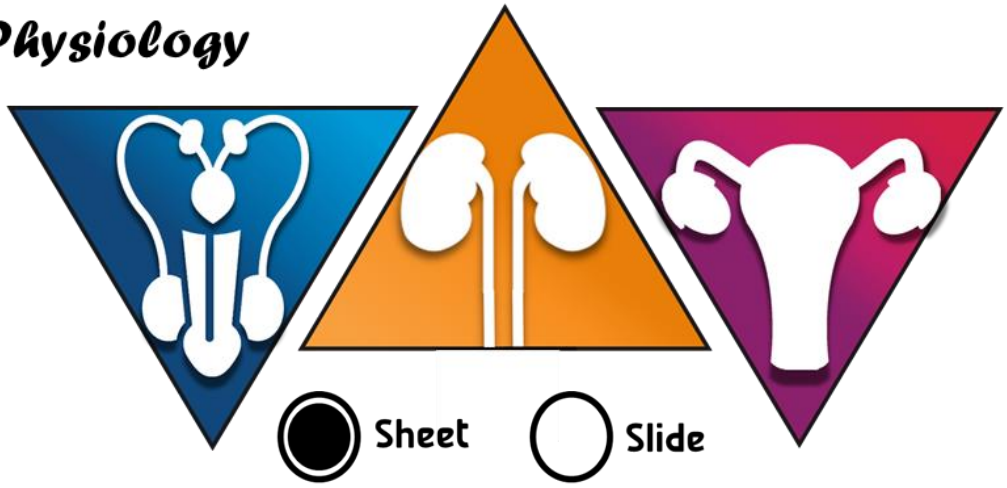
Urogenital system

Physiology



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Potassium balance in the body

The maintenance of potassium balance is essential for normal function of excitable tissues (nerves, skeletal muscles and cardiac muscles).

The potassium concentration gradient across excitable cell membranes sets the resting membrane potential (RMP), also changes in RMP alter excitability by opening or closing the sodium channels, which are responsible for the upstroke of the action potential.

Most of the total body potassium is located in the **ICF** (98%) and 2% is in the extracellular compartment. The concentration of potassium normally inside the cell = 150 mEq/L, and outside the cell = 4 mEq/L, this concentration gradient for potassium is maintained by the **Na-K ATPase** that is present in all cell membranes. This concentration gradient should be constant (potassium homeostasis), so if the intake increases, the excretion should increase too but this situation is applicable to a certain concentration, after this concentration, the potassium will accumulate in the blood which is very dangerous, the renal mechanism allow for excretion of the excess potassium as urinary excretion of potassium must be equal to potassium intake.(dietary potassium intake can vary from low as 50 mEq/day to as high as 150 mEq/day.)

Neuronal cell at rest has more permeability for K+ than for Sodium, so the equilibrium potential (Ek) for potassium determines the resting membrane potential in this cell; we can calculate Ek by using **Nernst's equation**:

Ek = -61 log ([k] inside / [k] outside)

If the potassium channels open, the potassium will move down its concentration gradient so it will go outside of the cell but this will generate negative charge inside the cell (because we are removing positive charges from inside the cell so what is left is negative), and this negative charge will prevent further removing of potassium to outside of the cell (keep the rest inside); so we conclude that there are two forces that control movement of potassium across the cell membrane:

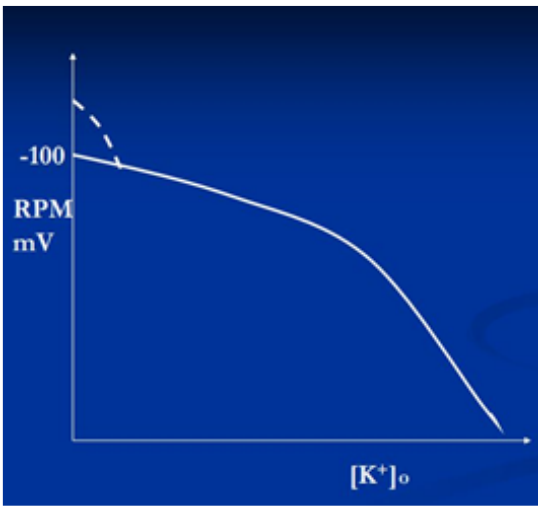
1- chemical gradient (favors outflux)
2- electrical gradient (favors influx)

When these two forces are equal; the potassium reaches its Ek; Ek = -61 log (150/4) = -90 mV and this is the resting membrane potential in cardiac cell (ventricular cell).

Note: in the peripheral neurons the resting membrane potential is less negative than the cardiac cell (around -60mV); but why? Because there is sodium contribution here (Sodium contributes in the resting membrane potential in these cells and when it gets inside it makes the resting membrane potential less negative).

So what happens if the K+ concentration outside the cell becomes more? to answer this question you should know first that the fast (voltage-gated) Sodium channels are in one of three states; open, closed active (capable of opening upon stimulation) or closed inactive. In the resting membrane potential of -90mV for example, the channels are closed and active, and it will become open when the stimulus reaches the threshold, after that, when the action potential becomes less negative and closer to zero it will become closed and inactive; the fast channels are now cancelled and the only working channels are slow sodium channels (during repolarization), when potential is back to resting membrane potential the channels will be in closed and active state again. But what is the relation of this with potassium?

When potassium concentration outside the cell becomes more (**hyperkalaemia**), the resting membrane potential is less negative and closer to zero (this is the same thing that happens in repolarization); so the fast sodium channels will be cancelled (closed and inactive) and slow sodium channels will only remain, so depolarization in cardiac muscle will be slow and this will lead to arrhythmias and cardiac arrest.



This graph from the slides demonstrate the relation between the concentration of K+ outside the cell and the resting membrane potential.

Cardiac muscles are in **syncytium**, Phase zero (Depolarization) of the first cell is so fast and is followed by the depolarization of the next cell by gap junctions (normally work by fast sodium channels), so the depolarization will move from the first cell to the last one in NO TIME.

Also, a decrease in [k+] outside the cell (**hypokalaemia**) is not good; it will increase the RMP and this will decrease excitability of the cell (more negative, away from threshold) and this will lead to paralysis. So the most important thing that we as doctors are afraid of in renal failure is an increase in potassium concentration in blood.

Note: Some people with renal failure have normal concentration of sodium; logically sodium will increase with renal failure, but also water excretion decreases and thus maintaining the same sodium concentration in the blood, however, they will have hypervolemia instead.

Normal K+ concentration in blood that should be maintained = 3.5-5.5 mmol/L. Potassium concentration is normally 4 mmol/L, if it exceeds 7 mmol/L, cardiac arrest will happen in the same mechanism we talked about. If a patient comes with K+ levels above 7 you go for an ECG, if there are any ECG changes, go for dialysis immediately (The purpose of this dialysis is the removal of K+ mainly, not urea or Creatinine).

Note: equivalent= number of moles* number of charge; in potassium=1 mol*1=1 so when we say 1mmol/L it is the same as we say 1mEq/L.

Daily intake of potassium in average is 100 mmol and the output is absolutely 100mmol but how? 95mmol is excreted by the kidneys and 5 mmol by other routes (GI, sweat…etc.), so the kidney is the major contributor for potassium excretion (by filtration or by secretion). If we have a meal with 50 mEq of potassium; the potassium will distribute in extracellular fluid in general by 50mEq/14L of extracellular fluid= 3.5mEq/L.

So in the blood, its concentration will be 4mEq (constant in the body) +3.5mEq (that we took from the meal) =7.5 mEq/L >>> arrhythmia and cardiac arrest will happen! But this situation is not compatible with life, it is not logical that death will happen if we eat anything with potassium! (we said that 100meq is the daily intake; how come 50meq cause death?), So our body will secrete **insulin** after the meal intake that will work on glucose and potassium and pushes potassium inside of the cell by activity of Na-K pump, instead of being outside the cell which is dangerous as we said, so inside the cell; the concentration will be 150(normally)+3.5(form meal) =153.5 mmol/L which is not a problem

because the cell will get rid of this extra potassium toward the blood slowly (instead of rising [k+] outside the cell form 4 to 7.5 suddenly; the cell with help of insulin will rise it form 4 to 4.1 or 4.4 mEq/L of blood which is compatible with life and then it will be excreted by the kidney without any problem).

Remember: total body water is 60% of the body weight, so if a person weight = 72 kg then his total body water amount is 42L; 28L intracellularly and 14L extracellularly (plasma and interstitial fluid). For plasma it is 3 litres and for the interstitial fluid it is 11 litres, from this 11 litre, 1 litre is free water and 10 litres as gel, the 1 litre free water is for conditions like bleeding to be quickly absorbed.

Potassium excretion by the kidneys:

Filtration load= GFR*[K+] in plasma,

GFR=125ml/min; 125*60min*24hour ml = 180000ml/day >>180L/day

Filtration load for potassium with 100mEq ingestion of K+ per day=180 L/day * 4mEq/L (our aim is to maintain this concentration in plasma) =720 mEq/day (in bowmen space).

We said that of this 100 mEq ingested per day; 95 mEq (95%) is excreted by the kidney, and 5 mEq (5%) is excreted by other routes. But how does this 95 mEq, as in our example, get excreted by the kidney? first of all to answer this question we should know that 65% of filtration load gets reabsorbed in proximal tubules, , zero reabsorption in descending limb of Henle and 25% reabsorbed by thick ascending limb of Henle. (90% is the total reabsorption) >> Reabsorption portion from 720 mEq filtration load is = 90% = 648 mEq/day reabsorbed by these routes. What is remained for excretion is 10% from filtered load = 10%*720=72 mEq/day (for simplicity we usually say 70) >>> 70 mEq of potassium is excreted by filtration per day form kidney. BUT, we said that we should excrete 95 mEq per day form kidney to urine! So, there is 25 mEq of this 95 mEq of potassium (of 100 mEq potassium intake per day) gets secreted per day in distal tubules by the help of **aldosterone**, so the net becomes 95meq in urine as we said and potassium homeostasis achieved.

Aldosterone works on principle cells of distal tubules to increase the reabsorption of Na+, and secrete K+ toward the lumen. **Notice that 70 mEq that we get from filtration does not change (constant), we can only manipulate the secreted part (increase it or decrease it according to our daily activity).** For example: if I eat a meal with 200 mEq potassium; I will get rid of this entire amount by two ways; 95% by kidney, and 5% by other routes. Of that, 95% =190 mEq is excreted by kidney; 70 mEq (constant) by filtration, and the rest, which is 120 mEq, is excreted by secretion (increased by increasing intake).

Difference between Na+ and K+:

Remember that Sodium get filtered and reabsorbed without secretion; while Potassium is affected by all three mechanisms: filtration, reabsorption and secretion.

Aldosterone affects principle cells in proximal tubules by:

1- Increase transcription of enzymes that generates ATP.

2-Generates Na+/k+ pump in basolateral surface of principle cell.

3-generates Na+ and k+ channels in luminal surface.

We all know that the concentration of sodium outside the cell is higher than inside the cell, and the opposite is for potassium, So to move potassium from plasma to principle cell we need a pump, and then from the cell to lumen (urine) we need a channel (passive diffusion). For sodium, to move it from the lumen to the cell (absorption) we need channel (that is why we have k+ and Na+ channels in luminal surface) and then from the principle cell to plasma (or interstitium) we need pump (that is why we have pump on basolateral surface). So in all, it will increase Sodium reabsorption and Potassium secretion.

How can I increase potassium secretion in the distal tubules? By Increasing Na-K pump activity and inserting K and Na channels in the luminal surface, these two mechanisms are dependent on aldosterone. Another way for increasing K secretion is by increasing flow through the distal tubules we can increase the flow by using diuretics, but how? Using diuretics will wash the potassium that is newly secreted form principle cells; and by that, it keeps the gradient difference across the membrane (between the cell and lumen) so more secretion of potassium will happen. >>> So diuretics (some of them) are potassium wasting agents, especially the first two groups; thiazide and furosemide.

In some cases these agents could lead to hypokalemia, if this happens we should compensate the loss of K by food or Aldosterone antagonist (potassium sparing agents).

-**Mannitol** a glomerular filtration marker is also osmodiuretic, **glucose** in high concentrations can become also osmodiuretic, that's why in diabetic patients it result in polyuria that leads to polydipsia. (osmodiuretic means it is able to reabsorb water and result in diuresis).

Diabetic ketoacidosis:

-Life threatening complication of diabetes type 1, especially in children.

-It results from H+ increase in the plasma which affects many enzymes activity especially in the CNS that could lead to coma and death.

-It leads to hyperkalaemia, as H+ exchange for potassium in the blood. As H+ enters the cells in exchange of potassium ions that will increase in the blood. It also inhibits the Na+-K+ pump which lead to more hyperkalaemia.

-We give the patient insulin to treat hyperkalaemia and acidosis. The doctor said we should give it with potassium supplements as potassium will be decreased severely by the administration of insulin.

-We need to check the blood every hour in search for hyperkalaemia and acidosis (we need arterial blood gas analyser for acidosis).

Concentrated urine formation

-Almost 1000 mOs/day waste products must be excreted from the kidneys in a normal healthy adult with normal diet and normal physical activity. These 1000mOs is a mixture of different materials as: Urea, Na+ (150 mOs), K+ (100 mOs), creatinine and other substances.

-Kidney can concentrate urine up to 1400mOs/L

-In hospitalized patients 700 mOs/day will be excreted from the kidneys, so the **minimum obligate urine output must be not less than 0.5 L/day or 20ml/hour**, this is important because in hospitalized patients we should check the urine output every hour and not wait a whole day because if there was an underlying problem we should know it early. Less than 20ml/hour will result of oliguria (decrease in urine) and renal failure.

- The urine is normally hyperosmolar (twice as much as the plasma).

-Other animals have the ability to concentrate urine differently depending on their environment and the structure of their kidneys. For example desert animals could concentrate about 10000 mOs/liter, other animals as fish does not need to concentrate the urine and the concetration of their urine will be very small.

-if you drink a sea water which has an osmolarity about 2400 mOsm/L then how much excretion will be? 1000 (normally you can make)+ 2400 (from sea water you drink)= 3400 mOsm; so the litters we need here are (3400/1400=2.4 litter) which is huge amount of water; because of that you get dehydrated after sea water drinking, and start drinking a lot of water to compensate.

- Minimal renal obligatory output is different from person to person depending on age, weight and other factors. For children it is less than adults (less than 0.5 Litre) .There is an equation to determine the minimal renal obligatory output that takes these factors into consideration, which = 300ml/m2 surface area/ day

Example: for an adult person with 1.5 m2 surface area, the minimal renal obligatory output will be 450 ml/day (approximately 500 ml / day as we said). A person with 2 m2 surface area the minimal renal output will be 600ml/day.

-**Oliguria < 300ml/m2 surface area/day**.

-Knowing the minimum renal output is important to indicate oliguria and thus a probable acute renal injury.

Water reabsorption:

-125ml/min of water is filtered in Bowman's capsule, 65% is reabsorbed in the proximal tubules, 15% in the descending loop, 0% in the thick ascending loop, 10% in the distal tubules and almost of the rest 10% in the collecting ducts. (I said almost because about 0.5-1% is excreted in the urine). The reabsorption in the collecting ducts is the most important because it is regulated by ADH which increase water reabsorption by inserting water channels in the collecting ducts. When ADH is absent you make large amount of diluted urine and if the ADH is present you make small amount of concentrated urine.

Urine formation:

-Urine could be hyperosmotic or hyposmotic depending on the presence of ADH.

-Production of Hyperosmotic Urine By definition urine has an osmolarity that is higher than blood osmolarity. Hyperosmotic urine is produced when the circulating levels of ADH are high, as occurs in water deprivation or in SIADH (syndrome of inappropriate ADH).

The following steps are involved in producing hyperosmotic urine:

1. The osmolarity of **glomerular filtrate** is identical to that of blood, 300 mOsm/L, because water and small solutes are freely filtered. The osmolarity remains at 300 mOsm/L along the entire proximal convoluted tubule, even though a significant volume of water is reabsorbed. This

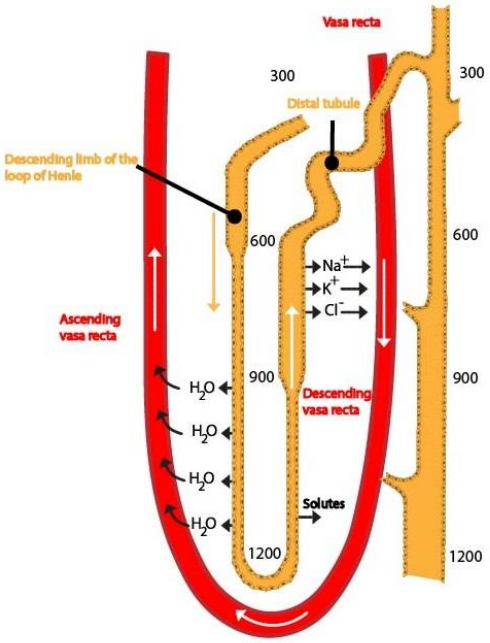
occurs because water is always reabsorbed in exact proportion to solute; that is, the process is **isosmotic**.

2. In the thick ascending limb of the loop of Henle, NaCl is reabsorbed via the **Na+ -K+ -2Cl− cotransporter**. However, because the cells of the thick ascending limb are impermeable to water, water reabsorption cannot accompany solute reabsorption. As solute is reabsorbed, water is left behind and the tubular fluid is diluted. The osmolarity of tubular fluid leaving this segment is 100 mOsm/L. Thus the thick ascending limb also is called the **diluting segment**.

3. In the early distal tubule, NaCl is reabsorbed by **an Na+ -Cl− cotransporter**. Like the thick ascending limb, cells of the early distal tubule are impermeable to water and water reabsorption cannot follow solute reabsorption. Here, the osmolarity of tubular fluid becomes even more dilute, as low as 80 mOsm/L. Thus the early distal tubule also is called the cortical diluting segment (cortical because the distal tubule is located in the cortex, rather than in the medulla where the thick ascending limb is found).

4. In the late distal tubule, the principal cells are permeable to water in the presence of **ADH**. Recall that the fluid entering the late distal tubule is quite dilute, 80 mOsm/L. Because the cells are now permeable to water, water flows out of the tubular fluid by osmosis, driven by the osmotic gradient across the cells (i.e., is reabsorbed). Water reabsorption will continue until the tubular fluid equilibrates osmotically with the surrounding interstitial fluid. The tubular fluid leaving the distal tubule is equilibrated with the interstitial fluid of the cortex, and it has an osmolarity of 300 mOsm/L.

5. In the collecting ducts, the mechanism is the same as that described for the late distal tubule. The principal cells of the collecting ducts are permeable to water in the presence of ADH. As tubular fluid flows down the collecting ducts, it is exposed to interstitial fluid with increasingly higher osmolarity (i.e., the corticopapillary osmotic gradient). Water will be reabsorbed until the tubular fluid equilibrates osmotically with surrounding interstitial fluid. The final urine will reach the osmolarity present at the tip of the papilla, which almost is 1200 mOsm/L.



-The ability of making concentrated urine

ADH is the key in making hyperosmotic urine in certain parts of the nephron, the most important part is the collecting ducts for determining urine concentration. A process of making hyperosmotic Interstitium that only takes place in the inner medulla between the collecting duct and the ascending thick limb.

In the ascending limb a process called the **single effect** which permits Na+, Cl-, and K+ reabsorption to the interstitium without being accompanied by water. In the collecting duct urea reabsorption occurs.

The reabsorption of urea and ions results in a **hyperosmotic Interstitium of 1400mOs**. The reason for making hyperosmotic Interstitium in the concentrated urine formation is to help reabsorb water, as water channels are inserted in the collecting duct under the effect of ADH and the hyperosmotic interstitium aids in water reabsorption.

The inner medulla is the only place where urea reabsorption occurs as urea is poisonous and should be excreted.

Urea will be less in vegetarian people so the osmolarity othe hyperosmotic interstitium will be less almost 900mOs rather than 1400mOs.

This whole process depends on ADH presence. In the absence of ADH hyposmotic urine will be formed (almost 50mOs/liter) and that means if we want to excrete the 1000mOs from our body we will need 20L of urine. And that what happens in **diabetes insipidus** as the posterior pituitary is unable to make ADH due to many factors commonly after head injury.

Acute kidney injury (AKI):

- Acute kidney injury (AKI), previously called acute renal failure (ARF), is an abrupt loss of kidney function that develops within 7 days. Its causes are numerous. ... People who have experienced AKI may have an increased risk of chronic kidney disease in the future.

-There are five stages for AKI, expressed in the word RIFLE.

1-**R**isk.

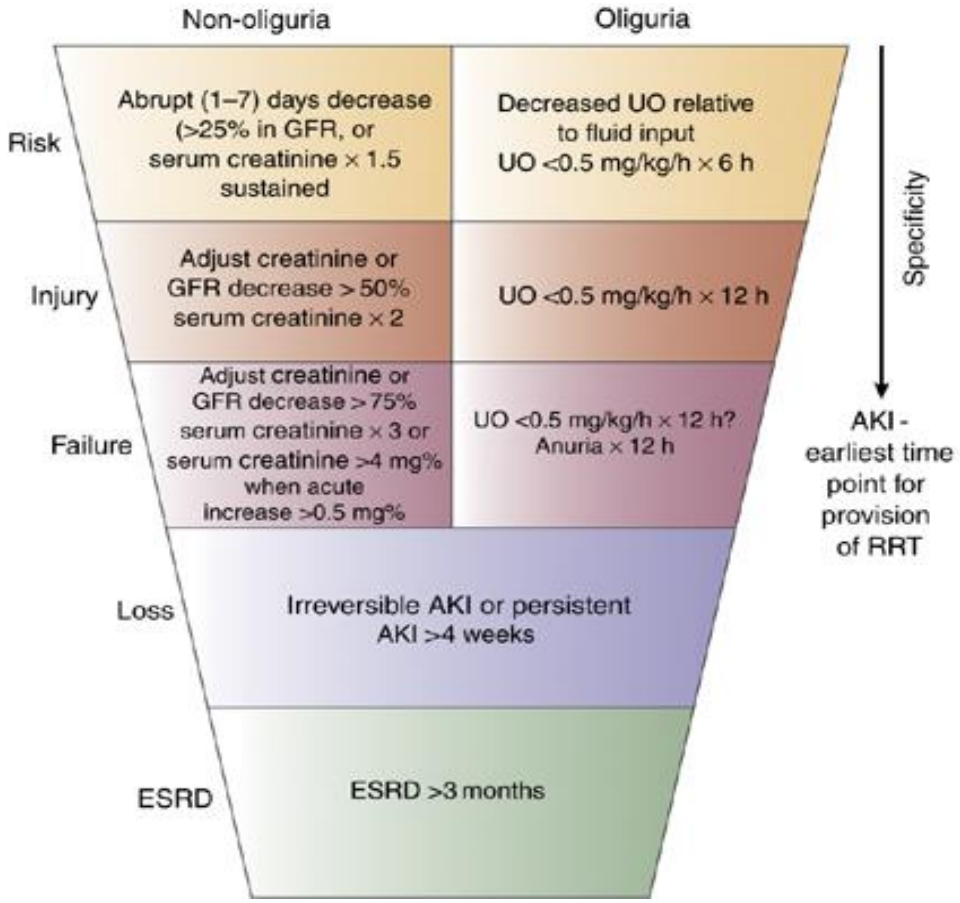
2-**I**njury.

3-**F**aliure.

4-**l**oss.

5-**E**nd stage renal disease (ESRD).

RIFLE defines three grades of increasing severity of acute kidney injury – risk (class R), injury (class I) and failure (class F) – and two outcome classes (loss and end-stage kidney disease).



(The doctor said that these stages are not for memorization).

The most important thing to know is the criteria for AKI which is :

- the creatinine plasma concentration
- and urinary output.

An increase in the creatinine plasma concentration and a decrease in the urinary output will indicate renal injury.

-Types of AKI:

1-**prerenal**: it means a problem in the blood flow to the kidney, the kidney itself is intact. The blood flow could be interrupted due to many causes as hypertension, hypotension, bleeding, etc.

The indication for prerenal injury will be low Na+ in the urine as the kidney reabsorb sodium to save water as the kidney indicates a problem as bleeding for example.

If the prerenal injury is not treated it could lead to intrarenal injury

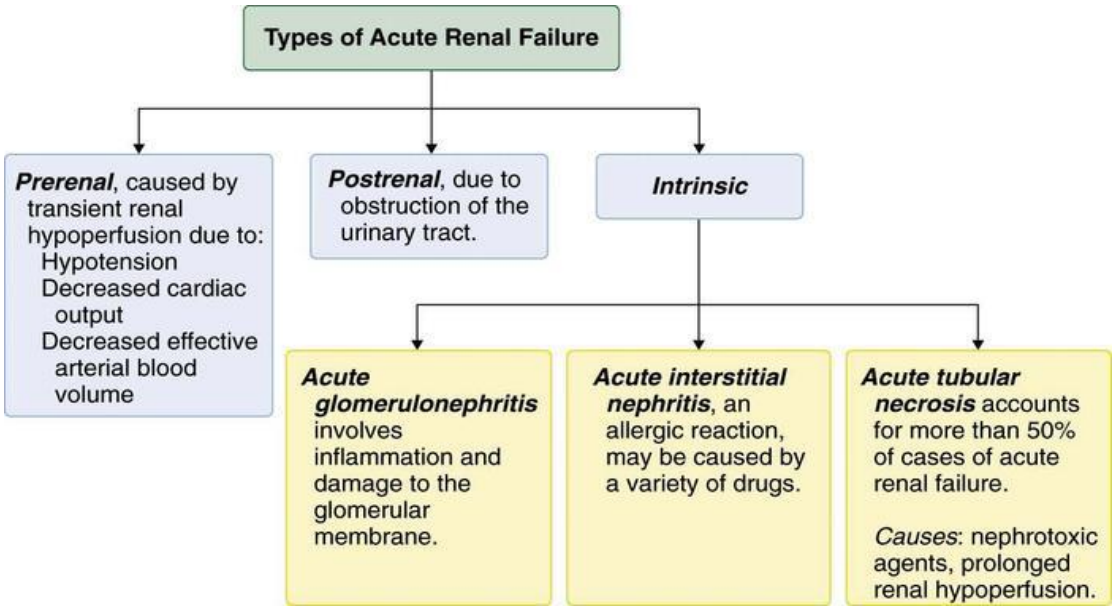
2-**intrarenal**: also called **acute tubular necrosis** that could result from certain medications as gentamycin, mercury and other nephrotoxic drugs.

Na+ will be high in this type of injury.

3-**postrenal**: as in kidney stones, it could result in urine flow obstruction Depending on the location of the stones if it is in the bladder it will affect both kidneys. Prostate hypertrophy could affect both kidneys too.

Painful kidney stones are called benign stones as it helps in early diagnosis and treatment in contrast to painless stones which are also called malignant.

-90% of acute renal injury is caused by the first two types and 10% is due to postrenal injury.



-Acute renal injury in general:

0.3% in the population.

3% in hospitalized patients.

30% in ICU patients.

-The best test for acute renal failure is to check if the kidneys could make concentrated urine. If osmolarity of urine is more than 1000mOsm/liter then the patient is fine and if it is less than 1000mOsm it could indicate a problem. To check for the urine osmolarity we need an osmometre which is not found in most hospitals, that's why we use another important test, **the specific gravity test**.

-A specific gravity test of 1.035 indicates a normal functioning kidney, as we take the last two digits and multiply it by 40 (35*40=1400), and a specific gravity test of 1.008-1.012 indicates a renal injury.