Chronic Kidney Diseases (CKD)

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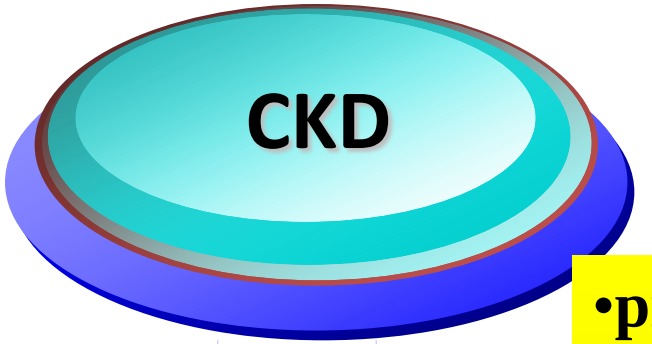
Contents

- **Definition, stage, epidemiology of CKD**
- **Causes and pathophysiology of CKD**
- **Clinical and laboratory manifestations of CKD**
- **Treatment of CKD**

Chronic Kidney Diseases (CKD) ---Definition (NKF-K/DOQI)



- GFR <60 mL/min
- with or without kidney damage
- ≥3 months

Loss of kidney function

- presence of kidney damage
  - pathologic abnormalities
  - markers of kidney damage
  - imaging tests
- ≥3 months

Kidney damage

Defining "Kidney Damage"

- Pathologic Abnormalities
  - By Radiology (US, CT, MR, etc)--e.g.
    - Multiple cysts consistent with PKD
    - Extensive scarring
    - Small kidneys
    - REMEMBER: Renal masses or complex cysts that are not simple should be referred to a UROLOGIST!!
  - By Histology--ie, renal biopsy

Defining “Kidney Damage”

- Markers of Kidney Damage
  - Proteinuria
  - Microalbuminuria
  - Hematuria (especially when seen with proteinuria)
    - Isolated hematuria has a long differential: infection, stone, malignancy, etc.
  - Casts (especially with cellular elements)

Definition

- Chronic kidney disease (CKD)
- Chronic renal failure (CRF)
- End stage renal diseases (ESRD)
- Uremia

Definition

- Chronic kidney disease (CKD)
  - A spectrum of different pathophysiologic processes associated with abnormal kidney function and a progressive decline in GFR
  - A spectrum of clinical problems beginning with abnormalities detectable only by laboratory testing to a late stage, labeled uremia.

Definition

- Chronic renal failure (CRF)
  - A pathophysiologic process with multiple causes that lasts > 3 months and results in progressive, irreversible attrition of the number and function of nephrons
  - Typically corresponds to CKD stages 3–5
  - Frequently leads to end-stage renal disease (ESRD)

Definition

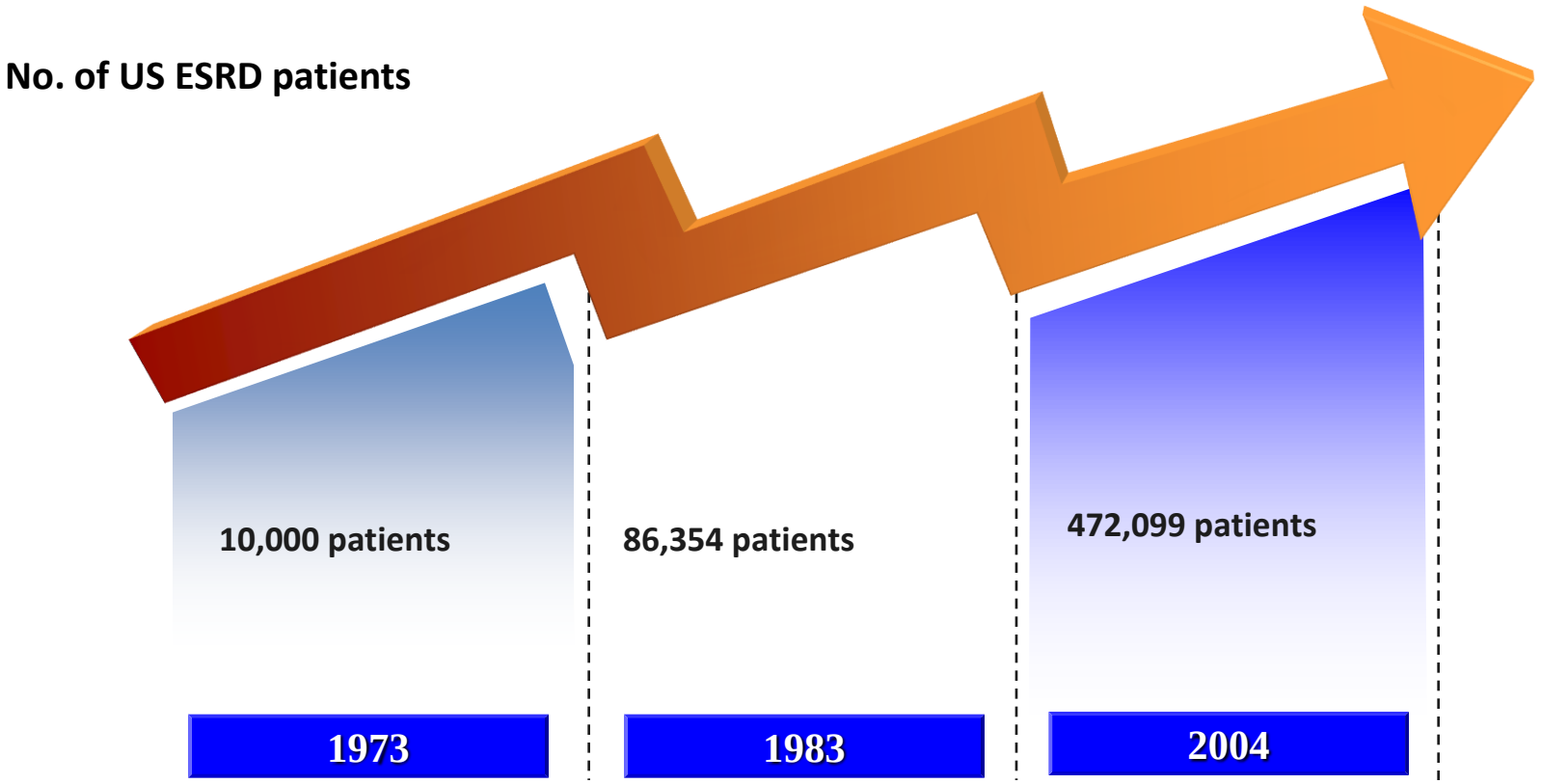
- End stage renal diseases (ESRD)
  - Clinical state in which irreversible loss of endogenous renal function has occurred
  - Patients are permanently dependent on renal replacement therapy to avoid life-threatening uremia.
  - CKD Stage 5

- Uremia
  - A clinical syndrome reflecting dysfunction of all organ systems due to untreated or undertreated acute or chronic renal failure

Stage and Prevalence of CKD

Stage	Description	GFR (ml/min/1.73 m^2)	Prevalence	
			N (1000s)	%
1	Kidney Damage with Normal or ↑ GFR	≥ 90	5,900	3.3
2	Kidney Damage with Mild ↓ GFR	60-89	5,300	3.0
3	Moderate ↓ GFR	30-59	7,600	4.3
4	Severe ↓ GFR	15-29	400	0.2
5	Kidney Failure	< 15 or Dialysis	300	0.1

Epidemiology
A rising incidence and prevalence of CKD



500 million CKD patients worldwide! 1 CKD patient every 10 people!

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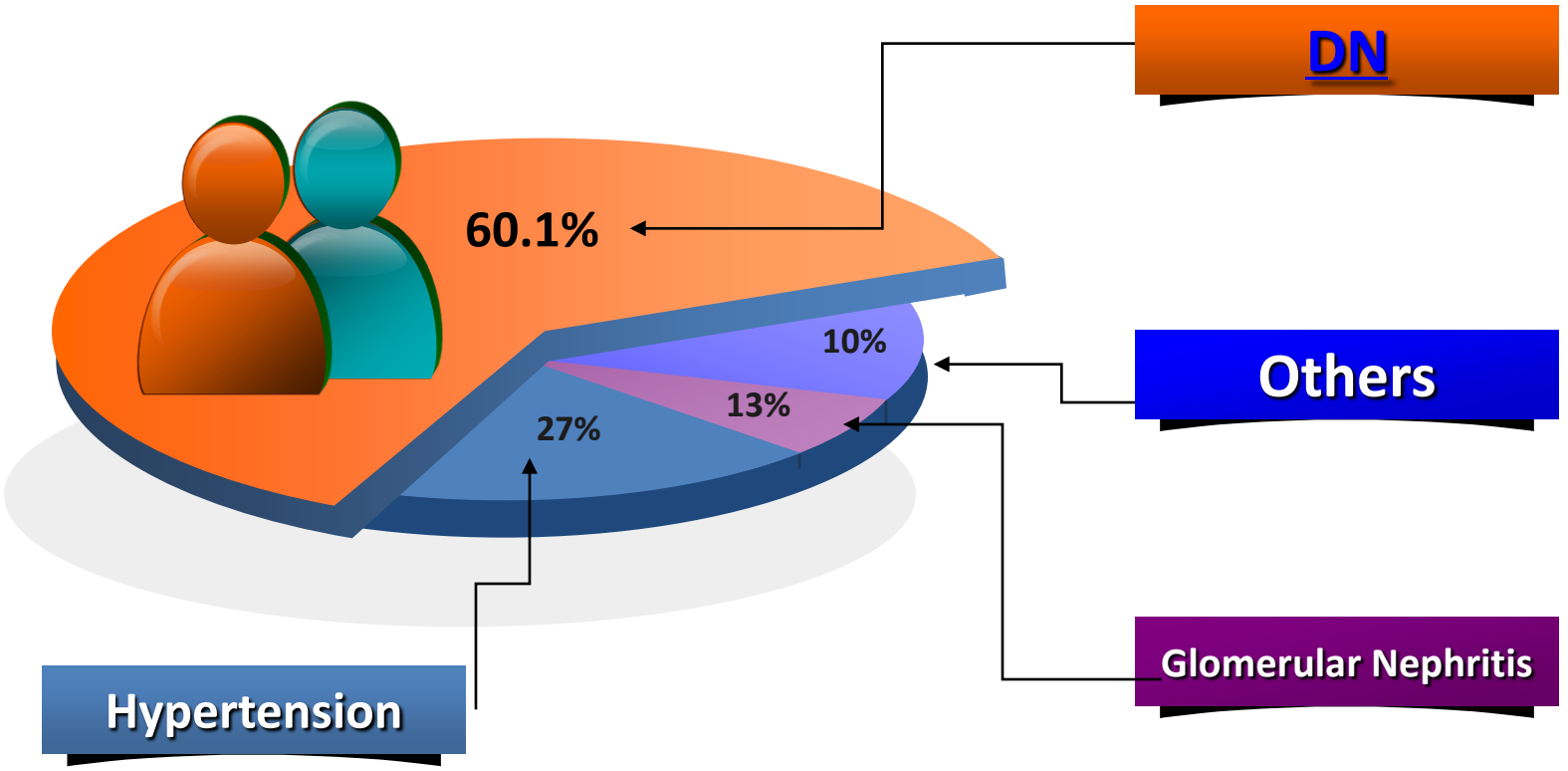
Causes of CKD

- Glomerular disease
- Diabetic glomerulosclerosis
- Hypertensive nephrosclerosis
- Tubulointerstitial disease
- Vascular disease
- Cystic diseases

Primary Diseases of CKD Stage 5 in US



United States Renal Data System. Annual Data Report. 2000

Pathophysiology of CKD

Functions of the kidney and problems due to impairment of kidney functions

Kidney Functions	Consequences of Dysfunction
Maintain concentrations and body contents of electrolytes and fluid volumes	Hyponatremia, hyperkalemia, low total potassium content, hypocalcemia, hyperphosphatemia, decreased tolerance to electrolyte or mineral loading
Regulate blood pressure	Hypertension, cardiovascular disease
Endocrine mediators	Anemia (low erythropoietin), hypertension (renin system activation), bone disease (secondary hyperparathyroidism), low vitamin D activation, prolonged half-lives of peptide hormones (e.g., insulin)
Waste product excretion	Anorexia, nausea, soft tissue deposition of oxalates and phosphates, neurologic dysfunction, loss of muscle protein

Pathophysiology of CKD

- **Balance and Steady-State Considerations**
- **The Tradeoff Hypothesis**
- **Hypertension**
- **Endocrine Disorders**
- **Accumulation of Uremic Toxins**

Balance and Steady-State Considerations

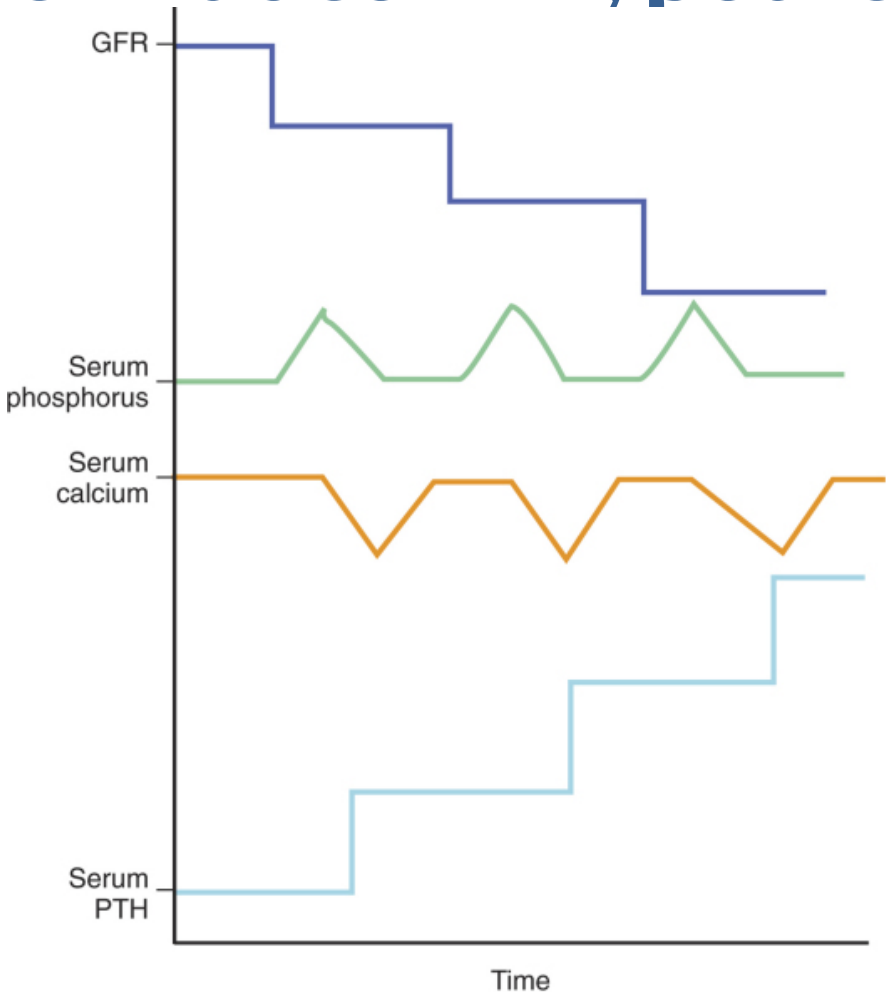
- **Balance state**
  - **the condition in which the intake or production of a substance equals its elimination**
- **Steady state**
  - **the intake or processes of production and elimination are not changing**

The Tradeoff Hypothesis

- A patient with CKD will achieve balance by activating pathophysiologic responses

- But the responses lead to a tradeoff that has the potential of causing adverse consequences

The Tradeoff Hypothesis



A decrease in glomerular filtration rate (GFR) is followed by an increase in serum phosphorus and a decrease in serum calcium. An increase in serum parathyroid hormone (PTH) returns phosphorus and calcium to normal levels.

Hypertension

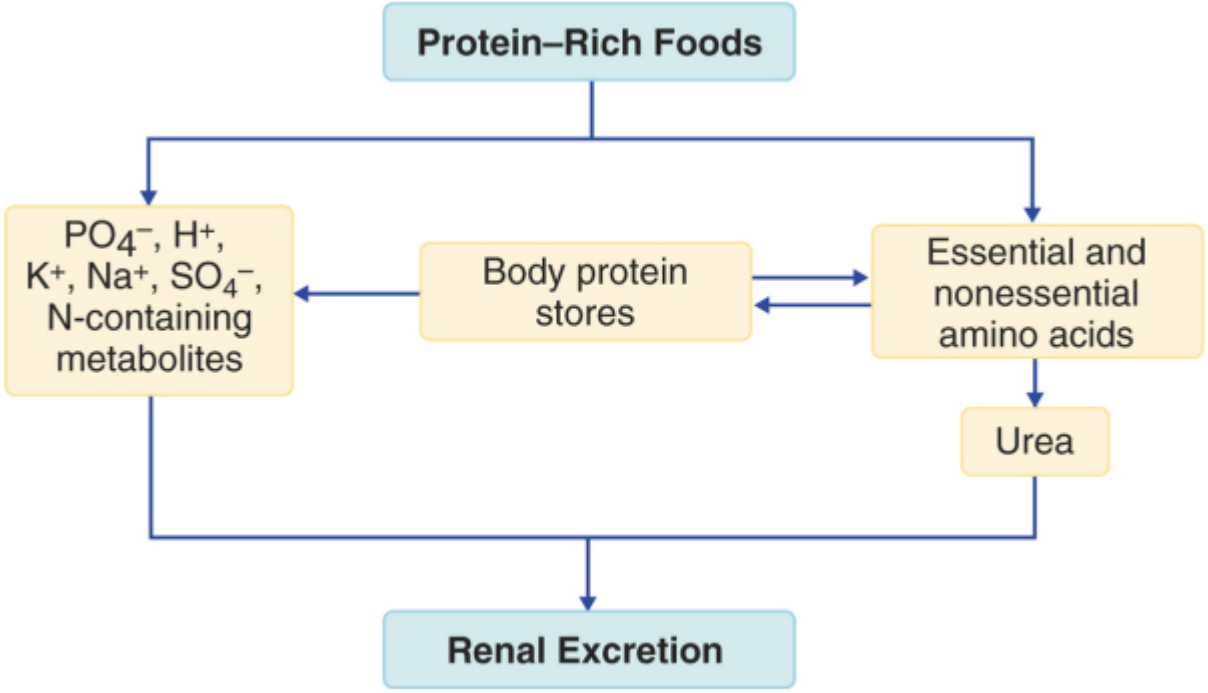
- **An expanded extracellular volume from a salt-rich diet and a decreased capacity for excretion of sodium**

- **Activation of the renin-angiotensin-aldosterone (RAA) system and the sympathetic nervous system**

Endocrine Disorders

- **Decreased function of 1,25-dihydroxyvitamin D_3**
- **Insulin resistance**
- **Decreased ability to degrade small proteins, including several hormones**
- **Impaired production of erythropoietin**

Accumulation of Uremic Toxins



Breakdown of dietary protein enlarges the pool of essential and nonessential amino acids that can be used to synthesize body protein. The amino acids are also used to produce urea, which must be excreted. Besides nitrogenous waste products, dietary protein catabolism yields inorganic ions that must be excreted.

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Clinical Manifestations

- Patients are often asymptomatic in the early stages

- Some symptoms and signs of CKD are associated with specific causes

Clinical Manifestations

- **General (systemic) symptoms of uremia**
  - Fatigue
  - Nausea
  - Vomiting
  - Shortness of breath
  - Edema
  - Weight change
  - Muscle cramps
  - Decreased mental acuity
  - Decreased urine output
  - Easy bleeding and bruising
  - Decreased sensation in hands and feet
  - Neuropathy

Complications

- Endocrine and metabolic
- Neuromuscular
- Cardiovascular and pulmonary
- GI
- Hematologic and immunologic
- Dermatologic

Complications

- **Endocrine and metabolic**
  - Secondary hyperparathyroidism
  - Osteitis fibrosa cystica
  - Osteomalacia
  - Hyperuricemia
  - Hypertriglyceridemia
  - Protein-energy malnutrition
  - Infertility and sexual dysfunction
  - Amenorrhea
  - Amyloidosis

Complications

- **Neuromuscular**
  - Peripheral neuropathy
  - Restless legs syndrome
  - Paralysis
  - Seizures
  - Sleep disorders

Complications

- **Cardiovascular and pulmonary**
  - Arterial hypertension
  - Cardiomyopathy
  - Congestive heart failure
  - Accelerated atherosclerosis

Complications

- **GI**
  - Peptic ulcer
  - GI bleeding
  - Constipation

Complications

- **Hematologic and immunologic**
  - Anemia
  - Splenomegaly and hypersplenism
  - Increased susceptibility to infection
  - Bleeding diathesis

Complications

- **Dermatologic**
  - Hyperpigmentation
  - Pruritus
  - Calciphylaxis
  - Nephrogenic fibrosing dermopathy

Laboratory Tests

- Chemistry in ESRD (stage 5 CKD)
  - Hyperkalemia
  - Metabolic acidosis
  - Hyperphosphatemia
  - Hypocalcemia
- Complete blood count
  - Anemia, usually normocytic and normochromic
    - Evaluate iron, B_{12}, folate levels.

Laboratory Tests

- Urinalysis
  - Proteinuria
  - Hematuria
  - Broad, waxy casts

- 24-hour urine collection
  - To quantify proteinuria
  - Heavy proteinuria (>3.5 g/d) in addition to hypoalbuminemia, hypercholesterolemia, and edema suggests nephrotic syndrome

Laboratory Tests

- Erythematosus and vasculitis
  - If history and physical examination warrant
- Serum and urinary protein electrophoresis in all patients > 35 years of age with unexplained CKD and anemia
  - Excludes paraproteinemia
- In the presence of glomerulonephritis, underlying infectious etiologies should be assessed.
  - Hepatitis B
  - Hepatitis C
  - HIV

Imaging

- **Renal ultrasonography**
  - Provides estimate of kidney size and symmetry and rules out renal masses and obstructive uropathy
  - Symmetric small kidneys support diagnosis of CKD.
  - Normal kidney size suggests possibility of an acute process.
    - Polycystic kidney disease, amyloidosis, diabetes, and HIV-associated renal disease may lead to CKD with normal kidney size.
  - Asymmetric kidney size suggests unilateral developmental abnormality or chronic renovascular disease.

Imaging

- Spiral CT without contrast
  - May be useful in assessing kidney stones
  - Reveals pathognomonic features
  - Avoid exposure to intravenous radiocontrast dye

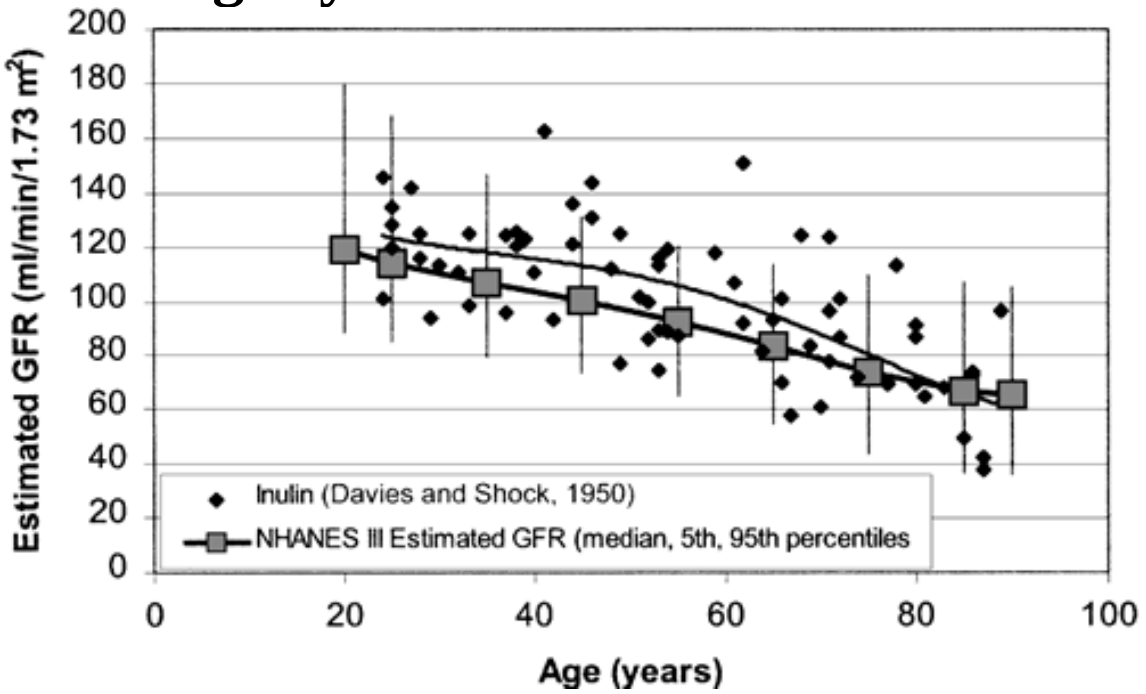
Imaging

- Vascular imaging
  - Duplex Doppler sonography of the renal arteries, radionuclide scintigraphy, or magnetic resonance angiography
    - Should be strongly considered if revascularization is possible

Estimation of GFR

The normal annual mean decrease in GFR with age beginning at age 20–30 years is 1 mL/min/m^2/1.73 m^2.

- **Reaches a mean value in men of 70 mL/min/m^2 at age 70 years**
- **GFR is slightly lower in women than in men.**



GFR normally decreases with age!

Measurement of glomerular filtration function

- GFR measurement by isotope
- Ccr (endogenous creatinine clearance rate)
- Estimation of GFR (MDRD, Cockcroft–Gault equation)
- Serum Creatinine

Serum Creatinine

- Serum Creatinine alone CAN NOT be used to accurately assess level of kidney function.
- S. creatinine is a function of production (muscle mass) and excretion (both GFR and tubular secretion).
- Age, sex, and lean body mass have to be taken into account.
- Factors Affecting Serum Creatinine Concentration

Factors Affecting Serum Creatinine Concentration

Increase	*Decrease*
• Kidney Disease • Ketoacidosis • Ingestion of cooked meat • Drugs: – Trimethoprim – Cimetidine – Flucytosine – Some cephalosporins	• Reduced Muscle Mass • Malnutrition

Cockcroft-Gault Equation to Predict GFR

- Prediction based on age, gender, creatinine and ideal body weight
  - Estimated creatinine clearance (mL/min) = [(140 – age) × body weight (kg)]/[72 × P_{Cr} (mg/dL)]
  - Multiply by 0.85 for women.

- **Used almost universally as the basis for drug dosing!**

MDRD Equation to Predict GFR

- Developed to follow GFR as part of the Modification of Diet in Renal Disease (MDRD) study
- Prediction based on age, gender, race and serum creatinine.
    - Estimated GFR (mL/min/1.73 m^2 body surface area) $= 1.86 \times (P_{Cr})^{-1.154} \times (age)^{-0.203}$
    - Multiply by 0.742 for women.
    - Multiply by 1.21 for African Americans.

Get it at
http://www.kidney.org/professionals/KDOQI/gfr.cfm

Diagnostic Approach

- Exclude acute kidney injury.
- Establish GFR to stage disease.
- Determine the cause of early-stage CKD.
  - Use clinical presentation and noninvasive tests, if possible.
  - Use renal biopsy if the cause cannot be established.
- In advanced CKD, definitive diagnosis is less feasible and of less therapeutic significance.

Differentiate from AKI

- **Past creatinine and urea concentrations**
- **Findings consistent with CKD**

Differentiate from AKI

- **Findings consistent with CKD**
  - **Bilaterally reduced kidney size (< 8.5 cm) on imaging studies**
  - **Normocytic, normochromic anemia**
  - **Evidence of chronic metabolic bone disease with hyperphosphatemia, hypocalcemia, elevated PTH level, and radiologic bone disease**
  - **Urinary sediment that is inactive or reveals proteinuria and broad casts**

Diagnostic Approach

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- Establish GFR to stage disease.
- Determine the cause of early-stage CKD.
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Diagnostic Procedures

- **Renal biopsy**
  - May be the only way to establish etiology in early CKD
    - Reserved for patients with near-normal kidney size, in whom diagnosis cannot be made by less invasive means and a reversible underlying disease process remains possible
  - Extent of tubulointerstitial scarring on kidney biopsy provides the most reliable pathologic correlate indicating prognosis for continued deterioration toward ESRD

Diagnostic Procedures

- **Renal biopsy**
  - Contraindications
    - Bilateral small kidneys
    - Polycystic kidney disease
    - Uncontrolled hypertension
    - Urinary tract or perinephric infection
    - Bleeding diathesis
    - Respiratory distress
    - Morbid obesity

Diagnostic Procedures

- **Renal biopsy**
  - Approach
    - Ultrasonography-guided percutaneous biopsy is favored
    - Surgical approaches, including laparoscopic biopsy, may be considered in special circumstances, such as biopsy of a solitary kidney

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Treatment

- Treatment of reversible causes of renal dysfunction
- Preventing or slowing the progression of renal disease
- Treatment of the complications of renal dysfunction
- Identification and adequate preparation of the patient in whom renal replacement therapy will be required

Reversible causes of renal dysfunction

- Decreased renal perfusion
- Administration of nephrotoxic drugs
- Urinary tract obstruction

Preventing or slowing the progression of renal disease

- Angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs)
- Blood pressure control
- Reduction in protein excretion
- Optimal level of protein intake, hyperlipidemia and metabolic acidosis control, smoking cessation

Treatment of the complications of renal dysfunction

- Hypertension
- Anemia
- Renal osteodystrophy
- Volume overload
- Hyperkalemia
- Metabolic acidosis
- Dyslipidemia

Clinical Practice Guidelines for Management of Hypertension in CKD

Type of Kidney Disease	Blood Pressure Target (mm Hg)	Preferred Agents for CKD, with or without Hypertension	Other Agents to Reduce CVD Risk and Reach Blood Pressure Target
Diabetic Kidney Disease	<130/80	ACE inhibitor or ARB	Diuretic preferred, then BB or CCB
Nondiabetic Kidney Disease with Urine Total Protein-to-Creatinine Ratio ≥200 mg/g			
Nondiabetic Kidney Disease with Spot Urine Total Protein-to-Creatinine ratio <200 mg/g		None preferred	Diuretic preferred, then ACE inhibitor, ARB, BB or CCB
Kidney Disease in Kidney Transplant Recipient			CCB, diuretic, BB, ACE inhibitor, ARB

Anemia

- **Erythropoietin**
- **Iron supplement**

Anemia

- **Erythropoietin**
  - **Initiation: 100u/kg/week**
  - **Increase 50% of the dose: Hct increase less than 2% per month**
  - **Decrease 25% of the dose: Hct increase more than 8% per month**
  - **Target: Hct 33%--36% Hb 11—12g/dl**

Anemia

- **Iron supplement**
  - **Target: serum ferritin >100 ng/mL or transferrin saturation (TSAT) >20 percent**
  - **Oral: 200mg elemental iron/day**
  - **Intravenous: 100mg elemental iron/time, for 10 times**

    After target reached, 25-125mg elemental iron/week

Renal osteodystrophy

- **Treating of hyperphosphatemia**
  - Dietary phosphate restriction
  - Phosphate binders : calcium carbonate
    sevelamer
    Lanthanum
- Calcitriol (1,25-dihydroxyvitamin D)
- Perathyroidectomy

Managing fluid, electrolyte, and acid–base disorders

- Extracellular fluid volume expansion
  - Loop diuretics, with dietary salt restriction
    - Mainstay of therapy
    - Occasionally in combination with metolazone
    - Side effects: hypovolemia, with precipitation of further decrease in GFR

Managing fluid, electrolyte, and acid–base disorders

- Hyperkalemia
  - Acute
    - Intravenous calcium chloride or gluconate
    - Intravenous insulin with glucose
    - Intravenous bicarbonate
    - Oral or *per rectum* ion exchange resin (sodium polystyrene sulfonate)
  - Chronic
    - Dietary potassium restriction
    - Avoidance of potassium-containing or -retaining medications or salt substitutes
    - Sodium polystyrene sulfonate 15–30 g PO qd in juice or sorbitol

Managing fluid, electrolyte, and acid–base disorders

- Metabolic acidosis
  - Sodium bicarbonate, calcium bicarbonate, or sodium citrate, 20–30 mmol/d, divided in 2 doses
  - Titrate to maintain bicarbonate at > 20 mEq/L.
- Hyponatremia
  - Uncommon in predialysis patients
  - Water restriction

Treatment of complications of ESRD

- Malnutrition
- Uremic bleeding
- Pericarditis
- Uremic neuropathy
- Thyroid dysfunction

Indications for renal replacement therapy

- Symptoms for emergency dialysis
  - Acute pulmonary edema
  - K^+>6.5mmol/L
  - Metabolic acidosis, TCO2<13mmol/L
  - Anuria >2 days, Oliguria>4 days

Indications for renal replacement therapy

- GFR
  - GFR of less than 15 mL/min per 1.73 m2 (2006 K/DOQI)
  - GFR is approximately 8 to 10 mL/min per 1.73 m2 (2005 European Best Practice Guidelines)

Choice of renal replacement therapy

- Dialysis
  - Hemodialysis
  - Peritoneal dialysis

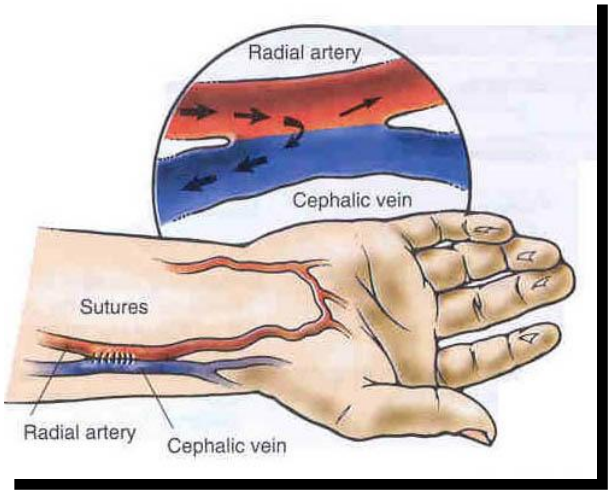
- Renal transplantation

Dialysis

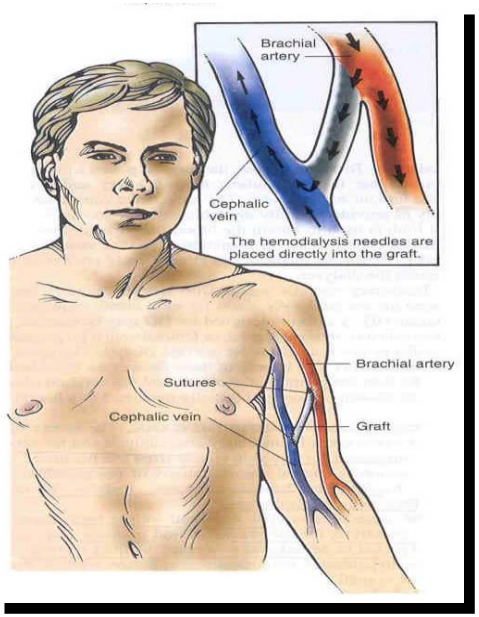
- Principles of dialysis
  - Diffusion , convection through the semipermeable membrane
- Semipermeable membrane
  - Hemodialysis: dialyzer
  - Peritoneal dialysis: peritoneum

Hemodialysis

Vascular Access



AV fistula

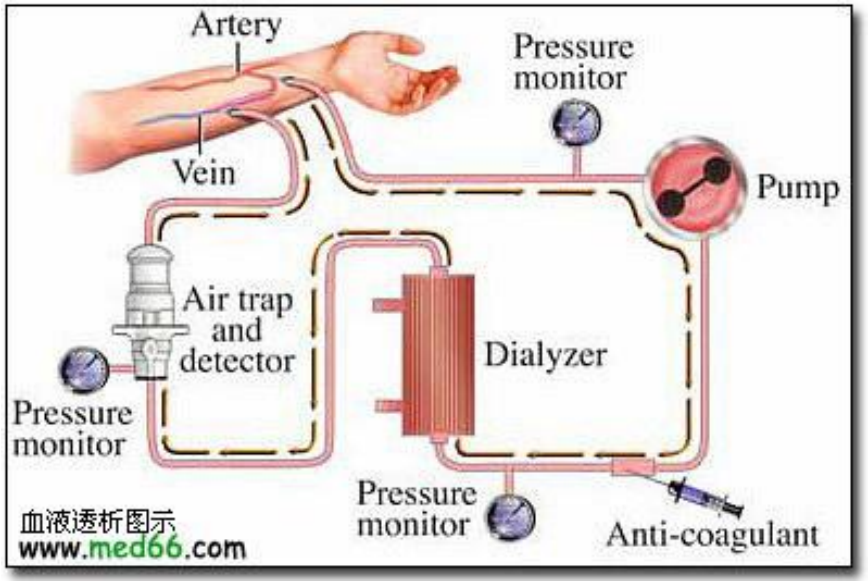


AV Graph Access

Catheter

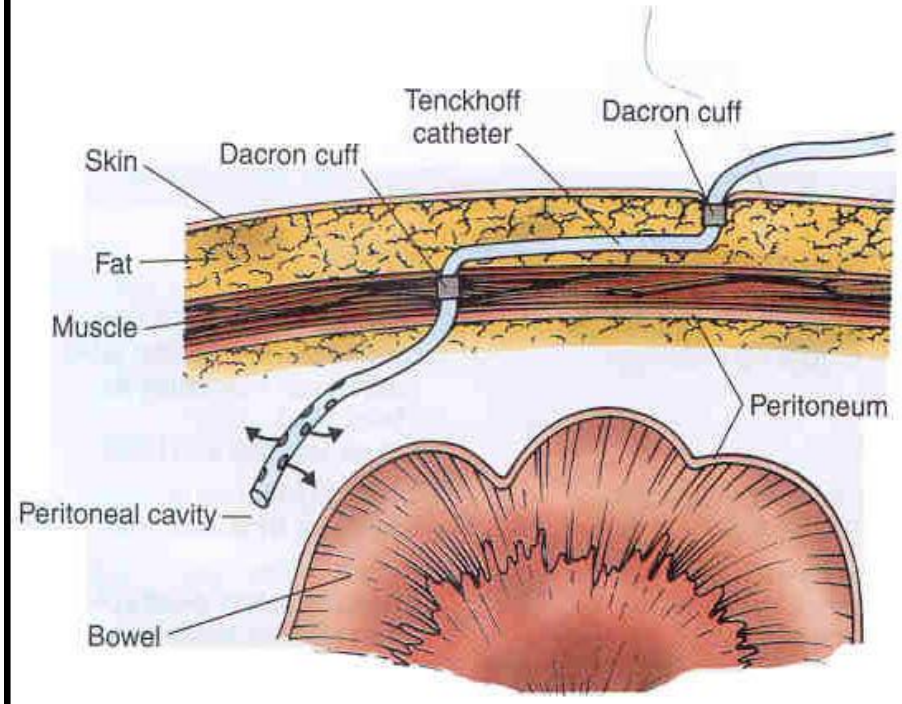
Hemodialysis

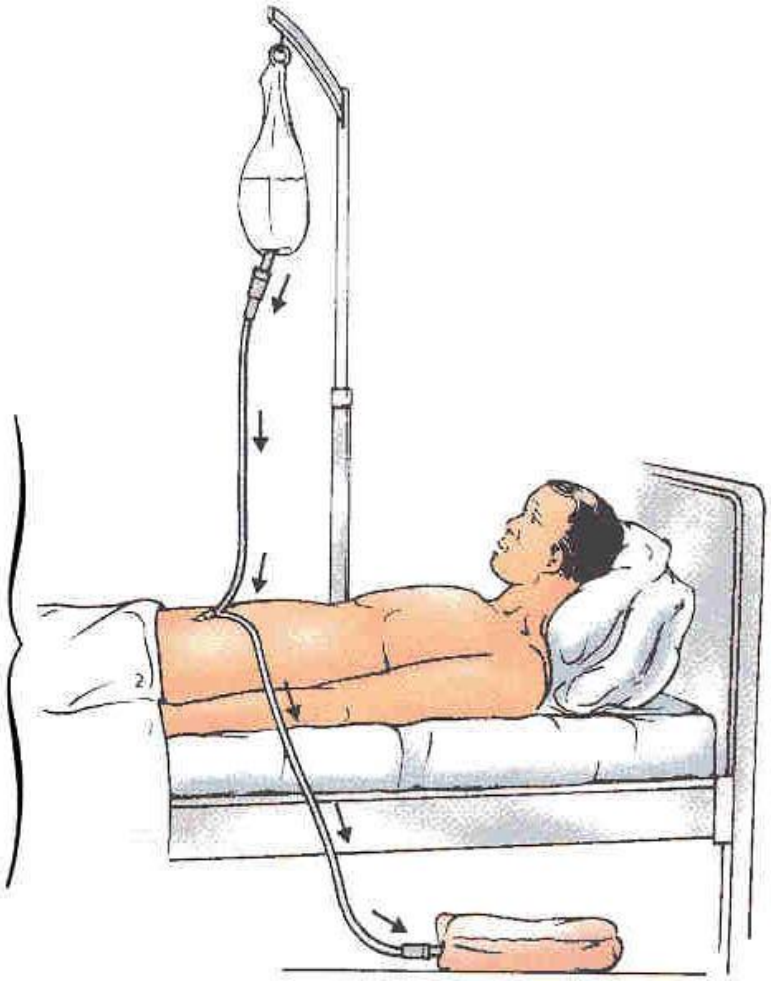
Hemodialysis circuit



Hemodialysis machine

Peritoneal Dialysis





Dialysis

Choice of dialysis methods

- **Hemodialysis:**
  - Hypercatabolism,
  - Recent abdominal operation,
  - Respiratory Failure

- **Peritoneal dialysis**
  - Active bleeding
  - Unstable cardiovascular function
  - Difficult to place vascular access

Clinical Practice Guidelines for the Detection, Evaluation and Management of CKD

Stage	Description	GFR	Evaluation	Management
	At increased risk		Test for CKD	Risk factor management
1	Kidney damage with normal or ↑ GFR	>90	Diagnosis Comorbid conditions CVD and CVD risk factors	Specific therapy, based on diagnosis Management of comorbid conditions Treatment of CVD and CVD risk factors
2	Kidney damage with mild ↓ GFR	60-89	Rate of progression	Slowing rate of loss of kidney function [1]
3	Moderate ↓ GFR	30-59	Complications	Prevention and treatment of complications
4	Severe ↓ GFR	15-29		Preparation for kidney replacement therapy Referral to Nephrologist
5	Kidney Failure	<15		Kidney replacement therapy

[1]Target blood pressure less than 130/80 mm Hg. Angiotension converting enzyme inhibitors (ACEI) or angiotension receptor blocker (ARB) for diabetic or non-diabetic kidney disease with spot urine total protein-to-creatinine ratio of greater than 200 mg/g.

Conclusions

- **CKD is a public health problem with poor outcomes and high cost. CKD is *underdiagnosed* and *undertreated*.**

- **Early CKD detection and intervention may increase opportunities for the prevention of ESRD and of complications of CKD, including death.**

Thank you!