Overview

• CKD – Metabolism & Elimination of Pharmacologic Agents
• Dialysis – Drug Therapy
• Drugs Commonly Used in CKD (including intradialytic Agents)

Renal Function – processes of

• Filtration
• Secretion
• Reabsorption
• Endocrine & Metabolic Fx’s

NEPHRON (1 million)/kidney
Is the functional unit of the kidney
Regions of the nephron
- Glomerulus
- Proximal tubule
- Loop of Henle
- Distal Tubule
- Collecting Duct

Renal physiologic functions affecting Pharmacology

Filtration
• Occurs at the glomerulus
• Determinants of a drug’s capacity to be filtered
• Most drugs are small enough for filtration except for high MW dextrans i.e. volume expanders
Protein Binding
• Displacement of highly bound drugs
• Only free drug can pass through the glomerulus

Active Learning Question?

Select ALL that apply: which of the following statement is TRUE about the kidneys?
__Filter, secrete and reabsorb
__Maintain water and electrolytes homeostasis
__Drugs do not process through the kidneys
__Produce and secrete erythropoietin
Measurement of Renal Function

- Quantify renal fx to use as a diagnostic indicator to monitor therapy.
  - success vs. failure
- Measurement of renal function is an indicator of the body’s ability to eliminate drugs from the body.
- Single best measure of renal fx = GFR
- Volume of plasma filtered across the glomerulus per unit of time
- Responsible for keeping the renal blood flow constant
- Normal GFR = 120 mL/min/1.73 m²

Mechanism of Kidney Clearance

- Kidney → Creatinine Clearance (GFR)

  (Filtration Process)

- Measurement of GFR
- Serum creatinine level, eClcr
- MDRD, CKD-EPI
- Cystatin C

PHARMACOLOGY IN RENAL DISEASE

- Measurement of GFR
- Inulin clearance
  - fructose polysaccharide obtained from plant tubers of the Jerusalem artichoke, chicory & dahlia plants.
  - Urine & blood samples
- Iothalamate clearance
  - 1-Iothalamate radiolabeled form

Intermittent availability, high cost, invasiveness, sample preparation, & assay variability limits its use in the clinical setting.

Estimation of Creatinine Clearance

- CLcr is the single most common clinical test for the assessment of renal fx.
- Cr is a product of creatinine metabolism on muscle mass.
- Normal Cr = 0.5 – 1.5 mg/dL
- Cockcroft and Gault Formula:

  \[
  \text{eCLcr} = \frac{(140 - \text{age})(\text{weight in kg})}{(72)(\text{sCr})} \times 0.85
  \]

  Women x 0.85

PHARMACOLOGY IN RENAL DISEASE

Calculating the CrCl

- 79 YO, Female
- sCr = 1.2 mg/dL
- 65 Kg

(140-79)(65) x 0.85
(1.2)(72)

eClcr = 39 mL/min

Important to note there is a normal loss of nephrons due to the aging process.

Modification of Diet in Renal Disease (MDRD) Study Formula

GFR (mL/min/1.73m²) = 186 x (Scr)^-1.154 x (age)^-0.203 x (0.742, if female) x (1.212, if black)

- Does not require weight as a variable
- More accurate for patients whose GFR is less than 90 mL/min
**CKD Epidemiology Collaboration (CKD-EPI)**

GFR = \(a \times \frac{\text{Scr}}{b} \times (0.993)^{\text{age}}\)

(see Appendix for more details)

- More accurate than MDRD if actual GFR >60 mL/min/1.73 m\(^2\)
- Pooled data from multiple studies

→ Better performance, less bias, greater accuracy

**Cystatin C**

- A low-molecular-weight protein
- Marker of kidney insufficiency
- May improve detection of early CKD
- Preliminary studies – superior eGFR in children, transplant patients & cirrhotic patients

**Children (Schwartz)**

\[\text{eGFR} = \frac{\text{height (cm)} \times k}{\text{Scr}}\]

- Infant (1 – 52 wks), \(k = 0.45\)
- Child (1 – 13 yrs), \(k = 0.55\)
- Adolescent male, \(k = 0.7\); female 0.55

**Others...(fyi)**

- Urea clearance
- Mayo Clinic
- Counahan-Barratt
- Salazar-Corcoran
- Rule’s
- Jellife
- Sobh
- Shlipak
- Akner

**CKD & CKD Classifications**

<table>
<thead>
<tr>
<th>Stages of CKD</th>
<th>Estimate Glomerular Filtration Rate (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>60 – 89</td>
</tr>
<tr>
<td>3a</td>
<td>45 – 59</td>
</tr>
<tr>
<td>3b</td>
<td>30 – 44</td>
</tr>
<tr>
<td>4</td>
<td>15 – 29</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

**PHARMACOLOGY IN RENAL DISEASE**

**Pharmacokinetics**

- measures rise & fall of drug concentrations in the serum & tissue
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
- \(T_{1/2}\) : the time it takes to eliminate 50% of the drug from the body

**Pharmacodynamics**

- What the drug does to the body
- incorporates kinetics
- integrates microbiological activity focusing on biological effects, particular growth inhibition and killing of pathogens
Pharmacokinetic alterations in CKD

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Alteration in CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>↓, believed to be reduced</td>
</tr>
<tr>
<td>Distribution</td>
<td>↓, reduced plasma protein binding</td>
</tr>
<tr>
<td>Metabolism</td>
<td>↑, accumulation of active metabolites</td>
</tr>
<tr>
<td>Elimination</td>
<td>↑, increased accumulation</td>
</tr>
</tbody>
</table>

Active Learning Question?
Which pharmacokinetic property is affected by CKD?
A. Absorption is reduced
B. Distribution is reduced
C. Metabolism does not change
D. Elimination changes

Pharmacotherapeutics
- Establish a therapeutic outcome for a specific patient
- Monitor patient’s therapy for effectiveness & clinical responses
- Evaluate potential side effects
- Drug Interactions:
  - Additive effect
  - Synergistic effect
  - Incompatibility
  - Adverse drug events
- All drugs are potentially toxic & can have cumulative effects. Knowledge of organs responsible for metabolizing & elimination will allow us to dose appropriately.
  - Especially in pts with compromised organ function

Drug dosing in CKD
- Anticipate problems
- Minimize polypharmacy
- Strategies:
  - Decrease dose
  - Increase Dosing Interval or BOTH
- Methods:
  - Estimate CLcr
  - Consult Dosing recommendations – guidelines
  - Individualize Dose
  - Monitor Serum Drug Concentrations

Drug Dosing in Dialysis
Influencing factors
- Protein Binding – unbound drug for dialysis
- Volume of Distribution-ige Vₐ less dialyzable
- Molecular Weight – MW > 500 not dialyzable
- Dialyzer Membrane Permeability – allow passage of drugs
- Dialyzer Surface Area – larger areas achieve greater clearance
- Blood Flow Rate – fast BFR may allow increased clearance

Dosing in Dialysis: Highly-bound drug

Johnson et al. 2005 Dialysis of Drugs
COMPLICATIONS FROM CKD

<table>
<thead>
<tr>
<th>Complications</th>
<th>Possible Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Blood loss, decreased erythropoietin production, decreased red blood cell lifespan, inadequate dialysis, inadequate iron store due to iron loss and decreased intake, and multiple co-morbid complications</td>
</tr>
<tr>
<td>Cardiovascular Problems</td>
<td>Tachycardia, congestive heart failure, hypertension, pericarditis</td>
</tr>
<tr>
<td>Bone Metabolism</td>
<td>Calculi, phosphate and vitamin D abnormalities (hypocalcemia, decreased vitamin D production, hyperphosphatemia)</td>
</tr>
<tr>
<td>Dialysis Related</td>
<td>Hypotension, dialysis reactions, dialysis technical problems</td>
</tr>
<tr>
<td>Electrolyte Disorders</td>
<td>Metabolic acidosis, hyperkalemia and electrolyte abnormalities</td>
</tr>
<tr>
<td>Fluid Retention</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Gastrointestinal Problems</td>
<td>Hepatitis, gastritis, duodenitis, peptic ulcer disease, colonic arteriovenous malformations, B or C virus</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Increased bleeding tendency</td>
</tr>
<tr>
<td>Infection</td>
<td>Vascular access issues, weakened immune system</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Diabetes mellitus, hyperlipidemia, hyperparathyroidism, hypercalcemia, hyperglycemia, hypoalbuminemia, hyperuricemia, hypoamyloidosis</td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>Muscle cramps, spinal cord compression, dystrophy, polyneuropathy, myopathy, cramps, weakness, fatigue</td>
</tr>
<tr>
<td>Oncologic</td>
<td>Cancer, lymphoma, leukemia, sarcoma, bone disease, recurrent infections</td>
</tr>
<tr>
<td>Perioperative Management</td>
<td>Transplantation, chemotherapy, radiation therapy, surgery, anesthesia, anesthesia complications, arrhythmias</td>
</tr>
</tbody>
</table>
| Special Issues | Acquired Immunodeficiency Syndrome, cancer, infection, malnutrition, fluid overload, electrolyte disorders, uremic encephalopathy, renal osteodystrophy, bone disease, vascular access, anemia, infection, bleeding, heart failure, kidney transplantation, mental health issues, smoking, obesity, diabetes, hypertension, hyperlipidemia, hyperparathyroidism, dyslipidemia, anemia, bone disease, renal osteodystrophy, bone disease, vascular access, anemia, infection, bleeding, heart failure, kidney transplantation, mental health issues, smoking, obesity, diabetes, hypertension, hyperlipidemia, hyperparathyroidism, dyslipidemia, anemia, infection, bleeding, heart failure, kidney transplantation, mental health issues, smoking, obesity, diabetes, hypertension, hyperlipidemia, hyperparathyroidism, dyslipidemia, anemia, infection, bleeding, heart failure, kidney transplantation, mental health issues, smoking, obesity, diabetes, hypertension, hyperlipidemia, hyperparathyroidism, 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**Antihypertensive in CKD: ACEIs & ARBs**

*HTN, a common complication of CKD*

Angiotensin Converting Enzyme Inhibitors
Captopril (Capoten), enalapril (Vasotec), enalaprilat (Vasotec IV), lisinopril (Prinivil, Zestril), ramipril (Altace), benazepril (Lotensin), quinapril (Accupril), fosinopril (Monopril), moexipril HCl (Univasc), spirapril (Renormax), trandolapril (Mavik), perindopril (Aceon).

**The Kidneys**

Produces **Renin** (response to a ↓ in BP)

*reacts with angiotensinogen*

Angiotensin I (ACEI)

(by angiotensin converting enzyme, ACE)

Angiotensin II (ACE II)

Stimulates the adrenal cortex to release

**Aldosterone**

(↑ BP)

(A mineralocorticoid, ↑ the reabsorption of Na+ & H2O by the kidneys, thereby ↑ blood Volume & BP)

**ACEIs**

- Beneficial in pts with HTN & diabetic damage to the kidneys & heart.
- HF – ACEIs significantly ↓ systemic vascular resistance (SVR), BP (afterload), pulmonary capillary obstructive pressure (PAOP or PCWP) (preload), pulmonary vascular resistance (PVR), and heart size; also ↓ CO, stroke index, & exercise tolerance time; Also block the sympathetic nervous system & therefore prevent ventricular remodeling (?end stage HF after an MI) *(↓'ed mortality from CHF by 25 to 31%)*
- Preventing diabetic nephropathy – ↓'ed GFR, **improved renal hemodynamics**, ↓'ed proteinuria, retarded glomerular hypertrophy, & a slower rate of decline in GFR.
- **Excreted primarily by the kidney**
- Half-life is prolonged in RD

**ACEIs: Precautions**

- **First dose effect** (a profound drop in BP); used in 2nd & 3rd trimesters of pregnancy is associated with fetal injury & death; cautious in RD (~20% associated with nephrotic syndrome); **hyperkalemia**.
- **CI**: bilateral renal artery stenosis, angioedema, pregnancy
- **AE’s**: orthostatic hotn, **angioedema**
- **Dry, hacking cough (15 – 20%)** (seem to be related to bradykinin & substance P)
- **Elevations of liver enzymes, BUN/SrCr, K**
- **DI**: Potassium-sparing diuretics, NSAIDs

**Angiotensin Receptor Blockers (ARBs)**

- Losartan potassium (Cozaar), candesartan (Atacand), eprosartan (Teveten), irbesartan (Avapro), olmesartan (Benicar), telmisartan (Micardis), valsartan (Diovan)
- **MOA**: Blocks the vasoconstriction & aldosterone effects of angiotensin, selectively blocking the binding of angiotensin II to angiotensin receptors.
- Have no effect on bradykinin metabolism & therefore more selective blockers of angiotensin effects than ACEIs; potentially have a more complete inhibition of angiotensin action compared with ACEIs b/c there are enzymes other than ACE that are capable of generating ACEII
- **AE’s**: **angioedema**, diarrhea, dizziness, cough *(less than ACE inhibitors)*

**HTN: Diuretics**

- **Thiazides** – early renal failure
  *(In the treatment AKI, large randomized trials have failed to prove diuretics to be effective)*
- Loop diuretics – effective in pts with residual renal fx
  - Furosemide (Lasix), Torsemide (Demadex)
  - Thiazide-like Diuretics – potent, use in CKD/ESRD
    - Indapamide (Lozol), metolazone (Zaroxoline)
  - Osmotic – Mannitol
  - K-Sparing – spironolactone (Aldactone), amiloride (Midamor) *(avoid in hyperkalemia)*
- Monitor: I/O, kidney function, lytes (e.g., K+), ototoxicity, lipid profiles, uric acid, allergy
Beta Adrenergic Blocking Drugs

- Propranolol HCl (Inderal)
- Acebutolol (Sectral)
- Metoprolol (Lopressor)
- Nadolol (Corgard)
- Atenolol (Tenormin)
- Pindolol (Visken)
- Betaxolol (Kerlone)
- Acarboseolol (Caristol)
- Penbutolol (Levatol)
- Timolol (Blocadren)
- Carvedilol (Coreg)
- Esmolol (Brevibloc)
- Sotalol (Betapace)
- Nebivolol (Bystolic)

- ↓ HR
- Bronchospasm
- Masked hypoglycemia
- ↑ triglycerides w/↓HDL

Calcium Channel Blockers

- Amlodipine (Norvasc)
- Nifedipine (Adalat, Procardia)
- Isradipine (Dynacirc)
- Felodipine (Plendil)
- Nisoldipine (Sular)
- Verapamil (Calan, Isoptin)
- Diltiazem (Cardizem)
- Others

- Also used as: antiangina, arrhythmias
- Cause negative inotropic
- Dizziness, HoTN

Other AntiHTN Drugs: Clonidine

MOA: α-2 adrenergic agonists → inhibition of peripheral sympathetic activities & vasodilation in the peripheral blood vessels.

Uses: mild to moderate HTN, lower both the supine & standing BP, therefore may produce orthostatic hypotension (HOTN)

AE’s: CNS-drowsiness, sedation, inability to concentrate, depression, forgetfulness, vivid dreams. Dry mouth, impotence. Orthostatic symptoms.

CI & Precautions: CNS effects, severe coronary insufficiency, recent MI, renal & hepatic disease.

Avoid abrupt cessation, may increases BP, nervousness, anxiety (should slowly taper)

Other AntiHTN Drugs: Minoxidil

- Very potent oral vasodilator.
- Has great potential for antiHTN effect, particularly effective in patients with renal failure & severe HTN or when not responding to Hydralazine
- Advantages: QD dosing, effectiveness in RF
- Disadvantages: fluid retention, hirsutism (~80%)

Active Learning Question?

Select all that apply: Which of the following is TRUE?

- Beta blockers may decrease heart rate
- ACEI’s may cause hypokalemia
- Amlodipine (Norvasc) is a calcium channel blocker
- Furosemide (Lasix) is more potent than HCTZ in CKD patients

STATINS

- Atorvastatin (Lipitor), Fluvastatin (Lescol), Lovastatin (Mevacor), Pitavastatin (Livalo), Pravastatin (Pravachol), Rosuvastatin (Creator), Simvastatin (Zocor)
- HMG Co-A Reductase inhibitor
- SE’s: LFT (AST/ALT), myopathy (muscle pain, rhabdo) (correct vit D, CoQ10, may help), dose adj in CKD (x/atorvastatin)
- DI’s: CYP450, Grapefruit juice
Analgesics in CKD

- **Mild (1-4):** APAP, +/- adjuvants prn
- **Moderate (5-6):** Tramadol (Ultram), Hydromorphone (Dilaudid)?
- **Severe (7-10):** Fentanyl, Methadone, +/- adjuvants

**Not recommended:** Codeine, Oxycodone, Morphine, NSAIDs

**AVOID:** Meperidine, Propoxyphene

CKD & Anemia Management

- **Transfusions**
- **Androgen tx – 1970**
  - Modest success
  - Only 50% of pts respond with a 5% increase in HCT’s
- **Recombinant erythropoietin**
  - EPO, Darbepoetin alfa
- **Iron Therapy (IV)**
  - Iron dextran (Infed), Sodium ferric gluconate (Ferrlecit), Iron Sucrose (Venofer), Ferumoxytol (Feraheme), Ferric carboxymaltose (Injectafer)
- **Adjuvants**

ESAs in CKD: Drug Safety Communication – Modified Dosing Recommendations (6/11)

- **Conservative dosing of ESA**
- ↑ risks of cardiovascular events
- Hb >11 g/dL – no benefits
- Risk vs. Benefits
- Inform patients
- Use the lowest possible dose given to reduce the need for transfusions

ESA: EPO & Darbepoetin alfa

- Revolutionized anemia management in CKD
- Stimulate the production of RBC

**Epoeitin alfa, EPO (Epogen, Procrit)**
- Nearly identical structure to endogenous erythropoetin
- Subcut administration > IV Push
- Usually TIW administration

**Darbepoetin alfa (Aranesp)**
- Similar to EPO but not identical chemical structures
- Differs by an addition of two sialic acid components at the N-glycosylation site
- Results with enhanced molecular weight & increased half-life (~3x longer compared to EPO)
- Usually Weekly or Q2W Administration

Onset of action: several weeks
Avoid rapid rise in Hb (>1 g/dL in any 2-wk period)
Common AE’s: infection, HTN/HoTN, myalgia, H/A, diarrhea, fever, chest pain
Serious AE’s: vascular access thrombosis, CHF, sepsis, cardiac arrh, PRCA

Black Boxed WARNINGS: ↑ ed the risk for death & serious CVS events when Hb >12 g/dL
Iron supplementation: TSAT >20%, sFerritin >200 ng/mL (HD)

NKF-KDOQI 2007

Active Learning Question?

Which of the following is NOT an adverse event associated with ESA drug?

A. Chest pain
B. Hypertension
C. Blood clot
D. Restless leg syndrome
Iron Physiology

- Is a key constituent of Hb & necessary as adjunctive thx to enhance the effectiveness of ESA
- **Ferritin**: Liver is the main storage site of Fe & in the form of ferritin
  - Acute-phase reactivity (↑ed in acute/chronic inflammation, malnutrition, liver disease)
- **Transferrin (TSAT)**: immediate iron on board is essential for erythropoiesis
  - Acute-phase reactivity (significant fluctuations, low in malnutrition/chronic disease)
- **Reticulocyte hemoglobin content**
  - “Real time” assessment of Fe status
  - Measures immediate incorporation of Fe into reticulocytes (in circulation for only 1 day)
  - Less variable/more accurate than sferritin/TSAT

IV Iron

- **Iron dextran** *(Infed, Dexferrum)*
- **Sodium ferric gluconate** *(Ferrlecit)*
- **Iron Sucrose** *(Venofer)*
- **Ferumoxytol** *(Feraheme)*
- **Ferric carboxymaltose** *(Injectafer)*

IV Iron administration

**Oral – not effective (HD)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Anaphylactic Risk</th>
<th>Test Dose</th>
<th>IV Push</th>
<th>Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron Dextran</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Iron Gelatinate</td>
<td>Low</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Iron Sucrose</td>
<td>Low</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ferric carboxymaltose</td>
<td>Low</td>
<td>No</td>
<td>Yes</td>
<td>100 mg, 2x, by 7 days</td>
</tr>
</tbody>
</table>

Iron Dextran: anaphylactic risk (0.6-2.3%), ~0.7% w/life-threatening rxns
Iron Sucrose & Gluconate: better safety profile, similar efficacy
Iron & Infection: microbes synthesize iron transport proteins that compete with transferrin for free iron; Depress sr iron values have been documented during infectious diseases

Iron: SE Profiles

- Anaphylactic-type reactions, pts may present with shock, clinically significant hotn, loss of consciousness, or collapse. Other common ADRs are hotn, h/a, HTN, tachycardia, N/V, and/or diarrhea, dizziness, dyspnea, CP, leg cramps & pain.
- Monitor during & after administration. Sign & symptoms usually resolved within one to two hours

Hyporesponsive Issues

Comorbidities: DM, HTN, Cardiovascular disease,
  - Frequent hospitalizations, blood loss, CA, AIDS
Infection, Inflammation
Iron deficiency (Absolute & Functional)
Aluminum toxicity
Pure Red Cell Aplasia (PRCA)
Hypoalbuminemia
Elevated C-reactive protein level
Temporary & permanent catheter insertions

Overcoming Hyporesponsive Issues?

L-Carnitine
  - A carrier involved in the transport of fatty acid
  - HD patients may have low level
  - No pathogenic mechanism that may contribute to anemia
Vitamin C (Ascorbate)
  - May help ↑ the release of Fe from ferritin & the reticuloendothelial system, which ↑ Fe utilization during heme synthesis
Conclusion: Insufficient evidence
Not recommended: Androgens
Mineral & Bone Disorders

- Severe Hyperparathyroidism (sHPT)
- Vitamin D’s analogs
- Phosphate-binding drugs
- Cinacalcet (Sensipar)
  - Calcium sensing receptors
  - Decrease PTH hormone
  - Lowering serum calcium levels
  - Dose sHPT – 30 mg po daily; increase q2-4w, prn
  - AE’s: N/V, hypocalcemia, seizures

NKF-KDOQI Target Treatment Goals for CKD Stage 5

<table>
<thead>
<tr>
<th>Serum Phosphorus</th>
<th>Corrected serum Calcium</th>
<th>Ca x P Product</th>
<th>Intact plasma PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5 – 5.5 mg/dL</td>
<td>8.4 – 9.5 mg/dL</td>
<td>&lt;55 mg²/dL</td>
<td>150 – 300 pg/mL</td>
</tr>
</tbody>
</table>

Ca-based binder: 1500 mg/day (elemental Ca)

The New KDIGO

Ca, P, PTH, Alk Phos - should be monitored regularly; adjust according to trends rather than specific target values

<table>
<thead>
<tr>
<th>PTH</th>
<th>CKD stages 3-5</th>
<th>Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above the assay’s upper limit</td>
<td>Evaluate for hyperP, hyperCa, &amp; vit D deficiency. Treatment w/vitamin D is suggested if progressively rises &amp; remains above the upper-normal limit.</td>
<td>Maintain ~2.9 times upper-normal limit (~10600 pg/mL).</td>
</tr>
</tbody>
</table>

Monitoring Intervals

<table>
<thead>
<tr>
<th>CKD</th>
<th>Ca &amp; P</th>
<th>PTH</th>
<th>Alk. Phos</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Q6-12m</td>
<td>Baseline &amp; CKD progression</td>
<td>Q6-12m.</td>
</tr>
<tr>
<td>4</td>
<td>Q3-6m</td>
<td>Q6-12m</td>
<td>Q12months, or more frequently if PTH is elevated</td>
</tr>
<tr>
<td>5</td>
<td>Q1-3m</td>
<td>Q1-3m</td>
<td>Q12months, or more frequently if PTH is elevated</td>
</tr>
</tbody>
</table>

Which binder?“Any one will do”, Dr. Martin KJ, Work Group for KDOQI

Lowering elevated P levels toward the normal range

Kalantar-Zadeh K et al, Kidney Int, 2008[in press]

Comparing PTH and Alkaline Phosphatase

Kalantar-Zadeh K et al

Serum levels of P, PTH, Ca & Risks of Death & CVS Disease in Individuals with CKD

- Treatment target levels: P, PTH, Ca
- Association of those levels with risks of death, cardiovascular mortality & nonfatal CVS events
- MEDLINE & EMBASE (1947 – 2010); 8380 citations, 47 cohort studies, N = 327,644

Serum Levels

<table>
<thead>
<tr>
<th>Serum Levels</th>
<th>Change in Levels</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>Every 1 mg/dL increase</td>
<td>18% ↑ed risk of death (RR 1.18, 95% CI, 1.12-1.25)</td>
</tr>
<tr>
<td>PTH</td>
<td>RR 1.01 per 100 pg/mL increase, 95%, 1-1.01</td>
<td>No significant association between all-cause mortality</td>
</tr>
<tr>
<td>Ca</td>
<td>RR 1.08 per 1 mg/dL increase, 95% CI, 1-1.16</td>
<td></td>
</tr>
</tbody>
</table>

Serum levels of P, PTH, Ca & Risks of Death & CVS Disease in Individuals with CKD

Conclusion: The evidentiary basis for a strong, consistent, & independent association between serum levels of Ca & PTH & the risk of death & CVS events in CKD is POOR. There appears to be an association between higher serum levels of P & mortality in this population.

Active Learning Question?
Which drug is not a vitamin D?
A. Cinacalcet (Sensipar)
B. Calcitriol (Calcijex)
C. Doxercalciferol (Hectorol)
D. Paricalcitol (Zemplar)

Antimicrobials
• Gram (+) coverage: Cefazolin, nafcillin, vancomycin, linezolid (Zyvox), quinupristin/dalfopristin (Synercid), daptomycin (Cubicin), Tigecycline (Tygacil), others
• Gram (-) coverage: aminoglycosides, fluoroquinolones, 3rd gen cephalosporins, others
• AntiFungals: e.g. Amphotericin, Fluconazole
• AntiVirals: e.g. Acyclovir
Dosages must be adjusted for renal failure

Antimicrobial: Cefazolin (Ancef, Kefzol)
SOA: sensitive staph & strep
Dose: nl 0.5-1.5 g, q8-6h, CLcr <10 mL/min, q24-48h.
PKs: renal excretion (56-100%), t1/2 1.5-2.5 hrs (nl), 11-13 hrs (renal failure), 40-70 hrs (anephric)
Dialyzable: Yes
HD: moderately dialyzable (20-50%), dose post-HD, or 0.5-1 g supplemental dose post-HD
PD: 0.5 g, q12h
CAVH/CAVHD: removes 30 mg/liter of filtrate/day
AE’s & Precautions: GI (diarrhea), renal impairment
Antimicrobial: Vancomycin
SOA: MRSA, Staph & Streph PCN allergic patients  
Dose: q12h→q24h→q48h→q96h→q5→7 days.  
PK: Renal excretion, t1/2 4-6hrs (nl RF), 7.5 days (avg anephric pts)  
Dialyzability: Conventional membranes - not dialyzable (0-5%), no longer used.  
Newer high-flux filter – dialyzable, dose post-HD  
Not significantly removed by CAPD, Clearance ~10-15 mL/min (CAHD)  
AE’s: rash (red neck), chills, drug fever.  
Slow infusion, not exceeding 10 mg/min, extremely irritating & may cause tissue necrosis  
Precautions: avoid IM, presence of renal impairments/drugs, pre-existing hearing loss, slow IV infusions  
Monitor: Trough, Random levels (avoid level w/in 6hr post-HD; wait ~20hrs)

Aminoglycosides: Gentamycin, Tobramycin, Amikacin
SOA: serious infections, gram negative, staph  
PK: Renal excretions (60-85%), t1/2 1.6-3 hrs (nl), 53 hrs (anephric)  
Dialyzable (HD, PD, Hemoperfusion): Yes, dose post-HD  
AE’s: ototoxicity, nephrotoxicity, neurotoxicity, edema, rash, GI’s  
Precautions: other nephro/ototoxicity agents, impair renal function.  
Monitor: Peak & trough, random levels

Unadjusted Associated ADRs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>ADEs Associated with Unadjusted Dosage Regimens in CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>Bleeding, seizures, tremors, thrombocytopenia</td>
</tr>
<tr>
<td>Imipenem</td>
<td>CNS toxicity, seizures</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Bleeding complications, prolonged PTT</td>
</tr>
<tr>
<td>Penicillin</td>
<td>CNS toxicity, lethargy, seizures</td>
</tr>
<tr>
<td>Acy/Ganci</td>
<td>Seizures, confusion, renal damage</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Nephropathy, ARF</td>
</tr>
<tr>
<td>Nitrofurantion</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Torsades de Pointes, Achille tendonitis with ruptures, hepatitis</td>
</tr>
</tbody>
</table>

Active Learning Question?  
Which statement is NOT true?  
A. Vancomycin is used primarily to treat gram positive infection  
B. Gentamycin may be administered anytime during dialysis  
C. Vancomycin should be administered slowly, no more than 10 mg/min  
D. Both Vancomycin and Gentamycin are dialyzable

Intradialytic Agents  
- Hypertonic Solutions: 23.5% NS, 5% NS, 3% NS  
  - Warning – JC Patient Safety High Alert  
- Normal Saline (NS)  
- Plasma expanders: Albumin, Mannitol  
- Sympatholytics: Midodrine  
  - Alpha agonist, activates phospholipase C, effects smooth muscle contraction increasing BP

Intradialytic Agents  
- Sympatholytics: Midodrine  
  - Alpha agonist, activates phospholipase C, effects smooth muscle contraction increasing BP
PHARMACOLOGY IN RENAL DISEASE: GI

Nausea, Vomiting / Hiccups / Peptic Ulcers –
- uremic toxins from the kidney directly irritate the GI tract

$H_2$ – antagonists: inhibit gastric acid secretion
- Cimetidine (Tagamet), Ranitidine (Zantac), Famotidine (Pepcid), others
- Required dose adjustment
- Pks: onset 30min-1hr
- AE’s: h/a, GI’s, CNS
- Precautions: renal/hepatic impairments, Drug interactions, CNS side effects, change in AST/ALT

PHARMACOLOGY IN RENAL DISEASE: GI

Proton pump Inhibitors: suppress acid secretion by inhibiting the parietal cell $H^+$/K$^+$ ATP pump
- Lansoprazole (Prevacid), pantoprazole (Protonix), omeprazole (Prilosec), others
- PK: onset ~1hr
- AE’s: h/a, dizziness, tachycardia, edema, GI’s, muscle cramps, C.diff, ICU-related infection
- DI: clopidogrel (Plavix)