moxifloxacin, macrolides, doxycycline, clindamycin, linezolid

• Careful monitoring of drug levels needed for:
  – Vancomycin, Aminoglycosides

• Trimethoprim/ sulfamethoxazole
  – May ↑SCR slightly due to ↓renal tubular creatinine excretion—no change in GFR.
  – Distinguish from AKI due to drug allergic interstitial nephritis
  – Hyperkalemia

• Imipenem/ cilastatin
  – High seizure risk in CKD patients, use carbapenem in CKD

Case Presentation

45 yo AA man with diabetes and HTN. He is on metformin with a HgbA1C 6.9, and has lost 5kg. Scr 1.5 mg/d last year, ↑1.6 mg/dl with eGFR of 59 ml/min/1.73m^2, ACR 200 mg/g, serum K^+ 4 mEq/l.

He is on losartan 100 mg/d with BP 130/80 mmHg. He has no complaints.

What should we do for his diabetes?

A. D/c metformin, add glyburide
B. D/c metformin, add glipizide
C. Add lisinopril
D. No medication changes
Antihypertensive Agents & CKD

• Discontinue ACEIs and ARBs when Srcr↑>30% or if K+ is ≥5.6mEq/L

• β-blockers need dose adjustment except metoprolol, propranolol and labetalol which are metabolized by the liver

• Ca-channel blockers do not require dose adjustment
Hypoglycemic Agents and CKD

• Sulfonylureas
  – Dose adjustment needed for renally excreted drugs: **chlorpropramide, glyburide**
  – Avoid above two if eGFR < 50 ml/min
  – Gliquidone is a biliary excreted drugs can be used safely

• Insulin
  – Partially renally excreted and dose adjustment may be needed for eGFR <30 ml/min
Metformin

- **Ideal agent**
  - Does not raise insulin levels
  - No hypoglycemia
- **Lactic acidosis**
  - ~3 cases per 100,000 pt-yr
- **Original cutpoints based on metabolizing 3 g in 24–48 h**
  - Females, SCr 1.4 mg/dL
  - Males, SCr 1.5 mg/dL

Proposed Metformin Use in CKD

- eGFR 45 to 60 mL/min/1.73m²
  - Continue metformin use and ↑ monitoring of eGFR to every 3 - 6 months
- eGFR 30 to 45 mL/min/1.73m²
  - Use metformin with caution with lower dose (50% maximal)
- eGFR < 30 mL/min/1.73m²
  - Stop metformin
- Avoid or hold if Acute Kidney Injury or high risk AKI
  - Iodinated contrast exposure
- Monitor Serum Bicarbonate in addition to eGFR
  - Stop metformin for any new acidosis

Lipid-Lowering Drugs

• Statins
  – No renal dose adjustment needed for atorvastatin
  – Dose adjustments needed when eGFR <30 ml/min for fluvastatin, lovastatin, pravastatin, rosvastatin and simvastatin

• Fibrates
  – Associated with AKI esp. in CKD patients
  – May transiently raise SCr by increased creatinine production rather than decreased GFR

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agents Requiring Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcotics</td>
<td>Codeine, morphine, avoid meperidine; other agents may also accumulate</td>
</tr>
<tr>
<td>Antipsychotic/antiepileptic agents</td>
<td>Chlortal hydrate, gabapentin, lithium, paroxetine, primidone, topiramate, trazodone, vigabatrin</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Allopurinol, colchicine, H2-receptor antagonists</td>
</tr>
</tbody>
</table>
Herbal Products

- Risk of metabolism acceleration (St. John’s work and ginkgo)
- Increase risk of bleeding in patients on aspirin (Ginkgo)
- Undisclosed amounts of K+
- May contain heavy metals
Modes of Drug-Related Adverse Events in CKD

- Direct kidney injury
- Dosing error
- Drug-drug interaction
Case Presentation

64 yo AA woman with weakness. PMH of HTN, hypercholesterolemia
CKD with Scr of 1.4 mg/dl, eGFR of 45 ml/min/1.73m², ACR 30 mg/g,
Meds: Diltiazem, Simvastatin, ASA
H. pylori. Rx: Clarithromycin, Metronidazole, Bismuth + PPI
7 d after starting regimen c/o severe weakness
Exam: 110/70 mmHg, tachycardia, ↓ lower extremity strength.
Na 138 K 6.4 Cl 98 HCO3 14 BUN 89 Cr 5.8.
CK 80,000 IU/L
Why did this happen?
Rhabdomyolysis with Statins: Cytochrome P450 3A4 interactions

Lova >/= Simva > Atorva – not Rosuva or Prava

- Azoles (ketoconazole the worst)
- Diltazem and Verapamil
- Clarithro and Erythro >>> Azithro
- Ritonavir in HIV patients
- Cyclosporine and FK506 (Tacrolimus)
CYP450 3A4 Interactions
Diltiazem with lovastatin and pravastatin

### INTERACTING CLASSES

| INTERACTING CLASSES | Calcium channel blockers | Combined oral contraceptives | Tricyclic antidepressants | Cyclosporine Tm 

| Antihistamines | Antihistamines | Antihistamines | Adverse effects: | Tm 

| Antihistamines | Antihistamines | Antihistamines | Adverse effects: | Tm 

| Antihistamines | Antihistamines | Antihistamines | Adverse effects: | Tm 

| Antihistamines | Antihistamines | Antihistamines | Adverse effects: | Tm 

### Potential interactions not to be missed

- **Warfarin and/or oral anticoagulants:** Increased risk of bleeding.
- **Levodopa and/or dopamine agonists:** Increased risk of dyskinesia.
- **Lithium and/or divalproex sodium:** Increased risk of toxicity.
- **Ocular hypotensive agents:** Decreased efficacy.

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*Note: The table above summarizes interactions between different medications. Always consult a healthcare professional for specific advice.*
Take Home message

- Appropriate and timely education and management (prevention of toxicity, vaccination) during the early stages of kidney disease reduces health care risk to the patient and lowers associated cost
- CKD patients at high risk for drug-related adverse events
- Several classes of drugs renally eliminated and dose must be adjusted
- Minimize pill burden as much as possible
- Remind CKD patients to avoid NSAIDs and drugs that may lead to acute injury
Collaborative Care

“A High Performing Team will simply find a way”

-Michelle Le