Renal with Rogers

October 31, 2014
Hosted by the UNM Student Pathology Association
An interpretation of **FIRSTAID** topics:

- **Embryology**
- **Anatomy**
  - Broadly
  - Nephron & Tubules
- **Filtration**
  - Physiology & Electrolytes
  - Acid/Base & Fluid Balance
  - Pharmacology & Hormones
  - Equations
Embryology

Pronephros
Mesonephros
Metanephros
Uretogenital sinus
Embryology

Pronephros
- Forms in 4th week & quickly regresses

Mesonephros
- Forms next and is functional until true kidney develops
  - Ductus deferens, epididymis, ejaculatory duct, seminal vesicle
  - Metanephric ureters, renal pelvis, calyces, collecting tubules

Metanephros (continued from mesonephros)
- Ureteric bud interacts with mesenchyme inducing differentiation of glomerulus through DCT. Aberrant interactions → malformation.

Uretogenital sinus
- Bladder, urethra
Embryology

Horseshoe kidney
- Inferior poles fused, ascent interrupted by IMA
- Risk Wilms tumor

Bilateral Renal Agenesis (Potter syn)
- Uteric bud doesn’t form
- Oligohydramnios
  - oligo Greek: few
- Facial & limb deformities
- Agenesis incompatible with life
Anatomy (broadly)
Anatomy (nephron)
Anatomy: the nephron

- Glomerulus
- PCT
- Descending loop
- Thick ascending loop
- DCT
- Collecting duct
Anatomy: the glomerulus

What are the parts?
Anatomy

Nephron key
A - renal corpuscle
B - proximal tubule
C - distal convoluted tubule
D - juxtaglomerular apparatus
1. basement membrane (basal lamina)
2. bowman’s capsule (parietal layer)
3. bowman’s capsule (visceral layer)
3a. podocyte foot process, aka pedicel
3b. podocyte
4. bowman’s space (urinary space)
5a. mesangium (intraglomerular cell)
5b. mesangium (extraglomerular cell)
6. granular (juxtaglomerular) cells
7. macula densa
8. myocytes
9. afferent arteriole
10. glomerular capillaries
11. efferent arteriole
Anatomy: another take on the glomerulus
Anatomy: glomerular filtration barrier

Charge & size selective filtration:

- Fenestrated capillary endothelium
- Glomerular basement membrane
  - heparan sulfate blocks large negatively charged solutes
  - small solutes +/- can pass
    - Na+, K+, Cl-, HCO3-
- Podocytes with diaphragms & filtration slit

Denied!

http://www.nature.com/ki/journal/v74/n3/fig_tab/ki2008260f1.html
Filtration
Or...

The nephron as a water treatment facility

IPHY 3410-100, Leif Saul
Filtration: a necessary homeostatic detour

25% → kidney
20% of that filtered

Aorta
- Renal artery
- Segmental artery
- Interlobar artery
- Arcuate artery
- Cortical radiate artery
- Afferent arteriole
- Efferent arteriole
- Glomerular capillaries

IVC
- Renal vein
- Interlobar vein
- Arcuate vein
- Cortical radiate vein
- Peritubular capillaries (vasa recta)
Filtration: So what’s in there?

- Uric acid: 0.3-2.0 g from purine degradation
- Creatine: 0.05-0.10 g from muscle metabolism
- Creatinine: 1.0-1.5 g from creatinine and creatine phosphate
- Urea: 20-35 g from proteins and amino acids

Volume: 0.5 - 2 L/day
pH: 5.8 (4.8 - 7.5)
Density: 1.015 - 1.022 kg/l
Osmolarity: 500 - 1300 mosmol/kg
Sedics: 50 - 52 g/day

Glucose: <0.16 g
Ketone bodies: <3 g
Proteins: <0.15 g
Amino acids: 1-3 g

Daily excretion (mmol):
- Cl⁻: 120-240
- SO₄²⁻: 30-60
- Na⁺: 100-150
- K⁺: 60-80
- H⁺: 10-60
- Ca²⁺: 3-11
- Mg²⁺: 3-5

Dissociation dependent on pH

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Filtration, reabsorption, excretion
Filtration: early PCT
Filtration: late PCT
Filtration: thick ascending limb
Filtration: early DCT
Filtration: late DCT & CD
Na+ and K+

Na+ Handling in the Nephron:
- Proximal convoluted tubule: 67%
- Distal convoluted tubule: 5%
- Thick ascending limb: 3%
- Thin descending limb: 25%
- Thin ascending limb: Excretion < 1%

K+ Handling in the Nephron:
- Proximal convoluted tubule: 67%
- Collecting duct: 20%
- Low K+ diet only
- Variable secretion
- Dietary K+
- Aldosterone
- Acid-base
- Flow rate
- Luminal anions
- Excretion 1%–110%
Ca²⁺, Mg²⁺, PO₄⁻
GFR = Kf \left[ (PGC - PBS) - (\pi GC - \pi BS) \right]
Filtration: Fluid volume

General principles:

- ECF is regulated by adjusting the rate of Na+ excretion.
- Osmolarity is regulated by adjusting the rate of free water excretion.
- Normal osmolarity of body fluids ~300 mOsm/L and can be estimated:

\[(2 \times \text{plasma Na+}) + (\text{glu}/18) + (\text{BUN}/2.8)\]
Filtration: Responses to osmolarity

- **Na⁺ INAKE**
  - ↑ ECF volume
  - ↑ EABV

- **SYMPATHETIC ACTIVITY**
  - Dilation of afferent arterioles (↑ GFR)
  - ↓ Na⁺ reabsorption (proximal tubule)

- **ANP**
  - Constriction of efferent arterioles (↑ GFR)
  - ↓ Na⁺ reabsorption (collecting ducts)

- **RENIN-ANGIOTENSIN-ALDOSTERONE**
  - ↓ Na⁺ reabsorption (proximal tubule and collecting ducts)

- **↑ Na⁺ EXCRETION**
### Filtration: Responses to osmolarity

<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
<th>ECF Volume</th>
<th>ICF Volume</th>
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<td>Isosmotic volume contraction</td>
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<td>↓</td>
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<tr>
<td>Hyposmotic volume expansion</td>
<td>SIADH</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
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Filtration: Systemic blood pressure

Myogenic mechanism of autoregulation

Tubuloglomerular mechanism of autoregulation

Hormonal (renin-angiotensin-aldosterone) mechanism

Neural controls

Intrinsic mechanisms directly regulate GFR despite moderate changes in blood pressure (between 90 and 180 mm Hg mean arterial pressure).

Extrinsic mechanisms indirectly regulate GFR by maintaining systemic blood pressure, which drives filtration in the kidneys.
All diuretics lower ECF volume by inhibiting tubular reabsorption of Na+.

Differences lie in where and by how much.

All diuretics, except K+ sparing, tend to increase K+ excretion, causing hypokalemia.

Loop diuretics can increase Ca2+ excretion.

Thiazides can increase Ca2+ reabsorption.
Filtration: Side effects by other drugs, i.e.:
Filtration: Side effects by other drugs

List of drugs with nephrotoxic effects: http://www.aafp.org/afp/2008/0915/p743.html
Filtration: Hormones

- **Aldosterone:** stimulates active Na+ absorption; H2O follows
- **ADH:** stimulates passive H2O absorption in CD
- **AT II:** efferent arteriole constriction
- **ANP:** increase GFR, decrease renin
What about acid?
Where does acid $\sim H^+$ come from anyway?

~ 50 mEq/day from phospholipid and protein catabolism
~ 20 mEq/day in titratable form
~ 30 mEq/day NH$_4^+$
First! We reabsorb our filtered HCO₃⁻

HCO₃⁻
- 99.9% reabsorbed mostly in the PCT
- brush border and intracellular CA
- no net secretion of H⁺
- angiotensin II stimulates Na+/H⁺ exchange → HCO₃⁻ reabsorption

acetazolamide
Second! We excrete titratable acid

H+ excreted with buffers (HPO4-2)
- alpha-intercalated cells of late DCT and CD
- 85% HPO4-2 still in tubule
- H+ ATPase
  - stim by aldosterone
- H+-K+ ATPase
- One HCO3- synthesized & reabsorbed for every H+ excreted

![Diagram of the excretion of titratable acid with labeled components and reactions.]
And! We excrete H+ as NH4+

H+ excreted with buffers (HPO4-2)

- PCT
  - NH4+ (from glutamine) is secreted via Na+-H+ exchanger

- TAL
  - NH4+ reabsorbed for osmotic gradient

- Alpha-intercalated
  - NH3 from medullary interstitial fluid combines with H+ and is secreted → NH4+ excreted
## Simple Acid-Base disorders

\[
\text{CO}_2 + \text{H}_2\text{O} \quad \leftrightarrow \quad \text{H}^+ + \text{HCO}_3^- \quad (\text{pH})
\]

<table>
<thead>
<tr>
<th></th>
<th>CO(_2)</th>
<th>H(_2)O</th>
<th>H(^+)</th>
<th>HCO(_3^-)</th>
<th>(pH)</th>
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</thead>
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<tr>
<td>Normal</td>
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<tr>
<td>(40 mmHg)</td>
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<td>Met Acidosis</td>
<td>low</td>
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<td>L</td>
<td></td>
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<tr>
<td>Met Alkalosis</td>
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<td>low</td>
<td>HIGH</td>
<td>H</td>
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<tr>
<td>Rsp Acidosis</td>
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<td>high</td>
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<td>L</td>
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<td>LOW</td>
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<td>low</td>
<td>H</td>
<td></td>
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Metabolic disturbances lead to respiratory compensations, adjusting [CO\(_2\)]
Respiratory disturbances lead to renal compensation, adjusting [HCO\(_3^-\)]

Winters formula calculates the **predicted** respiratory compensation:

\[
\text{PCO}_2 = 1.5 \times [\text{HCO}_3^-] + 8 +/- 2
\]

If **measured** differs significantly, there is likely a mixed acid-base disorder.
Acidosis/Alkalosis schematic

Check arterial pH

- pH < 7.4 Acidemia
  - PCO₂ > 40 mmHg
    - Respiratory acidosis
      - Hypoventilation
        - Airway obstruction
        - Acute lung disease
        - Chronic lung disease
        - Opioids, sedatives
        - Weakening of respiratory muscles
  - PCO₂ < 40 mmHg
    - Metabolic acidosis with compensation (hyperventilation)

- pH > 7.4 Alkalemia
  - PCO₂ < 40 mmHg
    - Respiratory alkalosis
      - Hyperventilation
        - Hysteria
        - Hypoxemia (e.g., high altitude)
        - Salicylates (early)
        - Tumor
        - Pulmonary embolism
  - PCO₂ > 40 mmHg
    - Metabolic alkalosis with compensation (hypoventilation)
      - Loop diuretics
      - Vomiting
      - Antacids use
      - Hyperaldosteronism

Check anion gap

Anion gap = Na⁺ - (Cl⁻ + HCO₃⁻)

- Anion gap
  - MUDPILES:
    - Methanol (formic acid)
    - Uremia
    - Diabetic ketoacidosis
    - Propylene glycol
    - Iron tablets or INH
    - Lactic acidosis
    - Ethylene glycol (oxalic acid)
    - Salicylates (late)
  - Normal anion gap (8–12 mEq/L)
    - HARD-ASS:
      - Hyperalimentation
      - Addison disease
      - Renal tubular acidosis
      - Diarrhea
      - Acetazolamide
      - Spironolactone
      - Saline infusion
Acid-Base assessment: anion gap

Plasma contains cations (Na+) and anions (HCO₃⁻, Cl⁻)

- Assess the gap for the unmeasured ions
  - Gap = [Na⁺] - ([HCO₃⁻] + [Cl⁻])
  - Normal Gap = 8 - 16 mEq/L

- In metabolic acidosis, [HCO₃⁻] is low
  - Another anion must take its place
    - if Cl⁻, no gap
      - HARDASS
    - if organic anion, “metabolic acidosis w/ an increased anion gap”

MUDPILES
BUN: Creatinine
Both are freely filtered within the glomerulus. What happens in the tubules?

BUN: Blood urea nitrogen
- Within the tubules, urea is secreted, reabsorbed, neither.

Creatinine
- Within the tubules, creatinine is secreted, reabsorbed, neither.
BUN:Creatinine

_________: the presence of abnormally high urea in blood

● 3 types
  ○ Prerenal, i.e. volume contraction, aka hypovolemia
    ■ Increased BUN:Creatinine ratio
    ● why?
    Decreased renal perfusion leads to decreased GFR, leading to an increase in both serum urea and serum creatinine. And since urea is reabsorbed while creatinine is not, BUN:Creatinine > 20
  ○ Primary renal
    ■ Decreased BUN:Creatinine ratio
    ● why?
    Renal disease leads to decreased GFR, leading to an increase in both serum urea and serum creatinine. Since urea is not being reabsorbed, BUN:Creatinine < 15
  ○ Postrenal
Equations

- GFR = Kf \[(PGC - PBS) - (\pi GC - \pi BS)\]
  \[= C(i) = U(i)V / P(i)\]
  
  \(i\) = inulin, though often use creatinine (which slightly overestimates)
  
  GFR usually \(~ 100\ \text{mL/min}\)
- Filtration Fraction = \(\text{GFR}/\text{RPF}\)
  
  FF usually \(~ 20\%\)
- Renal Blood Flow = \(\text{RPF} / (1-Hct)\)
- Filtered Load = \(\text{GFR}\times P(x)\)

<table>
<thead>
<tr>
<th>Changes in glomerular dynamics</th>
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<tbody>
<tr>
<td><strong>Effect</strong></td>
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<tr>
<td>Afferent arteriole constriction</td>
</tr>
<tr>
<td>Efferent arteriole constriction</td>
</tr>
<tr>
<td>↑ plasma protein concentration</td>
</tr>
<tr>
<td>↓ plasma protein concentration</td>
</tr>
<tr>
<td>Constriction of ureter</td>
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Equations

- **HH:** $\text{pH} = pK + \log \left[ \text{HCO}_3^- \right] / \text{PCO}_2$

- **Winters Formula:** $\text{PCO}_2 = 1.5 \left[ \text{HCO}_3^- \right] + 8 +/ - 2$

- **Renal Clearance:** $C(x) = U(x)V / P(x)$
  $C(x) =$ clearance of $(x)$ mL/min
  $U(x) =$ urine $(x)$ mL/min
  $V =$ urine flow rate mL/min
  $P(x) =$ plasma $(x)$

- **Filtered load =** $\text{GFR} \times P(x)$
  **Excretion rate =** $V \times U(x)$
  **Reabsorption =** filtered - excreted
  **Secretion =** excreted - filtered
Patient is injected with inulin and the following measurements are made:
urine flow rate: 3.0 ml/min
urine [inulin]: 11.0 mg/ml
plasma [inulin]: 0.25 mg/ml

What is their renal clearance?

\[ C(i) = \frac{U(i)V}{P(i)} = \frac{(11 \text{ mg/min}) \times (3.0 \text{ ml/min})}{0.25 \text{ mg/ml}} = 132 \text{ ml/min} \]
Practice

Renal blood flow = \( \frac{RPF}{1-Hct} \)

If \( RPF = 650 \text{ ml/min} \), and \( Hct = 45\% \), what is renal blood flow?

\[
650 \text{ ml/min} / (1-0.45) = 118 \text{ ml/min} \sim 1.2 \text{ L/min}
\]
Given the following, what is net filtration rate?

\[ P(gc) = \text{hydrostatic} = 75 \text{ mmHg} \]
\[ P(bs) = \text{hydrostatic} = 15 \text{ mmHg} \]
\[ P(gc) = \text{oncotic} = 25 \text{ mmHg} \]

\[ [(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})] \]
\[ (75 - 15) - 25 = 35 \]
Questions?

I’m sure somebody has the answer.


The interwebs’ image repository.
This notes document accompanies the powerpoint presentation, “Renal with Rogers” 10/31/14. This presentation is paired with “Kidneys by Kait” which discusses renal pathologies.

Note: Powerpoint images will be much larger (aka intelligible) than those included here.

Overview
Renal physiology and dynamics plays a central role in regulating homeostatic functions within our bodies. To approach this brief review I looked at FirstAID’s coverage of renal physiology and clumped concepts as they seemed logical to me. Some of the topics are reviewed in some depth, whereas others are only nominally included, simply to remind you that they need to be reviewed. The rough outline of the presentation is as follows:

An interpretation of FIRSTAID topics:
- Embryology
- Anatomy
  - Broadly
  - Nephron & Tubules
- Filtration
  - Physiology & Electrolytes
  - Pharmacology & Hormones
  - Acid/Base & Fluid Balance
  - Equations

Embryology
Embryology is easy money on STEP. These slides provide word and visual outlines of the key structures, precursors and ultimate derivatives during embryological development. The four stages of structures are:
Pronephros
Mesonephros
Metanephros
Uretogenital sinus
**Pronephros**
Forms during the 4th week of development & quickly regresses. It is never a functional structure.

**Mesonephros**
Forms next (toward the end of the 4th week) and is actually functional until the true kidney develops. The following structures develop from the mesonephros’s ureteric bud:
- Metanephric ureters, renal pelvis, calyces, collecting tubules

Additionally, the male’s ductus deferens, epididymis, ejaculatory duct, seminal vesicle derive from this stage

**Metanephros**
This is really just a continuation from the mesonephros. Within this stage the ureteric bud interacts with mesenchyme and inducing differentiation of the renal structures from the glomerulus through the distal convolutle tubules (DCT). If there are aberrant interactions during this time we see malformation.

**Uretogenital sinus**
The last structures to differentiate and canalize are the bladder and urethra.

**Developmental anomalies**
Two examples of developmental anomalies are the horseshoe kidney and bilateral renal agenesis, aka Potter’s syndrome.

Horseshoe kidney occurs when the inferior poles of the developing kidneys fuse, which causes their horseshoe-like appearance. The challenge here is that when the kidneys ascend into position, the loop of the horseshoe can catch on the inferior mesenteric artery (IMA) where it branches off of the aorta. There is also an increased risk of a Wilms tumor associated with this condition.

Potter’s syndrome occurs when the uteric bud doesn’t form (see mesonephros stage). Consequently the developing fetus is unable to produce urine, which normally mixes with the amniotic fluid in utero. Oligohydramnios is the term used for this (oligo: greek for few). Renal agenesis is incompatible with life.
Anatomy

Overview
Review the anatomy associated with the kidneys within the abdominal cavity. Note neighboring structures. Also review the anatomic regions of the kidney. Consider things such as, what is the significance of the cortex versus the medulla? What are the roles of the renal calyces? Which pathologies involve calyces and the renal pelvis? Which arteries ultimately lead into the nephrons? (More on that later) Etc.

Nephron
Most of what we discuss about kidneys comes down to the nephron. This is where all the homeostatic action is. The following diagram provides a nice overview of the nephron, and its shifting cell types.

Note that the cross cut of the proximal convoluted tubule (PCT) shows cells with prominent microvilli. Whereas the other cross cuts do not reveal prominent microvilli. This makes sense because of the role that the PCT plays in reabsorbing substances from within the filtrate coursing through the PCT’s lumen.

Nephrotoxic drugs lead to electrolyte imbalances when they affect the integrity of these reabsorbing/secreting tubules.

The Glomerulus
This structure is the key to filtration. Know it inside and out. What roles do each of the structures play?

i.e. Know that the afferent and efferent arterioles play key roles in the GFR and thus the fluid volume of the body. Know that Angiotensin II preferentially constricts the efferent arteriole.

i.e. Know what the macula densa cells are specialized to detect and how that affects homeostasis?

key
A - renal corpuscle
B - proximal tubule
C - distal convoluted tubule
D - juxtaglomerular apparatus
1. basement membrane (basal lamina)
2. bowman’s capsule (parietal layer)
3. bowman’s capsule (visceral layer)
3a. podocyte foot process, aka pedicel
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4. bowman’s space (urinary space)
5a. mesangium (intraglomerular cell)
5b. mesangium (extraglomerular cell)
6. granular (juxtaglomerular) cells
7. macula densa
8. myocytes
9. afferent arteriole
10. glomerular capillaries
11. efferent arteriole

Filtration barrier

Drilling down a bit further, the glomerulus provides a charge & size selective filter for the blood coming through the afferent arteriole. This barrier is made of three layers. Can you name them?
1) Fenestrated capillary endothelium
2) Glomerular basement membrane
   ○ heparan sulfate blocks large negatively charged solutes, i.e. albumin
   ○ small solutes +/- can pass, i.e.
     - Na+, K+, Cl-, HCO3-
3) Interdigitating podocytes (visceral epithelial cells) with slit diaphragms/filtration slits

What happens if filtration barrier compromised? One thing you'll see a loss of proteins from the blood which disrupts the π pressure of the capillaries throughout the body which disrupts fluid movement and leads to edema. What else will you see? (The subsequent lecture, “Kidneys with Kait” goes into glomerular pathology in great detail.)

Filtration
This silly cartoon is just a reminder that filtration within the glomerulus is just the beginning of the nephron’s work. As filtrate passes through the nephron substances will be reabsorbed out of the filtrate and secreted into it. The ultimate product is all excreted as urine.

Approximately 25% of the body’s blood supply is in the kidney at any given point in time, which is a huge percentage. Of this 25%, 20% of that will be filtered in the glomerulus. The remaining 80% continues directly to the efferent arteriole which then participates as the nephron’s peritubular capillaries. These eventually feed into the cortical radiate vein, arcuate vein, interlobar vein, renal vein, and ultimately the inferior vena cava (IVC).

As previously mentioned, during the filtrate’s course through the tubules, different substances are reabsorbed from or secreted into the tubular lumen. This graph provides a nice overview of the various concentrations of the filtrate’s components. Note that levels rise and fall in direct association with the part of the tubule that they are in.

Amino acids, for example, are almost entirely reabsorbed from the
proximal tubule, which is why their line (yellow) plummets so quickly. On the other hand, urea’s concentration increases throughout each portion of the nephron until it is ultimately excreted.

Again, note the cellular morphology within the different regions. The proximal tubule is designed for reabsorption, which reflects the patterns in the graph.

The following slides/images all really just reinforce the understanding of where filtrate components are reabsorbed and secreted. I find these visuals a helpful way to cement down which electrolytes are present where and how their movements across the tubular membranes affects homeostatic balance. Of course, knowing this helps predict electrolyte imbalances resulting from pathological syndromes and pharmaceutical side effects.

Note: Most of these images are taken from Costanzo’s Physiology text, because they are so clean and straightforward. They also show where diuretics are functioning.

**Filtration equation**

\[
GFR = K_f \left[ (P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS}) \right]
\]

- Recall that oncotic pressure of Bowman’s Space is approximately zero.
- Kf refers to the water permeability of the glomerular capillary wall.
- P(gc) is hydrostatic pressure in glomerular capillaries, favoring filtration
- P(bs) is hydrostatic pressure in bowman’s space, opposing filtration due to fluid in nephron
- \(\pi_{GC}\) is the oncotic pressure in the glomerular capillaries which also opposes filtration, and is determined by the protein concentration of blood. This increases as it progresses through the glomerular capsule as fluid is filtered out.
Filtration and total body water - principles:

- Extra Cellular Fluid (ECF) volume is regulated by adjusting the rate of Na⁺ excretion from the kidneys.
- Osmolarity is regulated by adjusting the rate of free water excretion from the kidneys.
- The normal osmolarity of body fluids ~ 290 mOsm/L and can be estimated by the following equation:

\[ (2 \times \text{plasma Na}^+) + \left( \frac{\text{glu}}{18} \right) + \left( \frac{\text{BUN}}{2.8} \right) \]

Plan on being 100% fluent with the movement of water between ECF and ICF spaces depending upon the circumstances, i.e. diarrhea vs sweating vs adrenal insufficiency, etc. There will be questions about this on STEP.

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<td>↑</td>
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<td>↑</td>
</tr>
<tr>
<td>Hyposmotic volume expansion</td>
<td>SIADH</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

Also be able to anticipate how systems globally interact to control fluid volume throughout the body. This graphic walks you through four different compensatory/reactive pathways to increased sodium ingestion. It includes the sympathetic, cardiac, renal and endocrine systems. Again, Costanzo is the source for this image and is a good place to clear up any gaps in knowledge about
fluid movement. This next graphic is simply another approach to visualizing and working through systemic responses to fluid volume, as told through the lens of blood pressure.

**Pharmacology: general rules**
As you have probably noticed already, FirstAID has a good graphic combining tubular reabsorption/secrection patterns along with pharmacological sites of action. Know these! Diuretics intentionally alter tubular action, mainly affecting the nephron’s affinity of H2O or Na+. Of course, nothing is so simple and the other electrolytes get involved in side effects. Understand how hypo/hyper-anything is going to affect systems, i.e. cardiac and cns. These organ & system side effects are easiest to understand when you know what should be happening in the tubules.

All diuretics lower ECF volume by inhibiting tubular reabsorption of Na+. The differences lie in where and by how much.

All diuretics, except K+ sparing, tend to increase K+ excretion, causing hypokalemia.

Loop diuretics can increase Ca2+ excretion where as thiazides can increase Ca2+ reabsorption.

ALSO be aware of the nephrotoxic side effects of other drugs. Top nephrotoxins are NSAIDs and antibiotics. The link included in the slides takes you to an AAFP article specifically about nephrotoxic side effects. We don’t need to know nearly all of the included drugs for STEP, but we need to know several.
Hormones

Can you name the biggest players affecting the nephrons? Can you explain the sequence of organs involved in producing the hormones, enzymes, etc and where they act within the kidney?

- **Aldosterone**: stimulates active Na+ absorption H2O follows
- **ADH**: stimulates passive H2O absorption in Collecting Duct
- **AT II**: efferent arteriole constriction, which increases the GFR due to a greater volume of fluid coming into the glomerular capsule (from the afferent arteriole) than is able to leave via the efferent arteriole
  - note: at higher concentrations it constricts both afferent and efferent arterioles
- **ANP**: increases GFR, decreases renin secretion

Acids and Buffers

In addition to being able to identify whether a patient is in acidosis or alkalosis, and determining whether that is due to metabolic, respiratory or mixed causes, you MUST know how the kidneys handle H+ and HCO3-. They excrete more H+ as well as synthesize more HCO3- when the body is acidic. They reabsorb less HCO3- when it’s alkalotic. But where and how?

First: HCO3- reabsorption:

- 99.9% reabsorbed mostly in the PCT due to the actions so carbonic anhydrase within the brush border and intracellularly.
- Acetazolamide is used to treat alkalotic states because it inhibits the brush border carbonic anhydrase, leading to reduced reabsorption of HCO3-
- At this location there is no net secretion of H+. The secreted H+ is incorporated into the HCO3- that is being reabsorbed
- By the way, angiotensin II stimulates the Na+/H+ exchange that facilitates HCO3-reabsorption
Second: titrateable H+ secretion:

Note, we excrete approximately 50 mEq/day of H+, 40% of which is excreted in a titratable form (H+) and the other 60% as NH4+.  

- This occurs via the alpha-intercalated cells of late DCT and CD
- 85% HPO4-2 is still in the tubules this far along the nephron to facilitate the excretion of these secreted H+
- An ATPase is required for this secretion, which is stimulated by aldosterone
- And K+ is reabsorbed in tandem with H+’s excretion
- Not only does this process rid the body of H+, it also synthesizes new HCO3- which is reabsorbed.

Third: we excrete H+ as NH4+  
(whoops this slide should not mention HPO4-2 again)

- Within the PCT, glutamine metabolisms generates NH3+. The Na+/H+ exchanger secretes H+ which combines to form NH4+.
- For osmotic gradient purposes, some NH4+ is reabsorbed within the Thick Ascending Loop
- Back in the alpha-intercalated cells, NH3 from medullary interstitial fluid combines with H+. This final step is where we see H+ excretion in the form of NH4+.

To assess arterial blood gases we look at pH, HCO3- and H+ concentrations. Because the body is dynamic, it will try to compensate for any initial imbalances metabolically or via respiration. Be familiar with the various approaches to assessing both simple and complex imbalances.

We learned to use both a flow diagram as well as a with the help of a Davenport diagram. Get
familiar with whatever works for you.

If a patient is in metabolic acidosis, their anionic gap will be affected because they have low HCO₃⁻ and something needs to take its place.

\[
\text{Gap} = [\text{Na}^+] - ([\text{HCO}_3^-] + [\text{Cl}^-])
\]

Normal Gap = 8 - 16 mEq/L

It’s important to know how big the gap is and what that replacement is.

If the HCO₃⁻ is replaced by an organic ion and the patient has “metabolic acidosis with an increased anionic gap,” this is likely due to the organic ions of **MUDPILES**:

- Methanol
- Uremia
- Diabetic Ketoacidosis
- Paraldehyde
- Infection
- Lactic Acidosis
- Ethylene Glycol
- Salicylates

If the gap is filled by Cl⁻ then it’s a **HARDASS** situation.

- Hyperalimentation
- Addison's Disease
- Renal Tubular Acidosis
- Diarrhea
- Acetazolamide
- Spironolactone
- Saline Infusion
Going back to that bit about nothing being simple, remember that metabolic disturbances lead to respiratory compensations, adjusting \([\text{CO}_2]\). Respiratory disturbances lead to renal compensation, adjusting \([\text{HCO}_3^-]\).

The Winters formula calculates the predicted respiratory compensation via:

\[
\text{PCO}_2 = 1.5 \times [\text{HCO}_3^-] + 8 \pm/\mp 2
\]

If the measured PCO2 differs significantly from the calculated PCO2 then there is likely a mixed acid-base disorder. How fun for you.

However, if it is a simple and straightforward imbalance then just follow this pattern:

<table>
<thead>
<tr>
<th>Normal</th>
<th>(\text{CO}_2) + H2O</th>
<th>(\text{H}^+) + HCO3-</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met Acidosis</td>
<td>low</td>
<td>high</td>
<td>LOW</td>
</tr>
<tr>
<td>Met Alkalosis</td>
<td>high</td>
<td>low</td>
<td>HIGH</td>
</tr>
<tr>
<td>Rsp Acidosis</td>
<td>HIGH</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>Rsp Alkalosis</td>
<td>LOW</td>
<td>low</td>
<td>low</td>
</tr>
</tbody>
</table>

**BUN:Creatinine & azotemia**

Both of these substances are freely filtered within the glomerulus. But in the tubules we see different behavior, which is what accounts for the usefulness of the Blood Urea Nitrogen:Creatinine ratio in assessing renal function. Within the tubules, urea is reabsorbed while creatinine is not.

In an instance of *prerenal azotemia*, we usually have an issue with volume contraction upstream from the kidneys. The kidney perceives decreased renal blood flow and consequent decreased GFR in the glomerulus. If this occurs, there will be a reduced amount of BUN and creatinine being filtered out of the blood so we will see an increased concentration of BUN and creatinine in the blood. But since the kidney increases reabsorption in situations of fluid deficiency, more urea is reabsorbed than usual. Therefore we see elevated concentrations of both substances, and an increased BUN:creatinine ratio > 20.

In *primary renal azotemia* the nephron itself is affected. This leads to compromised GFR and compromised reabsorption of urea. We therefore see increased serum BUN and creatinine, but since less urea is being absorbed due to the compromised tubular function, we see a lower BUN:creatinine ratio < 15.
In postrenal azotemia the issue is beyond the kidney. However, this issue (often an obstruction) can eventually cause fluid back up into the kidney and cause destruction of tubular epithelia, leading to decreased function. In this situation the BUN:creatinine ratio starts out normally but eventually drops due to compromised tubular function.

It seems that pre- and post- renal azotemia (which are both reversible situations) can lead to primary renal azotemia if unrecognized and unmanaged.

**Last but not least: Equations!**

My take on equations is that they are tools to help us assess the integrity of renal functioning by understanding renal blood flow, renal plasma flow, glomerular filtration rate and the clearance of various measured substances. Think of equations simply as ways to interpret the patterns of glomerular dynamics. There may be situations on STEP that do not ask you to specifically calculate anything, but the test writers expect that you will be able to assess renal function and develop diagnostic hypotheses based around filtration data. So get familiar with the equations. I included a lot of them but there are a few more. Many of them overlap one another and many others are fairly intuitive so it’s not quite as bad as it looks :)

<table>
<thead>
<tr>
<th>Changes in glomerular dynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect</td>
</tr>
<tr>
<td>Afferent arteriole constriction</td>
</tr>
<tr>
<td>Efferent arteriole constriction</td>
</tr>
<tr>
<td>↑ plasma protein concentration</td>
</tr>
<tr>
<td>↓ plasma protein concentration</td>
</tr>
<tr>
<td>Constriction of ureter</td>
</tr>
</tbody>
</table>

- **GFR** = Kf [(PGC − PBS) − (πGC − πBS)]
- **Filtration Fraction** = GFR/RPF
  - FF usually ~ 20%
- **Renal Blood Flow** = RPF / (1-Hct)
- **Filtered Load** = GFR x P(x)
- **Renal Clearance**: C(x) = U(x)V / P(x)
  - C(x) = clearance of (x) mL/min
  - U(x) = urine [x]
  - V = urine flow rate mL/min
  - P(x) = plasma [x]
Simple Practice Equations:

Patient is injected with inulin and the following measurements are made:
urine flow rate: 3.0 ml/min
urine [inulin]: 11.0 mg/ml
plasma [inulin]: 0.25 mg/ml

What is the renal clearance?

\[
C(i) = \frac{U(i)V}{P(i)} = \frac{(11 \text{ mg/min}) \times (3.0 \text{ ml/min})}{0.25 \text{ mg/ml}} = 132 \text{ ml/min}
\]

Note: use this equation for the clearance of anything (x)

If RPF = 650 ml/min, and Hct = 45%, what is renal blood flow?

\[
RPF / (1 - \text{Hct}) = \text{RBF}
650 / (1-0.45) = 118 \text{ ml/min} \sim 1.2 \text{ L/min}
\]

Given the following, what is net filtration rate?
P(gc) = hydrostatic = 75 mmHg  \quad P(bs) = hydrostatic = 15 mmHg
P(gc) = oncotic = 25 mmHg

\[
\text{GFR} = K_f [(P_GC - P_BS) - (\pi_GC - \pi_BS)]
= (75 - 15) - 25 = 35
\]