PHARMACOTHERAPY IN CKD PATIENTS
Definitions

- Renal Insufficiency
- Azotemia
- Uremia
- CKD
- ESRD
**ESRD**

- Définition
- Staging chronic kidney disease based-on GFR

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min/1.73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>At ↑risk</td>
<td>≥ 90 with CKD risk factor</td>
</tr>
<tr>
<td>1</td>
<td>Damage with normal/↑ GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Damage with mild ↓ GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15/ need for transplant</td>
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</table>
Patients at Risk

- Males
- Elderly
Etiology of CKD

- Diabetes: 33.8%
- HTN: 28.3%
- Glomerulonephritis: 12.6%
- Cystic kidney disease: 3%
- Interstitial nephritis: 3%
- Others: 19.3%
Main Causes of Death in ESRD

- Cardiac: 65%
- Septicemia: 15%
Complications of ESRD

- anemia
- renal osteodystrophy (hypo Ca, hyper P, sHPT)
- GI complications, bleeding
- neurological complications
- dermal complications
- leg cramps
- homeostatic complications
- cardiovascular complications (HTN, hyperlipidemia)
ESRD Complications Management

Anemia

Epoetin:

- Human erythropoietin
- Indication: Hgb<10, Hct<30%
- Recommended target range : Hct 33-36%, Hgb 11-12g/dL
- Hgb is more reliable; Hct depends on volume status, T, hyperglycemia, size of RBC
- SC: 80-120U/Kg/WK  IV: 120-180U/Kg/WK; 1-3 times weekly
- Side effects: HTN, flulike syn., H/A, seizure
ESRD Complications Management

Anemia

- IV vs SC administration of Epoetin:
  - $T_{1/2}$: 4-9 hrs (IV); 11-25hrs (SC)
  - Prolonged maintenance of active drug concentration and a slower decline in serum level with SC
  - SC administration is more physiologically similar to endogenous erythropoietin production
- SC administration is recommended by K/DOQI guideline
ESRD Complications Management

Anemia

- Darbepoetin
- Hyperglucosylated analogue of epoetin alfa
- Longer $T_{1/2}$ than epoetin ⇒ less frequent dosing (once weekly), 0.45μg/kg once/week or 0.75 μg/kg once every other week
ESRD Complications Management

Anemia

- Resistance to erythropoietic therapy:
  - iron deficiency,
  - infection,
  - inflammation,
  - chronic blood loss,
  - Al toxicity,
  - malnutrition,
  - hyperparathyroidism,
  - perhaps concomitant ACE inh. therapy
ESRD Complications Management
Anemia

**Iron:**
- **Goal:** TSAT: 20-50%, Ferritin: 100-800ng/mL
- **Dose:** 200mg/d to maintain sufficient iron status while receiving erythropoietic therapy
- **Take on an empty stomach to maximize absorption**
- **Drug interactions:** Antiacid, quinolones
- **Side Effects:** N, D, constipation, abdominal pain, dark stool
ESRD Complications Management

Anemia

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Iron percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulfate +7H2O</td>
<td>20</td>
</tr>
<tr>
<td>Ferrous sulfate anhydrous</td>
<td>30</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>11</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>33</td>
</tr>
</tbody>
</table>
ESRD Complications Management

Anemia

- IV iron preparation
  - Iron dextran (DexFerrum): dextran may cause anaphylactic reactions, administer a test dose of 25mg and observe pt for 1h before the total dose infusion
  - Sodium ferric gluconate complex in sucrose (ferrlecit)
  - Iron sucrose (iron hydroxide sucrose complex)(venofer)
ESRD Complications Management

Anemia

- Iron toxicity: *hemosiderosis* (may increase the risk of infection), *organ dysfunction* secondary to iron deposition in the heart, liver, pancreas
ESRD Complications Management

Anemia

- **Folic acid**: 0.8-1mg/d
- Why the folic acid dose is 5mg/d in dialysis pts?
ESRD Complications Management

Anemia

- Monitoring:
  - Hgb and Hct Q1-2wk at first; once stable, Q2-4wk
  - Iron indices Q3mo to ensure TSAT & ferritin do not exceed 50% & 800ng/mL res esp when using IV iron
ESRD Complications Management

Hyperphosphatemia

**Dietary P restriction** (milk, meat, legumens, carbonated beverage) to 800-1000mg/d

**Phosphate binders (esp when CrCl<30ml/min):**
1) Ca products
2) Al products
3) Mg products
4) Sevelamer hydrochloride (polymer-based)

All Phosphate binders must be administered with meal
Ca Products

Ca Carbonate (40% Ca)
Ca Acetate (25% Ca)
Ca citrate (21% Ca)

- P binding efficacy:
  Ca carbonate = Ca citrate
  Ca acetate = 2 × Ca carbonate

- Goal: Ca × P < 55; if exceed, switch to nonCa-based binders

- Max Ca provided by binders should not exceed 1500mg/d
Ca Products

- Side effects: nausea, constipation/diarrhea, hypercalcemia & calcifications
- Ca citrate increases Al absorption from GI; be careful
- Drug interactions (Fe, FQs, tetracycline)
Al products

- **Al hydroxide**
  - With meals
  - Side effects: constipation (docusate, sorbitol, **bisacodyl**), osteomalacia, microcitic anemia, fatal neurologic syndrome called dialysis encephalopathy
  - Considered on a short-term basis (up to 4 weeks) for pts with \(\uparrow\)Ca-P product
  - Antidote: deferoxamin

- **Sucralfate**
Mg Products

P binder in *dialysis* pts who do not respond to Ca
Sevelamer hydrochloride (Renagel)

- Ca & Al free Phosphate binder
- Is now considered a first line agent in pts with stage 5 CKD
- With meals
- It reduces LDL and total cholesterol as well
- Cap 403mg, tab 400, 800mg
- Serum P<7.5mg/dL: 800mg TID; Serum P≥7.5mg/dL: 1600mg TID
- Adjust dose at 2 weeks interval based on [P]
- 800mg sevelamer ≈ 169mg elemental Ca for P binding
Sevelamer hydrochloride

- Coadministration of elemental Ca (900mg/d) + sevelamer result in greater ↓ in both P and PTH than either agent alone without significant ↑ in serum Ca
- Administer sevelamer 1h before or 3h after administration of other agents with narrow therapeutic indices
- Administration of sevelamer to hemodialysis pts has been associated with ↓ serum bicarbonate
Lanthanum carbonate

- An elemental compound
- Currently being investigated as an alternative phosphate binder
Nicotinic Acid

- Some studies have shown the P lowering capacity of nicotinic acid with dosage of 500mg/d.

- Use SR form to ↓ side effects
ESRD Complication Management
Secondary Hyperparathyroidism

- Vit D analogues
  - Calcitriol (1,25 DHCC)
- IV over oral
  - Oral therapy is as effective as pulse IV therapy with a similar incidence of hypercalcemia
- Intermittent over persistent
  - 19-nor-1,25 dihydroxy vit D₂ (paricalcitol)
  - 1- hydroxy vit D₂ (doxercalciferol)
- Dihydrotachysterol

More important effect: ↓PTH

D₂ analogs cause less hypercalcemia than D₃
ESRD Complication Management
Secondary Hyperparathyroidism

- Strategy to minimize hypercalcemia while maximize PTH suppression
  - Administration calcitrol at bedtime or between meals
ESRD Complication Management
Secondary Hyperparathyroidism

- The calcimimetic agents
  - Enhance the affinity of Ca receptors for extracellular Ca and suppress PTH
  - Cinacalcet (Sensipar®); tab 30, 60, 90mg; start with 30mg/d with food
  - ADRs: Hypocalcemia, myalgia
  - Drug interactions: Major inhibitor of 2D6

- Biphosphonates
  - Block osteoclastic bone resorption
  - Be confined to the acute treatment of hypercalcemia resulting from hyperparathyroidism
ESRD Complication Management

Hyperkalemia

- Avoidance of drugs inducing hyperkalemia:
  - potassium-sparing diuretics
  - $\beta$-blockers, predominantly via $\beta_2$-antagonistic effects
  - ACEIs, ARBs
- Maintain a good bowel regimen
- Dietary potassium restriction of 50-80 mEq/d
- Sodium polystyrene sulfonate?
- Hemodialysis
- IV calcium gluconate, insulin+ glucose, nebulized albuterol
ESRD Complication Management

GI complications & bleeding

* Gastric emptying delay:
  Metoclopramide, cisapride

* Nausea/vomiting: antiemetic, dialysis

* Bleeding:
  Antacids, H2 Antagonists, PPIs

* H.pylori therapy
ESRD Complication Management
Neurological Complications

Peripheral neuropathy
- TCAs
- Anticonvulsants (Phenytoin, Gabapentin)
- Effect of transplant (ameliorate nerve dysfunction)
- Effect of dialysis (No)

Autonom (sympathetic/parasympat.) dysfunction
ESRD Complication Management
Psychological Complications

- Depression
- Anxiety
- Psychosis
ESRD Complication Management

Dermal Complications

- Hyperpigmentation, abnormal perspiration, dryness, pruritus

Pruritus management:

- dialysis, antihistamines, topical emollients, topical steroids, cholestyramin, nalteroxon (no success in some studies), ketotifen, epoetin, rifampin, activated charcoal, cromolin, UV$_B$ phototherapy
ESRD Complication Management

Leg cramps

- ↓ Ultrafiltration rate
- Isotonic/hypertonic saline
- Hypertonic dextrose
- Vit E 400U at bed time
- Stretching exercises
- Kinine sulfate
ESRD Complication Management
Homeostatic Complications
Uremic Bleeding

- Common complication in pts with CKD
- Primary mechanism
  - Platelet biochemical abnormalities and alterations in platelet-vessel wall interactions
  - Impaired binding of von Willebrand factor multimers to platelet membrane glycoprotein receptors
  - Anemia, hyperparathyroidism, uremic toxin accumulation, altered concentrations of PGs and coagulation mediators (ADP, serotonin, thromboxane A₂), ↑Nitric oxide
ESRD Complication Management
Homeostatic Complications
Uremic Bleeding

- Avoiding drugs that increase the risk of bleeding
  - anticoagulants, antiplatelet agents, NSAIDs and β-lactams
- PD cause less bleeding events than HD due to better removal of larger molecular weight uremic toxins
ESRD Complication Management
Homeostatic Complication
Uremic Bleeding

- Dialysis
- Cryoprecipitate
- DDAVP:
  - enhance release of von Willebrand factor multimers, serotonin
  - IV form: rapid onset, short duration
  - Nasal spray, solution 10mcg/puff, Inj 4, 15mcg/mL
  - Side effects: flushing, risk of thrombus formation, H/A, GI compliants
ESRD Complication Management
Homeostatic Complication
Uremic Bleeding

- Conjugated estrogen
  - **Mechanism**: antagonism of nitric oxide synthesis, perhaps through reduction of L-arginine
  - **High cost**, inconvenient administration but long duration, no tachyphylaxis has been reported
  - **Dosage**:
    - IV: 0.6mg/kg/day for 5 days
    - PO: 1-50mg/day
    - Transdermal: 50-100µg/24hrs, applied every 3.5 days for 2 months
ESRD Complication Management

Homeostatic Complication

- Cellular Immunity:
  - Vit B6: 10mg/day (HD); 5mg/day (PD)
  - Zn
Other requirements of ESRD patients

**Homocysteinemia:** Vit B6, B12, Folic acid (5mg/d)

**Levocarnitine** (IV not PO) improves quality of life, anemia, host cellular defence, muscular function and indicates in following pts who did not respond to standard therapies:

1) muscular cramps,
2) hypotension during dialysis
3) lack of energy
4) skeletal muscle weakness/ myopathy
5) cardiomyopathy
6) anemia
Other requirements of ESRD patients

- Vit A
ESRD Complication Management

Cardiovascular Complications

- Pericarditis *(dialysis, Indomethacin, Corticosteroids, surgery)*
ESRD Complication Management
Cardiovascular Complications

- HTN (furosemide (+thiazides/metolazone), ACE inh., ARBs, CCBs (nondihydropyridines))
ESRD Complication Management
Cardiovascular Complications
HTN

- ACEIs and CCBs may be the first choice for ESRD patients
- Bone marrow depression has been noted in 10% of renal failure patients receiving captopril
- Dosage of all ACEIs except fosinopril need to be adjusted in CKD
ESRD Complication Management
Cardiovascular Complications

HTN

- Is **dihydropyridines CCBs** effective in the treatment of HTN in ESRD patients?
  - Fail to adequately treat hypertension in patients receiving dialysis due to causing reflex stimulation of the sympathetic nervous system

- No dosage adjustment or replacement doses following dialysis is required
ESRD Complication Management
Cardiovascular Complications
HTN

- β-blockers are preferable in dialysis patients with MI
- Sympathetic nervous active agents
  - Prazocin, terazocin, doxazosin, clonidine, methyldopa
- Vasodilators
  - Hydralazine, minoxidil
  - Useful in patients resistant to combinations of other agents
Thanks for your attention