PHAR:8263 IP: Infectious Diseases

Assessment of Renal Function for TDM

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Objectives

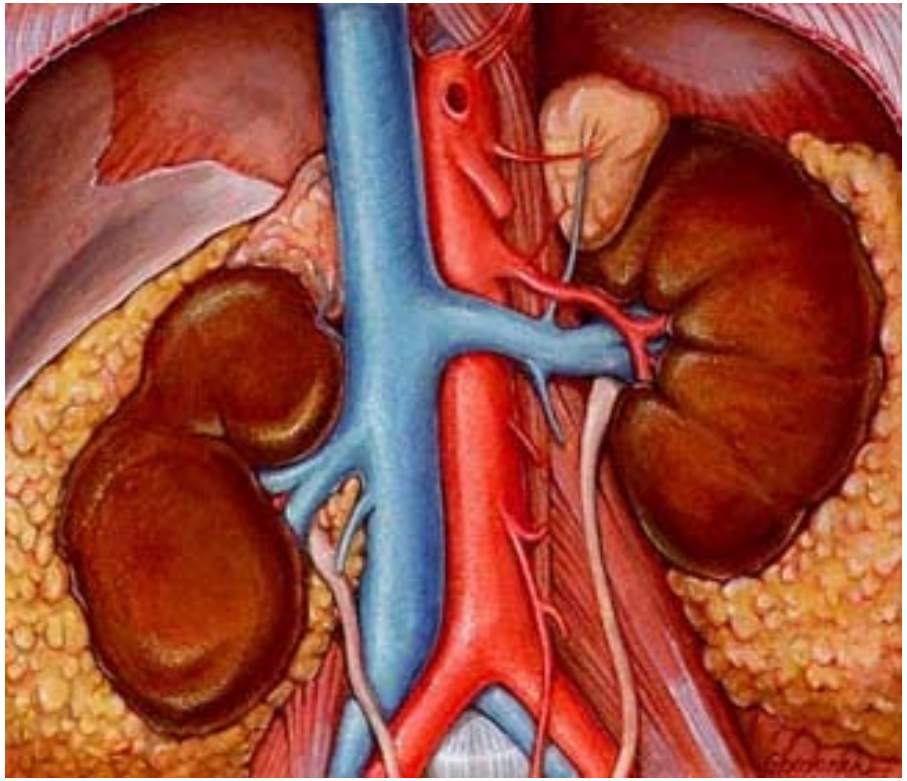
- Know the most commonly used methods of estimating creatinine clearance for all age groups.
- Describe how the GFR and CrCl relate to one another as measures of renal function.

Objectives

- Understand the controversy about actual body weight or lean body weight in the Cockcroft Gault equation.
- Know how to normalize creatinine clearance estimations.
- Use CrCl estimations to calculate PK parameters

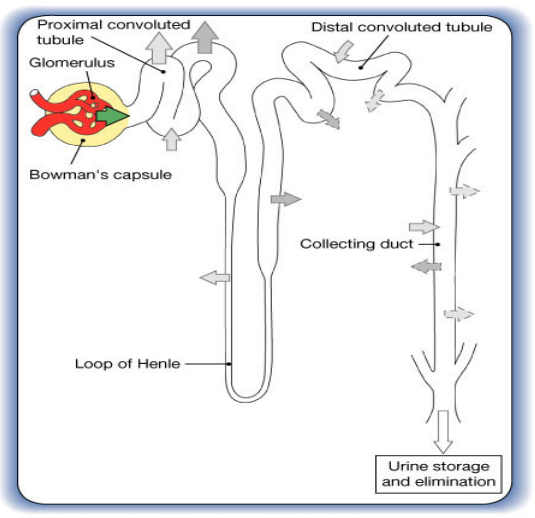
Introduction

- Functions of the kidney

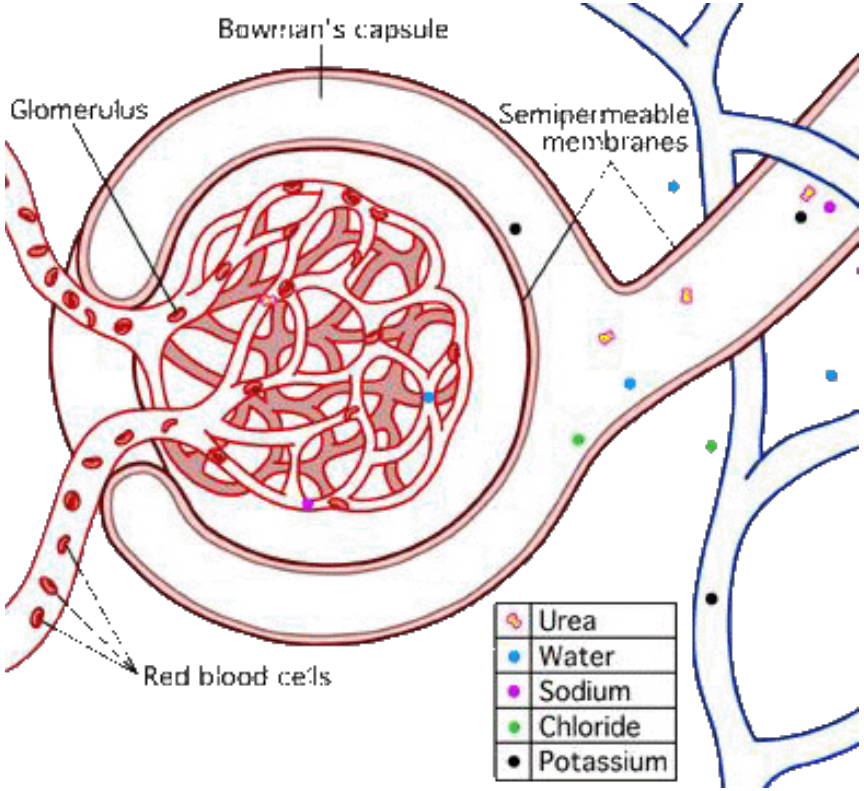


Functions of the Urinary System

- **Excretion**
  - The removal of organic waste products from body fluids.
- **Elimination**
  - The discharge of waste products into the environment.
- **Homeostatic regulation of blood plasma**
  - Regulating blood volume and pressure
  - Regulating plasma ion concentrations
  - Stabilizing blood pH
  - Conserving nutrients



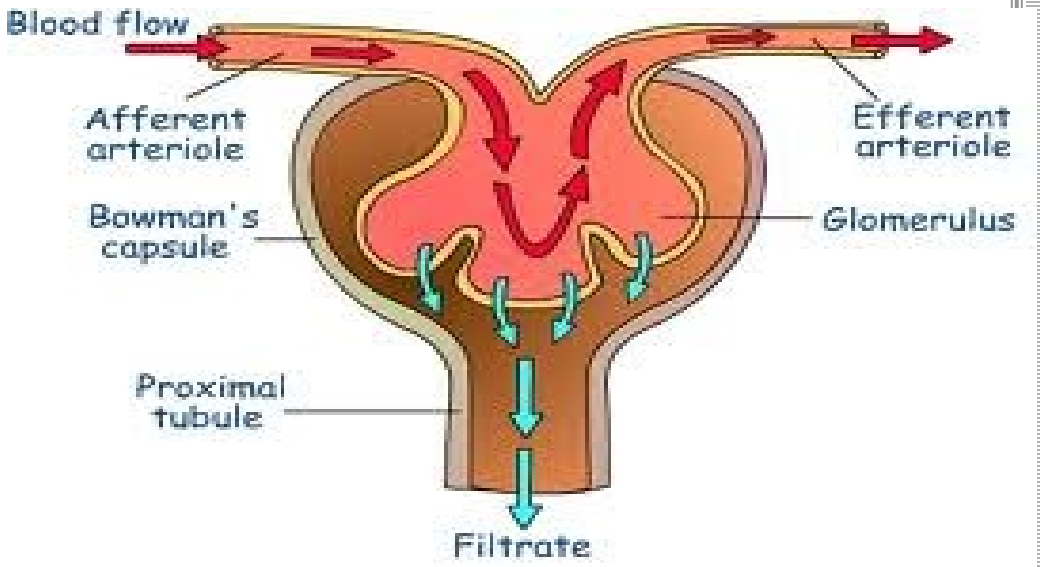
Drug Elimination



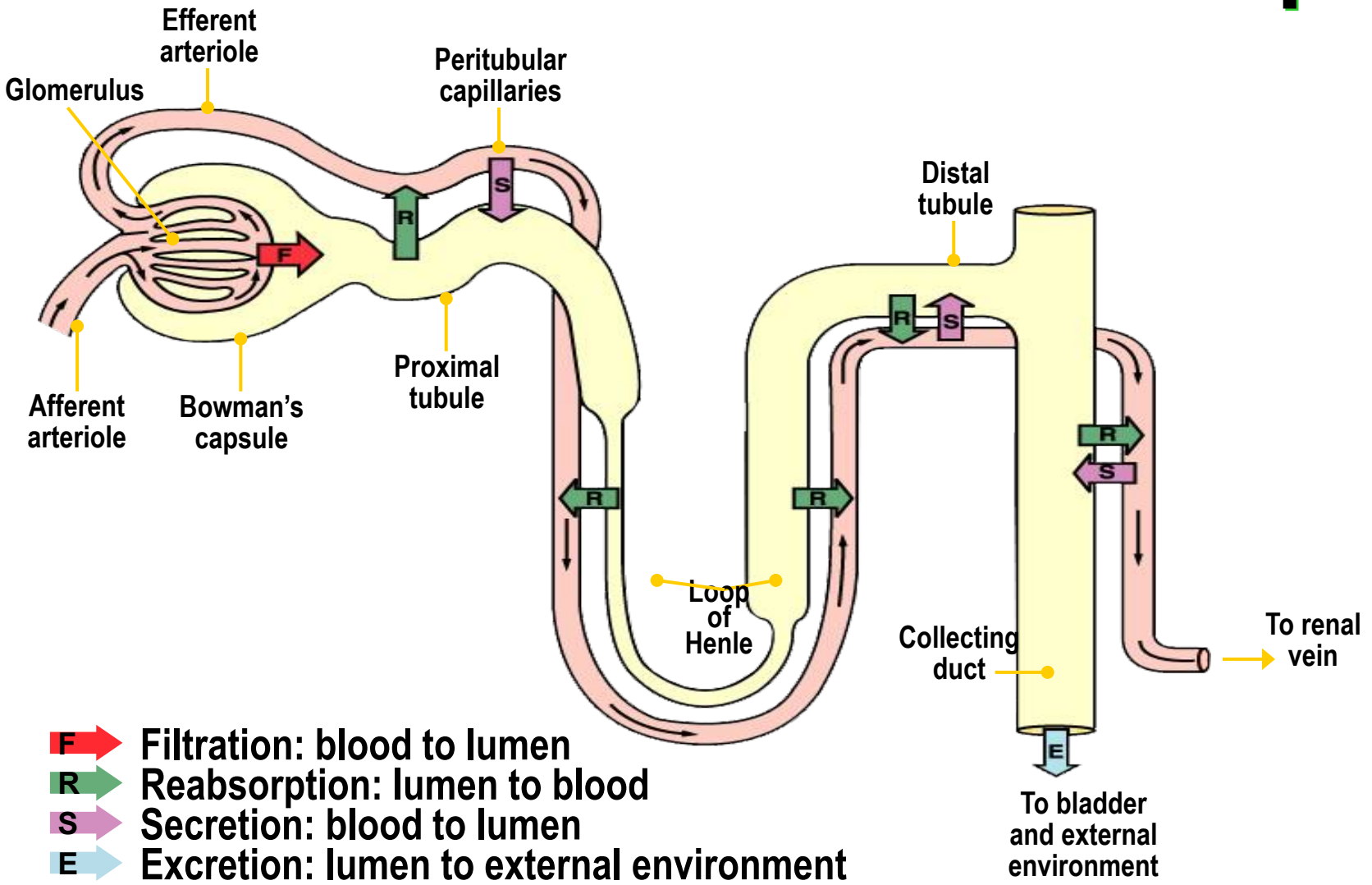
- **Glomerular Filtration**
  - Major route for elimination of small drug molecules.
- **Active Secretion**
  - Becomes important large, biotechnology medications.

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.



Renal Function Overview: The Nephron



Measures of Renal Function

- Glomerular Filtration Rate
  - Normal: 90-130 ml/min
- Methods for measuring GFR are
  - Too time consuming
  - Too expensive
  - The biomarker has some active secretion along with its filtration.

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

Evaluation of Kidney Function: GFR

- Serum creatinine is most widely used marker of GFR in clinical practice.
  - Metabolically inert product of muscle
- Various factors affect serum creatinine, and thus, the predictive accuracy of GFR
  - Muscle mass affects creatinine generation
    - Age, gender, weight, steroid use
  - Tubular secretion
    - Increased secretion when GFR is reduced
    - Secretion is inhibited by drugs (e.g., cimetidine, trimethoprim)
  - Variability in laboratory measurement
    - Intra-individual variability 7-20%

Assessment of Renal Function

- **MDRD**
  - **Modification of Diet in Renal Disease**
    - **Cross-Sectional Study**
    - **1628 Patients** – 1070 were use to develop regression models to predict GFR and 558 were used to test those models.
    - **GFR was measured with the renal clearance of ^{125}I-iothalamate.**
    - **Creatinine clearance was also measured.**

Assessment of Renal Function

- **Levey *et. al.* GFR-MDRD** **(ml/min/1.73 m^2)**

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

[Sex = 1 male, 0 for female, Black = 1 for Black, 0 for other races.]

	Measured	Predicted
GFR	**39.8 ml/min/1.73 m^2 (100%)**	**43.4 ml/min/1.73 m^2 (109%) MDRD**
CrCl	**48.6 ml/min/1.73 m^2 (119%)**	**46.2 ml/min/1.73 m^2 (116%) C-G**

Assessment of Renal Function

- **MDRD (CKD–EPI)**
  - **Modification of Diet in Renal Disease with Epidemiology Data**
    - **Took the previous 1628 Patients and added 6626 more patients that did not have chronic renal failure.**
      - –5504 were use to develop regression models to predict GFR and 2750 were used to test those models.

Levey and coworkers: *Ann Intern Med* 2009;150:604-12

Assessment of Renal Function

- **Levey *et. al.* GFR-MDRD (CKD-EPI)** **(ml/min/1.73 m^2)**

$$GFR\,(CKD-EPI) =$$

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

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

Creatinine Clearance Estimation

Schwartz *et. al.* (Neonates: < 2 months)

(ml/min/1.73 m^2)

$$CrCl = \frac{0.45 \cdot Ht}{SrCr}$$

Shull *et. al.* (Children: 2 months – 16 years)

(ml/min/1.73 m^2)

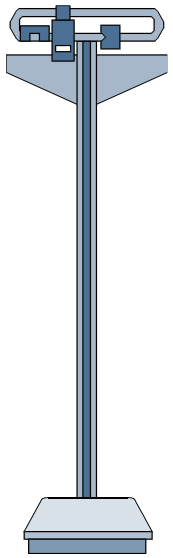
$$CrCl = \frac{(3.5 \cdot Age) + 23.6}{SrCr}$$

Creatinine Clearance Estimation

- **Cockcroft and Gault:** (ml/min)

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

Weight Adjustments



IBW (males) =

50 Kg + 2.3 Kg/inch over 5 feet

IBW (females) =

45.5 Kg + 2.3 Kg/inch over 5 feet

- **AdjWT = (ActBW - IBW)*(0.4) + IBW**
  - **If ActBW is > 30% over IBW** **DWT**
  - **If BMI ≥ 25 Kg/m²** **CrCl-Wt**

Cockroft & Gault: ABW, IBW or AdjWT?

- Original work of C&G used ABW.
- Creatinine is produced entirely by muscles, so there is no ↑'d production in obesity.
- C&G original work used ABW, but their patients were within 10% of their IBW.
- Winter and colleagues recommendations:
  - If the patient is < IBW, use CrCl-Wt = ABW
  - If the patient is > IBW and BMI < 25 Kg/m^2, CrCl-Wt = IBW
  - If the patient has a BMI ≥ 25 Kg/m^2, CrCl-Wt = AdjWT

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

Winter et al: Pharmacotherapy 2012;32(7):604-12

Cockcroft and Gault

- Things to remember:
  - This estimate is patient specific, not normalized.
  - Use the correct weight.
  - SrCr values, according to Winter and colleagues, should not be rounded

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

Reasons for Estimating CrCl

- To know if dosing adjustments are necessary.
- To use the CrCl estimate to estimate the rate of elimination of certain renally excreted drugs.

CrCl Estimations

- **Patient specific CrCl (ml/min)**
  - Used to calculate a patient specific rate of elimination (k_e).
- **Normalized CrCl (ml/min/1.73 m^2)**
  - To compare CrCl from one person to the next, the CrCl must be normalized to a standard (BSA).

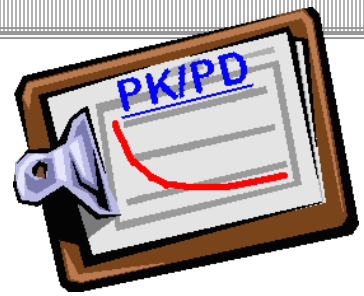
Creatinine Clearance Estimation

- **Cockcroft and Gault:** (ml/min)

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

To Normalize: $CrCl \bullet \frac{1.73}{BSA}$

Summary



- GFR is the most accurate estimate of renal function, however, therapeutic drug monitoring (at least to date) use population estimates that have been developed with CrCl.
- Therefore, in the clinical situation, we need to estimate renal function based on CrCl.
  - This estimate is necessary for PK dosage adjustments of drugs where we monitor serum concentrations.
  - However, it is also necessary to make dosage adjustments to many other drugs where we do not monitor serum concentrations.
- Therefore, we need to be able to quickly and accurately estimate CrCl in the clinical setting.