Diuretic Abuse and Electrolyte Imbalance

History of Presenting Illness

HYPOVOLEMIA
- Postural Hypotension
- Syncope (standing up too quickly)
- Light-headedness
- Dizzyness
- Confusion
- Drowsyness
- Lethargy
- Weakness
- Cramps
- Arrhythmias
- Polyuria
- Bradynoea (from alkalosis)

HYONATREMIA

HYPOKALEMIA

Differential Diagnoses of Hypovolemia:
- Extrarenal Na⁺ loss
  - Gastrointestinal (vomiting, nasogastric suction, drainage, fistula, diarrhea)
  - Skin/respiratory (insensible losses, sweat, burns)
  - Hemorrhage (?menstrual?)
- Renal Na⁺ and water loss
  - Diuretics
  - Osmotic diuresis
  - Hypoaldosteronism
  - Salt-wasting nephropathies
  - Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH)

Weird presentations due to abuse of a specific diuretic:
- DEAFNESS (from loop diuretics)
- GOUT (from thiazides diuretics)
- GYNACOMASTIA (from spironolactone)

MOST OFTEN SYMPTOMS ARE NON-SPECIFIC AND SECONDARY TO ELECTROLYTE IMBALANCE

DIMINISHED SKIN TURGOR and DRY MUCOUS MEMBRANES are poor markers of hypovolemia

Findings on History

Looking for any aetiological hint:

Has there been excessive...
- Vomiting
- Diarrhoea
- Urine output
- Sweating
- Blood loss
- Nasogastric drainage

Has there been any...
- ankle swelling
- muscle injury
- superficial burns

LOOK FOR END-ORGAN COMPLICATIONS:
- Palpitations
- arrhythmia
- tachycardia
- constipation
- seizures
- coma

ml blood loss 750 750-1500 1500-2000 >2000
% blood loss 15 15-30 30-40 >40
HR <100 >100 >120 >140
BP N N 80syst 60syst
Capillary refill N >2sec >>2sec >>2sec
Resp rate N 20 30 35
Urine ml/hr N 20-30 10 nil
Conscious N anxious confused lethargic

is there any history of...
- diabetes
- kidney disease
- alcohol abuse
- diuretic or laxative abuse
- psychogenic polydipsia
- anomalous salt-rich diet
- heart failure
- hyperaldosteronism
- Thyroid disease
Findings on Examination

MUST DEMONSTRATE HYPOVOLEMIA!

At the exam, one would be wise to mention
- skin turgor
- mucosal dryness
- peripheral perfusion

Otherwise:
Take blood pressure standing + supine
Take pulse standing + supine

Look for...
- Confusion
- Extremity weakness
- Nonfluent speech
- Dry mucous membranes
- Dry tongue
- Furrowed tongue
- Sunken eyes

Look at the heart sounds:
-may be arrhythmotic + dyssynchronous, with murmur?

Test for proximal muscle weakness
-normal distal power but proximal weakness = HYPOKALEMIA

Examine abdomen for ascites

Tests and Investigations

BUN: Blood Urea Nitrogen, [urea]
HIGH = AZOTEMIA (by definition)
= either increased protein catabolism or kidney malfunction
LOW = due to protein loss eg. nephrotic syndrome

Creatinine: measure of GFR
released from skeletal muscle at a steady rate; high level is associated with large muscle mass and exercise

Serum Biochemistry: expect ALKALOSIS
mainly interested in
- SODIUM
- POTASSIUM
- CALCIUM

Will all be low

TOTAL OSMOLALITY: should be
280 - 300
But in fact will be lower, ~ 270
(due to electrolyte-depleting action of loop diuretics)

Urinalysis
Tells you what is getting excreted; thus:
with diuretic abuse there will be lots of sodium + potassium

ECG: changes of hypokalemia:
- T wave flattening + splitting
- Depression of the ST segment
- Appearance of prominent u waves

Chest X-ray
Making sure that the ECG changes are not due to other pathology

Thyroid function tests
Hypothyroidism may mimic some of the presenting symptoms
TOTAL DAILY NORMAL LOSSES:
One and a half litres of urine

MASSIVE BLOOD TRANSFUSION?
Banked blood is ACIDOTIC (pH 6.7) and HYPERKALEMIC therefore….

ACIDOSIS WILL OCCUR!!
Thus, always give bicarbonate as well

FLUID REPLACEMENT RULES:
every casualty interns’ intracranial tattoo

NORMAL daily requirements of WATER: 2.5 to 3 litres = 35 to 40 ml per kg
Sodium 100 – 150 mmol
Potassium 70 mmol
Glucose : 100 grams per day is “protein sparing”
Chlorine: 210 mmol
Basic anatomy: WHERE ARE DEM KIDNEYS AT

**FACTOIDS**

- Gross size and weight (300-400 g) of kidneys (about 0.5% of body weight) in humans. BUT!! ~ 15% of the cardiac output!! THUS = most perfused organ by mass!!

A funny thing happened to me on the way to Anorexia:
Peri-renal fat depleted → kidneys drop in their position → ureters kink and become obstructed! THUS: ACUTE RENAL FAILURE

Superior poles are closer together

**THE LEFT KIDNEY IS ALWAYS THE HIGHEST**

Weighs 300-400g (0.5% of body weight) BUT gets 15% of cardiac output:
= MOST PERFUSED ORGAN BY WEIGHT

Pleural cavity is behind the kidney!
Abdominal vascular structures in PAINFUL DETAIL

The layers of fascia:
- FATTY = Campers
- MEMBRANOUS = Scarpas

HILUM is at L1
The KIDNEYS span T12 → L3

Horsehoe kidneys are always lower; @ L3-L5

Renal artery → segmental arteries → interlobar arteries → arcuate arteries → interlobular arteries → afferent arterioles → GLOMERULUS

Renal Vein ← Segmental veins ← Interlobar veins ← Arcuate veins ← Interlobular Veins ← Venules ← Peritubular capillaries ← Efferent arterioles ← GLOMERULUS

These are all END ARTERIES! = NO ANASTOMOSIS!

Fig. 42.6 The anterior surfaces of the kidneys.
UPPER AND LOWER URINARY TRACT

THE URETERS: 3 points most commonly obstructed:
@ the PELVIC RIM;
@ the BLADDER WALL ENTRANCE;
@ the RENAL PELVIS

STONES LODGE HERE! ➔ ➙ pain radiates to SCROTUM

THE URETHRA in CROSS SECTION

HIGHLY VASCULAR
ELASTIC LAMINA PROPRIA
Connective tissue
for reflection
Concentric smooth muscle
PARAURETHRAL GLANDS
open on each side of
the external urethral
opening
—Secret on ALKALINE FLUID

THE URINARY SYSTEM

COURSE OF THE URETER:
➔ over psoas
➔ around iliac vessels
➔ out, then in
➔ then post
➔ then ant

URETER is the MOST POSTERIOR STRUCTURE

The voluntary sphincter = pudendal nerve (S2-4 segments of spinal cord).
Sympathetic fibres (T11-L2)
= motor to internal involuntary sphincter
Parasympathetic fibres (pelvic splanchnic nerve, S2-4)
= inhibitory to internal involuntary sphincter

THE RENAL PELVIS IS FILLED WITH FAT

The voluntary sphincter = pudendal nerve (S2-4 segments of spinal cord).
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Parasympathetic fibres (pelvic splanchnic nerve, S2-4)
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**NORMAL FUNCTION:**

Blood → RBCs are filtered by endothelium

- **FENESTRATED ENDOTHELium:** free passage for all sizes of serum protein; Pores = around 400 → 375 angstrom

- **Lamina Rara Externa**
  - Lamina Rara Densa
  - collagen weave; pores = 40 angstrom negatively charged protein mesh repels negatively charged blood proteins

- **Glomerular Basement Membrane**
  - Heparan sulfate is responsible for the charge barrier; Type IV Collagen is responsible for the shape + size barrier

- **Podocyte foot processes**
  - like interlocking fingers: ARE NOT REPLACEABLE

- **@ TUBULE:** most low molecular weight non-polar proteins that get through this filter will end up being REABSORBED at PROXIMAL TUBULE by organic transporters

**Filtration Rate:** ~100 ml per minute; = Carefully controlled! Very steady between 90 and 200 systolic

**INCREASED BP** = reflex contraction of smooth muscle in afferent arteriole, thus reduced flow → GFR maintained at the same level

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**Mesangial Cell Function:**
- **Phagocytosis:** Remove trapped residues, keep the glomerulus free from debris
- **Provide Structural Support, + Contractility** (like smooth muscle) ← @ diabetic nephropathy: mesangial cell Ca++ release is inhibited, thus less contractility and hyperfiltration
- **Secret IL-1 and PDGF** in response to glomerular injury

**The Juxtaglomerular Apparatus:**
- Includes macula densa, juxtaglomerular cells and extraglomerular mesangial cells
- **Activates the Renin-Angiotensin System** in response to low sodium or renal ischaemia:
- **Macula densa cells** monitor the salt content of the afferent (incoming) arteriole:
- **Paracrine regulation of degranulation by juxtaglomerular cells which contain Renin granules**
- **Plus**: Macula densa controls Dilation + Constriction of Afferent Arteriole

- Nitrous Oxide @ afferent arteriole: ⇒ Dilation ⇒ Increased Filtration Rate
- Adenosine @ afferent arteriole: ⇒ Constriction ⇒ Reduced Filtration Rate
Mechanisms of concentration and solute handling

1) GLOMERULUS:
   - Free filtration of everything, thus ~300 mOsm/L.

2) PROXIMAL TUBULE:
   - Everything happens here!
   - Ions and organic molecules are sucked out actively.
   - This leads to a net movement of water out of the tubule.
   - Thus inside and outside remain isotonic.
   - About 40-30% of the filtrate left at this point (by volume).
   - Concentration still the same ~300 mOsm/L.
   - H+ is excreted here so as to join ammonium later.

3) DESCENDING LIMB:
   - Water-permeable but ion-impermeable.
   - This tubule descends into the solute-rich medulla (which has an ambient osmolality of ~1200 mOsm/L).
   - Medulla is so concentrated because its full of concentrated urea.
   - Thus: water wants to leave the tubule to dilute the medullary solutes.
   - This ultimately super-concentrates the tubular fluid.
   - About 15-20% of the filtrate left – at ~1200 mOsmol/L.

4) ASCENDING LIMB:
   - Impermeable to everything.
   - The ions are actively pumped out of the lumen but water can't leave the tubule...
   - Thus: Concentration decreases but the volume stays the same (15-20% at ~100 mOsm/L).
   - The ions involved are mainly Na+ and Cl-; urea now accounts for most of the osmolality.

5) DISTAL TUBULE + CORTICAL COLLECTING DUCT:
   - Potassium is secreted into the lumen here because aldosterone affects rate of sodium resorption.
   - And potassium secretion and thus potassium secretion here, + urea reabsorption.
   - Water will move out because the cortical collecting duct descends through the urea-rich medulla.
   - Thus: @ calyx the urine concentration may be anything between 100 and 1200 mOsm/L.

Stimuli to ADH release:
- Hyperosmolality
- Hypovolaemia
- Stress
- Nausea
- Hypoglycaemia
- Nicotine
- Morphine
- Other drugs
- Pregnancy

Inhibitors of ADH release:
- Hypo-osmolality (electrolyte loss)
- Hypervolaemia
- Ethanol
- Phenytoin

There's no active transport in the thin limbs.
Filtration and Reabsorption of Sodium

**Normal daily output** = 1.5 litres

**8.01**

100ml of fluid is required per 100 Cals consumed per day; plus:
- 3 mmol of Cl,
- 2 mmol Na,
- 1 mmol K

→ per kg per day

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**Glomerulus**

- **AFFERENT ARTERIOLE**
  - \(0.9 \text{ L/min}
  - = 20% of C.O.
  - = 0.5 \text{ L/min of actual plasma}

- **EFFERENT ARTERIOLE**
  - 80% returns to the blood
  - = cells, proteins etc.

**Ultrafiltrate**

- Na\(^+\) = 140 mmol/L
- Cl\(^-\) and HCO\(_3\)\(^-\) = 140 mmol/L
- K\(^+\), Mg\(^++\), Ca\(^++\), glucose = 10 mmol/L

**TOTAL OSMOLALITY** = 290 mmol/L

**HORMONAL MEANS OF CONTROL**

- **ANGIOTENSIN 2**
  - Sympathetic NS
  - High BP
  - more ECF volume
  - low plasma oncotic pressure
  - dopamine

- **ADH**
  - Prostaglandins
  - delivered load of Na\(^+\)
  - delivered load of Na\(^+\): !!! MACULA Densa located here!!
  - i.e. feedback to glomerulus (which is right next to the distal tubule) = if too muchNa\(^+\) in tubule, reduce GFR and vice versa (adenosine signal)

- **Aldosterone**
  - (increases EnaC activity)
  - ADH induces expression of AQUAPORINS on the membrane: like insulin for GLUT-4
  - Atrial Natriuretic Peptide
  - Glucocorticoids
  - prostaglandins

**H2O can cross** = follows Na\(^+\)

**H2O can cross**

- Na\(^+\), K\(^+\), Ca\(^++\), Mg\(^++\)

**Na\(^+\)**

- 25% of Na\(^+\)
  - EnaC channel blockers + Aldosterone Antagonists (amiloride)

- Electrically positive environment

**Early distal**

- 6% of Na\(^+\)
  - Carb. Anhydrase inhibitors, eg. acetazolamide: block H\(^+\) supply to Na\(^+\)/H\(^+\) exhanger

- **ThioZIDES**
  - Block Na, Cl cotransporter
  - mild but powerful in combination cause increased excretion of Na, K, Ca, uric acid, HCO\(_3\)\

**Cortical collecting duct**

- 2-3% of Na\(^+\)
  - **K-sparing Diuretics:**
    - EnaC channel blockers + Aldosterone Antagonists
    - (Spironolactone) (blocks aldosterone receptor @ cytoplasm)

**H2O can cross - but ONLY with ADH!!**

- (via aquaporins along osm. Gradient; not following Na\(^+\))

- **Principal cell**
  - If you block EnaC, there is no reason to for K\(^+\) to exit out
  - because its not too negative in the lumen and thus no gradient...

- **Intercalated cell** = acid/base balance
  - H\(^+\) = acid
  - Cl\(^-\) = base

**Back into circulation...**

**Filtration and Reabsorption of Sodium**

**Proximal tubule**

- Only 5 mmol of Na\(^+\) can be co-transported with organics as there is only ~ 5 mmol of organics in the ultrafiltrate:

- THUS some Na\(^+\) has to be exchanged with H\(^+\)
- PLUS some Na\(^+\) crosses via the tight junction

- = 65% of Na\(^+\) is removed in these ways

**Carbonic anhydrase**

- Na\(^+\), K\(^+\), Ca\(^++\), Mg\(^++\)

**H2O can cross**

- 2 K\(^+\) ATP
- 3 Na\(^+\)

**H2O can cross**

- Without a transporter! = via hydrostatic + oncotic pressures = “SHUNT PATHWAY”

**Normal daily output** = 1.5 litres

100ml of fluid is required per 100 Cals consumed per day; plus:
- 3 mmol of Cl,
- 2 mmol Na,
- 1 mmol K

→ per kg per day
ACID-BASE BALANCE and the kidney’s two cents in it
Two kinds of acid: NON-VOLATILE = NH4+ (60%), titratable acids (40%) and VOLATILE = CO2

LUNGS CORRECT METABOLIC ACID-BASE DISTURBANCES
KIDNEYS CORRECT RESPIRATORY ACID-BASE DISTURBANCES

Increased H+ = ACIDOSIS

BAD BUFFERING:
By proteins, which changes their function

“GOOD BUFFERING”:
HCO3− buffer: H+ ⇌ H2O, CO2 
Also by HEMOGLOBIN which sweeps up CO2

KIDNEYS GENERATE AMMONIA (NH3) and BICARBONATE HCO3−
ENZYMES must be generated, so there is a lag of 12-24 hrs

Intercalated cell @ collecting duct
AMMONIA BINDS H+ : Becomes AMMONIUM (NH4+) = is EXCRETED IN URINE

Decreased H+ = ALKALOSIS

BONE is a buffer for chronic acidosis: makes up as much as one third of the total buffering!
= release of mineral bicarbonate and mineral phosphate (MAINLY BICARBONATE)
THIS IS DANGEROUS: depletes integral elements of the hydroxyapatite matrix

Table: Reading Arterial Blood Gases:
1) Acidaemia or alkalaemia?
   Neither = mixed disorder or compensated

2) HCO3− and PCO2: both change
   IN DIRECTION OF pH = METABOLIC
   OPPOSITE TO pH = RESPIRATORY
   Change in opposite directions = mixed dz

3) BASE EXCESS:
   excess or deficit = METABOLIC
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Glutamine → glutaminase → Glutamate

Proximal tubule cell

Glutamine glutamase
Glutamate

→ tubule lumen
→ this way to ureter

Intercalated cell @ collecting duct

NH4+

Produced by carbonic anhydrase

ATP

H+ pumped by ATPase

Intercalated cell @ collecting duct

Increased H+ = ACIDOSIS

HCO3− retained

CO2 too low → Respiratory rate reduced (Rapidly, at a moments notice) → CO2 dissociates (until CO2 exceeds 55mmHg, when the medulla stimulates respiration again)

KIDNEY DUMPS HCO3− into urine: thus less alkali

AMMONIA BINDS H+ : Becomes AMMONIUM (NH4+) = is EXCRETED IN URINE

H2O

KHCO3−

KH2PO4

CO2

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NH4+
UREA SYNTHESIS AND METABOLISM: it is a product of amino acid breakdown, ammonia’s ticket out of you

Deamination @ the Liver
- Amino acid
- Aminotransferase
- Alpha keto-acid
  - Vit. B6
  - GLUTAMATE
    - H2O
    - NAD+
    - NADH+, H+
  - NH4+
  - Aspartate
  - Oxaloacetate
  - CO2
  - UREA

Detoxification @ the Liver
- (NH4+) is a cerebral toxin:
  - hepatic encephalopathy

50% Reabsorbed @ kidney (proximal tubule)
**Lecture: hypovolemia + hypervolemia**

8.01

### Intracellular
25-35% body weight

### Extracellular
20-30% body weight

### Intravascular
~7% body weight

### Extravascular
~20% body weight

#### Compensatory compartmental fluid shifts

- **Intracellular**
  - potassium
  - organic anions
  - bicarbonate
  - magnesium

- **Transcellular**
  - variable

- **Extracellular**
  - sodium
  - chloride
  - bicarbonate

### Ionic composition of body fluids

- **ICF**
- **ECF**
- **stomach**
- **diarrhoea**

### Normal daily maintenance requirements

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<th>Water</th>
<th>sodium</th>
<th>potassium</th>
<th>chloride</th>
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<td>1500 + 20/kg</td>
<td>100ml/100cals</td>
<td>1.5-2.5mmol/l</td>
<td>0.5-1mmol/l</td>
<td>2-3mmol/l</td>
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**eg for 65kg patient**

- **2400cals**
- **2400ml**
- **130mmol**
- **70mmol**
- **200mmol**

### Assessment of type of loss

- **Salt > water**
  - 
  - **S Na** (pre-treatment)
  - Fluid shift into cells
  - Falsely normal skin turgor
  - Early shock

- **Water > salt**
  - **S Na**
  - Fluid shift out of cells
  - More abnormal skin turgor

### Compensation for fluid loss:

- **water**: intracellular <-> extracellular (tonicity)
- **sodium**: intravascular <-> extravascular (Starling’s forces)

### Cardiac compensation
- force & rate

### Vascular compensation
- vasoconstriction
- vital organ protection (CNS)

### Renal compensation
- control of salt & water excretion

### Assessment:

- **History (unreliable guide)**
  - Blood pressure
  - Pulse rate and character
  - Mucous membrane appearance
  - Urine volume and concentration

- **Blood tests**
  - Hb/Hct
  - Plasma proteins
  - Blood urea

- **Urine tests**
  - SG/osmolality
  - **Na/K/Cl** concentrations
  - Creatinine concentration

### MANAGING:

- **Essential clinical information**
  - Initially, and repeatedly during fluid replacement
  - BP, pulse rate
  - Body weight
  - Clinical assessment of circulatory state
  - Clinical assessment of hydration
  - Observation of urine output

- **Essential laboratory information**
  - As early as possible
  - Blood: sodium, potassium, bicarbonate, urea, creatinine, total protein, haemoglobin
  - Urine: microscopy, sugar, ketones, sodium, potassium, osmolality, pH

### Management:

- **Phase 1**
  - Adequate restoration of circulating blood volume
  - Blood
  - Colloid plasma expanders
  - Crystalloid volume expanders - isotonic saline

- **Phase 2**
  - Appropriate further replacement and maintenance
  - once type of loss determined

### Replacement therapy in severe dehydration

- **Type and magnitude of loss**
  - **Phase 1**
    - Isotonic
    - 10% body wt
      - (100ml/kg)
    - Hypotonic
      - 7% body wt
      - (70ml/kg)
  - 2 hours

- **Phase 2**
  - Isotonic
    - 20-25% loss
      - (20-25ml/kg)
    - Hypertonic
      - (volume estimated from sodium)
      - (Na^+ - Na^+) x TBV%
      - eg (135-125)-0.5 x 10.6 mmol/kg
      - v=10/4 x 0.5 L/kg
  - 12-24 hours

### Crystalloid volume expanders

- Normal saline
  - 0.9% sodium chloride
  - (volume estimated from sodium)

### Acid-base equilibrium

- **Hydrogen ion concentration**
  - **pH**
  - **CO₂**
  - **bicarbonate**
  - **carbon dioxide**
  - **base excess**

### Sodium, potassium, bicarbonate, urea, creatinine, total protein, haemoglobin

### Blood: sodium, potassium, bicarbonate, urea, creatinine, total protein, haemoglobin

### Urine: microscopy, sugar, ketones, sodium, potassium, osmolality, pH

### Clinical assessment of circulatory state

### Clinical assessment of hydration

### Observation of urine output

### As early as possible

### Blood: sodium, potassium, bicarbonate, urea, creatinine, total protein, haemoglobin

### Urine: microscopy, sugar, ketones, sodium, potassium, osmolality, pH
Hypovolaemia
- Primary renal sodium retention
- Glomerulonephritis
- Acute renal failure

Hormone excess
- Conn’s syndrome
- Cushing’s syndrome
- SIADH

Disturbed Starling forces
- Increased venous pressure
  - (e.g. LVF, RVF, constrictive pericarditis, vena caval or portal vein obstruction)
- Reduced oncotic pressure (e.g. nephrotic syndrome)
- Combined abnormality (e.g. cirrhosis)

Summary
The composition of the body fluid compartments is held remarkably constant despite wide variations in solute and water intake. Homeostatic mechanisms can defend several simultaneous threats to this equilibrium.

Nevertheless, in debilitated hospital inpatients, disturbances of salt and water balance are common and can be life threatening. Understanding of the physiological processes controlling salt and water balance is essential to working out disturbances in clinical practice.

Separate consideration of disturbances of salt and of water balance is often needed to assist in deciding both volume and composition of replacement fluid for deficits.
**FACTOIDS:**

- Water = 60% of body weight
  - 33% of that is Intracellular
  - 27% is Extracellular
  - 20% is interstitial, and
  - 7% circulates (4.5% = plasma)

- Women drier than men (5% less total water)

**TRUTHISMS:**

- Urinary losses vary according to dietary intake (50-75 ml/100 Cals)
  - of these, 40 50ml/100 Cals are obligatory
  - + sweating = 1-50ml/100 Cals

- **WATER LOSS:**
  - **UNCONTROLABLE OBLIGATORY CHANNELS**
    - 1/3 through the lungs
    - 2/3 through the skin and stool losses
    - PLUS the kidney needs to excrete water to eliminate toxins, so here is some more water used as solvent and lost that way (also obligatory)

- **WATER GAIN:**
  - FOOD = (60-80% of food is water) as well as the water of oxidation

- **ABNORMAL GAINS AND LOSSES**
  - gain of water in excess of salt (hyponatraemic overhydration),
  - loss of salt in excess water (hyponatraemic dehydration),
  - gain of salt in excess water (hyperturamic overhydration),
  - or loss of water in excess salt (hyperuramic dehydration)

**TOTAL DAILY NORMAL LOSSES:**

- One and a half litres of urine

**FLUID HOMEOSTASIS**

Regulation of intracellular fluid: via ions (potassium INTRA, sodium EXTRA)

- maintained by Na+/K+ ATPase

- **Na+ reabsorption:** is @ whole tubule, but
  - 60% is @ proximal tubule
    - Na-H countertransporter (ANGIOTENSIN 2)
  - 25% is @ loop of Henle
  - 5% distal tubule
    - epithelial sodium channel (ENaC)
    - Na+/K+ ATPase (both = ALDOSTERONE)
    - also aldosterone simultaneously enhances secretion of potassium and acid
  - 4% collecting duct
  - **ANTIDIURETIC HORMONE**
    - influences collecting tubule
    - increases permeability via aquaporins
      - (thus more seepage into ECF from the tubule)
      - In states of water deficiency, ADH secretion is increased and aquaporins are inserted in the tubular epithelium and urine flow is decreased
  - **ATRIAL NATRIURETIC PEPTIDE**
    - inhibits Na+ resorption at the medullary collecting duct

- **WATER:**
  - Reabsorbed along with sodium in prox. Tubule
  - Reabsorbed alone in descending loop of Henle (where there is an osmolality gradient from tubule to medullary interstitium)
  - 99% of water is reabsorbed

**Rule of thumb:**

- 100ml of fluid is required per 100 Cals consumed per day
  - plus: 3 mmol of Cl, 2 mmol Na, 1 mmol K per kg per day

- hyponatraemic dehydration is always the result of initial isotonic dehydration followed by continued intake of water without salt:

- **ASSESSMENT**
  - **SEVERITY:**
    - 4% = mild
    - 7% = moderate
    - 10% = severe
    - beyond 10% = life threatening irreversible shock

- Magnitude of loss is assessed by observing blood pressure, pulse rate and rate of urine output, accurate measurement of body weight and assessment of the peripheral circulatory state and state of hydration

- **THE KIDNEY ALTERS EXTRACELLULAR FLUID VOLUME BY CHANGING Na+ CONCENTRATION**
  - thus:
    - increased blood volume
    - increased Na+ excretion, reduced reabsorption
    - thus increased H2O excretion,
**Pathological losses:**

**VISIBLE**
- from the gastrointestinal tract (mouth, fistulae, stomata, anus),
- kidneys,
- skin (e.g. burns),
- blood stream.

**HIDDEN**
- fluids sequestered around areas of inflammation (e.g. pancreatitis) or trauma (e.g. rhabdomyolysis),
- so-called third-spacing,
- into serosal cavities (e.g. pleural, peritoneal),
- into interstitial tissues (oedema).

**Electrolytes in body fluids:**

**Sweat** = hypotonic,
- \( \text{Na}^+ \) and \( \text{Cl}^- \) concentration of less than 60-80 mmol/L.

**Gastric juice** = mildly hypotonic or isotonic
- usual daily volume of 2-3 litres
- electrolyte composition dependent on the ratio of parietal cell (\( \text{H}^+ 135-160 \text{ mmol/L}, \text{mineral Na}^+, \text{high Cl}^- \)) to nonparietal cell secretion (plasma-like).

**VOMIT:**
- \( \text{K}^+ \) is not really lost in vomit as much as you would think.
- hypokalaemia occurring with vomiting is due to kaliuresis (renal \( \text{K}^+ \) loss accompanying \( \text{HCO}_3^- \)) - see lecture on Metabolic acid-base disturbances.

**Pancreatic, biliary and intestinal juices** are isotonic and alkaline;
- Metabolic acid-base disturbances accompanying gastrointestinal fluid loss (alkalosis for lesions above the pylorus, acidosis below the pylorus) can be corrected by the kidneys, provided they are not too severe and renal function is normal.

**Obligate and variable physiological losses** must be replaced and amount to 0.5 L (insensible water loss) + urine output + sweat.

**Clinical assessment.**
Clinical signs of extracellular volume loss (reduced skin turgor, dry mucous membranes, depressed jugular venous pressure, postural hypotension and tachycardia, shock) indicate the severity of fluid loss, and guide the volume of fluid replacement.

Measurement of electrolyte composition (and volume) of lost fluids, and osmolality and electrolyte (especially \( \text{Na}^+ \) and \( \text{K}^+ \)) concentration of plasma and urine indicate the relative balance of water and electrolyte loss, and guide the composition of fluid replacement.

**Replacement fluids**
- blood,
- colloids (containing a macromolecular solute confined to the intravascular compartment),
  - cause rapid movement of oedema into the bloodstream; thus increased blood volume
- crystalloids (electrolytes which will distribute initially throughout extracellular tissues)
  - can vary in osmolality:
    - hypertonic (e.g. 3 normal saline, 10% glucose),
    - isotonic (e.g. normal saline, 4% dextrose with 1/5 normal saline, 5% dextrose)
    - hypotonic (e.g. 5% normal saline).

- dextrose-based solutions (providing water without electrolytes).

\( \text{Na}^+ \) and \( \text{K}^+ \) are the predominant electrolytes that require replacement;
- other electrolytes include \( \text{Ca}^{2+}, \text{Mg}^{2+} \), and phosphate.

In general, once vital organ function is restored, losses can be replaced at the SAME RATE at which they have occurred.

DON'T BE TOO ZEALOUS WITH FLUID REPLACEMENT else = cardiac decompensation in patients with congestive cardiac failure,
- electrophysiological effects of potassium replacement
- osmotic cell shrinkage (e.g. osmotic demyelination) with hypertonic saline.
CONSEQUENCES OF HYPOKALEMIA  
= due to disruption of proper membrane polarisation in nerve and muscle
(plus intracellular acidosis)

**Cardiac Phenomena:**
- Arrhythmia
  - causes characteristic abnormalities in the ECG including
    - T wave flattening
    - depression of the ST segment
    - appearance of prominent u waves.

**Neuromuscular Phenomena:**
- reduced gastrointestinal motility resulting in symptoms ranging from constipation to ileus
  - MILD (serum K between 3.0 and 3.5 mmol/l) are often asymptomatic, but may complain of malaise, weakness, leg cramps or rarely myalgia.
  - Severe K depletion (K below 2.5 mmol/l) may cause rhabdomyolysis or paralysis.
  - In a K depleted state, muscle is susceptible to damage because the normal increase in blood flow is diminished
  - A low intracellular K reduces intracellular glycogen synthesis and thus energy stores for exercising muscle.

**Renal Effects:**
- do not usually cause symptoms in the patient.
- causes renal vasoconstriction
- reduced renal blood flow
- reduced glomerular filtration rate.
- SYMPTOMS: polyuria and secondary polydipsia due to a defect in tubular concentrating ability.
- increased renal ammonia production in the proximal tubule.
- This may at least partly account for the metabolic alkalosis observed in severe hypokalaemia.
- Pathologically, hypokalaemia has been associated with interstitial nephritis.

**Endocrine Effects**
- !! glucose intolerance !!
- Reversal of the carbohydrate intolerance occurs with correction of the hypokalaemia.
- Hypokalaemia decreases plasma aldosterone independent of volume status through a direct effect on the adrenal gland.

**Treatment**
The treatment of hypokalaemia is aimed at reversing the cause. However, if symptomatic then treatment is dictated by the degree of hypokalaemia and the urgency of the situation. The major issues in treatment relate to the quantity of K required, route of administration and rapidity of replacement.

CONSEQUENCES OF HYponATREMIA  
(below 135-145 mmol/L)

= in about 15% of hospital inpatients; associated with severe illness and relatively poor outcome.

!! NEURO SYMPTOMS !!
- nausea
- malaise,
- headache,
- lethargy,
- confusion,
- obtundation
- and eventually seizures and coma.

= better thought of as a water disturbance rather than a salt disturbance.

**Pathophysiology**
`Pathophysiologically, hyponatraemia may be spurious, dilutional, depletional or redistributinal.

. The slower the development of hyponatraemia, the less dramatic will be the cerebral manifestations. Unduly rapid elevation of plasma sodium by saline infusion carries the risk of induction of osmotic demyelination (central pontine myelinolysis).`

Common causes of hyponatraemia

1. Misleading result:
   - Biochemical error/ collection error (vein carrying an intravenous infusion)
   - Spurious
     - hyperlipidaemia
     - hyperproteinaemia
   - Solute excess
     - hyperglycaemia
     - mannitol
2. Water retention:
   - with elevated ECFV:
     - Congestive cardiac failure
     - Cirrhosis
     - Nephrotic syndrome
     - Renal failure
     - Water overload
   - without elevated ECFV:
     - Inappropriate ADH*
When considering the problems that can be caused by diuretics it helps to think about them in their functionally active groups. These can usefully be divided into:

- **Potassium Losing**
  - low potency eg thiazides
  - high potency or 'loop' diuretics eg frusemide
- **Potassium Sparing** eg amiloride, spironolactone
- **Combinations** eg moduretic (hydrochlorothiazide with amiloride)

A further useful subdivision is to consider those side effects which are a simple extension of the desired pharmacological action of the diuretics and those which are less intuitively obvious.

### Metabolic side effects due to extension of physiological actions

#### Potassium Losing Diuretics
- Fluid loss (hypovolaemia) - hypotension, dizziness, collapse
- Hyponatraemia (low sodium) - weakness, muscle cramps, confusion, drowsiness, seizures
  - Loop diuretics cause this problem less commonly than the thiazides because of their actions on the counter current system (interfering with urinary concentration).
- Hypokalaemia (low potassium) - weakness, muscle cramps, cardiac arrhythmias, polyuria
  - This is more of a problem in patients with high aldosterone, eg congestive cardiac failure, than it is in patients with uncomplicated hypertension.
- Alkalosis - commonly associated with hypokalaemia
- Hypercalcaemia - Thiazides reduce renal calcium excretion. (NB Frusemide has the opposite effect)

#### Potassium Sparing Diuretics
- Hyperkalaemia - leading to cardiac arrhythmias and muscular weakness. Care must be taken in using these drugs in renal failure and with ACE inhibitors which may also elevate potassium. They should not be given with potassium supplements.

#### Combination Diuretics
- Hyponatraemia plus hyperkalaemia

### Other side effects

#### Thiazides
- Hyperuricaemia; may lead to clinical attacks of gout
- Hyperglycaemia; may unmask diabetes in someone previously undiagnosed, or worsen control of blood sugar in a known diabetic
- Hyperlipidaemia - dose dependent increase in cholesterol and triglycerides

These side effects are seen more commonly with thiazides than with loop diuretics (indapamide which is related to the thiazide group is less likely to have these adverse effects but just as likely to cause the metabolic problems).

#### Loop Diuretics
Intravenously or in very high dose can cause deafness

#### Spironolactone
Is not a well tolerated drug. May cause gastrointestinal upset, painful gynaecomastia and impotence.

### Diuretic abuse
Such people may present with very low sodium and potassium with associated metabolic alkalosis. A specific history of diuretic use or abuse should be taken.

If diuretic use is denied, but still strongly suspected, a urine screen for the presence of diuretics can be performed.
INTERROGATING THE URINE

Box 25-1: Composition of urine

<table>
<thead>
<tr>
<th>Component</th>
<th>Concentration</th>
<th>Daily renal excretion</th>
<th>Finding/Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>500-2500 ml</td>
<td>&lt;500 ml/Nephropathy, shock &gt;2500 ml/Diabetes</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>60-70 mM</td>
<td>90 mmol daily</td>
<td>&lt;20 mmol daily/Low diet &gt;150 mmol daily/Rich diet</td>
</tr>
<tr>
<td>Sodium</td>
<td>50-120 mM</td>
<td>150 mmol daily</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>20 mg/l-1</td>
<td>500 mmol daily</td>
<td>Microalbuminuria/Diabetes</td>
</tr>
</tbody>
</table>

Anuria or oliguria (<500 ml daily) indicates the presence of hypotension or renal disease.
Polyuria (>2500 ml of urine daily) is the sign of diabetes
– both diabetes mellitus and diabetes insipidus.
Microalbuminuria (i.e. 50-150 mg per l) indicates glomerular barrier disorder
– such as diabetic glomerular disease.
Glucosuria with hyperglycaemia is the sign of diabetes mellitus,
and without hyperglycaemia it is a sign of a proximal reabsorption defect.
High urea excretion is seen in uraemia,
high creatinine excretion indicates a large muscle mass in a healthy person.
A low creatinine excretion is the sign of muscular atrophy or ageing.