
بسم الله الرحمن الرحیم

PHARMACOTHERAPY IN CKD PATIENTS

Definitions

- Renal Insufficiency
- Azotemia
- Uremia
- CKD
- ESRD

ESRD

- Définition
- Staging chronic kidney disease based-on GFR

Stage	Description	GFR (ml/min/1.73)
-	At ↑risk	≥ 90 with CKD risk factor
1	Damage with normal/↑ GFR	≥90
2	Damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	<15/ need for transplant

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 erythropoetin
- 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$\Rightarrow$ 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 erythropietic 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

Preparation	Iron percent
Ferrous sufate +7H2O	20
Ferrous sulfate anhydrous	30
Ferrous gluconate	11
Ferrous fumarate	33

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 increase 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 ↑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 analogus

  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 D_2(paricalcitol)

  1- hydroxy vit D_2(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
  - β-blockers, predmoninantly via β_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 emolients, 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 A_2),↑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 3.5days 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 deffence, 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)cardimyopathy

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

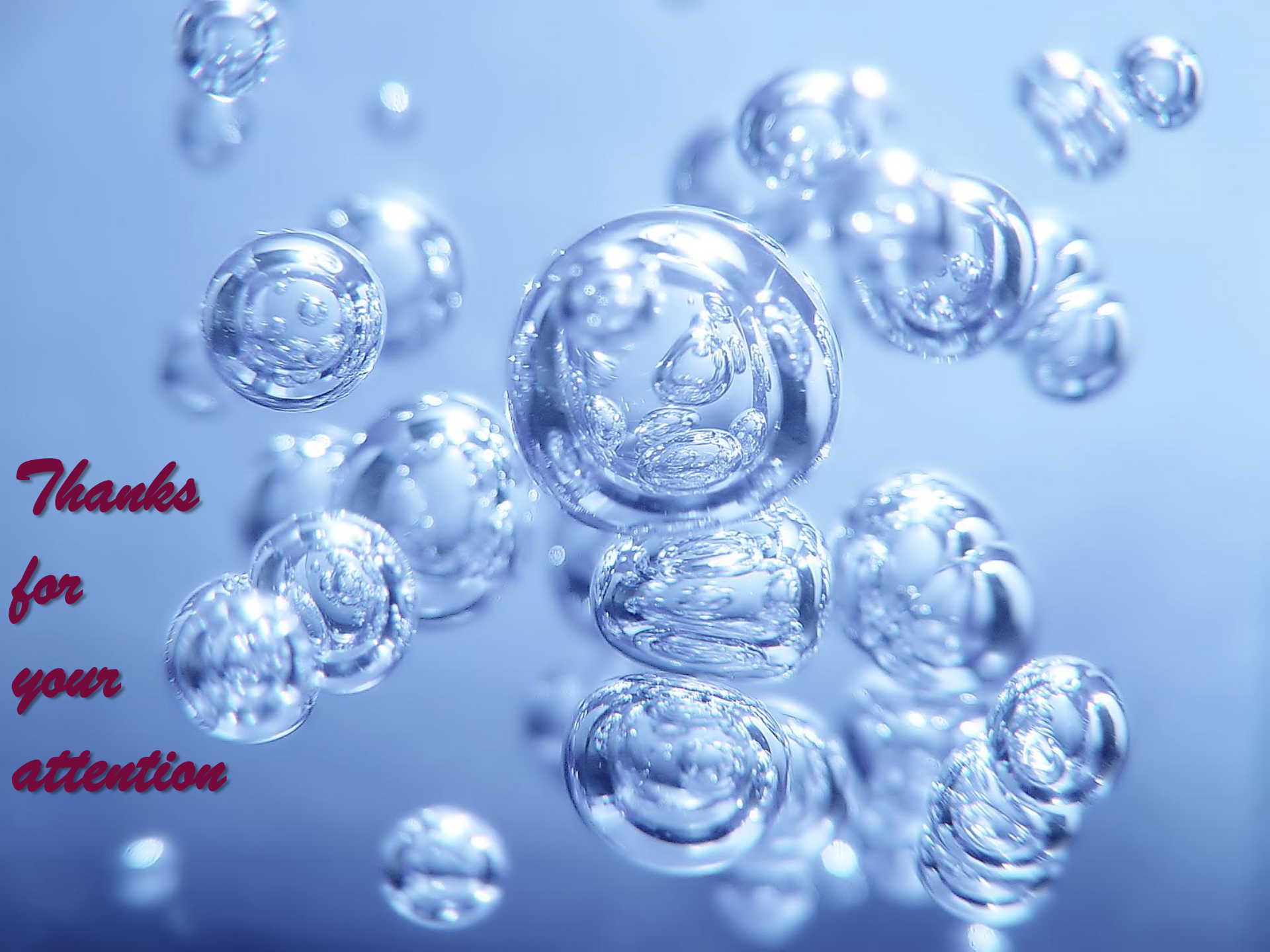
- Is dihydropyridines CCBs effective in the treatment of HTN in ESRD patients?
  - Fail to adequately treat hypertension in patients receiving dialysis due to causing reflex stimulation of the sympathetic nervous system
- No dosage adjustment or replacement doses following dialysis is required

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