

Renal Review lecture:

- I. Serum creatinine concentration as a reflection of GFR
 - A. GFR is our best index of overall kidney function.
 1. All of the functions of the kidney (excretory, acid/base, calcium/phosphorus balance, EPO production) are correlated with GFR.
 - B. In chronic renal insufficiency, there is a decrease in the number of functioning nephrons which decreases the GFR.
 1. The creatinine clearance is used as a measure of GFR because all of the creatinine that is filtered is excreted. The GFR is slightly overestimated by creatinine clearance due to a small amount of creatinine being secreted.
 2. It is cumbersome to measure timed urine collections in patients (creatinine clearance).
 3. It is much easier to draw a plasma sample of creatinine, which is inversely related to GFR.
 4. If GFR decreases from 100 ml/min to 50 ml/min, the creatinine concentration will increase from 1.0 mg/dl to 2.0 mg/dl.
 - a. If GFR decreases to 25 ml/min, the serum creatinine will double to 4.0 mg/dl.
 - b. If GFR decreases by 50% to 12.5 ml/min, the serum creatinine will double to 8.0 mg/dl.
 - c. Thus, GFR can be estimated from the serum creatinine concentration.
 - C. If you are seeing a patient whose serum creatinine is 0.9 mg/dl today and 1 year later the serum creatinine is still 0.9 mg/dl (and they are the same body mass as 1 year ago), then there has not been a change in GFR or kidney function.
 1. There was no need to measure urine. You only needed to measure their body weight. If there was not a change in skeletal muscle mass, then their serum creatinine did not change.
 2. If the serum creatinine had increased to 1.6 mg/dl, then you would know that their GFR had declined greatly.
 - D. At any point on any day, we make and excrete creatinine.
 1. Creatinine is made based on skeletal muscle mass.
 - a. The more muscle you have, the more creatinine you make each day.
 - b. If you are 80 years old, you have less muscle mass compared to a young person.
 - c. Females also typically have less muscle mass.
 2. Each day we excrete all of the creatinine that we made that day into the urine.
 - a. If you made a gram of creatinine, a gram of creatinine would be excreted into the urine, and the plasma level of creatinine stays the same.
 - b. If you only make 500 mg of creatinine each day, you excrete 500 mg of creatinine each day so you remain in a steady state.
 3. Creatinine gets into the urine via filtration. So every bit of creatinine that gets filtered ends up in the urine.
 - a. Filtered load = Plasma concentration X GFR
 - b. An example is an 80 year old female with a serum creatinine of 1.0 mg/dl and a 25 year old male with a serum creatinine of 1.0 mg/dl.

- c. They have the same serum creatinine, but they do not have the same GFR because they have a very different amount of muscle mass. If GFR decreases, then serum creatinine must increase to get all of the creatinine that was made into the urine. If there is less being filtered, the only way to get rid of the daily production is to increase the blood level.
 - a. If the GFR decreases by 50%, then serum creatinine will double to excrete the daily production.
 - b. Normal GFR is 120 ml/min and normal serum creatinine is 1 mg/dl. If GFR is decreased by 50%, then serum levels of creatinine must increase by 50% to keep filtered load the same (see equation in I.D.3.a).
 - c. Once the serum level is increased, you will be in steady state (excreting everything that you make).
 - 4. If a patient is the same size and GFR decreases, they will have the same creatinine production and excretion. Steady state will be maintained by increasing the blood levels of creatinine. Filtered load is the same.
 - a. Intuitively, you would think that if GFR decreases by 50%, then you are excreting 50% less creatinine.
 - b. This is not true- plasma creatinine will increase with a decrease in GFR to keep excretion equal.
 - c. So, you can monitor this blood level (creatinine) as an index of what is happening to GFR.
 - E. You can be more precise about the serum level representing the GFR by correcting for age and gender. This will improve the accuracy of a serum level representing GFR.
 - F. Serum level represents GFR if we are in steady state only.
 - G. Acute renal failure (ARF) is not steady state (kidney has quit working), so creatinine accumulates in the body.
 - 1. Their serum creatinine rises each day.
 - 2. Chronic renal insufficiency patients will have a slower increase in serum creatinine because they are in steady state on a day to day basis.
- II. Volume status
- A. volume status means extracellular fluid volume (ECFV) which we estimate clinically via heart rate and blood pressure and presence or absence of edema (along with other parts of the physical exam).
 - 1. The clinical volume status of the patient is noted as being low, normal or high.
 - 2. ECFV is a function of the total body Na^+ .
 - 3. total body Na^+ influences total body water (TBW) through osmolality.
 - 4. If we add salt to the body, serum osmolality will increase and water retention will occur via ADH. The patient will also get thirsty with an increase in serum osmolality which will increase intake.
 - B. For example, your patient has diarrhea and is vomiting with tachycardia, low blood pressure and no edema. In this scenario, intake of sodium is decreased (vomiting), loss of sodium is increased (diarrhea), and cardiac output is decreased clinically resulting in volume depletion.
 - C. If your patient is hypertensive and edematous, the patient will be hypervolemic
 - D. Quantitatively, we can determine volume status:

1. A patient weighs 70 kg and gains 3 kg in 2 weeks after eating a high salt diet.
 2. The weight gain is due to an increase in TBW (would not gain weight in muscle or bone in such a short period of time).
 3. The TBW increased 3 L.
 4. How much sodium did they retain in that period of time?
 - a. Measure their blood sodium concentration.
 - b. At the first visit:
 - i. Serum sodium concentration = 140meq/L
 - ii. Clinically the patient has normal volume status at this point.
 - iii. The serum sodium is used to estimate serum osmolality so serum osmolality is normal.
 - c. At the second visit:
 - i. Serum sodium = 140 meq/L so osmolality is unchanged
 - ii. TBW increased by 3 L
 - iii. Serum sodium is restricted to the extracellular space.
 - iv. $3 \text{ L} \times 140\text{meq/L} = 420 \text{ meq}$ of sodium has built up in the extracellular space over the last 2 weeks.
 - v. All of the extra 3 L is in the extracellular space.
 5. A patient who weighs 70 kg with a Na of 140 meq/L is given 3 L of plain water. If this is a dialysis patient and the kidney could not get rid of the 3 L of water, where would the water go?
 - a. The body weight would increase by 3 kg due to 3 L of TBW retention.
 - b. The water would diffuse into both the extracellular and intracellular space.
 - i. 60% of body weight is total body water.
 - ii. Two-thirds of TBW is in the intracellular space
 - iii. One-third of TBW is in the extracellular space
 - c. This patient looks less volume expanded than the patient in 4.
 - d. Their blood pressure is less affected either because the ECFV did not increase as much.
 - e. Serum sodium concentration decreases because the same amount of sodium is dissolved in more water.
 - i. The volume of distribution of water is intra- and extracellular whereas Na^+ is only distributed in the extracellular space.
- III. Serum sodium is a concentration
- A. Serum sodium concentration does not equal total body sodium content.
 - B. The number of meq of sodium is what determines the size of the extracellular fluid space.
 - C. The osmolality is measured via the concentration of sodium in meq/L of plasma.
 - D. If the serum sodium concentration is below normal, there is a tendency to say that the total body sodium is below normal and the volume is low. That is wrong!
 1. Serum sodium is ONLY a concentration.
 2. Serum sodium can decrease:
 - a. By losing more sodium than water

- b. By gaining water with a normal amount of sodium
- c. By gaining more water than sodium
- 3. The patient that lost more sodium than water is sodium and volume deficient.
- 4. The patient that gained more water is water expanded. But they all have the same serum sodium concentration.
- E. Serum sodium is not a measure of volume status.
- F. There is not a lab value that measures volume status. Volume status is a clinical measurement based on weight changes and features of the history and physical exam.

IV. BIG PICTURE- When a change occurs, think what would the kidney do (WWKD)?

- A. What is the kidney's job? Maintain homeostasis
- B. Too much solute in the body, what should the kidney do? Get rid of it.
 - 1. Clinically, this patient is hypertensive, swollen and edematous.
 - 2. The patient has too much sodium in the body. What should the kidney do?
 - a. Get rid of it.
- C. You can always know what the kidney is doing by measuring solutes in the urine.
 - 1. If you want to know what the kidney is doing in terms of sodium handling, you measure urine sodium concentration.
 - 2. If you want to know what the kidney is doing in terms of K, measure the urine K.
 - a. If the patient is hypokalemic, what should the kidney do?
 - b. Conserve K. How would you prove whether or not the kidney is conserving K?
 - c. Measure urine K. If the urine K is high, the kidney is the cause of the hypokalemia. It is wasting K when it should be conserving it.
 - d. Look for what is making the kidney waste K.
 - e. If the patient is losing K through diarrhea and blood levels of K are falling, what should the kidney do?
 - f. Conserve K. The urine K should be very low if the kidney is functioning properly.
 - 3. If you want to know what the kidney is doing in terms of water, what would you measure?
 - a. Urine osmolality. If there is too much water in the body, the kidney should be getting rid of it and the urine will be dilute. The urine osmolality will be below 100 mosm/kg.
 - b. If you drink a lot of water, you will turn off ADH and your urine will be very dilute.
 - c. If you are then deprived of water, your plasma osmolality will increase because you are losing more water than you are taking in.
 - d. If you raise plasma osmolality, what gets turned on?
 - i. ADH which tells the collecting duct to put water channels in the apical membrane and maximally conserve water.
 - ii. In a healthy person that is water restricted, the urine osmolality can increase up to ~1000 mosm/kg.
 - e. If a patient presents with a chief complaint of "peeing all of the time," what would you look at to see what the kidney was doing with water?

- i. The urine osmolality comes back as 88 mosm/kg. What does that tell you?
 - ii. The kidney is making incredibly dilute urine. Why?
 - iii. How would determine what was making the kidney get rid of so much urine?
 - iv. Lack of ADH or increased intake. How would you test for polydypsia?
 - v. Water restriction. Take the water away and repeat the urine osmolality in a couple of hours. If the urine osmolality increases, then the kidney is perfectly normal and the water intake is abnormal.
 - vi. If you water restrict, the TBW will decrease and the plasma osmolality will increase producing an increasingly concentrated urine by ADH directing the water pores to the apical membrane of the collecting ducts.
 - vii. If you water restrict (proven by a decline in body weight) and the urine osmolality is still low, either the patient is not making hormone or he is resistant to it. How do you tell which is going on?
 - viii. Give him hormone. Give him exogenous ADH and if his urine osmolality increases within the next hour, the problem was in producing ADH, central diabetes insipidus.
 - ix. If you give him exogenous ADH and the urine osmolality stays at 88 msom/kg, then he is resistant to ADH, nephrogenic diabetes insipidus.
 - x. Think of the children who have a defect in the receptor that binds vasopressin. If they can't bind vasopressin, they can't set off the cascade to insert water channels into the apical membrane of the collecting duct.
- D. Take any derangement and think- is the kidney doing what it should in this situation?
1. If there is too much of something, the normal kidney response is to get rid of it.
 2. If there is not enough of something, the normal kidney should conserve it.
 3. Check the urine to see how the kidney is handling solutes and water.
- V. What happens when we have a slight pathophysiology that changes our volume state?
- A. Volume deficiency or excess?
 - B. What should the kidney do if you are volume deficient?
 1. If you are volume deficient, then you are sodium deficient and the kidney should try to conserve Na.
 - C. If you are volume expanded with increased serum Na, the kidney should get rid of the excess Na.
 - D. What happens to a normal healthy person if you become volume deficient?
 1. If you become volume deficient because you can't eat and you are throwing up, what hormones are activated?
 2. Renin
 - a. Where is renin made? Solely by the kidney in the juxtaglomerular apparatus in the afferent arteriole.

- b. Less tone (pressure, flow) reaches the JG apparatus in the afferent arteriole when you become volume deficient because the cardiac output decreases and the renal blood flow decreases.
 - c. The decrease in tone (pressure, flow) signals for the JG apparatus to secrete renin.
 - d. Renin is just an enzyme (it does not vasoconstrict itself) that cleaves angiotensinogen to AI and sets off a cascade that ends in AII.
 - e. AII is a potent vasoconstrictor to help support blood pressure.
 - f. AII also activates aldosterone at the adrenal gland.
 - g. Aldosterone tells the cortical collecting duct to conserve Na avidly.
 - h. AII also has a direct effect on the proximal tubule to increase reabsorption of Na.
3. Atrial natriuretic peptide decreases due to decrease stretch in the atria.
 - a. Less ANP implies less natriuresis which helps the body conserve Na.
 4. Sympathetic nervous system is activated which activates the renin system via the receptor.
 5. All of the factors would be activated to maintain the blood pressure and tell the kidney to conserve Na.
 6. What hormone is turned on to tell the kidney to conserve water?
 - a. ADH only tells the kidney what to do with water. It has nothing to do directly with Na regulation.
 - b. Both Na and water would be conserved by the kidney by independent mechanisms.
 - c. The renin-aldo-angiotensin system is geared for Na. ADH is geared for water.
 - d. In a volume depleted patient, there would be non-osmotic vasopressin release which would tell the kidney to conserve water.
 7. The net effect of all of these actions is to tell the kidney to conserve salt and water and increase the volume status.

Question: Why would ADH increase if the serum osmolality decreased?

Answer: The blood volume in this situation is the activator of ADH. If there is low osmolality, the ADH should decrease..BUT because of the low blood volume, the baroreceptors tell the brain to increase ADH. The body would rather have a normal blood pressure than normal osmolality; ie there is non-osmotic ADH release

Question: If you have a non-osmotic activation of ADH, will aldosterone decrease causing hyponatremia?

Answer: These are two different issues. Aldosterone has absolutely nothing to do with water. It only affects Na. ADH has nothing to do with Na, it only affects water.

Question: If you have a volume depletion which causes hyponatremia, wouldn't you have ADH and aldosterone working and balancing each other?

Answer: Yes. If a person has heart failure with an inadequate pump, they will have non-osmotic AVP release and poor renal blood flow activating the aldosterone system which will conserve salt and water. The final serum Na concentration is a result of the amount of salt and water taken in. If they take in equal amounts of salt and water, then the concentration will stay the same and the volume will expand. If they take in more water than salt, the serum osmolality decreases.

8. If you are volume depleted, does the kidney quit working?

- a. Not unless the volume depletion is profound. The kidney function (GFR) remains constant.
 - b. Something must happen at the glomerulus to keep GFR constant.
9. Glomerular autoregulation
- a. The kidney is going to do its best to keep GFR constant despite a change in blood pressure and blood volume. How?
 - b. The kidney can autoregulate because it has a unique circulation with a resistant arteriole on each side of the glomerulus.
 - c. The key to maintaining GFR is to keep perfusion pressure high enough in the glomerulus to maintain the filtration force.
 - d. If the renal blood pressure decreases, how do we keep the filtration force constant?
 - e. We vasoconstrict the efferent arteriole which is very angiotensin sensitive.
 - f. We vasodilate the afferent arteriole which is prostaglandin sensitive.
 - g. The net effect is vasoconstriction of the efferent end and vasodilation of the afferent end keeping the glomerular capillary pressure and, therefore, filtration force constant.
 - h. Kidney function (GFR) stays the same.
10. If normal GFR is 120 ml/min and renal plasma flow is 600 ml/min, the filtration fraction equals 20%. Otherwise stated as, 20% of the renal plasma flow became filtrate.
- a. In the volume depleted state, the GFR remains 120 ml/min but the renal plasma flow decreased to 480 ml/min.
 - b. The filtration fraction increased to 25%.
 - c. GFR is kept constant by making a larger percentage of the renal plasma flow filtrate.
 - d. What does that influence?
 - e. When the efferent vessel leaves the glomerulus, it becomes the peritubular capillaries in the cortex.
 - f. Anatomically, all of the glomeruli are located in the renal cortex. Eighty-five percent of the nephrons are cortical nephrons with very short loops of Henle.
 - g. The cortex gets 90% of the total renal blood flow. This enormous flow allows for huge rates of reabsorption. This is important because we make 180 L of filtrate per day and 2 L of urine. We therefore must reabsorb 178 L of filtrate each day. Reabsorption occurs primarily in the cortex.
 - h. What tells the capillary to reabsorb filtrate? Starling forces:
 - i. What factors increase reabsorption in the capillary? Low hydrostatic pressure and high oncotic pressure.
 - ii. If there is an increase in the percentage of the renal plasma flow that becomes glomerular filtrate, what happens to the hydrostatic pressure in the capillaries?
 - iii. Hydrostatic pressure has decreased in the peritubular capillaries.

- iv. What has happened to the oncotic pressure in the capillaries?
Remember that the filtrate is protein free, so all of the protein was left in these vessels.
 - v. The oncotic pressure has increased in the peritubular capillaries.
 - i. These factors favor reabsorption in the peritubular capillaries surrounding the proximal nephron segments. The proximal tubule is built for large amounts of reabsorption. The proximal tubule usually reabsorbs 55%, but now the PT might reabsorb 60%.
 - j. Is this a good thing? Yes, it helps the kidney hang on to salt and water more avidly. If you reabsorb more in the proximal nephron, less gets to the distal nephron. The distal nephron is built for fine tuning (not bulk reabsorption). If you deliver less filtrate to the distal nephron, it is more efficient at conserving salt and water.
11. The net effect:
- a. Urine osmolality will be very high.
 - b. Urine Na is very low because we are reabsorbing most of it.
 - c. Fraction excretion of Na should be very low, <1%.
 - d. What is the solute in the concentrated urine if you reabsorb all of the Na?
Urea
- E. Everything would be opposite with volume expansion.
- 1. We would shut off the renin-aldosterone-angiotensin system.
 - 2. We would turn on the ANP system.
 - 3. We would not have to autoregulate to keep filtration fraction up.
 - 4. We would decrease filtration fraction to keep GFR constant with the increased blood pressure.
 - 5. If you reduce filtration fraction, there will be a higher hydrostatic pressure and less oncotic pressure which does not favor reabsorption as much. The proximal reabsorption will decrease helping you to get rid of salt and water.
 - 6. The distal is not getting hormonal signals to conserve so it excretes the salt and water.
- VI. Renal syndromes
- A. Glomerular disease
- 1. The glomerulus
 - a. mesangium with capillary loops You must have normal capillary loops to make GFR.
 - b. Glomerular capillary wall is highly impermeable to protein
 - c. If you have a lot of protein in the urine, it had to get there across the glomerular capillary membrane (abnormal permeability).
 - 2. Nephrotic syndrome
 - a. Damage to the glomerular capillary wall to allow leakage of protein into Bowman's space.
 - b. Every other function of making GFR may be fine, so GFR can be normal with heavy proteinuria.
 - i. 4+ protein on a urinary dipstick measures albumin only.
 - ii. Albumin is the main serum protein that is kept inside the capillary with a size and charge barrier.

- iii. Albumin is negatively charged and represents the bulk of the plasma anion gap (normally 10-12meq/l)
 - iv. The glomerular capillary is negatively charged to limit albumin from being filtered.
 - c. If albumin can get into the urine, some other serum proteins can get into the urine as well such as lipoprotein.
 - d. Urinary findings would show 4+ proteins and no other abnormality.
 - e. The serum creatinine would be normal because GFR is normal.
 - f. What would be the effect of Na in this nephrotic patient?
 - i. The kidney would increase Na reabsorption so the patients are in positive Na balance. They are retaining Na and developing edema.
 - ii. The edema is mostly in the interstitium seen as pitting edema.
 - iii. Blood volume is usually normal.
 - iv. It is not well understood what signals the kidney to hang on to Na, but it does so, primarily by increased distal nephron sodium reabsorption.
 - g. Edematous patient with normal blood pressure and creatinine. Albumin is low in the serum because it is being leaked into the urine.
 - h. If a patient presents with normal blood pressure, normal urinalysis and extreme proteinuria, think nephrotic syndrome.
3. Nephritic syndrome
- a. -itic means inflamed.
 - b. A glomerulus that is inflamed has cytokines and inflammatory cells infiltrating it.
 - c. What is the effect of this? The inflammation will cause the capillaries to swell and decreased the capillary surface area which decreases GFR.
 - d. A nephritic patient typically has reduced GFR.
 - e. A swollen, inflamed glomerular capillary wall will probably not have normal permeability characteristics either.
 - f. What would you look for in the urine to tell you that the capillary permeability is altered? Protein
 - g. A nephritic person frequently has proteinuria also, but the amount being excreted is less because there is less filtrate being formed.
 - h. The urine dipstick would be 2+ protein which correlates to about 1-2 g of protein per day. A nephrotic patient almost always has more than 3 g/day and can have 10-20 g/day.
 - i. Nephritic syndrome = bad GFR, some proteinuria
 - j. With all of this inflammation in the glomerulus, what else leaks out of the capillary into the urine? RBCs
 - k. Blood gets into the urinary space with inflammation of the mesangium or the endothelial cells.
 - l. Nephrotic patient has no blood in the urine.
 - m. Nephritic patients can also have RBC casts.
 - n. What would happen to the salt and water balance in this patient?
 - i. Positive balance, “
 - o. Plasma oncotic pressure didn't change very much. Where is the extra salt and water going?

- i. It is being distributed evenly between the extracellular and intracellular space
 - p. If ECFV goes up, then blood pressure will also increase.
 - q. The nephritic patient is retaining salt and water and a bigger portion of it is staying in the plasma volume. These patients will have symptoms of vascular congestion: shortness of breath, neck vein distention and hypertension.
 - r. This is a very different presentation than the swollen up, nephrotic who is not the least bit vascularly engorged. Because they have lost a lot of albumin, more of the retained salt and water is in the interstitium.
4. Chronic renal insufficiency
- a. A patient presents who had an episode of acute glomerulonephritis 10 years ago that knocked out 50% of their nephrons. The disease then went into remission with no further inflammation.
 - b. What happens to the serum creatinine over 10 years? It increased meaning the GFR decreased.
 - c. How does the glomerulus react to loss of nephrons?
 - i. The kidney will do its best to maintain homeostasis.
 - ii. Every nephron left must excrete more to maintain homeostasis.
 - iii. The kidney increases the single nephron GFR by vasodilating the afferent arteriole and increasing glomerular pressure.
 - d. Overtime the glomerular hypertrophy eventually leads to injury of the capillary and loss of more nephrons in a positive feedback cycle.
 - e. The kidney then must work harder and loses more nephrons.
 - f. That is the disappointment of chronic renal insufficiency. Homeostasis is maintained with glomerular hypertension at the expense of losing more nephrons over time.
 - g. How does a CRI patient look?
 - i. Can they get rid of salt load? No
 - ii. A high salt diet (American) diet causes volume expansion and hypertension. The most common cause of secondary hypertension is CRI which is volume mediated and Na driven.
 - h. Treatment regimen
 - i. Low salt diet- if you cannot get rid of salt, then decrease intake to help balance the amount of Na that is retained.
 - ii. Protein restriction- Increase in protein causes vasodilatation of the afferent arteriole which will increase glomerular hypertrophy
 - iii. Eating less protein leads to less K and Phosphorus intake and less hydrogen ion production. Usually the amount of K and P in the diet correlates with the amount of protein. With less nephrons to get rid of P, it is a good thing to eat less P.
 - iv. If you eat more P than the body can get rid of, then serum P levels increase turning on PTH. Hyperphosphatemia contributes to secondary hyperparathyroidism which will normalize Ca and increase P excretion with adverse side effects in the bones and muscles.

- i. CRI patient tends to be hypertensive and have an elevated serum creatinine.
 - j. The glomerular hypertension which causes disease independent injury will lead to focal segmental glomerular sclerosis (FSGS) which disrupts the capillary permeability. Even if the original disease was tubular, the disease independent injury will affect the glomerulus due to the earlier loss of nephrons.
 - k. What are the urinalysis findings?
 - i. Proteinuria (albumin) due to FSGS- not a huge amount because GFR is low
 - ii. No hematuria because there is no inflammation
 - iii. Casts? waxy casts (big, broad) which mean chronic disease. They do not tell you the cause of the disease, only that it is chronic. No RBC casts because the glomerulus is not inflamed. No lipid casts because the kidney is not nephrotic. No cellular casts because there is no inflammation.
5. Mesangial inflammatory process
- a. Inflammation in the mesangium only, sparing the capillary loops with immune complexes that are deposited in the mesangium causing some inflammation which does not affect the capillary loops
 - b. How will this affect GFR? The capillary loops are not affected so GFR is normal.
 - c. Will there be any proteinuria? No, the permeability of the capillary wall is not affected.
 - d. If the GFR is normal, then how do you know that there is inflammation occurring by looking at the urinalysis? Hematuria
 - i. Blood is the most sensitive marker of inflammation (even if it is only mesangial)
 - e. Serum creatinine is stable
 - f. What might the casts look like? RBC casts
 - i. RBC casts are pathognomonic for glomerular inflammation
- B. Tubular diseases
1. Without a functioning tubule, what happens to the glomerulus? It quits filtering.
 2. GFR will decrease with tubular and/or glomerular dysfunction.
 3. Acute renal Failure- What would be the affect on your kidney function of something that has damaged a bunch of tubules?
 - a. Kidney function = GFR, so if the tubules quit working, GFR decreases as well.
 - b. What happens to serum creatinine? It would increase
 - c. What would happen to the urinary output? If there was a complete loss of all of the nephrons, there would be oliguria. With a limited insult, urinary output stays absolutely normal.
 - d. What does urinary output tell you about GFR? Nothing
 - i. If there is oliguria or anuria, obviously GFR is in a sad state.

- ii. You can have severely reduced GFR and still be making an adequate urinary output.
- iii. Think about it- the tubule isn't reabsorbing well, but the glomerulus isn't filtering much either. Maybe only 14 L of filtrate was formed and the tubular could only reabsorb 12 L of the 14L so urine output looks normal.
- e. If this is an acutely damaged tubule, can it concentrate the urine well?
No.
 - i. Can it dilute the urine? No.
 - ii. So, what is the urine osmolality in this acute renal failure? The urine osmolality is equal to plasma osmolality because that is the concentration at which it was filtered. The plasma osmolality is 300 mosm/kg and the specific gravity is 1.010.
- f. Can the damaged tubule reabsorb Na efficiently? No, urine Na will be high. The fractional excretion of Na is high.
- g. Would there be proteinuria with a tubular injury? No, protein must come from the glomerulus. There may be some because it is difficult to damage tubules without damaging glomeruli, but it would only be a trace amount of protein.
- h. If this was a non-inflammatory injury to the tubular cells (for example, anoxic injury), would there be inflammatory cells in the urine? Not many
- i. Any casts? Granular casts that contain fragments of cells with Tamm horsfall protein
- j. If this was an inflammatory process that damaged the tubules (such as a renal transplant rejection or drug acting as a hapten), what would happen?
 - i. Decreased GFR
 - ii. Isoosmotic urine
 - iii. Fractional excretion of Na >1%
 - iv. Granular casts
 - v. Pyuria- a sterile inflammatory response in which neutrophils and eosinophils can be seen in the urine. This can be seen allergic interstitial nephritis.

C. Renal diseases

1. Glomerular OR Tubular
2. Acute OR Chronic
3. Inflammatory OR Non-inflammatory
4. Part of a systemic disease (SLE, DM) OR Disease confined to the kidney (renal transplant rejection)

VII. Acid/base balance

A. Approximations of H⁺ concentration and pH

1. Each time the H⁺ concentration doubles the pH will change by 0.3.
2. 7.70 = 20 nEq/L
3. 7.50 = 30 nEq/L
4. 7.40 = 40 nEq/L
5. 7.30 = 50 nEq/L
6. 7.10 = 80 nEq/L

- B. Think about acid/base balance in terms of people and their problems
1. If you change the arterial pH, either the acid changed via the lungs (carbon dioxide) or the bicarbonate levels changed Listen to the patient presentation, and consider what effect the history would have on the PCO_2 or HCO_3^- level.
- C. Acute Respiratory alkalosis:
1. If you are scared to death about taking the boards and you hyperventilate, the PCO_2 will decrease, decreasing acid acutely and causing a respiratory alkalosis.
 2. What organ will try to bring the arterial pH back to normal? The kidney (via HCO_3^- production and H^+ excretion).
 3. Can the kidney alter the pH quickly? No
 4. There will be only a small change in HCO_3^- acutely (~1-2 meq/l).
- D. Acute respiratory acidosis:
1. If you go out (after blocks of course) and get as drunk as an owl and quit breathing, your PCO_2 will increase causing a respiratory acidosis.
 2. What happened to the HCO_3^- ? The kidney hasn't had time to do anything yet, so the HCO_3^- will increase because the increase CO_2 shifts the equation to the right. $\text{H}_2\text{O} + \text{CO}_2 \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^-$
 3. Acidosis is due to the increase production in H^+
 4. Bicarbonate is a buffer so the change in HCO_3^- is very small, only 1-2 meq/L if normal is 24 meq/L.
- E. Chronic respiratory acidosis
1. If you have smoked like a stack for the last 40 years and develop chronic lung disease, you can't maintain normal PCO_2 .
 2. Because the abnormal PCO_2 is chronic, the kidney has had time to compensate by increasing HCO_3^- production (from 24 meq/L up to as much as 32 meq/L).
 3. How does the kidney do this? You always reabsorb the filtered load of HCO_3^- so there is another mechanism at work.
 - a. New HCO_3^- is produced by H^+ being pumped into the urine which exits as ammonium. The kidney upregulates its ammonia production to handle the extra H^+ .
 - b. Every H^+ that is excreted with NH_3 as NH_4^+ sends a HCO_3^- back into the blood.
 - c. Therefore, pH is only moderately increased rather than the large increase that is expected based on PCO_2 levels.
 - d. Acid leaves as titratable acids or ammonium. The amount of titratable acids is fixed whereas the amount of ammonium can be altered.
- F. Metabolic Acidosis
1. If you are out drinking again (celebrating after the boards) and start throwing up blood with a blood pressure of 60 mmHg, oxygen delivery decreases and lactate is produced via anaerobic metabolism.
 2. The patient has lactic acidosis. What happens to bicarbonate?
 3. HCO_3^- buffers the excess H^+ from lactate dissociation and the serum HCO_3^- levels decline.

4. What happens to the lactate? The kidney will conserve lactate because it is a nutrient and the kidney does not waste nutrients.
 5. How would you know that lactate was increased in the serum? Measure the plasma anion gap. Lactate is an unmeasured anion so the plasma anion gap will increase.
 6. We can suspect lactic acidosis from the patient's history and exam. We can confirm it with the plasma anion gap.
 7. What would the arterial pH be? Low
 8. How would the lungs respond to the low pH? Hyperventilate to get rid of acid (CO_2).
 9. How long does it take the lung to compensate? Seconds. You do not need to consider acute or chronic for metabolic disorders because the lung compensates instantaneously. The kidney is slower.
 10. You are taken to the emergency department and treated. Once the vital signs are normal, what happened to the acid/base problem?
 - a. Is there any need for anaerobic metabolism now? No, you will go back to aerobic metabolism
 - b. How do we get the HCO_3^- back up to 24 meq/L? The liver metabolizes the lactate. As lactate is metabolized a H^+ is consumed, which is equivalent to making a HCO_3^- . So, the HCO_3^- level goes back up, and we did not have to give any HCO_3^- .
 - c. What happened to the anion gap? It returned to normal with the lactate decrease.
 11. If you run the 200 meter dash and get transient lactic acidosis, the acid/base disorder returns to normal as soon as ventilation and perfusion return to normal.
- D. Metabolic acidosis by losing HCO_3^-
1. If you had a defect in the proximal tubule, you could not reabsorb HCO_3^- and you would lose it in the urine. This is not very common in adults.
 2. You can lose HCO_3^- via the GI tract because most of the GI secretions contain HCO_3^- (after the stomach).
 - a. Loss of HCO_3^- will cause metabolic acidosis (i.e. with diarrhea)
 - b. If you are vomiting, you will lose H^+ from the stomach and become alkalotic.
- E. Metabolic alkalosis
1. If you are "throwing your toenails up," what should the lung do? Decrease ventilation.
 2. The lungs cannot compensate precisely for metabolic alkalosis, because the lungs can only decrease ventilation to a certain point before hypoxemia would occur. (carbon dioxide is rarely $>55\text{mm Hg}$, even with severe metabolic alkalosis..)
 3. in contrast, you can hyperventilate very precisely and efficiently, reducing to as low as PCO_2 of $\sim 15\text{ mm Hg}$.

An aside that Dr. Wall just remembered: If clinical signs suggest lactic acidosis with a pH of 7.30 and a pCO_2 of 40 mm Hg, the patient has metabolic and respiratory acidosis

because the lungs did not respond to the lactic acidosis by increasing ventilation. Failure to ventilate appropriately is respiratory acidosis.