Renal Disease and PK/PD

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Drugs and Kidneys

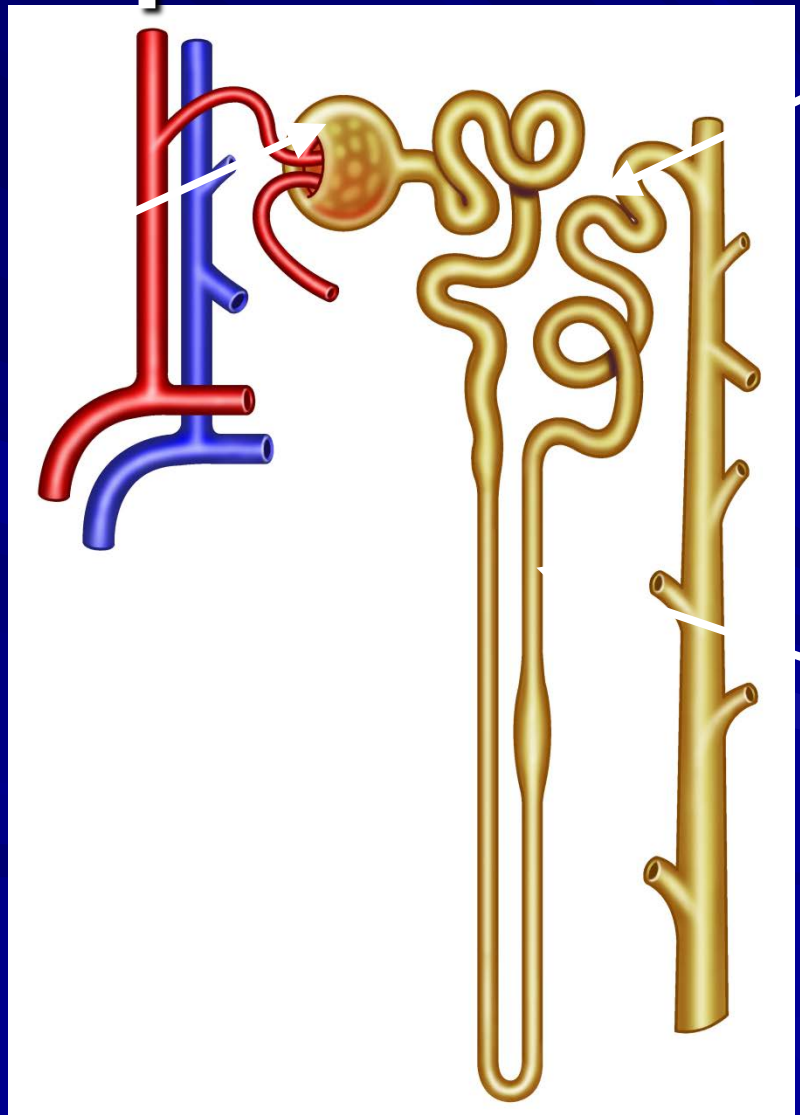
- Kidney is one of the major organ of drug elimination from the human body
- Renal disease and dialysis alters the pharmacokinetics and pharmacodynamics of most commonly used drugs
- Polypharmacy is common in renal disease patients with a median of 8 drugs being used
- Patients with renal disease on an average suffer from adverse effects as compared to the general population

Renal Disease and Drugs

- Decreased elimination
- Uremic effects
- Nephrotoxicity

- Estimation of renal function
- Effect of renal disease on PK and PD
- Drug Nephrotoxicity
- Management of poisoning

Nephron



Kidney regulates:

- **Water**
- **Acid-base balance**
- **Electrolytes**
- **Nitrogenous waste excretion**

GFR as an Indicator of Kidney Function

- GFR is an important indicator of CKD
- Reduced GFR in patients with renal disease results from irreversible loss of nephrons[1,2]
  - Greater burden is placed on remaining nephrons
  - Hyperfiltration predisposes to further nephron destruction
- 50% of nephrons can be lost without functional impairment[1]
- Patients may still be asymptomatic, but are progressing toward end-stage chronic renal failure[1]

1. Ix JH et al. *Lange Pathophysiology.* Lange Medical Books/McGraw Hill, Medical Publishing Division; 2006:456-481;
2. Eaton DC et al. *Vander's Renal Physiology.* Lange Medical Books/McGraw Hill, Medical Publishing Division; 2004:24-36.

Defining GFR

- Glomerular filtration
  - Process by which water and solutes in the blood pass from the vascular system through a filtration barrier into Bowman space
  - This filtrate is similar to blood plasma, with large plasma proteins excluded
- GFR
  - Volume of filtrate formed per unit of time
  - Normal young adult male: 180 L/d (125 mL/min/1.73 m^2)
  - Entire plasma volume is filtered by kidneys 60 times per day

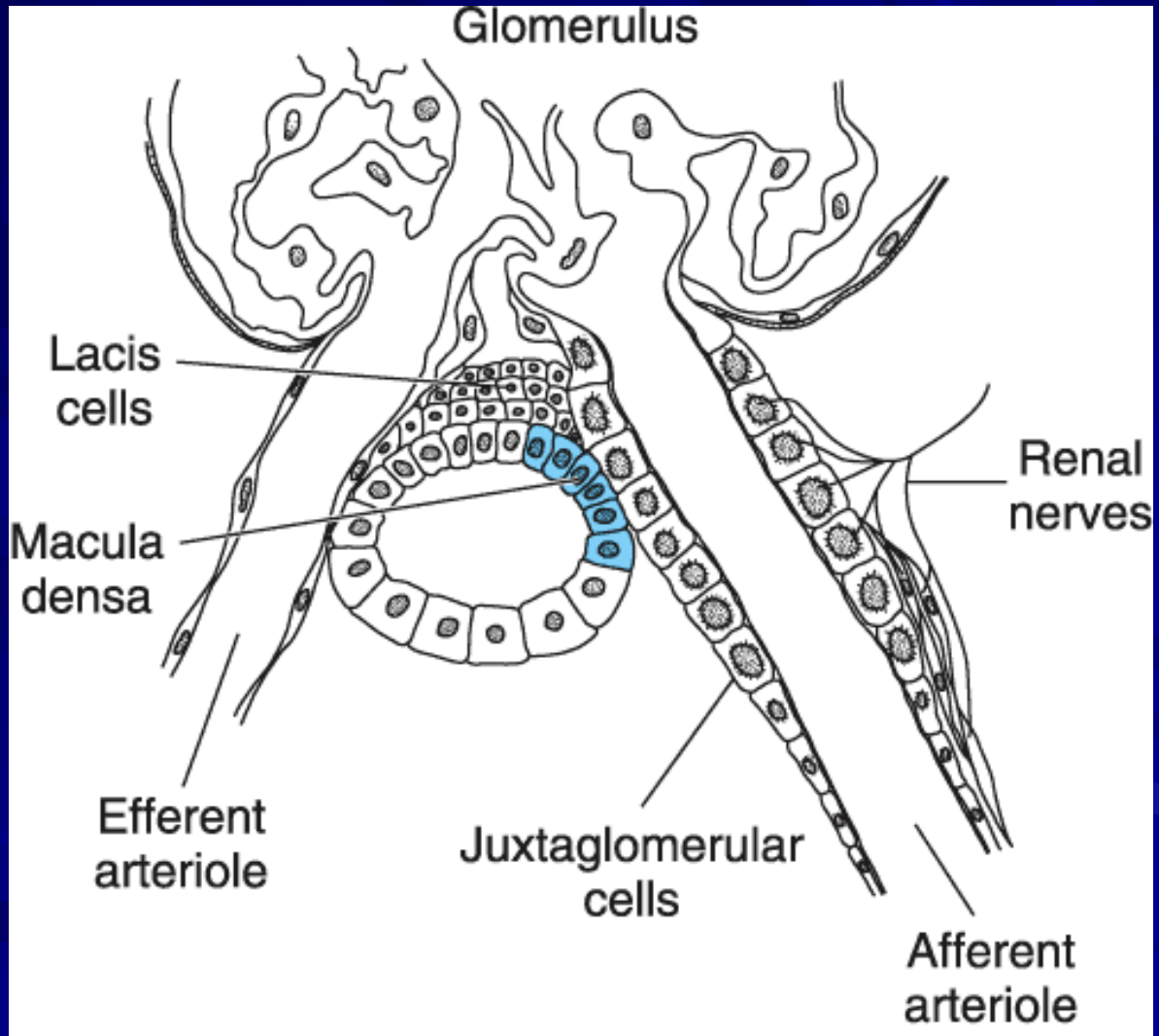
Eaton DC et al. *Vander's Renal Physiology.* Lange Medical Books/McGraw Hill, Medical Publishing Division; 2004:1-23.

Factors Affecting GFR

- Direct determinants of GFR
  - Permeability of capillaries and surface area (filtration coefficient)
  - Net filtration pressure (hydrostatic pressure in capillaries and in Bowman capsule, and glomerular capillary osmotic pressure resulting from proteins)
- Other factors that affect GFR
  - Changes in renal arterial pressure, renal arteriolar resistance (dilation or constriction), and renal plasma flow
  - ↑ Intratubular pressure—obstruction of tubule or urinary system
  - ↑ Osmotic pressure—increased protein concentration

Eaton DC et al. *Vander's Renal Physiology.* Lange Medical Books/McGraw Hill, Medical Publishing Division; 2004:24-36.

JGA



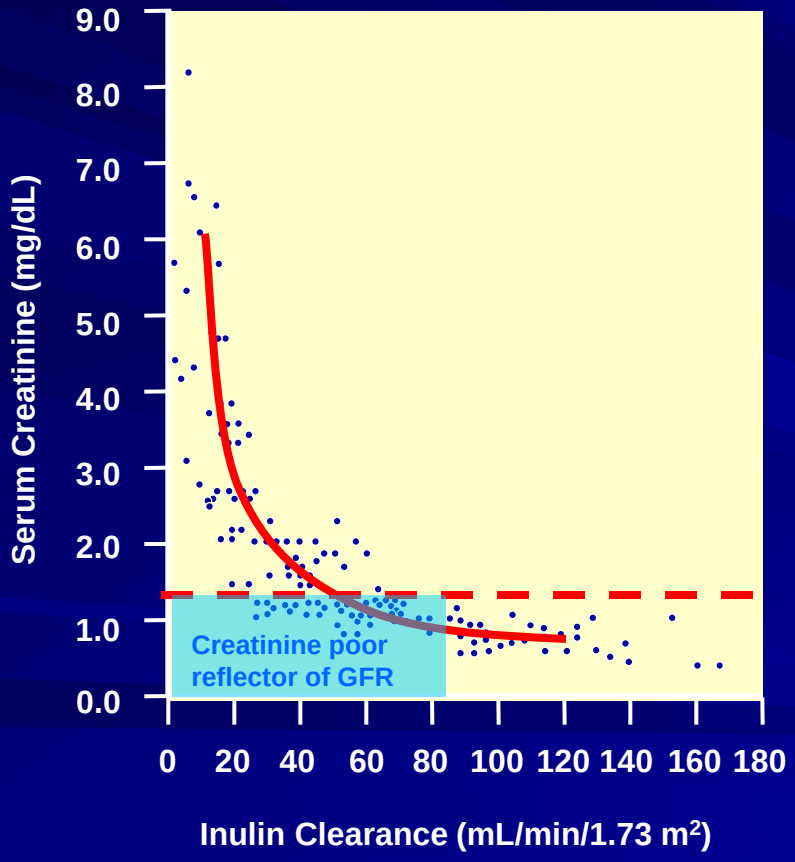
Source: Ganong WF: *Review of Medical Physiology*, 22nd Edition: http://www.accessmedicine.com

Estimation of GFR

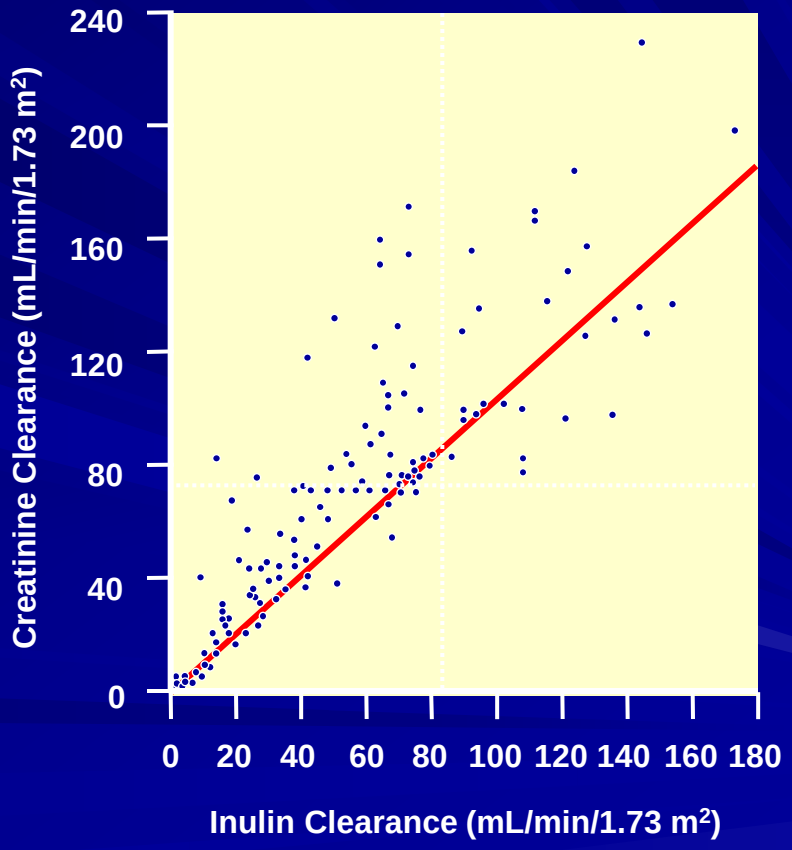
- Inulin clearance
- Iothalamate scans
- 24 hour urine collection
- eGFR
- Creatinine

GFR versus Serum Creatinine

GFR versus Serum Creatinine



GFR versus 24 hr Creatinine Clearance

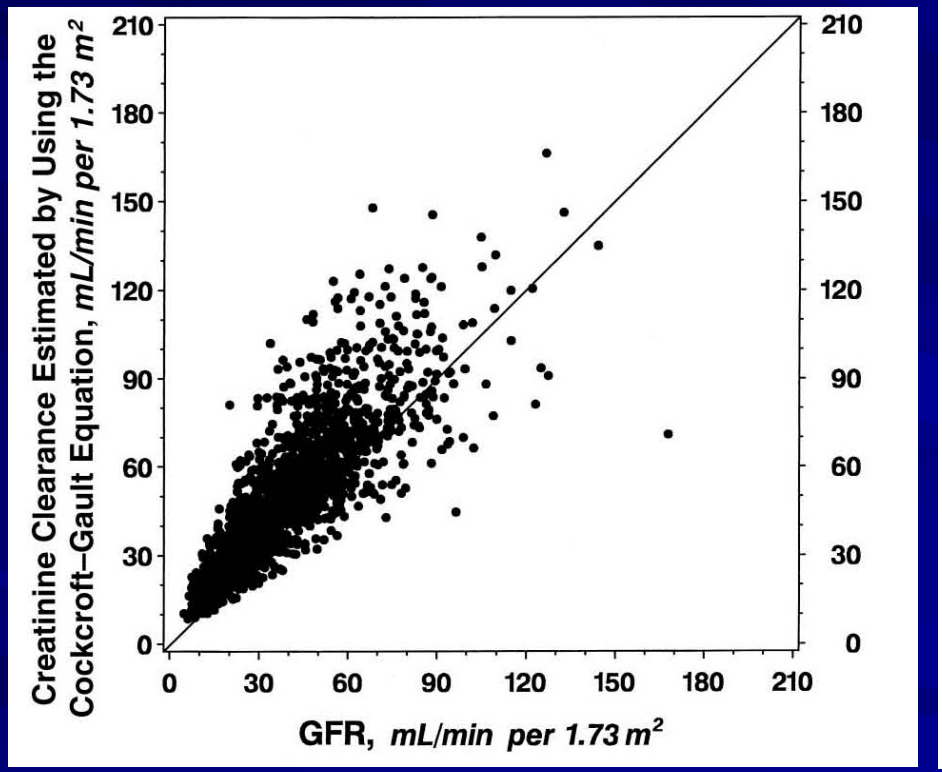


Available at: http//medical.dictionary.thefreedictionary.com/. Accessed on March 1, 2005.
Johnson R, et al. *Comprehensive Clinical Nephrology*. 2000. Mosby. St. Louis. 4.15.1–4.15.15.

GFR Equations Compared

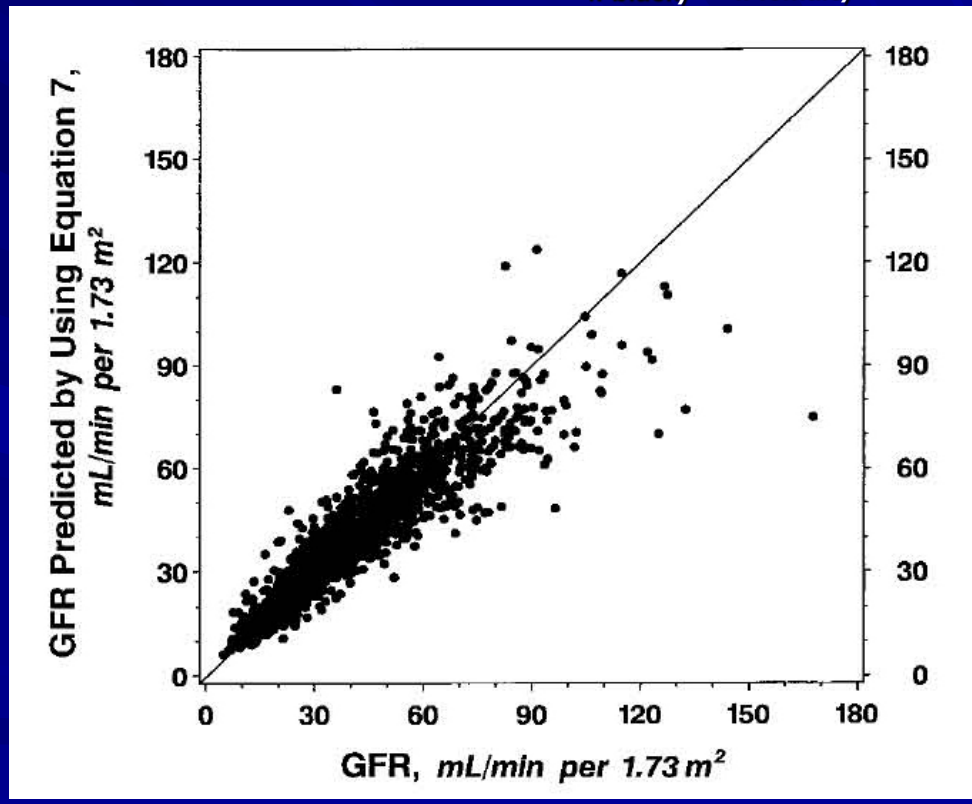
Cockcroft-Gault

$$\frac{[140 - \text{age}] \times \text{weight (kg)}}{[72 \times \text{PCr}]} \times (0.85 \text{ symbol for female})$$



MDRD

$$186.3 \times \text{PCr}^{-1.154} \times \text{age}^{-0.203} \times (1.212 \text{ if black}) \times (0.742 \text{ if female})$$



6 variable: Cr, BUN, age, alb, race, sex
4 variable: Cr, age, race, sex

Levey AS, et al. *Ann Intern Med*. 1999;130(6):461-470. Abstract

Pharmacokinetics

Pharmacokinetics

- Absorption and bioavailability
- Drug distribution
  - Volume of distribution
  - Protein binding
- Biotransformation and drug metabolism
- Elimination

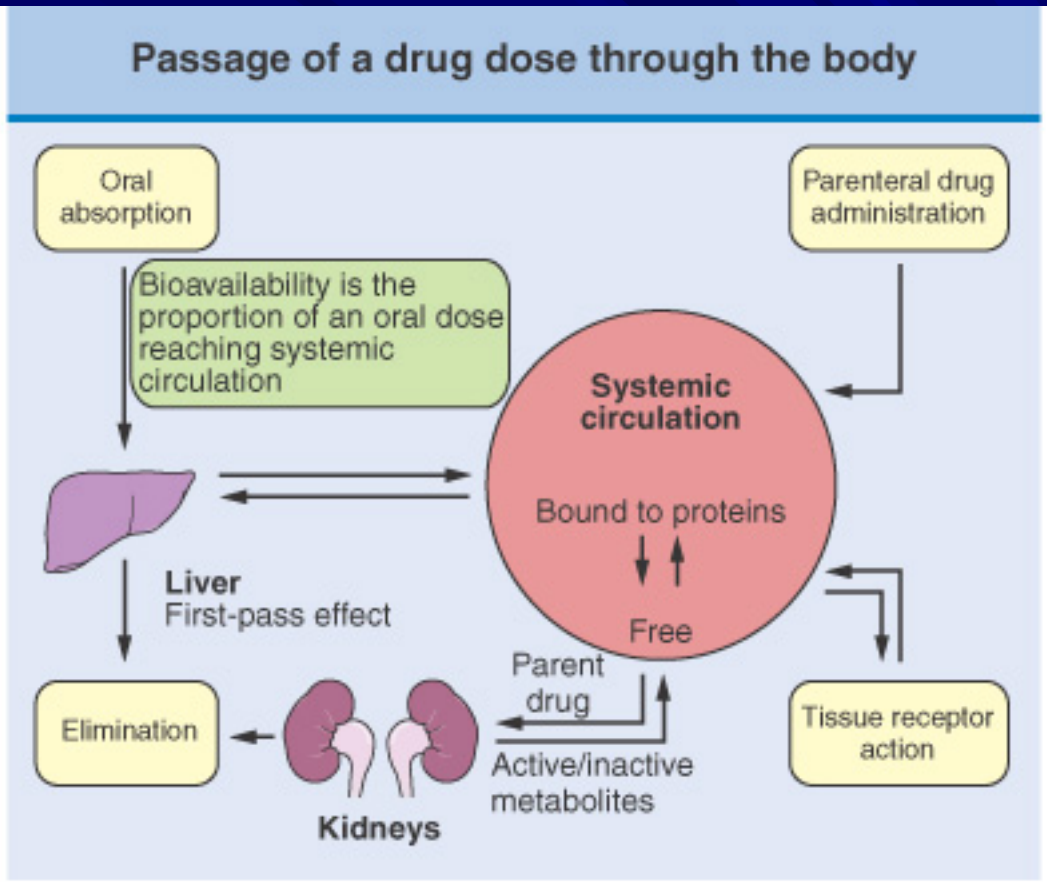


Figure 101.1 The passage of a drug through the body.

Bioavailability

- Proportion of oral drug reaching systemic circulation
- Affected by
  - Intestinal and drug permeability
  - First pass effect
  - Gut motility
  - pH

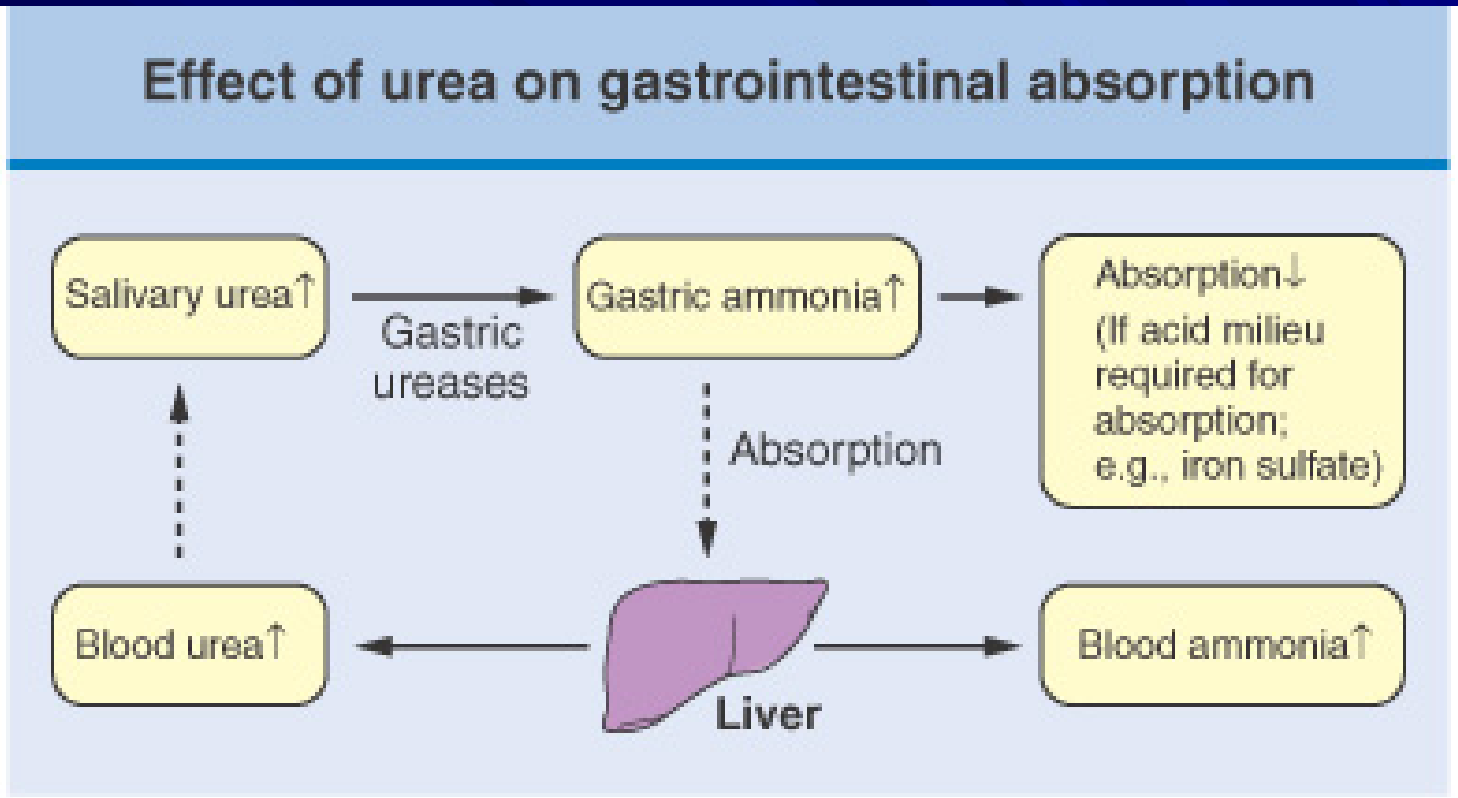
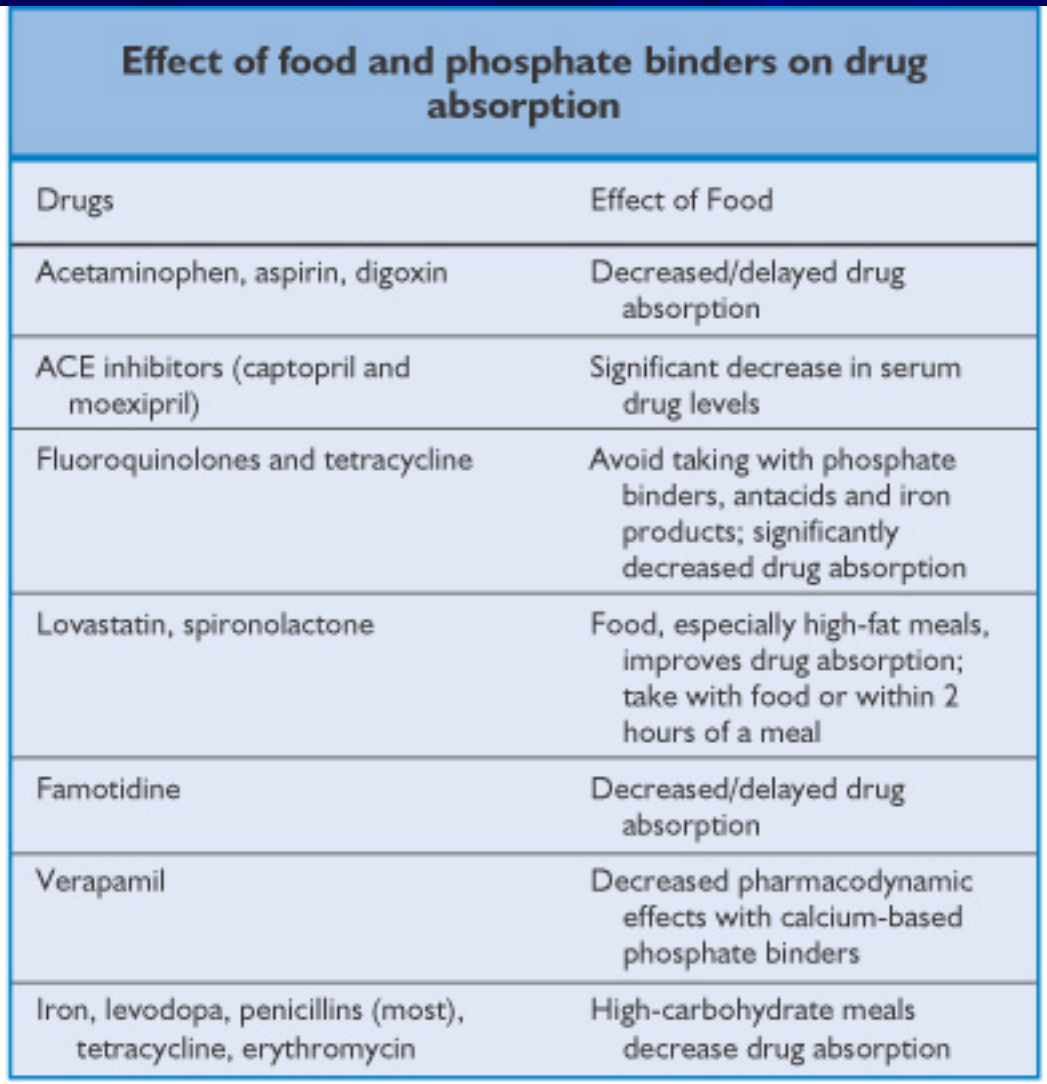


Figure 101.2 Effect of urea levels on gastrointestinal absorption.



Effect of food and phosphate binders on drug absorption

Drugs	Effect of Food
Acetaminophen, aspirin, digoxin	Decreased/delayed drug absorption
ACE inhibitors (captopril and moexipril)	Significant decrease in serum drug levels
Fluoroquinolones and tetracycline	Avoid taking with phosphate binders, antacids and iron products; significantly decreased drug absorption
Lovastatin, spironolactone	Food, especially high-fat meals, improves drug absorption; take with food or within 2 hours of a meal
Famotidine	Decreased/delayed drug absorption
Verapamil	Decreased pharmacodynamic effects with calcium-based phosphate binders
Iron, levodopa, penicillins (most), tetracycline, erythromycin	High-carbohydrate meals decrease drug absorption

Figure 101.3 Effect of food and phosphate binders on drug absorption. ACE, angiotensin-converting enzyme.

Plasma Protein Binding

- Acidic drugs bind to albumin and basic drugs to α_1-acid glycoprotein in the plasma
- There is a decrease in binding of acidic drugs in CKD which has been attributed to changes in the binding site, accumulation of endogenous inhibitors of binding and decreased concentrations of albumin.
- On the other hand the concentration of α_1-acid glycoprotein does not change that much and actually might be increased in patients on HD and transplanted patients

Protein binding of drugs in renal disease

Albumin: Binding Sites for Acidic Compounds	
Protein binding reduced in nephrotic syndrome (hypoalbuminemia) and renal failure (altered albumin affinity). Increased risk of drug toxicity	
Major Effects	Minor Effects
Barbiturates	Ascorbic acid
Benzodiazepine	Bilirubin
Carbamazepine	Fatty acids
Fibrates	Nafcillin
Furosemide	Phenylbutazone
Mycophenolate mofetil	Probenecid
Penicillins	Thiopental
Phenytoin	
Sulfonamides	
Tetracyclines	
Globulins: Binding Site for Basic Compounds	
Effect of altered protein binding less predictable in renal disease	
Major Effects	Minor Effects
Digitoxin	Adenosine
Methadone	Amitriptyline
Propranolol	Chloramphenicol
Warfarin	Chlorpromazine
	Nortriptyline
	Quinine

Figure 101.4 Protein binding of drugs in renal disease.

Nephrotic Syndrome

- Complex interaction
- Hypoalbuminemia may result in lesser protein binding with more free drug in the plasma while at the same time there might be loss of albumin bound drug in the urine
- Some drugs are also known to produce adverse effects more readily in patients with nephrotic syndrome eg clofibrate can produce severe muscle necrosis

Volume of Distribution (V_D)

$$V = \frac{\text{Amount of drug in body}}{C} \qquad (1)$$

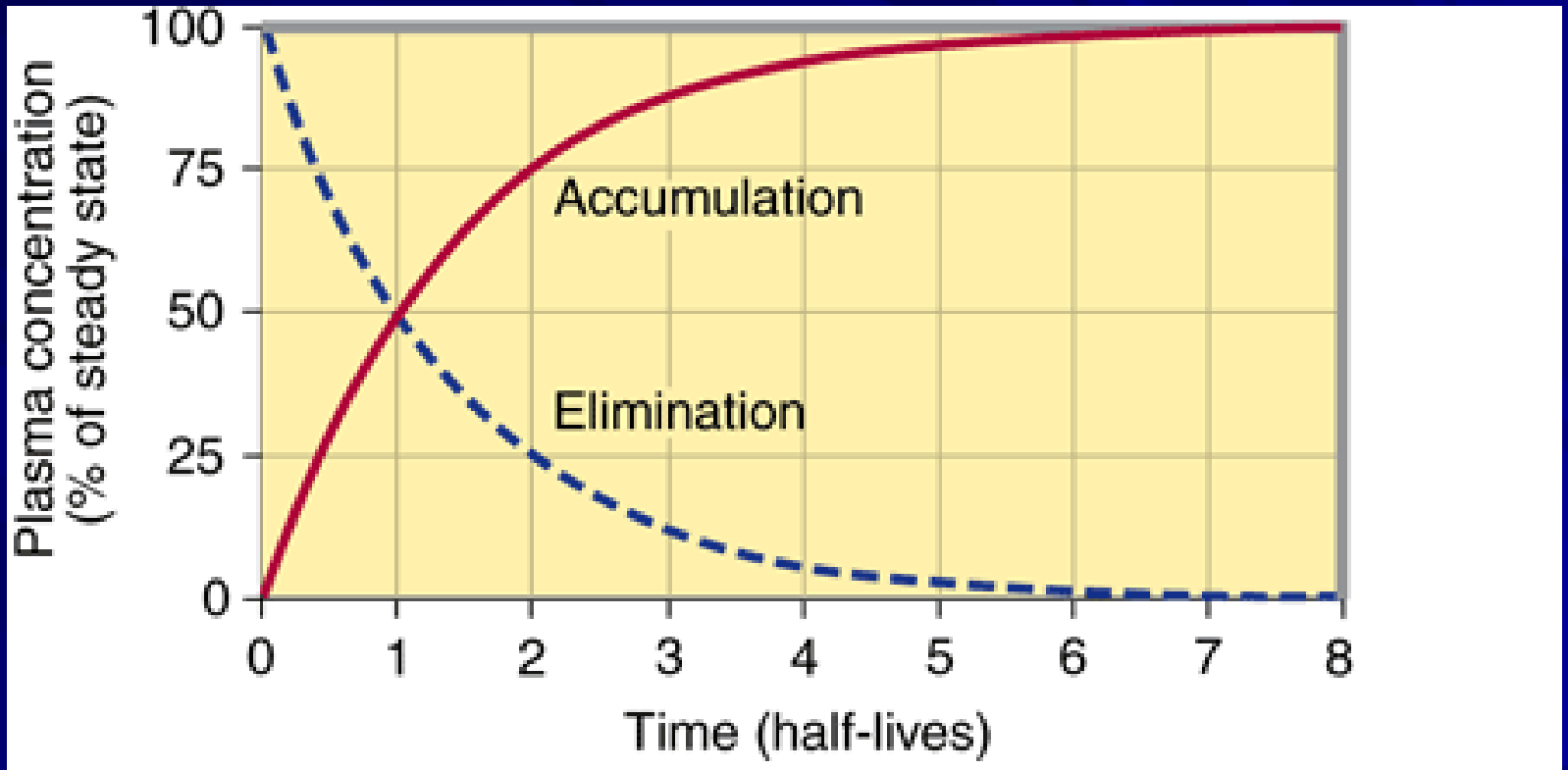
- **Apparent number** as it does not correlate with any defined anatomic space
- It is a ratio of the administered dose to plasma concentration at equilibrium
- Volume of distribution can vastly exceed any physical volume in the body because it is the volume *apparently* necessary to contain the amount of drug ***homogeneously*** at the concentration found in the blood, plasma, or water.
- Concept important for predicting the **loading dose**

Factors affecting V_D

- Protein and tissue binding
- Volume status

Half Life

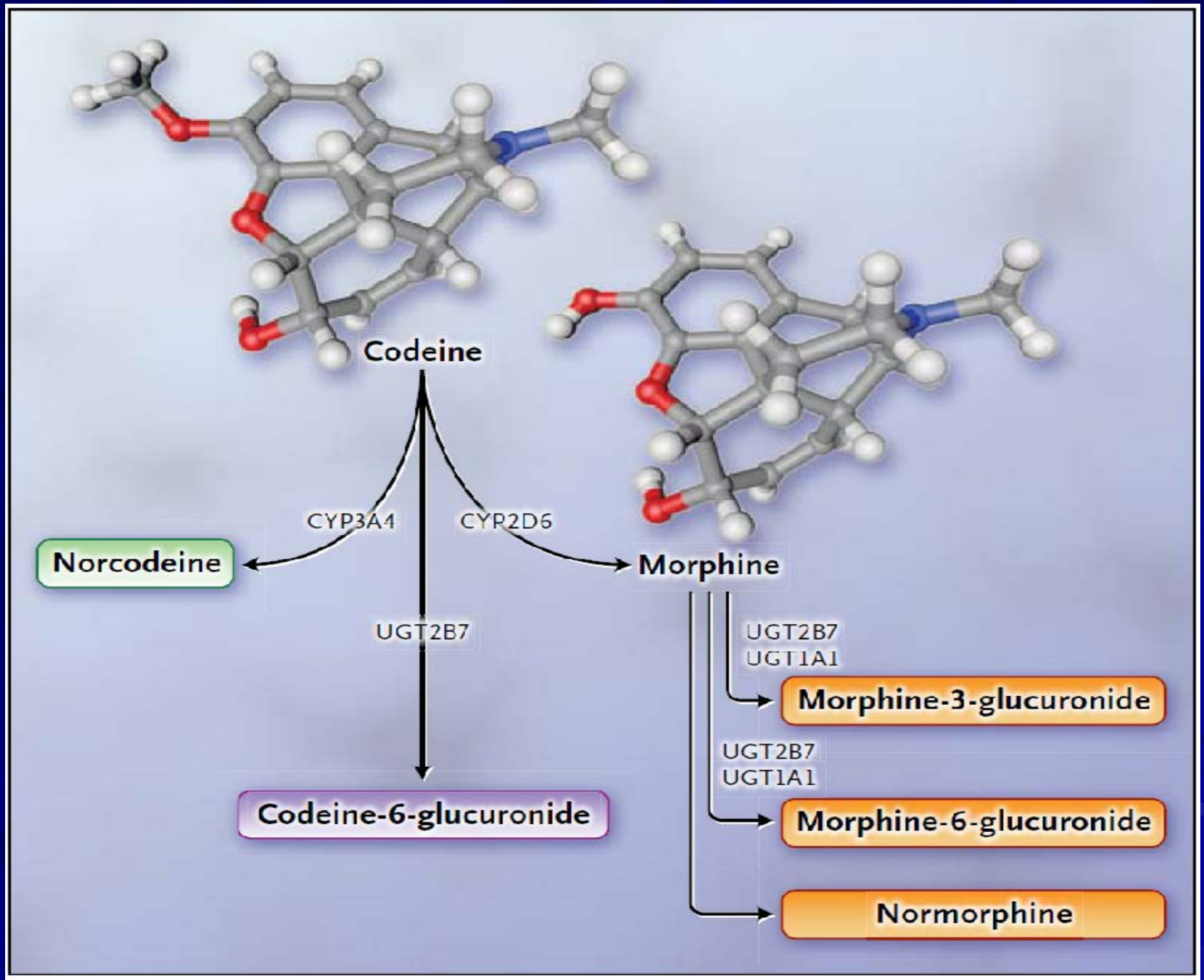
$$t_{1/2} = \frac{0.7 \times V}{CL} \qquad (6)$$



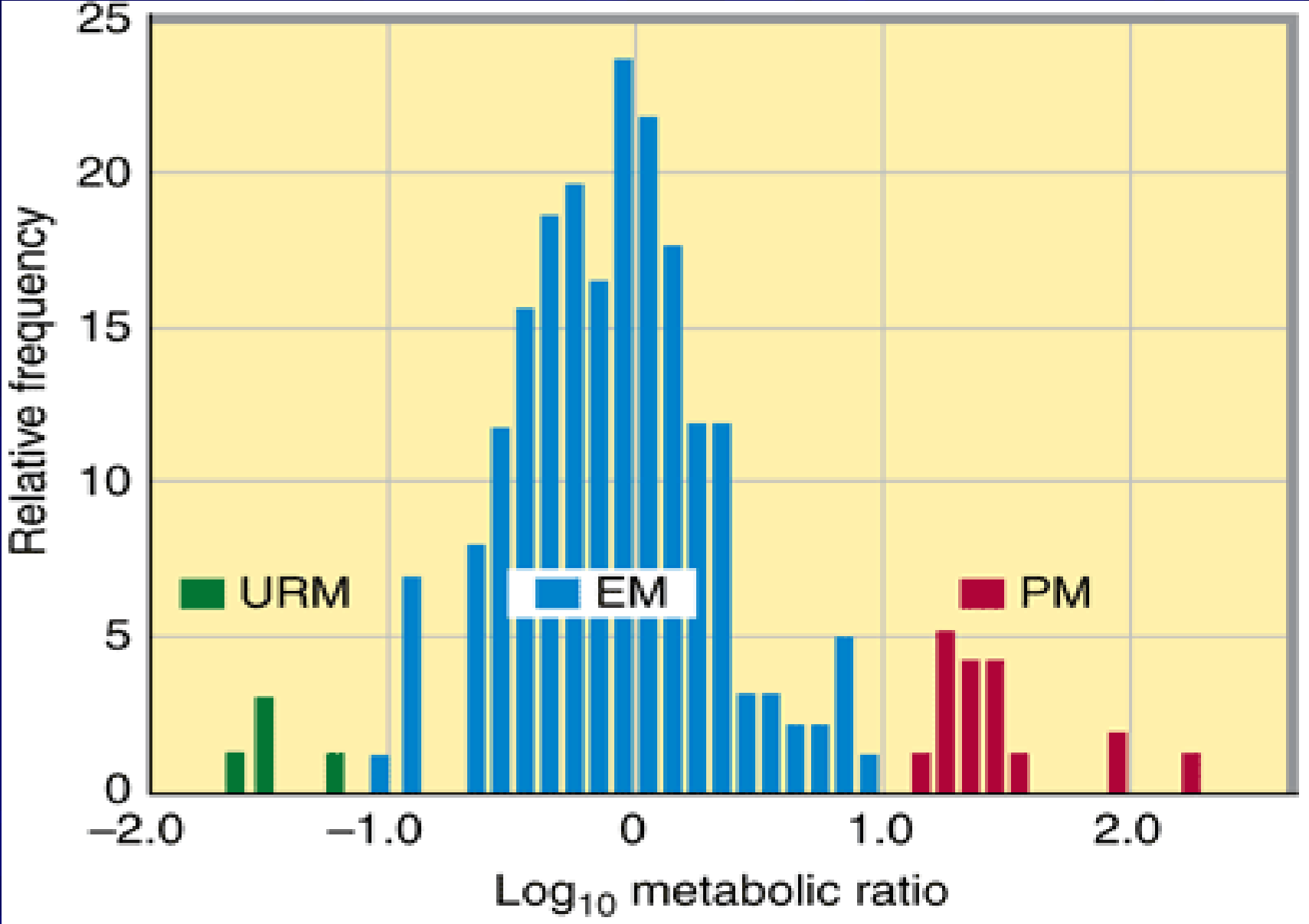
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

Metabolism

- Drug metabolism occurs in the kidneys but to a lesser extent than the liver
- Progressive CKD effects most body biochemical reactions including drug biotransformation
- Reduction and hydrolysis reactions are slowed but glucuronidation, sulfation, conjugation and microsomal oxidation reactions occur at normal rates
- Also important to keep in mind is the fact that even though the drug might not be eliminated by the kidney, their active metabolite might eg meperidine, nitrofurantoin and morphine



Codeine Metabolism Pathway.



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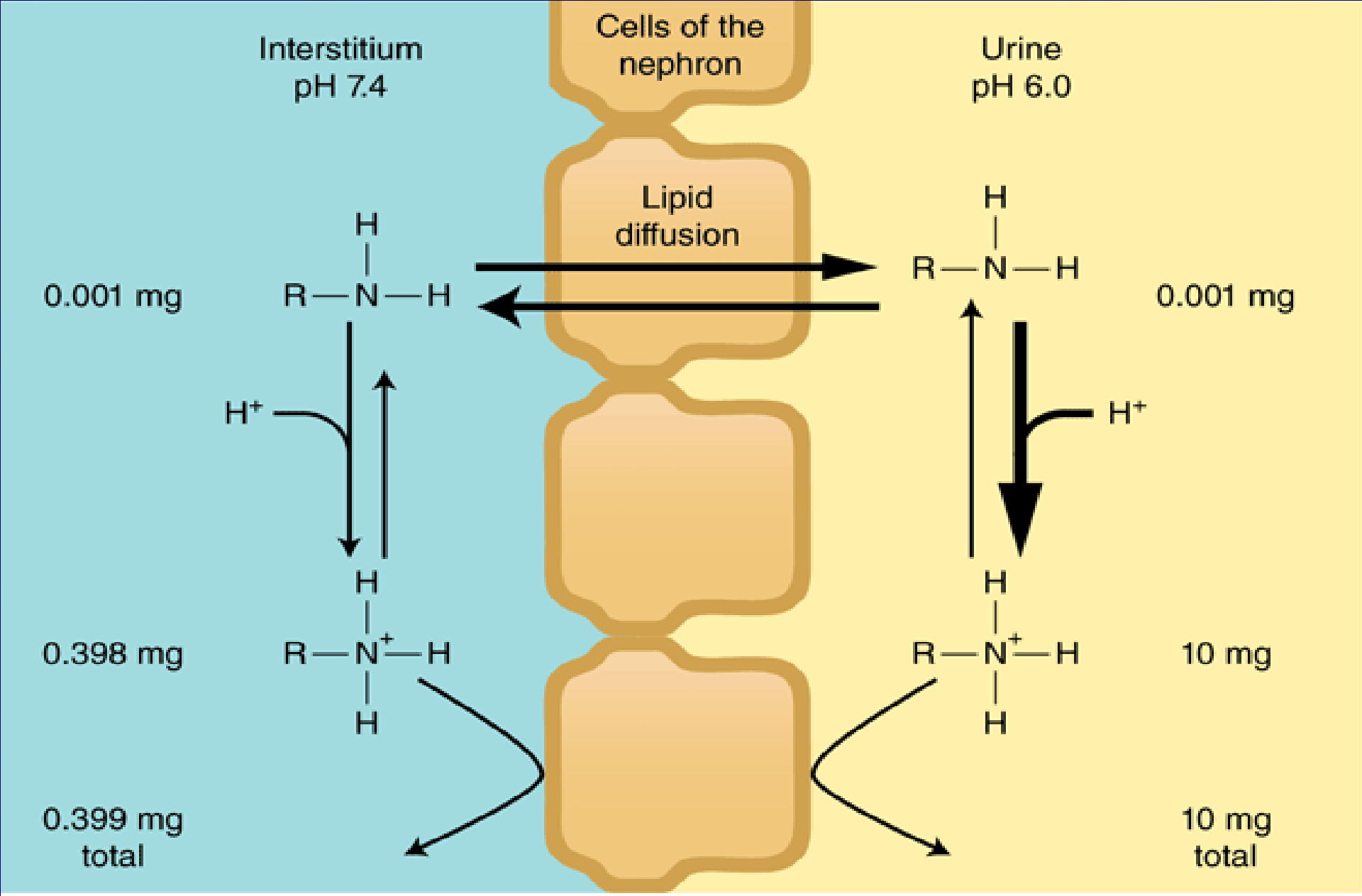

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Dosing in a patient with renal insufficiency

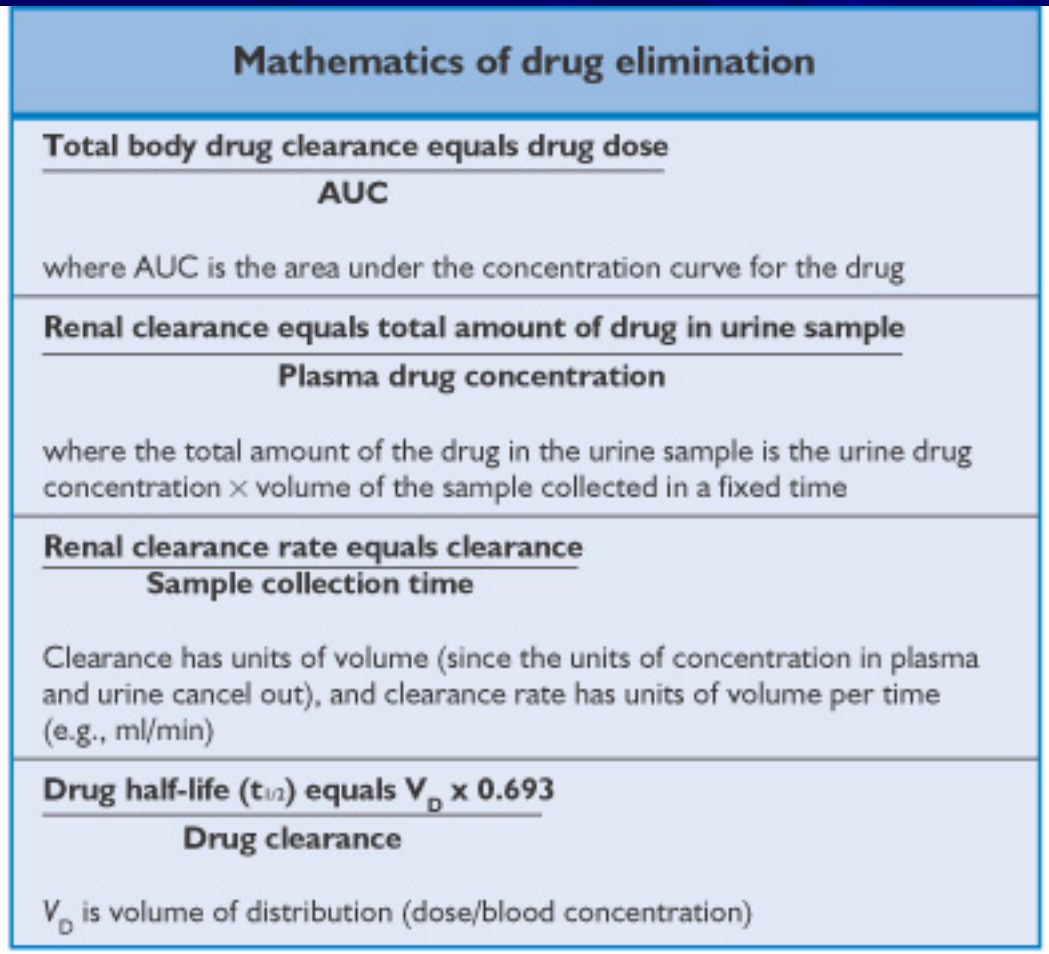
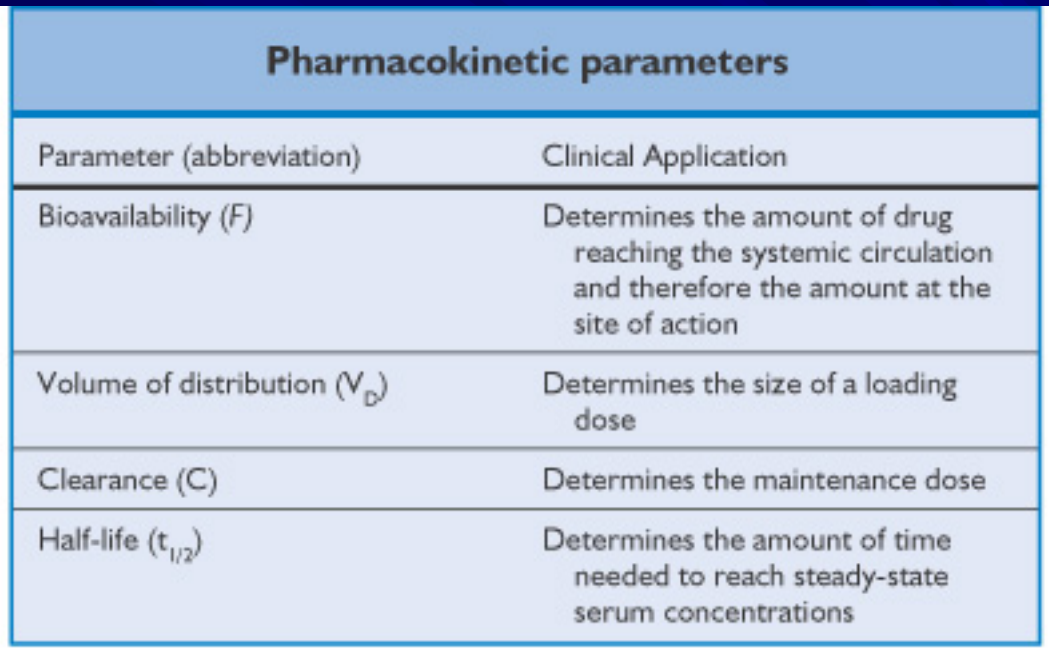


Figure 101.5 Mathematics of drug elimination.



Pharmacokinetic parameters	
Parameter (abbreviation)	Clinical Application
Bioavailability (*F*)	Determines the amount of drug reaching the systemic circulation and therefore the amount at the site of action
Volume of distribution (V_D)	Determines the size of a loading dose
Clearance (C)	Determines the maintenance dose
Half-life ($t_{1/2}$)	Determines the amount of time needed to reach steady-state serum concentrations

Figure 101.6 Pharmacokinetic parameters.

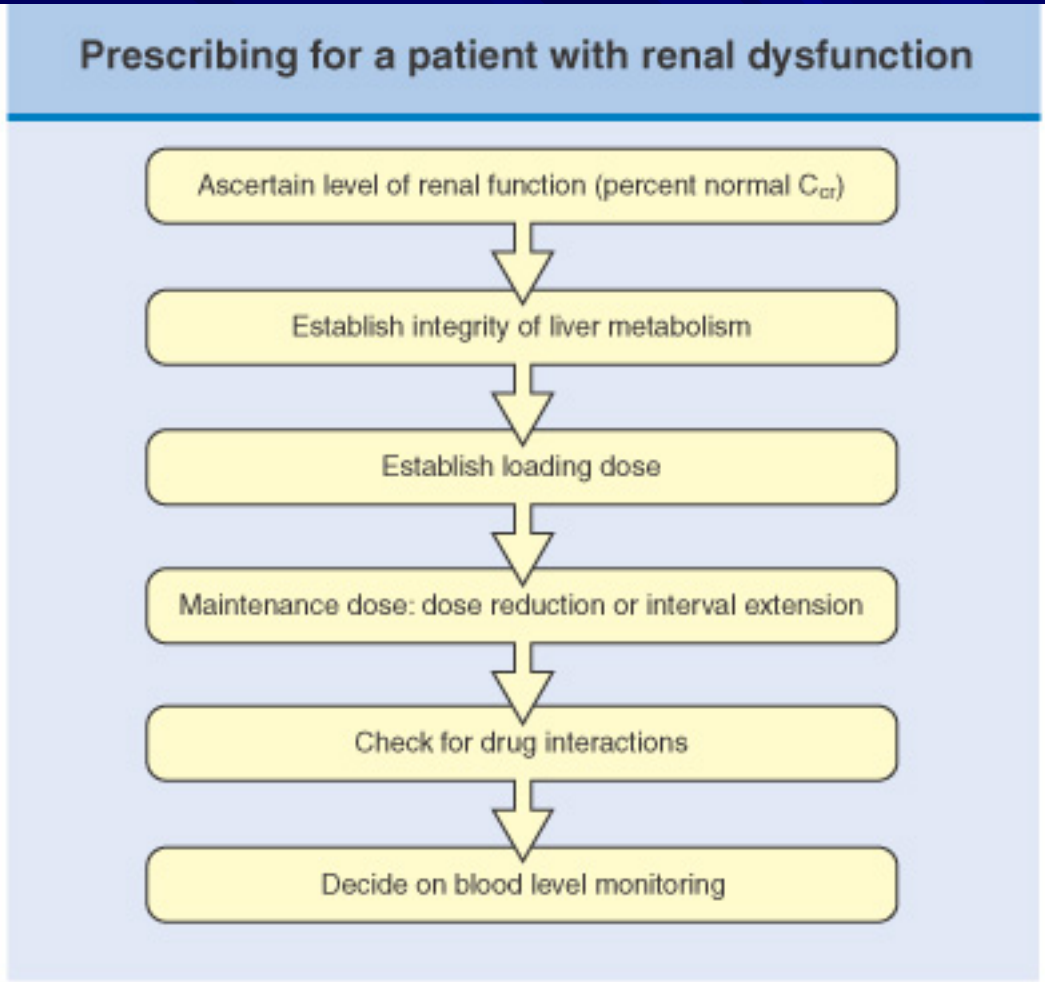


Figure 101.7 Prescribing for a patient with renal dysfunction. C_{cr}, creatinine clearance.

Extracorporeal Drug Losses

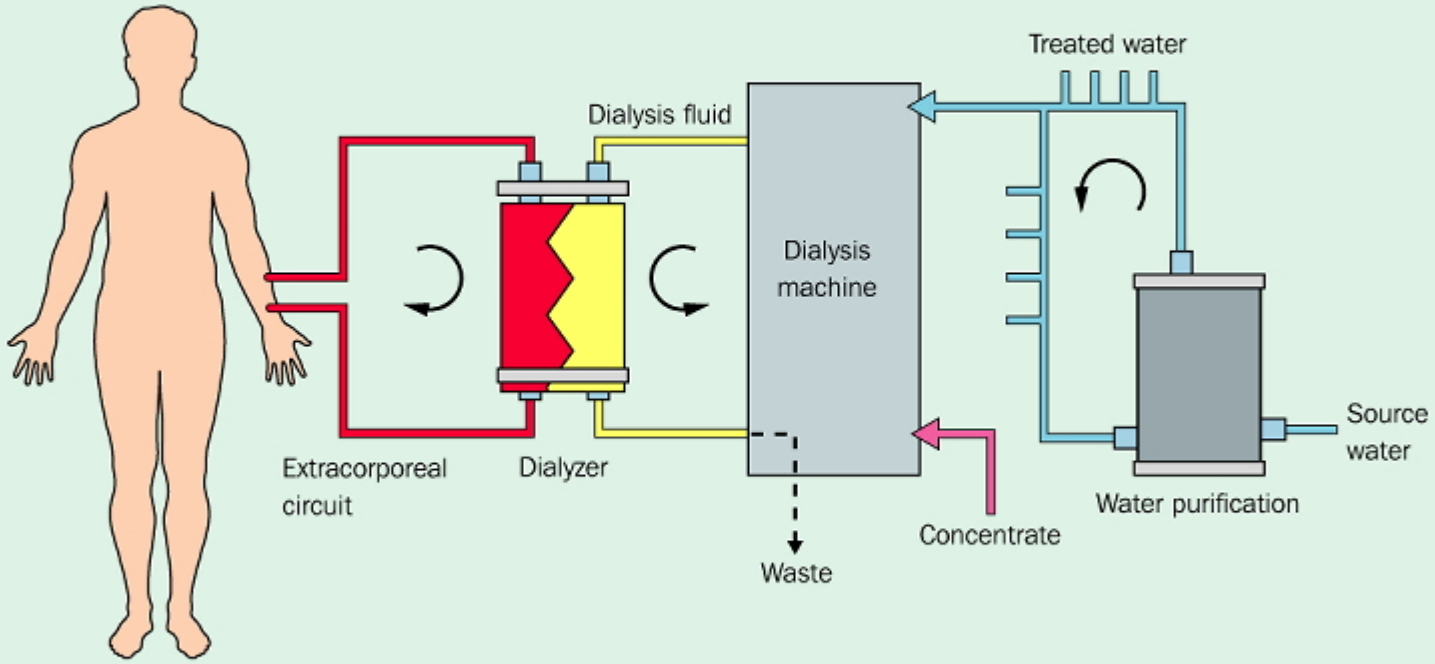
Dialysis

- Dialysis is extracorporeal purification of blood
- Artificial Kidney

Dialysis

Diffusion of small molecules down their concentration gradient across a semipermeable membrane

Components of the hemodialysis system



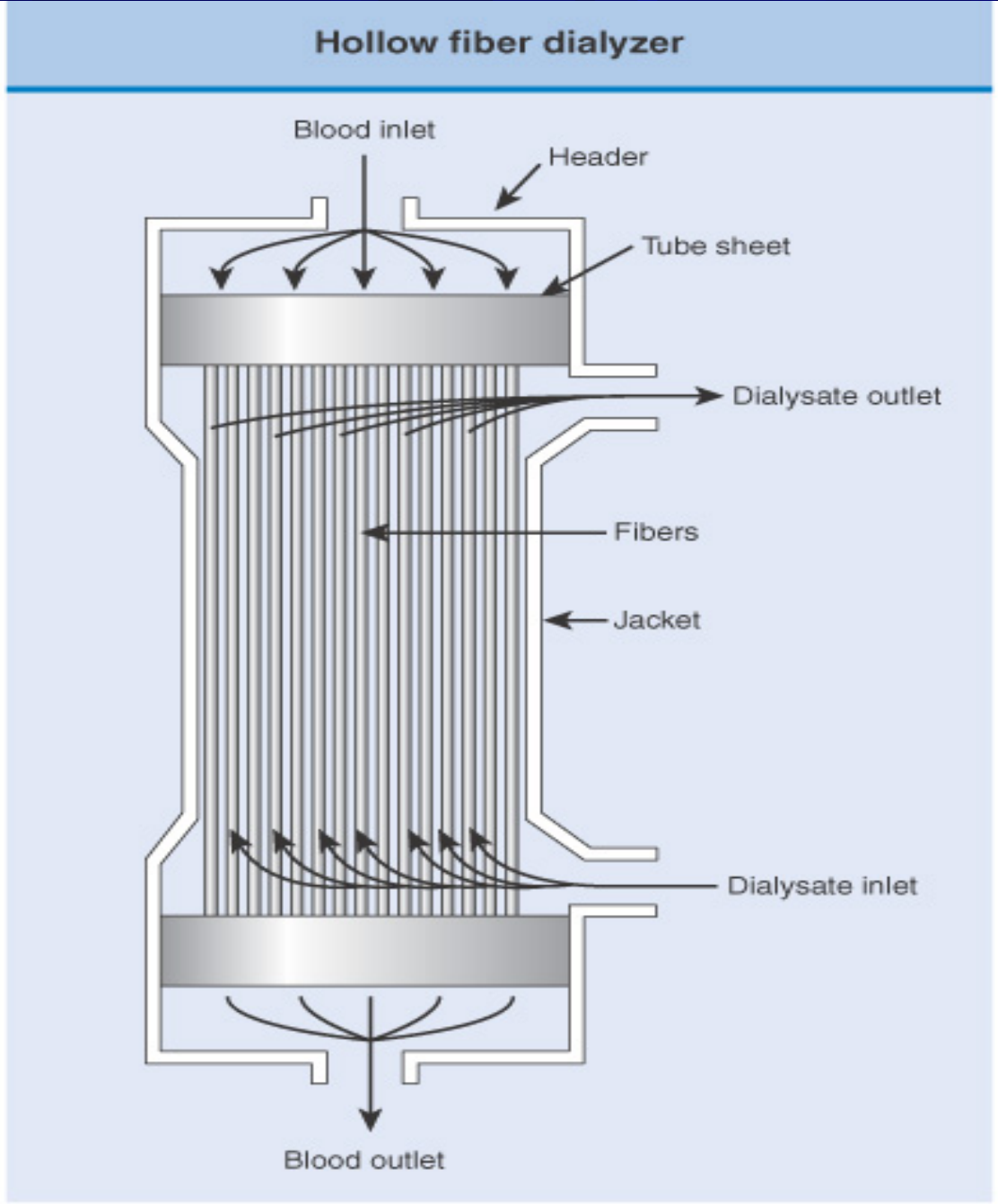
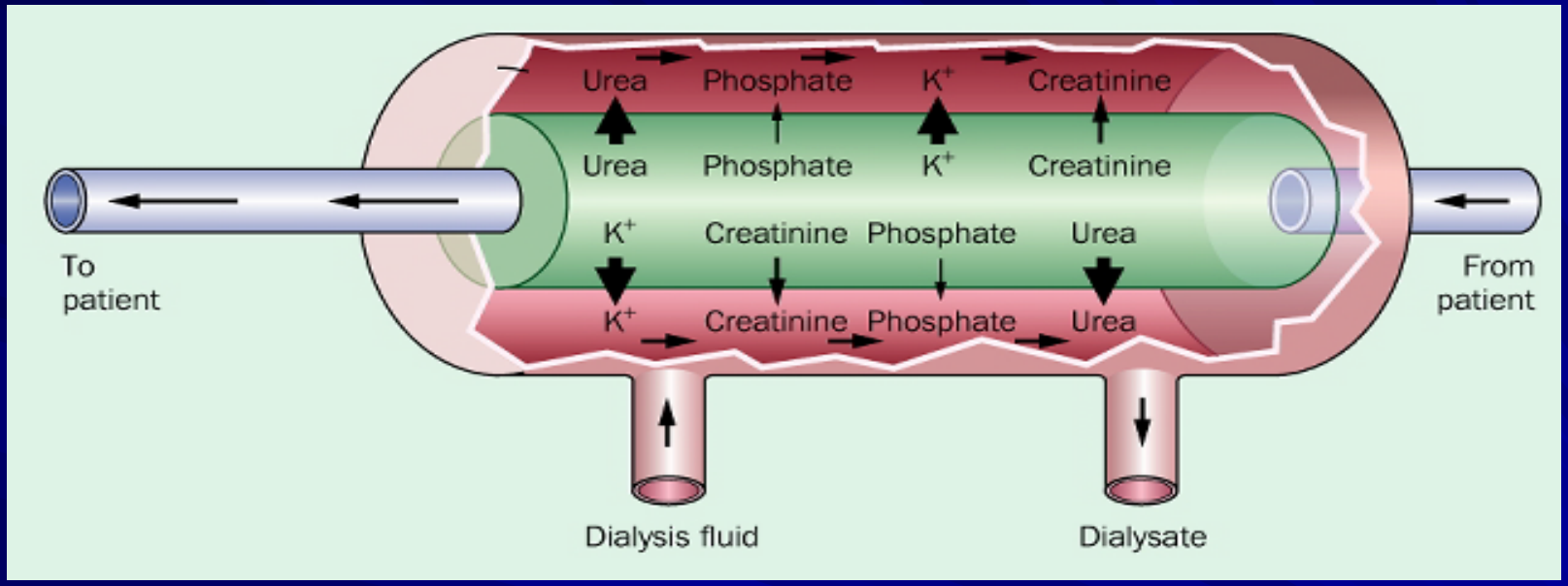


Figure 83.1 Design of a modern hollow-fiber dialyzer.

RRT

- Solute clearance
  - Diffusion
  - Convection
- Fluid clearance

Hemo-Dialysis (HD)



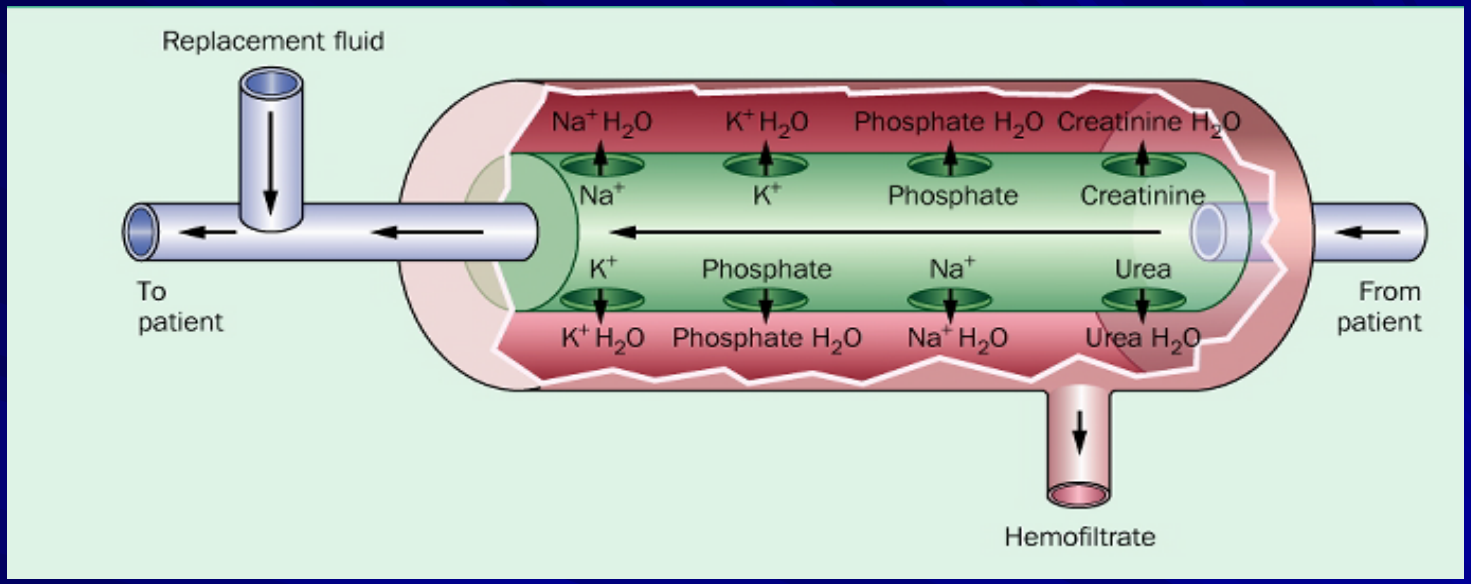
- Concentration difference across a semi-permeable membrane favors diffusive transport of small solutes (<300 Da)

Diffusion

Urea is used as the marker for small molecule diffusion during dialysis

Diffusive clearance is a function of

- Blood flow rate
- Membrane surface area
- Time


Replacement fluid
$Na^+ H_2O$
$K^+ H_2O$
Phosphate H_2O
Creatinine H_2O
Na^+
K^+
Phosphate
Creatinine
K^+
Phosphate
Na^+
Urea
$K^+ H_2O$
Phosphate H_2O
$Na^+ H_2O$
Urea H_2O
To patient
From patient
Hemofiltrate

Ultra-filtration

Removal of water during dialysis from the patients circulation

HD – Transmembrane pressure gradient

PD – Osmotically driven by glucose

Ultrafiltration

UF is a function of three factors

1. Transmembrane hydrostatic pressure
2. Ultra-filtration coefficient of dialysis membrane
3. Duration

Factors Affecting Drug Clearance by Dialysis

Drug

- Molecular weight
- Protein binding
- Volume of distribution

Factors Affecting Drug Clearance by Dialysis

Dialysis

- Composition of the dialyzer membrane
- Surface area
- Blood and dialysate flow
- Mode: IHD, PD or CRRT

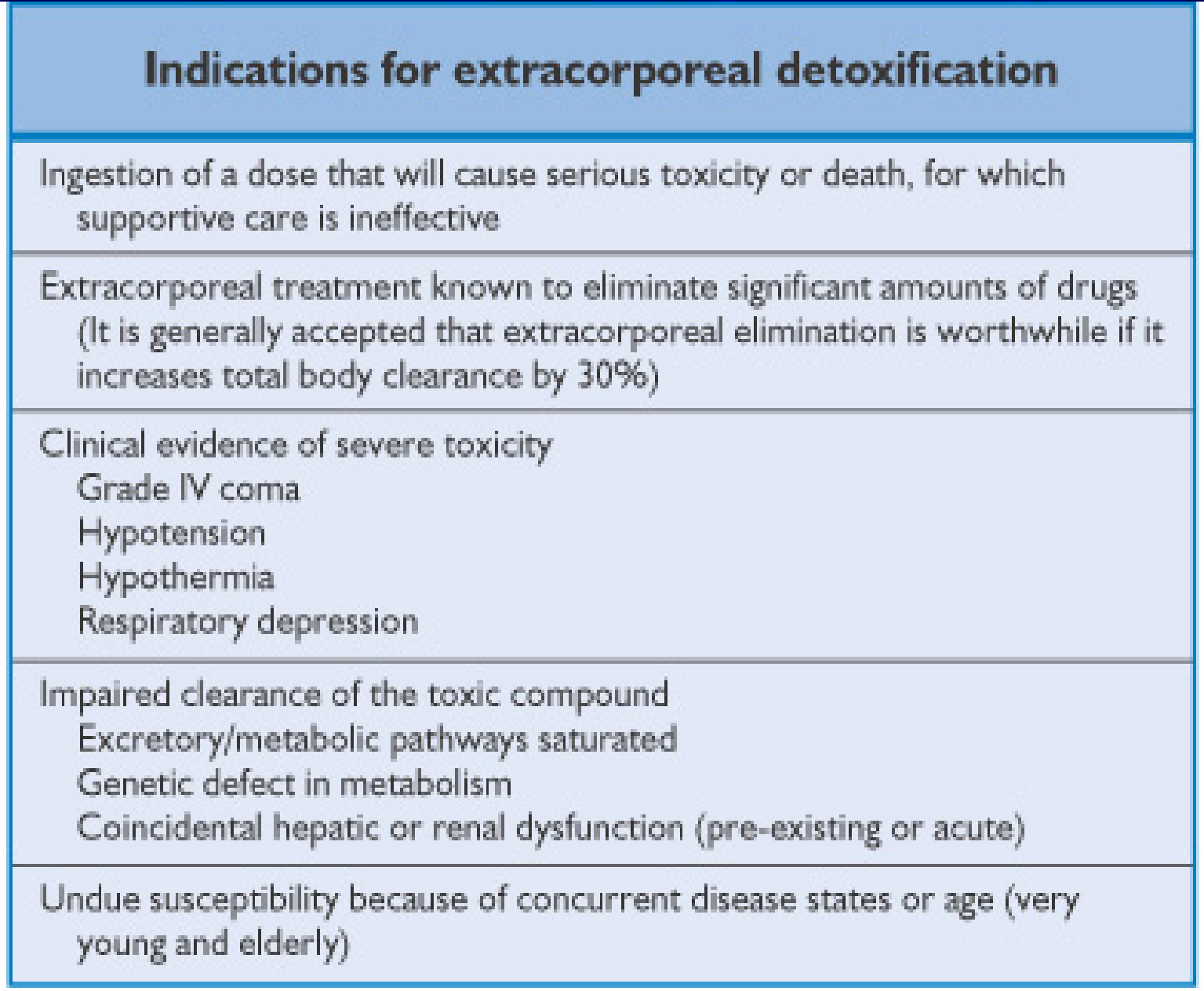


Figure 100.4 Indications for extracorporeal detoxification.

Common poisonings for which extracorporeal removal may be indicated

	Drug Level or Other Criterion for Extracorporeal Treatment	Comment
Hemodialysis		
Ethanol	>5 g/l (108 mmol/l)	Combine with fomepizole 15 mg/kg IV over 30 min, then 10 mg/kg every 4 hours during hemodialysis
Methanol	>50 mg/l (15 mmol/l)	
Ethylene glycol	>500 mg/l (8 mmol/l)	
Lithium	>4 mmol/l 2.5 mmol/l if severe symptoms	Postdialysis rebound as intracellular lithium diffuses into extracellular fluid
Methanol	>500 mg/l (15 mmol/l)	
Salicylate	>800 mg/l (5.8 mmol/l)	Lower threshold if renal impairment or if fluid overload restricts treatment with sodium bicarbonate
Hemofiltration		
Aminoglycosides	Various	
Hemoperfusion		
Amanita mushroom	Clinical severity	
Barbiturates	Phenobarbitone 150 mg/l (630 mol/l)	
Carbamazepine	Clinical severity	
Paraquat	Clinical severity	
Theophylline	Acute >100 mg/l	Chronic >40 mg/l
Valproic acid	>1 g/l	

Figure 100.10 Common poisonings for which extracorporeal removal may be indicated.

Hemoperfusion

- Extracorporeal form of treatment where large volumes of blood is passed over an adsorbent surface
- Activated carbon (irreversibly bound by van der Waals' forces) and resins (not irreversibly bound) are the adsorbents most commonly used.
- Higher MW (100-40,000 daltons) are well adsorbed with charcoal having greater affinity for water soluble and resin for lipid soluble compounds
- Time factor

Figure 100.5 A charcoal hemoperfusion cartridge.

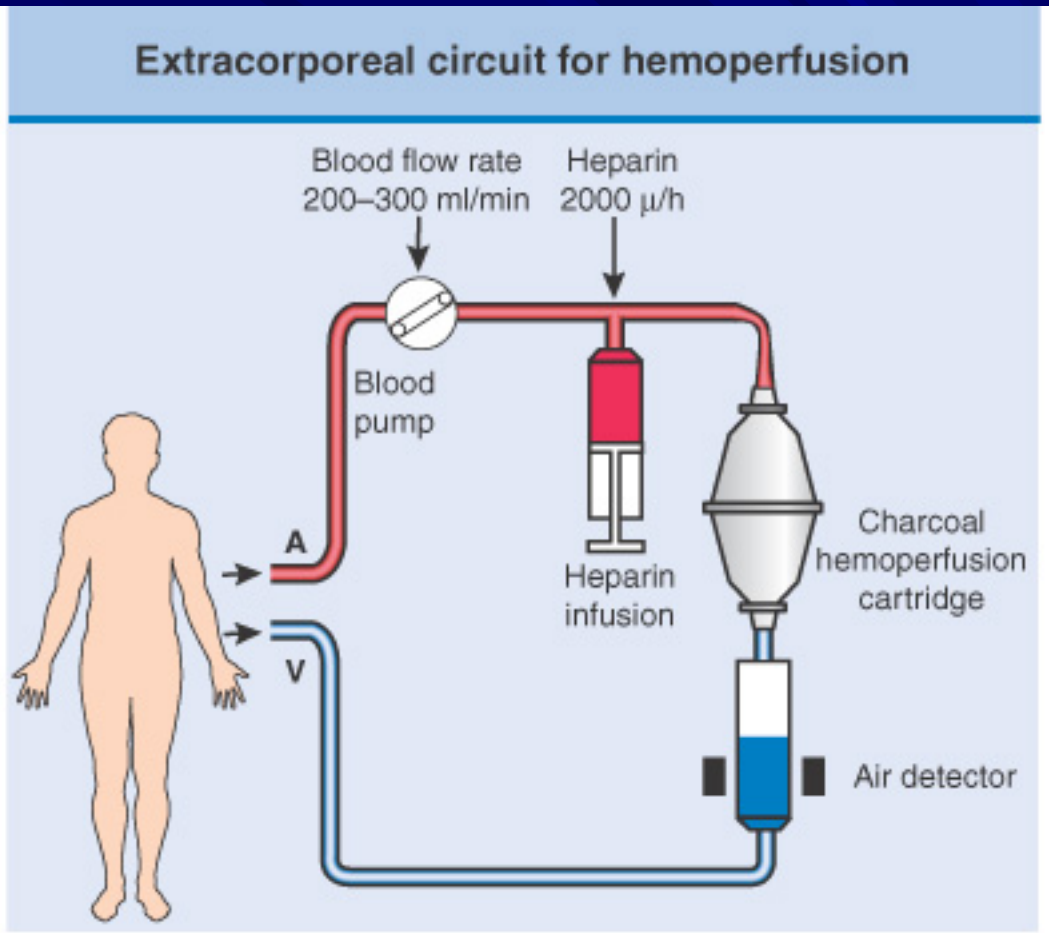


Figure 100.6 Extracorporeal circuit for hemoperfusion.

Kinetic characteristics that assist extracorporeal drug removal

Hemodialysis	Hemofiltration	Hemoperfusion
Relative molecular mass <500 d Small volume of distribution (V_D) (<1 l/kg) Poorly bound to plasma proteins Single-compartment kinetics Low endogenous clearance (<4 ml/min/kg)	Relative molecular mass less than cutoff of filter fibers (usually 40,000 d) Small V_D (<1 l/kg) Poorly bound to plasma proteins Single-compartment kinetics Low endogenous clearance (<4 ml/min/kg)	Adsorbed by activated charcoal Small V_D (<1 l/kg) Single-compartment kinetics Low endogenous clearance (<4 ml/min/kg)

Figure 100.9 Kinetic characteristics of drugs that assist extracorporeal drug removal.

MARS

- Molecular Adsorbent Recirculating System
- Effectively removes protein bound toxins

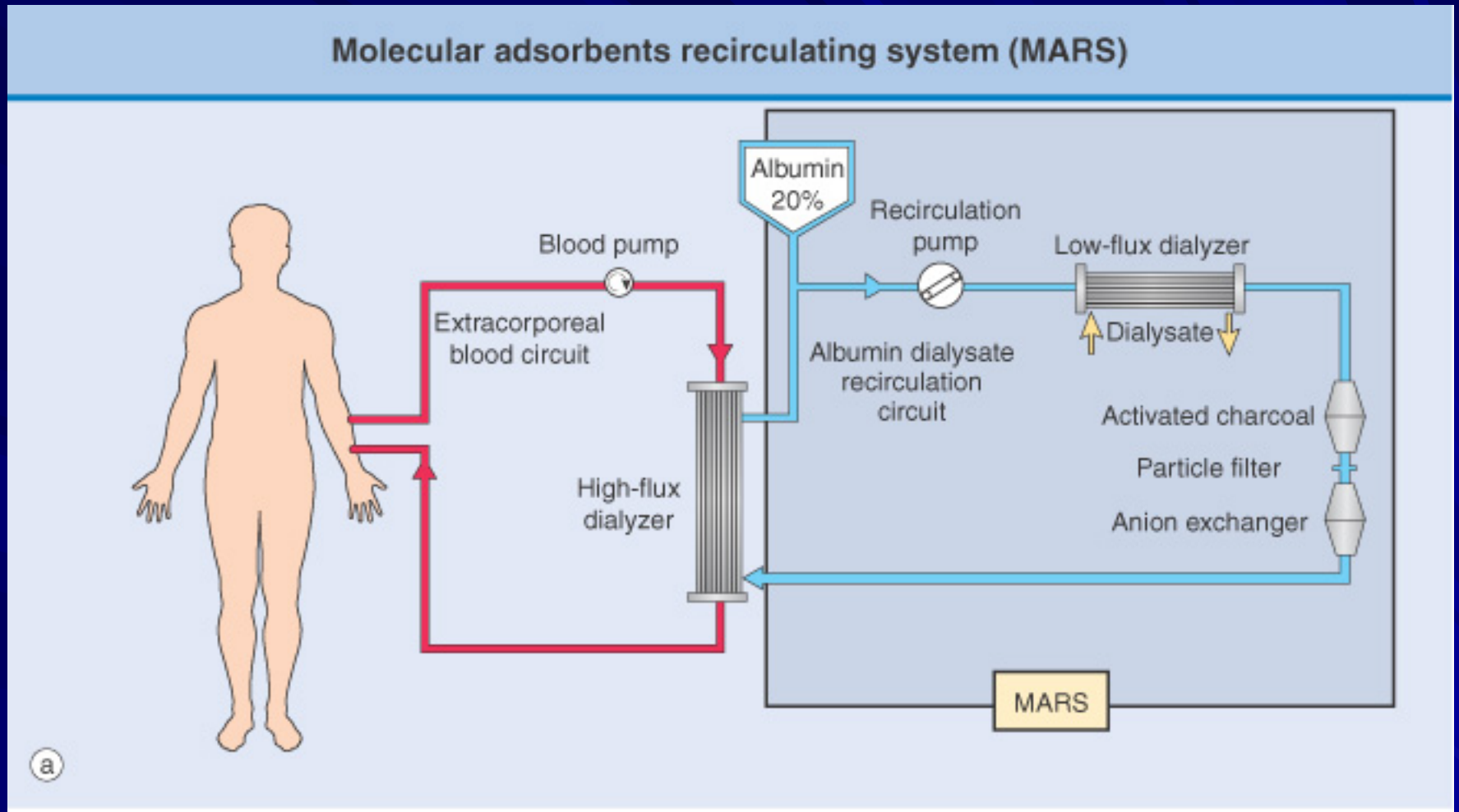
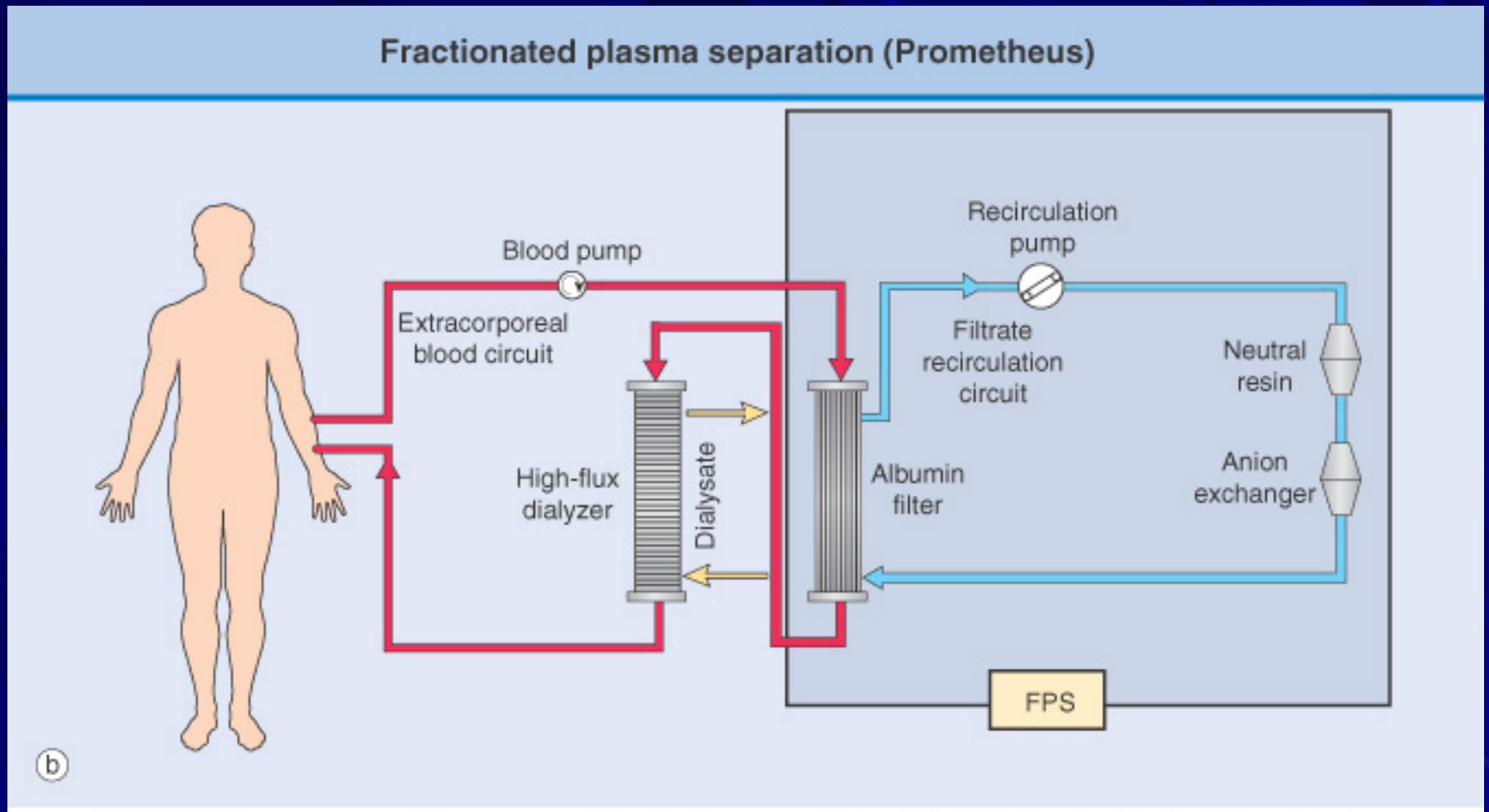


Figure 100.7A Extracorporeal liver support techniques. *a,* Molecular Adsorbents Recirculating System (MARS): an albumin-impermeable high-flux membrane is impregnated with human albumin and the dialysate enriched with albumin to facilitate removal of albumin-bound toxins from the blood. The albumin is regenerated by passage through activated charcoal and an anion exchanger. A low-flux dialyzer is in series to remove water-soluble toxins. *b,* Fractionated Plasma Separation (FPS) (Prometheus): blood passes through an albumin-permeable membrane; the albumin is removed by convection and then passes through neutral and anion exchange adsorbers to regenerate the albumin. A high-flux dialyzer is in series to remove water-soluble toxins.



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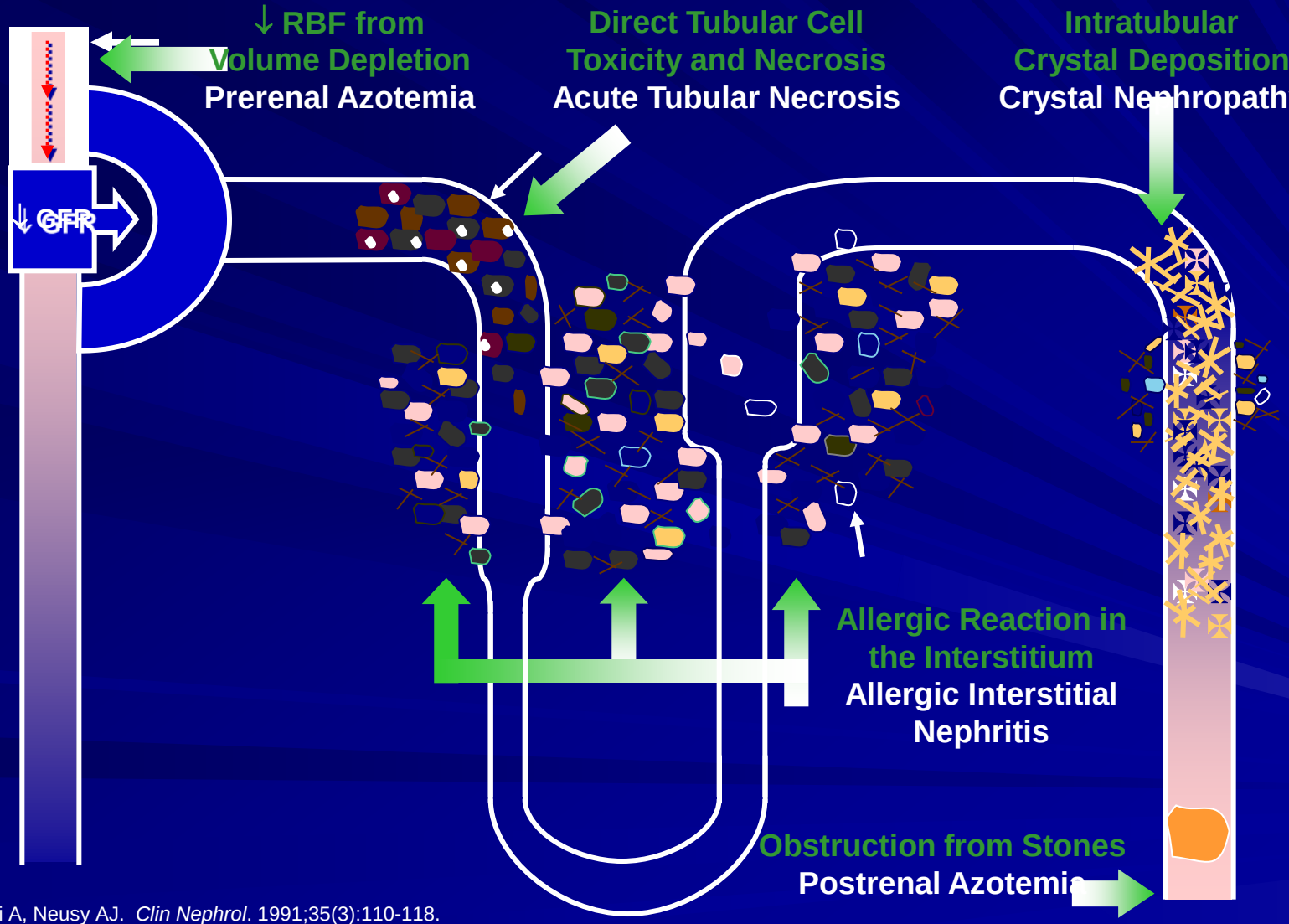
Diuresis at controlled pH

- Nonionized drugs are lipid soluble and will diffuse through cell membranes relatively easily, promoting passive absorption of filtered drugs. By contrast, drugs in the ionized states are poor absorbed. Alteration in the urine pH can alter the absorption of weak acids and bases.

Nephrotoxicity

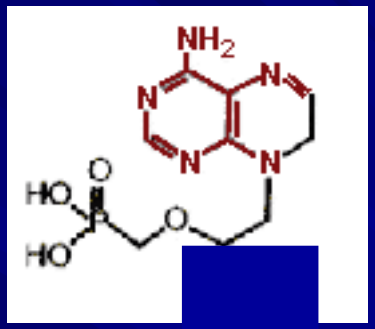
Causes of Acute Renal Failure



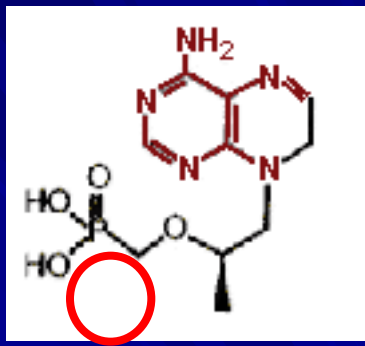
Valeri A, Neusy AJ. *Clin Nephrol*. 1991;35(3):110-118.
Rao TKS, Friedman EA. *Am J Kidney Dis*. 1995;25(3):390-398.
Perazella MA. *Am J Med Sci*. 2000;319(6):385-391.

TENOFOVIR

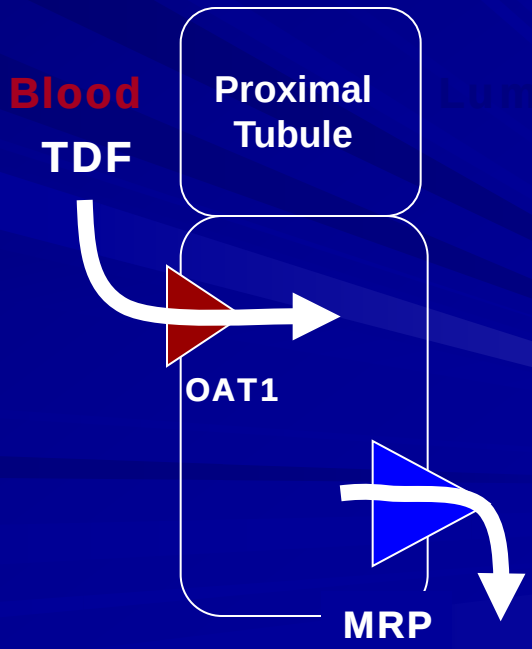
- Tenofovir closely related to adefovir
- Adefovir is a well described nephrotoxin
- Tenofovir freely filtered; also secreted by proximal tubule
- Nephrotoxicity vigilance in clinical trials



Adefovir



Tenofovir



Drug-induced kidney injury

Drug	Risk Factor	Incidence	Pathophysiology	Prevention	Management
			Antimicrobials		
Acyclovir	High dose, IV bolus dose	5%–25%	Deposition of acyclovir crystals → intratubular obstruction and foci of interstitial inflammation → ARF Crystal nephropathy Proximal tubulopathy	Avoid bolus dose, slow drug infusion over 1–2 hr Prior hydration (maintain urine output >75 ml/hr)	Discontinue hydration and loop diuretic
Adefovir dipivoxil	Dose ≥30 mg/day Duration of therapy Renal impairment Pre-existing tubular dysfunction	1% Fanconi syndrome	Depletion of mitochondrial DNA from proximal tubular cells → enlargement and dysmorphia of mitochondria of PCT → acute tubular degeneration		Discontinue
Aminoglycosides	Dose, duration, and frequency of administration Concurrent renal ischemia or administration of nephrotoxins Liver disease plasma concentration >10 mg/dl peak and >2–3 trough	5%–20%	In proximal tubule aminoglycoside bound to anionic phospholipid, delivered to megalin, endocytic uptake into the cell. Within cell, accumulates → direct toxicity → ARF	Maintain therapeutic range Give once-daily dose if necessary	Decrease dose, frequency, and duration of therapy
Amphotericin	High dose and long duration of therapy	5%–80%	Afferent vasoconstriction and direct action → ↓ GFR Distal tubular injury via creation of pores that increase membrane permeability → hypokalemia, hypomagnesemia, renal tubular acidosis, polyuria due to nephrogenic diabetes insipidus	Use liposomal formulation (does not contain deoxycholate) Sodium loading (500–1000 ml normal saline 30 min prior to administration Regularly monitor serum Na, K, Mg	
Cidofovir		8%	Induces apoptosis in proximal tubule → tubular dysfunction, diabetes insipidus, renal failure		Probenecid (human organic anion transporter inhibitor) →reduce tubular uptake of cidofovir
Foscarnet	Duration of therapy Renal impairment Pre-existing tubular dysfunction	27%	Direct tubular toxicity → acute tubular necrosis, nephrogenic diabetes insipidus Crystals in glomerular capillary lumen and proximal tubular lumen	0.5–1liters normal saline infusion	
Indinavir	Bolus dose	4%–14%	Crystal nephropathy, Nephrolithiasis → obstructive ARF	Hydration Establish high urine flow Avoid bolus dose	Discontinue
Sulfonamide (sulfadiazine and sulfamethoxazole)	High dose Urine pH <5.5	7%	Intrarenal precipitation → kidney stone formation	Fluid intake >3 l/day, monitor urine for crystals; if crystals seen; alkalinize urine to pH >7.1	

A

Figure 101.11A Drug-induced kidney injury. All drugs in this table should be dosed based on renal function. Avoid concomitant use of nephrotoxic medications and diuretics. Monitor renal function before and during treatment. Patient-related risk factors for all these drugs include age, pre-existing chronic kidney disease, volume depletion, concurrent use of nephrotoxic drugs. Adequate hydration prior to therapy and during the treatment of acute renal failure because volume depletion is one of the most important risk factors. ACE, angiotensin-converting enzyme; ARF, acute renal failure; FDA, U.S. Food and Drug Administration; GFR, glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs.

Drug-induced kidney injury—cont'd

Drug	Risk Factor	Incidence	Pathophysiology	Prevention	Management
Tenofovir	Dose Duration	Few case reports	Tubular cell karyomegaly, degeneration, and necrosis → interstitial nephritis, diabetes insipidus, ARF Fanconi syndrome		
Immune-modulating and Chemotherapeutic Agents					
Cyclosporine/ tacrolimus	Dose Age Postoperative ARF Diabetes Hypertension		↓ PG and ↑ 20-HETE acid production → vasoconstriction generation of H_2O_2 resulting in depleted glutathione → ↓ GFR, ischemic collapse or scarring of the glomeruli, vacuolization of the tubules, and focal areas of tubular atrophy and interstitial fibrosis	Maintain in therapeutic range Avoid drugs that raise levels (CYP 3A4 inhibitors) Calcium channel blockers	Discontinue or reduce dose
Interferon		15%–20% proteinuria	Prerenal ARF Tubulointerstitial nephritis Thrombotic microangiopathy Membranoproliferative glomerulonephritis		Discontinue
Intravenous immunoglob-ulin	Sucrose-containing product Dehydration	90% contained sucrose	Accumulation of sucrose in PCT forms vesicles, ↑ osmolarity → cell swelling, vacuolization, and tubular luminal occlusion	Infusion rate <3 mg sucrose/kg/min Avoid coadministration of radiocontrast Avoid sucrose-containing product	Hydration Discontinue sucrose-containing product
Methotrexate	Acidic urine High dose		Precipitates in the urine and induces tubular injury	Prior hydration Alkalinize urine to pH >7.0 (3 l of 5% dextrose in water + 44–66 mmol of $NaHCO_3$ per day)	Loop diuretic Leukovorin rescue with or without thymidine for systemic toxicities
Chemotherapeutic Agents					
Cisplatin	Low chloride High dose	25%–42%	Chloride in cis position replaced by H_2O → highly reactive hydroxyl radical via Cyp450 → DNA injury tubular cell death Nephrogenic diabetes insipidus Hypomagnesemia (may be persistent)	Forced diuresis: 2.5 l/hr normal saline before and several hours after administration Mannitol or furosemide Thiophosphate, thiosulfate	Discontinue Mg supplementation
Ifosfamide	Coprescription of cisplatin	Almost 100%	Direct tubular injury and mitochondrial damage → renal tubular acidosis, Fanconi-like syndrome, nephrogenic diabetes insipidus, hypokalemia	Mesna	Discontinue
Other Agents					
ACE inhibitor			Vasoconstriction → prerenal ARF	Avoid in bilateral renal artery stenosis	

B

Figure 101.11B Drug-induced kidney injury. All drugs in this table should be dosed based on renal function. Avoid concomitant use of nephrotoxic medications and diuretics. Monitor renal function before and during treatment. Patient-related risk factors for all these drugs include age, pre-existing chronic kidney disease, volume depletion, concurrent use of nephrotoxic drugs. Adequate hydration prior to therapy and during the treatment of acute renal failure because volume depletion is one of the most important risk factors. ACE, angiotensin-converting enzyme; ARF, acute renal failure; FDA, U.S. Food and Drug Administration; GFR, glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs.

Drug-induced kidney injury—cont'd

Drug	Risk Factor	Incidence	Pathophysiology	Prevention	Management
Lithium	Renal impairment Dehydration Hyponatremia Diuretic use, especially thiazide	20%–54% develop urine concentration defect 12% frank diabetes insipidus (defect persists in 63% despite withdrawal of lithium)	Impairment of collecting duct concentrating ability → diabetes insipidus Chronic tubulointerstitial nephropathy (tubular atrophy and interstitial fibrosis)	Therapeutic range (0.6–1.2 mmol/l) Prevent dehydration Avoid low-sodium diet Avoid thiazide	Amiloride for nephrogenic diabetes insipidus Fluid restoration Furosemide up to 40 mg/hr Acetazolamide + $NaHCO_3$ Na, K supplement Hemodialysis (rebound can occur if stop too early) Discontinue
NSAIDs	Volume and sodium depletion Diuretic use Large dose and long therapy Severe liver disease	1%–5%	Hemodynamically induced ARF due to vasoconstriction via reduced prostaglandin production → Acute and chronic tubulointerstitial nephritis,with or without nephrotic syndrome Direct toxicity → chronic interstitial nephritis and papillary necrosis	Avoid coprescription of diuretic Avoid large dose	
Radiocontrast media	Dose and frequency Osmolarity of contrast media	<10% in patients with normal GFR 12%–25% if GFR ↓	High osmolarity, medullary vasoconstriction, ↑ active transport in thick ascending loop of Henle → ↑ O_2 demand	Hydration before and after administration Acetylcysteine unproven	

C

Figure 101.11C Drug-induced kidney injury. All drugs in this table should be dosed based on renal function. Avoid concomitant use of nephrotoxic medications and diuretics. Monitor renal function before and during treatment. Patient-related risk factors for all these drugs include age, pre-existing chronic kidney disease, volume depletion, concurrent use of nephrotoxic drugs. Adequate hydration prior to therapy and during the treatment of acute renal failure because volume depletion is one of the most important risk factors. ACE, angiotensin-converting enzyme; ARF, acute renal failure; FDA, U.S. Food and Drug Administration; GFR, glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs.

Toxicology

Pattern of poisoning in accidental and deliberate self-harm		
Drug/Class	Specific Antidote Available	Extracorporeal Drug Removal May Be Indicated
Acetaminophen (paracetamol)	*N*-acetylcysteine	No
Benzodiazepines	Flumezanil	No
Antidepressants (most commonly amitriptyline)	No	No
Street drugs (including opioids and stimulants)	Naloxone	No
Other analgesics including opioids and NSAIDs	Naloxone	No
Aspirin	No	Yes
Anticonvulsants	No	Yes
Household compounds	No	No
Theophylline	No	Yes
Lithium	No	Yes

Figure 100.1 Pattern of poisoning in accidental and deliberate self-harm. The most common categories of drugs taken in deliberate and accidental self-harm listed in descending order of frequency. NSAIDs, nonsteroidal anti-inflammatory drugs.

(Adapted from data reported by National Poisons Information Service, United Kingdom [www.doh.gov.uk/npis.htm] and the American Association of Poison Control Centers [www.aapcc.org].)

Antidotes of proven value in common causes of poisoning	
Poison	Antidote
Acetaminophen	*N*-acetylcysteine, methionine
Benzodiazepines	Flumazenil
Carbon monoxide	Oxygen
Coumadin (warfarin)	Vitamin K
Cyanide	Amyl nitrite, sodium nitrite, sodium thiosulfate, dicobalt edetate
Digoxin	Digoxin-specific Fab antibodies
Ethylene glycol	Fomepizole, ethanol
Iron salts	Desferoxamine
Methanol	Ethanol
Methemoglobinemia	Methylene blue
Opioids	Naloxone
Organophosphate insecticides	Atropine, pralidoxime

Figure 100.3 Antidotes of proven value in common causes of poisoning.

Antidotes of proven value in common causes of poisoning	
Poison	Antidote
Acetaminophen	*N*-acetylcysteine, methionine
Benzodiazepines	Flumazenil
Carbon monoxide	Oxygen
Coumadin (warfarin)	Vitamin K
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Ethylene glycol	Fomepizole, ethanol
Iron salts	Desferoxamine
Methanol	Ethanol
Methemoglobinemia	Methylene blue
Opioids	Naloxone
Organophosphate insecticides	Atropine, pralidoxime

Figure 100.3 Antidotes of proven value in common causes of poisoning.

Indications for extracorporeal detoxification
Ingestion of a dose that will cause serious toxicity or death, for which supportive care is ineffective
Extracorporeal treatment known to eliminate significant amounts of drugs (It is generally accepted that extracorporeal elimination is worthwhile if it increases total body clearance by 30%)
Clinical evidence of severe toxicity Grade IV coma Hypotension Hypothermia Respiratory depression
Impaired clearance of the toxic compound Excretory/metabolic pathways saturated Genetic defect in metabolism Coincidental hepatic or renal dysfunction (pre-existing or acute)
Undue susceptibility because of concurrent disease states or age (very young and elderly)

Figure 100.4 Indications for extracorporeal detoxification.

Drug assays necessary for management of poisoning
Acetaminophen
Carbamazepine
Digoxin
Ethylene glycol
Ethanol
Lithium
Methemoglobin
Methanol
Phenobarbitone
Salicylate
Theophylline
Valproate

Figure 100.8 Drug assays necessary for management of poisoning. Drug assays that should be readily available around the clock for management of poisoning.

Kinetic characteristics that assist extracorporeal drug removal

Hemodialysis	Hemofiltration	Hemoperfusion
Relative molecular mass <500 d Small volume of distribution (V_D) (<1 l/kg) Poorly bound to plasma proteins Single-compartment kinetics Low endogenous clearance (<4 ml/min/kg)	Relative molecular mass less than cutoff of filter fibers (usually 40,000 d) Small V_D (<1 l/kg) Poorly bound to plasma proteins Single-compartment kinetics Low endogenous clearance (<4 ml/min/kg)	Adsorbed by activated charcoal Small V_D (<1 l/kg) Single-compartment kinetics Low endogenous clearance (<4 ml/min/kg)

Figure 100.9 Kinetic characteristics of drugs that assist extracorporeal drug removal.

Common poisonings for which extracorporeal removal may be indicated

	Drug Level or Other Criterion for Extracorporeal Treatment	Comment
Hemodialysis		
Ethanol	>5 g/l (108 mmol/l)	Combine with fomepizole 15 mg/kg IV over 30 min, then 10 mg/kg every 4 hours during hemodialysis
Methanol	>50 mg/l (15 mmol/l)	
Ethylene glycol	>500 mg/l (8 mmol/l)	
Lithium	>4 mmol/l 2.5 mmol/l if severe symptoms	Postdialysis rebound as intracellular lithium diffuses into extracellular fluid
Methanol	>500 mg/l (15 mmol/l)	
Salicylate	>800 mg/l (5.8 mmol/l)	Lower threshold if renal impairment or if fluid overload restricts treatment with sodium bicarbonate
Hemofiltration		
Aminoglycosides	Various	
Hemoperfusion		
Amanita mushroom	Clinical severity	
Barbiturates	Phenobarbitone 150 mg/l (630 mol/l)	
Carbamazepine	Clinical severity	
Paraquat	Clinical severity	
Theophylline	Acute >100 mg/l	Chronic >40 mg/l
Valproic acid	>1 g/l	

Figure 100.10 Common poisonings for which extracorporeal removal may be indicated.

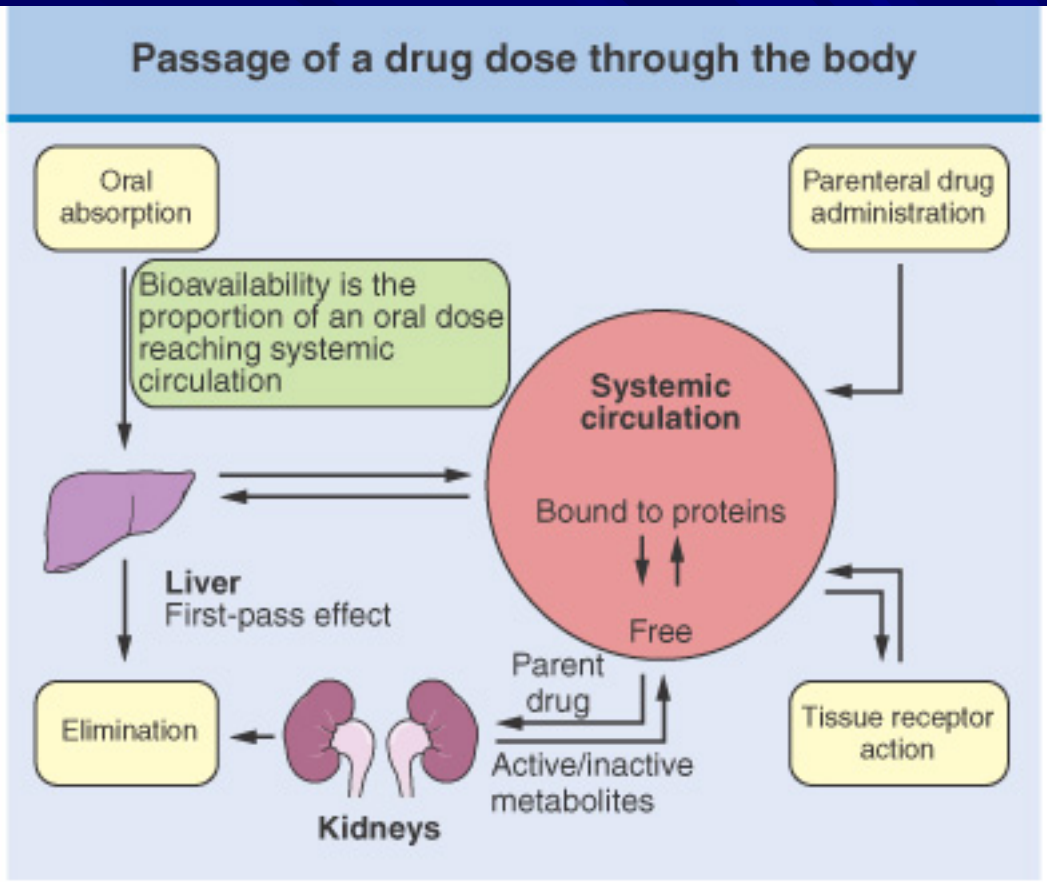


Figure 101.1 The passage of a drug through the body.

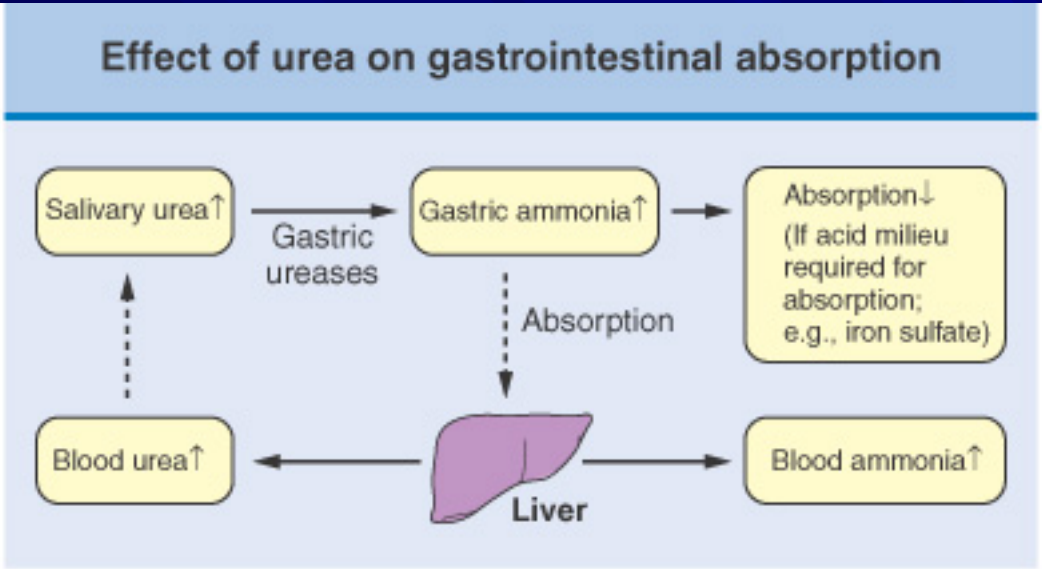
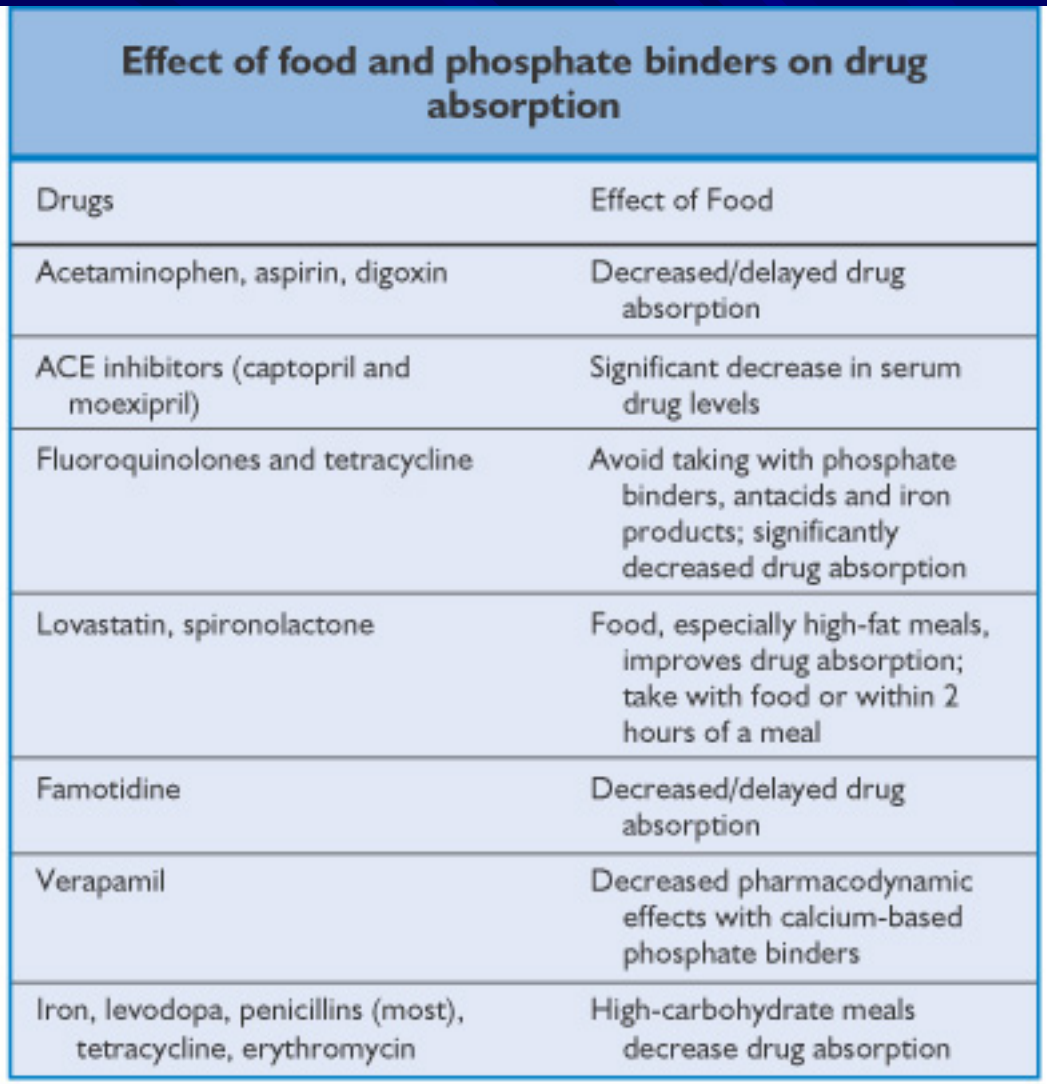


Figure 101.2 Effect of urea levels on gastrointestinal absorption.



Effect of food and phosphate binders on drug absorption

Drugs	Effect of Food
Acetaminophen, aspirin, digoxin	Decreased/delayed drug absorption
ACE inhibitors (captopril and moexipril)	Significant decrease in serum drug levels
Fluoroquinolones and tetracycline	Avoid taking with phosphate binders, antacids and iron products; significantly decreased drug absorption
Lovastatin, spironolactone	Food, especially high-fat meals, improves drug absorption; take with food or within 2 hours of a meal
Famotidine	Decreased/delayed drug absorption
Verapamil	Decreased pharmacodynamic effects with calcium-based phosphate binders
Iron, levodopa, penicillins (most), tetracycline, erythromycin	High-carbohydrate meals decrease drug absorption

Figure 101.3 Effect of food and phosphate binders on drug absorption. ACE, angiotensin-converting enzyme.

Protein binding of drugs in renal disease

Albumin: Binding Sites for Acidic Compounds	
Protein binding reduced in nephrotic syndrome (hypoalbuminemia) and renal failure (altered albumin affinity). Increased risk of drug toxicity	
Major Effects	Minor Effects
Barbiturates	Ascorbic acid
Benzodiazepine	Bilirubin
Carbamazepine	Fatty acids
Fibrates	Nafcillin
Furosemide	Phenylbutazone
Mycophenolate mofetil	Probenecid
Penicillins	Thiopental
Phenytoin	
Sulfonamides	
Tetracyclines	
Globulins: Binding Site for Basic Compounds	
Effect of altered protein binding less predictable in renal disease	
Major Effects	Minor Effects
Digitoxin	Adenosine
Methadone	Amitriptyline
Propranolol	Chloramphenicol
Warfarin	Chlorpromazine
	Nortriptyline
	Quinine

Figure 101.4 Protein binding of drugs in renal disease.

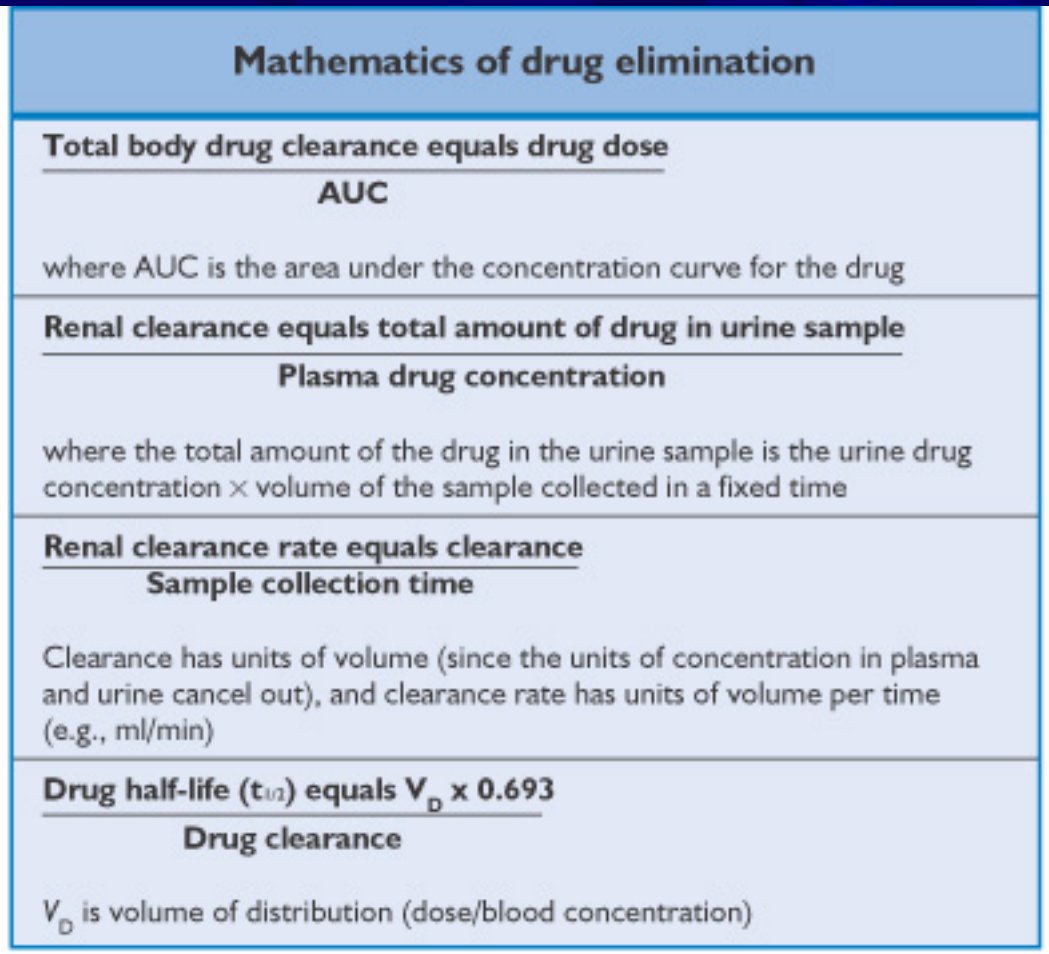
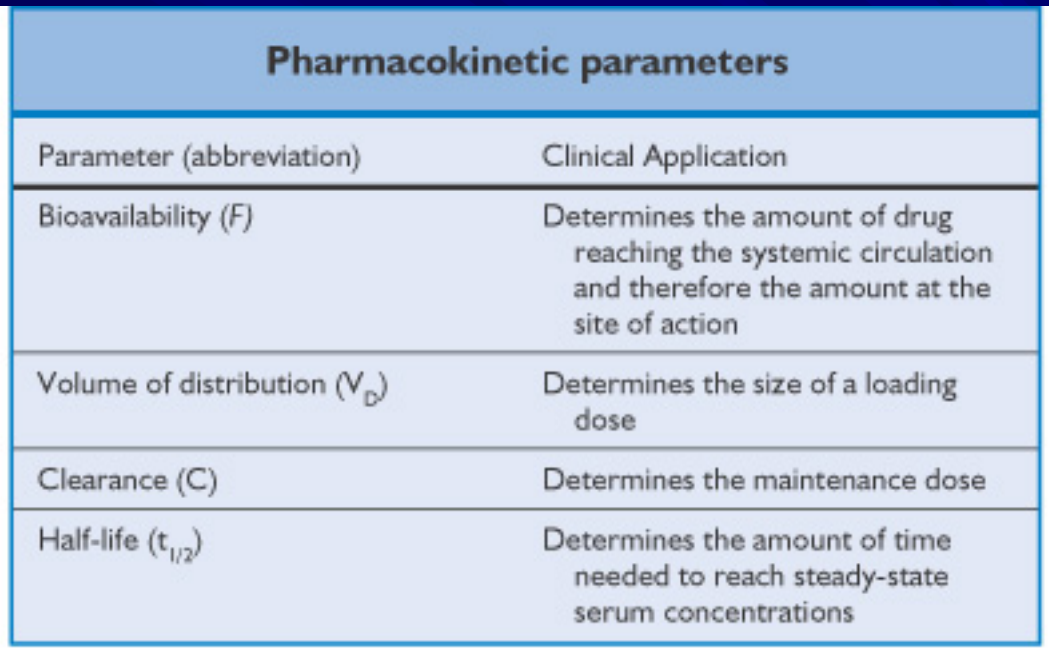


Figure 101.5 Mathematics of drug elimination.



Pharmacokinetic parameters	
Parameter (abbreviation)	Clinical Application
Bioavailability (*F*)	Determines the amount of drug reaching the systemic circulation and therefore the amount at the site of action
Volume of distribution (V_D)	Determines the size of a loading dose
Clearance (C)	Determines the maintenance dose
Half-life ($t_{1/2}$)	Determines the amount of time needed to reach steady-state serum concentrations

Figure 101.6 Pharmacokinetic parameters.

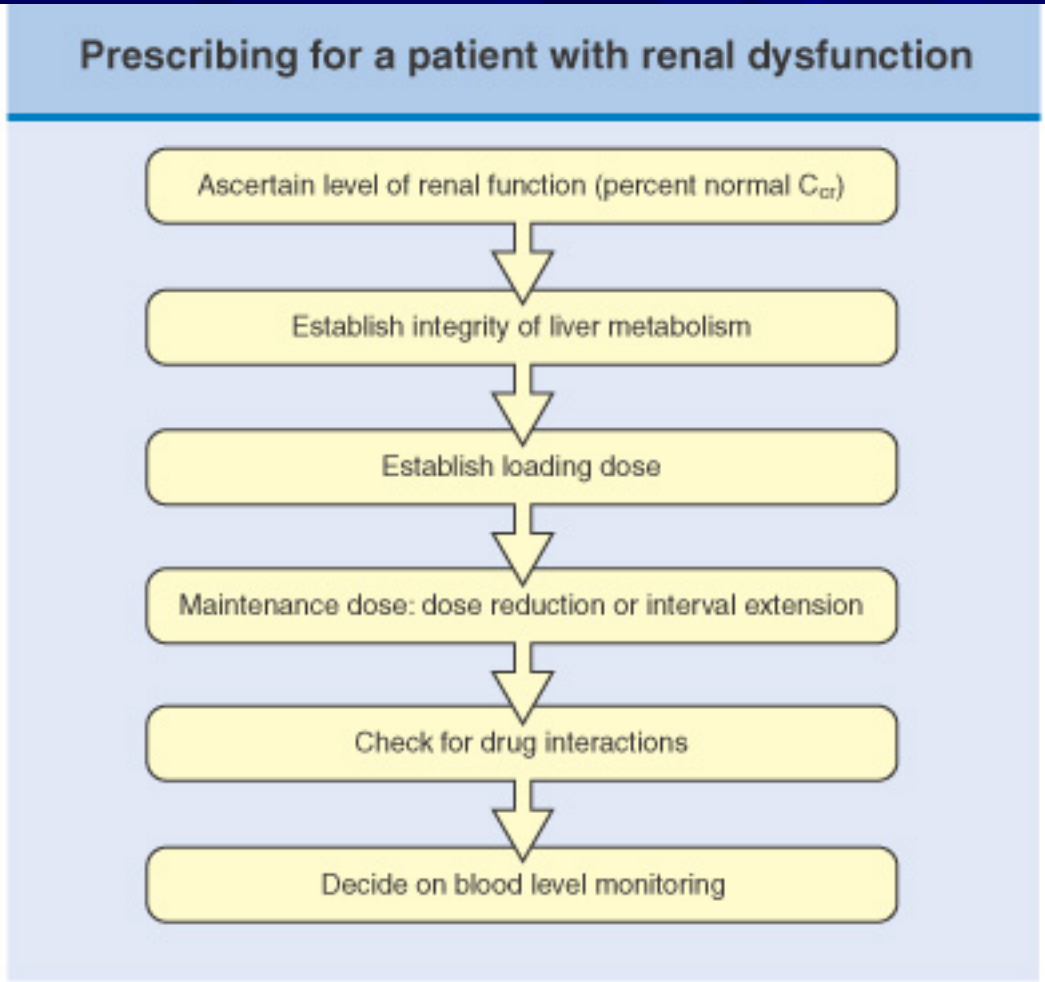


Figure 101.7 Prescribing for a patient with renal dysfunction. C_{cr}, creatinine clearance.

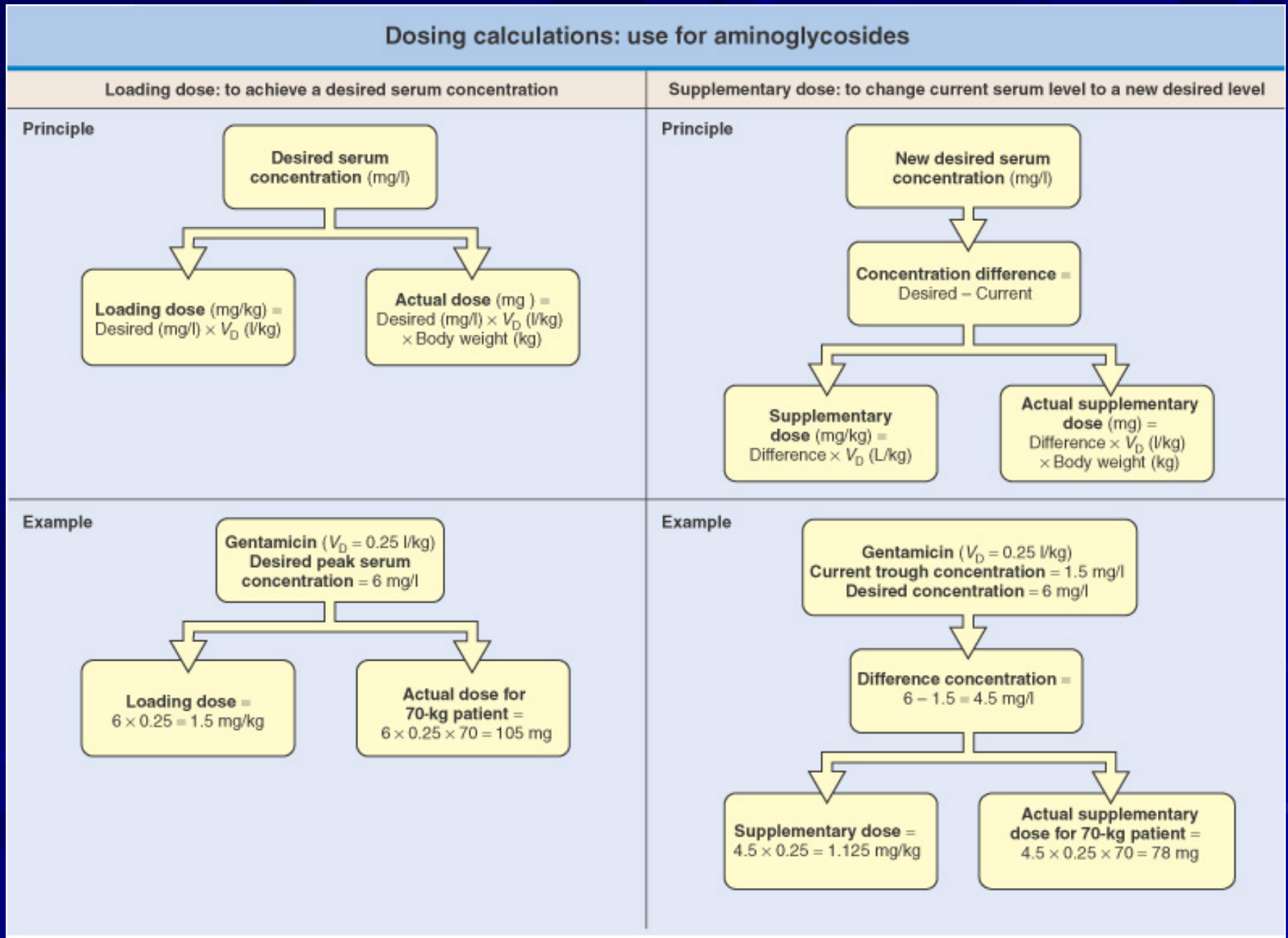


Figure 101.8 Dosing calculations.

Therapeutic drug monitoring in renal insufficiency

Drug Name	Therapeutic Range	When to Draw Sample	How Often to Check Levels
Aminoglycosides (conventional dosing): gentamicin, tobramycin, amikacin	Gentamicin and tobramycin Trough: 0.5–2 mg/l Peak: 5–8 mg/l Amikacin Peak: 20–30 mg/l Through: <10 mg/l	Trough: immediately prior to dose Peak: 30 min after a 30-min infusion	Check peak and trough with 3rd dose. For therapy 72 hr, levels not necessary. Repeat drug levels weekly or if renal function changes
Aminoglycosides (24-hr dosing): gentamicin, tobramycin, amikacin	0.5–3 mg/l	Obtain random drug level 12 hr after dose	After initial dose. Repeat drug level in 1 wk or if renal function changes
Carbamazepine	4–12 μg/ml	Trough: immediately prior to dosing	Check 2–4 days after first dose or change in dose
Cyclosporine	50–200 μg/ml	Trough: immediately prior to dosing	Daily for first week, then weekly
Digoxin	0.8–2 μg/ml	12 hr after maintenance dose	5–7 days after first dose for patients with normal renal and hepatic function; 15–20 days in anephric patients
Lidocaine	1–5 μg/ml	8 hr after IV infusion started or changed	
Lithium	Acute: 0.8–1.2 mmol/l Chronic: 0.6–0.8 mmol/l	Trough: before AM dose at least 12 hr since last dose	
Phenobarbitone	15–40 μg/l	Trough: immediately prior to dosing	Check 2 wk after first dose or change in dose. Follow-up level in 1–2 mo
Phenytoin Free phenytoin	10–20 μg/ml 1–2 μg/ml	Trough: immediately prior to dosing	5–7 d after first dose or after change in dose
Procainamide NAPA (*N*-acetyl procainamide), a procainamide metabolite	4–10 μg/ml Trough: 4 μg/ml Peak: 8 μg/ml 10–30 μg/ml	Trough: immediately prior to next dose or 12–18 hr after starting or changing an infusion Draw with procainamide sample	
Quinidine	1–5 μg/ml	Trough: immediately prior to dosing	
Sirolimus	10–20 μg/dl	Trough: immediately prior to dosing	
Tacrolimus	10–15 μg/ml	Trough: immediately prior to dosing	
Theophylline PO or aminophylline IV	15–20 μg/ml	Trough: immediately prior to dosing	
Valproic acid (divalproex sodium)	40–100 μg/ml	Trough: immediately prior to dosing	Check 2–4 days after first dose or change in dose
Vancomycin	Trough: 5–15 mg/l Peak: 25–40 mg/l	Trough: immediately prior to dosing Peak: 60 min after a 60 min infusion	With 3rd dose (when initially starting therapy, or after each dose adjustment). For therapy <72 hr, levels not necessary. Repeat drug levels if renal function changes

Figure 101.9 Therapeutic drug monitoring in renal insufficiency. Drugs for which monitoring of drug levels is routinely recommended.

Commonly used drugs that require replacement dosing following intermittent hemodialysis

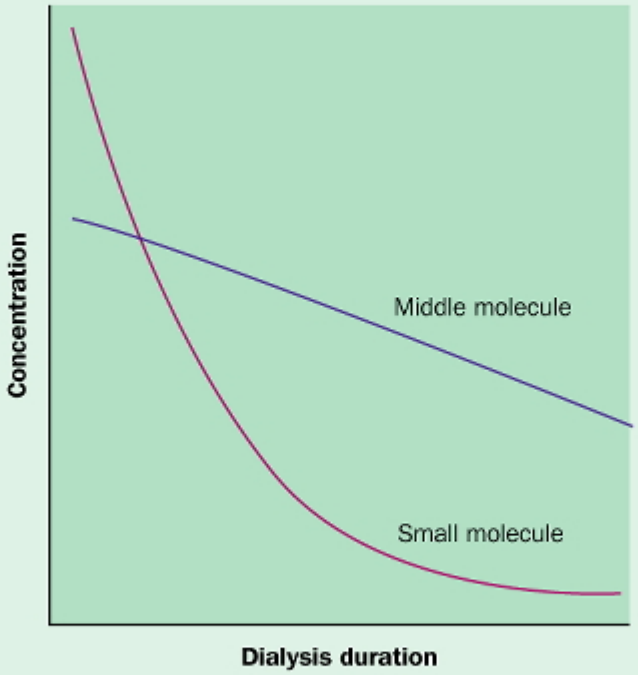
Acebutolol	Cefamandole	Ceftizoxime	Gabapentin	Metronidazole	Ticarcillin
Acetaminophen	Cefazolin	Cefuroxime	Ganciclovir	Mezlocillin	Tobramycin
Acyclovir	Cefdinir	Chloral hydrate	Gentamicin	Minoxidil	Trimethoprim
Allopurinol	Cefdroxil	Chloramphenicol	Ifosfamide	Nadolol	Valacyclovir
Amikacin	Cefepime	Cyclophosphamide	Imipenem	Ofloxacin	Vigabatrin
Amoxicillin	Cefmenoxime	Disopyramide	Iodixanol	Penicillin	Zidovudine
Ampicillin	Cefmetazole	Enalapril	Isosorbide	Piperacillin	
Aspirin	Cefotaxime	Esmolol	Lisinopril	Procainamide	
Atenolol	Cefotetan	Ethosuximide	Lithium	Pyrazinamide	
Aztreonam	Cefoxitin	Famciclovir	Loracarbef	Sotalol	
Captopril	Cefpirome	Fluconazole	Meropenem	Streptomycin	
Carboplatin	Cefradine	Flucytosine	Methotrexate	Sulfamethoxazole	
Cefaclor	Ceftazidime	5-Fluorouracil	Methylprednisolone	Sulfisoxazole	
Cefalexin	Ceftibuten	Foscarnet	Metoprolol	Theophylline	

Figure 101.10 Commonly used drugs that require replacement dosing following intermittent hemodialysis.

Aggravation by drugs of the metabolic effects of pre-existing renal impairment	
Metabolic effect	Drugs
Hyperkalemia	Potassium supplements, potassium-sparing diuretics (especially combination diuretics), nonsteroidal anti-inflammatory drugs, potassium citrate, tetracyclines, angiatensin-converting enzyme inhibitors, angiotensin II receptor antagonists
Uremia	Corticosteroids, tetracyclines
Sodium and water retention	Sodium chloride, sodium bicarbonate, sodium-containing antacids (e.g., Gaviscon), fludrocortisone, carbenoxolone
Metabolic acidosis	Acetazolamide, metformin
Coagulopathy	Aspirin

Figure 101.12 Aggravation by drugs of the metabolic effects of pre-existing renal impairment.

Molecular size and solute removal during HD



Sites of tubular Injury in ATN