University of Anbar
College of pharmacy
Therapeutic I, 5th stage
Lecturer : Yasir Farhan

Chronic Renal Failure

Chronic renal failure is defined as abnormalities in **kidney structure** or **function**, present for 3 months or longer, with implications for health.

Definitions

1. Azotemia - elevated BUN >28mg/dL) and creatinine (Cr>1.5mg/dL)
2. Uremia - azotemia with symptoms or signs of renal failure
3. End Stage Renal Disease (ESRD) - uremia requiring transplantation or dialysis
4. Creatinine Clearance (CCr) - the rate of filtration of creatinine by the kidney (GFR marker)
5. Glomerular Filtration Rate (GFR) - the total rate of filtration of blood by the kidney

Pathophysiology

A-**Susceptibility factors** increase the risk for kidney disease but **do not directly** cause kidney damage. They include

1- Advanced age.
2- Reduced kidney mass
3- Low birth weight
4- Racial or ethnic minority, family history, low income or education, systemic inflammation, and dyslipidemia.

B-Initiation factors <u>directly</u> result in kidney damage and are modifiable by drug therapy. They include :

1- Diabetes mellitus

2- Hypertension

3- Glomerulonephritis

4- polycystic kidney disease

5- wegener granulomatosis,

6- vascular diseases and human immunodeficiency virus (HIV) nephropathy.

C-Progression factors hasten the decline in kidney function after initiation of kidney damage.They include

1- Glycemia in diabetics

2- Hypertension

3- Proteinuria

4- Hyperlipidemia

5- Obesity and smoking.

Most progressive nephropathies share a final common pathway to irreversible renal parenchymal damage and ESRD

Key pathway elements include

— **1-** loss of nephron mass

— 2- Glomerular capillary hypertension.

— 3- Proteinuria.

Stages of chronic renal failure

The stages of chronic kidney disease are determined by the glomerular filtration rate(GFR). There are five stages of CRF , categorized in the following table :

Table 33. Stages of Chronic Kidney Disease: A Clinical Action Plan

Stage	Description	GFR (mL/min/1.73 m^2)	Action*
1	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment, Treatment of comorbid conditions, Slowing progression, CVD risk reduction
2	Kidney damage with mild ↓ GFR	60–89	Estimating progression
3	Moderate ↓ GFR	30–59	Evaluating and treating complications
4	Severe ↓ GFR	15–29	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	Replacement (if uremia present)

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

* Includes actions from preceding stages.

Abbreviations: CVD, cardiovascular disease

Clinical Presentation

Patients with stage 1 or 2 CRF usually do not have symptoms or metabolic derangements seen with stages 3 to 5 such as anemia, secondary hyperparathyroidism, cardiovascular disease (CVD), malnutrition, and fluid and electrolyte abnormalities that are more common as kidney function deteriorates.

Uremic symptoms include:

Fatigue, weakness, shortness of breath, mental confusion, nausea, vomiting, bleeding, and anorexia) are generally **absent** in stages 1 and 2, **minimal** during stages 3 and 4, and **common** in patients with stage 5 CRF who may also experience itching, cold intolerance, weight gain, and peripheral neuropathies.

Treatment

Goal of Treatment:

The goal is to **delay the progression of CKD**, minimizing the development or severity of complications.

Nonpharmacological therapy

A-Restrict protein to 0.8 g/kg/day if GFR is less than 30 mL/min/1.73 m2.

B-Encourage smoking cessation to slow progression of CKD and reduce the risk of CVD.

C- Encourage exercise at least 30 minutes five times per week and achievement of a body mass index (BMI) of 20 to 25 kg/m2.

Pharmacological therapy

A - Diabetes and Hypertension With CRF

Adequate blood pressure (BP) & DM control can **reduce the rate of decline in GFR** and **albuminuria** in patients without diabetes.

Target blood pressure is

140/90 mm Hg If urine albumin excretion is less than 30 mg/24 h ,

130/80 mm Hg If urine albumin excretion is greater than 30 mg/24 h .

1- **Initiate first-line** therapy with an (ACEI) or an angiotensin II receptor blocker (ARB).

2- Adding a **thiazide** diuretic in combination with an ARB if additional reduction in proteinuria is needed.

3- Nondihydropyridine (CCB) like amlodipine are generally used as second-line antiproteinuric drugs when ACEIs or ARBs are contraindicated or not tolerated.

Note

ACEI clearance is reduced in CRF; therefore, treatment should begin with **the lowest possible** dose followed by **gradual titration** to achieve target BP and, secondarily, to minimize proteinuria. No individual ACEI is superior to another.

B - Anemia of CRF

It can be defined by Hemoglobin (Hb) less than 13 g/dL for adult males and less than 12 g/dL for adult females.

Initiation with erythropoietic-stimulating agent (ESA) therapy in all CRF patients with Hb is between 9 and 10 g/dL.

1 - Epoetin alfa is given , Subcutaneous (SC) administration of epoetin alfa is preferred because IV access is not required, and the SC dose that maintains target indices is 15% to 30% lower than the IV dose.

2 - Darbepoetin alfa has a **longer half-life** than epoetin alfa and **prolonged biologic** activity. Doses are administered less frequently, starting at once a week when administered IV or SC.

Iron deficiency is the primary cause of resistance to treatment of anemia with ESAs, so, **Iron supplementation** is required by most CRF patients to replete iron stores depleted by ongoing blood loss and increased iron demands.

Parenteral iron therapy **improves response** to ESA therapy and **reduces the dose required** to achieve and maintain target indices. In contrast, oral therapy is limited by **poor absorption** and **nonadherence with therapy primarily due to adverse effects**

Adverse effects of IV iron include allergic reactions, hypotension, dizziness, dyspnea, headaches, lower back pain, arthralgia, syncope, and arthritis. Some of these reactions can be **minimized** by decreasing **the dose or rate of infusion.** Sodium ferric gluconate, iron sucrose, and ferumoxytol have a **better safety record** than iron dextran products.

Hypertension is the most common adverse event of ESA.

C – CRF related Mineral and Bone Disorders

The abnormalities in parathyroid hormone (PTH), calcium, phosphorus**,** vitamin D are related to CRF.

As kidney disease progresses, renal activation of vitamin D is **impaired**, which reduces gut absorption of calcium. **Low blood calcium** concentration stimulates secretion of PTH.

As renal function declines, serum calcium balance can be maintained by increased bone resorption, ultimately resulting in renal **osteodystrophy** (ROD).

Elemental calcium and phosphate binding agents **sevelamer and lanthanum carbonate** are used

Adverse effects of all phosphate binders are generally limited to GI effects, including **constipation, diarrhea, nausea, vomiting, and abdominal pain.**

Aluminum and magnesium binders are not recommended for regular use in CRF because aluminum binders have been associated with **CNS toxicity** and the **worsening of anemia**, whereas magnesium binders may lead **to hypermagnesemia** and **hyperkalemia.**

Vitamin D3 :

Calcitriol, 1,25-dihydroxyvitamin D3, directly suppresses PTH synthesis and secretion and upregulates vitamin D receptors. The dose depends on the stage of CRF.

The newer vitamin D analogues **paricalcitol and doxercalciferol** also used and may be associated with less **hypercalcemia** doxercalciferol and, less **hyperphosphatemia** for paricalcitol, **.**

D - **Dyslipidemia**

guidelines recommend treatment with a **statin (eg, atorvastatin** 20 mg, **fluvastatin 80 mg, rosuvastatin 10 mg, simvastatin 20 mg) in adults** aged 50 and older with stage 1 to 5 CRF not on dialysis.