Pharmacotherapy in Kidney Diseases

Scope

- Acute Kidney Injury
- Drug Induced Kidney Diseases
- Chronic Kidney Diseases

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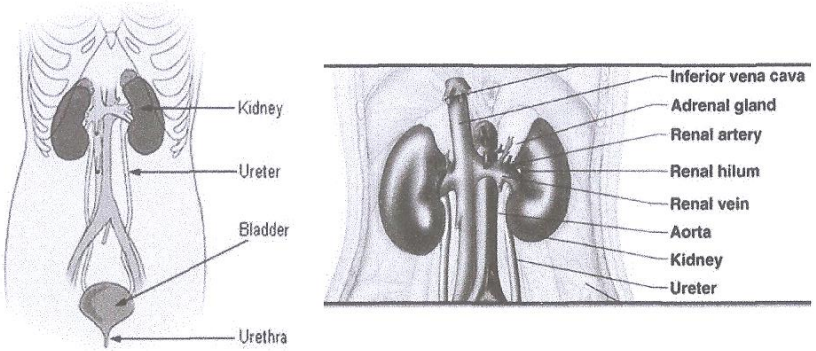


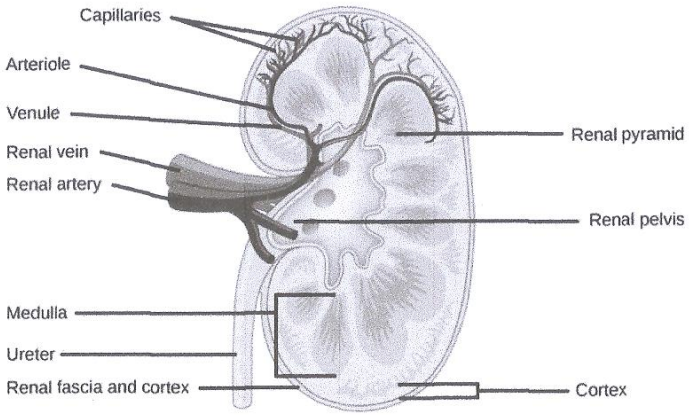


Figure 2. The internal structure of the kidney is shown. (credit: modification of work by NCI)

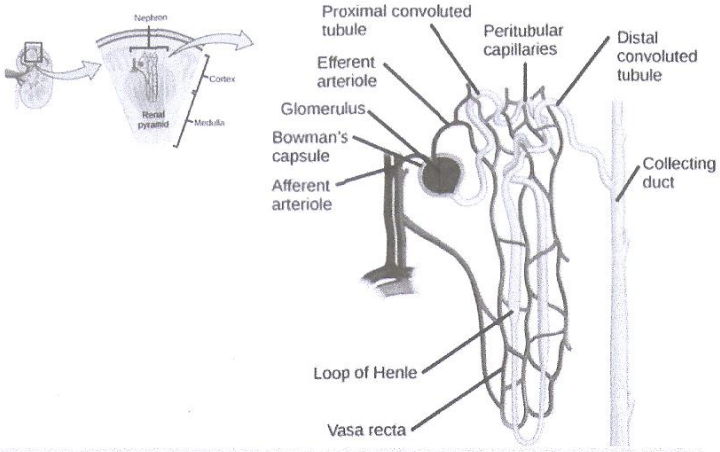
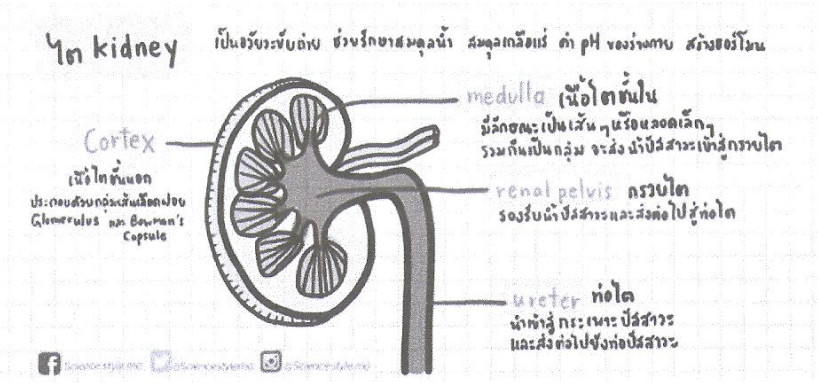
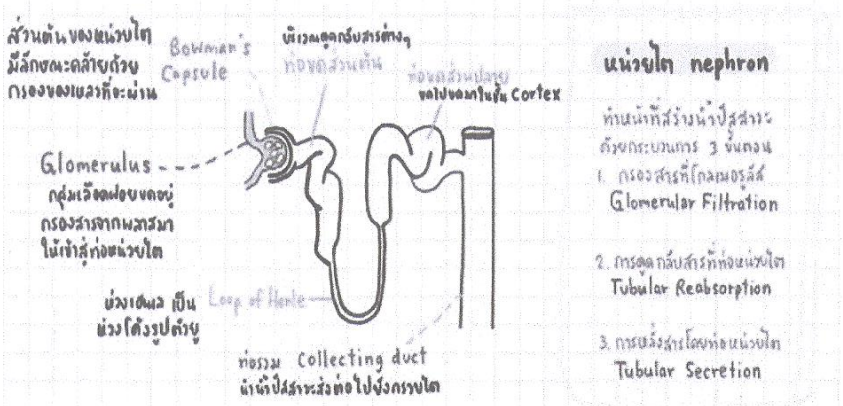


Figure 3. The nephron is the functional unit of the kidney. The glomerulus and convoluted tubules are located in the kidney cortex, while collecting ducts are located in the pyramids of the medulla. (credit: modification of work by NIDDK)





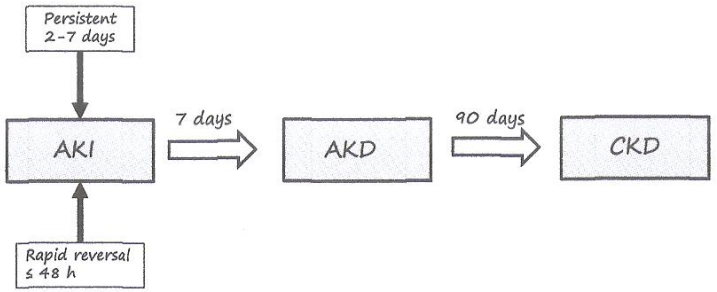
Acute Kidney Injury (AKI)

- Definition
- Classification system
- Category of AKI
- Treatment and Prevention

Definition : AKI

- An abrupt reduction in kidney function as evidenced by changes in Nitrogeneous wastes products (e.g. Scr, BUN) and urine output.
- No pharmacologic therapy that directly reverses the injury!!!
- AKI becomes AKD if kidney function is impaired > 7 days, and can ultimately transition into CKD if the duration > 90 days

Continuum of impaired kidney function



Classification systems: AKI

- **RIFLE (2004)**
  - The Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease
- **AKIN (2007)**
  - The Acute Kidney Injury Network
- **KDIGO (2012)**
  - Kidney Disease: Improving Global Outcomes

RIFLE Category

	Scr and GFR* Criteria	Urine Output Criteria
Risk	Scr ↑ to 1.5x or GFR ↓ > 25% from baseline	< 0.5 mL/kg/hr for ≥ 6 hrs
Injury	Scr ↑ to 2x or GFR ↓ > 50% from baseline	< 0.5 mL/kg/hr for ≥ 12 hrs
Failure	Scr ↑ to 3x or GFR ↓ > 75% from baseline or Scr ≥ 4 mg/dL + acute ↑ ≥ 0.5 mg/dL	Anuria for ≥ 12 hours
Loss	Complete loss of function for > 4 wks	
ESRD	Renal Replacement therapy > 3 mo	

GFR*= calculated GFR using the Modification of Diet in Renal Disease (MDRD) equation

AKIN Criteria

	Scr Criteria	Urine Output Criteria
Stage 1	Scr ↑ ≥ 0.3 mg/dL Or 1.5 to 2x from baseline	< 0.5 mL/kg/hr for ≥ 6 hrs
Stage 2	Scr ↑ 2 to 3x from baseline	< 0.5 mL/kg/hr for ≥ 12 hrs
Stage 3	Scr ↑ > 3x from baseline or Scr ≥ 4 mg/dL + acute ↑ ≥ 0.5 mg/dL Or need for RRT	< 0.3 mL/kg/hr for ≥ 24 hrs Or Anuria for ≥ 12 hours

KDIGO Criteria

	Scr Criteria	Urine Output Criteria
Stage 1	Scr ↑ ≥ 0.3 mg/dL Or 1.5 to 1.9x from baseline	< 0.5 mL/kg/hr for 6-12hrs
Stage 2	Scr ↑ 2 to 2.9x from baseline	< 0.5 mL/kg/hr for ≥ 12 hrs
Stage 3	Scr ↑ > 3x from baseline or Scr ≥ 4 mg/dL or need for RRT or eGFR* < 35 mL/min/1.73m² (< 18y)	Anuria for ≥ 12 hours

eGFR*= calculated GFR using the Schwartz formula

Epidemiology

- Varies widely depending on
  - the patient population studied
  - Criteria used to evaluate the patient
- Occurs in 3.0 to 18.3% of hospitalized noncritically ill patients and 30% to 60% of critically ill adults

Risk Factors

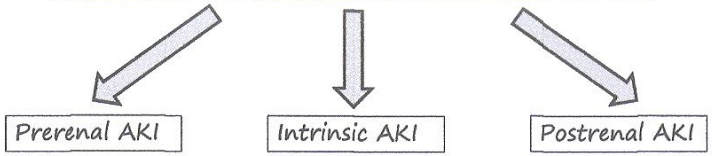
- Presence of CKD
- Diabetes
- Heart or liver disease
- Albuminuria
- Major surgery (esp. cardiac surgery)
- Acute decompensated heart failure
- Sepsis
- Hypotension
- Volume depletion
- Medications
- Advanced age
- Male gender
- Race (African American)

AKI-Risk Prediction Score

Risk factor	Points
Acute AKI	≥ 5
pH ≤ 7.30	3
Nephrotoxin exposure	3
Severe infection/sepsis	2
Mechanical ventilation	2
Anemia	1

Etiology

Clinical history: HPI, PMH
Physical exam: BP, fluid status, UO
Lab tests: chemistry assays, hematologic tests, U/A
Diagnostic test: imaging, biopsy



Prerenal AKI

- **Volume depletion**
  - Hemorrhage, GI losses, Renal losses, Skin losses, Third-space losses
- **Decreased circulatory blood volume**
  - Decreased cardiac output, pulmonary HTN, valvular diseases, systemic vasodilation, sepsis, liver failure
- **Functional**
  - NSAIDs, ACEIs, ARBs

Intrinsic AKI

- **Vascular damage**
  - Renal artery/vein thrombosis, atherothromboembolism, vasculitis, HTN, TTP
- **Glomerular damage**
  - Nephrotic/nephritic glomerulopathies, autoimmune diseases
- **Acute tubular necrosis**
  - Ischemic: Hypotension, sepsis
  - Endogenous toxins: myoglobin, hemoglobin, uric acid
  - Exogenous toxins: Nephrotoxic drugs, contrast dyes
- **Acute interstitial nephritis**
  - Drugs: NSAIDs, certain antibiotics
  - Infection

Postrenal AKI

- **Bladder outlet obstruction**
  - BPH, malignancy, anticholinergic drugs, displaced bladder catheter
- **Ureteral obstruction**
  - Malignancy, retroperitoneal fibrosis, nephrolithiasis
- **Renal pelvis/tubular obstruction**
  - Nephrolithiasis, drugs

Clinical Presentation

- Highly variable and largely dependent on the underlying etiology
- May be
  - Decreased urine output, anuria, oliguria
  - urine discoloration
  - Edema
  - Electrolyte disturbances
  - Sudden weight gain
  - Severe abdominal or flank pain

Clinical Presentation

- May be
  - Nausea, vomiting
  - Fatigue, malaise
  - Fever, rash, arthralgia

Patient Assessment

- Review of medical records with a particular focus on chronic conditions, laboratory studies, procedures, and surgeries
- Review of prescription and nonprescription medicines, herbal products and recreational drugs
- Assess the staging of AKI

Markers of Kidney Function

- Scr
- eCrCl,
- eGFR
- BUN
- Urine output e.g. 4-24 hrs
- Urine tests
- Urinary sediment

Parameters for differentiating causes of AKI

Lab test	Prerenal AKI	Intrinsic AKI	Postrenal AKI
Urine sediment	Hyaline casts, may be normal	Granular casts, cellular debris	Cellular debris
Urinary RBC	None	2-4+	Variable
Urinary WBC	None	2-4+	1+
Urine Na (mEq/L or mmol/L)	< 20	> 40	> 40
FE_{Na}* (%)	< 1	> 2	> Variable
Urine specific gravity	> 1.018	< 1.012	> Variable

Novel Biomarkers of Kidney Damage

- **TIMP-2:** Tissue Inhibitor of Metalloproteinases 2
- **IGFBP-7:** Insulin-like Growth Factor Binding Protein 7
  - Inhibit specific proteins that result in G1 cell-cycle arrest noted to occur during the very early phases of cellular stress or injury
  - Validated in critically ill and postoperative surgical patients
  - Approved by FDA in 2014 as the first point-of-care device to detect early AKI

Novel Biomarkers of Kidney Damage

- **Nephrocheck®**
  - Uses a fluorescent immunoassay
  - Results expressed as an AKI-risk score within 20 mins
    - Score > 0.3: high risk for moderate-to-severe AKI within 12 hours
    - Score 2.0: very high risk for AKI
  - Not to be used as a standalone test
  - Severe albuminuria and hyperbilirubinuria interfere the test results

Novel Biomarkers of Kidney Damage

- **NGAL**: Neutrophil Gelatinase-Associated Lipocalin
- **KIM-1**: Kidney Injury Molecule 1
- **IL-18**: Interleukin 18
- **L-FABP**: Liver-type Fatty Acid Binding Protein
- **NAG**: N-Acetyl-beta-D-Glucosaminidase

Novel Biomarkers of Kidney Damage

- **FST**: Furosemide Stress Test
  - Furosemide (a loop diuretic) secreted into the proximal tubules where it inhibits the Na-K-Cl cotransporter resulting in increased Na and water excretion
  - IV 1 mg/kg to patient then collected urine over the next 2 hours
  - If the collective urine output is < 200 mL, increased risk for progressing to AKI stage 3 and needing RRT

Prevention of Acute Kidney Injury

- Goals:
  - Screen and identify patients at risk
  - Monitor high-risk patients until the risk has subsided
  - Implement prevention strategies when appropriate

Prevention of AKI

- Depends on the patient's risk factors
  - Comorbidities, planned procedures, medications
- In some situations, the potential insult cannot be avoided but may be preventable or minimized
  - IV fluids, avoidance or removal of any additional insults, volume status optimization, hemodynamic support

Prevention of AKI

- **Electronic Alert Systems:** Electronic health record (HER)
  - Used for early detection of AKI lead to greater implementation of the intervention
  - Surveillance of patients on nephrotoxic medications
  - E.g. generated screening tool to identify patients receiving nephrotoxic medications, recommend daily Scr monitoring, switching a nephrotoxic drug to alternative, therapeutic drug monitoring

Prevention of AKI

- **Intravenous Fluids**
  - Shown benefit and routine used
  - Both isotonic crystalloids and colloid-containing solutions have been used
- **RenalGuard® System**
  - Closed-loop fluid management system
  - A bolus dose of IV isotonic saline and 0.25 mg/kg IV furosemide
- **Oral hydration**

Prevention of AKI

- **Remote Ischemic Preconditioning: RIPC**
  - Transient period of blood supply deprivation to a particular organ or tissue followed by a period of reperfusion
- **Ascorbic Acid**
  - Antioxidant properties
  - Alleviate oxidative stress caused by ischemia reperfusion injury

Prevention of AKI

- **N-Acetylcysteine (NAC)**
  - Antioxidant properties
  - The 2012 KIDGO suggest using NAC + IV isotonic saline
- **Statins**
  - Exhibit anti-inflammatory, antioxidant and endothelium protective effects
  - Reduce the risk of AKI in high-risk patients exposed to contrast agents

Prevention of AKI

- Glycemic control
  - Tight glycemic control (80-110 mg/dL) may significantly decrease the risk of AKI [but may also increase risk of hypoglycemia and mortality]

Treatment

- Desired Outcomes
  - Short-term goals:
    - Minimizing the degree of insult to the kidney
    - Reducing extrarenal complications
    - Expediting the patient's recovery of kidney function
  - Ultimate goal
    - The patient's kidney function restored to pre-AKI baseline

Treatment

- Currently available therapies are only supportive and focus on managing complications
  - Fluid overload: loop diuretics or RRT
  - Acid-base/electrolyte imbalances
  - Adequate fluid status: balanced solutions or isotonic saline

Treatment

- Intravenous fluids
  - To maintain or restore effective intravascular volume to assure adequate renal perfusion
  - Used judicious: volume depletion vs fluid overload
  - Be monitored for fluid intake and urine output (target ≥ 0.5mL/kg/hr), pulmonary and peripheral edema, blood pressure (MAP ≥ 65 mmHg), serum electrolytes

Treatment

- **Intravenous fluids**
  - In patients with anuria or oliguria → NSS or balanced crystalloid solution 250 mL bolus or 100 mL/hr short-term infusion to reduce the risk for pulmonary edema
  - NSS → hyperchloremic metabolic acidosis, esp. if dehydration from severe electrolyte imbalance e.g. severe diarrhea
  - If AKI is a result of blood loss or symptomatic anemia → RBC transfusion to reach Hb > 7 g/dL → balanced solutions or NSS can be used

Treatment

- **Intravenous fluids**
  - In patients with severe hypoalbuminemia 2nd to cirrhosis or nephrotic syndrome → Albumin
  - In critically ill patients with vasodilatory shock → norepinephrine, vasopressin or dopamine may be used in conjunction with fluids to maintain adequate hemodynamics and renal perfusion

Treatment

- **Electrolyte management**
  - Hypernatremia and fluid retention
    - Monitored unintended sodium intake: IV drugs (e.g. ATB) or foods
  - Hyperkalemia
    - Most common in AKI patients
    - May occur cardiac arrhythmias: $[K^+]$> 6 mEq/L
    - From some foods (oral phosphorus replacement powders) and alkalinizers or some medications

Treatment

- **Electrolyte management**
  - Hyperphosphatemia
    - Patients with significant tissue destruction (e.g. trauma, rhabdomyolysis and tumor lysis syndrome)
    - Restricted the dietary intake
  - Hypocalcemia
    - Frequent monitored unbound serum calcium concentrations
    - In CRRT patients→ citrate is used as the anticoagulant to bind serum calcium and prevent clotting→ calcium chloride or calcium gluconate is administered

Nutrition

- Derangements in glucose, lipid and protein metabolism
  - Hyperglycemia and insulin resistance
  - Hypertriglyceridemia
  - Protein catabolism and negative N balance
    - Increased amino acid turnover and skeletal muscle breakdown

Nutrition

- The KDIGO guidelines: 20 to 30 kcal/kg/day
- Non-catabolic AKI without dialysis
  - 0.8 to 1 g/kg/day of protein
- Patient with RRT
  - 1 to 1.5 g/kg/day of protein
- Patient with CRRT
  - Up to maximum 1.7 g/kg/day of protein