PHAR:8373 IP: Renal, Fluids and Electrolytes

Clinical PK and Renal Disease

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IOWA PHARMACY

Part 1 – Objectives

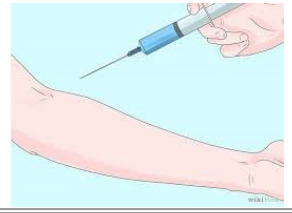
- Recall the key characteristics of basic pharmacokinetic terminology.
- Identify the 3 main processes in drug elimination from the kidneys.
- List the methods used to assess renal function and the levels of renal impairment.
- Describe the primary distinction between acute and chronic kidney disease.

Quick Review of Pharmacokinetics

- **Basic terminology**
  - The study of the processes of drug absorption, distribution and elimination.
  - The word itself comes from two root words
    - *pharmacon* which is the Greek word for drugs and poisons and
    - *kineticos* which pertains to the rate into and out of.
  - Hence literally pharmacokinetics is the rate of drugs into and out of the body.

Bioavailability

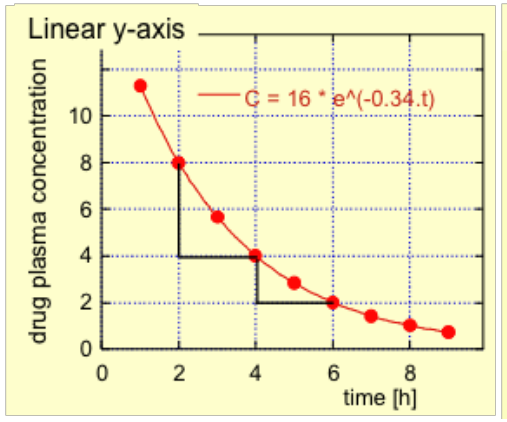
- It is fraction of the drug absorbed (F) and is influenced by the rate (T_{max}) and extent of absorption (C_{max}) of a particular dosage form.
  - It is not just a measure of how fast
  - or how much of the drug is absorbed
  - but is a function of both.

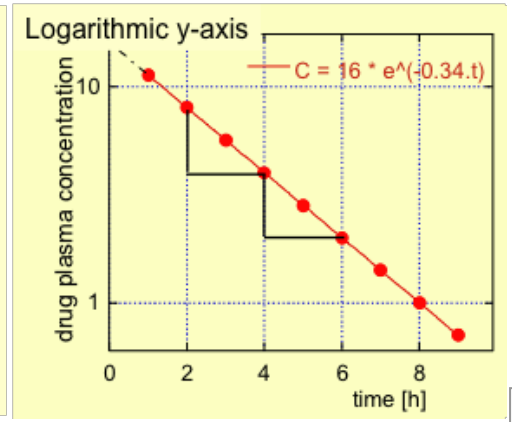




Rate of Elimination (K_e)

- **The rate at which drugs are eliminated from the body will determine how frequently they may be dosed again.**
  - **Most small molecule drugs are absorbed and eliminated from the body by diffusion through fluids, membranes and tissues.**
  - **This movement occurs not at a constant rate (zero order), but as a first order exponential process.**

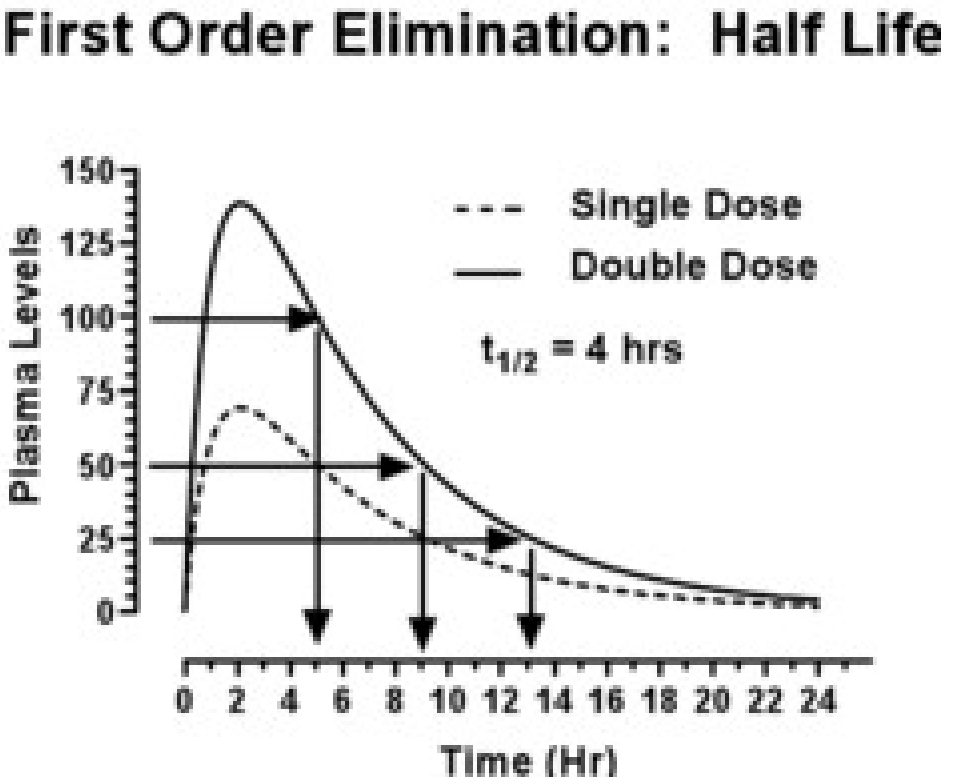




Half-life

- A half-life is the time it takes for the concentration of the drug to decrease by half of its initial value.

$$T_{1/2} = \frac{Ln\ 2}{K_e}$$

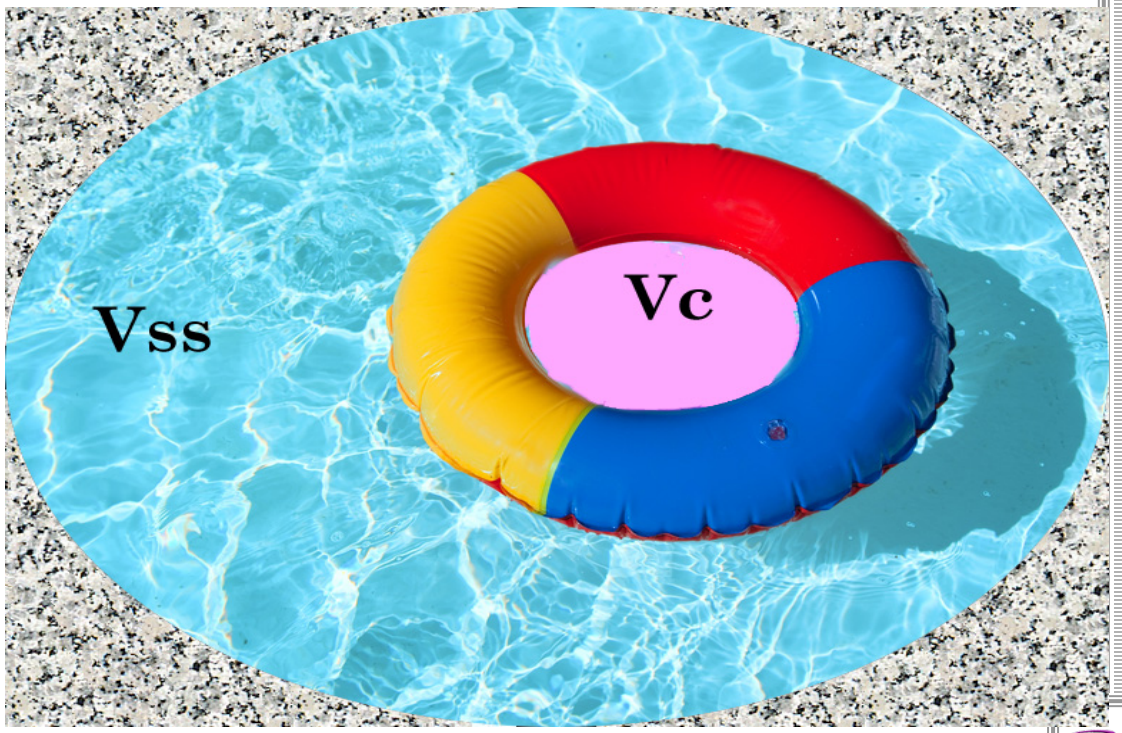


Volume of Distribution

- It is a factor that relates an amount of drug in a kinetic space (area or "compartment") to the concentration in that kinetic space.
- Volume of distribution is important because it gives an idea of the extent to which a drug is distributed to tissue, but does not have a physical meaning.
  - This is why it is sometimes referred to as the apparent volume of distribution.

Volume of Distribution

- There are several types of volumes of distribution that are commonly utilized.
  - Volume of the central compartment.
  - Volume of distribution at steady state.



Steady State

- Any exponential process reaches steady state in five half-lives.
- For example, drug elimination:
  - Goes from 100% - 50% in 1 half-life,
  - goes from 50% - 25% by the 2nd half-life,
  - goes from 25%-12.5% by the 3rd half-life,
  - goes from 12.5% to 6.25% by the 4th half-life, and
  - goes from 6.25% to 3.125% by the 5th half-life.

Clearance

- It is defined as the rate of removal of the drug normalized by the concentration.
  - amt./time / amt./vol. = vol./time
- For example:
  - If we determined that 576 mg of drug was removed from the body in 24 hours and if the concentration in the blood was 10 mg/L in the middle of that time, then clearance was:

Cl = 576 mg/24 Hr / 10 mg/L = 2.4 L/Hr = 40 ml/min

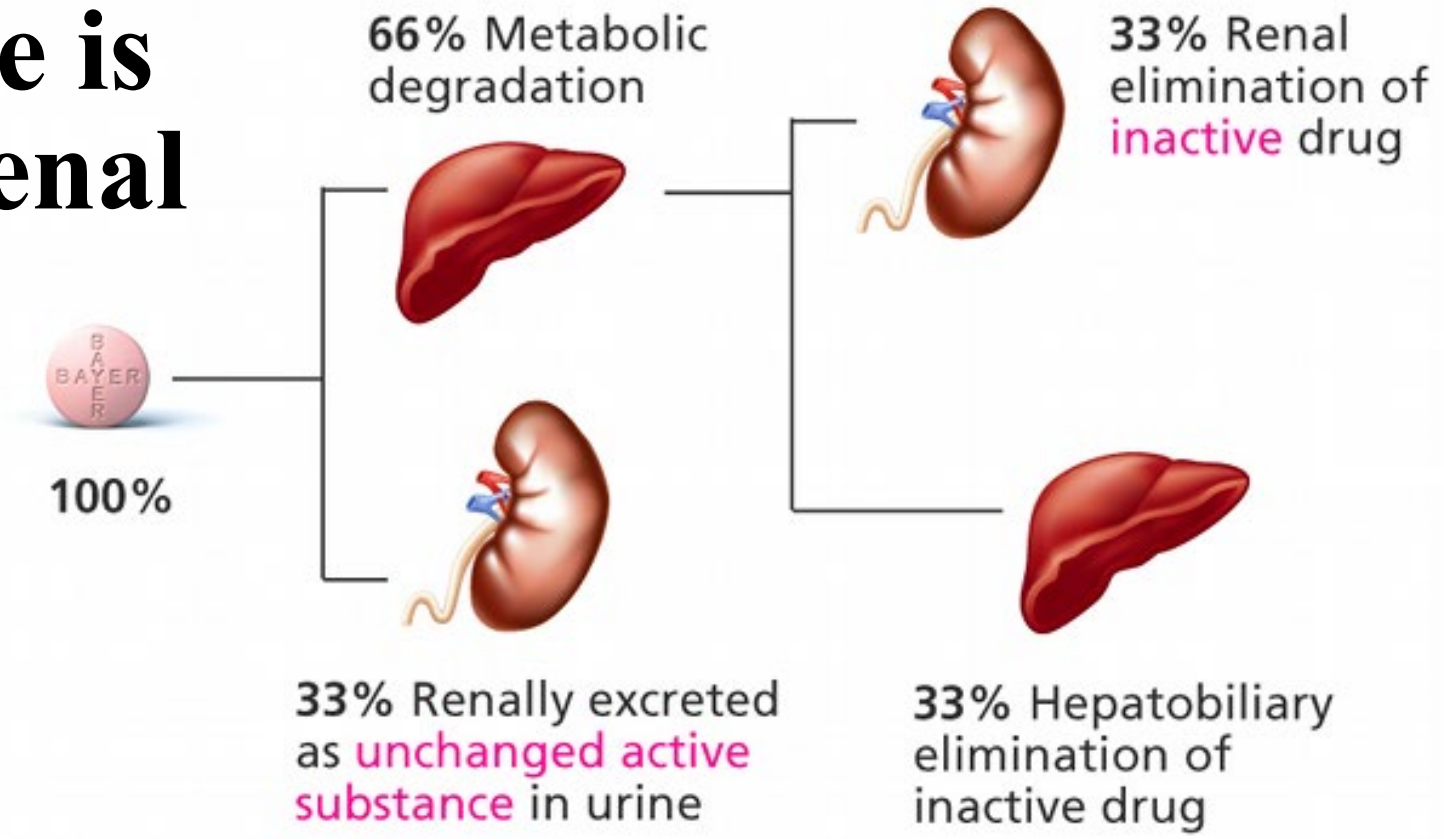
Clearance

- Literally, from a kinetic perspective the clearance is the product of the volume of distribution and the elimination rate constant.
  - $Cl = K_e * V_d$
    - ➢ So if $K_e = 0.10\ Hr^{-1}$ and Vd = 24 L, then:

      $Cl = 0.10\ Hr^{-1} * 24\ L = 2.4\ L/Hr = 40\ ml/min$
- It is the sum of the clearance from all routes out of the body

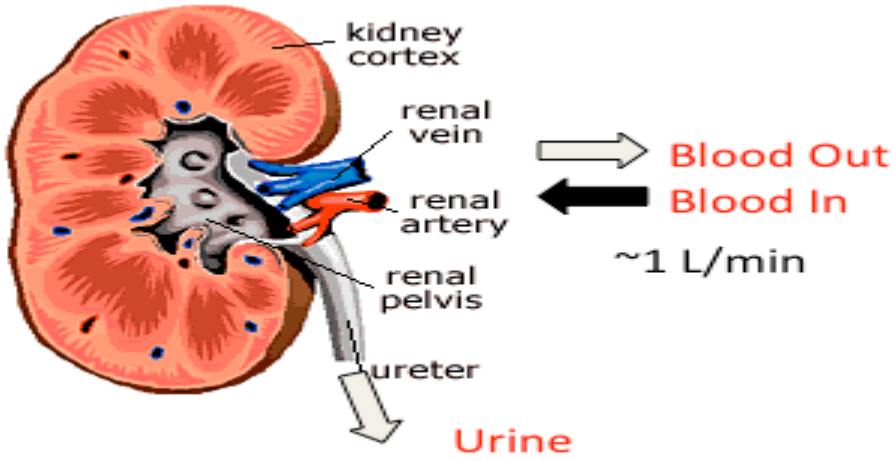
Clearance

- Total clearance is composed of renal and metabolic clearance.
- $Cl = Cl_R + Cl_H$

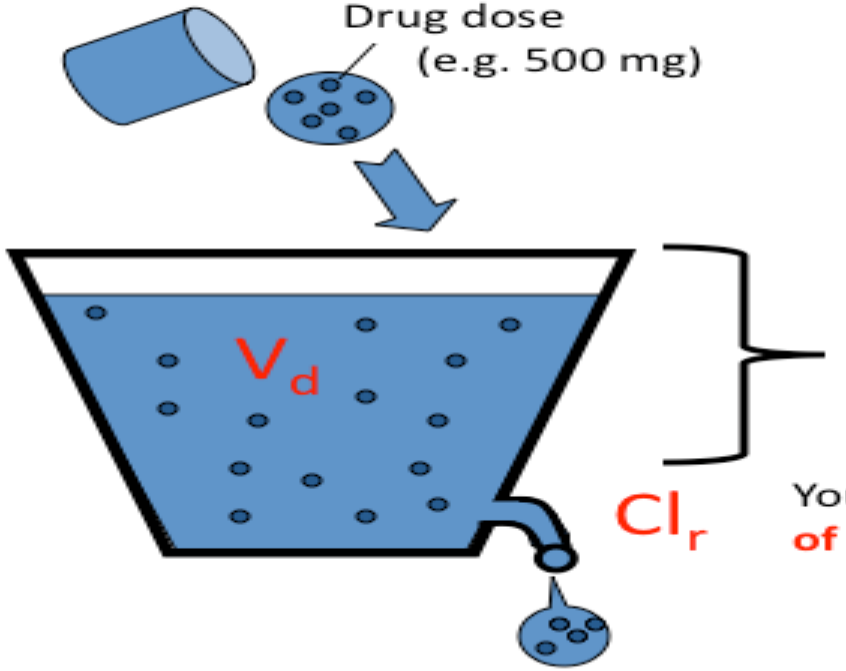


Clearance

Example:
Drug Clearance by the Kidney



Normal GFR ≈125 ml/min

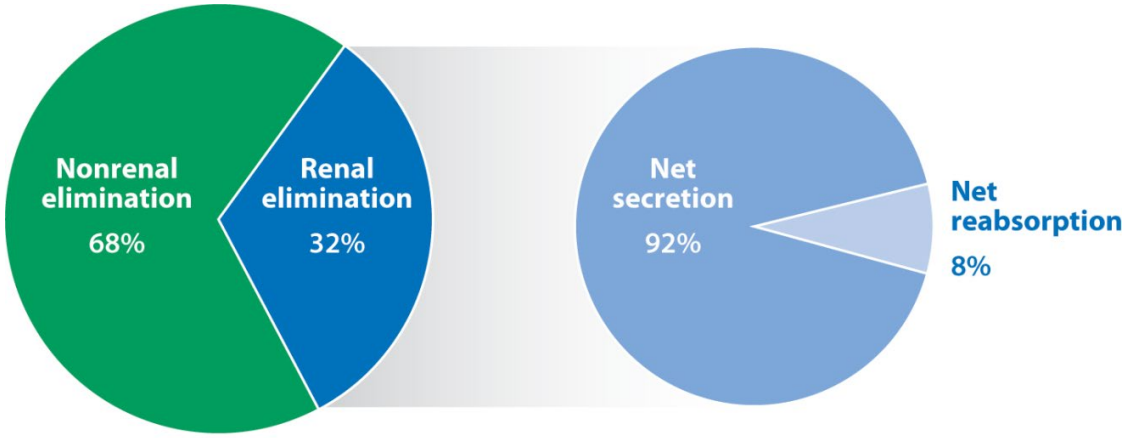


V_d (e.g. 10 L)

Your kidney (filter) will **clear a given volume of fluid per unit time "free of drug".**

L/hr/kg, ml/min etc.

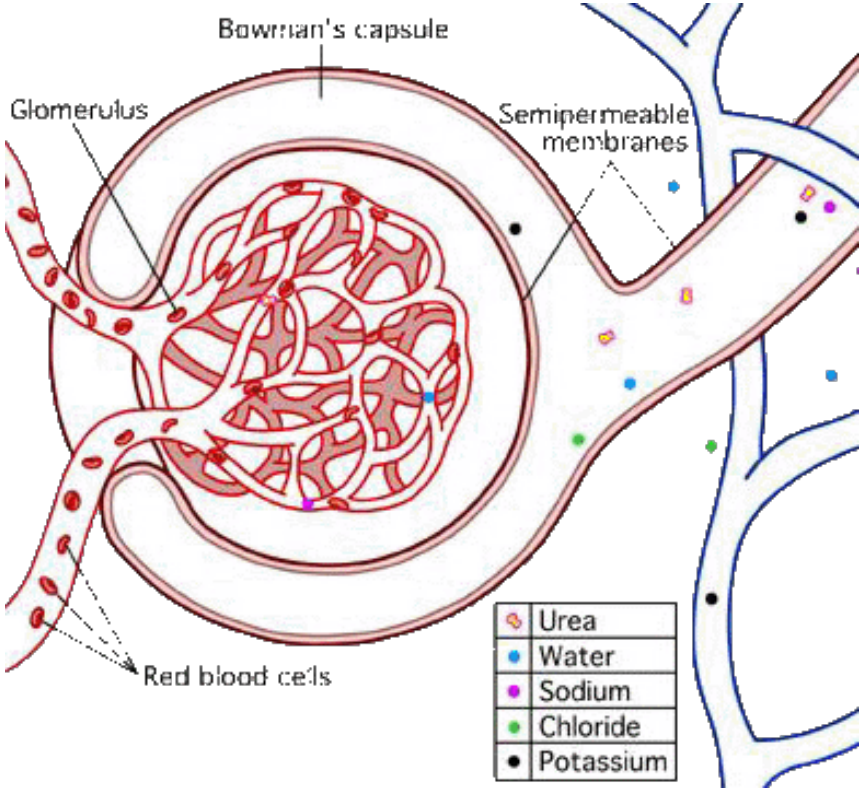
Renal Elimination of Top 200 drugs



Morrissey KM, et al. 2013.
Annu. Rev. Pharmacol. Toxicol. 53:503–29

- The contribution of the kidney to the elimination of the top 200 prescribed drugs in the US in 2010.
- Drugs are considered renally eliminated when ≥25% of their absorbed dose is excreted unchanged in the urine.
- Net secretion is designated for drugs whose renal clearances exceed their filtration clearances.

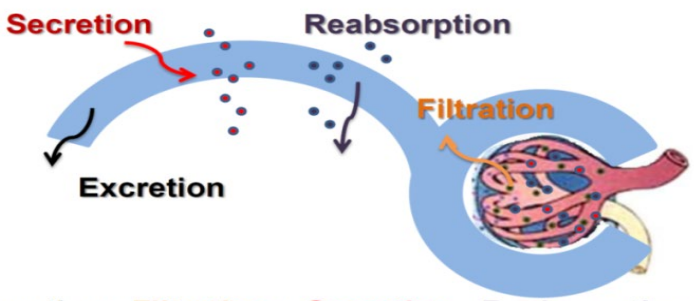
Renal Drug Elimination



- **Glomerular Filtration**
  - Major route for elimination of small drug molecules.
- **Active Secretion**
  - Becomes important large, biotechnology medications.

Renal Drug Elimination

- **Mechanisms of drug/solute/toxin elimination:**
  - Passive glomerular filtration
  - Active tubular transport / secretion
  - Reabsorption



Excretion= Filtration + Secretion - Reabsorption

- **Renal Failure**
  - Decreases elimination: accumulation & prolongs effects.
  - Dose adjustments may be necessary.
    - ➢ Guided by creatinine clearance (e.g. Cockcroft-Gault equation)
  - Dialysis: may remove drugs as well.

Verbeeck RK, *et al. EurJ Clin Pharmacol(2009) 65:757–773*

Renal Drug Elimination

- Renal impairment is the most common factor NOT accounted for in drug dosing adjustments[1-3].
  - Others: patient age, patient size, hepatic impairment
  - Without careful dosing & therapeutic drug monitoring, accumulation of drugs/toxic metabolites can occur.
- Renal disease (uremia) can alter drug disposition, protein binding, distribution and elimination (PK), and can also increase sensitivity to drugs (PD).

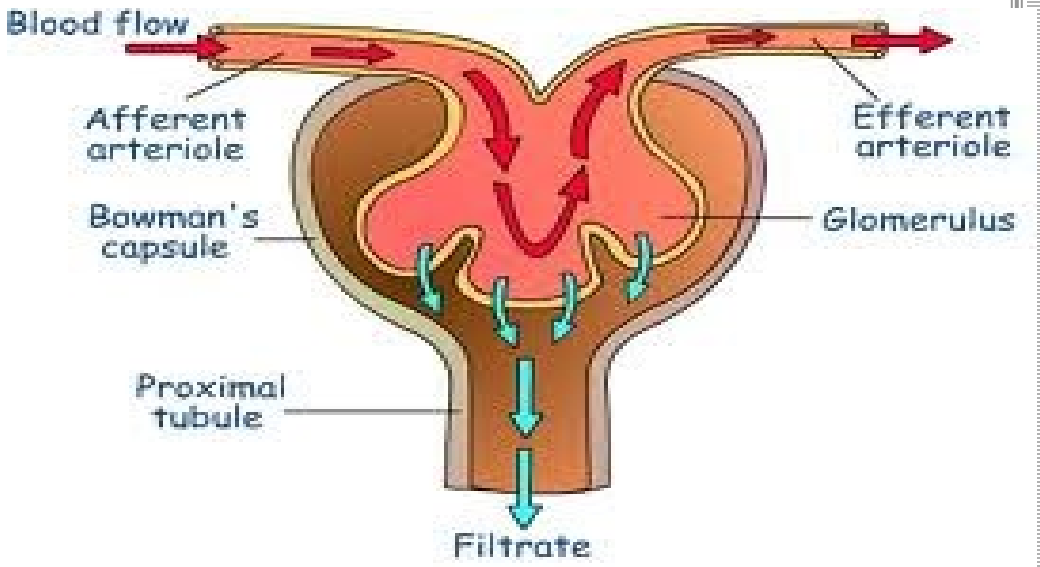
1) Salomon L, et al. Medication misuse in hospitalized patient with renal impairment. Int J Qual Health Care 2003;15:235-40;
2) AvanDijk E, et al. Drug dosage adjustments according to renal function at hospital discharge. Ann Pharm 2006;40:1254-60;
3) Chertow GM, et al. Guided medication dosing for inpatients with renal insufficiency. JAMA 2001;286: 2839–44.

Measures of Renal Function

- Serum Creatinine
  - Normal: 0.6 - 1.2 mg/dl
- Creatinine Clearance Normal:
  - Males: 97-137 ml/min
  - Females: 88 - 128 ml/min
- Blood Urea Nitrogen (BUN)
  - Normal: 7 - 20 mg/dl

Glomerular filtration rate (GFR)

- Amount of filtrate produced in the kidneys each minute.
- In normal adults 120-130 ml of fluid is filtered at the glomerulus per minute.
- Mol. Wt. > 60,000 daltons are not filtered.
- Factors that alter filtration pressure (e.g. blood flow rate, protein binding, etc.) change GFR.



Measures of Renal Function

- Methods for measuring GFR are
  - 24 hour urine collection for CrCl
    - ➢ Too time consuming.
    - ➢ The biomarker has some active secretion along with its filtration.
  - Inulin or iothalamate clearance
    - ➢ Too expensive.
    - ➢ Not available in many labs.

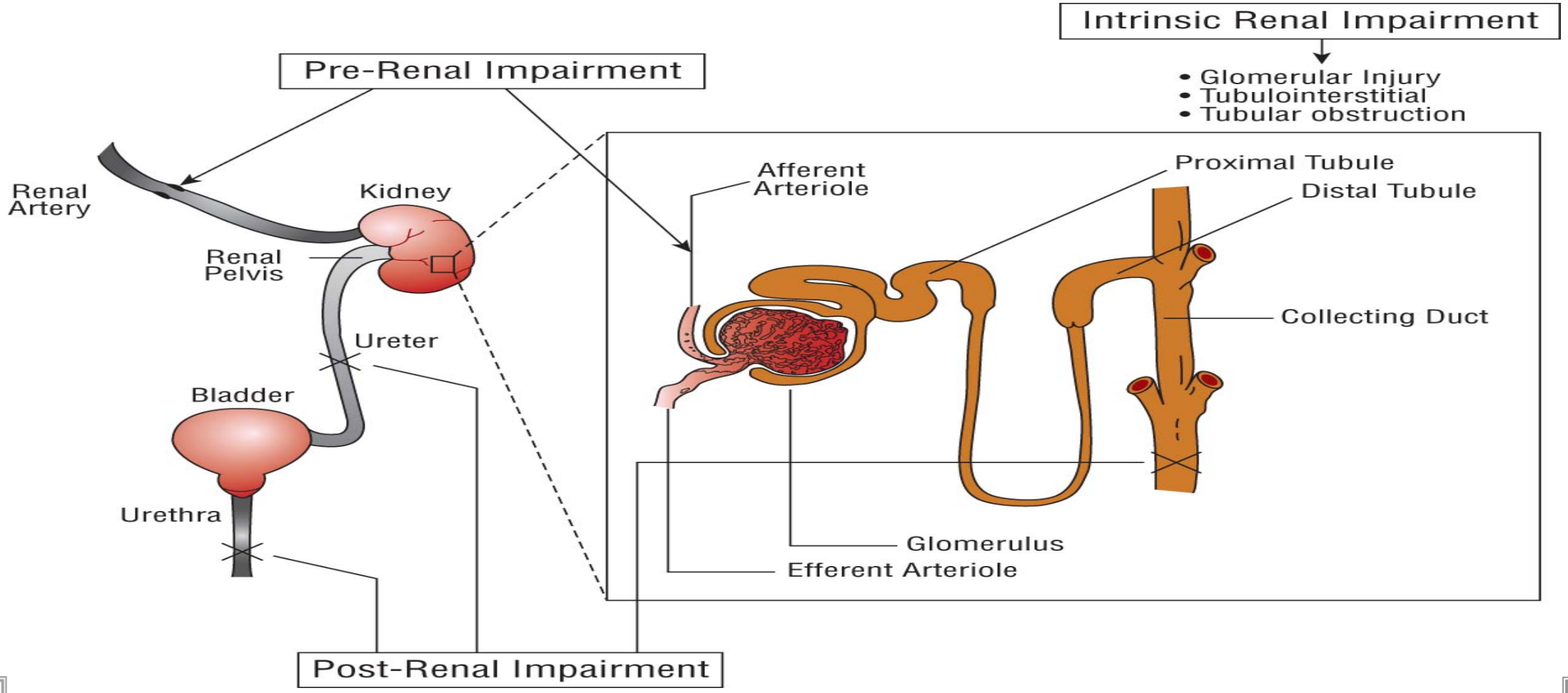
Estimation of Renal Function

- Cockcroft-Gault equation
  - Estimates CrCl: most commonly used in practice for drug dosing.
- Modification of Diet in Renal Disease (MDRD) study
  - Estimates GFR: NOT validated for drug dosing adjustments.
- Other adjunctive measures
  - Urine output
  - Electrolytes (potassium, phosphorous)
  - *Drug levels*

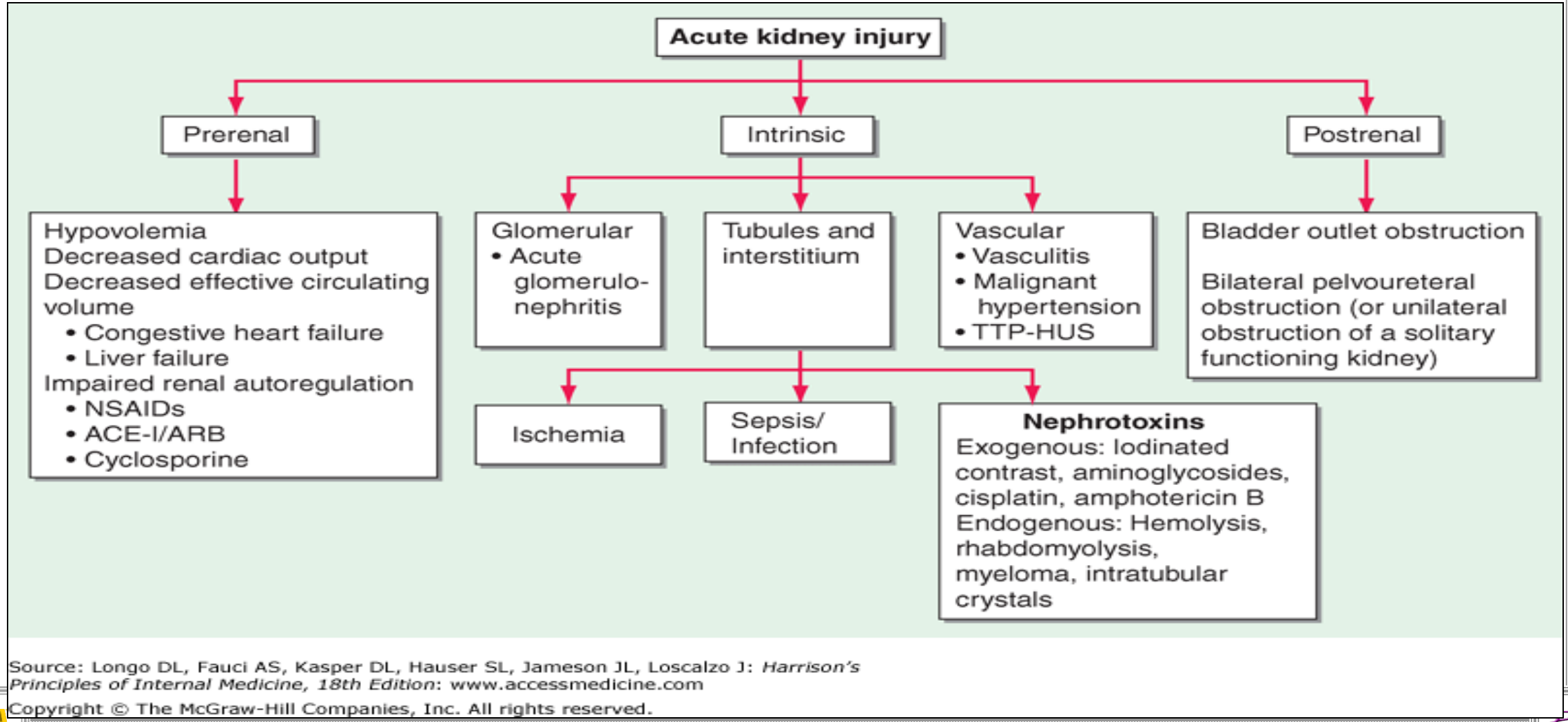
Renal Failure - Definitions

- **Acute Renal Failure (Acute Kidney Injury)**
  - **Rapid decline in the GFR over days to weeks.**
    - SrCr ↑ by >0.5 mg/dL, or
    - SrCr 1.5 fold increase over baseline, or
    - GFR <10mL/min, or <25% of normal, or
    - Anuria: No UOP, or
    - Oliguria: UOP < 400-500 mL/d, or < 0.5mL/kg/hr x 6 hours
  - **May be prerenal, renal, postrenal**

AKI Etiology - Overview



AKI Etiology - Overview



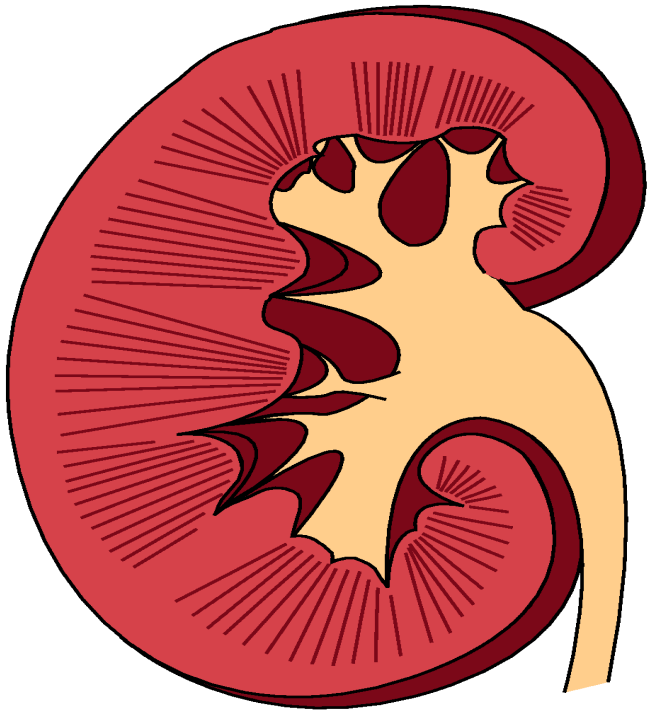
Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

Chronic Kidney Disease: Definition and Outcomes

- Kidney damage or abnormal kidney function for >3 mo.
- Abnormal kidney function: Glomerular Filtration Rate (GFR) < 60 mL/min/1.73 m^2
  - Kidney damage: Abnormal renal pathology or a surrogate marker (proteinuria, abnormal urinalysis or abnormal renal sonogram)
- Three important outcomes:
  - Progression to renal failure.
  - Cardiovascular disease.
  - Adverse event due to improper dosing of drugs primarily excreted by the kidneys.

Chronic Renal Disease

- Renal injury of a prolonged course often leads to progressive and irreversible destruction of nephron mass.
  - Reduction of renal mass causes structural and functional hyper-trophy of the remaining nephrons.
  - This compensatory response eventually predispose to sclerosis of the residual glomeruli.



Definitions - ESRD

- End Stage Renal Disease
  - GFR < 10 mL/min/1.73m^2, or 5% of normal
- Uremia: Excess of urea & other nitrogenous waste in the blood

Metabolic Consequences of ESRD

- "Uremia"- fatigue, nausea, dizziness, coma, death.
  - It is the term generally applied to the clinical syndrome that results from profound loss of renal function irrespective of the cause.

Metabolic Consequences of ESRD

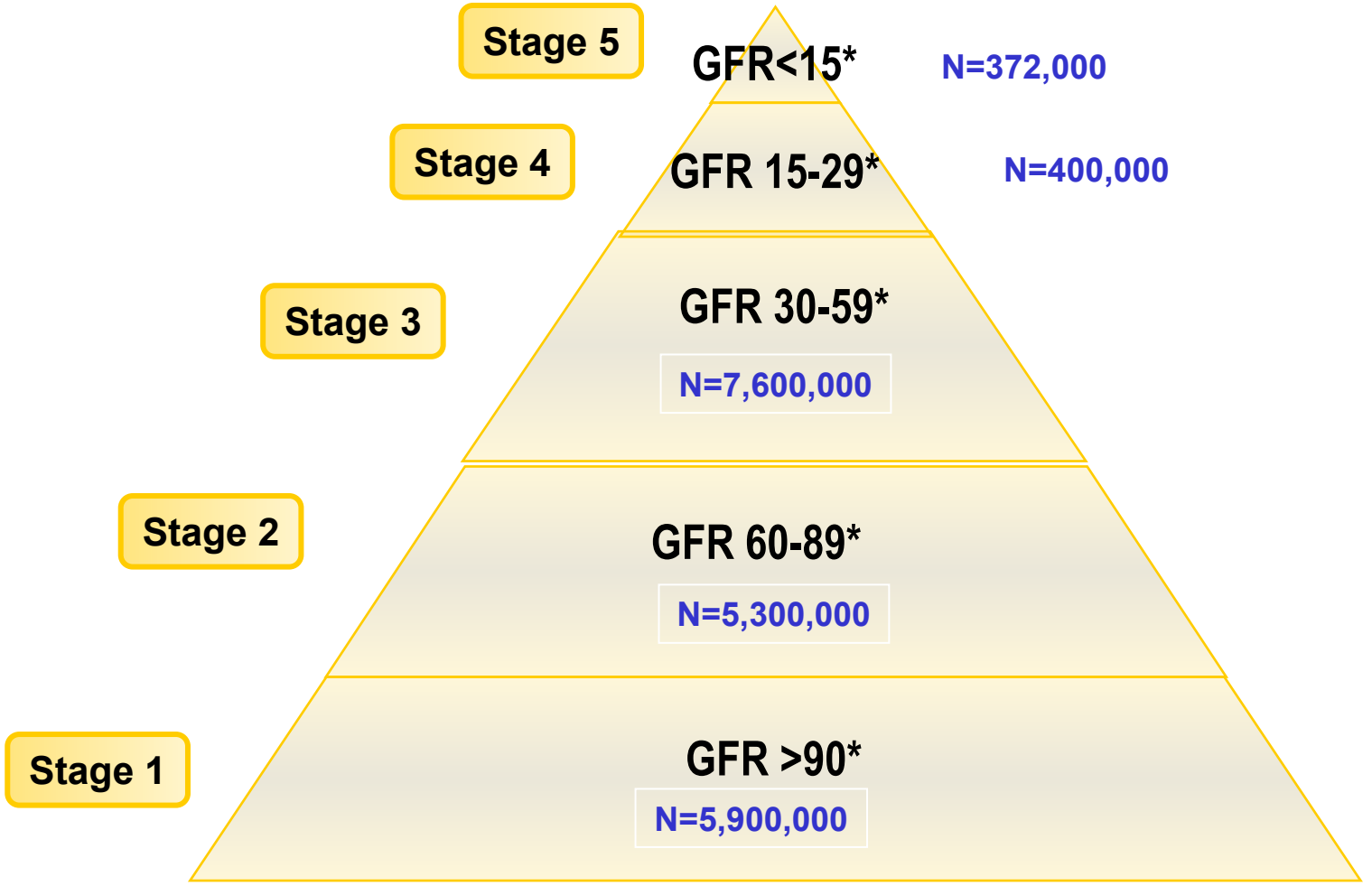
- Acid/Base disorders - pH of blood is lowered (7.33-7.37).
- Renal Osteodystrophy - bone pain, spontaneous fractures that heal slowly.
- Anemia

Stages of Chronic Kidney Disease (CKD)
[Guided by Glomerular Filtration Rate (GFR)]

Stage	Description	GFR (mL / min / 1.73m^2)
I	Kidney damage with normal or increased GFR	≥ 90
II	Kidney damage with mildly decreased GFR	60–89
III	Moderately decreased GFR	30–59
IV	Severely decreased GFR	15–29
V	Kidney failure	< 15 (or dialysis)

- GFR <60 mL/min/1.73 m^2 for 3 months classified as chronic kidney disease, irrespective of
- GFR <90 mL/min/1.73 m^2 would be abnormal in a young adult
- GFR of 60–89 mL/min/1.73 m^2 could be normal from approximately 8 weeks to 1 year of age and in older individuals

Prevalence of CKD in the United States



*GFR measurement is mL/min/1.73m^2

End Stage Renal Disease (ESRD)

- Kidney damage or abnormal kidney function for >3 mo.
- GFR is less than 10 ml/min/1.73m^2.
- Three important outcomes:
  - Progression to renal failure
  - Cardiovascular disease
  - Adverse event due to improper dosing of drugs primarily excreted by the kidneys

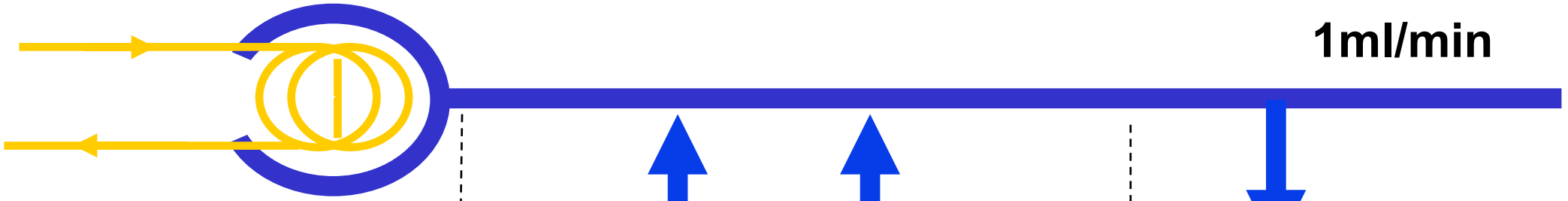
Quick Review of Part 1

- We reviewed 6 aspects of pharmacokinetics:
  - Bioavailability, rate of elimination, half-life, volume of distribution, steady state and clearance.
- We reviewed the 3 renal elimination processes:
  - Glomerular filtration, active secretion and active reabsorption.
- We revisited the methods to measure renal function.
  - Serum creatinine, creatinine clearance, BUN and glomerular filtration (GFR).
- We examined the classification of renal dysfunction:
  - Acute kidney injury, chronic renal disease & end stage renal disease.

Part 2 – Objectives

- Explain the interaction between glomerular filtration, tubular secretion and tubular reabsorption.
- Describe how transporters can affect active secretion of drugs.
- Identify for patients with acute kidney injury at least one change in bioavailability, distribution and elimination.

Mechanisms of Renal Excretion of Drugs



Urine
1ml/min

Plasma flow
650ml/min

Acid Base

99% of H_20 +
Lipid soluble drugs

Filtration
125 ml/min

Tubular Secretion

Tubular
Reabsorption

Molecular
Filtration

Active Secretion

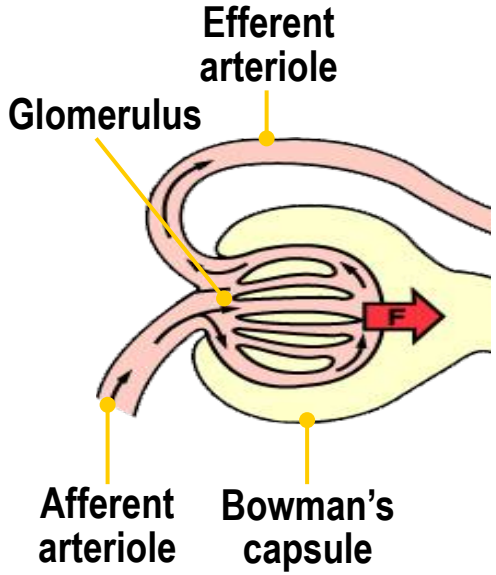
Passive
Diffusion

Glomerular Filtration

- If only excreted by Glomerular Filtration (or equal secretion / reabsorption), then: $CL_R = GFR \times f_u$
- If net tubular secretion occurs (Rate excretion > Rate filtration): $CL_R > GFR \times f_u$
- If net tubular reabsorption occurs (Rate excretion < Rate filtration): $CL_R < GFR \times f_u$

Drug filtration rate = $GFR \times f_u \times [drug]$

Glomerular Disorders



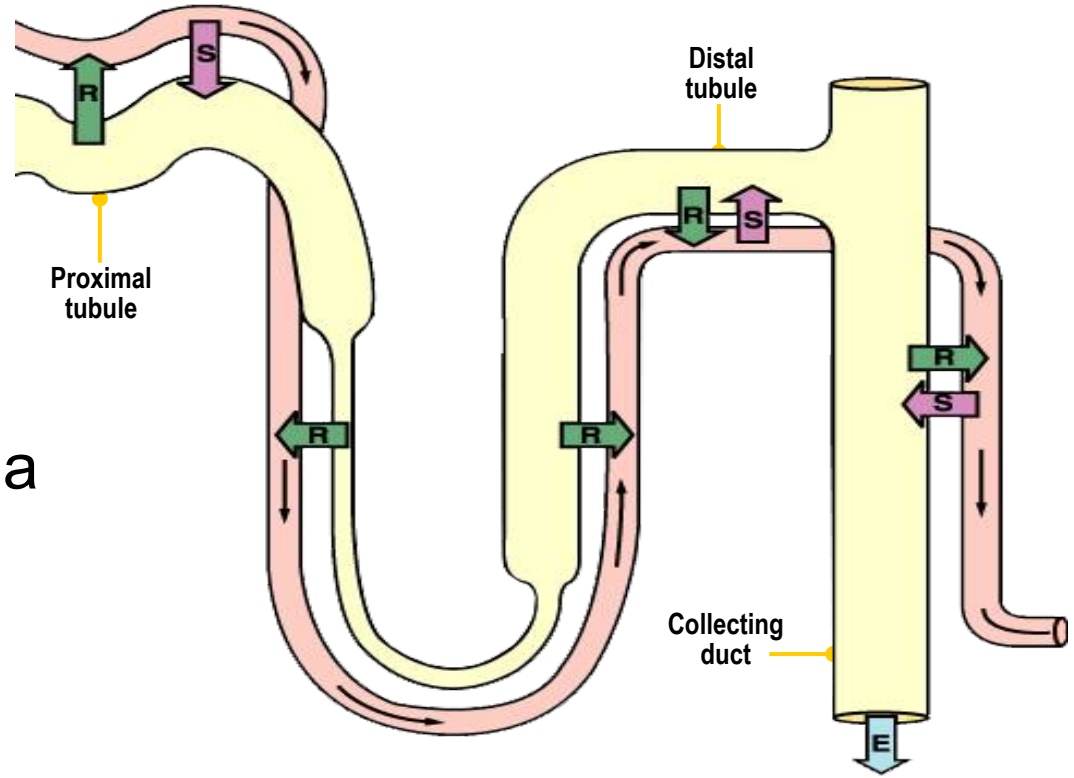
F Filtration: blood to lumen

- Proteinuria and/or red blood cell casts are the hallmarks of glomerular disease
- Drugs or metabolic disorders can alter renal hemodynamics
  - NSAIDS
  - Vasoconstrictors
  - ACE inhibitors
  - Hepatorenal syndrome

Tubular Disorders

- Characterized by:
  - Tubule proteinuria (Urine protein/ creatinine ratio < 1),
  - and an electrolyte imbalance.
- Can be due to:
  - Tubular damage,
  - Or can be associated with drug interactions with other drugs competing for drug transporter enzymes.

Renal Drug Secretion



Proximal Tubule

- Ischemia
- Prerenal azotemia
- Crystalluria
- Nephrotoxicity:

  Aminoglycosides

Distal Tubule

- Nephrotoxins: Amphotericin

Collecting Duct

- SIADH
- Nephrogenic diabetes insipidus

Interstitium

- Interstitial Nephritis (NSAIDS)
- Fibrosis

R **Reabsorption: lumen to blood**
S **Secretion: blood to lumen**
E **Excretion: lumen to external environement**

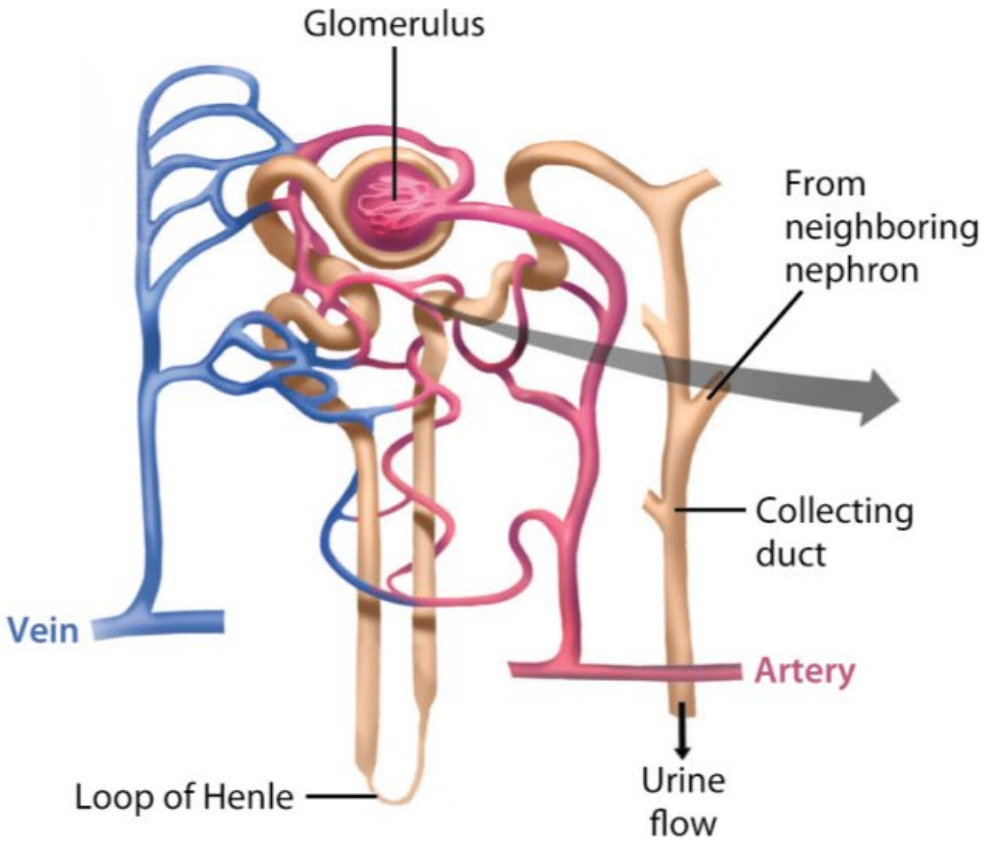
Transporters Involved in Renal Drug Secretion

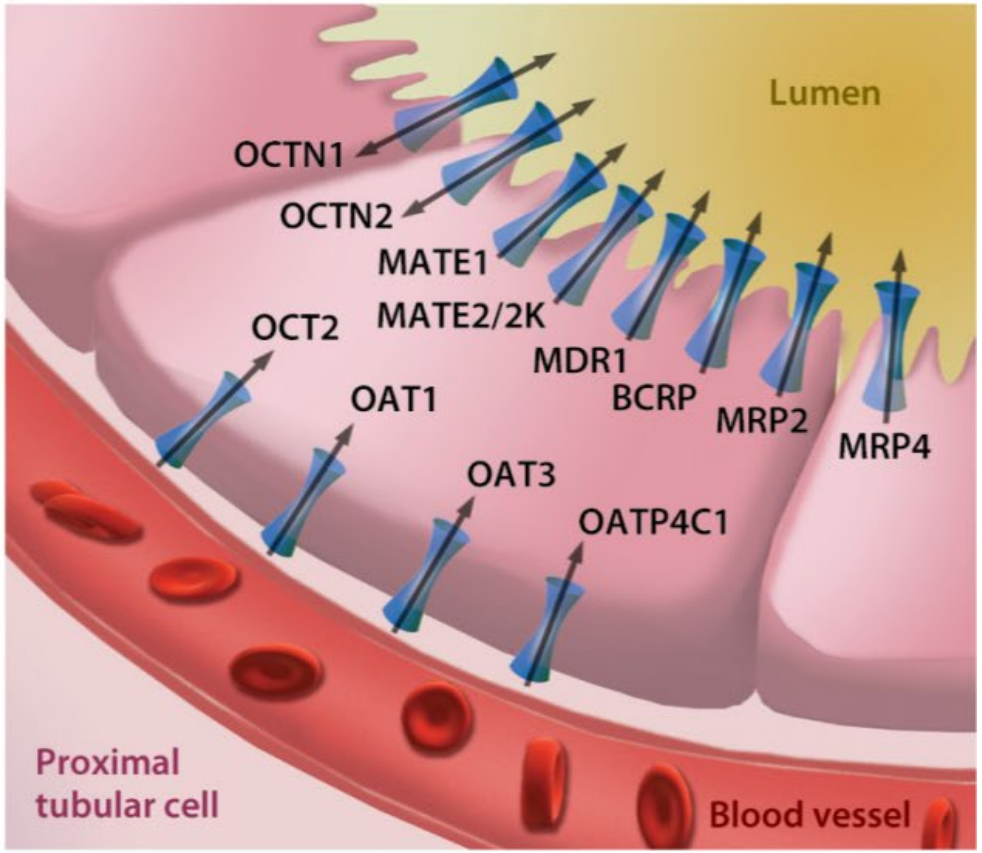
- Transporters expressed on basolateral and apical membranes of the renal tubule epithelium are generally found in the proximal tubule and work in systems to mediate renal drug elimination.
- For a small molecule to be actively secreted into the tubule lumen, at least two distinct transporters are required:
  - one at the basolateral membrane of the tubule cell to accept molecules from the blood
  - one at the apical membrane to mediate the exit of the molecule to the tubule fluid.

Renal Drug Secretion

- The transporters that play an important role in the renal elimination:
  - Newly identified transporters (e.g., OATP4C1, MATE1, MATE2K) are less well-characterized
  - Multidrug resistance protein 1 (MDR1), MRPs, OCT2, and OATs, are better characterized.

Drug transporters in the nephron of the kidney





BCRP, breast cancer resistance protein; MATE, multidrug and toxin extrusion protein; MDR, multidrug resistance protein; MRP, multidrug resistance-associated protein; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter. (Annu. Rev. Pharmacol. Toxicol. 53:503-29, 2013)

Renal Drug Secretion

Organic Anions (OATs)	Organic Cations (OCTs)
• Classical small anions e.g., Pravastatin , famotidine, cefoxitin, salicylates, sulfonamides • Interacting drug: probenecid	• Classical small cations e.g. Zidovudine, quinine, procaine, morphine, pindolol, metformin • Interacting drug: cimetidine
Multidrug Resistance Protein (MRP2)	P glycoprotein (Pgp or MDR1)
• Estradiol • Glutathione, Glucuronide, and Sulfate Conjugates of LTC_4	• Cyclosporine • Digoxin • Verapamil

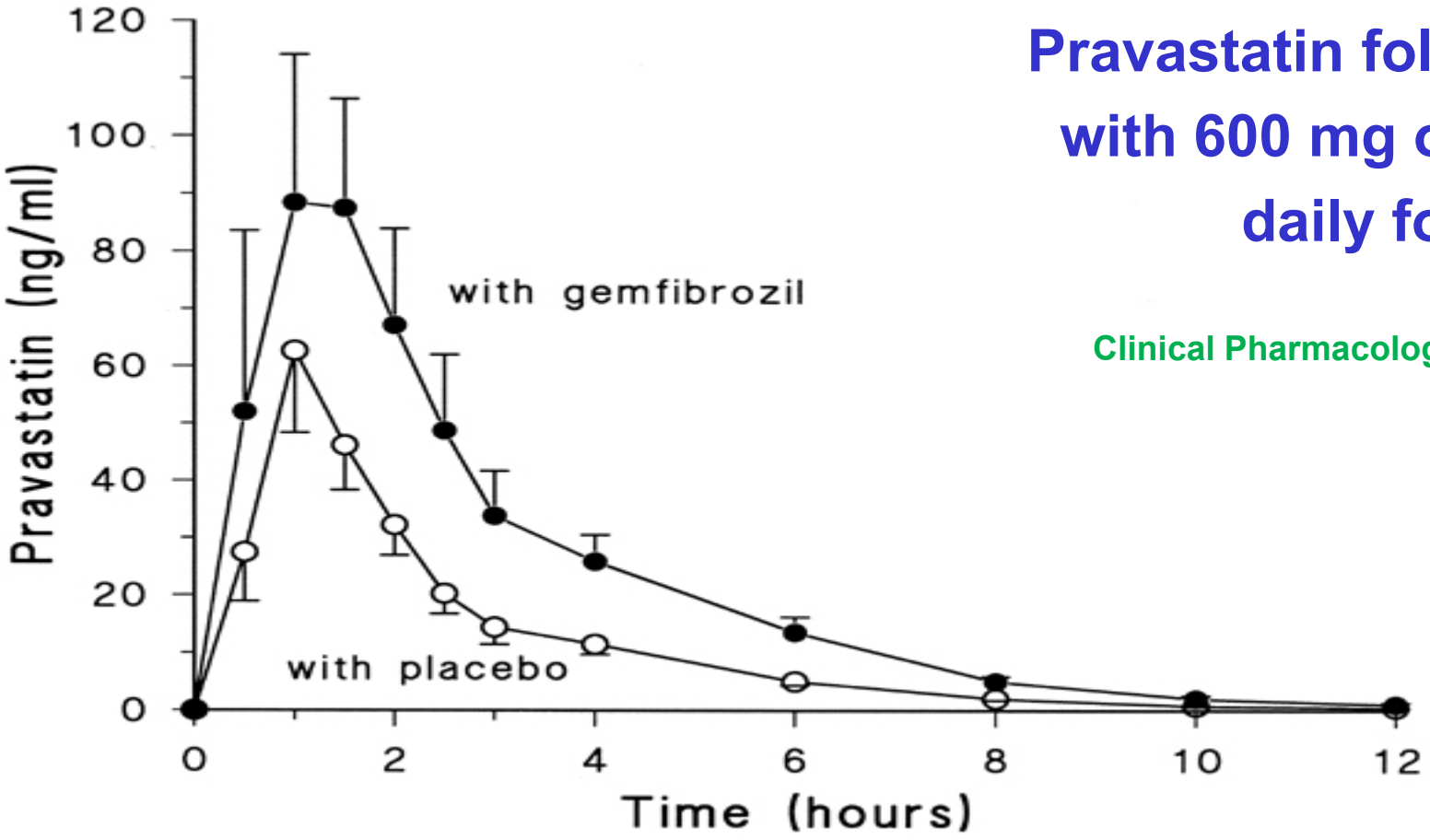
Examples of Drugs with Active Renal Secretion

- **Drugs are diverse in molecular weight, charge, and therapeutic classes:**
  - **Antibacterials (ciprofloxacin, cephalexin, levofloxacin),**
  - **Antihistamines (famotidine, ranitidine),**
  - **Diuretics (furosemide, trimethoprim),**
  - **Antidiabetics (metformin), and**
  - **Antihyperlipidemics (rosuvastatin, pravastatin).**

Altered Renal Drug Secretion

- Drugs that are eliminated in the kidney with a net tubular secretion are particularly susceptible to DDIs when coadministered with other medications that interact with the same transporters.

Drug-drug interaction mediated by renal secretory transporter



Pravastatin following pretreatment with 600 mg of gemfibrozil twice daily for three days

Clinical Pharmacology & Therapeutics (2003) 73, 538–544

Reabsorption by non-ionic diffusion

- Most drugs undergo reabsorption back into blood
- Passive process in distal tubules for lipophilic or not highly ionized drugs

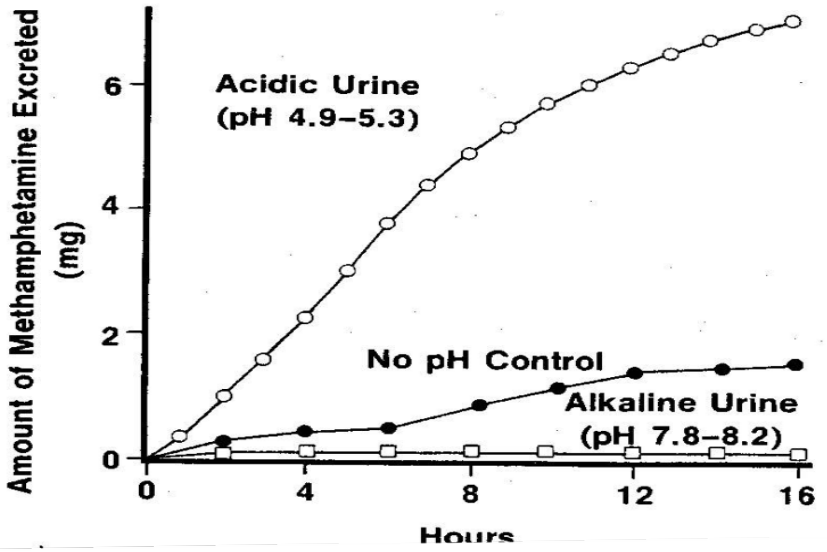
Reabsorption via Urine pH and pKa

- Urinary pH affects reabsorption of weak acids and bases
- Only important if excretion of free drug is major elimination path

Examples:

Weak acids	Phenobarbital
Weak bases	Quinidine

Urinary Elimination of a Weak Base



pKa = 10.0

$$pH = pK_a + \log([A^-]/[HA])$$

Table 11–4. Percent Un-Ionized of Selected Weak Acids and Weak Bases at Various Values of Urine pH[a]

Drug	Nature	pKa	Urine pH 4.4	Urine pH 6.4	Urine pH 7.9
A	Acid	2.4	1.0	0.01	0.0003
B		6.4	99	50	3
C		10.4	100	100	99.7
D	Base	2.4	99	100	100
E		6.4	1.0	50	97
F		10.4	0.0001	0.01	0.3
G		12.4	10^{-6}	0.0001	0.003

Tubular Reabsorption: Effect of Urine Flow Rate

- **Increased urine flow rate** (diuresis) causes dilution of tubular fluid drug conc. and **reduced transit time** which combine to reduce the efficiency of passive reabsorption.
- The greater the extent of reabsorption the bigger the effect of urine flow rate.

Active Reabsorption

- Is uncommon and is restricted to drugs that imitate endogenous cpds (salicylates, probenecid, benzoic acids).
- Glucose is normally 100% reabsorbed in the distal tubule
- Affects ions

Examples:

Halides: **Fluoride, bromide**

Alkaline metals: **Lithium**

Pharmacokinetic Alterations

- **Absorption / Bioavailability** ⇔⇩⇧
  - Absorption is influenced by gut blood flow, health & pH
    - ⇩ ➢GI disturbances: N/V/D, uremic gastritis, gastric motility, gut edema*
    - ⇩ ➢Uremia increases gastric pH: reduced absorption of some drugs
    - ⇧ ➢Uremia decreases 1st pass effect: enhanced absorption of some drugs

* Renal failure may be accompanied by *nephrotic syndrome* & subsequent leakage of proteins resulting in gut edema

Effect of Renal Disease on Drug Absorption

- The bioavailability of most drugs that have been studied in renal failure has not been altered.
- In chronic renal failure, D-xylose, a marker for small intestinal absorptive function:
  - Absorption was slower (0.555 h^{-1} vs. 1.03 h^{-1})
  - Less complete (48.6% vs. 69.4%)
- F ↓ for furosemide and pindolol in RF

Effect of Renal Disease on Drug Absorption

- Patients with renal failure experience nausea, vomiting, and/or diarrhea, which may cause drug malabsorption.
- Increased salivary urea in patients with renal failure convert urea to ammonia by gastric ureases, which increase gastirc pH and may cause decreased absorption of iron, ketoconazole, itraconazole and other drugs which require an acidic environment for optimal absorption.

Pharmacokinetic Alterations

- Drug Distribution ⇔ ⇑
  - ⇑ ✵ A drugs effect is influenced by the amount of unbound drug.
    - ➢ Hypoalbuminemia is common in renal failure.
      - – Increased unbound drug in renal failure: increase effects & toxicity.

Effect of Renal Disease on Drug Distribution

- Binding of acidic drugs (phenytoin, sulfonamides, warfarin, furosemide) is decreased in uremic patients.
- Displaced from albumin by organic acids that accumulate in uremia.
- Higher concentration of free drug may alter interpretation of therapeutic range.

Effect of Renal Disease on Drug Distribution

- Presence of edema and ascites may ↑ V of hydrophilic and highly protein bound drugs.
- In nephrotic syndrome (with extensive loss of plasma proteins) the binding of clofibric acid, the active metabolite of clofibrate, ↓. This results in an ↑ V.

Effect of Renal Disease on Drug Distribution

Volume of distribution (L/kg)		
Drug	**Normal**	**ESRD**
Increased V		
Furosemide	0.11	0.18
Gentamicin	0.20	0.29
Phenytoin	0.64	1.40
Trimethoprim	1.36	1.83
Decreased V		
Digoxin	7.30	4.10
Ethambutol	3.70	1.60

Example: Loading Dose

Loading dose = ($C_{initial}$) (V)

Target conc = $C_{initial}$ = 8 mg/L
V (normal) = 0.25 L/kg

Loading dose = (8 mg/L) (0.25 L/kg) = 2 mg/kg

If V is ½ the normal value, 0.125 L/kg

2 mg/kg = ($C_{initial}$) (0.125 L/kg)

$$C_{initial} = \frac{2mg/kg}{0.125L/kg} = 16mg/L$$

Need to pay attention to changes in V

Pharmacokinetic Alterations

- Metabolism ⇔ ⇩ ⇧
  - ⇩ Decreased renal metabolism (10-20% of metabolic capacity).
    - ➢ Accumulation of active metabolites.
  - ⇧ Increase unbound drug may increase hepatic metabolism.

Pharmacokinetic Alterations

- **Elimination** ⇔ ⇩
  - As kidney disease progresses, the kidney's ⇩ ability to excrete (eliminate) uremic toxins and select drugs decreases.
    - ➢ Altered glomerular filtration & active tubular secretion.
    - ➢ Metabolites may accumulate and lead to adverse events.

$$t_{1/2} = \frac{\ln 2}{k_e} \qquad V_{ss} = \frac{R_0}{k_e} \cdot \frac{1 - e^{-k_e t_{\inf}}}{(C_0 - C_{tr} \cdot e^{-k_e t_{\inf}})} \qquad C_{ss,pk} = \frac{R_0}{V_{ss} \cdot k_e} \cdot \frac{\left(1 - e^{-k_e t_{\inf}}\right)}{\left(1 - e^{-k_e \tau}\right)}$$

Quick Review of Part 2

- We examined the 3 mechanisms of renal excretion:
  - Glomerular filtration, tubular secretion and tubular reabsorption.
- We looked at the effect of renal disease on PK parameters:
  - Drug absorption and bioavailability, drug distribution, drug metabolism and drug elimination.

Part 3 – Objectives

- Identify the threshold for when renal dosing adjustments should be made.
- List at least 3 resources where information could possibly be found related to making dosing adjustments for a specific medication for a patient with chronic kidney disease.

Part 3 – Objectives

- Calculate an estimated GFR based on the MDRD approach and an estimated CrCl using the Cockcroft and Gault approach.
- Describe when it is appropriate to use the GFR-MDRD, GFR-Epi and CrCl.
- Explain what dosing adjustment often has to be made for patients who are receiving regular dialysis treatments.

General Principles of Drug Dosing in Patients with Renal Insufficiency

- Accumulation sufficient to be of clinical concern occurs if ≥ 30% of the drug or its active metabolite is eliminated unchanged in urine of patients with normal renal function.

General Principles of Drug Dosing in Patients with Renal Insufficiency

- In renal insufficiency endogenous organic acids accumulate in plasma.
  - Can compete with acidic xenobiotics for binding to albumin and thereby diminish protein binding.
  - Can compete with acidic drugs for active secretion by the kidney.
- Hypoalbuminemia from any cause results in diminished binding of drugs bound to albumin.

Dose Adjustments Based on Renal Function from Cockcroft-Gault Equation

	ADME	Renal function (ml/min)[a]	Fold-change in exposure (AUC)		Initial dose (mg)	Daily dose (mg)
Paliperidone[c]	fe = 60%	CrCl >80 CrCl 50–80 CrCl 30–50 CrCl 10–30 CrCl <10		Control 1.5-fold (mild) 2.6-fold (moderate) 4.8-fold (severe)	6 3 1.5 1.5 —[b]	3–12 3–6 1.5–3 1.5–3 —[b]
Telbivudine	fe = 40%	CrCl >50 CrCl 30–49 CrCl <30 ESRD		Control 1.9-fold (moderate) 3.4-fold (severe) 7-fold (ESRD)		600 q24h 600 q48h 600 q72h 600 q96h
Rosuvastatin	fe = 6% F = 20%	CrCl >80 CrCl 50–80 CrCl 30–50 CrCl <30		Control 1-fold (mild) 1-fold (moderate) 3-fold (severe)	10–20 10–20 10–20 5	5–40 5–40 5–40 5–10
Telithromycin	fe = 13% F = 57%	CrCl <30 CrCl <30[c]	0 1 2 3 4 5 6 7 8	Control 1.9-fold (severe) 4- to 5-fold (severe)[c]		800 q.d. 600 q.d. 400 q.d.[d]

Fe = Fraction of oral dose excreted unchanged in urine, F = Bioavailability

S-M Huang, et al, Clin Pharmacol Ther 86:475-479, 2009

Evaluation of Renal Drug Dosing Recommendations: Prescribing Info.

251	• Drugs approved by the FDA (1998-2007).
44	• Included renal dosing recommendations.
42	• Reported CrCl as index to guide dosage adjustments.
11	• Specified the equation to utilize (Cockcroft-Gault).
5	• Specified the weight to utilize (ideal body weight).
4	• Included hepatic dosing recommendations.

Dowling TC, et al. Evaluation of renal drug dosing: prescribing information and clinical pharmacist approaches. Pharmacotherapy 2010;30(8):776-786.

References to Guide Dosing Decisions

- **Drug Databases**
  - Micromedex®
  - Lexicomp®
  - Goodman & Gilman
- **Free Websites**
  - GlobalRph.com
  - DailMed®
  - Rxlist.com

- **Handbooks**
  - Drug Prescribing in Renal Failure
  - The Renal Drug handbook
  - The Handbook of Clinical Drug Data
  - Tarascon Pocket Pharmacopoeia
- **Institutional Guidelines**

Appendix II Table 1

Example from Goodman & Gilman

BioAVAIL-ABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE (mL/min/kg)	VOL. DIST. (L/kg)	HALF-LIFE (hours)	PEAK TIME (hours)	PEAK CONC.
Gentamicin [a]							
IM: ~100	>90	<10	$CL = 0.82CL_{cr} + 0.11$	0.31 ± 0.10	2-3[a]	IM: 0.3-0.75[b]	IV: 4.9 ± 0.5 µg/mL[b]
[a] Gentamicin has a very long terminal $t_{1/2}$ of 53 ± 25 hours (slow release from tissues), which accounts for urinary excretion for up to 3 weeks after a dose. [b] Following a single100-mg IV infusion (1 hour) or IM injection given to healthy adults.				*References*: Matzke GR, et al. Pharmacokinetics of cetirizine in the elderly and patients with renal insufficiency. *Ann Allergy,* **1987**, *59*:25–30. Regamey C, et al. Comparative pharmacokinetics of tobramycin and gentamicin. *Clin Pharmacol Ther,* **1973**, *14*:396–403.				

Estimating Renal Function to Make PK Dosing Adjustments

- **Predicting K_e**
  - Individualizing patient dosing for some drugs with a narrow therapeutic window and that are eliminated almost exclusively by the kidneys will often have identified an equation to predict the rate of elimination (Ke) for that drug.
  - For example, the vancomycin rate of elimination is estimated:
    - Ke = [44 + (8.3xCrCl)] / 10,000].
    - The volume of distribution can be estimated at Vss = 0.7 L/Kg x Actual body weight(Kg).
  - The CrCl that is to be used is either the measured CrCl, or estimated by the Cockroft & Gault (C&G) equation.

Estimating Renal Function to Make PK Dosing Adjustments

- **Adjustments based on CrCl**
  - **Some medications without a narrow therapeutic range, cephalosporins, for example, have recommended dosage adjustments at various levels of CrCl.**
    - **In these situations, if the dosing source says use the C&G estimate then use that because it is a patient specific estimate.**

Adults: (≥ 17 years)

$$\text{CrCl}\,(\text{ml/min}) = \frac{(140\text{-Age}) \cdot Wt}{72 \cdot SrCr} \cdot (0.85 + Sex \cdot 0.15)$$

If the patient is < IBW, use Wt = ABW.

If the patient is > IBW and BMI < 25 Kg/m^2, Wt = IBW

If the patient has a BMI > 25 Kg/m^2, Wt = AdjWT

Estimating Renal Function to Make PK Dosing Adjustments

- **Adjustments based on CrCl**
  - **If the dosing adjustment levels specified are normalize (e.g. 60 ml/min/1.73m2), then a GFR estimate can be used.**
    - **The GFR-MDRD equation is most frequently used. This equation was developed from a large number of patients with renal failure. However, it is not the best estimate of GFR in individuals that have normal renal function.**

$$GFR = 175 \cdot SrCr^{-1.154} \cdot Age^{-0.203} \cdot (0.742 + Sex \cdot 0.258) \cdot (1 + 0.21 \cdot Black)$$

Black = 1, else = 0,
Sex: Male = 1. female = 0

Black = 1, else = 0,
Sex: Male = 1. female = 0
$GFR = 175 \cdot SrCr^{-1.154} \cdot Age^{-0.203} \cdot (0.742 + Sex \cdot 0.258) \cdot (1 + 0.21 \cdot Black)$

Estimating Renal Function to Make PK Dosing Adjustments

- **Adjustments based on CrCl**
  - **A new version, GFR-Epi, is more accurate across the full range of renal function, but it is more complex to use.**
  - **These equations are listed on the equation sheet.**

$$GFR\ (CKD-EPI) = (144-(Sex*3))*(1+0.155*Black)*0.993^{Age}*\left(\frac{SrCr}{(0.7+(0.2*Sex))}\right)^{-0.329-SrCrExp}$$

[where Sex = 1 for male, 0 for female, Black = 1 for Black, 0 for other races. and
If SrCr > (0.7 + 0.2*Sex) Then SrCrExp = 0.88 , Else SrCrExp = Sex*0.082]

Drug Removal During Dialysis

- **Hemodialysis**
  - Is effective when the toxin in question has a small volume of distribution and low MW and is highly water-soluble and poorly protein-bound.
  - Hemodialysis is an important consideration when there are coinciding acid-base or electrolyte disturbances.
- **Charcoal hemoperfusion**
  - Involves placing a charcoal filter into the hemodialysis machine.
  - Substances effectively eliminated by this method must have a high affinity for charcoal and a small volume of distribution.
- **Hemofiltration**
  - Can remove compounds with a high MW.

Drug Removal During Dialysis

Table 19. Examples Of Agents Amenable To Extracorporeal Elimination

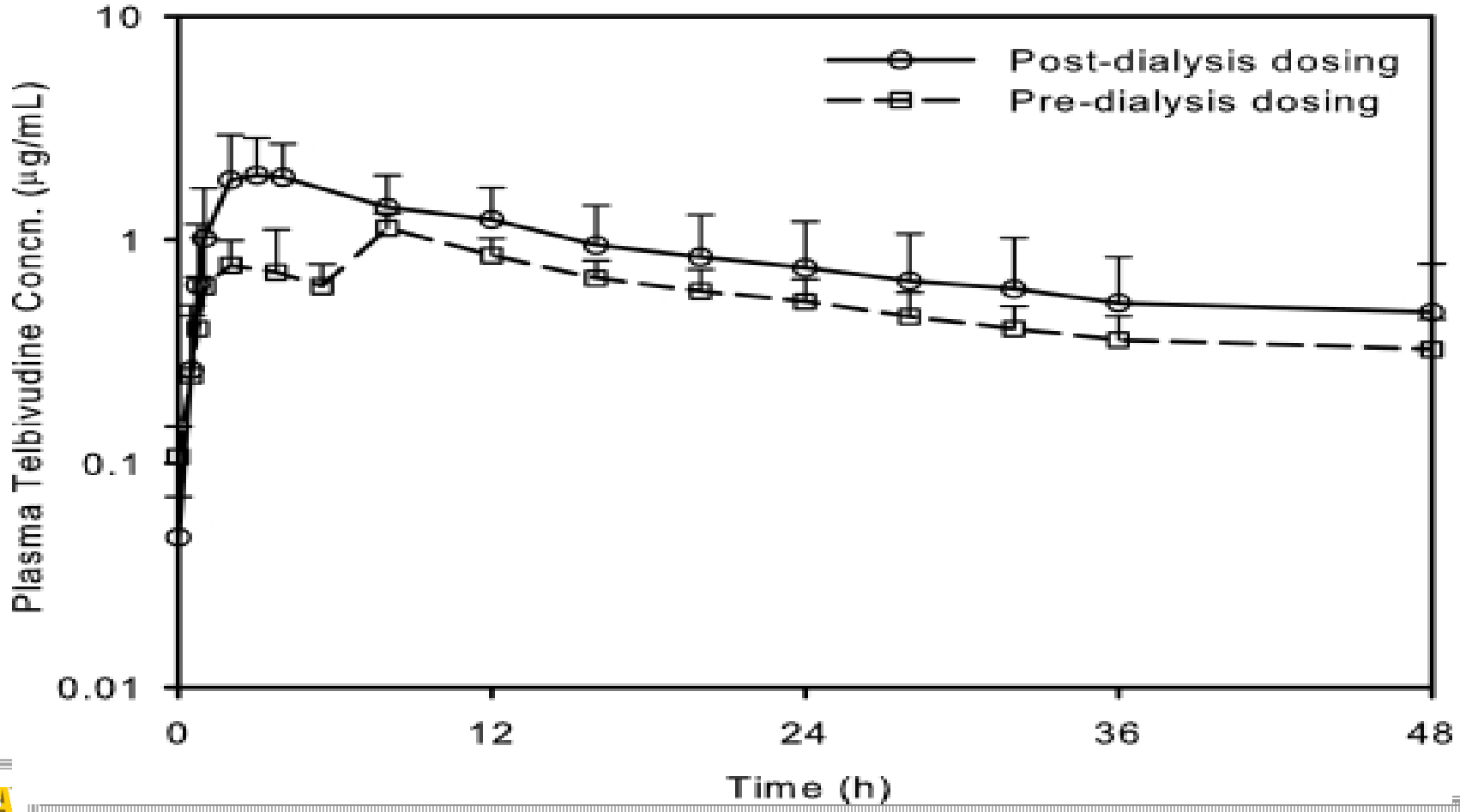
Hemodialysis	Hemoperfusion	Hemofiltration
Atenolol	Barbiturates	Aminoglycosides
Ethylene glycol	Carbamazepine	Iron
Isopropanol	Chloral Hydrate	Lithium
Lithium	Dapsone	Metal chelate complexes-iron/ desferoxamine, aluminum/ desferoxamine
Methanol	Diphenhydramine	Methanol ethylene glycol
Salicylate	Isoniazid	Metformin
Theophylline	Organophosphates	Theophylline
Vancomycin	Procainamide	Vancomycin

Dosage Adjustments in Dialysis

- Loading Dose
  - Does not need to be adjusted (Same post-dialysis dose as normal starting dose).
  - Loading dose depends solely on volume of distribution.
- Post-dialysis replacement dosing.
  - Telbivudine example to illustrate:

Mean (SD) plasma telbivudine concentration-time profiles in patients with ESRD

Administered a single oral dose of 200 mg of telbivudine



Mean Extraction Ratio = 44.7%

23% reduction in systemic exposure

Dosage Adjustments in Dialysis

- **Maintenance dose (Supplemental)**
  - **Based on standard reference tables, or**
  - **Based on measured loses.**
    - ➢ **Do frequent blood level determinations**
    - ➢ **e.g. Aminoglycosides, vancomycin**

$$Dose_{Suppl} = \left(C_{\text{Target}} - C_{\text{Measured}}\right) \bullet V$$