

# CORE CURRICULUM IN NEPHROLOGY

## Pharmacology

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### PHARMACOLOGY: GENERAL PRINCIPLES

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It is important to understand how to appropriately prescribe medications to patients with various levels of acute or chronic kidney disease (CKD), particularly those undergoing some form of renal replacement therapy. Drug effects and their handling by the body also are influenced by underlying comorbidities, age, liver function, nutritional status, critical illness, and other concurrently prescribed medications. This is best achieved by developing a firm grasp of the following concepts.

#### Definitions

##### *Pharmacokinetics*

- Defined as process by which a drug is absorbed, bound to protein (or not), distributed to various tissue compartments, and ultimately metabolized (biotransformation) or excreted intact
- Table 1 summarizes components of pharmacokinetics

##### Clinical pharmacokinetics.

- Refers to application of pharmacokinetic methods to drug therapy in humans
- Utilizes a multidisciplinary approach to individually optimize drug dosing strategies based on such patient characteristics as age, sex, disease state(s), genetics, and ethnic differences
- Table 2 demonstrates pharmacokinetic changes that occur with various patient characteristics

##### *Pharmacodynamics*

- Refers to how medications affect the patient
- Represents interaction of a drug with its target site (receptor) and the pharmacologic response that results
- Reflects relationship between achieved drug concentrations at receptor and associated pharmacologic response

##### *Pharmacogenetics*

- Refers to how genetic differences in patients influence their respective responses to drugs; these genetic differences give rise to interpatient variation in drug absorption, distribution, biotransformation, and elimination

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### PHARMACOKINETICS

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Absorption and bioavailability refer to the process of drug uptake into the body and ultimate level achieved within systemic circulation.

#### Absorption

- Drug must pass from absorption site through or around layers of cells, unless it is administered parenterally, before it gains access into the circulation
- Gastrointestinal absorption may be decreased in patients with advanced kidney disease for various reasons:
  - Absorption is dependent on physicochemical properties of drugs, nature of drug product, and anatomy and physiologic functions at site of drug absorption

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**Table 1. Pharmacokinetics of Drugs**

Absorption of medications into the systemic circulation	
Enteral (oral, buccal, rectal)	
Parenteral (IV, intramuscular, subcutaneous)	
Other (transdermal, inhalation)	
Distribution of drugs and metabolites in tissues	
Target (receptor) site	
Nonreceptor tissues	
Elimination organs	
Biotransformation (metabolism) of drugs	
Hepatic:	
Phase I metabolism:	
Microsomal enzyme mixed-function oxidase system	
Phase II metabolism:	
Conjugation system	
Elimination of drugs and metabolites from body	
Metabolism (as above)	
Excretion:	
Kidneys primarily	
Bile, sweat, saliva (minor contribution)	
Dialysis removal	

- Parenteral, enteral, inhalation, transdermal, or intranasal routes for systemic absorption are available (Table 3)
- There are 2 major factors to consider regarding drug absorption:
  - Extent of drug absorption
  - Rate of drug absorption

### Bioavailability

- Bioavailability of drugs is percentage or fraction of administered drug that reaches systemic circulation
- Drugs that are administered by intravenous (IV) route have complete bioavailability (F

= 1.0); bioavailability is  $\leq 1.0$  for all other administration routes because of incomplete absorption and “first-pass” hepatic metabolism

- Absorption from gastrointestinal tract can be reduced for several reasons:
  - Removal of drug:
    - Nasogastric suction and vomiting
  - Gastric pH change ( $\uparrow$  pH):
    - Salivary urea converted to ammonia in patients with kidney disease
    - Acid inhibition, ie, with  $H_2$ -blockers and proton pump inhibitors
  - Altered gastrointestinal peristalsis:
    - Gastroparesis (diabetic and uremic)
    - Ileus
  - Reduced gut function:
    - Pancreatitis
    - Complete or partial bowel obstruction
    - Uremia (decreased small-bowel absorptive function)
  - Diminished absorptive surface area:
    - Small-intestine resection of  $>100$  cm of ileum
  - Decreased splanchnic blood flow:
    - Intravascular volume depletion
    - Heart failure
  - Concomitant drug administration:
    - Phosphate binders, etc
- Presystemic metabolism or first-pass metabolism reduces drug levels in those that undergo significant intestinal mucosal cell or hepatic metabolism:
  - IV/oral dose ratio is low ( $\sim 1:4$ ) due to first-pass metabolism of drugs with 100% absorption

**Table 2. Pharmacokinetic Changes Associated With Various Comorbidities**

Kinetic Factor	Pathophysiologic Change	Drug Effect
Absorption	$\downarrow$ GI acidity and pill interactions* $\downarrow$ Small-bowel surface area	$\downarrow$ Absorption of certain drugs $\downarrow$ Absorption of certain sustained-release medications
Distribution	$\uparrow$ Adipose tissue $\downarrow$ Lean body mass* $\downarrow$ Albumin*	$\uparrow$ Half-life of lipid-soluble drugs $\downarrow$ Drug dose $\uparrow$ Active (unbound) drug
Metabolism	Phase I ( $\uparrow$ or $\downarrow$ ) Phase II ( $\uparrow$ or $\downarrow$ )	$\uparrow$ or $\downarrow$ Half-life of drugs metabolized by this route $\uparrow$ or $\downarrow$ Half-life of drugs metabolized by this route
Excretion	$\downarrow$ RPF, $\downarrow$ GFR*	$\uparrow$ Half-life of drugs that are excreted by kidneys

Abbreviations: GI, gastrointestinal; RPF, renal plasma flow.

\*Changes present in patients with CKD.



**Table 4. Major CYP450 Enzymes With Common Substrates, Inhibitors, and Inducers**

Enzymes	Substrates	Inhibitors	Inducers
CYP1A2	Phenothiazines, amitriptyline	Cimetidine, diltiazem, ciprofloxacin	Rifampin, phenobarbital, tobacco
CYP2C9	Naproxen, warfarin, glyburide	Fluconazole, cimetidine, isoniazid	Rifampin, secobarbital
CYP2C19	Phenytoin, diazepam, PPIs, amitriptyline	Fluoxetine, cimetidine, omeprazole	Rifampin, carbamazepine
CYP2D6	Oxycodone, haloperidol, phenothiazines	Bupropion, cimetidine, paroxetine	Rifampin, dexamethasone
CYP3A3/4	Benzodiazepines, SSRIs, steroids, macrolides	Cimetidine, erythromycin, diltiazem	Phenytoin, rifampin, St John's wort

Abbreviations: PPIs, proton pump inhibitors; SSRIs, selective serotonin reuptake inhibitors.

- Altered protein-binding affinity induced by uremia-associated changes in albumin structural orientation
- Accumulated endogenous substances that compete with drug binding to sites on proteins
- Drug solubility (water or lipophilic)
- Volume of distribution (apparent Vd):
  - Vd is ratio of amount of drug in body compared with its plasma concentration
  - Reflects a theoretical space that estimates initial dose of drug required to reach a therapeutic plasma concentration
  - Note that a large Vd is  $>0.7$  L/kg
  - Examples of Vd:
    - Small Vd (limited to extracellular fluid [ECF] space) = water-soluble drugs, high protein binding
    - Large Vd (penetrate body tissues) = lipid-soluble drugs
  - Influenced by several disease states:
    - Kidney disease ( $\uparrow$  Vd)
    - Liver disease ( $\uparrow$  Vd)
    - Edematous patients ( $\uparrow$  Vd)
    - Aging ( $\uparrow$  Vd)
    - Critically ill ( $\uparrow$  Vd)
    - Volume depletion ( $\downarrow$  Vd)
  - Increased Vd occurs in these patients due to expanded ECF volume and changes in concentrations and characteristics of binding proteins, while volume depletion ( $\downarrow$  ECF volume) decreases the Vd

- Clearance of a drug is expressed as half-life ( $T_{1/2}$ );  $T_{1/2}$  of a drug, which is time required for drug to decline to half its concentration, is proportional to Vd and inversely proportional to clearance

#### Biotransformation (Metabolism)

- Biotransformation of drug involves its enzymatic conversion to metabolite(s), some of which may be physiologically active
- Liver is primary organ of metabolism, with minor but sometimes relevant contributions from kidney
- Drug biotransformation is modulated by the following factors:
  - Age
  - Sex
  - Enzyme inhibition or induction
  - Genetic variability (genetic polymorphisms)
  - Pathologic states affecting hepatic function
  - Kidney disease and uremia slow reduction and hydrolysis reactions
- Drugs undergo metabolism by 2 basic reactions:
  - Phase I metabolism (microsomal enzyme mixed-function oxidase system):
    - Cytochrome P450 (CYP450) enzyme system metabolizes  $\sim 40\%$  to  $50\%$  of all medications
    - Primarily liver, small amounts in kidney, small bowel, and brain
    - CYP450 system consists of  $>20$  enzyme families; those noted in [Table 4](#)

- metabolize a significant number of drugs
- CYP450 enzymes possess genetic polymorphisms that influence drug metabolism (see later)
- Several medications that induce, inhibit, and act as substrates for CYP450 enzymes are prescribed to patients with various forms and levels of kidney disease, increasing potential for lack of efficacy, as well as toxicity (Table 4)
- Phase II metabolism (conjugation system):
  - Glucuronidation, sulfation, and acetylation of drugs into inactive compounds
  - Less important than CYP450 system

### Excretion

- Excretion of drugs involves removal of parent drug or its metabolite (from hepatic biotransformation) from the body
- Pathways of excretion follow:
  - Kidney (majority of excretion)
  - Bile
  - Sweat
  - Saliva
- Renal excretion of drugs occurs through glomerular filtration and tubular secretion and reabsorption; it is influenced by renal blood flow, glomerular filtration rate (GFR), and urinary flow rate:
  - Glomerular elimination is influenced by both degree of protein binding and molecular size of drug
  - Tubular secretion of drugs is higher with those that are protein bound and increases with uremia; however, with advanced kidney disease, drug clearance is significantly impaired despite tubular secretion
- All of these can be affected by the following factors, which can impair elimination of drug and cause potential toxicity:
  - ARF
  - CKD
  - Aging

- Medications that interact with either organic anion or cation transporters in proximal tubular cells (Fig 1):
  - Drugs that compete with organic anion transporter secretory pathways include nucleotide analogues, probenecid, penicillins, cephalosporins, salicylates, diuretics, and radiocontrast media; drug elimination is impaired
  - Drugs that compete with common organic cation transporter secretory pathways include trimethoprim, quinidine, cimetidine, acyclovir, and protease inhibitors; drug elimination is impaired

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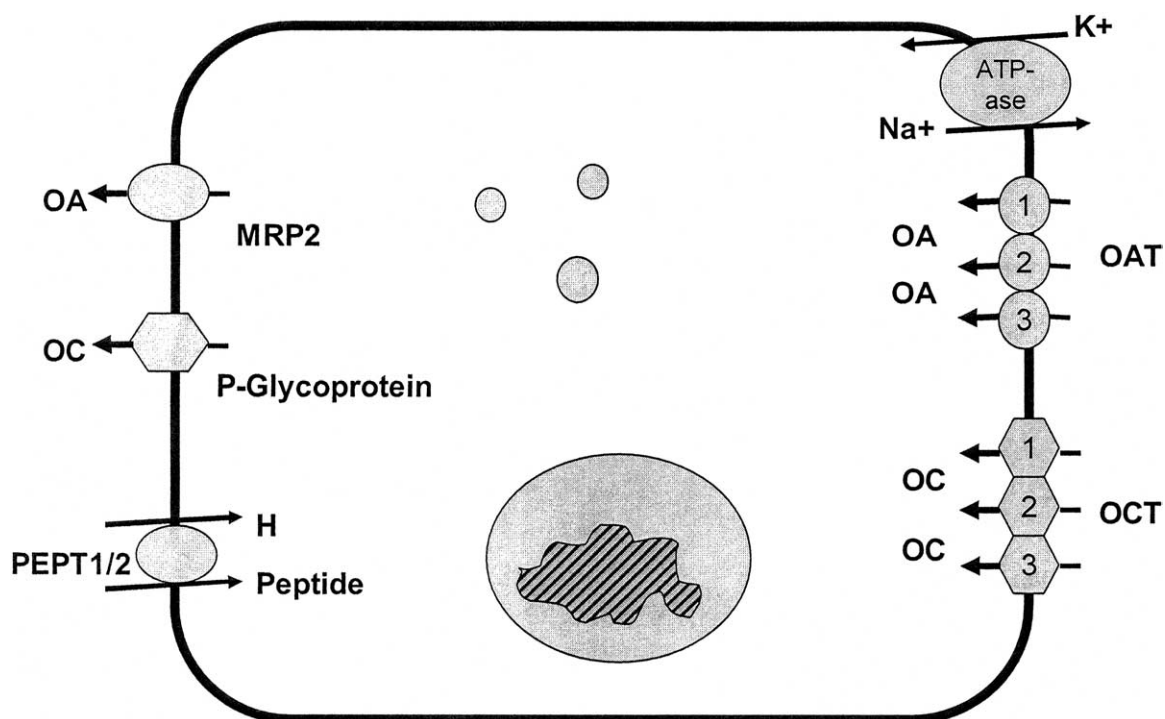
## PHARMACODYNAMICS

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### Pharmacodynamics of Medications

The term pharmacodynamics refers to the interaction of a drug with its target site (receptor), resulting in a pharmacologic response. It reflects the relationship between achieved drug concentrations at the receptor and associated pharmacologic response (linking drug dose to drug effect). The pharmacologic effect of the drug as measured by onset, intensity, and duration are dependent on the following factors (which primarily determine drug concentration at receptor):

- Drug dose
- Drug pharmacokinetics
- Other factors that modify the magnitude of drug effect:
  - Ability of target organ to respond to receptor activation
  - Receptor number at target organ
  - Counterregulatory influences (competing processes) at receptor



**Fig 1.** Schematic model of renal proximal tubule with organic anion and cation transporters. Both endogenous substances and drugs are secreted and reabsorbed by these transporters. Patients with renal failure may develop toxicity due to competition for these pathways of secretion due to endogenous substances and medications that compete for these transporters (see text). Abbreviations: OA, organic anion; OC, organic cation; OAT, OA transporter; OCT, OC transporter; PEPT 1/2, peptide transporters 1 and 2; MRP2, multidrug-resistant transporter.

- A number of pharmacodynamic changes are associated with pathologic processes, such as aging, acute and chronic illness, and renal dysfunction; they include:
  - Decreased receptor number
  - Diminished receptor binding
  - Altered signal transduction
- Numerous medications interact and compete for similar receptors, resulting in several clinical effects:
  - Synergistic effects
  - Antagonistic effects
  - Drug toxicity may result
- Examples of influence of various factors on pharmacodynamics, which may cause reduced efficacy or toxicity, include the following:
  - Older age delays onset of muscle relaxant effect compared with that seen in younger adults, despite equal achieved drug concentration
  - Female sex increases adverse events from a monoamine oxidase inhibitor independent of drug exposure level
  - Ethnicity influences sensitivity (Asian > white > African American) to  $\beta$ -adrenergic receptor antagonist despite similar drug exposure and  $\beta$ -receptor density
  - Interaction of warfarin and vitamin K affects anticoagulation; large amounts of vitamin K in diet reduce efficacy of warfarin
  - Exposure to nicotine, through its effect to increase blood pressure and heart rate, blunts effect of a  $\beta$ -adrenergic receptor antagonist to reduce these physiologic parameters

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## PHARMACOGENETICS

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### Pharmacogenetics of Patients

Genetic makeup of a patient importantly influences inherent pharmacokinetics, ultimately giving rise to interpatient variation in drug absorption, distribution, biotransformation, and elimination. These differences are explained in part by genetic variations in the following factors:

- Transport protein function (affect drug absorption):
  - P-Glycoprotein
  - Organic anion transporting polypeptide
- Drug target response (affect drug response):
  - $\beta_2$ -Adrenergic receptors
- Phase I and II enzyme system function (affect drug metabolism):
  - Phase I metabolism:
    - CYP450 enzymes
  - Phase II metabolism:
    - *N*-Acetyltransferase 2
    - Thiopurine *S*-methyltransferase

### Pharmacogenetic Polymorphisms

- This term refers to the setting where greater than 1% of a population has many different forms of CYP450 enzyme (or other) genes that give rise to interethnic variability in expression
- Clinical implication of this genetic variability is such that standard drug doses metabolized by a polymorphic enzyme cause the following effects:
  - Lack of drug effect
  - Prolonged therapeutic effect
  - Drug toxicity
- Phenotype expression related to genetic differences in a patient's enzyme activity includes the following metabolizer designations:
  - Poor metabolizer:
    - Dysfunctional or inactive enzymes
    - Impaired clearance of medications requiring biotransformation for elimination

- Intermediate metabolizer:
  - Decreased enzyme activity
  - Reduced drug metabolism
- Extensive metabolizer:
  - Normal enzyme activity
  - Standard medication response
- Ultrarapid extreme metabolizer:
  - Higher quantities of expressed enzymes due to gene duplication
  - Reduced or absent drug efficacy due to rapid metabolism
- Clinical genetics research will provide a future opportunity to incorporate pharmacogenetics into drug development, allowing individualization of drug dosing

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## DRUG DOSING IN KIDNEY DISEASE

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### Pharmacologic Alterations With Renal Dysfunction

- Drug dosing in patients with kidney disease requires knowledge of the pharmacologic alterations that occur with renal dysfunction (influence of uremia noted in parentheses):
  - Drug pharmacokinetics:
    - Absorption/bioavailability (decreased)
    - Distribution (increased or decreased)
    - Biotransformation (increased or decreased)
    - Elimination (reduced)
  - Drug pharmacodynamics:
    - Drug concentration at receptor (reduced)
    - Receptor function (reduced)
    - Receptor number (increased or decreased)

- Counterregulatory influences at receptor (increased or decreased)

### Clinical Evaluation

- For patients with kidney disease, the following should be undertaken to provide insight into factors that influence pharmacokinetics and pharmacodynamics:
  - History relevant to previous drug exposure, allergies, and toxicity
  - Current medication profile
  - Body weight and height (calculate body mass index)
  - Physical examination:
    - ECF volume:
      - Edema, ascites, pleural effusion (increase Vd)
      - Volume depletion (lower Vd)
    - Stigmata of liver disease
  - Laboratory data:
    - Renal function parameters
    - Tests of synthetic liver function
    - Albumin concentration

### Kidney Function Tests

- GFR is best measure of kidney function
- Drug elimination is highly dependent on prevailing level of kidney function; therefore, measurement (or accurate estimation) of GFR is crucial to appropriate drug dosing
- Estimation of GFR using clinically available tests:
  - Using serum creatinine (Scr) concentration:
    - Cockcroft-Gault creatinine clearance (CrCl) estimation equation (seldom used to quantify renal function):  $CrCl = (140 - \text{age}) \times (\text{ideal body weight})/72 \times \text{Scr (mg/dL)} [\times 0.85 \text{ in women}]$
    - GFR estimation equations:
      - Modification of Diet in Renal Disease (MDRD) equation:  $170 \times [\text{Scr (mg/dL)}]^{-0.999} \times [\text{age (y)}]^{-0.176} \times [0.762 \text{ if female}] \times [1.18 \text{ if African American}] \times [\text{blood urea nitrogen (mg/dL)}]^{-0.170} \times [\text{albumin (g/dL)}]^{+0.318}$

- Abbreviated MDRD equation:  $186 \times [\text{Scr (mg/dL)}]^{-1.154} \times [\text{age (y)}]^{-0.203} \times [0.742 \text{ if female}] \times [1.21 \text{ if African American}]$

- Using 24-hour urine creatinine collection and Scr concentration
- Measuring kidney function with tests that are not currently widely available in the clinical setting:
  - Cystatin C concentration
- Estimating GFR from Scr concentration assumes stable kidney function
- One can assume anuria has  $GFR = 0$ , while oliguria is generally associated with  $GFR = 10$  to  $30 \text{ mL/min}$  ( $0.17$  to  $0.50 \text{ mL/s}$ ; appropriate in ARF setting)

### Acute Renal Failure

- Scant data are available to estimate kidney function or guide drug dosing in this setting
- Pharmacokinetic parameters in patients with ARF may differ from those in patients with CKD:
  - However, elimination half-life values are not substantially different between ARF and CKD at similar GFR values
  - In ARF, preservation of nonrenal clearance of drugs contrasts to CKD, where nonrenal clearance decreases with prolonged duration of renal insufficiency
  - Patients with ARF may have a fluctuating Vd compared with CKD
  - Risk for underdosing or toxicity can occur in ARF patients where drug dosing is extrapolated from stable CKD
- Drug dosing must be individualized in patients with ARF and all available data used to guide therapy, including measuring drug levels when appropriate

### Drug Dosing in Kidney Disease

#### Drug dosing uses half-life ( $T_{1/2}$ )

- $T_{1/2} = (Vd \times 0.693)/\text{drug clearance (C)}$ 
  - $T_{1/2}$  determines amount of time needed to reach steady state and thus dosing frequency

**Table 5. Drug Prescribing in Patients With Kidney Disease**

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1. Ascertain level of kidney function
  2. Confirm integrity of liver metabolism
  3. Establish loading dose
  4. Determine maintenance dose (dosing interval or dose adjustment)
  5. Evaluate for drug interactions
  6. Perform drug blood level monitoring when appropriate
  7. Check dosing periodically in patients with rapidly declining kidney function
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- Four to 5 half-lives are needed for a drug to reach steady state

**Initial or loading dose**

- Vd determines size of initial or loading dose
- Same dose as in patients with normal kidney function unless drug in question has a large Vd and it is reduced in setting of renal failure (as in case of digoxin)
- Consider loading dose increase in presence of significant ECF volume excess for compounds with Vd approximating total-body water
- Reduce dose if volume depletion or significant debilitation is present

**Maintenance dose**

- Drug clearance (C) determines maintenance dose
- Doses need to be modified based on prevailing kidney function level and other appropriate pharmacokinetic considerations
- Maintenance dosing can be adjusted in kidney disease by altering either dosing interval or dose; rules of thumb are provided:
  - New dosing interval = (patient's Scr/normal Scr) × normal interval:
    - Dosing interval is increased in kidney disease
    - Subtherapeutic drug concentrations are potential risk
    - Used for aminoglycosides
  - New drug dose = (normal Scr/patient's Scr) × normal dose:
    - Dose is varied

- Typically reliable levels, but drug toxicity is potential risk
- Used for anticonvulsants, such as phenytoin
- Table 5 outlines simple approach to drug dosing in patients with kidney disease
- Dosage guidelines are available in books on subject of drug prescribing in renal failure

**Caution With Prescription Drugs**

- Certain commonly prescribed drugs can cause ARF and hyperkalemia in patients with underlying CKD and should be administered cautiously
- Partial list of common drugs is provided below:
  - ARF:
    - Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs)
    - Nonsteroidal anti-inflammatory drugs (NSAIDs), selective cyclo-oxygenase (COX)-2 inhibitors
    - Radiocontrast agents
    - Aminoglycosides
    - Amphotericin B
    - IV immunoglobulin, hydroxyethyl starch
  - Hyperkalemia:
    - ACE inhibitors, ARBs
    - NSAIDs, selective COX-2 inhibitors
    - Spironolactone, eplerenone, heparin
    - Trimethoprim, pentamidine
    - Cyclosporin A, tacrolimus
    - Nonselective  $\beta$ -blockers

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## EXTRACORPOREAL REMOVAL OF DRUGS

Drugs are eliminated to some degree by the various forms of dialysis, including hemodialysis (HD), peritoneal dialysis (PD), and continuous renal replacement therapies (CRRTs). Removal is difficult to predict and influenced by various factors:

- Molecular weight of drug:
  - >1,500 d limits diffusive clearance in low-flux membranes
- Vd of drug:
  - >0.7 L/kg reduces both diffusive and convective total drug clearance regardless of membrane type or dialysis modality; however, absolute drug clearance can remain high
  - Lithium and salicylates are examples of drugs with small Vd; tricyclic antidepressants are examples of drugs with large Vd
- Drug solubility:
  - Lipid-soluble drugs have reduced clearance compared with water-soluble drugs
  - Phenobarbital is example of lipid-soluble drug
- Protein binding:
  - High protein binding (>60%) reduces clearance
  - Theophylline is example of highly protein-bound drug, whereas lithium is not highly bound and is removed effectively with extracorporeal therapy
- Pore size and surface area of HD membrane:
  - Small pore size and surface area reduces clearance
- Blood and dialysate flow rates:

- Low blood and dialysate flows reduce clearance

## Hemodialysis

- Drug clearances reduced by low-flux membranes and medications with large Vd and extensive protein binding
- HD drug clearance can be estimated based on following relationship:
  - $Cl_{HD} = Cl_{urea} \times (60/MW_{drug})$ , where  $Cl_{HD}$  is drug clearance,  $Cl_{urea}$  is urea clearance by dialyzer,  $MW_{drug}$  is drug molecular weight, and urea clearance is 150 to 200 mL/min for most standard (high-efficiency) dialyzers
- Several drugs require dosing after HD; guidelines are available in books on subject of drug prescribing in dialysis

## Peritoneal Dialysis

- Low-efficiency drug clearance
- Drugs with small Vd and low protein binding are cleared well
- Peritoneal drug clearance can be estimated based on following relationship:
  - $Cl_{PD} = Cl_{urea} \times (\sqrt{60}/\sqrt{MW_{drug}})$ , where  $Cl_{PD}$  is drug clearance,  $Cl_{urea}$  is peritoneal urea clearance,  $MW_{drug}$  is drug molecular weight, and peritoneal urea clearance is 20 mL/min

## Continuous Renal Replacement Therapies

- Continuous arteriovenous hemofiltration (CAVH):
  - Convective transport is enhanced by a porous membrane
  - Clearance limited by erratic blood flow
- Continuous venovenous hemofiltration (CVVH):
  - Convective transport is enhanced by a porous membrane
  - Clearance more predictable with stable pump-driven blood flow
- Continuous venovenous hemodialysis (CVVHD):
  - Convective transport and diffusion-based drug clearance
  - CVVHD clearance > CVVH
- Continuous venovenous hemodiafiltration (CVVHDF):

- Convective transport and diffusion-based drug clearance
- Rate of drug removal dependent on sieving coefficient and ultrafiltrate volume
- CVVHDF clearance > CVVHD > CVVH

**Slow Low-Efficiency Daily Dialysis (SLEDD)**

- Diffusion-based clearance of drugs

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