Renal Disease

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- The kidney has metabolic and synthetic functions [1, 2]. The metabolic functions take place via a balance of filtration, reabsorption, and secretion.
- The functions of the kidney include the following:
  - Elimination of metabolic waste and nonessential materials.
  - Fluid balance, electrolyte balance, and composition.
  - Maintenance of acid/base levels.
  - Secretion of renin by the juxtaglomerular cells.
  - Secretion of erythropoietin, conversion of vitamin D, calcium and phosphorus homeostasis.
  - Regulation of blood pressure.
- Renal function is measured by the glomerular filtration rate (GFR).
  - GFR is estimated using the Cockroft-Gault formula = [(140−age) × (lean body weight in kg) × (0.85 if female)/(serum creatinine mg/dL) × 72].
  - GFR is expressed per 1.73 m^2 surface area; affected by age, sex, and body size.
  - Average GFR for adult male = 130 mL/min [3].
  - Average GFR for adult female = 120 mL/min [3].
  - Chronic kidney disease occurs when GFR is reduced by at least 50 mL/min or when it is lower than 60 mL/min/1.73 m^2 [3].
  - GFR is most commonly measured using the body's clearance of the creatinine; creatinine is a by-product of muscle metabolism; it is almost exclusively filtered through the glomeruli of the kidney, therefore, making it a good clinical indicator of renal function.

Stages of Renal Dysfunction and Failure

Acute Renal Failure (ARF)/Acute Kidney Injury (AKI)

- The loss of renal function over hours to days that results in disturbances in fluid, electrolyte, and acid-base homeostasis. Diagnosis is based upon a serum creatinine increase by more than 0.5 mg/dL or a serum creatinine concentration rise of more than 25% in a patient with chronic kidney disease and a reduction of GFR by 50% [4].
- This is most commonly measured using creatinine levels as it approximates GFR closely.

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- Blood urea nitrogen (BUN) levels are also helpful, but less reliable due to other distracting factors (e.g., GI bleeding, increased protein intake, low urine output/dehydration, use of catabolic drugs such as steroids and tetracycline) as they can cause false elevation [3]. Also, up to 50% of BUN can be reabsorbed, while a negligible amount of creatinine is secreted.
- The most accurate estimate of renal function is a 24-hour urine collection, which is used to compare differences in plasma to urine creatinine and nitrogen levels.
- ARF is classified into three categories (Table 15.1) [3, 4]:
  - Prerenal azotemia – conditions that cause a fall in GFR because of reduced glomerular perfusion pressure (BUN:CR > 20:1 and a FENA < 1%).
  - Intrinsic renal failure – direct damage to the structures of the kidney.
  - Post renal failure – obstruction from either upper or lower urinary tract.

Table 15.1 Causes of AKI

Pre-renal (60%)	Renal (intrinsic) (30%)	Post-renal (obstructive) (10%)
Hypovolemia – decreased renal perfusion: hemorrhage, diarrhea, diuretics Hypotension/ reduce blood flow: cardiac failure, sepsis, dehydration Drugs: ACE inhibitors, NSAIDs (altering PG and ATII levels that maintain renal perfusion) Intraoperative: stimulation of renin-angiotensin-aldosterone axis causes vasoconstriction Postoperative: intravascular volume depletion (redistribution of ECF, CHF, MI, vascular obstruction)	Acute tubular necrosis (ATN) – Injury that directly damages the tubular epithelial cells Common causes are toxic, septic and ischemic Toxins: ethylene glycol, contrast dye, myoglobinuria, NSAIDS, aminoglycosides and amphotericin B Ischemia: embolism, dissection, cardiovascular surgery, severe blood loss, and severe hypotension Sepsis Acute interstitial nephritis (AIN) – edema and inflammation of the renal interstitium Drugs implicated in AIN: penicillin, diuretics, cimetidine, NSAIDs	Renal vein occlusion Urinary tract obstruction Anticholinergic-associated bladder dysfunction from anesthetic agents or antihistamines

Evaluation for Acute Renal Failure

- Detailed history and physical including pertinent labs (CBC with differential, CMP, coagulation profile, urinalysis, urine electrolytes).
- FE_{Na} = fractional excretion of sodium in urine; measures the differences between sodium and creatinine in the plasma (P) and urine (U); (U Na/P Na)/(U Cr/P Cr) × 100%.
- Clinical signs include the following:
  - Patient may or may not be oliguric (<400 mL/d) or anuric (<50 mL/d).
  - Volume depletion: orthostatic hypotension, tachycardia, dry mucous membranes.
  - Dermatologic signs: rash, purpura, livedo reticularis (mottled reticular lace-like purplish skin discoloration caused by capillary obstruction), gangrene, digital cyanosis (AIN or renal artery occlusion) [3].
  - Cardiovascular signs: third heart sound, jugular venous distension, and peripheral and pulmonary edema (cardiac failure).
  - Upper quadrant tenderness (ureteral obstruction or renal infarction).
  - Laboratory findings of acute renal failure (Table 15.2).
- Urinalysis findings in ARF:
  - Brown granular casts and epithelial cells represent ischemia or nephrotoxic ARF.
  - Heme in the absence of red blood cells represents rhabdomyolysis.
  - Eosinophils associated with fever, rash, peripheral eosinophilia represent AIN.
  - Red cells casts, protein, red blood cells represent glomerulonephritis.

Table 15.2 Laboratory findings in acute renal failure

Pre-renal	Renal	Post-renal
Urinalysis normal BUN:CR ratio 20:1 (characteristic) Urinary Na < 20 mEq/L Urine osmolality >500 mOsm/kg FENa < 1%	Urinalysis abnormal and BUN:Cr ratio normal Urinary Na > 40 mEq/L Urine osmolality <350 mOsm/kg	Normal urinalysis BUN:Cr ratio elevated FENa > 1%

Management of ARF

- Preoperative hypotension and volume depletion can lead to perioperative renal ischemia and, therefore, the aforementioned must be addressed prior to surgery.
- Identify potential risk factors: volume depletion, hypotension, sepsis, nephrotoxic exposure, preexisting chronic kidney disease.
- Elective surgery should be postponed until abnormalities have improved.
- Discontinue or use NSAIDs cautiously. NSAIDs inhibit the synthesis of prostaglandins, which are vital in the maintenance of renal blood flow and GFR. This puts the kidney at risk for perioperative failure in the susceptible patient.
- Consider short-term discontinuation of ACE inhibitors and angiotensin receptor blockers (ARBs). These inhibit actions on the efferent arterioles and worsen ARF [3].
- Avoid radiocontrast (RC) dye in patients with elevated BUN/Cr or chronic renal insufficiency. RC dye can cause direct toxic effects on the kidney or alter the production of nitrous oxide leading to acute failure [3]. Consider pre-treatment with N-acetylcysteine or sodium bicarbonate, which are protective agents; always minimize contrast loads and administer post-procedure hydration.
- Treat underlying cause postoperative ARF [3]:
  - Identify and eliminate causative agents.
  - Aggressive hydration.
  - Eliminate all nephrotoxins.
  - If obstructive, relieve obstruction.
  - Dialysis is the last resort if there is fluid overload, significant electrolyte abnormalities, and acid–base imbalances that are not relieved by the preceding measures.

Chronic Renal Disease (CRD)/ Chronic Kidney Disease (CKD)

- CRD is permanent renal insufficiency that develops over months to years caused by the structural intrinsic damage of the glomerulus or tubulointerstitial system resulting in damaging and irreversible complications. CRD occurs when the GFR is reduced to 50 mL/min. CRD eventually leads to ESRD at which point dialysis or transplant is mandatory to prevent death (Table 15.3).
- Chronic renal failure: pathophysiologic process with several known causes that leads to a decrease in nephrons and function. Detected by combination of imaging, blood and urine analysis, and GFR <60 mL/min for 3 or more months [5, 6].
- End stage renal disease (ESRD): the irreversible loss of kidney function such that the patient is permanently dependent on renal replacement therapy (dialysis or transplantation); GFR <15 mL/min [5].

Comorbidities and Sequelae in Patients with CRD

- *Cardiovascular*:
  - Causes up to 50% of mortality in ESRD patients [3].
  - Dyslipidemia is a common finding. CAD is found in about 40% of ESRD patients.
  - 40% of all patients on end stage dialysis have CHF [3].

Table 15.3 Stage of chronic renal failure [5–7]

Stage	Description	GFR (mL/min/1.73 m^2)
1	Slight kidney damage with normal or increased filtration	>90
2	Mild decrease in kidney function	60–89
3	Moderate decrease in kidney function	30–59
4	Severe decrease in kidney function	15–29
5	Kidney failure/ESRD	<15

  - Left ventricular hypertrophy is found in about 75% of all ESRD patients.
  - Patients develop hypertension due to inability to regulate salt/water balance and chronically elevated levels of ATII.
- *Anemia*:
  - ESRD patients develop anemia of chronic disease due to altered and decreased production of erythropoietin that increases the production of red blood cells in the tissues in response to decreased oxygen levels.
  - In general, the hemoglobin level in ESRD patients should be maintained between 11 and 12 g/dL.
  - Transfusing ESRD patients can be complicated by the development of blood antibodies; this can decrease an ESRD patient's chance at a donor kidney. However, if transfusion is indicated, typically when a patient is symptomatic or hemoglobin falls below 7 g/dL, it should be performed [3].
- *Platelet Dysfunction*:
  - ESRD patients suffer from a qualitative platelet defect and are at increased risk of intraoperative and postoperative bleeding from uremic platelet dysfunction [3, 7].
- *Gastrointestinal*:
  - Patients tend to have nausea and vomiting and are predisposed to developing an ileus.
  - Increased risk of aspiration.
- *Glycemic Control*:
  - Many patients with CKD have DM, which may have been the causative factor leading to CKD.
  - Glucagon, growth hormone, cortisol, epinephrine, and norepinephrine can be released due to surgical stress and anesthesia, worsening insulin resistance and deficiency in diabetics. This can lead to hyperglycemia and ketogenesis.
  - Diabetics are also at increased risk of becoming hypoglycemic postoperatively.
- *Risk of Infection*:
  - Patients with CKD have impaired phagocytosis, neutrophil chemotaxis, and malnutrition.
- *Secondary Hyperparathyroidism*:
  - Occurs as the kidneys lose the ability to convert vitamin D with a concomitant decrease in intestinal absorption.
  - Patients will have a total body decrease in calcium and be hypocalcemic. This leads to secretion of parathyroid hormone, which acts to increase serum calcium by bony resorption and an increase in intestinal absorption. This leads to renal osteodystrophy, which can be seen radiographically.
- *Electrolyte/Acid –Base Disturbances*:
  - Patients may be hyperkalemic due to the inability of the kidney to secrete potassium. A concomitant metabolic acidosis may occur due to hyperkalemia and inability to secrete hydrogen ions.
- *Oral Manifestations*:
  - Halitosis
  - Stomatitis
  - Gingival bleeding and petechiae
  - Osteolytic changes in the jaws, loss of lamina dura around teeth in more severe cases
  - Accelerated accumulation of calculus
- Uremia
  - Syndrome characterized by anorexia, altered mental status, vomiting, anemia, fatigue, and coagulopathy that mirror the kidneys' inability to perform its excretory, secretory, and synthetic functions. BUN concentration correlates with symptoms and reflects the patient's response to therapy.

Drug Considerations in Patients with CKD (Table 15.4)

- Patients with CRD and ESRD have abnormalities in drug metabolism leading to decreased clearance and prolonged effect.

Dialysis

- Dialysis is the process of removing excess fluid, solutes, and nitrogenous wastes. It is also known as renal replacement therapy.

Table 15.4 Drug safety in patients with CRD

Drugs to avoid	Drugs safe to use in ESRD patients
Aminoglycosides Radiographic contrast media NSAIDs Benzodiazepines (may be considered in reduced doses) Meperidine Morphine (with caution) Most inhaled anesthetics (transient but reversible depression) Barbiturates (may be used in reduced doses) Succinylcholine (causes hyperkalemia and its active metabolite is renally excreted) Non-depolarizing muscle relaxants	First-generation cephalosporins (empiric prophylaxis) Fentanyl Halothane, desflurane, nitrous oxide Propofol (hepatic clearance) Atracurium (action not prolonged; muscle relaxant of choice)

- There are two primary types of dialysis: hemodialysis and peritoneal dialysis.

Hemodialysis:
- Filtering of blood by diffusion across a semipermeable membrane to remove toxins while adding required substances [8].
- The blood is heparinized and passed through a dialyzer.
- Requires patients to obtain indwelling arteriovenous access; this can be achieved through ports into central veins (typically used temporarily while awaiting fistula maturation, 3–6 months) and surgically created fistulas. Patients must visit a dialysis center 3 days/week to receive treatment.

- Complications: shunt infection, shunt thrombosis and failure, hypotension, chronic blood loss [8].

Peritoneal Dialysis
- The instillation of dialysate solution into the peritoneal cavity, allowing toxins to passively diffuse into solution for removal [8].
- This treatment may be done at home, allowing patients to travel and is well tolerated.
- It must be done up to five time per day lending to longer treatment times and clearance of toxins is sometimes inadequate.
- Complications: catheter tunnel infections, peritonitis.

Dialysis Indications (AEIOU)
- *A*cidosis
- *E*lectrolyte disturbances (e.g., hyperkalemia)
- *I*ntoxications (e.g., methylene glycol, lithium)
- *O*verload (volume)
- *U*remia

Patient Management of Renal Disease

- Patients with CKD are tenuous surgical and anesthesia candidates because they often have other comorbidities including myocardial dysfunction, coronary artery disease, and peripheral vascular disease.
- Work up for comorbidities: EKG, echocardiogram, hemoglobin A1C.
- Optimize medically by controlling comorbidities (e.g., DM, HTN, CHF).
- They are less capable in handling changes in fluids, electrolytes (e.g., sodium, potassium, and phosphorus), acid loads, and the metabolism or excretion of medications.
- They must also be considered immunocompromised and, therefore, are at an increased risk for infections.
- Antibiotic prophylaxis is indicated for the first 6 months after fistula placement as transient bacteremia can lead to infection.
- Clinically these patients are at an increased bleeding risk due to platelet dysfunction. Consider preoperative pharmacological hemostatic agents such as DDAVP (use with caution to prevent volume overload), cryoprecipitate, and conjugated estrogens to prevent bleeding (DDAVP – administered IV or intranasally at 0.3 μg/kg 1 hour before surgery/cryoprecipitate – 10 U over 30 minutes IV 1 hour before surgery/conjugated estrogens – 0.6 mg/kg/d IV or 2.5–25 mg PO 5 days before surgery).
- Patients should undergo dialysis the day before surgery to minimize uremic complications and decreased risk of bleeding in the set-

ting of being heparinized. The hemodialysis process also destroys platelets.
- Utilize good surgical technique by achieving primary closure and utilize agents such as Gelfoam, Surgicel®, Floseal®, and topical thrombin if necessary.
- Correction or normalization of abnormalities preoperatively (electrolyte and acid–base disturbances).
- Avoidance of nephrotoxic agents and tight glycemic control can significantly decrease the risk of perioperative complications and postoperative infection [3].
- Preoperative labs: CBC (rule out anemia), coagulation studies, CMP (assess creatinine, calcium, magnesium, and potassium levels), urinalysis, and bleeding time.
- Erythropoietin can be administered preoperatively in the setting of anemia. The hematocrit can be raised up to 30% by administration of erythropoietin.
- Discontinue diuretics to avoid intraoperative hypotension and volume depletion.
- Optimize blood pressure control and consider holding ARBs and ACE inhibitors to reduce the risk of hypotension.
- Avoid using arm with AV shunt for monitoring blood pressure and venipuncture.
- Consider anti-emetic and pro-motility medications preoperatively due to the risk of aspiration.
- Adjust dosages of drugs excreted by the kidney accordingly.
- General anesthesia with volatile inhalational anesthetics reversibly depresses renal function and is short lived once discontinued. Sevoflurane has a metabolite known as compound A, which is nephrotoxic. Halothane, enflurane, and isoflurane are generally safe in ESRD.
- Depolarizing agents such as succinylcholine can increase potassium. Potassium must be closely monitored. As long as the potassium is not acutely elevated, succinylcholine can safely be used in ESRD patients.
- All non-depolarizing agents undergo some degree of renal excretion with prolonged duration of action and, therefore, should be dose adjusted. Atracurium and cisatracurium undergo spontaneous degradation via Hofmann degradation and ester hydrolysis and are generally safe.
- Propofol is mainly metabolized by the liver (none of the metabolites have been shown to be active). The presence of renal failure and uremia does not have an effect on the pharmacology of propofol, and there is no significant decrease in the clearance in ESRD patients. Furthermore, no significant dosing adjustments are necessary in ESRD patients. However, propofol can decrease myocardial function and causes hypotension that can worsen renal failure.
- Fentanyl is very lipid soluble and rapidly redistributed to inactive tissues. It is slowly released into the plasma and then cleared. In moderate doses, it is safe for use in renal failure patients.
- Benzodiazepines undergo hepatic metabolism and can be used with caution. Be mindful of the by-products of conjugation; diazepam forms two active metabolites: desmethyldiazepam and oxazepam, which can cause prolonged sedation.
- Avoid nephrotoxic drugs, e.g., NSAIDs, diphenhydramine, chlordiazepoxide, cimetidine, aminoglycosides, IV contrast dye, cephalosporins, erythromycin, tetracycline, acyclovir [9].
- Lidocaine (amide anesthetics), codeine, clindamycin, metronidazole are safe to use.
- Avoid meperidine as the normeperidine metabolite can induce seizures.
- Consider discontinuing all antiplatelet agents (aspirin, dipyridamole) 72 hours prior to surgery.
- Must be judicious when administering fluids, as there is a narrow margin of safety as it relates to insufficient and excessive fluid administration.

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