Pathophysiology of Water and Electrolyte Metabolism

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A case of severe hyponatraemia – initial steps

- 75 yrs old female
- Diabetic, but who refused taking her medications and keeping diet
- Transferred to the hospital with severe, general weakness
- Looked severely volume depleted on admission
- Serum Na 117 mmol/l, K 5.5 mmol/l, Cl 81 mmol/l, blood sugar 79 mmol/l, total protein 82 g/l, CN 10.6 mmol/l, creatinine 119 umol/l
- Blood gas analysis: pH 7.4, pCO2 32 mmHg, HCO3 23 mmol/l, anion gap 15.6 mmol/l

What do you think about the hyponatraemia? Is her plasma hypoosmolar?
Is this a hypoosmolar condition?

- Calculated serum osmolality = \( \text{SeNa} \times 2 + \text{blood sugar} + \text{CN} \)
  
  \[
  117 \text{ mmol/l} \times 2 + 79 \text{ mmol/l} + 10 \text{ mmol/l} = 323 \text{ mosm/kg}
  
  This is a hyperosmolar condition!
  
- There is water movement from cells (IC space) to EC compartment
  
  By each 5 mmol/l increase in blood glucose, 1.5 mmol/l serum Na decrease can be expected
Real- or pseudohyponatraemia

Normal condition

1 litre serum

Na\(^+\) conc. 140 mmol/l

Plasma water

Lipids, proteins

Hyperlipidaemia, paraproteinaemia

1 litre serum

Na\(^+\) conc. 132 mmol/l

1 litre plasma

Na\(^+\) conc. 140 mmol/l

Plasma water

Lipids, proteins
Why is this old lady hyponatraemic?

- 93 yrs old female, admitted to hospital due to diarrhoea for two weeks, she was also vomiting, couldn’t eat, but forced drinking
- Her medications:
  25 mg hydrochlorothiazide,
  25 mg spironolactone,
  40 mg furosemide once a week,
  ramipril, bisoprolol, aspirin
- BP 100/45 mmHg. Looked severely volume depleted, but communicated appropriately.
Labs on admission

- Serum Na 104 mmol/l, K 4.2 mmol/l, CN 13.5 mmol/l, creatinine 118 umol/l,
- Urinary Na 49 mmol/l, K 35 mmol/l

Why is she hyponatraemic?
What does the urinary sodium concentration represent?
Is this acute or chronic hyponatraemia?
How aggressively would you treat the hypoNa?
Why is she hyponatraemic?

- Salt depletion + free water surplus
  (free water = water without solutes)
- Clinically is severe volume depletion
  + medical history
  + use of diuretics
  + low blood pressure
  + dry mucous membranes
- Urinary Na – should have been < 10 mmol/l
  But - diuretics still act!
SeNa concentration = ratio of Na and water

- HypoNa: water moves to IC space
- → swelling of the cells
ADH secretion

• **In physiologic conditions**
  - increased osmolality
  - increased serum Na

• **In pathophysiologic conditions**
  - stress, anxiety, pain, fever, nausea, vomiting
  - severe hypovolemia due to
    - fluid loss
    - diuretic use
  - effective volume depletion
  - SIADH
  - medications
Suggested treatment in volume depletion

- The major stimulus for ADH → volume depletion
- 0.9% NaCl infusion shuts off the stimulus of ADH secretion
- Hypertonic NaCl infusion is unnecessary and dangerous (exceptions will be discussed)
Treatment and the course of disease in our old lady

- 1500 ml normal saline (0.9%) infusion daily
- Labs on the following days:
  - Serum Na: 112, 124, 128, 133, 138 mmol/l
- Other results:
  - Creatinine: 89 umol/l, CN 6 mmol/l,
- Her mental condition on admission suggested that it was chronic hyponatraemia
Dangers in the hospital

- 84 years old female, admitted to hospital 12 days earlier because she had had diarrhea for 3 days
- On admission she looked volume depleted, had low BP (90/50 mmHg)
- Laboratory results: Hgb 9.86 g%, serum Na 134 mmol/l, K 3.0 mmol/l, BUN 21.9 mmol/l, creatinine 182 umol/l
- She got 0.9% NaCl infusion+KCl for 3 days the BP normalized (118/59 mmHg), the labs: Na 141 mmol/l, K 3.6 mmol/l, BUN 4.1 mmol/l, creatinine 86 umol/l
- The gastroenterology team decided to go on with GI work up in order to look for the cause of anemia
Sudden disaster on a Sunday afternoon ..... 

- Scheduled for colonoscopy on Monday (plan to preparing her by Fleet enema on Sunday evening)
- Instruction by the nurse on Sunday morning: „no solid food to eat, only fluids to drink”
- On Sunday morning – complaints free, ambulating, „looked nervous”
- In the afternoon: she suddenly lost her consciousness, had a convulsion, did not respond even to pain, had uncoordinated movements in all her extremities. Repeatedly vomited.
Sudden disaster on a Sunday afternoon.....

- Urgent labwork: serum Na 117 mmol/l, K 2.9 mmol/l, BUN 2.4 mmol/l, creatinine 98 umol/l
- Urinary osmolality 431 mOsm/kg, urinary Na 164 mmol/l, K 44 mmol/l hrs, 900 ml/12 hrs
- Brain CT:
  - no major abnormality can be seen
- She remained unconscious in the next day:
  Neurological examination:
  - no primary neurological abnormality,
  - EEG: diffuse functional cortical abnormality
Sudden disaster on a Sunday afternoon ..... 

- Why had she severe hyponatremia on the 12th day? 
- What do you think about the urinary osmolality of 431 mOsm/kg? 
- And about the urinary Na of 164 mmol/l? 
- What would you give her? How much?
Hyponatremia

ADH secretion + Water intake

Both need to be present

Why ???

Why is ADH secreted in spite of hypoosmolality?

Is this an acute or a chronic condition?
ADH secretion

- **In physiologic conditions**
  - increased osmolality
  - increased serum Na

- **In pathophysiologic conditions**
  - stress, anxiety, pain, fever, nausea, vomiting
  - severe hypovolemia due to
    - fluid loss
    - diuretic use
  - effective volume depletion
  - SIADH
  - medications
Treatment on the 12\textsuperscript{th} day

- **Acute**, severe hyponatremia, causing convulsion, coma, vomiting $\rightarrow$ very likely cerebral edema
- Urine osmolality: 431 mOsm/kg - proves **strong** influence of ADH (likely due to stress, anxiety, nausea)
- **Lots of fluid intake** according to the instructions
- Urine Na: 164 mmol/l means - no volume depletion
- Treatment: 3\% NaCl infusion
- How much?
Treatment on the 12th day

- Weight of the patient: 84 kg. Body water: 42 l
  - In order to elevate her serum Na by 1 mmol/l, she needs 42 mmol Na
  - In order to elevate serum her Na by 5 mmol/l, she needs 210 mmol Na
  - It means 408 ml of 3% NaCl infusion
- Follow urinary Na loss and replace it
- Check electrolytes frequently
Treatment on the 12th day

- She got 300 ml 3% NaCl infusion (154 mmol) and 4 g KCl
- 4 hours later serum Na 119 mmol/l, K 3.2 mmol/l
- During Sunday night 300 ml 3% NaCl infusion (154 mmol) and 4 g KCl
- On Monday morning 300 ml 3% NaCl infusion (154 mmol)
- In 24 hours: serum Na 130 mmol/l, K 3.9 mmol/l
- In summary she got 462 mmol Na in the 1st 24 hrs
- Urinary losses in 24 hrs: 230 mmol Na and 62 mmol K
- Next day: serum Na 134 mmol/l, she regained consciousness
- Two days later: serum Na 140 mmol/l
Do cirrhotic patients need sodium in hyponatremia?

- 70 yrs old male, treated on an internal medicine department
  He is a regular alcohol drinker, has liver cirrhosis, oedema on the legs and huge ascites
- On admission: serum Na 132 mmol/l, K 4.2 mmol/l, BUN 5.7 mmol/l, creatinine 82 umol/l
- Initial treatment: 100 mg spironolactone, 160 mg furosemide, 50 mg ethacrynic acid, 50 mg hydrochlorothiazide, 3 g KCl
- In three days BW 115 → 111 kg, Na 132 → 125 mmol/l, creatinine 82 → 126 umol/l
- Treatment: furosemide discontinued, others continued, + 5 g NaCl in Ringer infusion
Do cirrhotic patients need sodium in hyponatremia?

- In the next three days: BW → 120 kg, SeNa → 117 → 109 mmol/l, creatinine → 270 umol/l,
- Even more NaCl given
- Consultation asked for nephrology service because oliguria, deteriorating renal functions: SeNa 112 mmol/l, K 3,8 mmol/l, BUN 8,8 mmol/l, creatinine 307 umol/l
  Urinary Na excretion 2 mmol/day, K 8,6 mmol/day
- How would you manage this patient?
Hyponatremia in cirrhotic patients

Splanchnic vasodilatation, 
↓ systemic vascular resistance, ↓ MAP

Baroreceptor activation – 
„effective volume depletion”

↑ secretion of the „hypovolaemic hormones”

Renin → Ang.II.    ADH    Norepinephrine

Low distal delivery of filtrate:
Na and Cl reabsorption of the proximal tubule ↑↑ + low GFR
Hyponatremia in congestive heart failure

↓ cardiac output, ↓ systemic blood pressure

Baroreceptors sense low perfusion pressure (in the carotid sinus, aortic arch, afferent arterioles in the kidneys) „effective volume depletion”

↑ secretion of the „hypovolaemic hormones”

Renin → Ang.II.  ADH  Norepinephrine

Low distal delivery of filtrate:
Na and Cl reabsorption of the proximal tubule ↑↑ + low GFR
Hyponatremia in cirrhotic patients

- Severity of hyponatremia is proportional to the prognosis
- Correction of hyponatremia does not change the hemodynamical, pathophysiological abnormalities
- Mild hyponatremia usually does not cause major complaints, do not have to be treated (≈>125 mmol/l)
- Treatment: decrease fluid intake in order to achieve negative fluid balance
- „Delicate” diuretic administration, mainly loop diuretics (if peripheral edema present, ↓ BW: by 1-2 kg/d, if only ascites: <0.5 kg/d)
- Hypertonic saline infusion is contraindicated !!
- Vasopressin receptor antagonists: aquaretics (vaptans)
Therapy in CHF

- Survival is proportional to the degree of hyponatremia
- Its correction does not improve the prognosis of CHF
- ACEI/ARB
  - Improves cardiac output
  - ACEI decreases ADH’s effectivity in the cortical collecting duct, therefore water reabsorption
  - Decreases thirstiness
- Suggestion of moderate fluid restriction
- Administration of moderate doses of loop diuretics
- Vasopressin receptor antagonists: aquaretics (vaptans)
Vaptans

- Vasopressin receptor antagonists – increase electrolyte-free water excretion
- Conivaptan (V1a and V2), tolvaptan, (V2 receptor antagonists)
- Indicated in euvolemic and hypervolemic hyponatremia
- Contraindicated in hypovolemic hyponatremia
- Overcorrection of hyponatremia has to be avoided!
- Very expensive drugs
Why does she drink so much?

- 73 years old lady, in her past medical history: hypertension, schizophrenic psychosis and depression
- Between 2007-2009 practically spent the summers in hospital
- Reasons for admissions: weakness, bizarre pain sensations, numbness of her extremities, even unconsciousness developed several times
- Serum Na: 108-112 mmol/l
- Her complains: strong thirstiness, feeling of „salty skin”, therefore drank approximately 6 l/day
What happened in the hospital?

- XRs and ultrasound, head CT, chest CT, abdominal CT, gastroscopy, colonoscopy, cardiological examination, ACTH, cortisol, TSH tests
- All these results were normal
- But!
  - No data about urinary osmolality
  - No revision of her medications
  - Nobody told her to drink less!
Her medications

- Irbesartan + hydrochlorothiazide
- carbamazepine
- clomipramine
- bisoprolol
- amlodipine

- What is the etiology of her hyponatraemia? What would you suggest for her?
Hyponatremia

ADH secretion + Water intake

Both need to be present

Why ???

Why is ADH secreted in spite of hypoosmolality?

Is this an acute or a chronic condition?
On our Outpatient Clinic

- Likely psychogenic polydipsia (6L !) + medications may play role
- My suggestions:
  - maximum water intake: 1 L/day
  - salt can be consumed generously
  - discontinue thiazide diuretic
  - discontinue carbamazepine
  - consider discontinuation of clomipramine, if necessary
Follow up between 2010-2012

- SeNa 137-138-140-141-135-139-134-138-137-140-137 mmol/l
- Normal K, CN, creatinine, blood sugar
- Urinary Na 150-230 mmol/d, urinary osmolality 548-608 mosm/kg
- Urine output: 1000-1700 ml/day
- No hyponatraemic episodes with neurological symptoms!
The most frequent causes of hyponatremia

Clayton et al. Q.J.Med 2006

- Hyponatremia was found in 108 of the 9622 patients admitted to internal medicine department in 6 months

- **Etiology**
  - Thiazide diuretics - 29 cases
  - Congestive heart failure - 27 cases
  - Liver cirrhosis - 21 cases
  - In further cases: volume depletion, medications, malignancies, lung- and cerebral diseases, hypothyroidism, Addison disease, hypoNa postoperatively, primary polydipsia and chronic renal failure

- During the hospitalization 20% of the patients died
Risk factors for thiazide-induced hyponatremia

Chow et al. Q.J. Med 2003

- Between 1996-2002 223 thiazide caused hyponatremic patients were observed
- SeNa: 98-128 mmol/l (mean 116.7 mmol/l)
- Length of treatment 1-4479 day! (mean 105 day)
  - 42.8% indapamide, 15.4% HCT+triamterene
  - 16.1% HCT, 8.4% bendrofluazide
  - 17.3% HCT+amiloride,
- Thiazides were administered mainly for hypertension
- Risk factors for developing hyponatremia: age, low body weight, hypokalemia
A case of SIADH

- 66 yrs old male, acute lymphoid leukemia diagnosed 9 months ago
- Got monthly bolus cytostatic treatments
- Developed aspergillus pneumonia - Rx intaconazole
- Admitted secondary to feeling unwell, weak, dizzy, but he was ambulating, can properly communicate
- Labs: Na 117 mmol/l, K 3,5 mmol/l, Cl 85 mmol/l, bicarb 23 mmol/l, BUN 6,5 mmol/l, creatinine 75 umol/l, BS 8,3 mmol/l, serum osmolality 237 mOsm/kg, urinary Na 83 mmol/l, osmolality 456 mOsm/kg, normal TSH
- According to his chart: serum Na 123-133 mmol/l previously
- Why does he have ADH? Acute or chronic?
Inappropriate ADH secretion - SIADH

- **Malignancies**
  - small lung cell carcinoma
  - prostate, uterus cc.
  - pancreas, duodenum cc.
  - leukemia, lymphoma

- **Medications**
  - dDAVP, oxytocin, NSAID
  - antidepressants,
  - narcotics, nicotine
  - cytostatics
  - chlorpropamide
  - carbamazepine

- **Central nervous syst.dis.**
  - Tumors, abscess
  - infections
  - Demyelinization diseases
  - SAH, trauma

- **Lung diseases**
  - TBC, aspergillosis
  - pneumonia, abscess
  - obstructive lung disease
  - ventilation
Diagnosing SIADH

Essential criteria\(^1,2\)

- Hyponatraemia < 135 mmol/L
- Plasma hypo-osmolality < 275 mOsm/Kg
- Urine osmolality > 100 mOsm/Kg
- Clinical euvolaemia
- Increased urinary sodium excretion > 30 mmol/L with normal salt and water intake
- Absence of other potential causes of euvolaemic hypo-osmolality
  - Exclude thiazide use, renal disease, hypothyroidism and hypocortisolism

Treatment according to symptoms and acuteness

Symptomatic hyponatraemia: Neurological manifestations\textsuperscript{1,2}

- Headache
- Irritability
- Nausea / vomiting
- Mental slowing
- Unstable gait / falls
- Confusion / delirium
- Disorientation

Symptomatic but less impaired; usually chronic

The degree of symptomatology is a surrogate for the duration of hyponatraemia

Life-threatening; usually acute

Treatment of acute hypoNa
Treatment of severe, symptomatic chronic hypoNa (chronic hypoNa with acute deterioration)

- Increase serum Na by 5 mmol/l, then slow down and continue increasing the serum Na concentration by maximum 8-10 mmol/day as the total correction
Treatment of chronic hypoNa

- Maximum 8-10 mmol/day as the total correction
- Maximum 18 mmol/48 hours
And now the exceptions...

• Beer potomania/tea and toast hypoNa
• Primary polydypsia in psychotic conditions

• HypoNa develops because of more water ingested that can be excreted
• (Intermittent periods of ADH secretion can complicate these conditions
  → non-osmotic stimuli of ADH secretion)
Tea and toast hyponatraemia

- 62 yrs old patient with diabetic nephropathy
- Baseline kidney function: eGFR 18 ml/min
- Suffered from diverticulitis, and decided to keep a very strict diet: some soup and daily 200 ml liquid salt free Nutridrink
- His usual daily fluid intake 2.5-3 L
- He presented with serum Na of 107 mmol/l

Why did he develop hyponatremia?
What does the maximal urinary diluting capacity mean?

- **Healthy persons:**
  - Minimal urine osmolality: 50-80 mOsm/kg
  - Average solute excretion: 600-900 mOsm/day (300-450 mmol Na, K + the anions, and 300-450 urea)

- **How much can we drink without the risk of hyponatremia?**
  
  \[
  \text{Solute excretion} \div \text{diluting capacity} \div \text{L}
  \]

  - 900 mOsm and 50 mOsm/kg = 18 L
  - 600 mOsm and 80 mOsm/kg = 7.5 L
  - 200 mOsm and 50 mOsm/kg = 4 L

- **Beer potomania - „Tea and toast” hyponatremia:**
  - Low protein and salt intake, therefore low osmolar excretion and too much fluid intake
Polyuria and hypernatraemia
He drinks 8 L of fluid daily

- 54 yrs old male
- Had motorvehicle accident long ago
- Now presents with polyuria-polydipsia
- Se Na 139-144 mmol/l, measured se osmolality 290 mosm/kg
- Urinary osmolality: 97-188 mosm/kg
- Water deprivation test + 20 ug desmopressin:
  - maximal urinary osmolality: 293 mosm/kg
- Two days later, administering 10ug desmopressin/day
  - Uosm 605 molsm/kg, urine output 1600 ml/day
  - SeNa 139 mmol/l, SeOsm 287 mosm/kg
Some questions

• What is your diagnosis?
• Is this strange, that he has normal serum Na level?
• What do you think about the urinary osmolality of 97-188 mosm/kg
• Why was the urine osmolality „only” 293 mosm/kg during the test?
It gets complicated...

- He was well with this medication for more than 1 year, than refused to take the desmopressin, because having frequent headaches and dizziness.

- What do you think, what happened?
It gets complicated...

- He recently consumed 4 L fluid/day and took 10 ug of desmopressin, and then headaches and dizziness developed.
- His laboratory results:
  - SeNa 123 mmol/l, Se osmolality 258 mosm/kg
  - urine osmolality: 488 mosm/kg
- The question: What is the importance of the amount of fluid intake, when someone is treated with desmopressin?
Polydipsia-polyuria in pregnancy

- 35 yrs old female, 29th week of her first pregnancy
- Before pregnancy, her usual daily fluid intake was 3 L/day, but recently consumes 8 L/day
- Doesn’t have any complaints
- SeNa 140 mmol/l, K 4,0 mmol/l, creatinine 60 umol/l, blood sugar 4,9 mmol/l
- Delivers a healthy baby
- 2-3 weeks after delivery her fluid intake decreased 1 L/day

Why was she polyuric?
A rare complication of pregnancy

- Vasopressinase
  - can be released from the placenta
    (or later from retained necrotic placenta)
  - destroys N-terminal amino group of vasopressin
  - does not hydrolyze dDAVP — treatment of choice
What kind of i.v. infusion has to be given in hypernatremia?

- 81 yrs old male patient, admitted to hospital because of volume depletion and pneumonia. He was febrile, desoriented.
- Lab results: serum Na 156 mmol/l, K 5,0 mmol/l, BUN 22 mmol/l, creatinine 173 umol/l, glucose 6,1 mmol/l.
- Chest XR: pneumonia and pulmonary congestion
- Initial treatment: 500 ml of Ringer lactate + 500 ml 5% glucose infusion
- Was this appropriate? What kind of change do you expect in serum Na concentration?
What kind of i.v. infusion has to be given in hypernatremia?

- **Next morning:**
  - Se Na 157 mmol/l, osmolality 330 mOsm/kg
  - Urinary Na 40 mmol/l, K 48 mmol/l, osmolality 463 mOsm/kg
  (24 hrs collection could not be done)
What kind of i.v. infusion has to be given in hypernatremia?

- **Na balance**
  - the patient excreted 40 mmol/l sodium,
  - intake by RL: 67 mmol
  (Ringer lactate contains 132 mmol/l)

- **Treatment on the following day**
  - 1500 ml 5% glucose infusion
  - he was eating and drinking a little
  - Serum Na 159 mmol/l

- **Why? What can we do now?**
What kind of i.v. infusion has to be given in hypernatremia?

- Checking again the urinary excretion: Na 11 mmol/l, K 9,5 mmol/l
  osmolality 439 mOsm/kg
- He was excreting very little Na
- He was not able to increase his urine osmolality
- We gave 40 mg furosemide i.v. and 2500 ml 5% glucose infusion daily
- The urinary Na excretion increased to 52 mmol/l, K excretion to 30,2 mmol/l
- The serum Na decreased gradually and in 3 days normalized to 137 mmol/l
Potassium disorders
Hypokalemia – where does this huge amount of K go?

- A 62 yrs old female
- PMHx: collagen colitis – she had been well for years
- She presented with profuse, watery diarrhoea, several times daily. In the last days nausea and vomiting also occurred
- On admission: severely volume depleted, very weak, completely anuric, BP 60/40 mmHg.
Hypokalemia – where does this huge amount of K go?

Labs on admission:
Na 124 mmol/l, K 1,8 mmol/l, BUN 31,5 mmol/l, creatinine 665 umol/l

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<td>-</td>
<td>3,8</td>
<td>diuresis</td>
</tr>
</tbody>
</table>
Hypokalemia – where does this huge amount of K go?

- Why did she need so much K? (83 g = 1079 mmol)
- Did this patient have renal K wasting tubulopathy?
Hypokalemia – the first step in differential diagnosis

- Urinary K excretion
  - In our patient: 19.5 mmol/day
  - 18.8 mmol/day
Hypokalemia – where does this huge amount of K go?

- Body weight of the patient: 60 kg
  Extracellular water: 10 l
  Intracellular water: 20 l
- K content of EC: 10x4= 40 mmol
  K content of IC: 20x150=3000 mmol
An other hypokalemic patient ...

- 48 years old male
- PMHx: hypertension since his age of 30
- His mother, his sister and his son also have HTN
- Serum potassium between 2.5-2.9 mmol/l for years
- Meds on the first consultation: 20 mg amlodipin, 2x20 mg enalapril + hydrochlorothiazide, 4 mg prasosin, 2x2 g KCL
- Labs: serum Na 145 mmol/l, K 2.9 mmol/l, CN 7.7 mmol/l, creatinine 100 umol/l

What kind of tests would you order?
An other hypokalemic patient ...

- 24 hr urinary Na: 262 mmol/day
  24 hr urinary K: 104 mmol/day
- Blood gas analysis:
  pH 7.46
  HCO$_3$ 28.8 mmol/l
  pCO$_2$ 41 mmHg

What is the differential diagnosis?
An other hypokalemic patient ...

- Renin and aldosterone levels - repeatedly normal
- RAS - excluded
- Glucocorticoid overproduction – serum cortisol normal
- Rx: spironolactone – no change

What is your diagnosis and how would you treat this patient?
- Continually open ENaC
- Familiar HTN
- Suppressed renin and aldosterone
- Rx: amiloride, triamterene

**Liddle syndrome**
Is this an emergency?
Life threatening hyperkalemia

- 82 years old female with HTN, DM, and CRF
- Serum creatinine earlier 150 umol/l
- Rx: 20 mg lisinopril, 20 mg spironolactone, 5 mg amiloride, 50 mg hydrochlorothiazide, 100 mg metoprolol, trimetroprim-sulfamethoxasol for one week
- Extremely week, unable to walk, than respiratory insufficiency developed
- Labs: serum Na 133 mmol/l, K 10.0 mmol/l, Cl 102 mmol/l, HCO3 18 mmol/l, kreat 265 umol/l, CN 31.5 mmol/l, Vc 26.4 mmol/l, urinary K 16 mmol/l.

How much is the expected K excretion in hyperK?
How many reasons did she have for hyperkalemia?
Inhibitors of renal potassium excretion

- **↓ Renin**
  - metoprolol

- **↓ Ang II.**
  - ACEI

- **↓ GFR**
  - acute on chronic renal insufficiency

- **↓ aldosterone**
  - spironolactone

- **↓ ENaC**
  - amiloride
  - trimetoprim

(Lack of insulin
 - decreased K intake by cells)
Acid-base disorders
A bicarbonate of 2.3 mmol/l

- 78 yrs old male
  - PMHx: diabetes mellitus, hypertension
  - admission in very poor condition: BP 88/52 mmHg
  - Kussmaul-breeding, oligo-anuric
- Serum Na 139 mmol/l, K 5.8 mmol/l, Cl 99 mmol/l
  - BUN 39 mmol/l, creatinine 504 umol/l,
- Blood-gas analysis:
  - pH 6.97
  - HCO₃⁻ 2.3 mmol/l
  - pCO₂ 10.2 mmHg

What kind of acid-base disorder is this?
What should we do?
A bicarbonate of 2.3 mmol/l

- Anion gap
  \[ \text{Na}^+- (\text{Cl}^- + \text{HCO}_3^-) = 139 - (99 + 2,3) = 37,7 \text{ mmol/l} \]

- Decrease in bicarbonate
  \[ 25 - 2,3 = 22,7 \text{ mmol/l} \]

- Respiratory compensation: delta pCO\textsubscript{2}
  \[ 40 - \text{pCO}_2 = 40 - 10,2 = 29,8 \text{ mmHg} \]
A bicarbonate of 2.3 mmol/l

- The patient has: high anion gap metabolic acidosis
- His lactate level: 12.2 mmol/l
- He was taking metformin, which caused lactic acidosis
- He was dialysed, survived, but remained dialysis dependent
Etiology of wide anion gap metabolic acidosis

Gain of acids

Endogenous acid production
- ketoacidosis
- L-lactic acidosis (A and B-types)
  - D-lactic acidosis
  - advanced renal failure

Exogenous acids
- ethylene glycol
- methanol
Glucose

Glucose-6-phosphate

Piruvate

Lactate dehydrogenase

NADH

NAD+

Lactate

NADH

NAD+

Oxygen is necessary for the ATP production in the mitochondria. "A" type L-lactic acidosis develops, when there is no oxygen supply, therefore ATP is not produced. The consequence: increased glycolysis and lactate production.
The most frequent causes of „B” type L-lactic acidosis

Glucose → Glucose-6-phosphate → Piruvate → LDH → Lactate^-+H^+ → Ethanol → NADH → NAD^+ → Mitochondrial dysfunction → Mitochondria → Acetyl-CoA → Citrate cycle → CO2+H2O+ATP + NADH → NAD^+ → Metformin
Acidosis

\[ \text{pH} \downarrow \]

- **HCO_3^- \downarrow**
  - metabolic acidosis
    - \( \text{pCO}_2 \downarrow \)
      - respiratory compensation
        - 1:1
    - \( \text{pCO}_2 \uparrow \)
      - \( \text{HCO}_3^- \uparrow \)
        - metabolic compensation
          - 1:0.3
- **pCO_2 \uparrow**
  - respiratory acidosis
    - \( \text{HCO}_3^- \uparrow \)
      - 1:0.3
Alkalosis

pH $\uparrow$

HCO$_3^-$ $\uparrow$

- metabolic alkalosis

- respiratory compensation

pCO$_2$ $\uparrow$

1:0.7

pCO$_2$ $\downarrow$

respiratory alkalosis

HCO$_3^-$ $\downarrow$

- metabolic compensation

1:0.5
Deteriorating pH

- A 42 yrs old male patient
- He was admitted to the gastroenterology department in rapidly deteriorating physical condition
- Medical Hx: joint problems, hip replacement, on NSAIDs, aethyl abuse
- Labs on admission:
  - Serum Na 138 mmol/l, K 2.9 mmol/l, Cl 121 mmol/l, BUN 24.8 mmol/l, creatinine 432 umol/l, Hgb 9.6 g%
  - Blood gas analysis:
    - pH 7.3, bicarbonate 11 mmol/l, pCO₂ 14 mmHg
- Gastroscopy revealed bleeding from gastric ulcers
- **What kind of acid-base disorder is this?**
Deteriorating pH

- Anion gap
  \[ \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-) = 138 - (121 + 11) = 6 \text{ mmol/l} \]
- Decrease in bicarbonate
  \[ 25 - 11 = 14 \text{ mmol/l} \]
- delta pCO\(_2\)
  \[ 40 - \text{pCO}_2 = 40 - 14 = 26 \text{ mmHg} \]
Deteriorating pH

- Treatment: he got proton pump inhibitor, Na-bicarbonate infusion and furosemide, but did not improve
- Blood gas analysis few hours later:
  - pH 7.2, bicarb 9 mmol/l, pCO$_2$ 24 mmHg
  - (previous: pH 7.3, bicarb 11 mmol/l, pCO$_2$ 14 mmHg)

What happened to the pH?
Deteriorating pH

- Next day:
  - pH 6.84, bicarb 9 mmol/l, pCO$_2$ 58 mmHg
  - (previous: pH 7.3, bicarb 11 mmol/l, pCO2 14 Hgmm
    pH 7.2, bicarb 9 mmol/l, pCO2 24 mmHg)

What kind of acid-base disorder is this now?
Severe hypokalemia due to dRTA

40 years old female, admitted to intensive care unit with fever, pneumonia, respiratory failure

Serum Na 138 mmol/l, K 2,4 mmol/l, Cl 110 mmol/l
pH 7,32, $\text{HCO}_3$ 14,8 mmol/l, $\text{pCO}_2$ 28 Hgmm
AG 13,2 mmol/l
$U_{\text{Na}}$ 244 mmol/day, $U_{\text{K}}$ 52 mmol/day

Bicarbonate loading test:
Baseline urine: pH 6,8, $\text{HCO}_3$ 6 $\text{pCO}_2$ 35
Urine after loading: 7,1 12 36
Blood after loading 7,3 22 37

Urine $\text{pCO}_2$ – blood $\text{pCO}_2$ $\approx$ 0
Differential diagnosis of non-anion gap metabolic acidosis

Low plasma bicarbonate level

- Gastrointestinal bicarbonate loss
  - Urine Cl⁻ >> Na⁺+K⁺ (refers to NH₄⁺ production)

- Renal tubular abnormality
  - pRTA
  - dRTA
  - insufficient NH₄⁺ production
Physiologic bicarbonate reabsorption in the proximal tubule. pRTA develops due to reduced indirect bicarbonate reabsorption.
dRTA develops if the $H^+$ secretion is disturbed in the collecting duct
Bicarbonate-ammonia production is necessary for $H^+$ excretion.
Gastrointestinal disease diagnosed by blood pH

- A 41 year-old male patient, admitted to hospital secondary to nausea, vomiting and epigastric pain
- On admission he looked severely volume depleted, had a BP of 96/58 mmHg
- Labs: serum Na 123 mmol/l, K 3.5 mmol/l, BUN 24 mmol/l, creatinine 355 umol/l,
- Blood gas analysis: pH 7.65, bicarb 43 mmol/l, pCO$_2$ 55 mmHg.
- **What is your diagnosis?**
Gastrointestinal disease diagnosed by blood pH

- Metabolic alkalosis, hyponatremia and hypokalemia, acute renal failure
- According to the clinical picture – suspicion of pylorus stenosis
- Gastroscopy confirmed this abnormality (ulcer causing pylorus stenosis)