**Hyponatremia: classification**

An algorithm for investigations of hyponatremia:

1. **Measure Serum Osmolality**
   - **Hyper-osmotic**
     - Osmotic hyponatremia
       - Mannitol
       - Hyperglycemia
   - **Iso-osmotic**
   - **Hypo-osmotic**
     - Hyperlipidemia
     - Hyperproteinemia
     - Post – TURP hyponatremia

2. **Examine the Patients’ Hydration**
   - **Hypovolemic**
     - Urinary Sodium
       - over 20
       - Dry, with high urine sodium
         - Renal loss
           - Polyuric ATN
           - Chronic renal failure
           - Cerebral salt wasting
           - Excess diuretics
           - Mineralocorticoid deficiency
         - Extra-renal loss
           - Loss via the GIT
           - Loss via the skin
           - Abdominal loss, eg. sequestration in peritonitis or rapidly reaccumulated ascites
     - Under 20
       - Overloaded with high urine sodium
         - Renal failure, acute or chronic
     - Urinary Sodium
       - over 20
       - Dry, with low urine sodium
         - Extra-renal loss
           - Loss via the GIT
           - Loss via the skin
           - Abdominal loss, eg. sequestration in peritonitis or rapidly reaccumulated ascites
     - Under 20
       - Overloaded with low urine sodium
         - Heart failure
         - Cirrhosis
         - Nephrotic syndrome

3. **Hypervolemic**
   - Urinary Sodium
     - over 20
     - Euvolemic, high urine sodium
       - Renal failure, acute or chronic
     - Under 20
       - Euvolemic, low urine sodium
         - Polydipsia
         - Inappropriate IV fluid
     - Urinary Sodium
       - over 20
       - Euvolemic
     - Under 20

**How much sodium should there be?**

*Sodium deficit = 0.6 x body weight x (desired concentration -current concentration)*

In a 100 kg man with a sodium of 120mmol, when it ought to be 140mmol, the deficit is 1200mmol.
That’s about 8.5 litres of normal saline.

*From “Basic Assessment and Support in Intensive Care” by Gomersall et al, as well as “The Washington Manual of Critical Care” by Kellef et al, chapter 23, “Renal and Electrolyte Disorders” by Schrier and eMedicine article*
# Hyponatremia in summary

You find a low sodium in the blood results.
- Let's assume you know very little about the patient, and can't be bothered actually reading the notes.
- You order a urine sodium and a serum osmolality.

## The osmolality is high or normal
- Your patient either has **hyperglycaemia or high protein**.
  - They are unlikely to have **multiple myeloma or ridiculous hyperlipidaemia**
  - If they had **recent mannitol infusions or a recent TURP**, you should know about that.
    You might have overheard someone talking about it at hand-over.

## The osmolality is low
- You might actually have to think about this. Base it on the urine sodium.
- Either the urine sodium is going to be low, or high.
- THEN, maybe go and have a look at the patient. Are they wet or dry?

## The urine sodium is low
- **Extra-renal loss**:
  - Vomiting, diarrhoea,
  - Burns, peritonitis,
  - Ascites reaccumulating
- **Heart failure**
- **Cirrhosis**
- **Nephrotic syndrome**
- **Polydipsia**
- **Stupid IV fluid**

### Head Injury: you think, is it SIADH or cerebral salt wasting?
- In SIADH, the patient is well hydrated and oliguric
- In CSWS, the patient is dehydrated and polyuric

### Dehydrated and OLIGURIC: “renal success” rather than failure
- Overloaded and OLIGURIC
- Normovolemic and POLYURIC

## The urine sodium is high
- **Acute or Chronic Renal Failure**
- **Polyuric ATN**
- **Diuretics**
- **Cerebral salt wasting**
- **Mineralocorticoid deficiency**
- **SIADH**
- **Hypothyroidism**
- **Glucocorticoid deficiency**

### Overloaded and OLIGURIC
- Dehydrated and POLYURIC
- Normovolemic and OLIGURIC

From "Basic Assessment and Support in Intensive Care" by Gomersall et al, as well as "The Washington Manual of Critical Care" by Kollef et al; chapter 23, "Renal and Electrolyte Disorders" by Schrier and this eMedicine article
Hyper-osmotic hyponatremia

The evils of hyper-osmolarity

(serum osmolarity over 300 mOsm)

If a hyperosmolar solute is trapped in the extracellular fluid, free water will shift out of the cells and into the extracellular fluid.

Hyperglycemic hyponatremia

- Typically, in the setting of HONK or ketoacidosis, when the BSL is ridiculously high,

  For every 5.6 mmol/L of glucose, there is a 1.6mmol/L decrease in sodium
  sodium drops by 4 mmol/L at BSL 14,
  by 8 mmol/L at a BSL of 28,
  by 16 mmol/L at a BSL of 56

  …the relationship is not entirely linear, at BSL above 25 or so its more like 2.4 mmol sodium drop per 5.6 BSL

Mannitol hyponatremia

- This makes elegant sense because the whole point of mannitol therapy is to attract water out of the intracellular compartment, so as to reduce the oedema in brain tissue.
- Hyponatremia typically happens for the first few hours in a person with normal kidneys.
- Hypernatremia is the ultimate outcome because mannitol is a free-water-sucking osmotic diuretic.

From “Basic Assessment and Support in Intensive Care” by Gomersall et al, as well as “The Washington Manual of Critical Care” by Kollef et al, chapter 23, “Renal and Electrolyte Disorders” by Schrier and eMedicine article
Iso-osmotic hyponatremia

The confusing treachery of iso-osmolarity

(serum osmolarity around 275-290 mOsm)

This weirdness is the result of measurement artefact.

When you order an EUC

The plasma sample is taken to the biochem lab, and is diluted to 1/10th.

Then, this diluted result is run through either a flame emission spectrophotometer (i.e. it gets burned and the emission spectra measured), or run through an indirect ion-sensitive electrode.

Either way, the WHOLE PLASMA is used, not just the water fraction.

The amount of sodium found in this way is then “diluted” by calculation, with the assumption that it comes from a sample which originally consisted of 93% water.

Obviously, if you have 20% protein in that sample (eg. in multiple myeloma) then this assumption is false.

So, anything that causes there to be less water in your sample than the assumed 93%, will cause the test to show a falsely decreased sodium.

Iso-osmotic pseudohyponatremia

The abovedescribed measurement problem will confuse sodium measurements in the following conditions:

- High triglycerides (most common)
- High paraprotein (eg. multiple myeloma)

Post- TURP iso-osmotic hyponatremia: “TURP syndrome”

This bizarre complication can occur in as many as 5-10 TURP cases. It is due to absorption of irrigant solution through the distented urethra.

- In the course of a trans-urethral prostatectomy, small prostatic veins are cut. To keep the view clear, the irrigant solution needs to pump at pressure higher than venous pressure.
- THIS SOLUTION IS ISO-OSMOLAR: but it can’t be conductive, or the monopolar diathermy won’t work.
- The solution is made iso-osmolar by addition of glycine or sorbitol.
- As much as 6 litres of this crap gets infused into the periprostatic veins as the TURP is conducted.
- The bloodstream is thus inundated with glycine or sorbitol; these act in the same way as high lipids and high paraprotein, confusing the indirect ion-sensing electrode.
- This is a thing of the past: nowadays, progressive urologists use normal saline to irrigate, and a bipolar diathermy probe which doesn’t care how conductive your irrigant is.

From "Basic Assessment and Support in Intensive Care" by Gomersall et al, as well as "The Washington Manual of Critical Care" by Kollef et al, chapter 23, "Renal and Electrolyte Disorders" by Schrier and this eMedicine article
Hypo-osmotic euvolemic hyponatremia

Low urine sodium
You are just taking on extra fluid:
Your kidneys are normal, and they are trying to dump dilute urine, but you just keep on taking on more and more fluid, either because your insane, or the doctor gave you 10 bags of 5% dextrose.

Hypotonic fluid
(eg. 5% dextrose, toilet water)

The plasma is dilute, and there is more water than sodium

The urine is very dilute, there is a massive volume of it, and the sodium content is very low.

The kidneys are normal, and do a good job of concentrating the urine. If the intake of abnormal fluid stops, they will rapidly correct the hypo-osmolar state by getting rid of all the excess free water.

CAUSES
Psychogenic Polydipsia
Inappropriate maintenance or resuscitation fluids

High urine sodium
You are excreting an abnormal amount of sodium, but your kidneys can still conserve water somewhat.
Your kidneys can retain water, but can't stop dumping sodium. You either don't have enough tubules left to reabsorb the sodium (i.e. chronic renal failure), or you have too much ADH on board (as in SIADH).

Hypertonic fluid

The urine is concentrated, and there is not much of it.

Urinary sodium is high.

In SIADH, the natriuresis is a response to hypervolemia, and prevents volume overload or hypertension from developing. The urine is concentrated and its volume is low because the collecting ducts suck all the water out of it through ADH-activated aquaporin channels.

In renal failure (acute or chronic), the urinary sodium is high because the tubules are unable to reabsorb it (either they are too hypoxic, or there is not enough of them to cope). The urine is low volume and concentrated because the rate of fluid delivery to the nephron is low, and collecting ducts still suck all the water out of it (but there is not enough of them, and not enough delivered urine for them to work on, to maintain normal serum osmolality)

CAUSES

Common
SIADH
Acute or Chronic Renal Failure

Rare
Glucocorticoid deficiency
Hypothyroidism

SIADH

In SIADH, the plasma is dilute; there is too much free water because ADH is overproduced, and thus the collecting duct reabsorbs too much free water.

Acute or Chronic Renal Failure

In renal failure (acute or chronic), the plasma is dilute because there is not enough functioning collecting ducts left to excrete all the free water.

From "Basic Assessment and Support in Intensive Care" by Somersall et al, as well as "The Washington Manual of Critical Care" by Kollef et al, chapter 23, "Renal and Electrolyte Disorders" by Schrier and the eMedicine article
High urine sodium

This is a hyponatremia of increased renal losses. Losses of both water and sodium. Normally, you would want to conserve sodium in this setting. It’s a normal response to hypovolemia. If you are hypovolemic AND hyponatremic, there is all the more reason to conserve sodium. So, if you are hyponatremic, hypovolemic, AND losing more sodium, something must have gone wrong with all those sodium-defending and osmolality-defending mechanisms.

Cerebral Salt Wasting

In cerebral salt wasting, head injury abolishes sympathetic stimulation of proximal tubule sodium resorption, and releases brain natriuretic peptide which increase GFR, and inhibits aldosterone synthesis. The urine is thus very dilute, and full of sodium.

Plasma is dilute and the patient is dehydrated primarily because sodium is being dumped and water follows it.

Diuretics

Thiazides are notorious for this - they block resorption of sodium in the distal tubule. Mannitol and glucose act as osmotic diuretics. Either way, large amounts of sodium are excreted in a torrent of dilute urine.

Mineralocorticoid deficiency

Aldosterone activates the ENaC channel in the collecting duct, which causes resorption of sodium (and thus forces excretion of potassium). Loss of aldosterone, eg. Addisons disease, results in decreased sodium resportion, and increased potassium retention – thus the hyponatremia and hyperkalemia.

Polyuria Phase of Acute Tubular Necrosis

The proximal tubules and the thick ascending limb are the hardest hit. These are the ones where the oxygen tension is already low, and oxygen consumption high (most of the sodium transport happens there, and its all active ATP-dependent transport). So it’s little wonder that in ATN the damaged tubules are unable to reabsorb sodium.

In polyuric ATN, the plasma is dilute; this is largely due to a loss of sodium.

Chronic Renal Failure

In chronic renal failure which approaches the end stage, the renal tubules are too damaged to reabsorb sodium effectively. These people lack the capacity to concentrate urine (but they may still be able to dilute it). This is a mechanisms similar to the polyuric phase of ATN. These tubules are also unresponsive to aldosterone and ADH. This is not a very common complication of chronic renal failure, and their hyponatremia is typically hypervolemic.
This is a hyponatremia of increased EXTRA-renal losses. The findings reflect that the kidneys are compensating. That's right, it has been said that normally, any self respecting organism would want to conserve sodium in the setting of hyponatremia and conserve water in the setting of dehydration. With normal kidneys that’s exactly what you do in hypovolemic hyponatremia.

**Extra-renal losses** can be from the gut, the skin, into rapidly accumulating ascites, etc. Either way, the mechanism of loss typically results in hypovolemia, and the attempts to replace the fluid end up replacing too much free water, resulting in hyponatremia. Also, as a defence of osmolality (to prevent dehydration) ADH is secreted, which causes resorption of free water. The urinary sodium reflects the fact that sodium is being conserved.

**Hypo-osmotic hypovolemic hyponatremia with low urine sodium**

**Loss Via Burns**
- **Hypovolemia** is due to fluid shift into burnt tissue
- **Hyponatremia** is due to changes in cellular permeability: the heat-damaged cells absorb sodium from the ECF because the Na+/K+ ATPase no longer has enough ATP to keep the sodium out of the cells.

**Loss Via diarrhoea**
- **Hypovolemia** is due to net free water loss from the gut
- **Hyponatremia** is due to rehydration with hypotonic fluid; typically only Cholera and Shigella infections cause significant hyponatremia.

**Loss Via Rapidly Reaccumulated Ascites**
As ascites reaccumulates, the loss of intravascular volume is acted upon by the normal fluid and sodium conservation mechanisms.

The **cirrhotic patient is already hyponatremic**; the additional shift of fluid into the peritoneum also makes them hypovolemic. The kidneys attempt to compensate for this by reabsorbing sodium (thus the low urine sodium).

Treatment with spironolactone may actually turn this into a hypovolemic hyponatremia with normal or high urine sodium (because spironolactone blocks the sodium-reabsorbing actions of aldosterone in the collecting duct)

**Renal compensation**
To defend volume, osmolality and sodium concentration, the kidney focuses on reabsorbing as much sodium and water as possible.

**Sympathetic nervous system** causes the proximal tubule to reabsorb more sodium, leaving little for the distal nephron

**Aldosterone is released** which causes the ENaC channel to reabsorb what sodium is left in the collecting duct

**ADH is released** to defend osmolality, and increases aquaporin expression, causing water to be reabsorbed from the collecting duct.

The result is a concentrated urine with low urine sodium.

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From "Basic Assessment and Support in Intensive Care" by Comerota et al., as well as "The Washington Manual of Critical Care" by Kellef et al., chapter 23, "Renal and Electrolyte Disorders" by Schrier and the eMedicine article.
**Hypo-osmotic hypervolemic hyponatremia**

**Low urine sodium: oedema states.**

- **Cirrhosis:** The urine is concentrated and the patient is oedematous because there is too much ADH—there is no problem in the kidneys, as the ADH has not been metabolised. This is also why the patient is hyponatremic: the amount of free water retained is out of proportion to the retained sodium. The urine sodium is low because there is systemic vasodilatation and activation of the RAAS system, which leads to hyperaldosteronism, resulting in sodium resorption.

- **Heart Failure:** The urine is concentrated and the patient is oedematous again because of excess ADH—ADH is being secreted in response to the decreased cardiac output. The failing heart cannot mobilise the oedema, so on the other hand hand the patient is fluid overloaded. This is also why the patient is hyponatremic: the amount of free water retained is out of proportion to the retained sodium. The urine sodium is low because there is systemic vasodilatation and activation of the RAAS system, which leads to hyperaldosteronism, resulting in sodium resorption. The sympathetic nervous system responds to the reduced arterial filling by increasing sodium resorption in the proximal tubule.

- **Nephrotic syndrome:** Also, in this oedematous state the ECF volume is expanded, but the intravascular volume is reduced (as protein loss drives fluid out of the vessels and into the interstitial spaces). Thus, the kidneys avidly retain water and sodium because of the activated RAAS.

**High urine sodium: chronic renal failure**

Hyponatremia AND high urinary sodium always means something is wrong with the mechanisms of sodium defence. Chronic renal failure is typically where this happens. These are features of only end-stage renal failure.

- **The patient is oedematous,** because the kidneys are unable to excrete all that free water (not enough working collecting ducts).

- **The patient is hyponatremic,** because the kidneys are unable to reabsorb all the sodium it filters (as the few functioning tubules cannot reclaim it all effectively).

- **The urine sodium is high** because the kidneys are unable to conserve sodium, s too few functioning tubules are available.

- **The urine is concentrated and its volume is low** because the kidneys are unable to excrete all that free water (not enough working collecting ducts).

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