CHAPTER 1

SODIUM AND WATER PHYSIOLOGY

I. WATER

1. Body composition

50 - 70 % of the mass of the body is water. It is not always possible to relate total body water (TBW) to weight because of variations in the relative proportion of fat (has little water) and skeletal mass (has the bulk of water).

CLINICAL PEARL

A patient with a small muscle mass (less TBW) will have a much lower P_{Na} when a given volume of electrolyte-free water (EFW) is retained or lost

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2. Movement of water

Water will move if there is an osmotic driving force and channels to permit water to cross membranes. The only area with a variable permeability to water is the distal nephron.

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3. Effective osmoles

Effective osmoles are solutes that have a different concentration on each side of a membrane. The major effective osmoles in cells are K ions and small organic compounds such as phosphocreatine, ATP, carnosine, and amino acids. The effective osmoles in the ECF compartment are largely Na, Cl, and HCO_3. The major effective osmole in the vascular compartment is albumin.

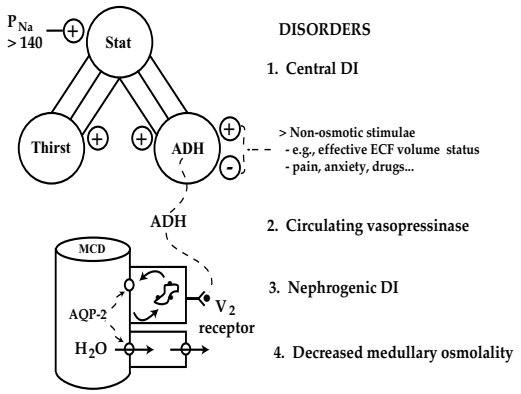
4. Central water control system

The sensor is the osmostat in the hypothalamus (Figure 1-1). It is connected to the thirst center. It is also connected to the ADH production center. When there is a water deficit (high P_{Na}), thirst is stimulated and ADH is released. The converse is true when there is a surplus of water (signal is a low P_{Na}).

Figure 1-1

Water control system

The primary sensor (stat) detects a change in volume in response to a change in the P_{Na}. These cells are linked to the thirst centre and to the ADH release centre. Non-osmotic stimuli also influence the release of ADH. ADH causes the insertion of water channels in the late distal nephron.



II. THE SODIUM CONTENT

1. Function of Na

Because most Na is located outside cells, the primary function of Na is to retain water in the ECF compartment (Table 1-1).

2. Sensing the Na content in the ECF compartment

The ECF volume is sensed by changes in the effective vascular volume. When this is low, a series of signals are sent to the kidney to prevent the excretion of Na. The converse is also true.

CLINICAL PEARL

In theory, the best way to identify a change in Na balance is to examine the ECF volume, but clinical methods to assess this volume are imprecise in quantitative terms

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TABLE 1-1

Causes of Low Effective ECF Volume

- ECF Volume Contraction
  - *Non renal Na loss*
    - GI tract (vomiting, drainage, ileus, diarrhea).
    - Skin (excessive sweating, burns).
  - *Renal Na loss*
    (diuretics, osmotic diuretics (glucose, urea), low aldosterone and tubular disorders).
- ECF Volume Normal but Maldistributed
  - *High interstitial and low vascular volume*
    (low plasma albumin e.g. liver disease, nephrotic syndrome or albumin leaks out of capillaries).
  - *Low arterial volume, high venous volume*
    (primary heart disease)

III. THE SODIUM CONCENTRATION

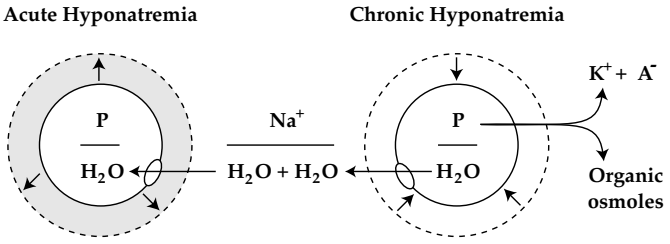
1. Na concentration and the ICF volume

The best indicator of the ICF volume is the P_{Na}, but in an inverse relationship (Figure 1-2). An exception is if there is a high concentration of organic solutes in the ECF compartment such as glucose or mannitol. Another exception is if there is a gain of ICF osmoles (acute seizure, rhabdomyolysis).

Figure 1-2

Relationship between the P_{Na} and the ICF volume

The solid circle represents the normal size of brain cells. Water crosses cell membranes and achieves osmotic equilibrium because there are water channels. The effective osmoles in the ICF are depicted as particles (P). In acute hyponatremia, shown on the left, brain cells swell (shaded area and dashed line). In chronic hyponatremia (shown on the right), brain cells have decreased towards their normal size by exporting some of their effective osmoles.



2. Basis for a change in the P_{Na}

A low P_{Na} can be due to a negative balance for Na or a positive balance for water, but both are almost always present. The ECF volume must be assessed quantitatively or a tonicity balance must be calculated

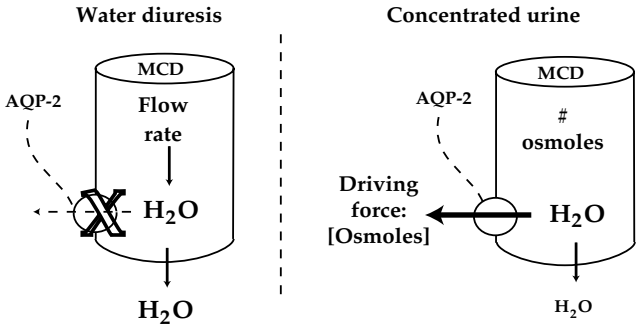
3. Maintain a low P_{Na}

A large intake of water is not enough to cause chronic hyponatremia. There must be a mechanism to prevent the excretion of the extra water. For this, ADH must be present without the most powerful stimulus for its release, a high P_{Na}. There could be a very low delivery of filtrate to the distal nephron (Figure 1-3).

Figure 1-3

Determinants of the urine volume

The factors required for a water diuresis are shown to the left of the dashed line and include the virtual absence of luminal aquaporin-2 (AQP-2) channels and a large distal flow rate. The factors required to excrete concentrated urine are shown on the right of the dashed line and include presence of luminal AQP-2 channels, a high osmolality in the medullary interstitial compartment, and the number of effective osmoles delivered to the medullary collecting duct (MCD).



4. Change in the ICF and ECF volumes

(i) ICF volume

Hyponatremia usually implies that the ICF volume has increased. This applies to brain cells if the duration of hyponatremia is short (< 48-hr). Brain cells have a unique response to hyponatremia that has been present for > 48-hr—they extrude effective ICF osmoles. Roughly half are K salts and the other half is a family of small organic solutes. The most important issue now is once the P_{Na} rises, it will take time to re-

accumulate these effective ICF osmoles. Therefore the major danger in the patient with chronic hyponatremia is a rise in the P_{Na} that is too rapid because this may cause the osmotic demyelination syndrome (ODS).

(ii) ECF volume

The ECF volume may be high, normal, or low in the patient with hyponatremia, depending on the balances for Na and water and whether other effective osmoles are present in the ECF compartment

5. Use of the P_{osm} to decide if hyponatremia is associated with cell swelling

Consider a gain of effective osmoles in a solution that is isotonic to plasma. For osmoles like mannitol that do not enter the ICF compartment of all organs, the result will be a fall in the P_{Na}, but the ICF volume will not change. Recognize this picture by finding no change in the P_{osm}. Consider a gain of effective osmoles in a solution that has an effective osmolality that is lower than that of the ECF (e.g., half iso-osmolar mannitol). In this setting, the fall in P_{Na} is associated with a rise in the ICF volume, but this rise is much less than anticipated from a fall in P_{Na} due to water gain (see Chapter 4 for more details). The change in ICF volume can be deduced from the measured P_{osm}.

Consider a gain of effective osmoles in a solution that has an effective osmolality that is greater than that of the ECF (e.g., hyper-osmolar mannitol). In this setting, the ICF volume will fall despite the presence of hyponatremia. The change in ICF volume can be deduced from the measured P_{osm}

6. Glucose and the P_{Na}

Glucose is an effective osmole for some cells, but not in other cells (e.g., the liver). Therefore hyponatremia will not always be equated with cell volume expansion (Figure 1-4).

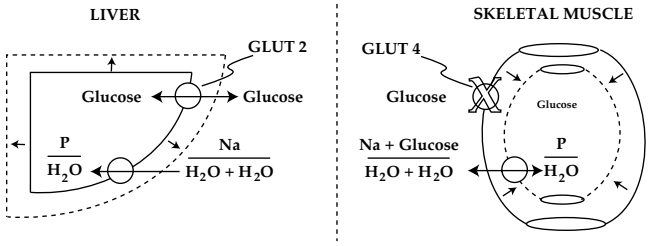
CLINICAL PEARL

There is no reliable quantitative relationship between the $P_{Glucose}$ and the P_{Na}.

Figure 1-4

Size of organs when the $P_{Glucose}$ changes

The solid line represents the normal size of the organs whereas the dashed line represents their size during hyperglycemia. The X-symbol represents the low ability to transport glucose into muscle cells in the absence of insulin so the concentration of glucose in these cells is very low (represented by a smaller font).



IV. URINE VOLUME AND Na CONCENTRATION

1. Normal values in the urine

CLINICAL PEARL

There are <u>no</u> normal values! There are only expected values dictated by stimuli for excretion.

When there is a deficit of water, the urine volume should be as low as possible and the urine osmolality (U_{osm}) should be as high as possible (maximum 1200 mOsm/kg H_2O). The converse is also true.

2. Urine flow rate

Typically, the urine volume in an adult is 1 to 1.5 L/day—this is an average flow rate of ~ 1 ml/min. There are often large variations throughout the day.

In an osmotic diuresis, the urine flow rate is dependent on the number of effective osmoles in the urine (exclude ethanol and possibly urea) and the osmolality in the medullary interstitial compartment when the MCD is permeable to water (and urea) (ADH acts, see equation below).

Urine flow rate (L/day) = # mosmoles excreted/day/U_{osm}

In a water diuresis, the urine flow rate is dependent on the volume delivered to the distal nephron and the ability of these nephron segments to be impermeable to water (lack of ADH, Figure 1-3).

3. Basis for an abnormal urine flow rate

Although you only measure two of the parameters in the equation above (urine flow rate and the U_{osm}), you should always calculate the osmole excretion rate. The osmole excretion rate is 600 –900 mosmoles per day in adults on a typical western diet. This information is useful to assess distal volume delivery and whether there is an osmotic diuresis (or an impending one once a water diuresis is curtailed by giving ADH).

V. NORMAL VALUES

1. P_{Na} is 140 ± 2 mmol/l

A low P_{Na} is the commonest electrolyte disorder in hospitalized patients.

2. Na content in the ECF compartment

Multiply the P_{Na} times the ECF volume.

3. Excretion of water

The objective is to keep the P_{Na} close to 140 mmol/l.

- Hence water will be excreted when the P_{Na} is low and water will be retained when the P_{Na} is high.

4. Assess ADH

While the level of ADH is rarely available in a timely fashion in clinical medicine, you must ask two questions in patients with a low P_{Na}.

(i) Why is ADH present?

(ii) Will the release of ADH cease and cause a rapid water diuresis in a patient with chronic hyponatremia?

This is especially important because the ODS may develop, especially in the patient who is malnourished, catabolic, and/or K deficient.

VI. TOOLS TO USE IN PATIENTS WITH AN ABNORMAL SALT OR WATER BALANCE

Tools that are useful to design therapy for an abnormal P_{Na}:

1. Assess the ECF volume to determine the balance for Na

There are two ways to change the P_{Na}, change the balance for Na or water. To distinguish between these two possibilities, one must have a reliable estimate of the volume of the ECF compartment. Clinical assessment of the ECF volume is not sufficiently precise to gain the needed quantitative information. Hemodynamic measurements provide useful information at times, but they too lack the quantitative data that are needed. While urine electrolytes are useful in many patients, the caveats of using drugs that inhibit the renal reabsorption of Na such as diuretics, agents that bind to the calcium-sensing receptor (Ca-SR) in the loop of Henle, and disorders that lead to renal or cerebral salt wasting make them less reliable indicators of the effective circulating volume in these patients

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CLINICAL PEARL

Use the hematocrit or the total plasma protein concentration to gain quantitative information about the ECF volume if you can.

(i) Use of hemoglobin/hematocrit or total plasma protein concentration:

Under the right setting, these measurements provide the most reliable way to assess the plasma volume. Based on this information and an assessment of the Starling forces, the degree of ECF volume contraction can be deduced.

CAUTIONS

There will be a problem if the patient has blood loss, a severe hemolytic disorder, if he has received a transfusion, or if polycythemia is present.

CALCULATION

The hematocrit is the ratio of the RBC volume to the blood volume (RBC + plasma)—its normal value is ~ 40% (0.40) in a healthy young male. In a patient with a hematocrit of 60 %, the plasma volume is decreased by 56 %.

Hematocrit of 0.40 = 2 L RBC/(2 L RBC + 3 L plasma)

Hematocrit of 0.60 = 2 L RBC/(2 L RBC + X L plasma)

∴ plasma volume = 1.33 L

(ii) Information from the venous Vs the arterial PCO_2

While not providing quantitative data, these measurements provide information about the rate of blood flow to a specific area relative to its demand for O_2. In normal subjects, the PCO_2 in the brachial vein is ~ 6 mm Hg higher than in the arterial blood. With a very low cardiac output, blood flow to peripheral organs declines. For example, in a patient with diabetic ketoacidosis, we observed that the venous PCO_2 was 26 mm Hg higher than the arterial PCO_2, suggesting that the effective blood flow rate and by inference, the ECF volume was sufficiently contracted to cause this very big arteriovenous (A-V) PCO_2 difference. In support of this impression, this A-V PCO_2 difference fell promptly to ~ 7 mm Hg when sufficient saline was infused.

(iii) Indirect information from other laboratory tests

This information is not quantitative (Table 1-2).

TABLE 1-2

Clues to suspect that the ECF volume is contracted

- Urine electrolytes
- Plasma K concentration
- Plasma HCO_3 concentration
- Plasma creatinine concentration
- Plasma urea concentration (BUN)
- Plasma urate concentration

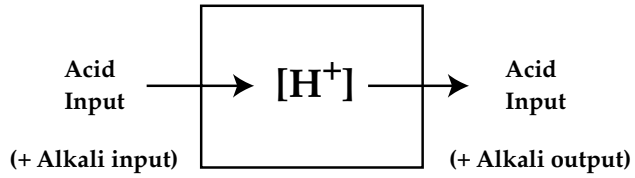
2. Tonicity balance to determine the quantitative contributions of Na and water balances

To calculate a tonicity balance, one needs to measure the water and electrolyte contents of all inputs and outputs. When the balances for water and Na + K balance are known, one knows why the P_{Na} changed and what therapy is needed to rectify the ECF and ICF volumes and compositions. We call this a tonicity balance (Figure 1-5).

Figure 1-5

Calculation of a tonicity balance

The rectangle represents all body compartments. To calculate a tonicity balance, one must have separate balances for water and for Na + K. The data can predict how the P_{Na} should change and this should be compared to measured values. It also defines the goals for therapy.



Quantitative analysis

***Na + K*:**

For every mmol retained or lost per L of total body water, the change in P_{Na} will be 1 mmol/l.

***Water*:**

A deficit or surplus of 1 L of water should change the P_{Na} by: P_{Na} times (TBW/TBW ± 1 L).

Tool that is not useful to design therapy for an abnormal P_{Na}:

EFW balance

An EFW balance cannot assess the basis for the abnormal P_{Na}. The calculation requires an imaginary separation of a solution into isotonic saline (same P_{Na} as the patient) and the residual is either EFW or Na without water (Figure 1-6). Because a gain of Na and a deficit of water are identical in EFW balance terms, one cannot distinguish between them as the cause of the abnormal P_{Na} (Table 1-3).

Figure 1-6

Calculation of EFW content

The total volumes are shown above the rectangles while the Na + K concentrations in these solutions are shown in the ovals inside the rectangles

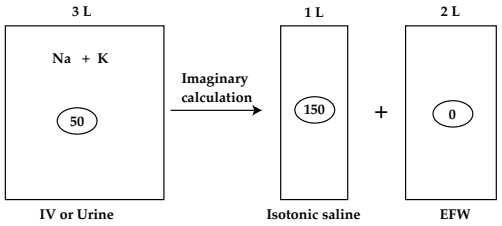


TABLE 1-3

Comparison of an EFW and a tonicity balance as a cause for a change in the P_{Na}

Three situations are described where the P_{Na} rose from 140 to 150 mmol/l. The only difference is the volume of isotonic saline infused over the time period of observation. In all three settings, there is a negative balance of 2 L of EFW. Nevertheless, the goals of therapy to correct the hypernatremia are clear only after a tonicity balance is calculated.

	Na + K (mmol)	Water (L)	EFW (L)	Therapy from balances EFW	Tonicity
Case 2-2					
Input	450	3	0	+ 2 L	+ 0 L water
Output	150	3	2	? Na	–300 mmol Na
Balance	**+300**	**0**	**-2**		
Case if 4 L of isotonic saline was infused and the urine output was unchanged					
Input	600	4	0	+ 2 L	–1 L
Output	150	3	2	? Na	–450 mmol Na
Balance	**+450**	**+1**	**–2**		
Case if no intravenous fluid was administered and the urine output was unchanged					
Input	0	0	0	+ 2 L	+ 3 L
Output	150	3	2	? Na	+150 mmol Na
Balance	**–150**	**–3**	**–2**		

VII PRINCIPLES OF INTRAVENOUS FLUID ADMINISTRATION

This section will deal with factors required to make clinical decisions in patients with a salt and water problem. The factors to analyze in intravenous solutions are:

- Need for cations (Content of Na = ECFV, K for hypokalemia)
- Need for anions (is bicarbonate needed?)
- Tonicity (is electrolyte-free-water needed or should it be lost?)

1. Questions to be answered

- Should the ECF volume rise, stay the same, or fall?
- How fast should the changes in ECF volume occur?
- Should the intravascular volume rise in a patient with an expanded ECF volume, but contracted intravascular volume (ascites, edema and hypotension)?
- Should the ICF volume rise, stay the same, or fall?
- How fast should the changes in ICF volume occur?
- Are there any dangers to anticipate with therapy?

2. Principles

- The ECF volume is determined primarily by the content of Na in the body.
- The vascular Vs interstitial volume is determined principally by the concentration of albumin in plasma (and the hydrostatic pressure).
- The P_{Na} is the best indicator of the ICF volume (Figure 1-2).
- In a patient with hyponatremia that is not due to hyperglycemia, there is an excess of water in cells.
- Leverage in therapy can be exerted upon:
  - input (intravenous, oral routes)
  - output (urine)
  - if the aim is to change the P_{Na}, create a tonicity balance (Figure 1-5).
  - In a patient who has very little output of urine, the concentration of Na in intravenous solutions must be matched to the P_{Na}. If this is difficult to do, attempt to raise or lower the U_{Na}.
  - In a patient with polyuria, infuse an equal amount of Na and water to that lost in the urine.

The goals of therapy and the solutions available for use are outlined in Table 1-4.

TABLE 1-4

Distribution of One Litre of Intravenous Therapy

Goals of Therapy	Solution	Vol ECF (ml)	Vol ICF (ml)
1. Expand ECFV	Isotonic saline (152 mmol/l)	1000	0
2. Expand ECFV, and also ICF volumes	• Half-normal saline (76 mmol/l)	667	333
	• 2/3 D_5W, 1/3 NS	555	445 [a]
	• 1/3 normal saline (51 mmol/l)	555	445
3. Expand ICFV	• D5W	333	667 [a]
4. Expand ICFV, but shrink ECFV	• D_5W + loop diuretic	< 333	> 667 [a,b]
5. Contract ICF volume[c]	• Hypertonic (3%,) saline, 507 mmol/l)	+ 2.1	(2.1) [d]

Footnotes

[a] Providing glucose is metabolized
[b] Depends on volume and quantity of Na lost in the urine
[c] Assume 70 kg individual with ECF volume of 14 L and ICF volume of 28 L
[d] Parenthesis denotes loss of ECF volume

Sample calculations

Raise the P_{Na} 4 mmol/l in 24-hours.

(i) Gain of Na strategy:

- Data needed:
  - Total number of L of water in the body, not the ECF volume as water equilibrates across ICF–ECF interface (50-60% of the weight (70 kg) will do most of the time).
  - Amount of water and Na lost on that day.

- Therapy:
  - Give 4 mmol of Na per L of body water plus the amount of Na and water that were lost.

(ii) Loss of water strategy

- Data needed:
  - P_{Na} value
  - Total body water as above
  - Balance of water and Na in that day,

- Therapy:
  - If the P_{Na} is 120 mmol/l and you want to raise it to 124 mmol/l in 24-hours, the total body water must decline by ~ 2.5 %.
  - If the total body water is 40 L, then a negative balance of 1 L of water must be created over 24 hours and replace all electrolytes that were lost.

3. Clinical aspects of intravenous fluid administration

Hyponatremia is the commonest electrolyte disorder in hospitalized patients. This is due in large part to an error in the selection of intravenous fluids. With respect to maintenance fluids, the traditional strategy is to use a prescription of *"one size fits all"*. What then are the issues?

(i) Oxidative metabolism generates heat

To avoid hyperthermia, heat must be dissipated. One form of heat loss is evaporation. The question is, *"Can we predict how much evaporation will be needed for thermal balance in a given hospitalized patient?"* This topic will be considered in section 4, '*Analysis of insensible water loss*'.

(ii) What should be the source of the water needed for evaporative heat loss?

There are two possible sources, endogenous water in excess of physiological needs, and exogenous water (e.g., intravenous fluids). Exogenous water should NOT be given if a patient has a surplus of endogenous water.

(iii) Currently recommended maintenance fluids contain electrolyte-free water

Common examples are 0.2 % saline in children and 2/3 D_5W with 1/3 isotonic saline in adults. The danger of administering EFW is when the body cannot rid itself of this water because renal mechanisms to excrete it have been removed (ADH is present).

(iv) Patients often have non-osmotic stimuli for the release of ADH

When this electrolyte-free water is retained, the P_{Na} will fall acutely. This causes cells to swell because the ICF volume is inversely related to the P_{Na} (Figure 1-2). Because brain cells occupy approximately 2/3 of the intracranial volume, brain cell swelling is very likely to increase intracranial pressure and predispose to brain herniation because the brain is encased in the skull and there is only a small volume of intracranial water that can be lost when there is a small rise in intracranial pressure (the volume in the cerebrospinal fluid). Children are at greater risk because their brains have a larger ICF volume (more cells) per total skull volume.

(v) Usual reasons for intravenous fluid administration

Three common reasons to give intravenous fluids are provided below.

(a) Re-expand a contracted effective circulating volume

Infuse isotonic saline only if there is a hemodynamic emergency. There is one caution, however—there is a danger if the patient also has an acute and major fall in their P_{Na}. Another instance with a low effective circulating volume is when an anaesthetic agent diminished venous tone sufficiently to cause a fall in the blood pressure. Infuse a large enough volume of isotonic saline to prevent hypotension in this setting.

(b) Replace a large water deficit in the ICF compartment

This is usually indicated by a $P_{Na} > 145$ mmol/l. Infuse electrolyte-free water (often 5 % dextrose in water (D_5W)). Care must be taken to avoid inducing hyperglycemia ($P_{Glucose} > 10$ mmol/l (180 mg/dl)).

(c) Infuse maintenance fluids to match insensible losses

The traditional guidelines for maintenance fluid infusion focus on the need to replace insensible loss of water for evaporative heat dissipation—the latter was related incorrectly to caloric expenditure based on data and deductions published almost 50 years ago. This error is compounded by a perceived need to excrete a larger urine volume with a more 'comfortable' urine osmolality. There have been a number of recent publications that questioned this practice. The rationale is provided below.

4. Maintenance fluid administration

This topic is mainly concerned with the need of the body to lose the heat produced during oxidative metabolism.

(i) Analysis of insensible water loss

Heat loss is a vital function served in part by evaporation of surface water from the skin and the respiratory tract. While this rationale is qualitatively correct, it may not always be correct from a quantitative perspective and you do not need to infuse water if there is a surplus present in the body.

(a) Water loss via the lungs

This component of water loss does NOT change the P_{Na}. My rationale is that metabolic production of CO_2 and water occur in a 1:1 proportion during the oxidation of carbohydrates ($C_n(H_2O)_n$) (equation 1) and fatty acids ($-CH_2)_n$ (equation 2, Figure 1-7). In addition, these two end products are eliminated together in alveolar air in a 1:1 proportion providing that the arterial PCO_2 is close to 40 mm Hg. The reason for this parallel excretion of water and CO_2 is that the partial pressure of water vapour and CO_2 are virtually equal in alveolar air (47 and 40 mm Hg) and in inspired air (close to zero after air is warmed to 37° C). Therefore water loss via exhaling alveolar air is equal to its metabolic production so these two pathways can be ignored unless the patient is hyperventilating and/or is on a ventilator and is inspiring humidified air warmed to body temperature. Only water evaporation from the upper respiratory tract results in a negative water balance.

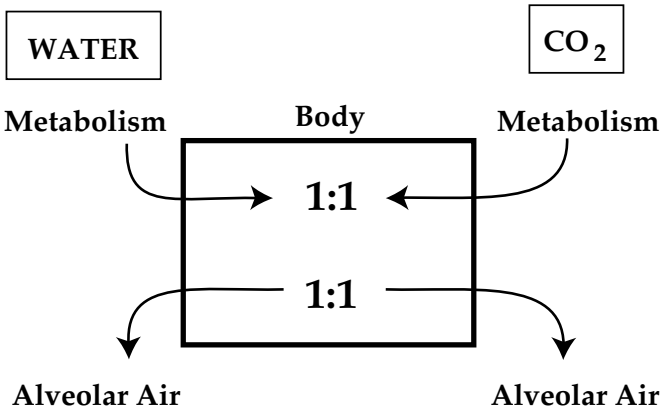
$$\mathbf{C_n(H_2O)_n + n\,O_2 + ADP \rightarrow n\,CO_2 + n\,H_2O + ATP} \qquad \mathbf{(1)}$$

$$\mathbf{(-CH_2)_n + 1.5n\,O_2 + ADP \rightarrow n\,CO_2 + n\,H_2O + ATP} \qquad \mathbf{(2)}$$

Figure 1-7

Daily balance for metabolic water

The body is depicted by the large rectangle. The balance for water is shown to the left while the balance for CO_2 is shown to the right of this rectangle. Production of water and CO_2 (top arrows) as well as their loss (bottom arrows) are in ~ 1:1 proportion. Hence there is no net change in water balance as a result of metabolism and alveolar ventilation.



(b) Water loss in sweat

This type of water loss is the major reason to have a source of electrolyte-free water for heat dissipation. It is clear that an exogenous source of water should be replaced only in patients who have a $P_{Na} > 140$ mmol/l because this indicates that there is not a surplus of intracellular water.

The link between water evaporation (heat dissipation) and caloric expenditure (heat production) is the cornerstone for the traditional prescription for maintenance fluid administration. These two components are analyzed in the following paragraphs.

Heat dissipation

In a healthy, fed, 70-kg adult male in steady state, approximately 2500 kcal are ingested and expended each day. If 1 L of water were to evaporate, this would cause a loss of only slightly greater than 500 kcal. Hence ~ 2000 kcal of heat are removed daily by radiation, conduction and convection. The exact quantitative contribution of

these latter routes of heat loss depends on environmental factors such as temperature, air circulation, humidity, cutaneous blood flow, clothing, etc. Hence they cannot be quantitated to generate guidelines that would apply to every patient.

When additional heat loss is needed, there is an increased production of sweat together with its evaporation. Therefore an appreciable volume of sweat can be anticipated during exercise or a febrile state unless heat loss by conduction and/or convention can be augmented. Conversely, little loss water in sweat might occur when caloric expenditure declines if there is little change in heat loss by conduction and convection.

Heat production

The rate of fuel oxidation depends on how quickly ADP is regenerated during biological work and/or if oxidative phosphorylation is uncoupled.

(i) Work

There are three categories of biologic work, biosynthetic, mechanical, and electrical work. To digest food, enzymes must be synthesized. For absorption of nutrients, there is a need for ATP formation to drive ion transport. During the conversion of dietary fuels to storage forms of energy, there is biosynthesis of proteins, glycogen, and triglycerides. Hence it is not surprising that caloric expenditure is much lower when there is little physical activity (e.g., bed rest) and little dietary intake. In quantitative terms, there is a 50% decline in daily caloric expenditure during prolonged fasting with inactivity. In summary, if a hospitalized patient is afebrile, does not eat, and is physically inactive, much less heat production can be anticipated and thereby there is a diminished need for evaporation of water for heat loss.

(ii) Uncoupled energy metabolism

Caloric expenditure (heat production) exceeds that needed for metabolic work if there is uncoupling of oxidative phosphorylation. This form of heat production is catalyzed by uncoupler proteins. The major uncoupler proteins that have an impact on the endogenous heat production in human subjects are those in skeletal muscle—their estimated contribution to energy metabolism in the rat is about 25% of resting energy turnover. In summary, it is unlikely that the contribution of uncoupler protein-catalyzed energy metabolism will be constant in a patient and it

should be extremely difficult to predict their total caloric expenditure while receiving much of his/her caloric supply from endogenous sources. Therefore relating body needs for electrolyte-free water in an individual patient is dependent on unreliable criteria—estimated energy expenditure based on body weight.

5. Excretion of concentrated urine and extra renal work

One reason proposed to infuse electrolyte-free water to hospitalized patients is to minimize the work of the kidney. This again is not really valid for the following reasons. Energy is expended for active, but not passive reabsorption of Na. While it seems obvious that work is required to excrete concentrated urine, I doubt that extra renal work is required for this task. My rationale is that normal kidneys reabsorb 99.5% of filtered Na whether or not the final urine is concentrated. Water reabsorption in the kidney is passive and is controlled by the induction of water permeability of luminal membrane of the distal nephron)—this requires the expenditure of very little energy so it can be ignored in the overall quantitative analysis of renal work.

6. Prescription for intravenous fluid administration

It is important to recognize that intravenous fluid prescriptions should be individualized. The priorities for the infusion of fluids were summarized above. Focusing on maintenance fluid administration, my view is that caloric expenditure should NOT be used to quantitate its need.

(i) Contraindications concerning the infusion of hypotonic fluids

Do not infuse hypotonic solutions if the P_{Na} is < 138 mmol/l. In contrast, hypotonic fluids should be given to match the daily loss of electrolyte-free water in sweat in a patient who has a P_{Na} > 138 mmol/l. This volume is less than 1 L/day unless the patient is febrile or if there is a large renal loss of electrolyte-free water in a water or osmotic diuresis, or if there is a non-renal loss via the GI tract or by the skin.

(ii) Unique factors that place patients at greater risk of developing a more severe decline in their P_{Na} when given a given absolute volume of electrolyte-free water

Two factors should be considered. The first is the age of the patient because brain cell number decreases with age. Therefore children and young adults are at a greater risk. The second factor

concerns skeletal muscle mass relative to body weight because 50% of body water is in skeletal muscle in normal subjects. Therefore in patients who have marked muscle atrophy due to disuse, nutritional problems, and/or a disease that involves skeletal muscle, much less electrolyte-free water needs to be retained to cause a serious decline in P_{Na} and, as a result, a greater degree of swelling of brain cells if the hyponatremia is acute.

CHAPTER 2

POLYURIA

I. ESSENTIAL POINTS

1. Definition

The following case example illustrates that this definition should be based on physiological principles rather than 'usual' or 'normal' volumes. A list of causes of polyuria is presented in Table 2-1.

TABLE 2-1

DIFFERENTIAL DIAGNOSIS OF POLYURIA

Basis	Key features	Tools
Water diuresis		
• Primary polydipsia	• Lack of stimulus for ADH	• P_{Na} < 138 mmol/l
• Central DI	• CNS pathology	• Responds to exogenous ADH
• Vasopressinase	• Pregnancy, necrotic tissue	• Responds to dDAVP, not ADH
• Nephrogenic DI	• Often lithium intake	• Not respond to dDAVP
Osmotic diuresis		
• Organic agents (glucose, urea, mannitol) • Electrolytes (Na + Cl)	• U_{osm} > 300 mOsm/l and osmole excretion > 900 mosmoles/day	• U_{osm} & $U_{flow\ rate}$ • Seek nature of the urine osmoles
Renal concentrating defect medulla	• U_{osm} max 300-600 mOsm/l	• Diseases or drugs that affect the renal

2. Illustrative case to define polyuria

CASE 2-1

How to define polyuria

The daily urine volume in a 22-year old woman is 4 L/day and its U_{osm} is 80 mOsm/kg H_2O. On that day, her P_{Na} is 130 mmol/l.

Question

- **Is this polyuria?**
- **What are the risks for the patient?**

Discussion of Case 2-1

Is this polyuria?

(i) Conventional interpretation

Polyuria is present because the urine volume is > 3 L/day. This is a water diuresis because the U_{osm} is considerably < the P_{osm}. The presence of hyponatremia indicates that the patient has primary polydipsia.

(ii) Physiology-based interpretation

The observed urine flow rate (~3 ml/min) is much lower than expected if ADH is absent (> 10 mil/min) because of the low P_{Na}. Hence this is not physiological polyuria.

She could have SIADH or a low delivery of hypo-osmolar filtrate to the distal nephron. The latter could be inferred because her osmole excretion rate was low {320 instead of 600 - 900 mosmoles/day (80 mOsm/kg H_2O X 4 L/day)}

.

(iii) Implications

Making a diagnosis of polyuria because the urine output was 4 L/day does not reveal that the urine volume was not large enough. This helps identify the following risks for the patient.

What are the risks for the patient?

(i) Acute hyponatremia:

This patient is at risk of a substantial gain of water if she were to:

- Ingest more water

• Have a non-osmotic stimulus for the release of ADH (Table 2-2)
• Diminish her non-renal loss of water in sweat (fails to run).

The resulting sudden fall in her P_{Na} will place her at risk of developing acute brain cell swelling with possible herniation.

(ii) Sudden rise in her P_{Na}

If she were to increase her intake of NaCl, there could be a large increase in the distal delivery of filtrate and thereby a large and acute excretion of EFW because there was no stimulus to release ADH (hyponatremia is still present). This very rapid correction of chronic hyponatremia could place her at risk of developing the ODS, especially if her dietary intake is poor or if she was K depleted.

TABLE 2-2

CAUSES FOR THE RELEASE OF ADH

A more detailed list is provided in Table 4-3, page 47.

ADH release in response to physiologic stimuli
• Non-osmotic stimuli
- Excessive pain, nausea, vomiting. anxiety.
- Low effective circulating volume

ADH release without a physiologic stimulus
• CNS or lung lesions.
- Neoplasms, granulomas such as tuberculosis.
• Metabolic disorders such as acute intermittent porphyria.
• Administration of agents that have an antidiuretic effect
- dDAVP (e.g., treatment for diabetes insipidus or urinary incontinence)
• Drugs that stimulate the release of ADH:
- Examples include nicotine, clofibrate, tricyclic antidepressants, antineoplastic agents (probably via nausea and emesis), morphine,
• Drugs that promote the actions of ADH on the kidney by increasing cyclic AMP levels or augmenting its bioactivity:
- Examples include oral hypoglycemics (e.g., chlorpropamide), methylxanthines (e.g., caffeine, aminophylline), analgesics that inhibit prostaglandin synthesis (e.g., aspirin, non-steroidal anti-inflammatory drugs), anticonvulsants such as tegretol.

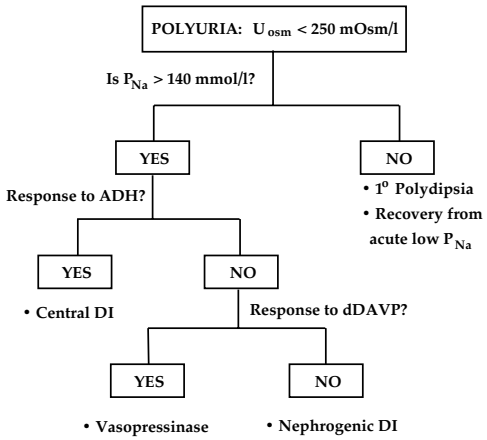
II. CLINICAL APPROACH TO THE PATIENT WITH POLYURIA

The differential diagnosis of polyuria is provided in Table 2-1 and the steps to take are illustrated in Flow Chart 2-1 when polyuria is caused by a water diuresis and in Flow Chart 2-2 when polyuria is caused by an osmotic diuresis.

Flow Chart 2-1

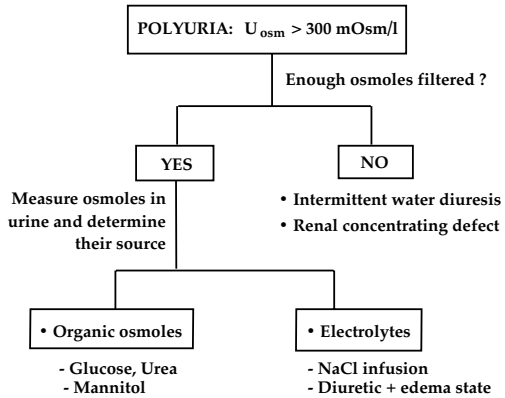
Approach to the Patient with Polyuria

A bullet symbol precedes the final diagnostic categories.



Flow Chart 2-2

Investigation of a patient who has an osmotic diuresis



III. CASES TO ILLUSTRATE THE CLINICAL APPROACH

CASE 2-2

Water diuresis following neurosurgery

A craniopharyngeoma was resected today from a 16-year-old male (weight 50-kg, total body water 30 L). During neurosurgery, his urine flow rate rose to 10 ml/min (3 L in 300 min). His P_{Na} rose from 140 to 150 mmol/l. Over this period, he received of 3 L of isotonic saline. His U_{osm} was 120 mOsm/kg H_2O, and his urine Na + K concentration was 50 mmol/l. After dDAVP, his urine flow rate fell to 6 ml/min, the U_{Na} was 175 mmol/l, and his U_{osm} was 375 mOsm/kg H_2O.

Questions

- **Is this a water diuresis?**
- **What is his <u>expected</u> renal response to dDAVP?**
- **What is his basis for his high osmole excretion rate?**

Note: The basis for hypernatremia will be discussed in Chapter 3, Case 3-1.

Discussion of Case 2-2

Please proceed using Flow Chart 2-1.

Is this a water diuresis?

Step 1. What is the U_{osm}?

Because his U_{osm} is 120 mOsm/kg H_2O, he has a water diuresis.

Step 2. Is the P_{Na} high enough to stimulate the release of ADH?

Yes because the P_{Na} is 150 mmol/l. Hence his water diuresis appears to be due to diabetes insipidus.

Step 3. Renal response to ADH

This raises an interesting problem. Should we compare the patient to us or should we compare his response to others with a similar osmole excretion rate and a prior water diuresis?

If we compare the patient to us, he does not have an appropriate response to ADH because we would have a U_{osm} of > 900 mOsm/kg H_2O and a flow rate of < 1.0 ml/min.

If we compare the patient to a suitable control, he does have an appropriate response to ADH because his medullary interstitial compartment was washed out from the prior osmotic diuresis and because he had a high osmole excretion rate (120 mOsm/kg H_2O times a 24-hr volume of 15 L (1800 mosmoles/day). When ADH acts, he will have an osmotic diuresis.

What is the basis for his high osmole excretion rate?

Because his major urine osmoles were electrolytes (100 of the 120 mOsm/l), this is an electrolyte-induced osmotic diuresis. In fact, the rate of Na + K excretion was 500 µmol/min (50 µmol/ml X 10 ml/min—this extrapolates to 720 mmol/day or 5 times the usual values on a typical Western diet).

The positive balance of saline expanded his ECF volume and this induced the natriuresis. This electrolyte-induced osmotic diuresis will continue as long as his effective circulating volume is expanded.

This electrolyte-induced osmotic diuresis will be very important when we examine its influence on his PNa in Chapter 3.

CLINICAL PEARLS

- *A patient can have more than one reason for polyuria, but one cannot have a water diuresis and an osmotic diuresis at the same time because poor water permeability in the distal nephron is required for a water diuresis while an osmotic diuresis requires water to be permeable in this nephron site.*
- *When interpreting the post-dDAVP urine flow rate, do not think that there is an incomplete response to dDAVP if the patient had a prior high osmole excretion rate or a water diuresis.*
- *The absolute value of the U_{osm} in a water diuresis depends on the rate of excretion of osmoles.*

CASE 2-3

Polyuria in a patient who had a bone marrow transplant

A 70-kg male had a recent bone marrow transplant. He was given drugs that could lead to a catabolic state. His 24-hour urine volume was 6 L/day and the U_{osm} was 500 mOsm/kg H_2O. He did not receive mannitol, his $P_{Glucose}$ was 180 mg/dl (10 mmol/l), and his P_{Urea} was 75 mmol/l (BUN 210 mg/dl).

Questions

- **Does he have an osmotic diuresis?**
- **What was the nature of the urine osmoles?**
- **What is the source of the urine urea?**
- **What is the major aim of therapy with respect to urea excretion?**

Discussion of Case 2-3

Please use the right side of Flow Chart 2-2.

Does he have an osmotic diuresis?

Step 1. What is the U_{osm}?

Because his U_{osm} was > 300 mOsm/kg H_2O and his osmole excretion rate was 3000 mosmoles/day, an osmotic diuresis was present.

What was the nature of the urine osmoles?

Step 2. Estimate the rate of filtration of the major urine osmoles:

One can make a reasonable estimate of a solute's likelihood of causing polyuria if its concentration in plasma is measured, the GFR is estimated, and the renal handling of that solute is known. For example, his $P_{Glucose}$ of 180 mg/dl (10 mmol/l) so his filtered load of glucose does not exceed the maximum amount of glucose that can be reabsorbed. Hence he does not have a glucose-induced osmotic diuresis. In contrast, he also does have a high enough P_{Urea} to cause a urea-induced osmotic diuresis.

Step 3. Measure urine osmoles and determine the source of extra osmoles:

He did have a high enough urine urea concentration (400 mmol/l) to confirm that he had a urea-induced osmotic diuresis. The next objective

was to determine if the source of urea is from exogenous protein or tissue catabolism.

What is the source of the urine urea?

The patient excreted approximately 2400 mmol of urea that day (6 L/day x 400 mmol urea/l). For every 100 g of protein oxidized, 16 g of nitrogen is converted to urea (572 mmol of urea). Therefore, this amount of urea represents the breakdown of close to 400 g of protein. On that day, the patient was given 60 g of protein by nasogastric tube. Therefore, he catabolized approximately 340 g of endogenous protein.

What is the major aim of therapy with respect to urea excretion?

Each kg of lean body mass has 800 g of water and close to 180 g of protein. Therefore his urea excreted today represents the catabolism of ~ 2 kg of lean body mass. Should this continue, he would ultimately undergo marked muscle wasting. This could compromise respiratory muscle function and lead to bronchopneumonia. Furthermore, this catabolic state could affect his immunological defense mechanisms.

Once this metabolic problem was recognized, therapy included a nutritional emphasis. More exogenous calories and protein were given. Anabolic hormones such as high dose insulin (with glucose to avoid hypoglycemia) or anabolic steroids and/or the provision of nutritional supplements such as glutamine might minimize endogenous protein catabolism. In addition, one should be cautious about the use of drugs that can augment catabolism such as glucocorticoids.

CLINICAL PEARL

By identifying the nature of the osmoles causing an osmotic diuresis, polyuria was a clue to reveal the very large endogenous protein catabolism with its need for treatment options to minimize this threat to survival.

CHAPTER 3

HYPERNATREMIA

I. ESSENTIAL POINTS

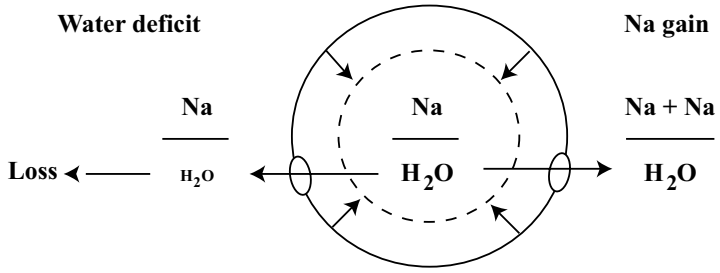
1. Definition:

Hypernatremia = P_{Na} > 144 mmol/l; its causes are Na gain and/or water loss. Hypernatremia signals that the cell volume has decreased in size (Figure 3-1).

Figure 3-1

Cell size during hypernatremia

The solid circle represents the normal ICF volume and the dashed line the new shrunken ICF volume due to hypernatremia independent of whether the basis is water deficit (left side) or Na gain (right side). The ovals represent APQ-1 water channels in the cell membrane.



2. Expected physiological responses:

(i) Brain: Thirst; if absent, look for a CNS lesion.

(ii) Renal: Expect the release of ADH and the excretion of the minimum urine flow rate (~ 0.75 L/day) with a maximum U_{osm} (> 900 mOsm/kg H_2O).

3. Causes of Hypernatremia:

These are summarized in Table 3-1.

TABLE 3-1

CAUSES OF HYPERNATREMIA

The most important aspect is that hypernatremia is always accompanied by a water intake problem. The danger is from brain cell volume changes. Abbreviations: Diabetes insipidus = DI.

- **Net primary water loss**
  - Reduced water intake
    - Defective thirst due to altered mental state, psychological disorder, disease involving the osmoreceptor or thirst center
    - Inability to gain access to, or to drink water
    - Lack of water
  - Increased water loss
    - Renal loss: central DI, nephrogenic DI, osmotic diuresis, vasopressinase
    - Gastrointestinal loss: vomiting, osmotic diarrhea
    - Cutaneous loss: sweating
    - Respiratory loss: hyperventilation
  - Water shift into the ICF
    - Gain ICF particles (convulsion, rhabdomyolysis)
- **Net primary Na gain**
  - Hypertonic NaCl or $NaHCO_3$ infusion
  - Ingestion of sea-water or NaCl replacing sugar in the feeding formula
  - IV saline with a higher [Na] than during osmotic or water diuresis

II. QUESTIONS TO ASK OF THE PATIENT WITH HYPERNATREMIA

1. Is hypernatremia due to a positive balance for Na?

Answer: Yes, if the ECF volume is normal or expanded, thirst and excretion of the minimum volume of very concentrated urine.

This can occur during DKA when 150 mmol/l saline is infused and the U_{Na} is < 100 mmol/l or infusing fluid with a higher Na concentration than in the urine in a patient with DI.

2. Has there been non-renal water loss?

Answer: If this is the case, the patient will be thirsty and cannot obtain water; expect a minimum volume of maximally concentrated urine.

3. Is the cause a water shift into the ICF?

Answer: This is a muscle problem where the number of ICF particles has increased (mild rhabdomyolysis, convulsions). In this case, there will not be weight loss.

4. Is the cause excessive renal water loss?

Answer: The 2 major groups of causes are DI (central or nephrogenic, Table 3-2) or an osmotic diuresis due to glucose or urea.

The differential diagnosis is shown in Flow Chart 2-1, page 24 and hinges upon whether the large volume of urine has a U_{osm} that is very low or in the 400-500 mOsm/kg H_2O range.

TABLE 3-2

ETIOLOGY OF DIABETES INSIPIDUS

- **Central Diabetes Insipidus**
  - Trauma (especially basal skull fractures)
  - Neurosurgery
  - Space occupying lesions (craniopharyngeoma, granuloma, other)
  - Infection (meningitis, encephalitis)
  - Vascular (aneurysm)
  - Post hypoxia
  - Drugs interfering with ADH release (e.g.phenytoin)
  - Idiopathic (may be familial)

- **Nephrogenic Diabetes Insipidus**
  - ADH fails to act
    - Drugs (lithium, demethylchlortetracycline)
    - Congenital nephrogenic diabetes insipidus
    - Loss of medullary hypertonicity
      - Interstitial disorders including obstructive uropathy
      - Loop diuretics
      - Hypokalemia
      - Occupancy of the Calcium sensing receptor in the LOH (hypercalcemia, cationic drugs or protein)

- **Vasopressinase from necrotic tissues**

III. CLINICAL EMPHASIS

Hypernatremia is not a specific disease; look for the underlying disorder (Table 3-1). In acute hypernatremia, there is brain cell shrinkage (Figure 3-1). In chronic hypernatremia, brain cells tend to re-expand slowly by accumulating solutes. This means that water replacement must be slow; lower the P_{Na} by close to 10% /24 hr.

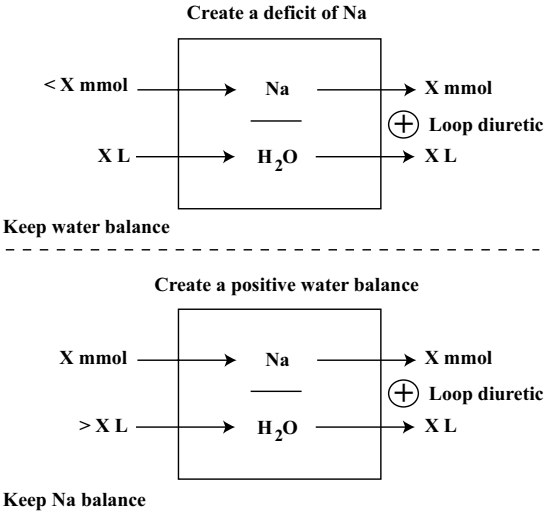
Assess the hypothalamic response. If thirst is absent, suspect a CNS lesion or a communication problem.

Assess the renal response. Hypernatremia almost always involves water loss and this implies that ADH should be released. Failure to find a very low urine volume and/or a high U_{osm} suggests a renal problem. The major renal causes of hypernatremia are diabetes insipidus or an osmotic diuresis. Distinguish these with the U_{osm}.

Figure 3-2

Create a fall in the P_{Na} using a loop diuretic

The rectangle represents the body with its Na and H_2O ratio in the ECF compartment. To lower the P_{Na} by inducing a Na deficit, create a loss of Na + H_2O with a loop diuretic and replace all the water, but not all the Na. To create a positive water balance after giving a loop diuretic, replace all the Na and give more water than was lost—e.g., give 2 L 75 mmol/l saline when 1 L of 150 mmol/l NaCl was lost.



Treatment has 2 main objectives. Stop ongoing water loss (ADH will be needed in central DI). Give water; the oral route is the safest. IV solutions must have a lower [Na] than ongoing losses in a polyuric state. The 2 options are 5% glucose in water (limited by the rate of glucose metabolism, do not exceed 0.3 L/hr) or hypotonic saline (33-75 mmol/l), the limit being the Na load (Figure 3-2).

IV. CLINICAL APPROACH TO THE PATIENT WITH HYPERNATREMIA

I divide my approach into three stages.

1. Determine the relative importance of a gain of Na and a deficit of water.
2. Does the patient have a CNS lesion?
3. Is his renal response appropriate?

V. CASES TO ILLUSTRATE THE CLINICAL APPROACH

CASE 3-1

Hypernatremia during neurosurgery

A craniopharyngeoma was resected from a 16-year-old male (weight 50-kg, total body water 30 L). During neurosurgery, his urine flow rate rose to 10 ml/min (3 L in 300 min) and his P_{Na} rose from 140 to 150 mmol/l. Over this period, he received of 3 L of isotonic saline. His U_{osm} was 120 mOsm/kg H_2O, and his urine Na + K concentration was 50 mmol/l.

Questions

- **Why did hypernatremia develop?**
- **Does he have a CNS lesion?**
- **Is his renal response appropriate?**
- **What are the goals for therapy?**

Discussion of Case 3-1

Why did hypernatremia develop?

A tonicity balance (Figure 1-5, page 10) is especially useful in an acute care setting because the data needed are already on the chart (IN and OUT data in the nurses notes).

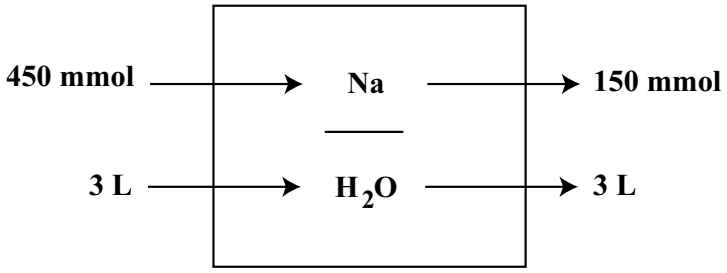
The patient received 3 L of isotonic saline and excreted 3 L of urine with a $U_{Na} + U_K$ of 50 mmol/l. Accordingly, there is a gain of 300 mmol of Na and a nil balance of water (Figure 3-3).

Balance data for Na can also be deduced using the change in P_{Na} and an estimate of the ECF volume if one has an accurate assessment of this volume

.

Figure 3-3

Tonicity balance in Case 3-1



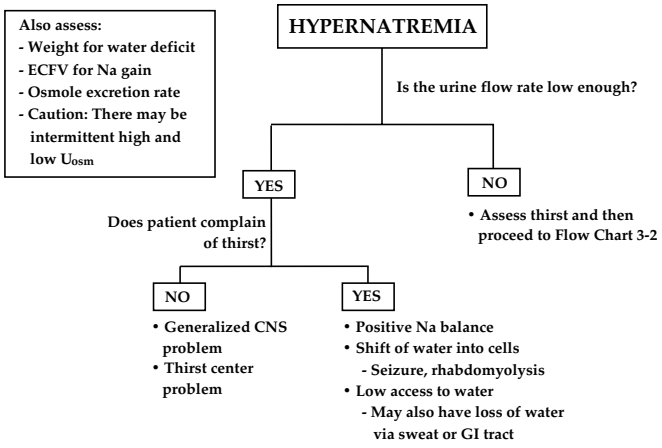
Does he have a CNS lesion?

The objective is to define whether there is a lesion involving the central osmostat, the thirst control center, and/or the site of synthesis of ADH in the hypothalamus, the pathway to the posterior pituitary and/or in this latter location (Figure 1-1). The steps to take are summarized in Flow Chart 3-1.

Flow Chart 3-1

Hypernatremia: Assess the hypothalamic responses

The first step is to assess whether vasopressin is present and acting on the kidney. The second step is to assess the reason why there was too little intake of water.



Step 1. Is the flow rate very low?

No, the urine flow rate is enormous (10 ml/min). In response to hypernatremia, ADH should be released and the urine output should be ~ 0.5 ml/min in an adult on a typical western diet.

Because the urine flow rate is so high, proceed to Flow Chart 3-2 after assessing the thirst response.

Step 2. Does the patient complain of thirst?

The expected response to hypernatremia is thirst, but thirst may be absent because of a generalized disturbance of CNS function (anaesthesia), so a lesion involving the central osmostat and/or the thirst center cannot be assessed at this time.

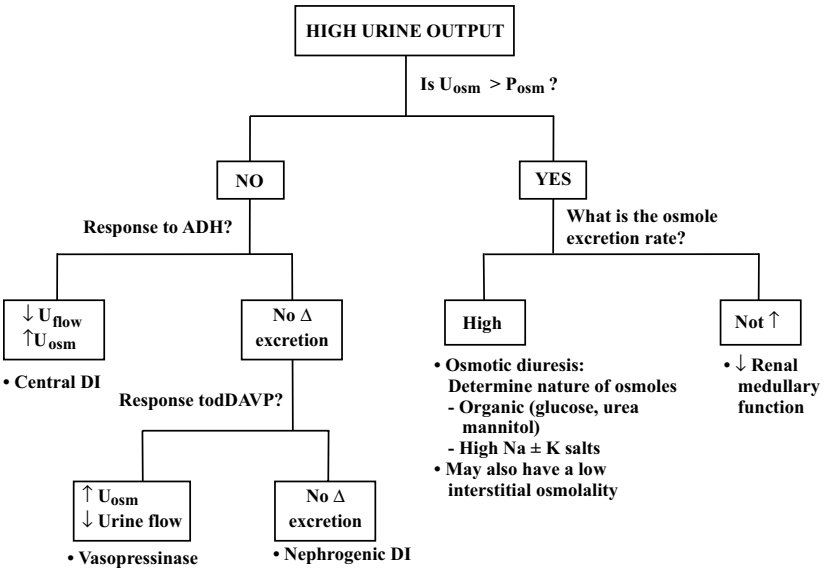
Is his renal response appropriate?

In the patient with hypernatremia and a large urine output, the steps to follow to distinguish between a water or an osmotic diuresis are outlined in Flow Chart 3-2. Because his U_{osm} is much less than his P_{osm}, he has a water diuresis. Because he had a response to ADH, this is central DI (see discussion of case 2-2, chapter 2).

Flow Chart 3-2

Hypernatremia: Assess the renal responses

The steps taken permit the clinician to separate a water diuresis from an osmotic diuresis.



What are the goals for therapy?

The goal of therapy is now clear—create a negative balance of 300 mmol of Na (+ Cl), but do not induce a change in water balance. This therapy will correct the hypernatremia and return both the ICF and ECF compartment volumes and composition to normal.

CASE 3-2

Hypernatremia due to an osmotic diuresis

A 73-year old male has congestive heart failure with a large volume of edema fluid. He was treated with a loop diuretic and passed 5 L of urine that day. Of note, his P_{Na} rose and he was thirsty.

		Before	After loop diuretic	
		Plasma	Plasma	Urine
Na	mmol/l	140	150	55
K	mmol/l	3.7	3.0	30
Urea	mmol/l	20	10	150
Glucose	mmol/l (mg/dl)	10 (180)	10 (180)	0
Osmolality	mOsm/l	310	325	320

Questions

- **Why did hypernatremia develop?**
- **Is there a CNS component to the hypernatremia?**
- **Is the renal response appropriate?**

Discussion of Case 3-2

Why did hypernatremia develop?

The first step is to identify whether there was a positive balance for Na and/or a negative balance for water to explain the basis for his rise in P_{Na}. Given the absence of input and his urinary excretion of Na + K, the basis for his rise in P_{Na} is a negative balance for water. To understand why he had this change in P_{Na}, determine why his $U_{Na} + U_K$ was lower than his $P_{Na} + P_K$.

Is there a CNS component to the hypernatremia?

Follow the steps outlined in Flow Chart 3-1.

Step 1. Is the urine flow rate low enough?

No because when his P_{Na} was 152 mmol/l, his ADH level should be high enough to cause his daily urine volume to be ~ 0.75 L/day; it was 5 L that day. This polyuria will be explored using Flow Chart 3-2.

Step 2. Does the patient complain of thirst:

Yes, so his hypothalamic osmostat and thirst center are intact.

Is there a renal basis for the hypernatremia?

Follow the steps outlined in Flow Chart 3-2.

Step 1. Is the U_{osm} greater than his P_{osm}?

His U_{osm} is 320 mOsm/kg H_2O, high enough to rule out a water diuresis and suggests that there was some release of ADH. Hence, proceed to the right side of the flow chart.

Step 2. What is the osmole excretion rate?

In subjects on a typical Western diet, one would expect a value less than 900 mosmol/day. His osmole excretion rate was 1600 mosmol/day. Hence he has an osmotic diuresis.

Step 3. What is the nature of these osmoles?

The urine contained a combination of urea and electrolytes. The high urea excretion rate was the result of elimination of part of his large urea pool (high P_{Urea} and the edema fluid). The high rate of excretion of electrolytes was due to the loop diuretic his expanded ECF volume.

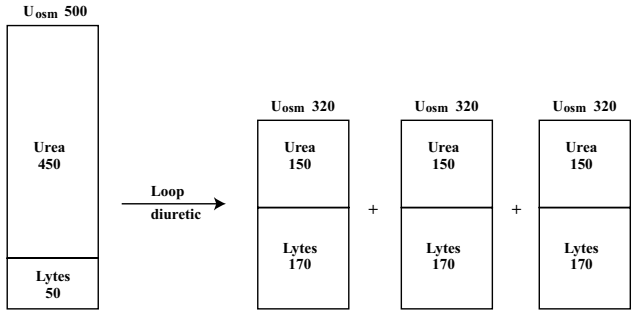
There was another important factor in this patient, the diuretic-induced low medullary interstitial osmolality. This will cause a higher urine flow rate for any given osmole excretion rate.

The combination of this ceiling on the U_{osm} and that urea accounts for an appreciable proportion of the urine osmoles, there will be a lower $U_{Na} + U_K$ and a higher volume of EFW in each litre of urine (Figure 3-4). When the loop diuretic effect wore off, his U_{osm} rose to 700 mOsm/kg H_2O, ruling out central or nephrogenic DI.

Figure 3-4

Urine composition before and after the loop diuretic

Each rectangle represents a urine volume of 1 L. The numbers represent concentrations in mOsm/kg H_2O. At a U_{osm} of 320 – 150 mosmol of urea, or 170 mOsm/l for electrolytes, the $U_{Na} + U_K$ = 85 mmol/l.



What therapy will be needed to bring his P_{Na} to normal?

To lower his P_{Na}, either create a negative balance for Na and/or a positive balance for water.

ECF analysis:

Because he still has edema fluid, one should create a negative balance for Na. This aim can be achieved by giving a loop diuretic and replace the urine volume with water, but no Na (Figure 3-2). K replacement as KCl may be needed to replace the urinary K loss if his P_K falls appreciably.

ICF analysis

When the P_{Na} decreases at the appropriate rate, water will shift into cells, re-expanding the ICF volume.

CLINICAL PEARL

When there is a low ceiling for the maximum U_{osm} (low medullary interstitial osmolality) and a high rate of excretion of organic osmoles (e.g. urea), the $U_{Na} + U_K$ will be much lower than their concentrations in plasma so a rise in the P_{Na} can be expected.

VI. TREATMENT OF THE PATIENT WITH HYPERNATREMIA

A tonicity balance will be very helpful to design therapy because we know whether to focus on a negative balance for Na and/or a positive balance for water.

ICF analysis:

A high P_{Na} indicates that there is a water deficit in the ICF compartment with rare exceptions (Figure 3-1). The amount of water needed to restore the ICF tonicity and volume can be estimated as in the equation below. To perform this calculation, an estimate of normal ICF volume (2/3 of body water) is required. Another assumption is that the number of particles in the ICF did not change appreciably.

ICF H_2O deficit = Normal ICFV x (Current P_{Na} - 140 mmol/l)/140 mmol/l

Sample calculation

Two 50-kg females have a P_{Na} of 154 mmol/l. The analysis is divided into two steps. After each is performed, you must add the results to obtain the appropriate therapy.

ICF Analysis

This is similar for both patients. Because the P_{Na} is now 10% higher, each will need a positive balance of ~ 10% of their normal ICF volume of 20 L—they must retain 2 L of water.

ECF Analysis

Patient 1 has a normal ECF volume (10 L)

A deficit of 140 mmol of Na will correct her ECF composition and volume (154 - 140 mmol/l x 10 L).

Patient 2 has an estimated ECF volume of 7 L instead of 10 L

Because the Na content in her ECF is 1078 mmol (154 mmol/l x 7 L), she will require a positive balance of 322 mmol of Na (1400 – 1078 mmol) plus a positive balance of 3 L of water to restore the tonicity and the volume of the ECF compartment to normal.

VII. ADDITIONAL ILLUSTRATIVE CASE

CASE 3-3

Polyuria and hypernatremia following a head injury

A 19-year old male fell 15 feet from a balcony and suffered multiple soft-tissue bruises and fractures including a skull fracture. He is currently comatose. Over a 3-day period, his P_{Na} rose from 140 to 154 mmol/l, his urine volume is now 4 L/day and his latest U_{osm} is 500 mOsm/kg H_2O. His $P_{Glucose}$ is 9 mmol/l (162 mg/dl) and his P_{urea} is 3 mmol/l (8 mg/dl). The U_{Na} was 65 mmol/l and the U_K was 15 mmol/l.

Question

- **What is the basis for his polyuria?**
- **What is your therapy for his polyuria and hypernatremia?**

Discussion of Case 3-3

What is the basis for polyuria?

Please examine Flow Chart 2-1, page 24.

Step 1. What is his U_{osm}?

With a U_{osm} of 500 mOsm/day, this is an osmotic diuresis because his calculated osmole excretion rate is 2000 (4L X 500 mOsm/l) instead of the expected 800 mosmoles/day.

Step 2. Were enough osmoles filtered?

Because his $P_{Glucose}$ was 9 mmol/l and his P_{urea} was 3 mmol/l, there were insufficient endogenous organic osmoles filtered to cause an osmotic diuresis. He was not given mannitol or similar agents. Although he was given an infusion of saline, urine electrolytes accounted for ~ half of his urine osmoles ($2 \times (U_{Na} + U_K)$). Because it is very difficult to explain why he has an osmotic diuresis, perhaps he has a water diuresis.

Step 2. Left side. Is this a water diuresis?

The high U_{osm} in his spot urine suggests that if a water diuresis is present, it is intermittent. This could be due to a form of central DI (history

of head injury) with the release of ADH provoked by non-osmotic stimuli but not to hypernatremia (Figure 3-5). Alternatively, consider a non-constant release of an enzyme that destroys circulatory ADH (vasopressinase) released from necrotic tissue. The fact that the U_{osm} rose to 900 mOsm/kg H_2O after dDAVP was given is compatible with either of these diagnoses. Direct measurements of circulating vasopressinase will be needed to establish the correct diagnosis.

FIGURE 3-5

Lesion in the CNS causing intermittent water diuresis

The 3 circles represent areas in the hypothalamus, the top one labeled 'stat' is the sensor ('osmostat'), the circle on the lower left is the thirst center and the circle on the lower right is the ADH release centre. There are two major mechanisms to consider: first, virtually all of the fibres connecting the 'osmostat' to the ADH release centre were cut, but non-osmotic stimuli could cause the release of ADH (site 1). Second, necrotic tissues released a vasopressinase (site 2).

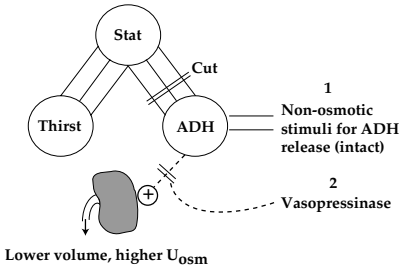


TABLE 3-5

Intermittent water diuresis in a patient with high P_{Na}

- Primary polydipsia with intermittent intake
- CNS lesion affecting osmostat or its link to ADH release
  - Need non-osmotic stimuli + intact ADH center
- Exogenous administration of ADH
  - dDAVP to control bedwetting or in therapy of central DI
- Limited water diuresis by low distal delivery of filtrate plus
  - Infusion of saline to have increased distal delivery

What is your therapy for his polyuria and hypernatremia?

When given dDAVP after the loop diuretic wore off, his urine flow rate declined and his U_{osm} rose to 800 mOsm/kg H_2O. Knowing that dDAVP can control the urine output and that his osmole excretion rate was no longer abnormal, it was easy to bring his P_{Na} back to the normal range using a tonicity balance approach. A list of possible causes for intermittent actions of ADH is provided in Table 3-5.

CLINICAL PEARLS

- *Do not multiply a spot urine value (U_{osm}) by the 24-h urine volume. One needs to know the stimulus at the time of the high urine output to interpret the data properly*
- *Wide variations in flow rate within a short time period suggest vasopressinase as the cause of the lesion.*

CHAPTER 4

HYPONATREMIA

I. ESSENTIAL POINTS

1. Definition:

Hyponatremia = P_{Na} < 136 mmol/l. The Na concentration is the Na to water ratio; thus there are 2 primary factors to evaluate: Na deficit and water surplus.

2. Expected physiological responses:

- **Na Deficit Type:** With non-renal causes, the urine [Na] (U_{Na}) and/or [Cl] (U_{Cl}) is usually < 15 mmol/l (Table 4-1).
- **Water Surplus Type:** No longer excrete the maximum volume (0.5 - 1 L/hr) of the most dilute urine (~ 60 mOsm/kg H_2O).

TABLE 4-1

Urine Electrolytes in the Differential Diagnosis of Hyponatremia and a Low ECF Volume

A high value for the U_{Na} or U_{Cl} is > 15 mmol/l whereas a low value for the U_{Na} or the U_{Cl} < 15 mmol/l unless there is a polyuric state where the concentrations should be adjusted downwards.

Condition	Urine Electrolyte	
	Na	Cl
• Vomiting		
- Recent	High	Low
- Remote	Low	Low
• Diuretics		
- Recent	High	High
- Remote	Low	Low
• Diarrhea or laxative abuse	Low	High
• Bartter's or Gitelman's syndrome	High	High

II. CLINICAL APPROACH TO THE PATIENT WITH HYPONATREMIA

Hyponatremia does not represent a single disease state. Hence there is no treatment that applies to all patients with hyponatremia.

The only useful initial classification will ask, "Is hyponatremia acute?" (Flow Chart 4-1, Table 4-2). This concept is the most important one in dealing with patients who have hyponatremia. If it is acute, the danger is brain cell swelling and possibly herniation. Acute identifies what is needed for therapy. Hypertonic saline to draw water out of the skull.

TABLE 4-2

CLASSIFICATION OF HYPONATREMIA

- **Acute hyponatremia (< 48 hr duration)**
  - Source of water:
    - Exogenous (IV or oral)
    - Endogenous
      - Desalination of a large infusion of isotonic saline (Figure 4-1)
        - Cerebral salt wasting
        - Thiazide diuretic to an edematous patient
        - A large infusion of isotonic saline to a patient with SIADH.
  - Seek reason for ADH, see Table 4-3.

- **Chronic hyponatremia**
  - Source of water is not usually the most important component of the problem.
  - Seek reason for ADH, see Table 4-3.

Figure 4-1

Desalination generates electrolyte-free water

The rectangle to the left of the arrow represents 2 L of infusate whereas the rectangles to its right represent 1 L volumes. The concentration of Na in each L is shown in the ovals inside the rectangles. The first rectangle to the right of the arrow represents 1 L of hypertonic urine and the second rectangle to the right of the arrow represents 1 L of EFW generated and retained in the body due to ADH actions.

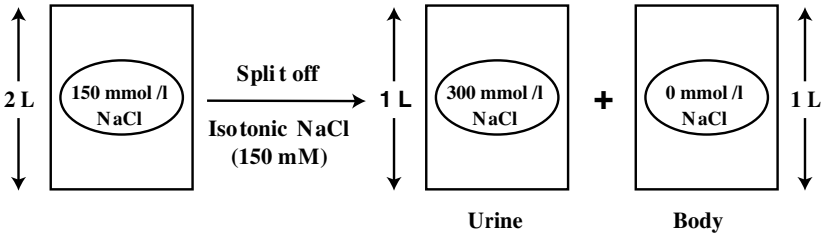


TABLE 4-3

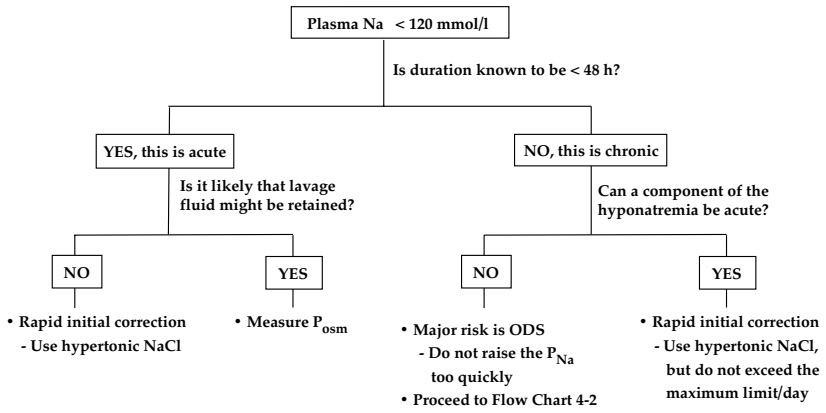
REASONS FOR HIGH ADH LEVELS

- **ADH release in response to physiologic stimuli:**
  - Low "effective" circulating volume
- **Non-osmotic stimuli for ADH release:**
  - Excessive pain, nausea, vomiting or anxiety.
- **ADH release without a physiologic stimulus:**
  - CNS or lung lesions.
  - Neoplasms, granulomas such as tuberculosis.
  - Exogenous administration of agents with ADH actions
    - dDAVP (e.g., treatment for diabetes insipidus or urinary incontinence)
    - Oxytocin for labor induction.
    - Drugs that stimulate the release of ADH such as nicotine, morphine, clofibrate, tricyclic antidepressants, antineoplastic agents (probably act via nausea).
    - Low glucocorticoids to suppress the release of corticotropin releasing factor
- **Drugs that augment ADH actions on the kidney**
  - Examples include hypoglycemics, methylxanthines (e.g., caffeine, aminophylline), analgesics that inhibit prostaglandin synthesis (e.g., aspirin, NSAIDs).

Flow Chart 4-1

Clinical Approach to the Patient With Hyponatremia

Identify if this is acute. Aggressive therapy is needed in acute symptomatic hyponatremia.



ILLUSTRATIVE CASE 4-1

This is far from ecstasy

Amy-Sue, age 19, is very thin because she suffers from anorexia nervosa. She went to a rave party—many hours later, she began to feel unwell—her main symptoms were lassitude and headache. Because there was no improvement, she was brought to hospital. In the emergency department, she had a grand mal seizure. Blood was drawn and the major abnormality was a P_{Na} of 130 mmol/l.

Questions

- **Is this acute hyponatremia"?**
- **Why did she have a seizure with a P_{Na} of 130 mmol/l?**
- **What is your therapy?**
- **What role might anorexia nervosa have played?**

Discussion of Case 4-1

Is this acute hyponatremia"?

Turn to step 1 of Flow Chart 4-1.

Step 1. Is the duration of hyponatremia known to be < 48-hours?

Yes, so the situation can become catastrophic, even if symptoms are mild (e.g, headache, drowsiness, mild confusion).

- Proceed quickly to step 2a, left side of the flow chart.

Step 2a. Is it likely that lavage fluid was retained?

No, so act quickly to prevent irreversible brain damage. Urgent therapy with hypertonic saline is needed to raise the P_{Na} by 5 mmol/l quickly to shrink the size of brain cells before seizures and/or respiratory arrest with irreversible brain damage develop. Give 5 mmol NaCl per L of body water (150 mmol hypertonic NaCl in this case).

If the answer had been yes, measure the P_{osm} to determine the likelihood that the acute fall in P_{Na} is associated with brain swelling.

Why did she have a seizure with a P_{Na} of 130 mmol/l?

There two options: First, she had an underlying CNS lesion that made her more sensitive to develop a seizure with a smaller degree of brain cell swelling. Second, the seizure caused her P_{Na} to rise because of a shift of water into muscle cells due to the generation of many new small effective osmoles in these cells.

What is your therapy?

Control the seizure. Repeat the P_{Na} and give her 5 mmol hypertonic NaCl per L of total body water (~ 60% of her weight) to raise the P_{Na} acutely; then raise the P_{Na} to normal over 24-hours.

What role might anorexia nervosa have played?

Approximately 50% of water in the body is located in skeletal muscle cells. She has a very small muscle mass so a smaller positive water balance can cause a greater fall in her P_{Na}. There is not a similar decline in the number or size of her brain cells.

CLINICAL PEARLS

- *During a seizure, the P_{Na} can rise by ~ 15 mmol/l due to a shift of water into muscle cells. Therefore do not rule out hyponatremia as acause of a seizure if the P_{Na} is much higher than 120 mmol/l.*
- *Younger patients are more likely to become symptomatic with acute hyponatremia because they have a larger number of brain cells.*
- *Recognize the role of a small muscle mass.*
- *A patient with an underlying seizure disorder may become symptomatic with a smaller decline in P_{Na}.*

ILLUSTRATIVE CASE 4-2

Tea and toast hyponatremia

Sadie, age 71, has hypertension (BP 150/90 mm Hg). She began treatment with a diuretic one month ago. Fatigue became evident 1 week ago. Her current blood pressure is 130/85 mm Hg and there was a small postural drop in BP. The laboratory data are:

Parameter		Plasma	Urine
Na	mmol/l	103	3
K	mmol/l	3.1	12
Cl	mmol/l	60	11
HCO_3	mmol/l	29	0
pH		7.47	5.9
Urea (BUN)	mmol/l (mg/dl)	5.0 (14)	-
Osmolality	mOsm/kg H_2O	220	422

Discussion of Case 4-2

Please follow the steps outlined in Flow Chart 4-1.

Step 1. Is the duration of hyponatremia known to be < 48-hours?

No, so proceed to step 2b right side of the flow chart.

Step 2b. Can there be a component of acute hyponatremia?

No, so the main danger will appear after therapy begins—too rapid or an excessive rise in the P_{Na} that may result in the ODS.

Caution

One must identify conditions in which ADH levels may decline rapidly and/or distal volume delivery will increase dramatically and predispose this patient to the danger of developing ODS.

We shall return to Case 4-2, page 50, when the emphasis will be on the patient with chronic hyponatremia

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III. QUESTIONS TO ASK OF THE HYPONATREMIC PATIENT

1. Is the hyponatremia real?

Answer: Hyperlipemia and hyperproteinemia did not cause hyponatremia if the P_{osm} is low.

2. Is hyponatremia due to hyperglycemia?

Answer: Yes, if the $P_{Glucose}$ is elevated and the P_{osm} is not low. There is no reliable relationship between the rise in the $P_{Glucose}$ and the fall in the P_{Na}.

3. Is hyponatremia due solely to excess water intake?

Answer: Almost never! If so, the urine will be maximally dilute and flow at 0.5-1 L/hr.

4. Is hyponatremia due to high ADH levels?

Answer: Almost always. Determine why ADH being present.

5. What is the best way to treat hyponatremia?

Answer: Separate acute Vs chronic hyponatremia.

IV. ACUTE HYPONATREMIA

1. What is the reason for the low P_{Na}?

Ask, "Where did that patient get ~ 3.5 L of water to cause the low P_{Na}?" The clinical settings are listed in Table 4-4.

TABLE 4-4

CLINICAL SETTINGS WITH ACUTE HYPONATREMIA

- **Inside the hospital**
  - Post-operative hyponatremia
  - Hyponatremia following transurethral resection of the prostate
  - Hyponatremia in young children
- **Outside the hospital**
  - Vigorous exercise with the consumption of a large volume of water
  - Use of Ecstasy in a rave party

2. What are the likely clinical settings?

Gender issues in acute hyponatremia:

Acute hyponatremia has different implications in females and males because the basis for this hyponatremia is often different in hospitalized patients (Table 4-5).

Females: Most commonly, there is a surgical procedure that leads to the release of ADH. This together with an infusion of D_5W completes the picture (the source of water). This form of acute hyponatremia leads to brain cell swelling because 2/3 of the water retained is in the ICF (Table 4-5). If the intracranial pressure is too high, the patient may die.

Males: ADH release is again due to a surgical procedure (Table 4-5). The common setting for males is transurethral resection of the prostate (TURP). The basis for, and impact of this type of hyponatremia on brain cell volume is different from a simple retention of water. There are two reasons to develop hyponatremia; they become obvious after dividing the absorbed fluid into its two constituent parts.

Osmole-free (and electrolyte-free) water: This is simple water gain that causes cells to swell. It has the same impact as the infused hypotonic fluid in females. This is not the major cause for the hyponatremia (Table 4-5).

Isosmolar fluid: Solutes such as mannitol behave early on as if they do not cross cell membranes at an appreciable rate and they remain in the ECF and because they are Na-free, they cause hyponatremia. This form of hyponatremia is not associated with brain cell swelling nor will it pose a threat of brain herniation.

TABLE 4-5

COMPARISON OF EFW AND HALF-OSMOTIC MANNITOL ON THE DEGREE OF HYPONATREMIA

Examples are provided to illustrate the effects of retaining 3 L of water or 3 L of half-isotonic mannitol on the P_{Na} and the ICF and ECF volumes in a patient who has 30 L of total body water, 2/3 in the ICF compartment. The retention of lavage fluid illustrates the problem of relating the P_{Na} and the ICF volume in what is incorrectly called, translocational hyponatremia'.

Parameter Values		Normal	Gain 3 L EFW	Gain 3 L	Mannitol Excrete mannitol
Total body water	L	30	33	33	31.5
- ICF volume	L	20	22	21	21
- ECF volume	L	10	11	12	10.5
- P_{Na}	mmol/l	140	127	114	133
- Change in P_{Na}	mmol/l	0	- 13	- 26	- 7

Quantities

For simplicity, I shall assume both the male and the female have 30 L of total body water and have a positive balance of 3 L of fluid.

Females: Distribution of 3 L of water—2 L to the ICF and 1 L to the ECF. This resulted in a gain of ECF volume of 10% and a fall in the P_{Na} to 127 mmol/l (Table 4-5).

Males: The 3 L consist of 1.5 L of osmole-free water and 1.5 L of iso-osmolar mannitol (all retained in ECF). 2/3 of the osmole-free water will be retained in the ICF (half that with 3 L EFW). The ECF gain of Na-free water is 0.5 L of EFW plus the 1.5 L of isosmolal mannitol, so the P_{Na} falls twice as much in males (Table 4-5), but its impact on ICF volume is half as much. After the mannitol is excreted as an isosmolal solution (300 mmol/l), the ECF volume declines by 1.5 L to 10.5 L and the P_{Na} rises to 133 mmol/l. Note this 20-mmol/l rise in P_{Na} is <u>not</u> accompanied by a change in the ICF volume.

3. Therapy for the patient with acute hyponatremia

Emergency treatment

If hyponatremia is definitely acute (usually ~ 120 mmol/l), give hypertonic saline.

Sample calculation

Patient has 30 L of total body water (50% of body wt (60 kg)). Aim to raise the P_{Na} by 5 mmol/l to shrink the size of brain cells. Create a positive balance of 150 mmol NaCl without water (30 L X 5 mmol/l = 150 mmol).

Prevention of acute hyponatremia

The approach here can be divided into input and output therapies (Table 4-6).

(i) Input therapy

Do not give hypotonic fluids. Give as little isotonic saline as needed to maintain blood pressure during anesthesia. Once hyponatremia is present, infuse fluids with the same tonicity and volume as the urine to prevent a further fall in the P_{Na}. Wait for a dilute urine, then stop intravenous therapy.

(ii) Output therapy

When the U_{Na+K} is very high, give an agent which will lower the U_{Na+K} to an isotonic solution. This in effect means a loop diuretic because you must destroy the ability of the kidney to excrete concentrated urine. An alternative is to give an osmotic diuretic (urea). Isotonic intravenous fluids should be given at the same rate as the urine output to preserve water and Na + K balance. Once the reason for the release of ADH is no longer present, this therapy will not be required; the patient will begin to excrete dilute urine and hence the P_{Na} will rise. Do not give agents like lithium, demeclocycline, or ADH antagonists to cause nephrogenic diabetes insipidus. The former act too slowly and the latter may cause unwanted hypernatremia.

TABLE 4-6

PREVENTION OF ACUTE HYPONATREMIA

- Do not infuse electrolyte-free water in the acute peri-operative setting.
- Even mild symptoms (mild nausea, headache) might be followed by a sudden and catastrophic herniation of the brain.
- Be very suspicious of a 'good' urine output because this might be hypertonic to the infused solutions and generate EFW.
- Do not give more isotonic saline than the patient needs for hemodynamic purposes.
- Be extremely cautious with the volume given to a smaller patient.

V. CHRONIC HYPONATREMIA

1. Classification of chronic hyponatremia:

The usual ways to classify patients with chronic hyponatremia are often not helpful because we cannot assess small changes in the ECF volume at the bedside (Tables 4-7 and 4-8).

TABLE 4-7

CLASSIFICATIONS FOR CHRONIC HYPONATREMIA

None of these classifications are very useful for the reasons outlined.

Basis	Comment
P_{osm}	• Identifies patients with hyperglycemia or those who retained lavage fluid
Effective ECFV	• Cannot determine ECFV at the bedside unless changes are marked
Dilutional/depletional	• Applies to almost all patients

TABLE 4-8

CAUSES OF HYPONATREMIA

- **Pseudohyponatremia (normal plasma osmolality)**
  - Hyperlipidemia, hyperproteinemia
  - True hyponatremia, but high urea, ethanol
- **Addition of particles largely restricted to the ECF**
  - Hyperglycemia, mannitol (hyperosmolality)
- **Decreased "effective circulating" volume**
  - ECF volume contraction (loss of Na)
    - May be difficult to detect at the bedside
  - Low arterial volume but expanded venous volume (heart problems) or interstital fluid expansion (edema states)
- **Primary Water Gain (and secondary Na loss)**
  - ADH release from the posterior pituitary without a tonicity or "effective circulatory volume" stimulus
    - Drugs (see Table 4-3)
    - Other (excessive pain, emesis, vagal nerve stimulation, etc)
    - CNS diseases
    - Metabolic disorders (e.g. porphyria)
  - ADH from other sources (neoplasms, exogenous administration)
  - Drugs potentiating ADH action
- **Drugs interfering with free-water formation (e.g. loop diuretics) plus need for water intake.**

---

2. Clinical approach

Calculate the magnitude of the deficit of Na and the gain in water to understand why the P_{Na} was low. There are two important issues raised in Case 13-5, page 211 in this context. If the negative balance of Na is very large, look for conditions that could cause such a large deficit of Na. If the patient has a low muscle mass, a small positive balance for water can cause a large fall in the P_{Na}. This also has an important implication for therapy—creating this same small negative balance for water might cause an excessive increase in the P_{Na} and thereby predispose the patient to ODS, especially if there is K depletion or malnutrition.

3. The major issue is the reason for the release of ADH

The level of ADH might decline suddenly so the P_{Na} might rise abruptly. Examples include re-expansion of the ECF volume or removal of non-osmotic stimuli for ADH release.

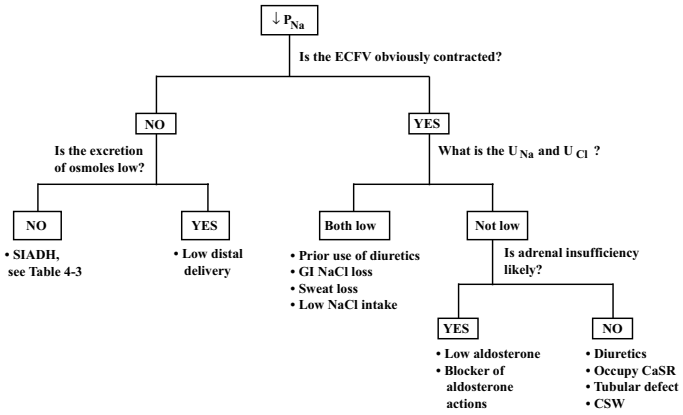
Low distal delivery of filtrate: Even if the effective circulating volume is not appreciably low, the distal delivery of filtrate can be low enough to reduce the excretion of water to a major extent (Figure 1-3, page 3). Because the inner MCD has intrinsic permeability to water even in the absence of ADH, water can be reabsorbed from the inner MCD if their interstitial fluid compartment has a high osmolality. This can be called *'Trickle-down' hyponatremia*'.

4. Proceed using Flow Chart 4-2

Flow Chart 4-2

Steps to take in the patient with Chronic Hyponatremia

In chronic hyponatremia, determine why ADH is present. If the reason for the release of ADH is reversible, patients might be at risk of having a water diuresis if the release of ADH is suppressed—e.g., when their ECF volume is re-expanded. Abbreviation: CSW = cerebral salt wasting.



ILLUSTRATIVE CASE 4-2 RETURNS

Tea and toast hyponatremia

Sadie, age 71, has hypertension (BP 150/90 mm Hg). She began treatment with a diuretic. Fatigue became evident 1 week ago. Her current blood pressure is 130/85 mm Hg and there was a small postural drop in BP. The laboratory data are:

Parameter		Plasma	Urine
Na	mmol/l	103	3
K	mmol/l	3.1	12
Cl	mmol/l	60	11
HCO_3	mmol/l	29	0
pH		7.47	5.9
Urea (BUN)	mmol/l (mg/dl)	5 (14)	-
Osmolality	mOsm/kg H_2O	220	422
Volume	L/day	-	1.0

Questions

- **Is the basis of hyponatremia water gain?**
- **Is the basis of hyponatremia a deficit of Na?**
- **Is adrenal insufficiency a likely cause of her Na deficit?**

Discussion of Case 4-2, revisited

Is the basis of hyponatremia water gain?

Step 1. Is the ECF volume obviously contracted?

Yes, but this is not the whole story. The history, physical exam and lab data all suggest that there is a degree ECF volume contraction. The degree of the hyponatremia is so severe that there is also a surplus of water.

***Conclusion*: An important basis of the hyponatremia is a positive balance of water, so proceed first down the left side of the flow chart.**

Step 2. Is the excretion of osmoles low?

Yes, she has two reasons for the inability to excrete enough of her habitual water intake (tea). The low ECF volume could stimulate the release of ADH. A low excretion of water could also be due to a low distal delivery of filtrate.

Is the basis of hyponatremia a deficit of Na?

To evaluate her low ECF volume, proceed down the right side of Flow Chart 4-2 to determine where and why there was a loss of Na.

Step 2. What is the U_{Na} and the U_{Cl}?

Because both the U_{Na} and the U_{Cl} are low, loss of NaCl could have occurred by non-renal routes such as the GI tract or in sweat are likely. Nevertheless, given the history and her diet, the loss of NaCl probably was the result of her prior use of diuretics.

Is adrenal insufficiency a likely cause of her Na deficit?

Step 3. Might this patient have adrenal insufficiency?

While I recognize that diuretic use is what caused her low ECF volume, I emphasize this question because of the danger of not recognizing this potentially important condition. The presence of hypokalemia makes this diagnosis very unlikely.

CLINICAL PEARL

Patients with adrenal insufficiency usually have hyperkalemia and low rate of excretion of K. Nevertheless, hyperkalemia is not present in as much as 1/3 of the patients with adrenal insufficiency.

CLINICAL PEARLS

- *The acute discovery of a chronic condition does not make it an acute disorder.*
- *In a patient with chronic hyponatremia, there can still be an acute component to hyponatremia.*
- *The rates of correction of chronic hyponatremia should <u>not</u> be taken as rates that must be achieved, but rather as rates that must <u>not</u> be exceeded.*
- *A rate < 8 mmol/l/day is likely to avoid ODS. A rate of < 4 mmol/l/day is the upper limit in a patient who is K-depleted or malnourished.*
- *Too rapid or too extensive a water loss can produce an ODS. If anticipated, prevent this by giving dDAVP early in therapy*

TABLE 4-9

REVIEW OF ISSUES WITH CHRONIC HYPONATREMIA

- **If ADH release is due to a low ECF volume or non-osmotic stimuli for the release of ADH, or if water excretion is low because of a low distal delivery of filtrate, be aware that a rapid water diuresis can occur once the ECF volume is re-expanded.**
  - If this is suspected, give enough ADH early on to diminish the rate of excretion of water.

- **If the patient is symptomatic**
  - Only correct hyponatremia initially at a more rapid rate if the patient is suffering from a seizure or coma.
    - Raise the P_{Na} by up to 5 mmol/l over 1-2 hr, but do not to exceed 8 mmol/l/24 hr.

- **Rate of correction of hyponatremia: Choose a maximum limit, not a target to be achieved.**
  - The rate is one not associated with ODS.
  - A rise of < 12 mmol/l/24 hr is safe in most cases, but go slower.
  - An even slower rate of < 8 mmol/l/24 hr, is a better choice.
  - In a patient with hypokalemia, malnutrition, a catabolic state, and/or hypoxia, go much slower (< 4 mmol/l/24 hr).
  - If you have any doubts about a recent intake of water, choose a rate of 0-4 mmol/l/24 hr, and slower in the first 12-hr.

- **Chronic hypornatremia occurs in a variety of settings**
  - If the ECF volume is not contracted, a negative water balance is the major form of therapy.
  - If the ECF volume is contracted, a positive Na balance is the major form of therapy.

SECTION II

POTASSIUM

CHAPTER 5

POTASSIUM PHYSIOLOGY

I. ESSENTIAL POINTS

1. Overview

Regulation of K homeostasis has two important aspects:
- Short-term control is by the movement of K across cell membranes. This limits acute changes in the P_K.
- Longer-term control is by K secretion in the cortical collecting duct (CCD). This maintains total body K balance.

2. K Distribution

Close to 98% of total body K is in the ICF compartment. K ions are kept inside the cell by an electrical force (a negative voltage in cells) that is generated by the Na-K-ATPase (it exports 3 Na ions while importing 2 K ions). Entry of Na into cells needs to occur in an electroneutral fashion via the Na/H^+ exchanger (NHE) (Figure 5-1). Flux through the Na-K-ATPase is enhanced by an increased $[Na]_{ICF}$ or by hormones (insulin, β-adrenergics).

There are three reasons for a shift of K out of cells during metabolic acidosis. The causes have one mechanism in common—a diminished negative voltage (less negative resting membrane potential (RMP)).

(i) Low NHE activity

The cause of acidosis diminishes insulin-induced activation of NHE {diabetic ketoacidosis (DKA)}.

(ii) Mechanism of anion entry

To cause a K shift, the anion produced with the H^+ cannot enter cells on a cotransporter with H^+. Thus no shift of K ions occurs when the acids are L-lactic acid or β-hydroxybutyric acid because they enter cells via a specific, electroneutral monocarboxylate transporter. In contrast, a shift of K ions occurs with inorganic acidosis and with organic acids that have more than one carboxyl group (e.g., citric acid).

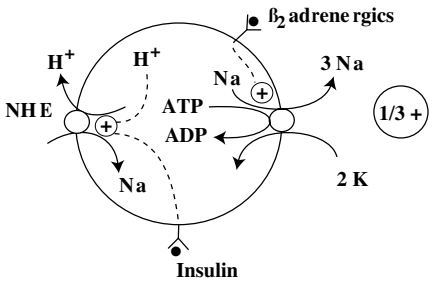
(iii) Tissue anabolism/catabolism can affect the P_K.

Hypokalemia may be seen in conjunction with rapid cell growth or during therapy of DKA if enough K is not given. In contrast, hyperkalemia may be seen with cell destruction. If hyperkalemia is chronic, factors that compromise the kidney's ability to excrete K are usually present as well.

Figure 5-1

Na-K-ATPase activity and the export of positive voltage

The Na-K-ATPase generates the electrical driving force for K ion entry into cells providing that the source of Na ions pumped was either Na ions that existed in cells or entered via the electroneutral NHE. Insulin activates NHE. $ß_2$-Adrenergics activate Na-K-ATPase via phosphorylation.



3. Excretion of K

Control of the renal excretion of K maintains overall daily K balance. The usual rate of excretion of K reflects its dietary intake. K excretion can decline to 10-15 mmol/day with very little K intake. In contrast, K excretion can easily match an intake of > 200 mmol/day with only a minor P_K rise.

Two factors influence K secretion in the CCD, the flow rate in the terminal CCD and net secretion of K raises its luminal K concentration ($[K]_{CCD}$).

$$\textbf{K excretion} = \textbf{Flow rate}_{CCD} \textbf{ X } [K]_{CCD}$$

(i) Flow rate in the CCD

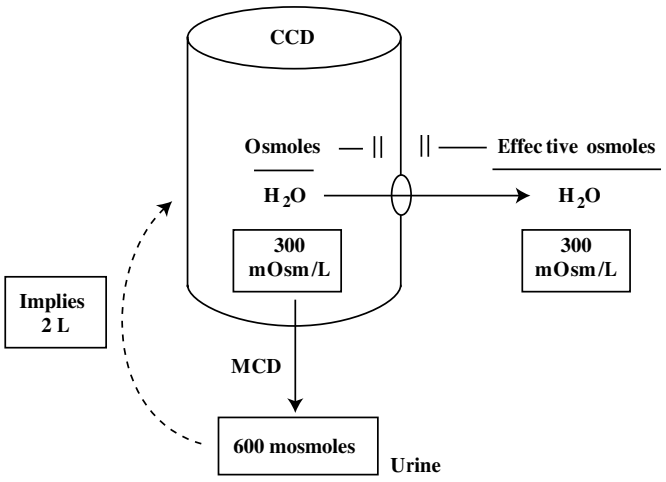
When ADH acts, the flow rate in the CCD is reflected by the rate of excretion of osmoles because the osmolality of fluid in the terminal CCD is equal to the P_{osm} (Figure 5-2, equation below) and most of the osmoles delivered to the terminal CCD are excreted. The two major urinary osmoles are urea and Na (+ Cl).

$$\textbf{(Flow rate)}_{CCD} = (U_{osm} \textbf{ X Urine volume})/P_{osm}$$

Figure 5-2

Non-invasive estimate of the Flow Rate in the terminal CCD

The barrel-shaped structure represents the CCD. When ADH acts, the P_{osm} and the osmolality in the luminal fluid of the CCD are equal (represented as 300 mOsm/kg H_2O for easy math). For example, if 600 mosmol are excreted in a given time, the minimum flow rate in the terminal CCD is 2 L.



(ii) [K] in the lumen of the terminal CCD

The secretory process for K in principal cells has two elements. First, a lumen negative voltage must be generated via electrogenic reabsorption of Na via the epithelial Na ion channel (ENaC). Second, open K channels must be present in the luminal membranes of principal cells.

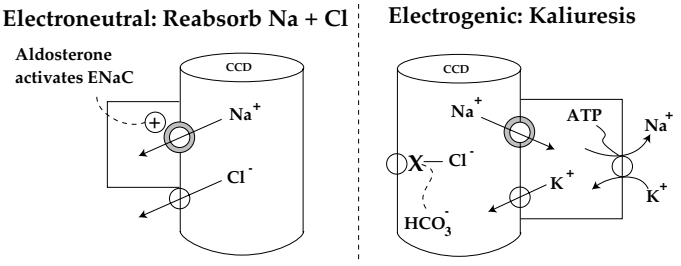
The reabsorption of Na in the CCD can be electroneutral or electrogenic depending on whether Cl is reabsorbed as fast as Na (electroneutral) or slower than Na (electrogenic) (Figure 5-3). Faster reabsorption of Na than Cl in the CCD can occur for three reasons. First, Na is delivered to the CCD with little Cl. A key finding in these patients is Cl-poor urine (Figure 5-4, top-left panel). Second, reabsorption of Cl in the CCD may be inhibited. This mechanism is suspected when the urine is not Cl-poor (Figure 5-5, top-right panel). It appears that HCO_3 and/or an alkaline luminal pH in the CCD could inhibit Cl reabsorption. Third, a higher lumen-negative voltage in the CCD could develop when the delivery of Na and Cl are very high and the capacity for Cl reabsorption is less than that for Na (Figure 5-4, lower-left panel). This requires a stimulated reabsorption of Na via ENaC in the CCD (high aldosterone level due to low effective circulating volume).

If Na is **not** reabsorbed faster than Cl in the CCD, a lumen-negative voltage does not develop. Two factors are important to achieve this near-equal rate of ion transport in the CCD (Figure 5-4, lower-right panel). First, low delivery of Na and Cl to the CCD occurs because the reabsorption of Na and Cl was augmented in the distal convoluted tubule because of increased activity of Na-Cl-cotransporter (NCC). Second, ECF volume expansion suppresses the release of aldosterone and this will diminish the rate of excretion of K.

Figure 5-3

Electrogenic and Electroneutral reabsorption of Na in the CCD

The barrel-shaped structures represent the CCD and the rectangles represent principal cells. Na is reabsorbed via ENaC; this reabsorption is increased by aldosterone (the shaded enlarged circle). Net secretion of K occurs through its specific ion channel (ROM-K). Electroneutral reabsorption of Na is shown on the left and an example of electrogenic reabsorption of Na (HCO_3 or an alkaline luminal pH decreasing the apparent permeability for Cl in the CCD) is shown to the right of the dashed horizontal line.

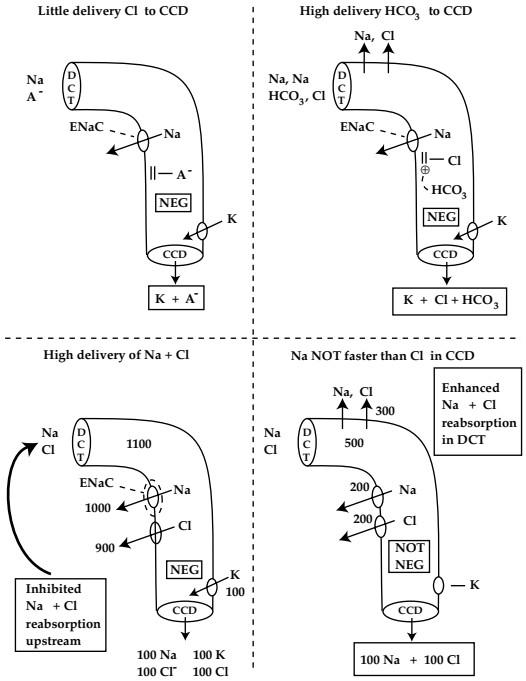


Cortisol can exert a mineralocorticoid effect in three circumstances. First, if the activity of 11 ß-hydroxysteroid dehydrogenase (11 ß-HSDH) is decreased (e.g., apparent mineralocorticoids excess syndrome). Second, if 11 ß-HSDH is overwhelmed by an extreme abundance of cortisol (e.g., patients with an ACTH producing tumor). Third, if 11 ß-HSDH is inhibited (e.g., by glycyrrhizic acid in licorice).

Figure 5-4

Secretion of K in the Cortical Collecting Duct

The early portion structure represents the distal convoluted tubule (DCT) and the CCD. A negative voltage is created in the lumen of the CCD by reabsorbing Na faster than Cl. This will occur if there is delivery of Na with little Cl to the CCD (top left)) or if the reabsorption of Cl in the CCD is inhibited by HCO_3 (top right). Should there be a very high delivery of Na and Cl together with a larger capacity to reabsorb Na than Cl in the CCD, a lumen-negative voltage will be generated (bottom left). In contrast, a low delivery of Na and Cl to the CCD can occur when NaCl reabsorption is stimulated in the DCT. At these low delivery rates to the CCD, Na and Cl are reabsorbed at comparable rates so lumen-negative voltage is not generated in this nephron segment (bottom right).



II. TOOLS TO ASSESS THE CONTROL OF THE RENAL EXCRETION OF K

1. Examine the rate of excretion of K

To assess the renal response in a patient with hypokalemia or hyperkalemia, I use the expected rate of K excretion when these electrolyte abnormalities are due to non-renal causes. With a K deficit, the expected response is to excrete < 15 mmol/day. With a surfeit of K, the expected response is to excrete > 200 mmol/day.

To assess the rate of excretion of K, a 24-hr urine collection is not necessary. Use the $U_K/U_{Creatinine}$ (despite the diurnal variation in K excretion) because creatinine is excreted at a near-constant rate throughout the day. A $U_K/ U_{Creatinine}$ in spot urines provides information that is more relevant because the stimulus to drive K excretion (e.g., P_K) should be known at that time.

- With hypokalemia, the $U_K/ U_{Creatinine}$ should be < 1 mmol K/mmol creatinine (< 10 mmol K/g creatinine).
- With hyperkalemia, the $U_K/ U_{Creatinine}$ should be > 15 mmol K/ mmol creatinine (>150 mmol K/g creatinine).

2. Estimate the flow rate in the terminal CCD

The critical factor is the rate of excretion of osmoles, typically ~0.5 mosmol/min or 720 mosmol/day. A minimum estimate of the flow rate in the terminal CCD is obtained by dividing the rate of excretion of osmoles by the osmolality of luminal fluid in the terminal CCD (equals the P_{osm} when ADH acts) (Figure 5-2).

3. Estimate the $[K]_{CCD}$

A reasonable approximation of the $[K]_{CCD}$ can be obtained by adjusting the U_K for water reabsorbed in the MCD. This is done by dividing the U_K by the $(U/P)_{Osm}$ (equation below).

$$\mathbf{[K]_{CCD} = [K]_{urine}/(U/P)_{Osm}}$$

Another way to evaluate the driving force for the net secretion of K in the CCD is to calculate the transtubular [K] gradient (TTKG). In this calculation, the $[K]_{CCD}$ is divided by the P_K (Figure 5-5, equation below). The expected value for the TTKG in a patient with

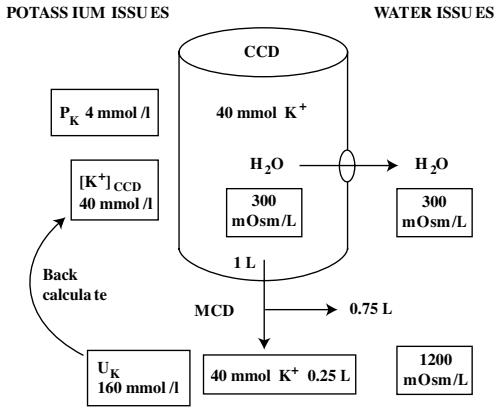
hypokalemia due to a non-renal cause is < 2, whereas the appropriate renal response in a normal subject given a K load is > 7.

$$\mathbf{TTKG = [K]_{CCD}/P_K}$$

Figure 5-5

Transtubular K Concentration Gradient

The barrel-shaped structures represent the CCD and the arrow below the CCD is the MCD. In this example, the luminal K concentration is 40 mmol/l or 10-fold larger than the peritubular K concentration of 4 mmol/l. Consider what happens when 1 L of fluid traverses the MCD where 75% of the water is reabsorbed. In this example, no K is reabsorbed or secreted in the MCD. Therefore the U_K is 4-fold higher (40 to 160 mmol/l) as is the U_{osm} (300 to 1200 mOsm/kg H_2O). This should be taken into account in assessing the U_K.



4. Establish the basis for the abnormal $[K]_{CCD}$

In a patient with hyperkalemia and a lower than expected $[K]_{CCD}$, this usually implies that the lumen-negative voltage is abnormally low due to less electrogenic reabsorption of Na. In rare cases, there can be limitations by K channels (less open). The converse is true in a patient with hypokalemia.

The basis for the change in the rate of electrogenic reabsorption of Na can be deduced from an assessment of the ECF volume, the ability to conserve Na and Cl in response to a contracted effective ECF volume, and measurement of the activity of renin and the level of aldosterone in plasma (see Chapter 6).

CHAPTER 6

HYPOKALEMIA

I. ESSENTIAL POINTS

1. Definition

Hypokalemia = plasma [K] (P_K) < 3.5 mmol/l (exact cut-off is arbitrary).

2. Expected physiologic response

Excretion of < 15 mmol (0.2 mmol/kg) K per day if non-renal K loss.

3. Clinical evaluation

The main danger of hypokalemia is a cardiac arrhythmia (examine the EKG). Notwithstanding, EKG changes and the absolute P_K are not tightly correlated.

Evaluate whether there may be a shift of K into cells. Your suspicion should be high if the time course is short. Suspect hypokalemic periodic paralysis (HPP) if weakness was provoked by an adrenergic surge or a high carbohydrate intake in a young, Asian male, especially if there is a positive family history, hyperthyroidism, low K excretion, and the absence of an acid-base disorder.

The clinical manifestations of hypokalemia may be subtle. A high degree of suspicion can arise from the clinical setting (vomiting, diuretics, laxative abuse or diarrhoea) to identify patients at risk. Beware of deceptions! Patients may not admit to vomiting or abuse of diuretics or laxatives. The presence of hypertension is helpful, but it is difficult to be certain about the ECF volume status. When hypokalemia is very severe (< 2.5 mmol/l), look for causes in addition to diuretic intake.

4. Differential diagnosis

Causes include a decreased daily K intake, but this is rarely a sole cause of hypokalemia. A shift of K from the ECF to the ICF

compartment is often present and the major causes are insulin or catecholamine excess, anabolism, metabolic alkalosis, or HPP. Most often, excessive urine K loss is present. Evaluate the renal excretion of K by either a timed collection or the $U_K/U_{Creatinine}$ ratio. Also, examine the components of K excretion, the flow rate in the CCD and the $[K]_{CCD}$ if $U_{osm} > P_{osm}$. Determine why each of these components may be abnormal.

5. Laboratory features

An abnormal EKG makes at least part of the hypokalemia a potentially urgent medical problem. The tests for K excretion should be examined bearing the P_K in mind. A note of caution is worthwhile. The renal K loss may be intermittent.

Urine electrolytes as diagnostic features

- U_K Suspect renal K wasting if $U_K > 30$ mmol/l. Renal K wasting if > 15 mmol of K are excreted/day. Suspect activated K secretion if TTKG > 4.
- U_{Na} If U_{Na} not < 20 mmol/l when ECF volume is low, determine why renal Na wasting.
- U_{Cl} If $U_{Cl} < 10$ mmol/l, suspect vomiting or remote diuretics
  If $U_{Cl} > 20$ mmol/l, suspect recent ingestion of diuretics if ECF volume is low or if U_{Cl} high intermittently.
  U_{Cl} can be high if there is a reason to excrete NH_4^+.
- U_{pH} If urine pH > 7, suspect recent vomiting.

6. Treatment

If there are EKG changes, an anticipated fall in the P_K or a $P_K < 2.0$ mmol/l, this may be an emergency. You must distinguish between a shift of K into cells and large K deficit because treatments will be very different. If you suspect hyperthyroidism in HPP, ß-blockers are very effective in therapy.

Be sure that bowel sounds are present if you use the oral route to administer K. The usual K salt is KCl but $KHCO_3$ may be an appropriate therapy later in the acidotic patient. Intravenous K should not be given too quickly (> 60 mmol/hr) or be infused at too high a [K] (> 40 mmol/l) by a peripheral route.

II. QUESTIONS TO ASK OF THE HYPOKALEMIC PATIENT

1. Did a K shift into cells cause hypokalemia?

Answer: Yes if the time period is short. The causes are listed in Table 6-1.

2. What features should be stressed on history?

Answer: Diuretics, vomiting and laxative abuse are common causes but the patient may deny them. If digitalis is being used, the danger of arrhythmias is much greater. As mentioned above, establish the time course.

3. What should be stressed on physical exam?

Answer: ECF volume, hypertension and psychological problems.

4. What should be stressed on lab exam?

Answer: EKG, blood acid-base and electrolyte status, U_K, U_{Cl}, U_{Na}, urine flow, osmolality and the TTKG.

5. When is hypokalemia most dangerous?

Answer: When the K deficit is severe or sudden. In combination with digitalis or heart disease. In combination with severe metabolic acidosis where hyperventilation is needed. When associated with DKA because therapy will unmask the severe K deficit. Overaggressive iv K therapy producing transient, severe hyperkalemia.

6. How much K should be given during therapy?

Answer: Usually several hundred mmol, but answer depends on muscle mass and if there is a shift of K into cells. Use the oral route if possible (bowel sounds present). IV K must not be given too quickly.

TABLE 6-1

CAUSES OF HYPOKALEMIA

- **Decreased intake of K**
  - Rarely a primary cause unless K intake is very low and duration is prolonged
  - Can augment the degree of hypokalemia if there is ongoing K loss

- **Shift of K into cells**
  - Hormones (insulin and ß-adrenergics are most important)
  - Metabolic alkalosis
  - Anabolic state (e.g., recovery from DKA)
  - Other (anaesthesia, hereditary hypokalemic periodic paralysis)

- **Increased Urine K Loss**
  - Large volume in CCD (diuretics)
  - High $[K]_{CCD}$
    - Faster reabsorption of Na in the CCD
      - High aldosterone levels (see Figure 6-1)
      - Constitutively active ENaC (e.g., Liddle's syndrome)
      - Artificial ENaC (e.g., amphotericin B)
      - Cortisol acts as a mineralocorticoid
        - Low 11-ßHSDH activity (AME)
        - Inhibitors of 11-ßHSDH (e.g., licorice)
        - Very high cortisol level (e.g., ACTH-producing tumor)

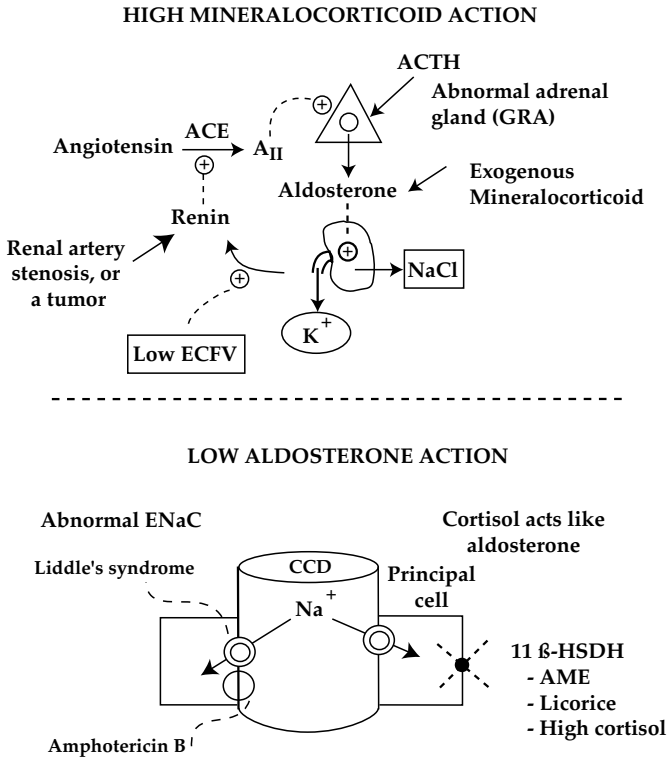
    - Relatively slower reabsorption of Cl in the CCD
      - Delivery of Na without Cl to the CCD & a low ECF volume
      - Inhibition of Cl reabsorption in the CCD (e.g., bicarbonaturia)
      - High delivery of Na and Cl to the CCD and a V_{max} for Na reabsorption that exceeds that for Cl (inhibition of NaCl reabsorption in an upstream nephron segment plus ECF volume depletion)

- **Loss of K via the GI tract or skin**

Figure 6-1

Hypokalemia with augmented K excretion

The top portion of the figure deals with hypokalemia associated with high levels of aldosterone or an aldosterone-like compound in plasma; the bottom portion represents high aldosterone bioactivity when aldosterone levels in plasma are low. The triangular shaped figure is the adrenal gland.



GRA = Glucocorticoid Remedial Aldosteronism
AME = Apparent Mineralocorticoid Excess

III. CLINICAL APPROACH TO THE PATIENT WITH HYPOKALEMIA

I shall illustrate the step-by-step approach by working our way through Case 6-1. The initial approach is summarized in Flow Chart 6-1. Because there is an acute component to the hypokalemia, the following facts about hypokalemic periodic paralysis (HPP) should be borne in mind. He also has hypertension so please examine Table 6-2 for a list of diseases where there is both a low P_K and an abnormal blood pressure.

Hypokalemic periodic paralysis

This can be familial or associated with thyrotoxicosis. The major clues to suggest thyrotoxic hypokalemic periodic paralysis are the ethnic origin (most common in Asians), gender (males most often), signs associated with hyperthyroidism (tachycardia, high systolic blood pressure). There is no acid-base disorder and the rate of excretion of K is low; in addition, there are signs of left ventricular hypertrophy on the EKG, and a low plasma phosphate level in conjunction with a high urine calcium to phosphate ratio.

TABLE 6-2

HYPOKALEMIA AND BLOOD PRESSURE

- **Associated with high blood pressure**
  - Overactive renin angiotensin system (e.g., renin-secreting tumour, renal artery stenosis, malignant hypertension)
  - Adrenal hyperplasia or adenoma
  - Liddle's syndrome
  - Low 11-ßHSDH activity (AME)
    - Inhibitors of 11-ßHSDH (e.g., licorice)
    - Very high cortisol level (e.g., ACTH-producing tumor)
  - Use of diuretics to treat essential hypertension

- **Associated with a low blood pressure**
  - Diuretics
  - Vomiting, laxative abuse, diarrhea
  - Bartter's and Gitelman's syndrome
  - Stimulation of the calcium-sensing receptor (e.g., hypercalcemia, cationic drugs such as aminoglycosides)
  - Other (e.g., cisplatin, distal RTA due to low H^+ secretion, ureteral diversion)

CASE 6-1

Hypokalemia and paralysis

A 76-year old Asian male presented to the emergency department because of an inability to walk because of weakness. He had a low P_K (3.3 mmol/l) first noted 1-year ago. His family history is negative for hypertension and electrolyte disorders. He denies taking medications. On physical examination, his blood pressure was 160/95 mm Hg and his pulse rate was 72/min. There were no signs of a contracted ECF volume. He displayed extreme weakness and hyporeflexia. There was no evidence of hyperthyroidism. His laboratory examination is described below. His 24-hour urine volume was 1.5 litres.

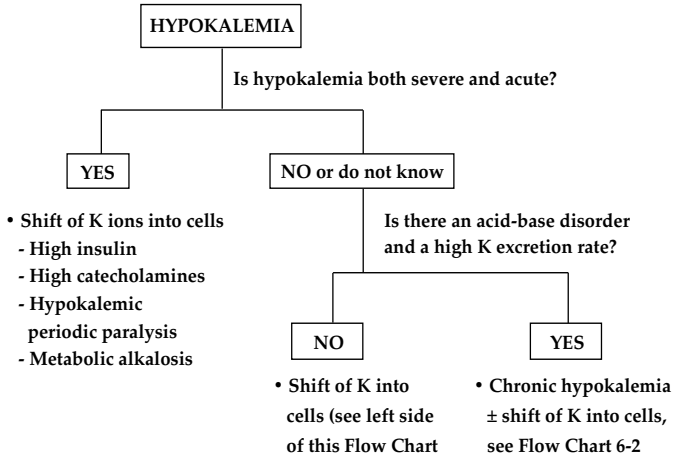
		Plasma	**Urine**
Na	mmol/l	147	100
K	mmol/l	1.8	26
Cl	mmol/l	96	103
HCO_3	mmol/l	38	-
pH		7.55	-
PCO_2	mm Hg	39	-
Urea	mmol/l (mg/dl)	5.0 (14)	-
Creatinine	µmol/l (mg/dl)	70 (0.8)	6 mmol/l
Glucose	mmol/l (mg/dl)	5.0 (90)	0
Osmolality	mOsm/kg H_2O	295	482
Mg	mmol/l	0.8	-
Special studies			
Renin	Very low	-	
Aldosterone	Very low	-	
Cortisol	Normal	-	

Discussion of case 6-1

See flow chart on page 78.

Flow Chart 6-1

Initial evaluation of the patient with Hypokalemia



Step 1. Is hypokalemia known to be acute?

Both the time frame and the clinical setting are important elements to consider. Despite having chronic hypokalemia, there was an acute component to make his hypokalemia severe in degree because he presented with an extreme weakness of both upper and lower limbs of recent onset. Because he is an Asian male, the initial presumptive diagnosis was hypokalemic periodic paralysis (HPP). Nevertheless, there was little to support this diagnosis because he did not have a family history of paralysis, evidence of thyrotoxicosis, and he was very old for this being his first episode of HPP.

Overall: His extreme weakness might be due to an acute shift of K into cells in conjunction with a chronic disorder that caused excessive excretion of K.

Step 2. Is there an acid-base disorder and/or a high rate of excretion of K?

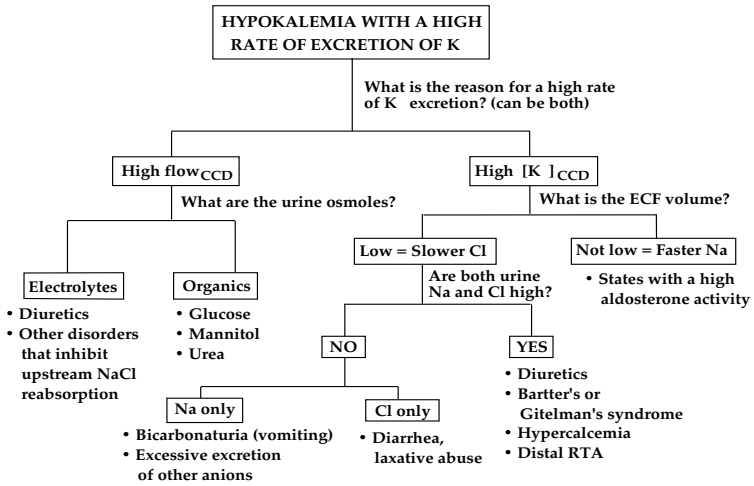
He had two laboratory findings that are not characteristic of HPP. First, he had a high rate of excretion of K because his $U_K/U_{Creatinine}$ was 5, a value that is > 2-fold higher than what is expected if the hypokalemia was due to a shift of K into cells or a non-renal loss of K. Second, he had

an acid-base disorder. The presence of metabolic alkalosis is not seen in patients with HPP.

Proceed to Flow Chart 6-2 to examine why he had a high rate of K excretion and consider both the flow rate in the CCD and the $[K]_{CCD}$.

Flow Chart 6-2

Clinical Approach to Hypokalemia Due to Renal K Loss



Step 1. Left side of the flow chart. What is the flow rate in the terminal CCD?

The flow rate in the terminal CCD was not high because the rate of excretion of osmoles was 723 mosmoles/day (1.5 L x 482 mOsm/l).

Step 1. Right side of the flow chart; What is the $[K]_{CCD}$?

The TTKG was ~ 9, a value that is very high in the presence of hypokalemia. This reflects a high lumen-negative voltage in the CCD, due to either a faster rate of reabsorption of Na or a relatively slower rate of reabsorption of Cl. This aspect needs further exploration as indicated below.

Step 2. Right side of the flow chart; What is the ECF volume?

On clinical assessment, his ECF volume did not seem to be contracted. Furthermore, his blood pressure is elevated and he had been told by his family physician, his blood pressure was elevated a year ago. Therefore the increased lumen-negative voltage in his CCD was likely due to a faster rate of reabsorption of Na. His plasma renin activity was very low, consistent with a degree of ECF volume expansion. Moreover, he had an undetectable level of aldosterone in plasma (Table 6-3). A diagram depicting his possible lesions is shown in Figure 6-2

TABLE 6-3

PLASMA RENIN AND ALDOSTERONE TO ASSESS THE BASIS OF HYPOKALEMIA

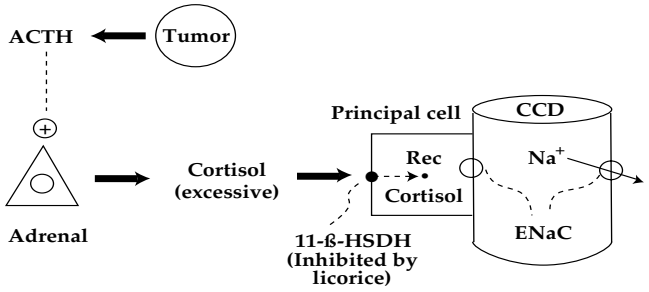
Abbreviations: AME = apparent mineralocorticoid excess, 11ß-HSDH = 11ß-hydroxysteroid dehydrogenase: GRA = glucocorticoid-remediable aldosteronism.

	Renin	Aldosterone
• **Adrenal gland lesion**		
- Primary hyperaldosteronism or adrenal tumor	low	high
- ACTH causes aldosterone synthesis (GRA)	low	high
• **Kidney lesions**		
- Renal artery stenosis	high	high
- Malignant hypertension	high	high
- Renin-secreting tumor	high	high
- Liddle's syndrome	low	absent
- Bartter's syndrome	high	high
- Gitelman's syndrome	high	high
- 11ß-HSDH fails to remove all cortisol		
- Hereditary defect (AME)	low	low
- inhibition (e.g., licorice ingestion)	low	low
- saturation because of ectopic ACTH	low	low

Figure 6-2

Influence of 11ß-hydroxysteroid dehydrogenase on aldosterone-like actions in the CCD

Cortisol has a very high affinity to the aldosterone receptor. As cortisol enters principal cells of the CCD, 11ß-HSDH (shown by the larger solid dot in the membrane) inactivates it before it can bind to the aldosterone receptor (Rec, the smaller dot in the cell). There are three circumstances in which cortisol will successfully bind to the aldosterone receptor. First, when there is a deficiency of 11ß-HSDH (apparent mineralocorticoid excess syndrome), second, when an inhibitor 11ß-HSDH is present (e.g., licorice), and third, when the supply of cortisol exceeds the ability of 11ß-HSDH to inactivate it (e.g., ectopic production of ACTH by a tumor).



Shift of K into cells

His acute symptom of weakness and the severity of his hypokalemia suggested that there was an acute shift of K into cells. Nevertheless, the high rate of K excretion and the presence of an acid-base disorder did not support a diagnosis of hypokalemic periodic paralysis.

Renal K wasting

The diagnostic category to account for his high $[K]_{CCD}$ was a faster Na reabsorption in his CCD. Because both the level of aldosterone and the activity of renin in plasma were suppressed (Table 6-3), the differential diagnosis was between disorders in which cortisol acts as mineralocorticoid and those with an open ENaC despite the undetectable levels of aldosterone (Figure 6-1).

A chest X-ray did not reveal a lung mass and cortisol levels were not elevated. Inherited disorders where ENaC is constitutively active (Liddle's syndrome) seemed unlikely considering the patient's age. While the patient denied consuming licorice or chewing tobacco, it turned out that he used large amounts of glycyrrhizic acid (the active principle in licorice) to sweeten his tea. Discontinuing this intake led to a normal P_K and a fall in his blood pressure.

IV. SPECIFIC CAUSES OF HYPOKALEMIA

A summary of the causes of hypokalemia based on their pathophysiology is provided in Table 6-1.

V. THERAPY OF HYPOKALEMIA

Our approach is to first recognize when hypokalemia may be life threatening (Table 6-4).

TABLE 6-4

INDICATIONS FOR THE ADMINISTRATION OF K

- **Absolute indications**
  - Therapy for diabetic ketoacidosis
  - Symptomatic (e.g. respiratory muscle weakness causing hypoventilation)
  - Very severe hypokalemia (less than 2.0 mmol/l) as in HPP
  - Digitalis therapy

- **Strong indications**
  - Myocardial disease
  - Anticipated hepatic encephalopathy
  - Anticipated increase in another factor causing a K shift into cells ($ß_2$ - adrenergics)
  - Less severe hypokalemia (P_K < 3.0 mmol/l)

VI. MEDICAL EMERGENCIES, AN ACUTE SHIFT OF K INTO CELLS

The major emergencies include cardiac arrhythmias and extreme weakness causing respiratory failure. When either is present, enough K must be given to raise the P_K quickly to a safe range (~ 3.0 mmol/l). The total body K deficit should be replaced much more slowly. Because large doses and high concentrations of K might be needed, K must be administered via a central vein and the patient should be on a cardiac monitor. In general, the infusion should not contain glucose or HCO_3 because this might aggravate the degree of hypokalemia.

CASE 6-2

An adrenergic surge

A 57-year old male had an acute traumatic brain injury after a fall from a large height. Within the first few hours, his P_K fell from 3.7 mmol/l to a nadir of 1.3 mmol/l and ventricular tachycardia developed.

1. Diagnosis

Given the short time course, the basis for the fall in P_K was a sudden and marked shift of K into cells. The cause of this K shift was the extreme adrenergic response and the adrenergic agents administered to maintain hemodynamics.

2. Therapy

The goal is to raise his P_K by 1 mmol/l in 1 min, recognizing that there would be a much smaller increase in K concentration in interstitial fluid in the heart. To achieve this goal, 3 mmol of K needs to be infused in 1 min (cardiac output is 5 L/min, blood volume 5 L, and plasma volume 3 L). If the EKG changes do not improve, repeat this procedure. Following this initial K bolus, the rate of infusion of K should be reduced to 1 mmol/min and the P_K should be monitored very closely. Stop the infusion for 60 sec to avoid a spuriously high P_K.

The patient in this report was given 618 mmol of K, but his P_K never exceeded 2.4 mmol/l. The predominant K salt infused was a HCO_3 derivative, not KCl.

3. Therapy of Hypokalemic periodic paralysis

In the absence of a cardiac or respiratory emergency, small doses of KCl should be given to patients with hypokalemic periodic paralysis to minimize the risk of severe rebound hyperkalemia because they do not have a large deficit of K. If associated with hyperthyroidism, a non-selective ß-blocker (propranalol 3 mg/kg) can provide effective therapy. Clues to suggest the presence of 'occult' hyperthyroidism were listed above.

4. No medical emergency

(i) Magnitude of the K deficit

There is no useful quantitative relationship between the P_K and the total body K deficit because there may also be a shift of K into cells. Hence careful monitoring of the P_K during replacement of the K deficit is mandatory.

(ii) Route of K administration

The oral route is preferred if bowel sounds are present. When a peripheral intravenous route is used, the K concentration should not be > 40 mmol/l. The rate of K administration should not be > 60 mmol/h in all but emergency settings.

(iii) K preparations

Increasing the intake of K rich foods (e.g., bananas, fruit juice) has the danger of inducing a large weight gain. Oral KCl (e.g., salt substitutes like co-salt provide 14 mmol of K per gram) is generally well tolerated and inexpensive. Liquid K supplements have an unpleasant taste and are often poorly tolerated. Most preparations used are "slow-release", either microencapsulated or in a wax matrix. Although usually well tolerated, they may cause ulcerative or stenotic lesions in the GI tract.

In patients with a deficit of KCl (e.g., chronic vomiting or diuretics), KCl is needed. In patients with a $KHCO_3$ deficit (e.g., diarrhoea), $KHCO_3$ may be needed in addition to giving KCl. Because the administration of HCO_3 may lead to a shift of K into cells, KCl should be given initially and alkali should be withheld until the P_K approaches a safe level of (~ 3 mmol/l) unless there are ongoing and large losses of HCO_3. K phosphate may be needed when there is rapid anabolism and little oral intake. I give K as KCl in treatment of DKA and rely on the patient's diet to supply the phosphate needed to restore a normal ICF composition later in time. If given, limit phosphate infusion to < 50-mmol/8 h to minimize the risk of hypocalcemia and metastatic calcification.

(iv) Adjuncts to therapy

Using K-sparing-diuretics may reduce renal loss of K, but this is only useful on a chronic basis. Amiloride and triamterene are better tolerated than spironolactone as they lack the gastrointestinal and hormonal (ammenorhea, gynecomastia, decreased libido) complications of spironolactone. Hyperkalemia may develop, especially when K is given with K-sparing diuretics and if other conditions which compromise K excretion are present; note that these drugs have a long half-life.

There is a problem when blockers of the luminal ENaC are combined with diuretics because these latter drugs can cause a high distal flow rate. As a result, the luminal concentration of

these ENaC blockers declines because of the higher volume delivered to the CCD. Thus ENaC might not be inhibited sufficiently to reduce the excretion of K.

(v) Risks of therapy

With prolonged hypokalemia, the CCD may become temporarily hyporesponsive to the kaliuretic effect of aldosterone. Hence, it is important to monitor the P_K frequently during the treatment of hypokalemia. Hyperkalemia has been observed in ~ 4% of patients taking K supplements. The risk is highest in patients with renal failure and diabetes mellitus. The simultaneous use of ACE inhibitors or angiotensin II receptor blockers, ß-blockers or non-steroidal anti-inflammatory drugs and K-sparing diuretics (e.g., spironolactone) may also predispose to the development of hyperkalemia.

CHAPTER 7

HYPERKALEMIA

I. ESSENTIAL POINTS

1. Definition

Hyperkalemia = plasma [K] (P_K) > 5.0 mmol/l (exact cut-off is arbitrary).

2. Expected physiological response:

Excretion of > 200 mmol (3 mmol/kg) K per day.

3. Clinical evaluation

The main danger of hyperkalemia is a cardiac arrhythmia (examine the EKG). This threat and the absolute P_K are not tightly correlated.

Evaluate whether there may be a shift of K out of cells. Suspect it if the time course is short and if there is little K intake. Also suspect it if there is cell breakdown, insulin deficiency, or metabolic acidosis (loss of $NaHCO_3$ type).

Evaluate the renal excretion of K. This is an important factor in all patients with chronic hyperkalemia. Use either a timed collection or the $U_K/U_{Creatinine}$ ratio. Examine the components of K excretion, flow rate in the CCD and $[K]_{CCD}$ if $U_{osm} > P_{osm}$. Determine why each of these components may be abnormal

4. Laboratory features

One must be certain that hyperkalemia is not the result of the technique for drawing blood or the lysis of cells in blood. An abnormal EKG makes at least part of the hyperkalemia a real medical problem.

The tests for K excretion should be examined bearing the P_K in mind. Use the K excretion rate, an assessment of the flow rate in the CCD, and the $[K]_{CCD}$ or the TTKG.

5. Treatment

If there are EKG changes, an anticipated rise in the P_K or a $P_K > 7.0$ mmol/l, this may be an emergency. Antagonize the effects of hyperkalemia with Ca if an emergency. You will also have to stop K

intake, shift K into cells, and promote K loss into the gastrointestinal tract or the urine. If you anticipate a problem, prepare the patient for dialysis sooner rather than later.

II. QUESTIONS TO ASK THE PATIENT WITH HYPERKALEMIA

1. When is hyperkalemia an emergency?

Answer: If there are EKG changes, an anticipated rise in the P_K or a $P_K > 7.0$ mmol/l.

2. Is hyperkalemia due to a lab problem?

Answer: Rule out hemolysis or thrombocytosis. EKG changes exclude a lab problem as the sole cause of hyperkalemia.

3. What should be stressed on history?

Answer: Dietary K intake, catabolism, diabetes mellitus, drug intake (Table 7–1). The symptoms of adrenal insufficiency may be non-specific. A family history may be helpful.

4. Is hyperkalemia due to high K intake alone?

Answer: No. High K intake will contribute only if K excretion is compromised.

5. Did K shift from the ICF?

Answer: Yes if the time course is short and if K intake is low. Look for cell damage, low insulin levels, §-adrenergic blockade, or metabolic acidosis due to a deficit of $NaHCO_3$, drugs that cause depolarization and a K shift from the ICF. If the family history is positive, suspect hyperkalemic periodic paralysis.

6. What should be stressed on physical exam?

Answer: Examine the blood pressure,and skin pigmentation. Use laboratory and clinical tools to assess the ECF volume.

7. What should be stressed on lab examination?

Answer: EKG, acid-base status, glucose, urea, plasma and urine electrolytes, TTKG, osmole excretion rate, response to mineralocorticoids. The hematocrit, plasma renein activity, and aldosterone levels may be helpful to assess the ECF volume.

8. Is K excretion compromised?

Answer: K excretion is determined by the [K] X flow rate; therefore decreased K excretion will occur if there is a problem with K secretion (low $[K]_{CCD}$) and/or low urine $flow_{CCD}$ (low osmole excretion rate).

9. What are the main options for therapy?

Answer: Eliminate the intake of K. Shift K into cells with insulin and possibly ß-adrenergics. Increase renal K excretion. For the latter, if the U_{Na} is low, raise it with a loop diuretic + enough NaCl. Give aldosterone ± $NaHCO_3$ or acetazolamide if the $[K]_{CCD}$ is low. Give urea or a loop diuretic (+ NaCl) if the flow rate in the CCD is low. Promote GI K loss with resins. If severe hyperkalemia, EKG changes and/or an acute P_K rise, give Ca to antagonize cardiac effects of hyperkalemia and prepare to dialyze.

TABLE 7-1

DRUGS THAT CAN CAUSE HYPERKALEMIA

- **Drugs containing K**
  - Only increase P_K if renal function is compromised.
  - KCl, table salt substitutes
- **Drugs causing a K shift from ICF to ECF**
  - Cell depolarizers such as succinylcholine
  - Drugs causing cell necrosis
  - Drugs impairing insulin release from ß-cells such as α-adrenergic agonists
  - Hormone antagonists, e.g., $ß_2$-adrenergic receptor blockers
- **Drugs which interfere with K excretion in the urine:**
  - Drugs causing renal failure
  - Drugs interfering with aldosterone action
  - Drugs that block ENaC, e.g., amiloride, trimethoprim
- **Low aldosterone release from adrenal gland:**
  - Drugs that can cause adrenal gland destruction (e.g., heparin)
  - Converting enzyme inhibitors and angiotensin II receptor blockers
- **Block aldosterone binding to its renal receptor**
  - Spironolactone, aldactone
  - Drugs causing interstitial nephritis
- **Post-receptor blockers:**
  - ENaC blockers in the CCD (e.g., amiloride, trimethoprim).

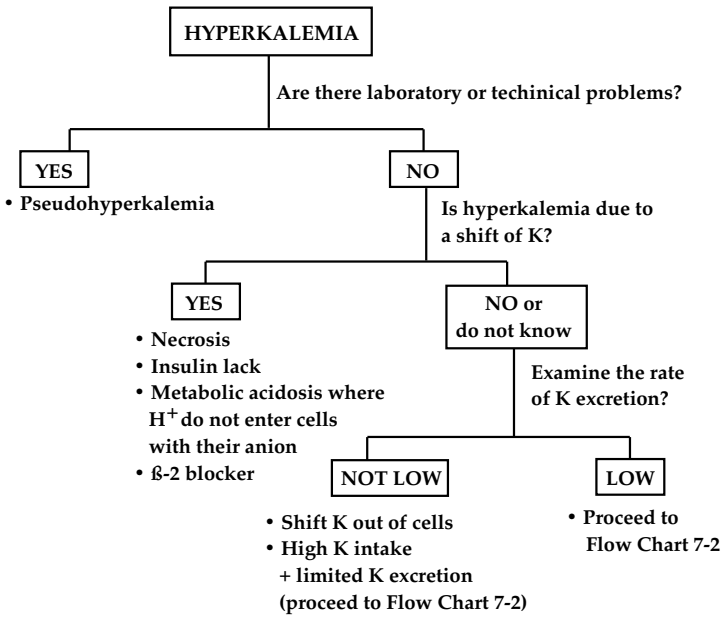
III. CLINICAL APPROACH TO THE PATIENT WITH HYPERKALEMIA

It is imperative to recognize when hyperkalemia represents a medical emergency because therapy must take precedence over diagnosis. In the absence of an emergency, follow the step-by-step approach outlined in Flow Chart 7-1. I shall use Case 7-1 to illustrate these steps.

Flow Chart 7-1

Initial steps in the patient with Hyperkalemia

The final diagnostic categories are preceded by a bullet symbol.



IV. ILLUSTRATIVE CASE

CASE 7-1

Hyperkalemia, A shift in thinking

A 23-year old male has a long history of AIDS, which is now complicated by PCP pneumonia; he began treatment with trimethoprim several days ago. His dietary intake was poor and he appeared to be malnourished. Over the past several days, there was no change in his pneumonia, but hypotension developed secondary to a reduced ECF volume. The EKG showed changes consistent with hyperkalemia. His laboratory data today are summarized below.

		Plasma	Urine
Na	mmol/l	130	60
K	mmol/l	6.8	14
Cl	mmol/l	105	43
HCO_3	mmol/l	15	0
pH		7.30	5.1
Urea (BUN)	mmol/l (mg/dl)	5 (14)	100 mmol/l
Creatinine	µmol/l (mg/dl)	100 (0.9)	7 mmol/l
Osmolality	mOsm/kg H_2O	268	270
Volume	L/day	-	0.8

Questions

- **Are there laboratory or technical problems?**
- **Is hyperkalemia due to a shift of K?**
- **What is the rate of K excretion?**

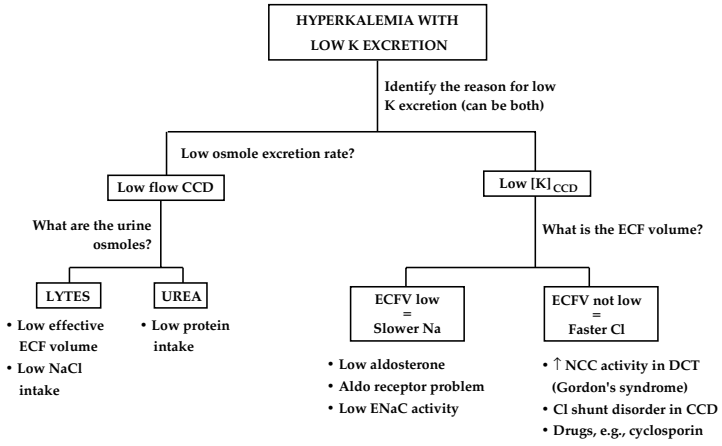
Discussion of Case 7-1

Are there laboratory or technical problems?

Although an element of pseudohyperkalemia was suspected in this cachectic patient, it was not the only or the major cause of hyperkalemia because his EKG showed signs of hyperkalemia. Pseudohyperkalemia can be present in cachectic patients because the normal T-tubule architecture in skeletal muscle may be disturbed. This permits more K to be released into venous blood, even without excessive fist clenching.

Flow Chart 7-2

Renal Causes for Hyperkalemia and a low rate of excretion of K



Is hyperkalemia due to a shift of K?

A shift of K from cells rather than a large positive balance for K was the major cause of hyperkalemia because the rise in P_K occurred over several days and the patient consumed little K. This is important to recognize because one should not induce a large loss of K and cause an overall total body K deficit during therapy since this may lead to a severe degree of hypokalemia when K shifts back into cells. The shift of K out of cells could be due to insulin deficiency secondary to the α-adrenergic effect of catecholamines released in response to the low ECF volume. Other causes for K exit from cells could be cell necrosis and/or metabolic acidosis due to an added acid whose anion cannot cross cell membranes.

What is the rate of K excretion?

Because his U_K was 14 mmol/l and his 24-hour urine volume was 0.8 L, his rate of excretion of K is very low in the face of hyperkalemia. It is important to determine why he had such a low rate of K excretion (see Flow Chart 7-2).

Assess the (Flow rate)$_{CCD}$

Step 2. Left side of the flow chart. What is the urine osmole excretion rate?

Because his osmole excretion rate is low (0.8 L x 270 mOsm/l = 218 mosmol/day), he has a low flow rate in his CCD. The low protein intake will cause a low urea excretion. The low salt intake and the low ECF volume will cause a low excretion of Na + Cl.

Assess the $[K]_{CCD}$

Step 1. Right side of the flow chart. What is the $[K]_{CCD}$?

The $[K]_{CCD}$ ($< 7 \times P_K$) and the TTKG of ~ 2 were both very low in this setting. The low $[K]_{CCD}$ usually implies a less negative lumen-negative voltage in the CCD due to less electrogenic reabsorption of Na. Seek the basis for an inability to reabsorb Na faster than Cl. The two groups of causes are a slower Na reabsorption and a relatively faster Cl reabsorption

Step 2. Right side of the flow chart. What is the ECF volume?

Because he had a low ECF volume and a U_{Na} and U_{Cl} that were inappropriately high in the presence of a contracted ECF volume, his low $[K]_{CCD}$ was probably due to slower Na reabsorption resulting from inhibition of ENaC by trimethoprim. Both his plasma renin activity and aldosterone level (which became available later) were high suggesting that there was not an important adrenal lesion (Table 7-2).

From a therapeutic point of view, the question arose as to whether trimethoprim should be discontinued. The drug was needed to treat his pneumonia. To remove its renal ENaC-blocking effect, the objective was to lower the concentration of trimethoprim in the lumen of the CCD. To achieve this aim, the flow rate in the CCD was increased using a loop diuretic (Figure 7-1). To avoid a further contraction of his ECF volume, enough NaCl was infused to re-expand his ECF volume. Inducing bicarbonaturia could also be considered to lower the concentration of H^+

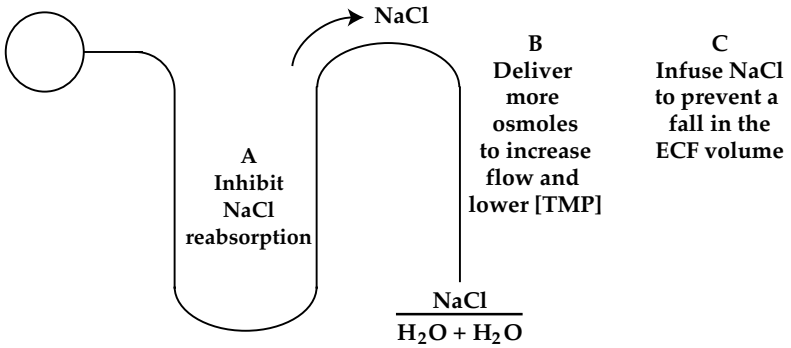
in the luminal fluid in the CCD and thereby the cationic form of the drug that blocks ENaC..

$Trimethoprim^{o} + H^{+} \leftrightarrow Trimethoprim^{+}$ (active form)

Figure 7-1

Method to lower the concentration of Trimethoprim in the CCD

The steps to follow are listed as A, B,and C.



Synopsis:

The step-by-step approach illustrated in Flow Charts 7-1 and 7-2 revealed the basis of hyperkalemia and provided a rational approach to therapy. The effect of trimethoprim to block ENaC caused renal salt wasting and contributed to ECF volume contraction. This led to a shift of K out of cells because of inhibition of insulin release by α-adrenergics. Because of the low ECF volume (and the low intake of proteins), there was a low rate of flow in the CCD. This, in addition to diminishing the rate of K excretion, caused the concentration of trimethoprim in the lumen of the CCD to be higher (same amount of trimethoprim in a smaller volume), and hence it became a more effective blocker of ENaC, leading to a diminished $[K]_{CCD}$. Re-expanding the ECF volume and increasing the rate of flow in the CCD provided the rationale for therapy. Care was taken to avoid inducing too large a K loss and thereby, aggravating his total body K deficit and producing a severe degree of hypokalemia later on.

TABLE 7-2

PLASMA RENIN AND ALDOSTERONE TO ASSESS THE BASIS OF HYPERKALEMIA

• **Effective ECF volume**	**Renin**	**Aldosterone**
- Low	high	- should be high
- High	low	- should be low
• **Adrenal gland problem**		
- Adrenal insufficiency	high	low
• **Renal lesions**		
- Gordon's syndrome	low	low

V. SPECIFIC CAUSES OF HYPERKALEMIA

A list of conditions associated with hyperkalemia is shown in Table 7-3

TABLE 7-3

CAUSES OF HYPERKALEMIA

- **High dietary K intake (an unlikely sole cause of hyperkalemia).**
- **Shift of K from the ICF to the ECF**
  - Cell necrosis or depolarization
  - Hormone deficiency or blockade:
    - Insulin
    - $ß_2$-adrenergics
    - Aldosterone (possibly)
    - Metabolic acidosis due to loss of $NaHCO_3$ or where the anion does not distribute in the ICF compartment
    - Rare causes (e.g., hyperkalemic periodic paralysis)
- **Decreased renal K excretion**
  - Lower K loss in the urine
    - Low flow rate in terminal CCD (low osmole excretion rate)
    - Low $[K]_{CCD}$
      - Na not reabsorbed faster than Cl
        - Very low delivery of Na to the CCD,
        - Low levels of aldosterone (e.g., Addison's disease)
        - Blockade of the aldosterone receptor (e.g., spironolactone)
        - Low ENaC activity (hereditary disease)
        - Blockade of ENaC (e.g., amiloride, triamterene, trimethoprim-like drugs)
      - Na reabsorbed at a similar rate as Cl
        - Faster NaCl reabsorption inthe CCD (Gordon's syndrome)
        - Drugs (e.g., cyclosporin)

Blood pressure and Hyperkalemia

A list of conditions where hyperkalemia is associated with an alteration in blood pressure is shown in Table 7-4.

TABLE 7-4

HYPERKALEMIA AND BLOOD PRESSURE

Because hyporeninemic hypoaldosteronism has multiple causes, it is not listed as a specific entity in this Table.

- **Associated with a high blood pressure**
  - Enhanced Na and Cl reabsorption in the DCT (e.g., Gordon's syndrome, diabetes mellitus, calcineurin inhibitors)
  - Advanced renal disease

- **Associated with a low blood pressure**
  - Low aldosterone bioactivity
  - Pre-receptor level (e.g., adrenal insufficiency)
  - Receptor level (e.g., defective aldosterone receptor)
  - Post-receptor level (e.g., drugs that block ENaC)
  - Tubulointerstitial disorders

VI. THERAPY OF HYPERKALEMIA

1. Medical emergencies

The major danger of a severe degree of hyperkalemia is a cardiac arrhythmia. Because mild EKG changes may progress rapidly to a dangerous arrhythmia, any patient with an EKG abnormality related to hyperkalemia should be considered as a potential medical emergency. In certain circumstances, I would treat patients with a P_K > 7.0 mmol/l aggressively, even in the absence of EKG changes—exceptions include extremes in exercise, most patients on chronic hemodialysis, and in infants.

(i) Antagonize the cardiac effects of hyperkalemia

Ionized Ca is the best agent and its effects are usually evident within minutes (Table 7-5). It is usually given as 20-30 ml of a 10% calcium gluconate solution (2-3 ampoules) or 10 ml of 10% $CaCl_2$ (one ampoule). This dose can be repeated in 5 minutes if EKG changes persist. The effect usually lasts 30-60 minutes.

TABLE 7-5

TIME COURSE FOR THE ACTION OF MODES OF TREATMENT OF HYPERKALEMIA

Onset of Action (hr)	Agent
0.1	Calcium salts
0.5 - 2	Insulin, but prevent hypoglycemia $ß_2$-adrenergics may be added Promote renal K excretion with NaCl, furosemide ± aldosterone
2 - 10	K binding resins by enema
12 - 24	Oral K-binding resins
At onset	Dialysis

(ii) Induce a shift of K into the ICF

Insulin is important to shift K into cells. Large doses of insulin (20 units of regular insulin) may be needed. Give glucose to avoid the development of hypoglycemia.

$ß_2$-adrenergics may lower the P_K in patients with renal failure. However, 20 –40 % of patients are resistant to this therapy and it is not possible to predict non-responders; hence I do not recommend their use as a sole emergency therapy. There are concerns about the safety of these drugs in the doses used for the treatment of hyperkalemia (20 mg of nebulized albuterol), doses that are 4 to 8 times that prescribed for the treatment of acute asthma.

A number of recent studies have found $NaHCO_3$ to be ineffective as a sole treatment of hyperkalemia.

2. No medical emergency

(i) Remove K from the body

Much less K loss is needed to lower the P_K from 7.0 to 6.0 mmol/l than to lower it from 6.0 to 5.0 mmol/l. Hence creating a small K loss can be very important when there is a severe degree of hyperkalemia.

(ii) Enhance the excretion of K in the urine

If a patient has a low rate of K excretion because of a low urine volume, a loop diuretic may induce kaliuresis by increasing the flow rate in the CCD. One can avoid unwanted ECF volume contraction by replacing the NaCl lost in the urine. This NaCl should be given at the same tonicity as the urine to avoid creating a dysnatremia.

If the U_K is unduly low, giving an exogenous mineralocorticoid (100 μg florinef) and possibly inducing bicarbonaturia with a carbonic anhydrase inhibitor may cause a substantial kaliuresis. If HCO_3 is lost in the urine, it might need to be replaced.

(iii) Cation exchange resins to promote the loss of K

A cation exchange resin can exchange bound Na (Kayexalate) or ionized Ca (calcium resonium) for K. Kayexalate contains 4 mEq of Na per gram, but only 1 mmol of Na appears to exchange for K in the GI tract. The only favorable location for the exchange of Na for K is in the lumen of the colon but a number of factors limit the magnitude of this process.

Other cations may exchange for resin-bound Na, apart from K. Even if K were secreted in the colon, the low stool volume would limit the total K loss. Hence there may be little benefit of resins in the treatment of <u>acute</u> hyperkalemia.

(iv) Dialysis

Hemodialysis is more effective than peritoneal dialysis for removing K. Removal rates of K can approximate 35 mmol/hr with a dialysate bath K concentration of 1-2 mmol/l. A glucose-free dialysate is preferable to minimize a glucose-induced shift of K into cells, lessening the removal of K.

VII. ADDITIONAL CASE

CASE 7-2

Hyperkalemia and hypertension after a renal transplant

A 23-year old woman had a renal transplant 6 months ago with an excellent result; the treatment included the drug, cyclosporin. Over the

past 3 months, there were two new findings, her blood pressure rose from 120/90 to 160/100 mm Hg where it has remained, and her plasma P_K rose to the mid-5 range. All antihypertensive medications were discontinued for the past 3 days to permit a definition of her electrolyte disorder. The laboratory data are provided below. The plasma renin activity was very low and the EKG showed signs of hyperkalemia.

Parameter		Plasma	Urine
Na	mmol/l	133	147
K	mmol/l	5.8	36
Cl	mmol/l	109	145
HCO_3	mmol/l	20	0
pH		7.35	5.1
Pco_2	mm Hg	35	-
Glucose	mmol/l (mg/dl)	5 (90)	0
Creatinine	µmol/l (mg/dl)	138 (1.2)	10 mmol/l
Urea (BUN)	mmol/l (mg/dl)	5 (14)	280
Osmolality	mOsm/kg H_2O	280	690
Volume	L/day	-	1.0

Question

- **What is the basis for chronic hyperkalemia?**

Discussion of Case 7-2

What is the basis for hyperkalemia?

Begin by following the steps in Flow Chart 7-1.

Step 1. Are there laboratory or technical problems?

Pseudohyperkalemia was not present. Moreover, even if it were present, it would not be the major cause of hyperkalemia because the EKG showed signs of hyperkalemia.

Step 2. Is hyperkalemia due to a shift of K?

A shift of K from cells could play a minor role in the chronic hyperkalemia because there was a mild degree of metabolic acidosis due to a deficit of $NaHCO_3$.

Step 3. What is the rate of K excretion?

Because the U_K was 36 mmol/l and the 24-hour urine volume was 1 L, the rate of excretion of K was very low in the face of hyperkalemia. It is important now to determine why there was such a low rate of K excretion (see Flow Chart 7-2).

Assess the $(\text{Flow rate})_{CCD}$

Step 1. Left side of the flow chart. What is the urine osmole excretion rate?

Because his osmole excretion rate was in normal range (1 L x 690 mOsm/l = 690 mosmol/day), there was not a low flow rate traversing the terminal CCD.

Assess the $[K]_{CCD}$

Step 1. Right side of the flow chart. What is the $[K]_{CCD}$?

The $[K]_{CCD}$ (36 mmol/l/(690/285) = 15 mmol/l) and the TTKG (15 / 5.8 mmol/l = 2.6) were both very low in the face of hyperkalemia. This usually implies a diminished lumen-negative voltage in the CCD due to less electrogenic reabsorption of Na.

I shall now seek the basis for an inability to reabsorb Na faster than Cl in the CCD. The two groups of causes are a slower Na reabsorption and a relatively faster Cl reabsorption in the CCD.

Step 2. Right side of the flow chart. What is the ECF volume?

The physical examination is just not adequate to assess the ECF volume when changes are modest in degree. Therefore I turn to the plasma renin activity for help. A low renin activity suggests that the ECF volume was high. This rules out conditions with a slower Na reabsorption in the CCD. Therefore the differential diagnosis is shown in the bottom right segment of Flow Chart 7.2.

One other comment is helpful. The current values for the excretions of Na, K, and Cl represent their intakes in a person in steady state (this is a chronic condition). Therefore the U_{Na} and U_{Cl} are not helpful to assess the ECF volume unless you are assessing them in the presence of a stimulus for distal Na reabsorption, a contracted ECF volume. Had this stimulus been present, they would be extremely low because there is no limitation being imposed on the reabsorption of Na and Cl in the distal nephron in this patient.

Synopsis

The low $[K]_{CCD}$ was probably due to an inability to reabsorb Na faster than Cl. The most likely basis is a faster reabsorption of Na and Cl in an upstream nephron segment, probably the DCT. The net result is a very much lower delivery of Na and Cl to the CCD so that Na cannot be reabsorbed faster than Cl in this nephron segment (delivery limitation). This pathophysiology is depicted in the lower right segment of Figure 5-4, page 57.

Hypertension is the result of vasoconstriction and/or a higher circulating volume. The hyperkalemia and hypertension can be linked in the following way. Because of enhanced reabsorption of Na and Cl, the ECF volume will be expanded. As a result, the blood pressure will rise if the patient is more sensitive to blood volume than to vasoconstrictor level with respect to their blood pressure.

The low arterial pH and P_{HCO3} indicate that metabolic acidosis is present. It is not due to added acids because the anion gap is normal and there are no unusual anions in the urine. Therefore its basis is a deficit of $NaHCO_3$. There was no urinary loss of $NaHCO_3$ or a history of GI $NaHCO_3$ loss. Hence I suspected that there would be a low rate of excretion of NH_4. This suspicion for the basis for the acidosis is supported by the fact that both the urine net charge and urine osmolar gap fail to indicate a high rate of excretion of NH_4. The low urine pH suggests that the low NH_4 excretion rate is due to low NH_3 in the renal medullary interstitium, probably secondary to hyperkalemia.

SECTION III

ACID BASE

CHAPTER 8

ACID-BASE PHYSIOLOGY

I. BACKGROUND

This chapter will supply background information for the next 4 chapters that deal with more specific issues in the acid-base area. The first goal will be to understand how acid balance is achieved (Figure 8-1). The second goal will be to understand how base balance is achieved (Figure 8-1).

FIGURE 8-1

How acid is eliminated

The new H^+ produced in metabolism (in the liver) that require NH_4 excretion for their elimination come from the oxidation of sulphur-containing amino acids depicted as methionine (see starting point at the top left). These new H^+ are removed by reacting with ECF HCO_3, forming CO_2, which is exhaled via the lungs. The SO_4 anions are excreted in the urine with NH_4. For the latter process, an equal quantity of HCO_3 is added to the ECF—overall, equal equivalent amounts of NH_4 + SO_4 are excreted in the urine.

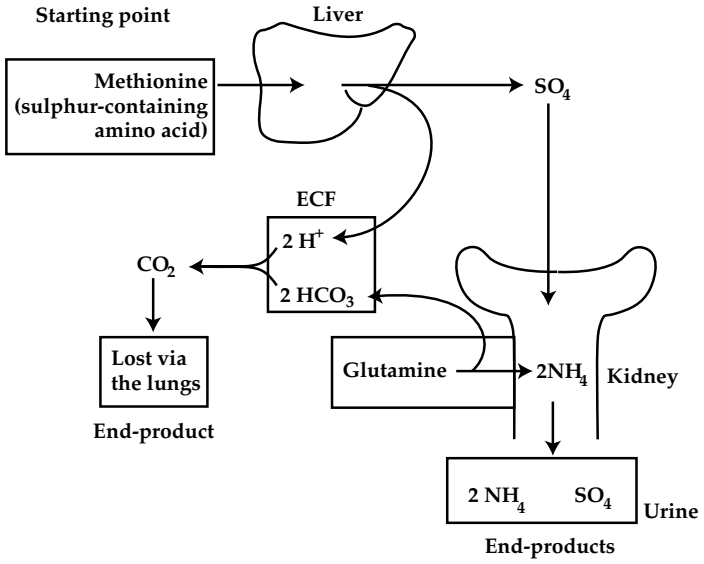
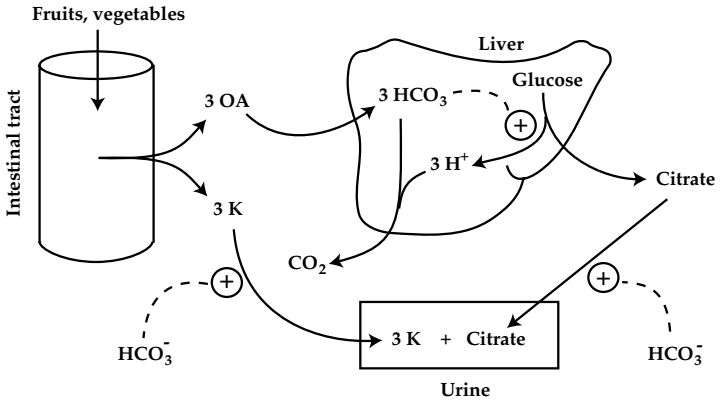


FIGURE 8-2

How alkali is eliminated

The alkali load of the diet is derived primarily from ingested K-salts of organic anions. These organic anions (OA) are converted to HCO_3 in the liver. The liver also produces citric acid; its H^+ remove the HCO_3 and the citrate anions will be excreted in the urine with K. HCO_3 ions augment the excretion of both K and citrate anions. Thus the urine can be virtually HCO_3-free.



II. SYNOPSIS OF PERTINENT PHYSIOLOGY

1. Production of Acids

When there is a gain of an acid, identify new H^+ by finding a fall in the content of HCO_3 and a rise in the free H^+ concentration in plasma. Identify new anions in plasma, urine and/or feces.

Clinical context

The plasma and urine anion gaps become useful clinical tools to detect new acids.

2. Production of Alkali

Ingested $NaHCO_3$ or the K salts of organic acids yields a HCO_3 load (Figure 8-2). Fruits and vegetables contain organic anions + K.

Clinical context

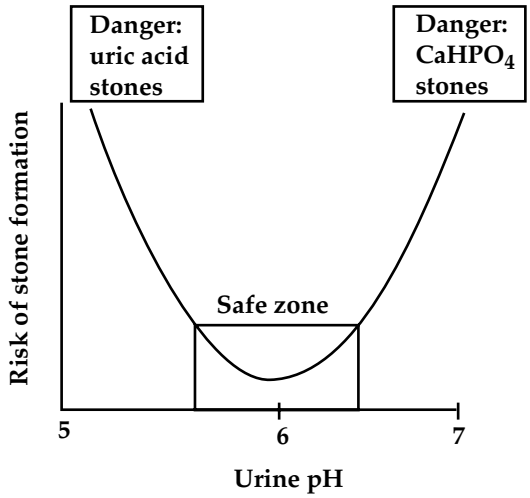
The daily alkali ingestion provides the stimulus for organic anion excretion. Citrate is the most important one because it chelates ionized calcium in the urine. Bicarbonaturia would increase the likelihood of

forming calcium-containing kidney stones as a consequence of an alkaline urine pH (Figure 8-3).

FIGURE 8-3

Urine pH and the risk of kidney stone formation

The ideal range (safe zone) for the urine pH is a value close to 6.0 to minimize the risk of kidney stone formation.



3. Buffer H^+

In physiologic terms, the objective is to minimize the likelihood of H^+ binding to proteins by forcing H^+ to react with HCO_3 ions (Figure 8-4). The latter is achieved by lowering the Pco_2 in cells.

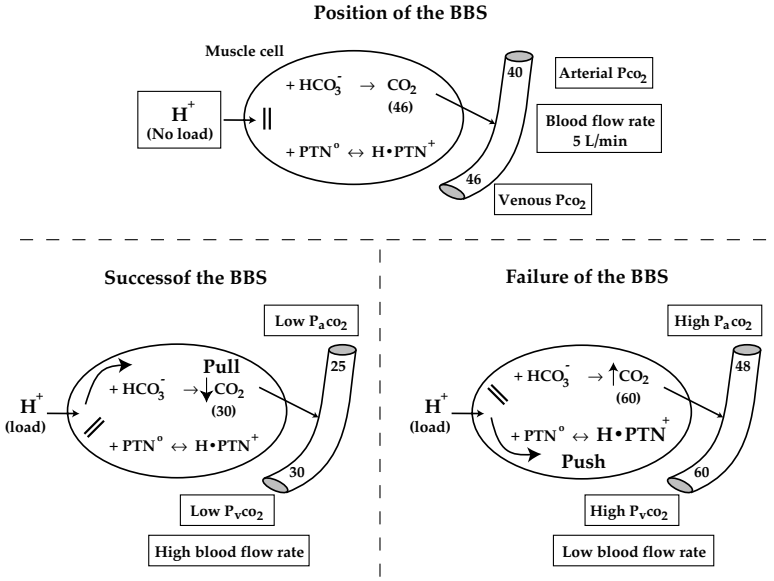
Clinical context:

Respiratory acidosis should be defined in acid-base terms as a condition where the Pco_2 is too high <u>in cells</u> so that cells cannot use their bicarbonate buffer system to buffer H^+—rather H^+ will bind to proteins (Figure 8-4). Do <u>not</u> rely on the arterial Pco_2 to indicate how many H^+ can be buffered by HCO_3. You must also assess the blood flow rate to individual organs and the rate of production of CO_2 to know the Pco_2 in cells. Measure the venous Pco_2.

Figure 8-4

Role of tissue Pco_2 in the selection of intracellular buffer systems

There are two major potential H^+ acceptors in cells, but at rest, there are few H^+ to buffer (top portion of the figure). Success of the BBS to remove a H^+ load (bottom left) is when the tissue Pco_2 falls and this pulls new H^+ to bind with HCO_3 rather than intracellular proteins with their ideal charge (PTN^o). This success depends on having a low arterial Pco_2 and a high blood flow rate. Failure of the BBS to remove a H^+ load (bottom right) is when the tissue Pco_2 cannot fall because the arterial Pco_2 is not low and/or the blood flow rate is too low. This rise in tissue Pco_2 increases the $[H^+]$ in cells, pushing H^+ to bind to intracellular proteins ($H{\bullet}PTN^+$). When the blood flow rate rises, the tissue and venous Pco_2 will fall. As a result, H^+ will be released from $H{\bullet}PTN^+$) in the ICF.



4. Kidney in acid-base balance

There are two roles: First, H^+ are eliminated (new HCO_3 are formed) when NH_4 is excreted in the urine (U_{NH4}) (Figure 8-1). Second, alkali is eliminated when a family of organic anions is excreted in the urine as their K or Na salts; there is very little excretion of HCO_3 (Figure 8-2).

Clinical context

The body strives to achieve a urine pH that is ~ 6.0 to minimize the risk of kidney stone formation ((Figure 8-3)—this means excrete NH_4 instead of H^+ and citrate anions instead of HCO_3.

5. Control of the cell pH and voltage

The cell defends its H^+ concentration by exporting H^+ or HCO_3. The Na/H^+ ion exchanger (NHE) is electroneutral and normally inactive It can be activated by insulin (high level) or by an intracellular acidosis (Figure 8-5, left side). The Cl/HCO_3 anion exchanger (AE) is electroneutral and normally inactive (Figure 8-5, right side). It is not clear how it can be activated. The cell defends its voltage by exporting H^+ or HCO_3 on NHE or AE.

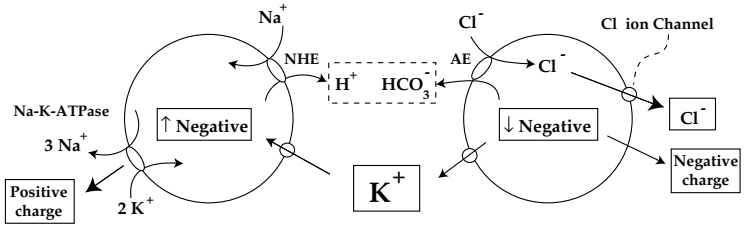
Clinical context

A more important function may be the regulation of the voltage in cells because this regulates K distribution and thereby the plasma K concentration (P_K).

Figure 8-5

NHE exports H^+ and makes the cell interior more negative

The circles represent cells with their usual net negative ICF voltage. Because of the higher Na concentration outside cells and the higher H^+ concentration in cells, the NHE catalyzes H^+ exit and Na ion entry into cells in an electroneutral fashion (left portion). This transport requires activation by insulin or intracellular acidosis. When Na ions are exported by the Na-K-ATPase, the voltage in cells becomes more negative. The net effect is to shift K ions into cells. As shown on the right, because of the much higher Cl ion concentration outside cells, the AE catalyzes HCO_3 exit and Cl ion entry into cells in an electroneutral fashion. The combination of flux through the AE and the Cl ion channel tends to decrease the negative ICF voltage and cause intracellular acidification and ECF alkalinization. This transporter required activation but the mechanism is not clear. The net effect is to shift K ions into cells.



III. EVALUATE ACID-BASE DISORDERS

1. Normal values are:

pH 7.40 or $[H^+]$ 40 nmol/l

Method 1: To convert pH to $[H^+]$ in the pH range of 7.25 - 7.55, do the following. Drop the 7 and the decimal point. Subtract the value obtained from 40. Add this value to 40 = the $[H^+]$ in nmol/l.

Example: The pH is 7.30. Drop the 7 and the decimal point = 30. Subtract 30 from 40 = +10. Add +10 to 40 = 50 nmol/l. For pH 7.50, you will add –10 to 40 yielding a $[H^+]$ of 30 nmol/l.

Method 2: For pH 7.00, the $[H^+]$ is 100 nmol/l. If the pH rises 0.1 unit multiply by 0.8. Thus a pH of 7.10 is a $[H^+]$ of 80 nmol/l. Conversely, if the pH falls by 0.1 unit, divide by 0.8. Therefore a pH of 6.90 is a $[H^+]$ of 125 nmol/l.

2. Pco_2

This is important to select the HCO_3 buffer system. The Pco_2 in arterial blood (40 mm Hg) reflects alveolar ventilation. The Pco_2 in venous blood (46 mm Hg) is more critical for buffering. It is influenced by factors other than the arterial Pco_2, the rate of CO_2 production, and most importantly, the blood flow rate in that organ.

3. Plasma $[HCO_3]$ 25 mmol/l

This is a concentration term and is influenced by its numerator (HCO_3) and its denominator (ECF volume).

4. Plasma anion gap (AG)

$$\mathbf{P_{Na} - P_{Cl} - P_{HCO_3} = 12 \pm 2\ mEq/l:}$$

This equation is numerically valid if the level of albumin is normal (40 g/l). For every decline of 10 g/l, subtract 4 from the normal value for the AG. There must not be a difference in the ECF volume as compared to normal because you are comparing concentrations rather than amounts

Conclusion: Using the pH, Pco_2, P_{HCO3}, and the AG in plasma, one can recognize mixed acid-base disorders (Table 8-1).

5. Is there a lab error?

Insert the pH, Pco_2 and measured P_{HCO3} in the Henderson equation below. If the values for calculated and measured P_{HCO3} differ by > 10% and the patient is afebrile, there is a laboratory error in the pH, Pco_2 or P_{HCO3}. Repeat these measurements to avoid making a decision based on an error.

$$[H^+] = Pco_2 \times 24/P_{HCO3}$$

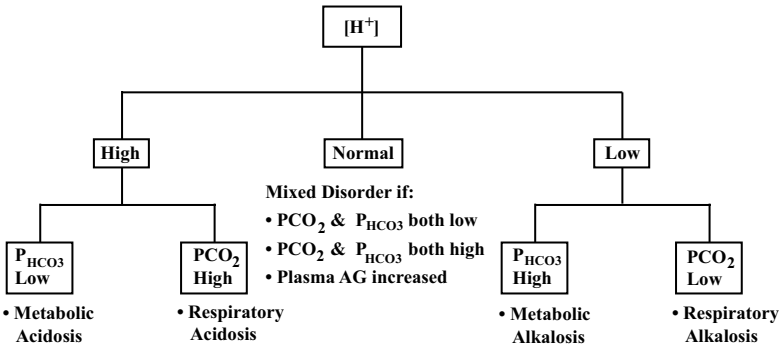
6. Mixed acid-base disorders

More than one acid-base disorder can exist in a patient (Flow Chart 8-1).

Flow chart 8-1

IDENTIFY ACID BASE ABNORMALITIES FROM PLASMA DETERMINATIONS

The final diagnoses are shown in the hatched boxes.



7. Deficit of $NaHCO_3$

This category can be divided into 3 groups. The expected effect in each of them is the presence of metabolic acidosis without a rise in the anion gap in plasma corrected for the concentration of albumin in plasma. It is important to assess the expected renal response to metabolic acidosis, the rate of excretion of NH_4.

(i) Direct loss of $NaHCO_3$

The word direct is used to signify that Na and HCO_3 were lost together in the same solution (e.g., via the GI tract or urine, Figure 8-6). In the absence of a renal defect, expect to find the highest rate of NH_4 excretion (~ 3 mmol/kg body weight).

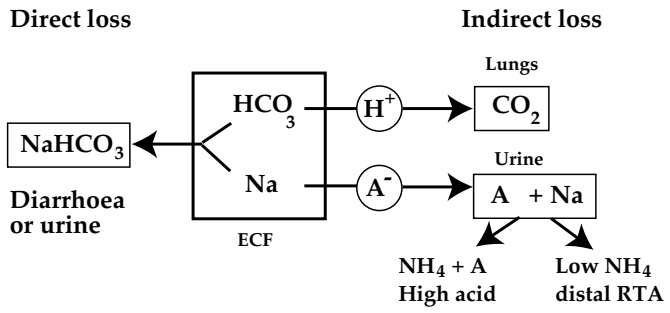
CLINICAL PEARLS

- *If the ECF volume is contracted, the GFR might fall and this will diminish the rate of excretion of NH_4.*
- *If the ECF volume is contracted, the concentration of albumin in plasma should rise and this can cause an elevated anion gap in plasma (see Case 9-3, page 144).*

Figure 8-6

DEFICIT OF $NaHCO_3$

The central rectangle represents the ECF compartment. For simplicity, it contains only Na and HCO_3. $NaHCO_3$ can be lost directly in GI fluids or the urine (left part of the Figure). Alternatively, Na and HCO_3 can be lost by separate routes after an acid is added. The anion of that acid (A) must be secreted or filtered and not reabsorbed by the kidney. If NH_4 excretion is high, the basis is over-production of an acid whereas if NH_4 excretion is low, the diagnosis is RTA.



(ii) Indirect loss of $NaHCO_3$

The word indirect is used to signify that Na and HCO_3 were lost separately via 2 different routes (Figure 8-6). The first step in this process is the addition of an acid. Its conjugate base (anion) must have unique properties—it is either filtered and poorly reabsorbed by the kidney, or it is secreted by the proximal convoluted tubule (e.g., hippurate anions in the glue sniffer). The conjugate base must be excreted with Na and not NH_4 to cause the metabolic acidosis. The H^+ of the acid combines with HCO_3 in the body to become CO_2 and H_2O, while the CO_2 is excreted via the lungs.

Therefore the acid over-production type is characterized by a high rate of excretion of NH_4. In contrast, if the rate of NH_4 excretion is not appropriately elevated, there is a renal disorder characterized by a low rate of NH_4 excretion (called renal tubular acidosis (RTA)).

(iii) Ingestion of HCl or $CaCO_3$

This converts $NaHCO_3$ to NaCl. It is simply mentioned for completeness.

IV. ILLUSTRATIVE CASE

Illustrative Case 8-1

Mixed acid base disorder

A 24-year old 50-kg male had severe diarrhea that resulted in a deficit of $NaHCO_3$. Because of the continuing loss of Na, his ECF volume became contracted. As a result of the very low circulating volume, there was not enough oxygen delivery to tissues to meet their demand so anaerobic production of ATP was stimulated. This results in a net production of L-lactic acid. This accumulation of 10 mmol of L-lactate anion per L of plasma should raise the plasma AG by 10 mEq/l (Table 8-1). Simultaneously, the 10 mmol of H^+ added per L will lower the P_{HCO3} by 10 mmol/l. Continuing with this scenario, the release of aldosterone (due to a contracted ECF volume) stimulates the excretion of K. As a result, a deficit of K occurs and this could lead to muscular weakness. If

the respiratory muscles are involved, there may be an inability to lower the arterial Pco_2 to the expected degree.

Discussion of Case 8-1

By working backwards beginning at the far right of Table 8-1, each of the 3 acid-base disorders can be identified.

Respiratory acidosis

The Pco_2 in blood should be as low as possible (less than 20 mm Hg) with such a low value for the P_{HCO3} (5 mmol/l). Hence an arterial Pco_2 of 30 mm Hg is too high for this clinical setting.

Metabolic acidosis due to a gain of acid

The elevated value for the plasma AG of 10 mEq/l with a normal concentration of albumin in plasma suggests that 10 of the 20 mmol/l fall in P_{HCO3} was due to the added L-lactic acid.

Metabolic acidosis due to loss of $NaHCO_3$

The fact that the fall in the P_{HCO3} is much greater than the rise in the plasma AG suggests a deficit of $NaHCO_3$. This deficit of $NaHCO_3$ is even larger than what is apparent from this calculation because of the significant ECF volume contraction (HCO_3 concentration Vs HCO_3 content).

TABLE 8-1

IDENTIFICATION OF A MIXED ACID-BASE DISORDER

The value for albumin in plasma is 4 g/dl (40 g/l), a normal level, which does not change throughout the course of illness in this patient. Hypoventilation in this case is due to a deficit of K.

Abbreviation: H•L = L-lactic acid.

Plasma	Normal		Loss $NaHCO_3$ (10 mmol/l)	Gain H•L (10 mmol/l)	Effect of hypoventilation
pH		7.40	7.30	7.13	6.83
HCO_3^-	mmol/l	25	15	5	5
Anion gap	mEq/l	12	12	22	22
Pco_2	mm Hg	40	30	15	30

V. SPECIAL TESTS IN THE URINE

One should examine the following tests in the urine from the perspective of the group of diseases characterized by a deficit of $NaHCO_3$. The most important test to subdivide these patients will be to measure the rate of excretion of NH_4.

1. Concentration of NH_4

There are times when it is important to know the U_{NH4}; however, clinical labs will not provide a direct assay for the U_{NH4}. Accordingly, you have to deduce the U_{NH4} from the concentrations of Na, K, and Cl in the urine.

2. Urine net charge

This only detects NH_4 excreted with Cl. Because NH_4 is a cation, it can be assumed to be present if the sum of the $U_{Na} + U_K$ is *less* than the U_{Cl} (called a *negative urine net charge*). Urines containing little NH_4 will have more Na + K than Cl (*urine net charge is positive*). When $U_{Cl} = (U_{Na} + U_K)$, $NH_4 = 80$ mmol/l if the urine volume is close to 1 L per 24 hr.

$$\textbf{Urine } NH_4 = U_{Cl} - U_{Na} - U_K + 80$$

3. Urine osmolal gap

This is the best test to detect U_{NH4}. If NH_4 is excreted with an anion other than Cl, deduce the U_{NH4} as follows: where calculated $U_{osm} = 2(U_{Na} + U_K) + U_{glucose} + U_{urea}$, all in mmol/l terms.

$$U_{NH4} = (\text{measured} - \text{calculated } U_{osm})/2$$

4. Urine Pco_2

In patients with metabolic acidosis, a normal plasma AG and a low NH_4 excretion rate, you may want to confirm that the cause is a low rate of distal nephron H^+ secretion. Measuring the Pco_2 in alkaline urine accomplishes this task (Figure 8-7).

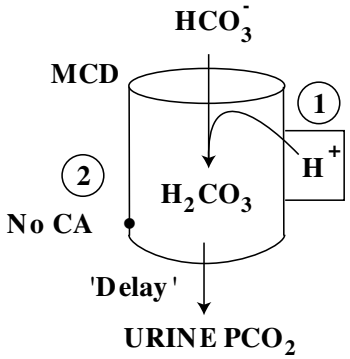
Technique

Discard urine if the pH of the previous urine was < 7 to avoid a Pco_2 rise due to mixing of acid and alkaline urines. If the urine Pco_2 is > 70 mm Hg then distal H^+ secretion is normal whereas values < 55 mm Hg suggest that this H^+ secretion process is defective.

Figure 8-7

The urine PCO_2

When $NaHCO_3$ is given, there is a large delivery of HCO_3 ions to the distal nephron so this HCO_3 is virtually the only H^+ acceptor in its lumen. Because there is no luminal carbonic anhydrase (CA), the H_2CO_3 formed will be delivered downstream and form CO_2 plus water. Thus if the urine Pco_2 is appreciably higher than the plasma Pco_2, this provides evidence for distal H^+ secretion.



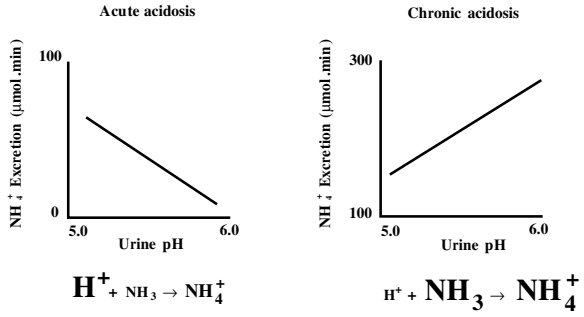
5. Use of the urine pH to evaluate the rate of excretion of NH_4

The urine pH is NOT helpful to assess the rate of excretion of NH_4 or its concentration in the urine (Figure 8-8). It does become useful once you know that the rate of excretion of NH_4 is low to decide whether its basis is a low concentration of H^+ in the lumen of the MCD or whether its basis was a low concentration of NH_3 in the lumen of the MCD. Hence the urine pH is most helpful once you are investigating a patient with distal RTA, a renal disease in which there is impaired renal excretion of NH_4.

Figure 8-8

USE OF THE URINE pH TO DETECT U_{NH4}

As shown on the left, the rate of excretion of NH_4 is modestly higher while the urine pH is low due to enhanced distal H^+ secretion during acute metabolic acidosis. This is the case before there is time to increase the rate of renal production of NH_4. In contrast, during chronic metabolic acidosis shown on the right, the rate of renal production of NH_4 is so high that the availability of NH_3 in the medullary interstitial compartment provides more NH_3 in the lumen of the MCD than H^+ secretion in this nephron segment. Therefore note the much higher NH_4 excretion rate at a urine pH of 6.



$$H^+ + NH_3 \rightarrow NH_4^+$$

$$H^+ + NH_3 \rightarrow NH_4^+$$

CHAPTER 9

METABOLIC ACIDOSIS

I. ESSENTIAL POINTS

The goal of this chapter is to define elements that are common to many diagnostic entities that present with metabolic acidosis. A more detailed analysis of ketoacidosis is provided in Chapter 10.

1. Definition

The usual definition is based on concentrations—a high [H^+] (low pH) and low P_{HCO3}. Metabolic acidosis may be suspected by finding a high plasma AG (> 16 mEq/L) without a pH or HCO_3 change.

Metabolic acidosis can also be defined in content instead of concentration terms—a low pH and a decrease in the content of HCO_3 in the ECF compartment (e.g., loss of $NaHCO_3$ in diarrhoeal fluid). There may not be a change in the pH or P_{HCO3} if the ECF volume is sufficiently decreased (Case 9-1).

2. Expected physiological responses

(i) Lower Pco_2 in cells: This forces H^+ to bind to HCO_3 rather than proteins (Figure 8-4; it can be examined in two ways:
Arterial Pco_2: The fall in Pco_2 from 40 mm Hg should equal the fall in P_{HCO3} from 25mmol/l.
Venous Pco_2: You can measure the Pco_2 in the brachial vein, but not in veins draining most organs.

(ii) Excrete NH_4 to make new HCO_3: The kidneys usually excrete 20 - 40 mmol NH_4/day (0.5 mmol/kg/day). During chronic metabolic acidosis, this should be 200 - 300 mmol/day (3 mmol/kg/day).

3. Clinical classification

There are 2 major categories, acid gain and $NaHCO_3$ loss (Table 9-1).

(i) Acid gain

Recognize them by finding new anions in plasma, urine or GI losses. In *quantitative* terms, the rise in the plasma AG should equal the fall in the P_{HCO3} if the ECF volume is normal.

The P_{osm} gap is very helpful to recognize the intoxicants, methanol and ethylene glycol. It will also be elevated by ethanol.

P_{osm} gap = measured P_{osm} – (2 P_{Na}) – $P_{glucose}$ – P_{urea} in mmol/l.

There are several properties of individual acids that help in this analysis. First, one needs information concerning the principles of physiology of added acids (Table 9-2).

(ii) Loss of $NaHCO_3$

When a deficit of $NaHCO_3$ develops, the patient should have metabolic acidosis without a rise in the AG in plasma. Notwithstanding, if the ECF becomes very contracted, the P_{HCO3} can rise to the normal range and the plasma AG can be higher than normal due to a large increase in the concentration of albumin in plasma (see Case 9-3 at the end of this Chapter).

(a) Direct loss of $NaHCO_3$

The main routes of loss of $NaHCO_3$ are via the GI (diarrhoea, ileus, fistula or nasogastric drainage, vomiting & achlorhydria) or in the urine (proximal RTA, acetazolamide). Nevertheless, most patients with proximal RTA do not have HCO_3 in their urine—their metabolic acidosis is due principally to a low rate of excretion of NH_4 in steady state.

(b) Indirect loss of $NaHCO_3$

The description of this disorder was provided in Chapter 8, Figure 8-6, page **102**. The loss of Na and HCO_3 occurs via 2 separate routes—the HCO_3 is converted to $CO_2 + H_2O$ when a H^+ is added and the CO_2 is exhaled. The Na is lost in the urine along with the conjugate base of the acid (its anion). There are two major types of indirect $NaHCO_3$ losses. The first has a high NH_4 excretion rate and it is caused by a large addition of acid whose conjugate base is readily excreted by the kidney (secreted or filtered and poorly reabsorbed). The second does not have overproduction of an acid. Its basis is a very low NH_4 excretion rate despite metabolic acidosis (distal RTA).

Bottom line

Knowing the rate of excretion of NH_4 provides the essential clue for the differential diagnosis of $NaHCO_3$ loss.

TABLE 9-1

MECHANISMS RESPONSIBLE FOR THE DEVELOPMENT OF METABOLIC ACIDOSIS

- **Acid gain**
  - **With retention of anions in plasma**
    - Fast addition of acids
      - L-lactic acidosis (hypoxia, problems with pyruvate metabolism)
      - Ingested acids
    - Slow addition of acids
      - Ketoacidosis (relative insulin lack and low GFR or CNS function)
      - Toxic alcohol ingestion (e.g., methanol, ethylene glycol)
      - D-lactic acidosis (and other organic acids produced by gastrointestinal bacteria)
      - Pyroglutamic acidosis
  - **With a high rate of excretion of anions in urine**
    - Glue-sniffing (hippuric acid overproduction)
    - Diabetic ketoacidosis with excessive ketonuria
- **$NaHCO_3$ loss**
  - **Direct**
    - Via the GI tract (e.g., diarrhea, ileus, fistula)
    - Via the urine (proximal RTA or low carbonic anhydrase II or IV activity)*
  - **Indirect loss (low urinary excretion of NH_4)**
    - Low urine NH_3 (urine pH ~ 5) = Problem with PCT ammoniagenesis:
      - Decreased GFR, hyperkalemia, alkaline pH in PCT cells, decreased glutamine availability, fuel competition (organic acids, TPN)
    - Defect in net distal H^+ secretion (urine pH often ~ 7):
      - H^+ ATPase defect or alkaline α–intercalated cells
      - H^+ back-leak (e.g., amphotericin B)
      - HCO_3 secretion in the collecting ducts (anion exchanger trafficking disorder)
    - Problem with both distal H^+ secretion and medullary NH_3 (urine pH ~ 6):
      - Diseases involving the renal interstitial compartment

* These patients also have a low rate of excretion of NH_4.

TABLE 9-2

PRINCIPLES OF PHYSIOLOGY WHEN ACIDS ARE ADDED

PRINCIPLE	COMMENT
1. A high H^+ concentration per se rarely is life threatening.	The threat to survival is usually due to the cause for the acidosis rather than the pH per se.
2. Finding a new anion means a new acid was added.	Look in plasma (AG) and urine (net charge) to identify the new anions.
3. Identify the acid by thinking of the properties of the anion.	Rate of production, rapidity of removal from plasma, and unique toxic effects may all provide clues.
4. Metabolic acidosis develops when the kidney fails to add new HCO_3 to the body.	The kidney generates HCO_3 by excreting NH_4, (usually with Cl), in the urine
5. Ketoacids are brain fuels, produced when there is a prolonged lack of insulin.	The usual causes are DKA, alcoholic KA, starvation or hypoglycemia-induced KA, or ketoacidosis associated with salicylate overdose.
6. GI bacteria produce many useful products.	Propionate is useful to synthesize oxaloacetate, a TCA cycle intermediate. Butyrate is an important colonic fuel.

4. Differential diagnosis

Look for underlying disease because metabolic acidosis is often an expression of a more serious disorder requiring specific therapy (Table 9-3). Use the anion and osmolal gaps in plasma and urine to help with decision-making. Another property that is important is the speed of production of acids (Table 9-4).

5. Rules to memorize

- Arterial Pco_2 fall from 40 mm Hg should equal fall in P_{HCO3} from 25 mmol/l.
- Corollary: "Big Thumb Rule"
  - Cover the 7 and decimal point in the pH of plasma; this is what the arterial Pco_2 should be in simple metabolic acidosis.

- In simple acid gain type of metabolic acidosis, the rise in the anion gap from 12 mEq/l should ~ = the fall in the P_{HCO3} from 25 mmol/l if the ECF volume is normal.
- In intoxications with methanol and ethylene glycol, the P_{osm} gap will be elevated.
- In metabolic acidosis with a normal plasma AG, the kidney should excrete > 80 mmol NH_4/day.
- Use the hematocrit or the total protein (g/dl) to calculate the plasma volume. This should reflect the ECF volume in the absence of edema.

Hct (%/100) = RBC volume/(RBC volume + plasma volume)

Suggested reading

Napolova O, Urbach S, Davids MR and Halperin ML. How to assess the degree of extracellular fluid volume contraction in a patient with a severe degree of hyperglycemia. *Nephrol Dial Trans* 18: 2674-2677, 2003.

TABLE 9-3

THREATS TO LIFE WITH HIGH ANION GAP METABOLIC ACIDOSIS

Cause	Threats
• L-Lactic acidosis	Underlying lesion such as cardiac arrest, sepsis, tumours,B vitamin deficiencies, hepatic failure, etc
• Ketoacidosis	Severe ECF volume contraction and later hypokalaemia in DKA and alcoholic KA; cerebral edema in children with DKA.
• Methanol, ethylene glycol	Toxic aldehydes; renal failure and pulmonary edema with ethylene glycol.
• Renal failure	Hyperkalemia, pulmonary edema, encephalopathy.
• D-Lactic acidosis	Rarely life-threatening. Danger due to other compounds.
• Toxicity due to anions	e.g., Chelation of ionized Ca^{2+} in plasma during citric acidosis.
• Acetaminophen overdose	Mitochondrial reactive oxygen species accumulate in pyroglutamic acidosis

TABLE 9-4

RATES OF PRODUCTION AND REMOVAL OF H^+

The rates are in mmol/l.

	Rate	Comments
Production of H^+		
• Lactic acid		
-Anoxia	72	• Complete anoxia
• Ketoacids	1	• Lack of insulin
• Toxic alcohols	< 1	• Toxins rather than H^+ are the major threat
Removal of H^+		
• Kidney		• Has a lag period
(excretion of NH_4)	0.05 to 0.2	• Metabolic acidosis is needed for rapid rates
• Metabolism		
-Lactate	4 - 8	• Half by oxidation and half by glucogenesis
-Ketoacids	0.8	• Oxidized primarily in brain and kidneys

II. QUESTIONS TO ASK OF THE PATIENT WITH METABOLIC ACIDOSIS

1. Is the respiratory response normal (really, "Is the Pco_2 in cells too high?")?

Answer: The fall in arterial Pco_2 from 40 should be ~ = to the fall in P_{HCO3} from 25. The venous Pco_2 should be measured and compared to the arterial Pco_2.

2. Is there a reason for the plasma AG to be lower than normal?

Answer: Look for hypoalbuminemia, error in P_{Na}, P_{Cl} or P_{HCO3}, halide ingestion or dysproteinemia. Save a sample of plasma and urine for later analyses. Compare the rise in AG to the fall in P_{HCO3} to determine if there is a mixed type of acid-base disorder.

3. What should be done if the AG in plasma is increased?

Answer: Suspect the cause clinically and confirm with lab studies (serum ketones or plasma [ßHB] for ketoacidosis, plasma creatinine ($P_{Creatinine}$) for renal failure (at least 5 x normal), plasma L or D-lactate if appropriate, P_{osm} gap for methanol or ethylene glycol intoxications). If the P_{osm} gap is high and you cannot detect ethanol on the breath, give the patient ethanol to prevent damage due to the products of metabolism of methanol or ethylene glycol.

4. What do I do if there is metabolic acidosis and a plasma AG that is normal?

Answer: Establish the renal role in acidemia by estimating the U_{NH4} from the urine *net charge* or the U_{osm} gap. If the $U_{NH4 \bullet V}$ is high, the most likely cause is GI $NaHCO_3$ loss. If U_{osm} gap is < 100, the cause is renal. If there is a renal cause (low NH_4 excretion), the P_K is very helpful. Hypokalemia suggests a H^+ secretion defect (confirm with urine Pco_2). Hyperkalemia suggests a problem with aldosterone action (may be called type IV RTA).

5. When should therapy with $NaHCO_3$ be started?

Answer: If very severe acidosis, P_{HCO3} < 5 mmol/l and P_K is > 3 mmol/l, give $NaHCO_3$ to raise the P_{HCO3} 2-fold (based on a HCO_3 space = 50% of body weight; more $NaHCO_3$ is required when the P_{HCO3} is very low. Other situations to use $NaHCO_3$ are a very rapid production of H^+, a patient who cannot make HCO_3 quickly (i.e. by metabolism of high [lactate] or [BHB]), a very low pH (in the hope that heart function will improve), and kidneys that cannot make appreciable new HCO_3.

III. HOW TO THINK ABOUT CHRONIC METABOLIC ACIDOSIS

The following concepts form the foundation for understanding how metabolic acidosis can develop and persist in a patient.

1. Balance must be present during a steady state:

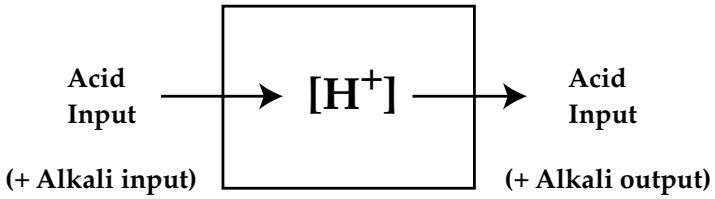
Balance requires a quantitative analysis of both input and output (Figure 9-1). For H^+ balance, one must consider balances for acids and bases.

Suggested reading

Halperin ML and Goldstein MB. *Fluid, Electrolyte and Acid-Base physiology; a problem-based approach*. Philadelphia: W.B. Saunders, 1998

FIGURE 9-1

The need for H^+ balance in Steady State



2. Electroneutrality must be maintained

A common misconception in acid-base physiology is to consider single ion terms.

Term	More correct term
H^+ load	Positive balance of acid
Cl-depletion	Negative NaCl, KCl or HCl balance

3. Use kinetic terms to understand the basis of an acid-base disorder

When examining the rate of a single reaction or an entire metabolic process (Figure 9-2), there are two major ways to influence that rate.

(i) Substrate concentration

In simplest terms, the rate (or velocity of that process) will increase as the substrate concentration rises until the enzyme that catalyzes the process is saturated with its substrate (Figure 9-3). Once saturated, the velocity of that reaction is called its maximum velocity (V_{max}). The substrate concentration that permits a velocity equal to 1/2 the V_{max} is called the K_m.

(ii) Maximum velocity

This terms depends on how much enzyme is present—if you double the amount of enzyme, you double the V_{max} of that reaction. The converse is also true (Figure 9-3).

FIGURE 9-2

Analysis of Metabolism emphasizing Metabolic Process

In a metabolic process, one only considers its starting point and its end products (ATP or storage forms of energy). All metabolic cofactors and intermediates can be ignored because they are present in tiny amounts and they are both synthesized and removed in that metabolic process. Metabolic processes may involve more than one organ. Examples are shown for the fed and fasted states.

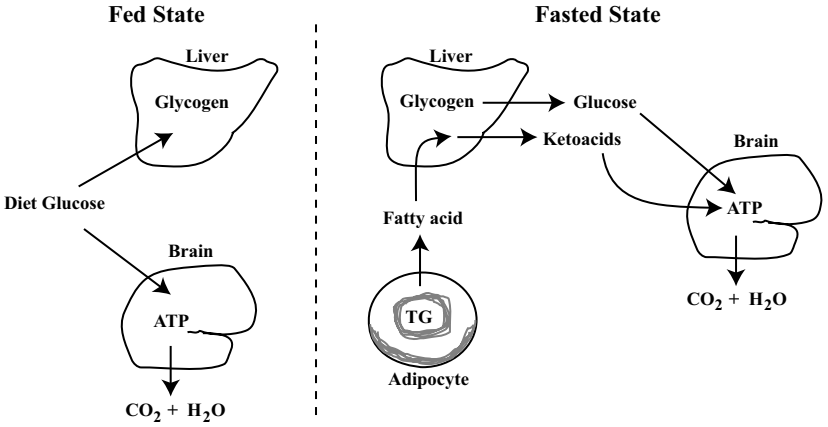
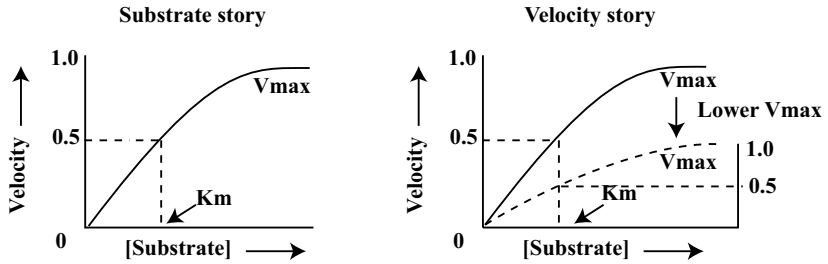


FIGURE 9-3

Emphasis on enzyme kinetics

The sub**s**trate concentration is on the X-axis and the velocity of the reaction is shown on the Y-axis. The substrate concentration that causes a velocity that is 1/2 the V_{max} is the K_m. Notice in the Figure on the right that when the V_{max} is reduced (dashed line, y-axis to the right) the K_m is unchanged.



Suggested reading

Halperin ML and Rolleston FS. *Clinical Detective Stories: A Problem-Based Approach to Clinical Cases in Energy and Acid-Base Metabolism*. London, England: Portland Press, 1993.

4. Difference between acute and chronic metabolic acidosis

(i) Acute

The point to emphasize is that an acute perturbation is not a steady state. The focus will be primarily on a sudden increase in the rate of input and/or a decrease in the rate of output of an acid. One mechanism can influence both of these rates.

(ii) Chronic

With a chronic disorder, there is a major problem in both the production of the acid and in the rate of removal of that acid. Examples include non-hypoxic L-lactic acidosis and DKA.

5. Theoretical analysis of chronic metabolic acidosis

I shall examine three forms of chronic metabolic acidosis in terms of both limbs of the balance diagram (Figure 9-1) and use a kinetic analysis (Figure 9-3).

(i) Diabetic ketoacidosis (DKA)

This topic will be discussed in detail in Chapter 10. A high rate of production of ketoacids usually occurs when there is a lack of insulin. It has an upper limit set by the rate of production of ADP in the liver (hepatic work) (Figure 9-4). The major cause of severe ketoacidosis is due to decreased removal of ketoacids by the major organs that can oxidize them.
(a) Kidney: Less oxidation of fuels due to low GFR
(b) Brain: Less oxidation if coma, sedatives, high tissue Pco_2.

(ii) Hypoxic L-lactic acidosis

There is not enough O_2 to meet demands so the production of L-lactic acid rises. This is due to the fact that the concentration of ADP rises and this stimulates anaerobic glycolysis (Figure 9-5). Removal of L-lactate + H^+ is diminished because the mitochondria do not have sufficient O_2 (left side of Figure 9-5). The kinetics are summarized in Figure 9-6.

FIGURE 9-4

Basis for Ketoacidosis in DKA

The rectangle represents the liver, the site where ketoacids are synthesized when there is a lack of insulin. The removal of ketoacid is primarily via the brain and the kidneys. Oxidation of ketoacids will be diminished when work in these organs declines (brain work is primarily due to ion pumping and renal work is primarily due to the reabsorption of filtered Na).

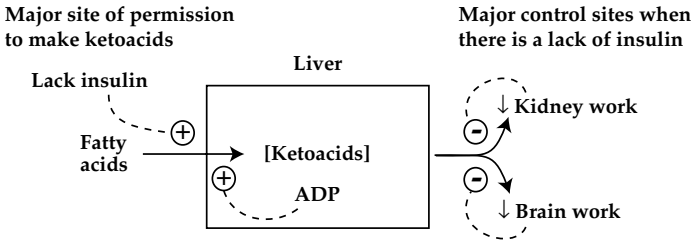


FIGURE 9-5

Overproduction of L-lactic Acid during Hypoxia

The starting point is an inadequate supply of O_2 at the far left. This leads to a failure of conversion of ADP to ATP. The high ADP level stimulates anaerobic glycolysis (shown to the right of the dashed vertical line). This combined with ATP hydrolysis to permit continuing work leads to the net production of H^+.

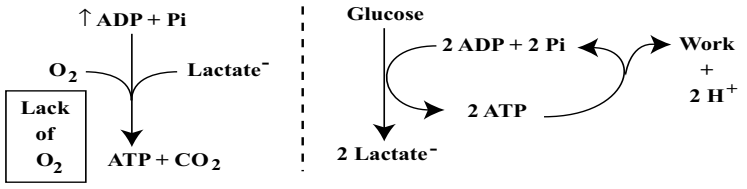
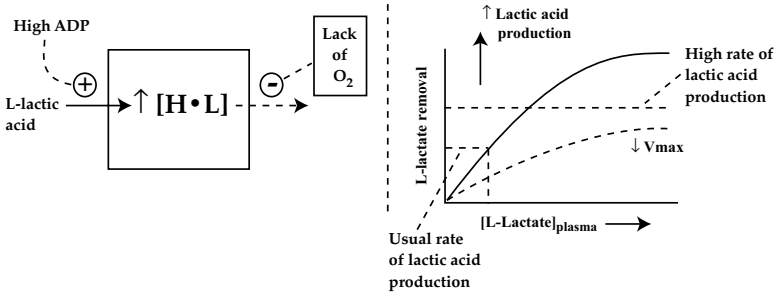


FIGURE 9-6

Hypoxic L-lactic acidosis

In kinetic terms, this type of L-lactic acidosis has a rate of L-lactic acid production that is markedly increased and this exceeds the V_{max} of L-lactate removal. The rise in $P_{Lactate}$ and the fall in pH occur very quickly and are progressive; hence a steady state cannot be achieved.

Abbreviation: H•L = L-lactic acid



(iii) Chronic L-lactic acidosis without hypoxia:

In a chronic setting, there is a steady state. There will usually be a small increase in the rate of L-lactic acid production along with a lower V_{max} for the removal of L-lactic acid. As shown in Figure 9-7, one needs to have a higher concentration of L-lactate in plasma in order to have a rate of removal of L-lactic acid that matches its higher production rate. There are two major pathways for L-lactate removal, conversion to glucose (primarily in the liver) and oxidation to CO_2 and water. The latter pathway needs flux through pyruvate dehydrogenase (PDH) (Figure 9-8).

FIGURE 9-7

Kinetic analysis in Case 9-1

The rise in L-lactate in plasma is due in part to an increase in its production (move from A to B on the y-axis). This alone causes only a small increment in the $P_{Lactate}$. Because the V_{max} of L-lactic acid removal is lower due to hepatic metastases (dashed curve), now the same increase in L-lactic acid production causes a much large rise in the $P_{Lactate}$ (from point B to C, 10 mmol/l).

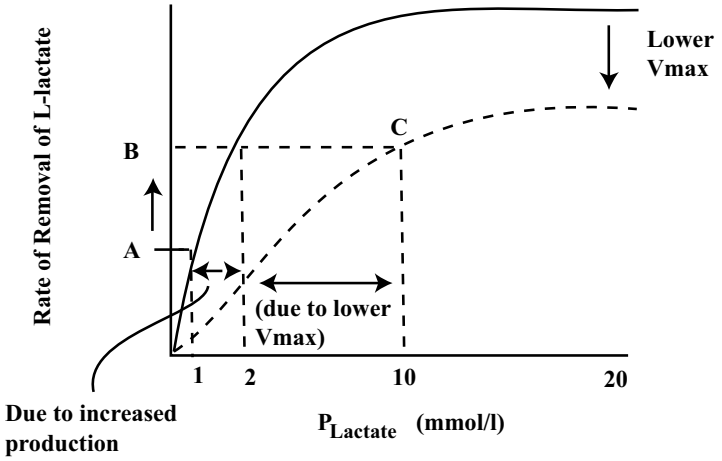
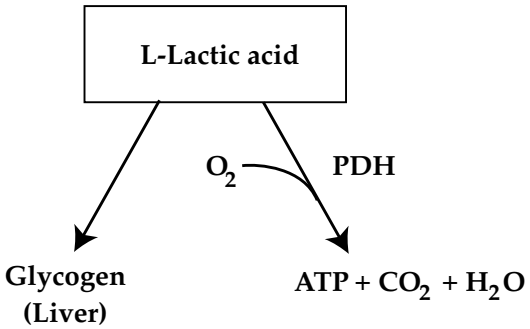


FIGURE 9-8

Pathways for the removal of L-lactic acid



ILLUSTRATIVE CASE

CASE 9-1

Tumour with hepatic metastases and metabolic acidosis

A 70-year old patient has metastatic cancer; there are multiple metastases in her liver. There is chronic metabolic acidosis (pH 7.30, P_{HCO3} 15 mmol/l, anion gap 12 + 10 mEq/l); blood L-lactate is 10 mmol/l. These results were similar one month ago. There is no problem with circulation or O_2 in blood. There is no drug intake or a nutritional deficiency.

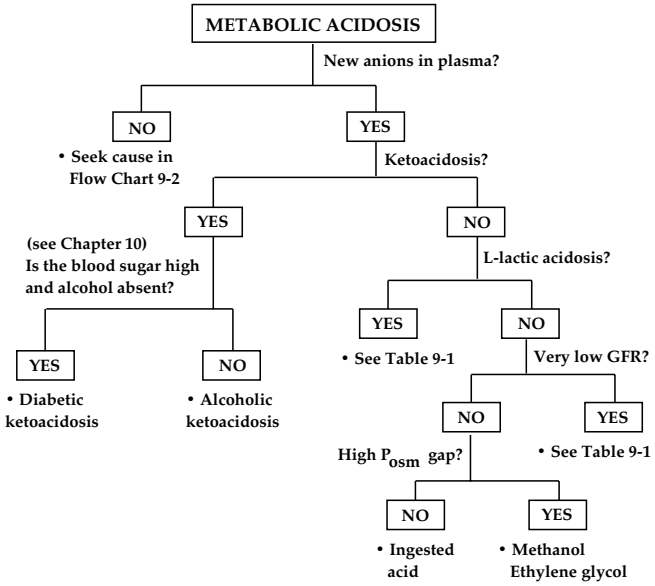
Questions

- **What is the basis of L-lactic acidosis?**

Flow chart 9-1

Approach to the patient with Metabolic Acidosis and a high plasma AG

The starting point is a patient with metabolic acidosis (low pH and P_{HCO3}) and a high plasma A/G. Final diagnoses are shown after the bullet symbols.



Discussion of Case 9-1

Begin by following the steps in Flow Chart 9-1.

Step 1: Are new anions present in plasma?

Yes, there are new anions in plasma, so proceed with the steps on the right side of this flow chart.

Step 2: Are ketoacids present in plasma?

No, there are no new extra ketoacid anions present in plasma.

Step 3: Is L-lactic acid present in plasma?

Yes, so determine why L-lactic acidosis is present.

What is the basis of his L-lactic acidosis?

Increased production of L-lactic acid

Tumour cells are known to have an increased rate of aerobic production of L-lactic acid. This could be a contributing factor, but it is not a complete explanation for her L-lactic acidosis (Figure 9-7).

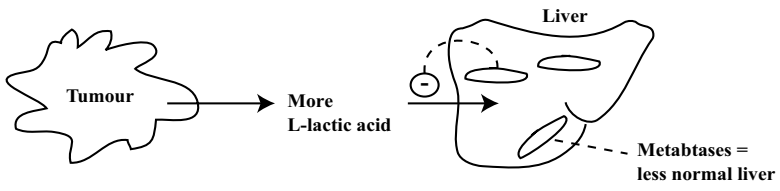
Decreased removal of L-lactic acid:

One of the major sites of L-lactate removal is via conversion to glucose or glycogen in the liver (Figure 9-8). Her hepatic metastases decreased the number of normal liver cells and decreased the rate of L-lactate removal. Having a somewhat higher $P_{Lactate}$ can make this rate equal to his rate of L-lactic acid production (Figure 9-9).

FIGURE 9-9

L-lactic acid balance in Case 9-1

The tumour cells produce and release L-lactic acid even though they have sufficient delivery of oxygen. The hepatic metestases damaged enough liver parenchyma to lower the V_{max} for the rate of removal of L-lactate.



Kinetic analysis

As shown in Figure 9-7, the combination of both an increased L-lactic acid production and a lower V_{max} for L-lactic acid removal result in a large increase in the $P_{Lactate}$.

IV. SPECIFIC DISORDERS

1. High anion gap type of metabolic acidosis

(a) Diabetic ketoacidosis (see chapter 10)

(b L-Lactic acidosis

Diagnosis

The main cause is tissue hypoxia (other causes are listed in Table 9-5). Expect an increased AG type of metabolic acidosis, hyperventilation, and circulatory collapse (hypotension, shock). Look for sepsis, or problems related to ethanol. Be suspicious of a B-vitamin deficit in a malnourished patient with chronic L-lactic acidosis (e.g., thiamin in an alcoholic).

Treatment

This is not a specific disease but has a number of causes; the patient will survive if the underlying disease can be treated. The major priority is usually to restore delivery of O_2 to the tissue by treating the circulatory defect. If hypoxia is absent, measures such as vitamin B_1, dichloroacetate, insulin, and $NaHCO_3$ could be useful. $NaHCO_3$ will only buy a little time and has the danger of the Na load as very large infusions are required.

c) Methanol or ethylene glycol

Diagnosis

There may be a history suggestive of intoxication. On laboratory examination, there should be an increased P_{osm} gap (especially in the absence of ethanol), metabolic acidosis with an increased plasma AG. The ECF volume is usually normal . Overall, you must have a high index of suspicion.

Treatment

Give ethanol as soon as methanol or ethylene glycol intoxication suspected (46 g load, 15 g/hr). Lavage the stomach and possibly give iv ethanol. Dialyze if methanol >15 mmol/l (add ethanol to bath). Treat severe acidemia with $NaHCO_3$.

With ethylene glycol, acute renal failure may occur, necessitating less $NaHCO_3$ infusion and even earlier dialysis.

TABLE 9-5

CAUSES OF L-LACTIC ACIDOSIS

- **Type A (hypoxic)**
  - Circulatory failure (cardiogenic shock or secondary to sepsis)
  - Severe hypoxemia (lung problem or high altitude)
  - Severe anemia
  - Excessive demand for oxygen (e.g. generalized seizure, vigorous exercise)

- **Type B (compromised metabolism of L-lactate)**
  - A variety of diseases that severely affect the liver
    - Inhibition of gluconeogenesis (e.g. by ethanol)
  - Inborn error of metabolism affecting pyruvate dehydrogenase, the tricarboxylic acid cycle, or the electron transport system
  - Nutritional deficiencies
    - Thiamin (vitamin B_1)
    - Riboflavin deficiency or low bioactivity (vitamin B_2)
    - Isoniazide (vitamin B_6 deficiency).

d) D-Lactic acidosis

Diagnosis

Bacteria are normally segregated from dietary sugar by GI 'geography'; they are primarily in the colon and glucose is absorbed in the jejunum (Figure 9-10). For over-production of D-lactic acid, bacteria in the lower GI tract must mix with sugars. Therefore the supply of sugar is critical for organic acid production. Bacteria can migrate up to and proliferate in the small intestine when there is a GI motility problem. The most abundant abnormal organic acid that accumulates is D-lactic acid. Humans metabolize this D-isomer more slowly than L-lactate.

Three factors that act in concert to make extra D-lactic acid:

(i) Slow GI transit
  - Examples include drugs that slow motility, blind loops, obstruc ion

(ii) Change of the normal flora (usually with antibiotic therapy)
  - Migration of these bacteria upstream to sites before all the glucose is absorbed.

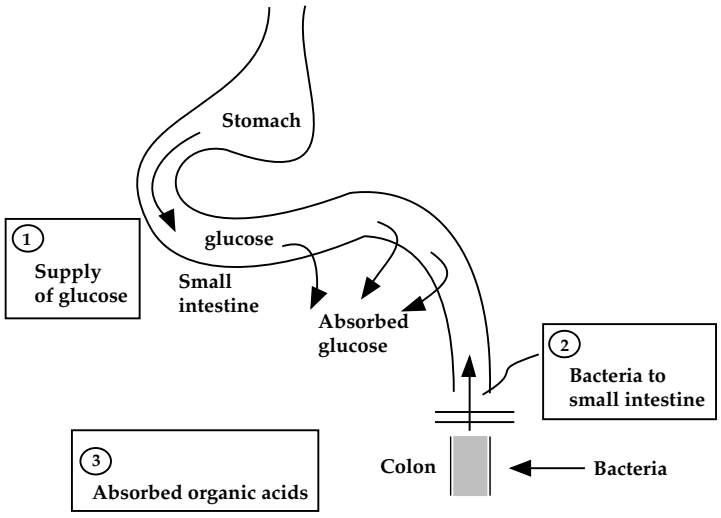
(iii) Carbohydrate must be supplied to these bacteria
- Aggravated by ingestion of food, fructose or sorbitol (Figure 9-10). Can be exacerbated by antacid therapy because there is a more favourable pH for bacterial growth and metabolism.

There are three points that should be noted with respect to D-lactic acidosis. First, the usual clinical laboratory test for lactate is specific for the L-lactate isomer. Hence the laboratory measurement for lactate will not be elevated. Second, GI bacteria produce amines, mercaptans, and other compounds that may cause the clinical symptoms related to CNS dysfunction (personality changes, gait changes, confusion, etc.). Third, some of the D-lactate will be lost in the urine (if the GFR is not too low). Hence the degree of rise in the plasma AG may not be as high as expected for the fall in the P_{HCO3}.

Figure 9-10

D-Lactic acidosis

For details, see page 121



Acid-base issues

The acidosis is rarely the major threat to life. There must be enough mucosal surface area to transport these acids into the body and cause the high plasma anion gap; otherwise the H^+ produced might simply destroy luminal HCO_3 from the secreted $NaHCO_3$ and lead to the loss of Na plus D-lactate in the stool (a normal anion gap type of metabolic acidosis). The degree of the acidosis also depends on the rate that these organic acids can be oxidized and/or converted to glucose or fat (primarily in the liver).

Fermentation produces a variety of organic acids and noxious alcohols, aldehydes and amines; these latter compounds cause important neurological abnormalities (largely cerebellar signs and symptoms).

Treatment:

Treatment should be directed at the GI problem. Stop the oral intake of carbohydrates. Antacids should be avoided. Stop the GI antimotility drugs. You may have to change the bacterial flora.

Suggested reading

Halperin ML and Kamel KS. Turning sugar into acids in the gastrointestinal tract. *Kidney Int* 49: 1-8, 1996.

e) Pyroglutamic acidosis

Diagnosis

There have been an increasing number of case reports where PGA accumulated and caused metabolic acidosis with an increase in the AG in plasma. When plasma levels of PGA rose to the 5-10 mmol/l range, the 24-h urine contained 50- 150 mmol of PGA.

Although we tend to focus on acid-base issues in this disorder, failure of the detoxification of reactive oxygen species (ROS) is far more important for patient care. The major function of reduced gluathione (GSH) is to detoxify ROS. When ROS accumulate, the consumption of GSH increases.

PGA is formed at a more rapid rate when there is a lower concentration of GSH (Figure 9-11). GSH feeds back to inhibit the first enzyme that leads to the synthesis of glutathione. A

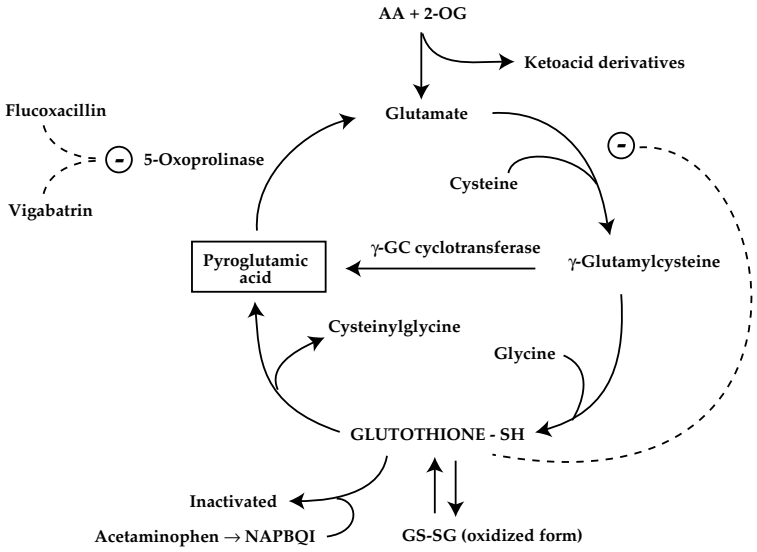
number of drugs have been identified as potential causes of PGA acidosis (Figure 9-11). Acetaminophen complexes with NADP and lowers the amount of GSH. The antibiotic flucloxacillin and the anticonvulsant, vigabatrin inhibit the removal of PGA. Inborn errors of metabolism (e.g., G6PDH deficiency) that result in a diminished concentration of NADPH, the cofactor that reduces GS-SG to GSH (equation below), can cause PGA acidosis. Hypothyroidism may also predispose to PGA acidosis because thyroid hormone is needed to allow reduction of the oxidized form of glutathione, GS-SG.

2 GSH + ROS → GS-SG + Inactive ROS
GS-SG + NADPH → GSH + NADP

FIGURE 9-11

Production of pyroglutamic acid

The pathway begins with glutamate, a key intermediate in transamination reactions. When there are low levels of reduced glutathione (GSH), the first step in its synthesis is stimulated. There is an overflow pathway that is largely responsible for PGA accumulation in this setting (γ-glutamylcysteine cyclotransferase). In addition, if 5-oxyprolinase is inhibited, pyroglutamic acid will also accumulate. As described in the text, a diminished ability to detoxify ROS is likely to be more important than the acidosis



2. Normal anion gap type of metabolic acidosis

(i) Loss of $NaHCO_3$ via the GI tract

Diagnosis

This is usually obvious from the history, but occasionally, ileus may be difficult to detect. The renal response should be normal (i.e. have > 80 mmol NH_4/day detected by a negative urine net charge). For significant acidosis, GI losses must be very high and/or there is an overproduction of acids with the excretion of their conjugate base or a renal lesion (low excretion of NH_4). Two facts act in concert to change the P_{HCO3}. First, the amount of HCO_3 in the ECF and second, the ECF volume; each must be analyzed in a quantitative fashion.

Treatment

Treat the underlying disease and give $NaHCO_3$ if the acidosis is very severe. The patient may need a considerable amount of K as well. The anticipated response depends on the underlying disease and the severity of the loss of $NaHCO_3$ by the GI tract. With a severely contracted ECF volume, the P_{HCO3} can be close to the normal range (see Case 9-2).

b) Loss of $NaHCO_3$ via the urine (proximal RTA)

Diagnosis

The hereditary forms usually occur in children. In adults, suspect dysproteinemias, an intake of heavy metals or drugs such as Chinese herbs. There may be multiple proximal defects such as glucosuria, aminoaciduria, phosphaturia, etc. (Fanconi syndrome). Loss of $NaHCO_3$ in the urine may also result from the use of carbonic anhydrase inhibitor type of diuretics.

Treatment:

This depends on the specific cause. In general, do not be over-aggressive with $NaHCO_3$—the P_{HCO3} will rarely be maintained in the normal range in patients with proximal RTA.

c) Failure of the kidney to make new HCO_3 (distal RTA)

Diagnosis

All have low urine NH_4 excretion rates and this is reflected by a positive urine *net charge or low* U_{osm} *gap*. Now the urine pH is helpful to further define the etiology (Flow Chart 14-1, page 232). A urine pH ~ 5 suggests a defect in NH_3 production (low GFR or hyperkalemia) or medullary interstitial disease, a urine pH > 6.5

23suggests that there is a defect in distal H^+ secretion, and a urine pH ~ 6 suggests involvement of both H^+ secretion and NH_3 availability.

The P_K helps subdivide those with a low rate of NH_4 production (high P_K) from those with a defect in distal H^+ secretion (low P_K).

Treatment

This depends on the specific cause. In the group with hyperkalemia, treat its cause. For the low H^+ secretion group, in addition to treating any underlying disease, the patient will need $NaHCO_3$ sufficient to replace the HCO_3 deficit and titrate the daily acid load (< 70 mmol H^+/day).

d) Acid production with the excretion of the anion without H^+ or NH_4

Diagnosis

A high degree of suspicion is required. The diagnosis is established by finding the anions in the urine, i.e., the urine *net charge* is positive. However, when NH_4 is measured in the urine, it will be high. An increased U_{osm} gap will suggest the presence of urine NH_4 plus an anion other than Cl. Most often, the diagnosis is a patient who has sniffed glue. In this setting, toluene is converted to hippuric acid and acidosis occurs because hippurate anions are secreted into the urine and excreted with Na and/or K.

Treatment

Stop the input of toluene. The accumulated toluene may take several days to be removed by metabolism that produces hippuric acid.

V. CLINICAL APPROACH

The step-by-step approach is summarized in Flow Charts 9-1 and 9-2. To illustrate their utility, Cases 9-2 and 9-3 are discussed below.

VI. ILLUSTRATIVE CASES

CASE 9-2

Anions have effects too

Hugh, age 42, has a long history of alcohol abuse, but all his past medical tests were normal. He drank a solution of unknown composition 6 hours ago. In the past hour, he developed non-specific complaints, but he denied blood loss, feeling faint, excessive sweating, diarrhoea, and vomiting. Suddenly, 15 minutes later during the physical examination, he appeared very ill; blood pressure fell to 80/40 mm Hg, pulse rate rose to 180/minute with normal sinus rhythm, and jugular venous pressure was below the sternal angle. Respirations were rapid and deep. There were no other positive findings. Surprisingly, during the initial minutes of therapy, his blood pressure and pulse rate became normal.

Laboratory findings from arterial blood on admission were:

pH		7.20	Na	mmol/l	143
Pco_2 (arterial)	mm Hg	25	K	mmol/l	6.3
HCO_3	mmol/l	11	Cl	mmol/l	99
Albumin	g/L	51	Osmolality	mOsm/l	303
Creatinine	mg/dl	1.9	Creatinine	µmol/l	161
BUN	mg/dl	8.4	Urea	mmol/l	3.0
Glucose	mg/dl	180	Glucose	mmol/l	10
L-Lactate	mmol/l	2.0	Ca	mmol/l	2.5

EKG: Tall peaked T waves

Questions

- **Judging from the time frame, which acids accumulated?**
- **Why was his blood pressure so low?**
- **Does his low arterial Pco_2 value ensure that he buffered most of the H^+ load in his cells with HCO_3?**
- **Why was hyperkalemia present on admission?**
- **What component of therapy led to the dramatic recovery of his blood pressure?**

- **What component of therapy led to the dramatic recovery of his blood pressure?**

Suggested reading

DeMars C, Hollister K, Tomassoni A, Himmelfarb J, and Halperin ML. Citric acidosis: A life-threatening cause of metabolic acidosis. *Ann Emerg Med* 38: 588-591, 2001.

Discussion of Case 9-2

Step 1. Are there new anions in plasma?

Yes, because the plasma AG has a higher value than normal. Therefore the most likely cause is the addition of an acid (Table 9-1). Acids dissociate into H^+ and new anions. New H^+ have appeared if there is a deficit of HCO_3, and a rise in the H^+ concentration (or fall in pH) in plasma. Therefore hunt for new anions in this case. Because his plasma AG was elevated ($Na - Cl - HCO_3$ = 33 mEq/l and the normal value is 12 mEq/l), he retained new anions in plasma. His high albumin concentration (51 g/l) will contribute ~4 mEq/l to the rise in the AG.

Judging from the time frame, which acids accumulated?

The only acid that is made endogenously at a very rapid rate is L-lactic acid during hypoxia (Table 9-4), but his L-lactate was 2 mmol/l so this is not the correct answer.

The most likely diagnosis is that he ingested an acid.

Step 2. Right side of the Flow Chart: Are the tests for ketoacids positive?

No, the serum tests for ketoacids were negative. Other features also make this diagnosis unlikely. For example, the $P_{Glucose}$ is not elevated, the time frame is too short, and there is no history of diabetes mellitus.

Step 3. Right side of the Flow chart: Is the story suggestive of L-lactic acidosis?

Yes, there are two major findings that he had L-lactic acidosis; first there is a low blood pressure, and second the time frame is very short.

Of greater importance, his $P_{L\text{-lactate}}$ is not elevated and this rules out L-lactic acidosis.

Why is his blood pressure so low?

Blood pressure is a function of cardiac output and peripheral resistance. Cardiac output is a function of heart rate and stroke volume. Because his heart rate was rapid, we are looking for a process that could compromise his stroke volume and possibly his peripheral resistance. Because he did not have evidence of blood loss, or salt deficiency (vomiting, diarrhoea), a problem with contractility of his heart and blood vessels was suspected. One factor that is essential for contractility is ionized calcium. Therefore it is reasonable to speculate that the new anions might be able to chelate ionized calcium in the circulation. We learned later that he drank citric acid.

Step 4. Right side of the Flow chart: Might the basis of the metabolic acidosis be due to renal insufficiency?

No, because the $P_{Creatinine}$ and P_{urea} are not high enough. Moreover, the time frame is too short.

Step 5. Right side of the flow chart: Is the acidosis due to the ingestion of a precursor of an acid.

On the one hand, this is not the ingestion of a toxic alcohol like methanol or ethylene glycol because his P_{osm} gap is not elevated and the time course is too short.

On the other hand, he did drink an acid. As commented on above, the anion accompanying these H^+ was able to chelate ionized Ca; it was $citrate^{3-}$.

Does his low arterial Pco_2 value ensure that he buffered most of the H^+ load in his cells with HCO_3?

No because the Pco_2 in cells is influenced not only by the arterial Pco_2, but also by the rate of production of CO_2 and the rate of blood flow past these cells (see Figure 8-4, page 108). He might have buffered H^+ on proteins if he had a high venous Pco_2 due to the hypotension and low myocardial contractility, forcing each L of venous blood to carry more CO_2 with a higher venous Pco_2. The Pco_2 in cells must be as high or

higher than the venous Pco_2. As a result, he cannot use his HCO_3 buffer system effectively. This a tissue form of respiratory acidosis.

Why was hyperkalemia present on admission?

When an acid is added and the conjugate base cannot cross cell membranes on the monocarboxylate transporter, there is a shift of K out of cells because the ICF voltage becomes less negative (Figure 9-12).

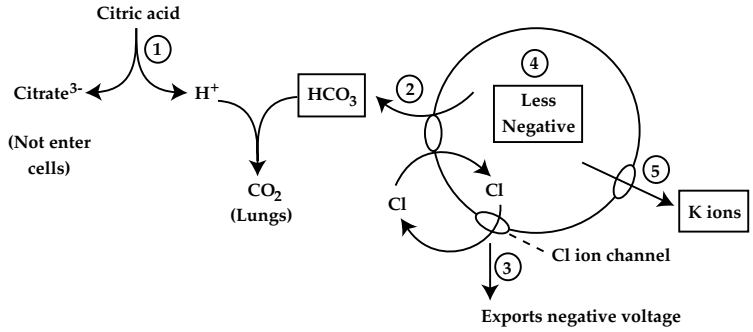
Final comments

What component of therapy led to the dramatic recovery in his blood pressure?

Figure 9-12

Hyperkalemia due to a shift of K from cells when acids are added

The crucial event is a diminished net negative voltage in cells. This occurs when an anion, Cl, is forced to leave cells via its specific Cl ion channel. The net effect is to export K and HCO_3 from cells.



CASE 9-3

Metabolic acidosis due to diarrhoea.

A 25 year old male was perfectly healthy until 24-hours ago. He developed acute, massive diarrhoea due to cholera today. He had no input and now has no urine output. Acid-base measurements in arterial blood revealed a pH 7.36, P_{HCO3} 22 mmol/l, and a PCO_2 of 38 mm Hg. His diarrhoeal fluid (5 L today) has the following composition in mmol/l of water.

Cations		Anions	
Na	140	Cl	110
K	15	HCO_3	45

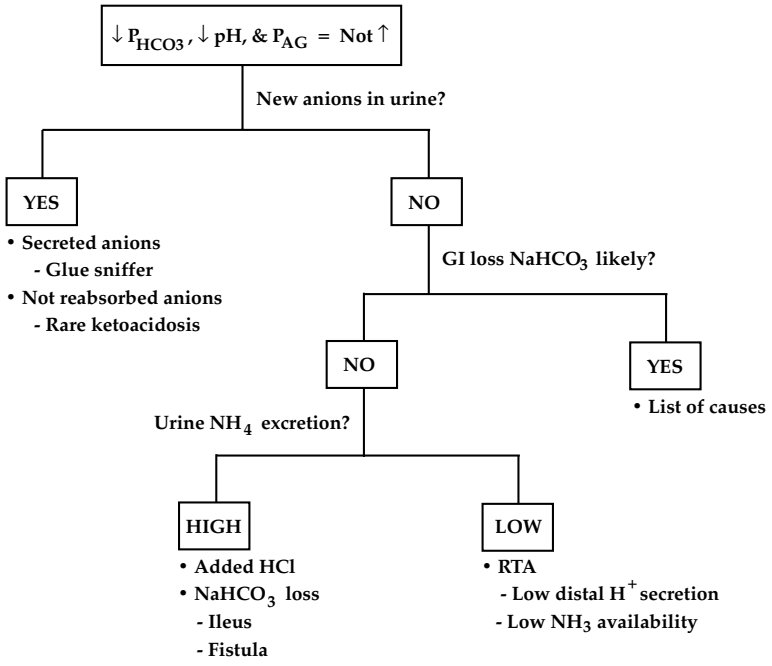
Question

- **Is a serious degree of metabolic acidosis present?**
- **What do you predict his P_{HCO3} to be?**
- **Does he have respiratory acidosis?**

Discussion of Case 9-3

Flow chart 9-2

Metabolic acidosis with no new anions in plasma



Is a serious degree of metabolic acidosis present?

Loss of diarrhoeal fluid should cause the P_{HCO3} to fall and metabolic acidosis to be present.

What do you predict his P_{HCO3} to be?

Concentrations have both the numerators and denominators (Figure 9-13)!

Numerator analysis

The loss of $NaHCO_3$ should cause the P_{HCO3} to fall. A loss of 5 L of diarrhoeal fluid (and with no HCO_3 input) will cause a deficit of 225 mmol of HCO_3 (5 L x 45 mmol/l). The ECF HCO_3 content in a 70-kg male is 375 mmol (15 L ECF x 25 mmol/l). Hence the quantity of HCO_3 remaining in the ECF is 150 mmol (375 – 225 mmol).

Denominator analysis

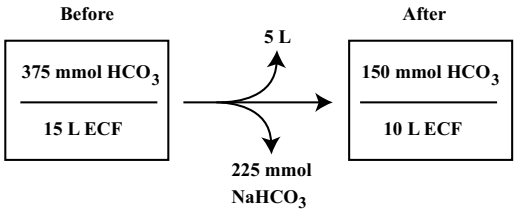
The P_{HCO3} will be higher due to a contracted ECF volume. The normal ECF volume is 15 L and the fluid lost is isotonic to the body fluids. The deficit is 5 L, so the new ECF volume is 10 L (15 – 5 L).

Expected P_{HCO3}

He now has 150 mmol HCO_3 in 10 L of ECF, so the P_{HCO3} should be 15 mmol/l. The measured P_{HCO3} was 22 mmol/l so we would need an input of ~ 70 mmol of HCO_3. Nevertheless, there was no HCl trapped in the stomach, virtually no NH_4Cl in the urine and he had no intake of $NaHCO_3$. Therefore look for the generation of H_2CO_3 with H^+ bound to proteins. To determine if this may be important, see discussion of the respiratory acidosis question below in this Case.

FIGURE 9-13

Concentration of HCO_3



Does this patient have respiratory acidosis?

(i) Ventilatory type of respiratory acidosis

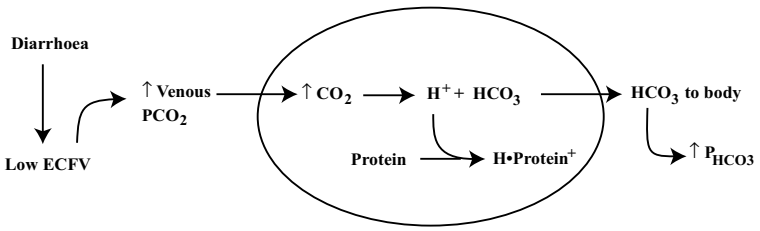
No, because his arterial Pco_2 is appropriate for his pH and P_{HCO3}.

(ii) Tissue form of respiratory acidosis

Yes, because of his marked degree of ECF volume contraction, he has a reduced blood flow rate to tissues. Thus his venous Pco_2 should be much higher than his arterial Pco_2—the venous Pco_2 was 69 mm Hg. This high venous Pco_2 means that the cells drained by this vein have a Pco_2 of at least 69 mm Hg (CO_2 moves via diffusion). A high Pco_2 leads to the generation of new HCO_3 and this could explain his higher than expected arterial P_{HCO3} of 22 mmol/l (Figure 9-14).

FIGURE 9-14

Tissue type of respiratory acidosis



Conclusion

You cannot understand an acid-base disorder if you rely solely on the blood tests. There is an even larger error if you do not factor for the ECF volume, rely solely on the arterial values, and do not assess both types of respiratory acidosis.

Suggested reading

Watten RH, Morgan FM, Songkhla YN, Vanikiati B, and Phillips RA. Water and electrolyte studies in cholera. *J Clin Invest* 38: 1879-1889, 1959.

Zalunardo N, Lemaire M, Davids MR and Halperin ML. Acidosis in a patient with cholera: A need to redefine concepts. *Quart J Med* 97: 681-696, 2004.

CHAPTER 10

KETOACIDOSIS

I. ESSENTIAL POINTS

1. Biochemical features

Ketoacids are synthesized during the partial oxidation of fatty acids. The signal for this synthesis is a relative deficiency of insulin (low insulin, high counter-insulin hormones). The causes for low activity of insulin are shown in *Table 10-1 and Flow Chart 10-1*. Virtually all ketoacids are synthesized in the liver, but it usually takes several days to get the maximum rates of ketogenesis (Figure 10-1).

Ketoacids are the water-soluble, fat-derived fuel for the brain when the other major brain fuel (glucose) is in short supply. Ketoacids are also oxidized in the kidney. There is a near-perfect balance between ketoacid formation in the liver and their oxidation in the brain and kidneys during starvation. In DKA, the major accumulation of ketoacids is due to slower oxidation in the brain and kidneys.

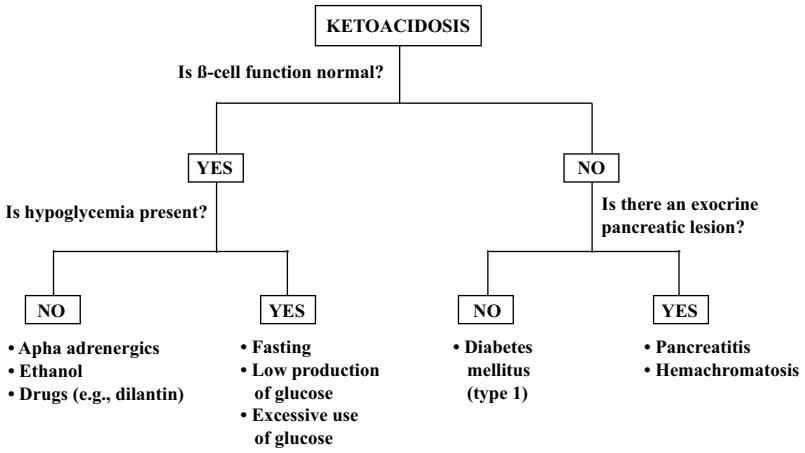
TABLE 10-1

REASONS FOR LOW INSULIN ACTIVITY

- **Pre-receptor (low levels of insulin)**
  - Lack of stimulator (low $P_{Glucose}$)
  - Damage or destruction of pancreas (diabetes mellitus (usually type 1), pancreatitis)
  - Inhibitors of the release of insulin (high α-adrenergics, drugs (e.g., dilantin)
- **Receptor problems**
  - Abnormal receptors (rare disorders such as acanthosis nigricans)
- **Post-receptor problems**
  - Extreme obesity
  - Drugs activating lipolysis

FLOW CHART 10-1

Etiology of ketoacidosis



2. Balance between ketogenesis and the oxidation of ketoacids

(i) Production

Production of ketoacids can be as high as 1500 mmol/day or 1 mmol/min. This rate is similar in chronic fasting, DKA or alcoholic ketoacidosis (AKA).

(ii) Utilization

During chronic fasting, ketoacids are oxidized in brain (750 mmol/day) and kidneys (250 mmol/day). Of the remaining 500 mmol, 150 are excreted in the urine (with NH_4), 150 mmol are converted to acetone + CO_2, and 200 mmol are oxidized, largely in muscle and the intestinal tract. This explains the net balance between production and utilization of ketoacids.

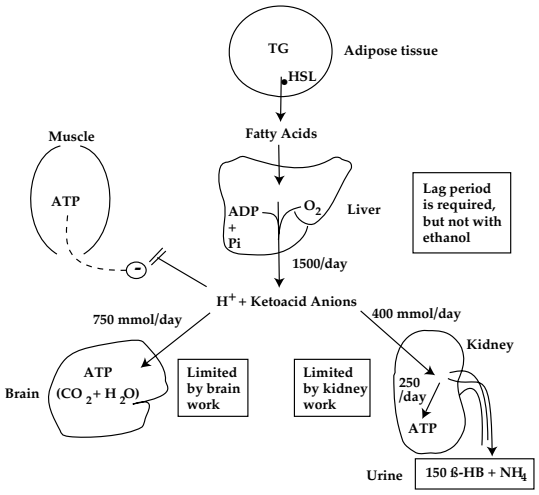
(iii) Balance of ketoacids

There is little opportunity to increase the rate of ketogenesis further. In contrast, the major site where leverage occurs in increasing the degree of ketoacidosis is to decrease the rate of removal of ketoacids. This, in effect, means to slow the rate of oxidation of ketoacids in the brain (coma, sedatives, anaesthesia) or the kidney (low GFR) (Figure 10-1).

FIGURE 10-1

Factors Influencing the Degree of Ketoacidosis

Ketoacidosis requires a low net insulin activity. It becomes severe if there is a decreased rate of removal of ketoacids. In the ketotic phase of fasting or in DKA, the total rate of production of ketoacids in one day exceeds the ECF HCO_3 body pool size by 4-fold. Metabolism of ketoacids in the brain consumes half and removal of ketoacids by the kidneys eliminates 1/4 of the ketoacids produced each day. HSL = Hormone Sensitive Lipase



II. QUESTIONS FOR THE PATIENT WITH KETOACIDOSIS

The causes of ketoacidosis are listed in Table 10-2.

1. Why is insulin low?

(i) Is this the result of hypoglycemia?

If yes, the $P_{Glucose}$ will be ~ 3.3 mmol/l (60 mg/dl) early in fasting, but somewhat higher (4-5 mmol/l, 72-90 mg/dl) after several weeks of starvation. If the $P_{Glucose}$ is < 2.5 mmol/l (45 mg/dl), look for a cause of hypoglycemia in addition to, or instead of, starvation.

(ii) Is there an inhibitor of the release of insulin present?

Look for an a-adrenergic response (marked hypovolemia) drugs such as dilantin, diazoxide, etc. Hyperglycemia will usually be seen when there is low insulin bioactivity, but it need not be present (e.g. AKA).

(iii) Are the ß-cells of the pancreas destroyed?

An example is DKA in children. In these circumstances, always expect hyperglycemia.

2. Are there other causes of ketoacidosis, or why is lipolysis so high?

(i) Rarely

In the post-exercise period, the sudden decline in the rate of oxidation of FFA leads to the formation of ketoacids owing to the rapid rate of lipolysis stimulated by catecholamines. In addition, the rate of oxidation of ketoacids in muscle cells declines.

(ii) Drugs

Ketoacidosis may follow the administration of drugs that augment hepatic lipolysis; ASA is a possible example.

TABLE 10-2

CAUSES OF KETOACIDOSIS

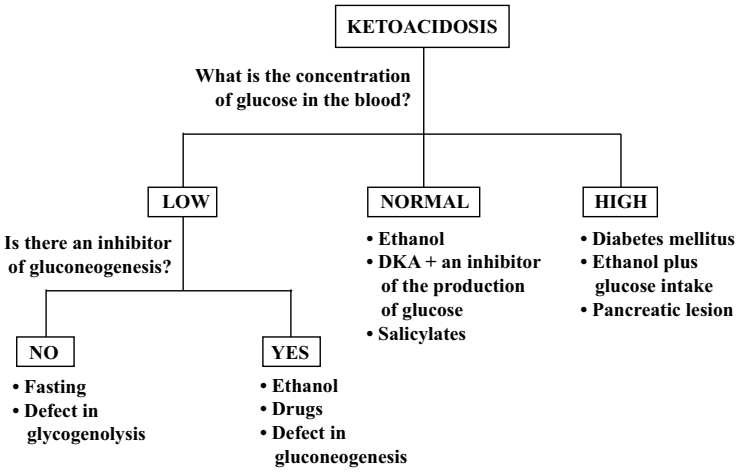
- Diabetic ketoacidosis
- Alcoholic ketoacidosis
- Hypoglycemic ketoacidosis (including inborn errors of metabolism)
- Starvation ketoacidosis
- Inhibitor of insulin release causing ketoacidosis (e.g., α-adrenergics, diazoxide)
- Acetic acid overload & inhibition of acetyl-CoA carboxylase (see Case 10-2)

III. CLINICAL CLUES CONCERNING THE CAUSE OF KETOACIDOSIS

Examine the clinical setting (alcohol, age, etc, Table 10-2 and Flow Chart 10-2) and the degree of hyperglycemia or hypoglycemia. For AKA, the patient almost always has profound contraction of their ECF volume. This is due to protracted vomiting in almost every case. Never overlook the underlying or associated illness.

FLOW CHART 10-2

Blood sugar and ketoacidosis



IV. DIABETIC KETOACIDOSIS

1. Definition

The key diagnostic features are hyperglycemia and accumulation of ketoacids. Patients with this disorder lack insulin and are typically young. The potential threats to life are hypovolemia, acidosis, underlying illness and complications. In children, the major cause of morbidity is cerebral edema (0.5 – 1 % of DKA), usually 5-15 hr after therapy begins.

2. Expected physiological response

Lack of insulin plus high counter-insulin hormones lead to the synthesis of ketoacids in the liver (~ 1 mmol/min) after a lag period of > 1 day. The oxidation of fatty acids and ketoacids inhibits the oxidation of glucose and contributes to hyperglycemia. There is also an increased production of glucose due to the catabolism of glycogen and proteins.

Another aspect of the expected response is an osmotic diuresis, which leads to contraction of the ECF volume (loss of Na).

3. Clinical features

These can be divided into 5 major groups.

(i) Hypoglycemia: If an insulin-dependent diabetic presents in coma, one might not be sure if the cause is DKA or a hypoglycemic reaction. Physical findings of a low circulating volume, the intensity of the adrenergic response, the history, etc., should leave little doubt as to the cause. A quick measurement of $P_{Glucose}$ (< 1 min) indicates the diagnosis.

(ii) Hypovolemia: Tachycardia, hypotension, and dizziness due to a contracted ECF volume because Na was lost in the urine.

(iii) Ketoacidosis: Expect hyperventilation and a fruity odour of acetone on the breath.

(iv) CNS signs: Confusion and later coma are manifestations of serious DKA.

(v) Underlying disorder and complications: Infections are common, but the list is long and will not be discussed here.

4. Differential diagnosis

This is usually not a problem.

(i) Hypoglycemic coma: If an insulin-dependent diabetic presents in coma one might not be sure if the cause is DKA or a hypoglycemia reaction. Physical findings of a low circulating volume, the intensity of the adrenergic response, the history etc should leave little doubt as to the cause. A quick measurement of $P_{Glucose}$ (< 1 min) provides the key confirmation.

Do not rely on glucosuria to make this differential diagnosis. With a profound reduction of the GFR, glucosuria may be absent, despite hyperglycemia. In contrast, glucosuria in a diabetic may represent "old" urine containing glucose, but the patient now has hypoglycemia owing to the actions of administered insulin.

(ii) Alcoholic ketoacidosis (AKA): Because the intake of ethanol is not uncommon in the insulin-dependent diabetic population, AKA may be present. Key features to suggest AKA are ingestion of a large quantity of ethanol, more profound vomiting which led to a more marked degree of contraction of the ECF volume, a higher

P_{HCO3} and a lower $P_{Glucose}$ if ethanol is still present; the P_{osm} gap will be high in this setting.

5. Laboratory features

The hallmarks of the diagnosis are hyperglycemia and ketoacidosis.

(i) Hyperglycemia: The $P_{Glucose}$ is often in excess of 30 mmol/l (540 mg/dl) and indicates a very low GFR and/or excessive intake of glucose. Glucosuria is almost always 4+, but it can be absent when the GFR is very low, owing to marked hypovolemia. The $P_{Glucose}$ is often less elevated in children with DKA.

(ii) Ketoacidosis: A high anion gap type of metabolic acidosis is the most common presentation. Nevertheless, the fall in the P_{HCO3} (from 25 mmol/l) should not equal the rise in the plasma AG (from 12 mEq/l) because there is a component of indirect loss of Na and HCO_3 (ketonuria without NH_4) and also because the ECF volume is low.

The side-room test for ketones measures acetone and acetoacetate. The former is responsible for the "fruity odour" on the breath. Both acetone and acetoacetate might be low despite DKA if the NADH/NAD ratio is high (for example, the presence of hypoxia or ethanol metabolism). In this case, the diagnosis can be confirmed by measurement of the β-OH butyrate level in plasma.

(iii) Potassium: The usual P_K is in the 5.5 mmol/l range. This hyperkalemia reflects a shift of K out of cells secondary to the lack of insulin (not the acidosis) and a large deficit of K (osmotic diuresis). The absence of this degree of hyperkalemia indicates that a greater degree of K depletion is present.

(iv) Creatinine and urea: Both are elevated in plasma, primarily reflecting the low GFR. Hyperglycemia may yield lower than expected values for creatinine in enzyme-based analyses whereas ketonemia yields a higher value for creatinine in the picric acid method.

TABLE 10-3

TYPICAL DEFICITS IN A PATIENT WITH DKA

	Quantity	Comment	Danger
• Na	• 5-10 mmol/kg	• Restore quickly only if an emergency	• If effective P_{osm} falls in children, cerebral edema may develop
• K	• 5-10 mmol/kg	• K will shift into cells once insulin acts	• Initial: hyperkalemia • > 1-2 hr: hypokalemia
• H_2O	• Many L	• Focus initially on ECF	• Fall in effective P_{osm}
• HCO_3	• Depends on $P_{ß\text{-}HB}$ & ECFV	• Do not give $NaHCO_3$ unless $P_{HCO3} < 5$ mmol/l	• Strong opinions, but no clear data

6. Treatment

Typical deficits to expect in a patient with DKA are shown in Table 10-3. The anticipated results of therapy are summarized in Table 10-4 and the dangers are summarized in Table 10-5.

(i) Expand the ECF volume. Give isotonic saline rapidly only if there is a hemodynamic emergency, especially in children.

(ii) Give insulin to stop the production of ketoacids: Do not give a bolus of insulin to children. Infuse 1 unit of insulin per hour until the biochemical disorder has been reversed. The only early reliable clue that insulin has acted is a fall in the P_K of > 1 mmol/l.

(iii) P_K problems: Give IV KCl to avoid hypokalemia after insulin acts (> 1-1.5 hours later).

TABLE 10-4

ANTICIPATED RESULTS OF THERAPY OF DKA

• $P_{Glucose}$	• Will fall 5.5 mmol/l/hr (100 mg/dl/hr) over first 6 hr. Reasons for this fall are dilution (early), glucosuria (mid-time) and metabolism (late).
• P_{HCO3}	• Will not rise for several hours. This reflects some production of HCO_3 from ketoacid anion oxidation and a fall from dilution (administered NaCl). • The P_{HCO3} will be close to 18 mmol/l once ketoacidosis disappears.
• **Ketoacids**	• Slow steady decline over 8 hours to < 1 mmol/l • Serum quick test for ketones will be positive much, much longer.
• **Plasma AG**	• Fall in parallel with ketoacids, will return to normal in 8-12 hours.
• P_K	• Sudden fall over 1-2 hours owing to shift of K into cells. • Adjust administered dose of KCl to avoid hypokalemia.
• P_{Na}	• Defend effective P_{osm} ($2\ P_{Na} + P_{Glu}$) by permitting P_{Na} to rise above 140 mmol/l in children.
• **Underlying lesion**	• Be vigilant!
• **Complication**	• Early, avoid aspiration pneumonitis and look for thromboembolic events. ~ 10 hours, watch out for cerebral edema, especially in children.

TABLE 10-5

POTENTIAL CAUSES OF DEATH DURING DKA

CAUSE	TIME	TREATMENT
• Hyperkalemia	• Admission	• Insulin
• Aspiration	• While CNS depressed	• NG suction, position, etc.
• Hypokalemia	• 2+ hours after insulin is given	• KCl to yield P_K of 4.0 mmol/l
• Relative hypoglycemia	• 6-8 hours later	• IV D_5W when $P_{Glucose}$ is 15 mmol/l (270 mg/dl)
• Underlying lesion and complications	• All times	• Vigilance • Specific measures

7. Questions to stress in the patient with DKA

(i) Questions in the history: Is the patient likely to be ketosis-prone (young, IDDM)? If not, is there reduced oxidation of ketoacids (coma) or severe resistance to the actions of insulin (infection, pancreatitis, drugs)? Are there drugs inhibiting the release of insulin? Are there expected sequelae (hyperventilation, acetone on the breath)? Are there complications? Has aspiration occurred (or is it likely)? Is there an underlying illness?

(ii) Questions on physical exam: Is there marked contraction of the ECF volume? Is acetone on the breath? Is hyperventilation evident? Is there an underlying lesion? Is there distension of the stomach? Are complications present?

(iii) Questions when evaluating the lab exam: Are the hallmarks of DKA present (hyperglycemia, high anion gap type of metabolic acidosis, positive ketones in plasma, glucosuria)? What is the P_K and the effective P_{osm}? Is the GFR low? Are there complications evident? Is there an underlying lesion?

V. ALCOHOLIC KETOACIDOSIS (AKA)

1. Definition

The clinical picture must contain a reason for lack of insulin and high levels of counter-insulin hormones (almost always protracted vomiting), which are responsible, in large part, for the ketoacidosis ($P_{ßHB} > 5$ mmol/l). Ethanol need not be present on admission. One should rule out other causes of insulin-lack such as DKA, drugs, which inhibit the release of insulin, or hypoglycemia *(Table 10-1)*.

2. Pathophysiology

The key components of AKA are the ingestion of large quantities of ethanol and marked contraction of the ECF volume. Ethanol may be detected in the breath, in the circulation (high P_{osm} gap) and in tissues (intoxication), but this is not an absolute requirement on admission. Toxic effects of ethanol lead to protracted vomiting (alcoholic gastritis or possibly pancreatitis). The expected response to protracted vomiting is a marked contraction of the ECF volume, which leads to hypotension, a higher P_{HCO3}, a lower P_K, and inhibition of the release of insulin (α-adrenergic response).

3. Clinical features

The patient has consumed an excessive quantity of ethanol and is intoxicated, but can usually be aroused. Frequently, the patient does not have diabetes mellitus. Vomiting is a key factor—this leads to a profound contraction of the ECF volume. There is no major age or sex predilection. One need not be a chronic alcoholic. The laboratory findings depend on whether alcohol is present in the circulation.

4. Differential diagnosis

The situations to distinguish are DKA and intoxications with other alcohols as specific treatments are required in each case. Further, complications may differ in AKA.

(i) DKA: The key feature on history is the reason for the lack of insulin (IDDM Vs α-adrenergic response). Physical exam of AKA reveals very severe hypovolemia; be cautious of this diagnosis without it. If the $P_{Glucose}$ is < 15 mmol/l (270 mg/dl), this suggests AKA rather than DKA as the cause of the ketoacidosis. The plasma AG is higher than expected when compared to the fall in the P_{HCO3} in patients with AKA because of the history of excessive vomiting and the very contracted ECF volume. Patients with AKA will have a high P_{osm} gap if ethanol is present in the circulation.

(ii) Intoxication with methanol or ethylene glycol: Aside from the history of ingestion, the absence of severe contraction of the ECF volume suggests methanol or ethylene glycol. The rise in the plasma AG will not exceed the fall in P_{HCO3} in most cases with these intoxications. Do not let level of ethanol fall until these intoxications are ruled out.

5. Laboratory features

The features will vary, depending on the presence or absence of ethanol in the circulation and the duration over which food was not ingested (Table 10-6).

TABLE 10-6

LABORATORY FEATURES IN THE PATIENT WITH AKA

Plasma	
• **$P_{Glucose}$**	The $P_{Glucose}$ may be lower if the patient has no input of glucose, time for glycogen stores in liver to be depleted (fasting for several days) and ethanol is present in the blood. In the absence of any of the above, the $P_{Glucose}$ will be elevated, but usually to a lesser extent than in DKA.
• **Ketoacids**	Usually elevated, and possibly very high. If ethanol is present, the quick test for ketones in plasma may underestimate the degree of ketoacidosis.
• **Acid-base**	The P_{HCO3} will be higher than expected from the very high plasma AG.
• **Ethanol**	If present, there will be a high P_{osm} gap.
• **P_{K}**	The P_{K} can be high or low depending on how much K was lost in urine Vs shifted out of cells (lack of insulin).
• **P_{Na}**	Usually quite hyponatremic owing to large water intake with ethanol. If hyperglycemia is present, it will contribute to hyponatremia, but now the P_{osm} is higher.
• **$P_{Creatinine}$**	Expect very elevated values (BUN as well).
Urine	
• **Volume**	Usually very low as patient may be in shock.

6. Treatment

(i) Re-expand the ECF Volume: This often needs to be done quickly initially. The tonicity of this saline depends on the degree of hyponatremia. The sum of Na + K per L of IV should not exceed that of plasma if the patient has severe hyponatremia. For the first L of saline, isotonic saline is the simplest choice and should not have significant danger associated with it.

(ii) Potassium: The large deficit of K cannot be replaced early as the relative lack of insulin has led to a shift of K from the ICF. Once the ECF volume is restored there will be a rapid shift of K into cells owing to release of insulin from β-cells. In addition, there will be a large kaliuresis once the urine volume increases as aldosterone is still acting and bicarbonaturia may develop. Attempt to keep the P_K in the normal range; the quantity of K needed will have to be determined from repeated laboratory results. KCl is the best initial source for K, but wait to replace the entire ICF deficit.

(iii) Thiamin: B vitamins should be added to the first IV bottle in malnourished patients.

(iv) Factors that are not so important:
Insulin: Insulin need not be given unless there is life-threatening acidemia. Insulin could cause problems such as hypokalemia or hypoglycemia.

Glucose: Glucose need only be given if hypoglycemia is present. If given, the patient will only need a small quantity as long as the levels of ketoacids and FFA are high. To raise the $P_{Glucose}$ by 5 mmol/l (90 mg/dl), only 100 mmol (1.8 g) of glucose are needed (3.5 ml $D_{50}W$).

Acid base: Specific attention to acid base problems is generally not necessary as two offsetting conditions are present, metabolic alkalosis to raise the P_{HCO3} and ketoacidosis plus lactic acidosis to lower it. The re-expansion of the ECF with saline and K replacement will reverse all these disorders.

Phosphate and magnesium: These deficits can be replaced more slowly. Oral supplementation is usually adequate. However, if levels of magnesium are extremely low, magnesium could be given intravenously.

(v) Expected response: The electrolyte and acid base abnormalities should be reversed in 24 hours.

(vi) Complications: The complications to avoid during therapy are listed in *Table 10-7*. Special precautions concerning a possible subdural hemorrhage should be taken; this becomes more difficult to detect as there are many factors that can contribute to confusion.

7. Questions to ask of the patient with AKA

1. Questions on history

(i) Why is insulin low? Is this due to underlying type 1 diabetes mellitus? Was a drug ingested that inhibits the release of insulin or opposes its action? Most commonly, the cause is profound vomiting – is the ECF volume very low?

(ii) Is ethanol still present? If so, expect a higher $P_{Lactate}$ and lower $P_{Glucose}$. Watch out for symptoms and signs to suggest that delerium tremens is present.

(iii) What is the nutritional state? If the patient is likely to be malnourished, give B vitamins right away.

(iv) Are underlying lesions or complications present?

2. Question on physical exam

(i) Is the ECF volume very contracted? If not, suspect that your diagnosis may be incorrect.

(ii) Is confusion present? This may be due to alcohol, withdrawal of alcohol, or an underlying lesion (possible subdural hematoma).

3. Questions on lab exam

(i) Is ethanol the only agent involved? Look at toxic drug screen or for unexpected lab findings.

(ii) Are complications present (Table 10-7)?

(iii) How will lab tests change once ethanol disappears from the body? When ethanol is present, the P_{osm} gap is high and pyruvate is converted to L-lactate and not to glucose. Hence L-lactate levels tend to be close to 4 mmol/l and the $P_{Glucose}$ will fall if glycogen stores in liver are depleted (fasted for a few days) and no glucose was ingested (Figure 10-2).

There is no change in the rate of formation of ketoacids when ethanol is absent. There may be a change in the relative proportion of acetoacetate and ß-hydroxybutyrate such that the side-room test for ketones in plasma will be more strongly positive in the absence of ethanol *(*Table 10-6*)*.

FIGURE 10-2

Ethanol and the presence of a lower $P_{Glucose}$

The metabolism of ethanol will lead ultimately to high level of ketoacids and a low $P_{Glucose}$ in patients who have a deficiency of insulin. Key to this feature is the high NADH, which steals pyruvate and converts it to lactate instead of glucose.

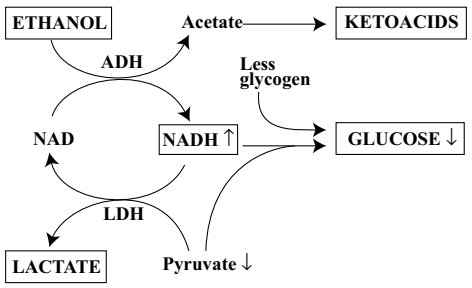


TABLE 10-7

COMPLICATIONS TO AVOID DURING THERAPY

- Brain lesions secondary to a deficit of thiamin
- Shock
- Aspiration pnemonitis
- Thrombotic episodes
- Hyperkalemia and hypokalemia as they can cause cardiac arrhythmias
- Too rapid correction of hyponatremia (osmotic demyelination)
- Rhabdomyolysis secondary to electrolyte deficits (K, Mg, PO_4)
- Ileus with accumulation of oral K salts and secreted $NaCO_3$; later patient must be able to excrete this electrolyte load once it is absorbed.
- Delirium tremens (alcohol withdrawal syndromes)
- Complications of the underlying illness (e.g., subdural hematoma)

7. Questions to ask of the patient with AKA

8. Expected deficits
These may vary considerably form case to case.

9. Dangers
The possible causes of death are outlined in Table 10-8.

TABLE 10-8

POSSIBLE CAUSES OF DEATH IN A PATIENT WITH AKA

Cause	Time	Comment	Therapy
• Shock-	• On admission	• Beware if ECFV not very low	• IV NaCl quickly, initially
• Hypokalemia with cardiac arrhythmia	• Mainly once insulin acts	• Large K deficit, but K shift due to lack of insulin	• No initial insulin • Do not give large oral K load if ileus
• CNS damage due to L-lactic acid	• Once ketoacids fall	• Brain needs active PDH or L-lactic acid will be made rapidly	• Give thiamine (vitamin B_1) on admission
• Delerium tremens	• After $P_{Ethanol}$ falls	• A major danger	• Sedation, close observation
• Hypoglycemia	• After ketoacids disappear	• Over-rated!	• Glucose
• Underlying lesion and/or complications	• At any time	• Always be on the alert	• Specifics not discussed here

VI. ILLUSTRATIVE CASES

CASE 10-1

Hyperglycemia and acidosis

Andy, age 12, was feeling well until he had the 'flu' 2 weeks ago. Since that time, his urine output was large. He became thirsty and drank large volumes of juices. Despite eating well, he lost weight. Today, he is confused and difficult to rouse. On physical examination, his ECF volume is very contracted, respirations are rapid and deep, and acetone is detected on his breath.

		Plasma	Urine
Glucose	mmol/l (mg/dl)	30 (540)	300 (5400)
pH		7.25	5.4
HCO_3	mmol/l	10	0
PCO_2	mm Hg	25	-
Na	mmol/l	130	47
K	mmol/l	5.5	15
Cl	mmol/l	93	24
Anion gap	mEq/l	27	38
Ketones		4+	4+
Creatinine	μmol/l (mg/dl)	250 (2.8)	-
Urea (BUN)	mmol/l (mg/dl)	20 (56)	300
Osmolality	mOsm/kg H_2O	310	750

Questions

- **Are there any other tests that you need to confirm the diagnosis of DKA?**
- **What are the major threats to Andy's life?**
- **How does the depressed sensorium contribute to the degree of ketoacidosis?**
- **Should the physician administer $NaHCO_3$ to Andy?**

Discussion of Case 10-1

Are there any other tests that you need to confirm the diagnosis of DKA?

This is DKA because the patient is in the right age range, the history is strongly suggestive, the physical findings are characteristic, and the laboratory findings are all consistent with this diagnosis. Therefore, additional blood tests for diagnostic purposes are not needed. However, the possibility of an underlying illness and complications should be evaluated further. To minimize this risk, ensure that the effective P_{osm} ($2 P_{Na} + P_{Glucose}$ in mmol/l terms) does not fall appreciably by infusing isotonic saline + KCl as needed for at least the first 12-hours.

What are the major threats to Andy's life?

The major threats to Andy's life are shock and possibly aspiration pneumonitis on admission (Table 10-5). After insulin acts (1.5-2 hours later), there is an acute danger of a cardiac arrhythmia secondary to hypokalemia. After 6 hours, neuroglucopoenia can be a problem owing to down-regulation of glucose transporters in the blood-brain barrier. Several hours later, cerebral edema is the major danger. Complications and an underlying lesion can be a threat at any time.

How does the depressed sensorium contribute to the degree of ketoacidosis?

The depressed sensorium can lead to a more severe degree of ketoacidosis because the brain will oxidize fewer ketoacid anions.

Should the physician administer $NaHCO_3$ to Andy?

$NaHCO_3$ should not be given because the degree of acidosis is not life-threatening. Expect that the P_{HCO3} will be ~ 18 mmol/l after 8-12 hours of therapy (normal anion gap) and the P_{HCO3} will return to normal in 24-36 hours providing there is sufficient renal function to excrete NH_4 in the urine.

CASE 10-2

Ketoacidosis without diabetes mellitus

This is the fourth admission with similar findings in a 22-year old male who has mild cerebral palsy. He is normal between episodes, taking the same medications for control of depression. There was no history to suggest that he has diabetes mellitus.

Acute episode: The syndrome began with extreme agitation and an inability to sleep. His intake of sweetened soft drinks increased markedly. He complained of crampy lower abdominal pain. He denied the intake of alcohol or toxins (P_{osm} gap was not elevated). On physical examination, there were no signs of ECF volume contraction. Acetone was detected on his breath. The laboratory data in plasma before therapy are:

pH	mmol/l	7.20
HCO_3	mmol/l	8
Anion gap	mEq/l	26
Albumin	g/l	41
Glucose	mmol/l (mg/dl)	5 (92)
§-HB	mmol/l	4.5
L-Lactate	mmol/l	1.0
K	mmol/l	4.2
Creatinine	µmmol/l (mg/dl)	115 (1.0)
Osmolality	mOsm/kg H_2O	285

Because diabetic ketoacidosis was considered, his plasma insulin level was measured and found to be in the normal range; his hemoglobin A_1C was not elevated 4.4%.

Course: His treatment consisted of 1 L of isotonic saline and 1 L of D_5W and his acid-base values were normal within 24-h.

Questions:

- **What makes diabetic ketoacidosis an unlikely diagnosis?**
- **What makes alcoholic ketoacidosis an unlikely diagnosis?**
- **What makes ketoacidosis of starvation, hypoglycemia, or drug ontake an unlikely diagnosis?**
- **How might his intake of fructose contribute to the development of ketoacidosis?**

What makes diabetic ketoacidosis an unlikely diagnosis?

DKA is unlikely because his $P_{Glucose}$ is in the normal range, he is not diabetic, and he does not have a high P_K or ECF volume contraction. Moreover, his therapy did not include insulin. On further testing, his plasma insulin level was in the normal range.

What makes alcoholic ketoacidosis an unlikely diagnosis?

AKA is unlikely because he had no intake of alcohol, his ECF volume is not contracted, and his P_{osm} gap is not elevated.

What makes ketoacidosis due to starvation, hypoglycemia or drug intake an unlikely diagnosis?

Starvation and hypoglycemic ketoacidosis were ruled out because he had a normal $P_{Glucose}$ and a large intake of sugar. He denied the intake of drugs that inhibited the release of insulin

How might his intake of fructose contribute to the development of ketoacidosis?

Ketoacids are produced in the liver from acetyl-CoA (Figure 10-3). An unusual source for acetyl-CoA formation in the liver should be suspected because of the failure to find insulin lack. Acetyl-CoA can be produced during the metabolism of acetic acid. Acetic acid is produced by bacterial metabolism in the GI tract. This production depends on the delivery of a metabolic fuel to intestinal bacteria (fructose is a bacterial fuel because there are no specific intestinal transporters catalyzing the absorption of fructose). Thus this patient could have had a very large delivery of acetic acid to his liver (Figure 10-4). Moreover, the usual sites of regulation of ketogenesis are bypassed when acetic acid is its precursor. In this setting, a *lack of insulin* may not be needed for ketogenesis. When a large amount of acetyl-CoA is formed, inhibition of other hepatic fates of acetyl-CoA such as fatty acid synthesis should be important for ketoacid overproduction.

What other factors might have increased the degree of ketoacidosis?

Oxidation of ketoacids might be reduced by the brain because the patient had cerebral palsy due to a birth injury and he was taking a sedative drug. Nevertheless, this is not simply ketoacidosis because the $P_{\beta HB}$ was only 4.5 mmol/l yet the plasma AG was elevated by 14 mEq/l. Perhaps there was an unusually high concentration of acetoacetate. Alternatively,

short-chain fatty acids produced by bacterial fermentation could account for the unmeasured anions in plasma.

FIGURE 10-3

Metabolism of acetic acid in the liver

As shown in the top portion of the figure, a major source of acetic acid is from bacterial fermentation of poorly absorbed carbohydrates such as fructose. ATP is consumed during the formation of acetyl-CoA from acetic acid so there is no feedback control of this process by ATP turnover (site 1). As shown in the bottom portion of the figure, one does need inhibition of fatty acid synthesis (site 2) to have rapid rates of ketoacid formation.

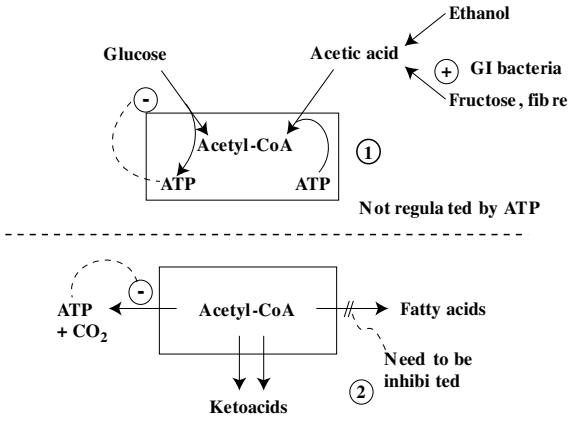
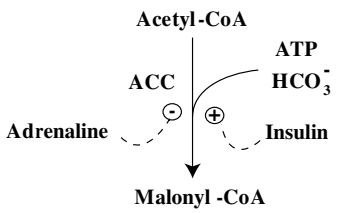


FIGURE 10-4

Role of Acetyl-CoA carboxylase in the liver

The longer vertical arrow represents the enzyme, acetyl-CoA carboxylase (ACC). This enzyme is activated by insulin and inhibited by adrenaline. This latter regulation has greater control strength and plays the dominant role in this case. The product, malonyl-CoA is an inhibitor of the entry of fatty-acyl groups into mitochondria for fatty acid oxidation.



CASE 10–3

Bud went on a drinking spree

Bud had vomited on many occasions; he drank only "store-bought" liquor. He was not known to have diabetes mellitus. On physical examination, he responded only to painful stimuli. He had a marked degree of contraction of his ECF volume and there was a normal rate and depth of respiration. Laboratory values in arterial blood and urine are provided below.

		Plasma		Urine
Glucose	mmol/l (mg/dl)	15	(270)	0
pH		7.30		5.4
P_{HCO3}	mmol/l	15		0
Pco_2	mm Hg	30		-
Na	mmol/l	116		1
K	mmol/l	3.5		15
Cl	mmol/l	66		1
Anion gap	mEq/l	35		+ 15
Ketones		1+		-
Creatinine	μmol/l (mg/dl)	250	(2.8)	-
Urea (BUN)	mmol/l (mg/dl)	20	(56)	-
Osmolality	mOsm/kg H_2O	350		600

Questions

- **Is this AKA?**
- **Why did ketoacidosis develop?**
- **What are the threats to life?**
- **What are the issues for therapy?**

Discussion of Case 10–3

Is this AKA?

The clinical setting of ethanol abuse, protracted vomiting, marked contraction of the ECF volume and the laboratory features including high anion gap type of metabolic acidosis, a rise in the anion gap (from 12 mEq/l) which exceeds the fall in the P_{HCO3} (from 25 mmol/l), modest hyperglycemia are all consistent with the diagnosis of AKA. The lower

than expected $P_{Glucose}$ is due to an inhibition of glucose production in the liver when ethanol is being metabolized (Figure 10-2). The ketoacids did not cause academia because there is another acid-base disorder—vomiting caused the loss of HCl. The markedly contracted ECF volume raises the plasma AG and the P_{HCO3}.

Why did ketoacidosis develop?

Ketoacidosis is due to relative lack of insulin. Bud did not have diabetes mellitus. There are other possible mechanisms to explain a lack of insulin. For example, the release of adrenaline secondary to the poor circulatory volume will inhibit the release of insulin from ß-cells of the pancreas. Because his $P_{Glucose}$ is elevated, this is not the ketoacidosis of fasting.

What are the threats to life?

AKA raises several areas of great concern that must be dealt with to permit the patient to survive (Table 10-8). The clinician must be on the alert for possible complications (Table 10-7) and any underlying disorders throughout the hospital course.

What are the issues for therapy?

Thiamin deficiency

B-vitamins must be added to the first intravenous solution so that energy metabolism in the brain will not be compromised once ketoacidosis disappears, an expectation following re-expansion of the ECF volume in a chronic alcoholic.

Hypovolemia

The ECF volume should be re-expanded so that the circulation will not be compromised. Initially, this should be done rapidly. The dangers of this therapy are raising the P_{Na} too rapidly (> 0.3 mmol/l/hr), hypokalemia (see below) and over-expansion of the ECF volume. Bearing this in mind, isotonic saline (150 mmol/l) should be given for the first L. At this point, re-evaluate carefully and slow the rate of infusion before the ECF volume is restored (a clinical decision).

Too rapid a rise in the P_{Na}

To avoid raising the P_{Na}, two strategies are employed. First, solutions isotonic to the patient (or the urine if large volumes of urine are excreted) are given. Second, if a water diuresis begins, a small dose of ADH should

be given to stop the uncontrolled loss of free water in the urine and thereby, the precipitous rise in the P_{Na}. Should the patient need K, KCl should be added to the intravenous solution (you may need to add 40 mmol KCl to half-isotonic NaCl to avoid raising the P_{Na} excessively).

Potassium

The patient is likely to have a very large deficit of K (several hundred mmol) owing to a large loss of K in the urine. Despite this deficit, the shift of K out of cells owing to the low levels of insulin causes a rise in the P_K. The problems to anticipate are a significant shift of K into cells (restoring the ECF volume removes the α-adrenergic response which inhibited the release of insulin from ß-cells) and a large kaliuresis (accentuated by bicarbonaturia in the presence of aldosterone). Sufficient K must be administered to match losses in the urine and shifts into cells. KCl is the preparation of choice. Phosphate will be needed during the anabolic phase of recovery.

CASE 10-4

Is this DKA?

A 7-year old, 20-kg female had a 2-week history of polydipsia, polyuria, and a 2.5 kg weight loss. She was drowsy, but easily roused and answered questions appropriately. There was no history of diabetes mellitus. Her blood pressure was 100/60 mm Hg, heart rate was 148 / min, and respiratory rate was 12/min. There was no urine output in the first 2-hours. Laboratory data in venous blood are:

Abbreviations: P_aco_2 is the arterial Pco_2 and P_vco_2 is the venous Pco_2.

Glucose	mmol/l	110	WBC	10^9/L	10.6
Glucose	mg/dl	2000	Hemoglobin	g/dl	17.8
pH		7.19	Hematocrit	%	61
P_{HC03}	mmol/l	25	Platelets	10^9/L	154
P_vCO_2	mm Hg	69	P_aCO_2	mm Hg	43
Na	mmol/l	129	Creatinine	µmol/l	82
K	mmol/l	5.7	Creatinine	mg/dl	0.9
Cl	mmol/l	80	Urea	mmol/l	10
Albumin	g/l	78	Urea	mg/dl	28

Questions

- **How do you interpret the normal value for the P_{HCO3} and high $P_{Anion\ gap}$?**
- **How contracted is her ECF volume? Please choose a number (10%, 25 %, 40 %, > 45%).**
- **What is the basis for her very high $P_{Glucose}$?**
- **How did the high $P_{Glucose}$ help her hemodynamics?**

Discussion of Case 10-4

How do you interpret the normal value for the P_{HCO3} and high $P_{Anion\ gap}$?

While the concentration of HCO_3 in plasma is normal, the content of HCO_3 in her ECF compartment is low (25 mmol/l * 1/2 ECF volume, vide infra). Therefore she has metabolic acidosis (deficit of HCO_3) and a second acid-base disorder, contraction metabolic acidosis, which raises the P_{HCO3}. The acidosis will become much more severe when Na is infused to restore her ECF volume unless that solution also contains 25 mmol HCO_3 per L.

The increased plasma anion gap suggested that she metabolic acidosis due to the addition of acids. The increase in plasma anion gap was magnified by the ECF volume contraction that raised the concentration of albumin in plasma. Because her plasma L-lactate concentration was 1 mmol/l, I suspected that she might also have DKA—unfortunately her plasma ß-HB concentration was not measured.

How contracted is her ECF volume?

It is virtually impossible to quantitate the degree of ECF volume contraction on clinical grounds. Therefore laboratory data must be examined. While many parameters can provide qualitative information, I rely on the hematocrit or the plasma albumin level for quantitative information if the patient does not have another disorder that affects these markers.

Hematocrit: When normal, her blood volume would be ~1.5 L (75 ml/kg). With a hematocrit of 40%, her red blood cell (RBC) volume would be 0.6 L and plasma volume 0.9 L (equation below).

Hematocrit = RBC volume/total blood volume

With a haematocrit of 61% and the same RBC volume, her blood volume would be ~1 L. Thus with the same 0.6 L RBC volume, her plasma volume would be 0.4 L, reduced by > 50%.

The combination of a low hydrostatic and high colloid osmotic pressure (high albumin concentration) implies a greater % decline in her interstitial than plasma volume. For simplicity, I shall assume that her ECF volume was reduced from 4 L (20% weight) to 2 L. Her blood volume should be better preserved because of the unchanged RBC volume.

Venous Pco_2: Normally, the P_vco_2 is ~ 6 mm Hg > the arterial P_aco_2. With a low cardiac output, there is a disproportionate rise in P_vco_2. On admission, her P_vco_2 was 69 mm Hg (P_aco_2 43 mm Hg), implying a very low blood flow rate.

Oliguria: The extreme degree of hyperglycemia (P_{Glu}), and oliguria together with the modest elevation in plasma creatinine concentration suggested a recent, but marked fall in GFR—its likely basis was very poor renal perfusion. Perhaps her high blood viscosity decreased flow, especially in the smaller arterioles.

What is the basis for her very high $P_{Glucose}$?

Hyperglycemia is due to either more glucose in the ECF compartment and/or a low ECF volume. A 50% decline in ECF volume raised her P_{Glu} 2-fold. Hence with the same glucose input from her GI tract, the very low ECF volume and GFR (she is now anuric) could virtually quadruple her P_{Glu} from 27.5 mmol/l (500 mg/dl) to 110 mmol/l (2000 mg/dl).

How did the high $P_{Glucose}$ help her hemodynamics?

Hyperglycemia leads to a higher ECF volume because glucose is an effective osmole for skeletal muscle. Using an imaginary redistribution, her 2 L ECF and 220 mmol of glucose (2 L X 110 mmol/l) can be divided into two iso-osmotic solutions. This is helpful because the glucose-containing one will be excreted rapidly when the GFR rises.

In this calculation, the glucose solution will have a $P_{Glucose}$ equal to her effective P_{osm}—368 mOsm/kg H_2O in 0.6 L (220 mmol/368 mmol/l). The other 1.4 L contains all the Na with an identical P_{osm} (P_{Na} 184 mM (1/2 of 368 mmol/l)). Hence this severe degree of hyperglycemia permitted her to have an ECF volume that was 30% higher than it would have been in the absence of hyperglycemia!

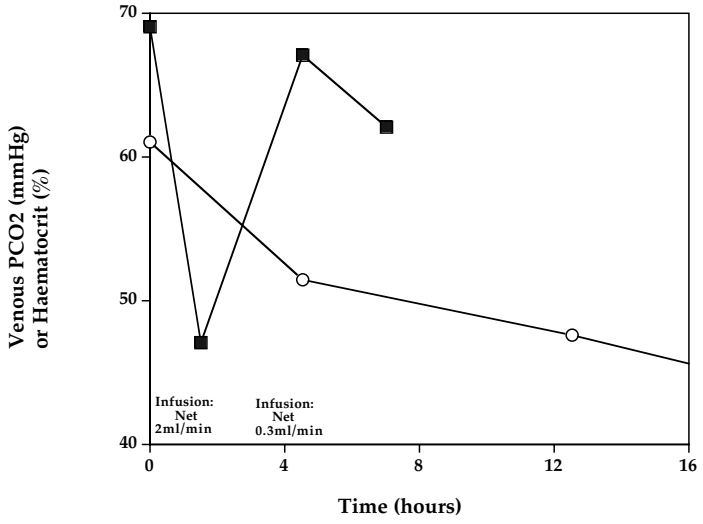
Therapy for ECF volume contraction:

The patient received a bolus of 160 ml saline over 80 min—her P_vco_2 fell to 47 mm Hg (Figure 10-5). Unfortunately, the hematocrit was not measured at this time. Because there was no urine output, this infusion should lower the viscosity of arterial blood to a greater extent because on first pass, it has not reached systemic capillaries. Over the next 120 min, 235 ml of isotonic saline was infused and 200 ml of urine was excreted. Hence her net fluid gain was only 0.3 ml/min and her P_vco_2 rose to 67 mm Hg with no change in P_aco_2. Of note, her urine output declined appreciably. This P_vco_2 change illustrates the initial benefit of re-expanding the arterial plasma volume and its abrogation by a marked decline in the rate of net fluid addition to this compartment.

Figure 10-5

Time course for changes in hematocrit and venous Pco_2

The P_vco_2 is shown in the solid square symbols and the hematocrit is shown in the open circle symbols. Note the fall in P_vco_2 at 80 min, a time when there was intravenous fluid administration and no urine output. Between 80 and 270 min, the intravenous input was only somewhat larger than the urine output and the P_vco_2 rose.



Avoiding a fall in the effective P_{osm}:

The $P_{Glucose}$ will fall due to dilution (infused saline) and glucosuria when the GFR rises. This will lower the effective P_{osm} unless the P_{Na} rises by ~1/2 the fall in $P_{Glucose}$. To achieve this constant effective P_{osm}, the tonicity of the intravenous fluids should equal the P_{osm} during oliguria and the U_{osm} during polyuria. Fortunately, the effective P_{osm} and U_{osm} are similar during a profound glucose-induced osmotic diuresis. Even luckier, the osmolality of isotonic saline plus 20-40 mM KCl is similar to this U_{osm}. Her effective P_{osm} on admission was 368 mOsm/kg H_2O and 12-h later it fell to only 359 mOsm/kg H_2O ($P_{Glucose}$ 27 mmol/l and P_{Na} 166 mmol/l). Later, the decline in P_{Na} should occur gradually to minimize rapid brain cell swelling.

CLINICAL PEARLS

- *The magnitude of ECF volume contraction was best revealed by the hematocrit while the response to therapy was reflected by the venous P_vco_2 and the change in urine output—the rate of saline infusion should be influenced by the urine output and the clinical assessment of the CNS status.*
- *A fall in the effective P_{osm} should be avoided because of the risk of cerebral edema. To achieve this aim, the rise in the P_{Na} should be 1/2 the fall in the $P_{Glucose}$.*

CHAPTER 11

METABOLIC ALKALOSIS

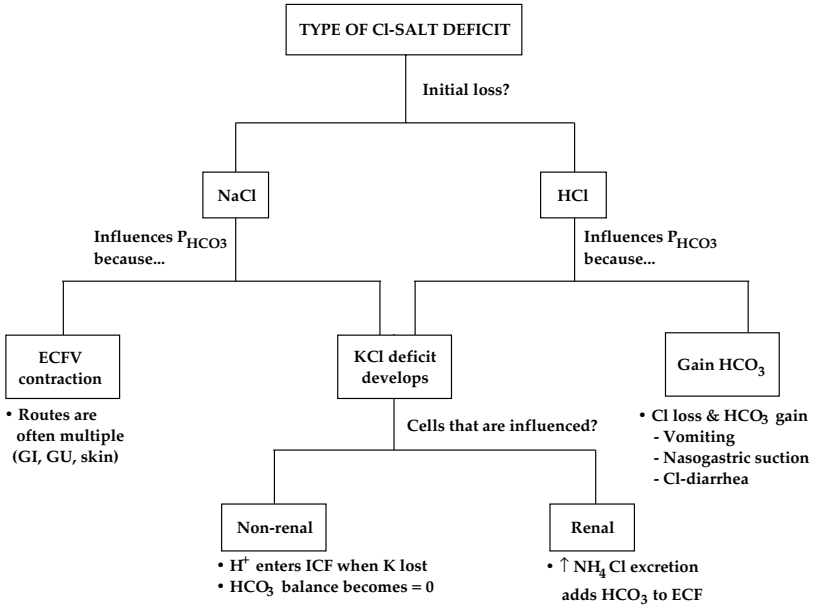
I. ESSENTIAL POINTS

1. Definition

Metabolic alkalosis is not a specific disease; it is usually the net result of an HCl, NH_4Cl, KCl, and/or NaCl deficit (Flow Chart 11-1). Its hallmarks are an increased P_{HCO3} and pH in plasma; however, it can still be diagnosed with a lower pH and P_{HCO3} if there is a large increase in the plasma AG.

FLOW CHART 11-1

Pathophysiology of Metabolic Alkalosis due to a deficit of Cl salts



Balance data

Balance data for the major cations (Na and K) and the anion Cl provide essential clues to understand the basis for this disorder. Data are incomplete if they do not lead to electroneutrality in all body compartments and the urine. If the P_{Na}, P_K, P_{Cl} and P_{HCO3} and their balances are measured, the ionic composition in the ECF and the ICF compartments can be deduced. During treatment, deficits must be replaced and surpluses must be lost. Balance data for the selective loss of HCl are shown in Table 11-1.

TABLE 11-1

BALANCE DATA IN STEADY STATE: SELECTIVE DEPLETION OF HCL

These data were derived from Kassirer and Schwartz (AJM 40: 10-18, 1966).

Duration		Cumulative balance (mmol)		
Drainage	**Day**	**Na**	**K**	**Cl**
During	2	-16	-145	-345
Post	5	-30	-181	+21
Cumulative		**-46**	**-336**	**-324**
Cumulative balance after treatment with NaCl				
		+1034	-288	+648

Electroneutrality

During drainage: Because of the negative balance of 16-mmol of Na, a deficit of 16-mmol of NaCl was created in this initial period. Similarly, because of a deficit of 145-mmol of K, a deficit of 145-mmol of KCl was created. The remaining deficit of Cl (345 – 16 – 145 or 184 mmol) was accompanied by H^+ so there was a deficit of 184-mmol of HCl was created at this time.

Post-drainage: Analyzing the cumulative data in Table 11-1, there was an overall deficit of 46-mmol of NaCl and 278-mmol KCl, with a 58-mmol K deficit with an anion other than Cl (336 – 278 mmol K). This deficit of K was most likely due to the excretion of sulphate anions (SO_4). This excretion of SO_4 anions with K reflects a gain of H^+ in the ICF compartment to ensure that there is electroneutrality in the ECF, ICF,

and in the urine (Figure 11-1). For the urine, the delivery of Na + SO_4 to the cortical collecting duct (CCD) results in the excretion of K with SO_4 because aldosterone leads to an open ENaC and the generation of a lumen-negative voltage in the CCD (Figure 11-2).

Figure 11-1

Mass Balance in the ICF Compartment in the Post-drainage Period

The large square represents the ICF compartment. The bulk of K in the body is in the ICF compartment. During selective depletion of HCl, there is a deficit of Cl and a gain of HCO_3 in the ECF compartment (Figure 11-3). In response to the daily production of H_2SO_4 from sulphur-containing amino acids (AA), there is a renal excretion of K and SO_4 along with a shift of H^+ into and K out of the ICF compartment (see Figure 11-2).

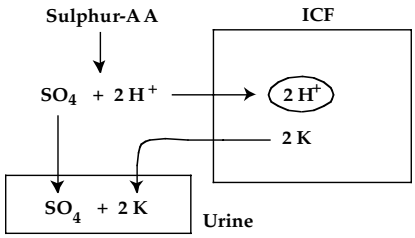
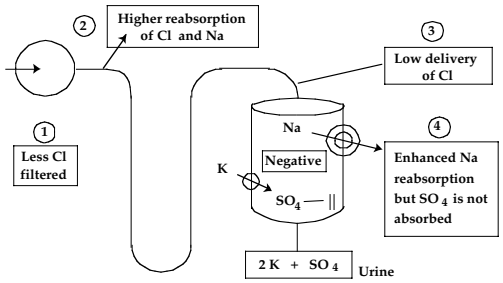


Figure 11-2

Requirements for Renal K Loss in Selective HCl Depletion

There are two major reasons for a low delivery of Cl to the CCD (site 3). First, a low P_{Cl} and the low GFR caused a lower filtered load of Cl (site 1). Second, due to the low 'effective' ECF volume, there is enhanced reabsorption of Cl (and Na) in nephron segments upstream to the CCD (site 2). Because the filtered load of SO_4 exceeds its reabsorption in the PCT, some SO_4 will be delivered to the CCD along with Na (site 4). Since Na ion reabsorption occurs in the CCD via ENaC, but SO_4 anions do not follow, the resultant lumen negative voltage drives the secretion of K so that its excretion will be in near-equi-equivalent amounts to that of SO_4 in the urine.



2. Expected physiological responses

(i) Lungs

The degree of respiratory compensation is small. For every 1.0 mmol/l rise in P_{HCO3}, the arterial Pco_2 often rises by 0.7 mm Hg.

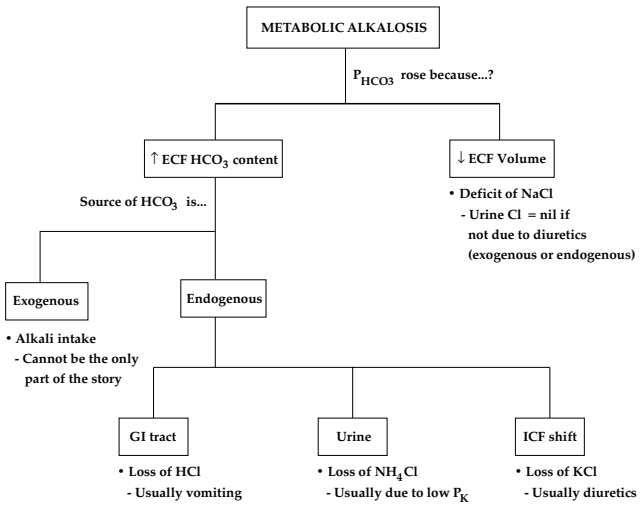
(ii) Kidneys

Because there are many different possible causes for metabolic alkalosis, there is no single expected renal response. In HCl deficiency, the U_{Cl} should be virtually zero—this is the hallmark of this disorder. In response to ECF volume contraction, little Na and Cl should be excreted. However, if there was recent vomiting, there might be an appreciable excretion of HCO_3 and/or organic anions. In this setting, the U_{Na} may not be low, but there will be little Cl in the urine unless there is recent use of a diuretic. When the basis of metabolic alkalosis is diuretic use, the urine will contain Cl even when there is no recent use of diuretics due to the high excretion of Na, K, and/or NH_4. The urine U_K is often high due to a low distal delivery of Cl; K is excreted with anions other than Cl or HCO_3.

FLOW CHART 11-2

Basis for a high P_{HCO3} in Metabolic Alkalosis

This Flow Chart is most useful to understand why the P_{HCO3} rose.



3. Differential diagnosis

Divide them based on ECF volume (Flow Chart 11-2). The majority will have ECF volume contraction due to vomiting or diuretics. Urine electrolytes help in the diagnosis (Table 11-2).

TABLE 11-2

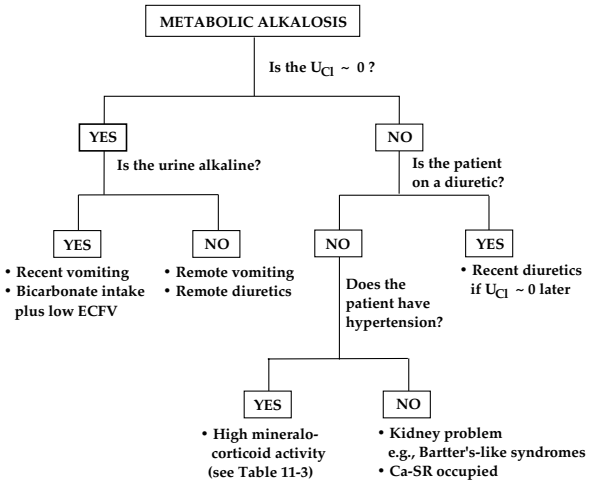
Urine electrolytes in the differential diagnosis of metabolic alkalosis

Urine 'lyte	With Low ECFV	Rare Causes
Cl (most valuable)	• < 10 mmol/l unless on diuretics	• > 20 mmol/l
Na	• < 20 mmol/l unless recent vomiting, diuretics	• > 20 mmol/l
K	• May be high if distal Na delivery without Cl (recent vomiting)	• Usually high as aldosterone is acting

Flow chart 11-3

Diagnostic approach to the patient with Metabolic Alkalosis

Ca-SR = calcium-sensing receptor in the loop of Henle.



4. Clinical evaluation

Most patients will have ECF volume contraction due to vomiting or diuretics. Patients may not admit to either vomiting or diuretic intake; be suspicious of paramedical people or those concerned about their body image

.

The presence of hypertension is an important observation; it usually signals primary hyperaldosteronism, renal artery stenosis, malignant hypertension, renin producing tumour or exogenous or endogenous compounds with mineralocorticoid actions.

TABLE 11-3

CAUSES OF METABOLIC ALKALOSIS

Abbreviation: DRA = down-regulated Cl/HCO_3 exchanger in adenoma/adenocarcinoma; ECF = "effective" circulating volume

- **Causes usually associated with a contracted ECF**
  - Low U_{Cl} (unless a diuretic is acting)
    - Loss of gastric secretions (e.g., vomiting, nasogastric suction)
    - Remote use of diuretics
    - Delivery or non-reabsorbable anions plus a reason for Na avidity
    - Posthypercapnia
    - Loss of HCl via lower GI tract (e.g., congenital Cl loss, acquired DRA)
  - Persistent high U_{Cl}
    - Current diuretic use
    - Bartter's or Gitelman's syndrome

- **Causes associated with an expanded ECF**
  - Large reduction in GFR (ESRD) plus a source of HCO_3
  - Enhanced mineralocorticoid activity
    - Primary aldosteronism
    - Secondary hyperaldosteronism (examples include renal artery stenosis, malignant hypertension, renin-producing tumor, low effective blood volume plus an alkali load)
    - Endogenous or exogenous mineralocorticoids, licorice ingestion, ACTH-driven mineralocorticoid secretion

- **Causes that were difficult to classify with respect to ECF volume**
  - Hypomagnesemia

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5. Diagnostic approach (Flow Chart 11-3 & Table 11-3)

II. ILLUSTRATIVE CASE

CASE 11-1

Metabolic alkalosis due to the selective deficit of HCl

Please explain the basis for the urine electrolyte excretion pattern in a subject who has chronic metabolic alkalosis induced with selective depletion of HCl while studied in a clinical research center (Figure 11-3). When the deficit of Cl was present for more than one week, the U_{Cl} was zero mmol/l. There was no detectable change in the ECF volume. Before answering the questions below, perform a clinical analysis of these data.

Questions:

- **What does the loss of HCl represent in ECF terms?**
- **How was electroneutrality maintained in the ICF compartment?**
- **What anion was produced along with the H^+ that entered cells?**
- **What are the issues for therapy?**

Discussion of Case 11-1

In the clinical approach, begin by examining the left side of the Flow Chart 11-3.

Step 1. Is the $U_{Cl} \sim 0$?

A $U_{Cl} \sim 0$ indicates that the 'effective' ECF volume is low. Therefore proceed to the left side of the Flow Chart.

Step 2. Is the urine alkaline?

Yes, because the urine pH is ~ 7. Therefore suspect recent vomiting or an input of $NaHCO_3$ plus a contracted ECF volume. The diagnosis was removal of HCl. At this point, the physiologic analysis begins and the questions posed at the outset will be addressed.

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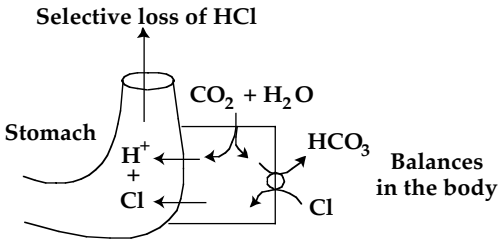
What does the loss of HCl represent in ECF terms?

As shown in Figure 11-3, there is a loss of Cl and a gain of HCO_3 in equimolar amounts.

Figure 11-3

Effect of selective depletion of HCl

The loss of HCl results in a loss of Cl and an equimolar gain of HCO_3 in the ECF compartment as shown in the far right portion of this figure.



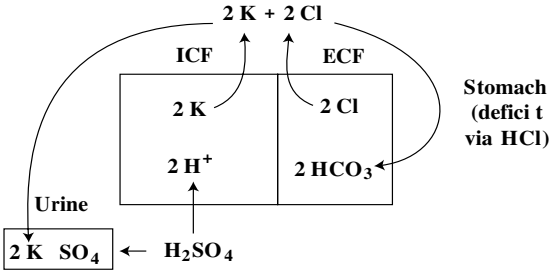
How was electroneutrality maintained in the ICF compartment?

The major site of the deficit of K is from the ICF compartment (Figure 11-4). To achieve electroneutrality, there must be an equimolar gain of a cation in the ICF compartment (Na and/or H^+) or a loss of K with an intracellular anion (phosphate for the most part, but there was no deficit of phosphate). Moreover, if an appreciable quantity of Na entered cells when K was lost, the ECF volume would have decreased and there would no longer be electroneutrality in the ECF compartment. Because of the need for electroneutrality, the obvious candidate is a gain of H^+ in the ICF compartment (Figure 11-2) .

Figure 11-4

Electroneutrality in the ICF and ECF compartments

With a deficit of KCl and metabolic alkalosis, there is a gain of HCO_3 in the ECF compartment and H^+ in the ICF compartment, but different routes are used.



What anion was produced along with the H^+ that entered cells?

H^+ are produced in normal metabolism when sulphur-containing amino acids are oxidized to produce H_2SO_4 (Figure 11-1). The physiological response is to excrete NH_4 with the SO_4 because an acid load augments the renal excretion of NH_4. This normal pattern of physiology cannot occur initially when there is a selective deficit of HCl because the resulting alkalemia raises the pH of PCT cells and thereby inhibits the production of NH_4. Therefore SO_4 is excreted in the urine with a cation other than H^+ (due to the low pK of H_2SO_4), but the cation is not NH_4 (due to alkalemia) or Na (balance data). Hence a loss of K in the urine was the means of achieving overall electroneutrality (Figure 11-1).

What are the issues for therapy?

(i) KCl

It is obvious that KCl must be given to replace the KCl deficit. When K and Cl are retained, K enters the ICF compartment in conjunction with the net transfer of H^+ to the ECF compartment. These exported H^+ combine with HCO_3 to form H_2O and CO_2. After the CO_2 is exhaled, the intracellular acidosis and extracellular alkalosis are corrected. Cl remains in the ECF compartment replacing the deficit, and this preserves electroneutrality.

(ii) NaCl

NaCl is the correct treatment for a deficit of NaCl. NaCl cannot be the sole replacement therapy for a deficit of KCl because Na cannot replace a deficit of K. Notwithstanding, a significant number of patients who were treated with NaCl plus their usual diet did ultimately replace their K deficit because dietary K was retained while extra Na from NaCl was excreted along with the anion that accompanied K in the diet.

(iii) Summary

The deficits of Cl and K did not occur simultaneously or via the same route. The loss of Cl was from the GI tract in the form of HCl. This resulted in a gain of HCO_3 in the body. The excretion of K occurred in the urine with a sulphate anion from H_2SO_4 formed during the metabolism of sulfur-containing amino acids. Thus this deficit of K was associated with a gain of H^+ in the body. Since the source of urinary K was from the ICF compartment, there was a net shift of H^+ into and K out of cells. If the deficits of K and Cl were equal, the overall gain of HCO_3 in the ECF would be equal to the gain of H^+ in the ICF compartment. Hence there would not be a total body surplus

of HCO_3; rather there was an intracellular H^+ gain and an extracellular HCO_3 gain of the same magnitude. In addition, there was an appropriate renal response that prevented the excretion of HCO_3 with Na or K in the urine.

(iv) Note

Please go to Chapter 14 to examine more sophisticated cases with metabolic alkalosis. To understand their pathophysiology, one must use principles of integrative physiology.

CLINICAL PEARL

The above calls into question the standard approach of calling metabolic alkalosis a 'selective' Cl-depletion type (rather than a KCl depletion type) or believing it is saline-responsive by simply looking at the fall in P_{HCO3} when the ECF volume is over-expanded by the administration of excessive amounts of NaCl (Table 11-1, note the large positive balances for Na and Cl). Furthermore, appreciable bicarbonaturia need not occur during correction of this type of metabolic alkalosis because there is little if any net surplus of HCO_3 as compared to H^+ in the body

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CHAPTER 12

RESPIRATORY ACID-BASE DISORDERS

I. ESSENTIAL POINTS

1. Definition

In respiratory acid-base disorders, the arterial and/or the venous Pco_2 is/are too high or too low to meet the body's needs. There are two types of respiratory acidosis.

The ventilatory form is present when the arterial Pco_2 is > 40 mm Hg in normal subjects. In metabolic acidosis, the expected arterial Pco_2 is 40 – $\downarrow P_{HCO3}$ from 25 mmol/l.

The tissue form is present when the venous Pco_2 is too high; this latter form is due to slow blood flow and/or an increased production of CO_2. For this, one needs to extract more O_2/L of blood yielding more CO_2/L.

2. Ventilatory response to a pH change

This response ignores the tissue form of respiratory acidosis. To assess this, measure the venous Pco_2.

- In acute respiratory acidosis, the P_{HCO3} will remain close to 25 mmol/l and the plasma $[H^+]$ will rise almost 1 nmol/l/mm Hg rise in Pco_2.
- In chronic respiratory acidosis, remember 0.3: both the P_{HCO3} (mmol/l) and $[H^+]$ (nmol/l) rise 0.3/mm Hg rise in Pco_2.
- In acute respiratory alkalosis, the changes are almost the same as in respiratory acidosis but opposite in direction (almost no change in P_{HCO3} and a 1 nmol/l fall in plasma $[H^+]$/mm Hg fall in Pco_2.
- In chronic respiratory alkalosis, the plasma $[H^+]$ remains quite close to normal. The P_{HCO3} falls ~ 0.5 mmol/l/mm Hg fall in arterial Pco_2.

3. Diagnosis

Integrate the clinical and lab findings: Use clinical criteria to determine if an acute respiratory disorder is present. Compare the change in Pco_2 to the quantitative change in plasma $[H^+]$ and P_{HCO3}.

Alveolar – arterial (A-a) Pco_2 difference: This is < 15 mm Hg, but it is also age-dependent. Be careful, there are many drawbacks. An increased A-a difference suggests that there is underlying lung disease.

4. Clinical evaluation

In respiratory alkalosis, look for a serious underlying disorder.

II. QUESTIONS TO ASK OF THE PATIENT WITH A RESPIRATORY ACID BASE DISORDER

1. Is this an acute or chronic disorder?

Answer: This is based on clinical findings.

2. Is this a simple acid-base disorder?

Answer: Use the Rules to Memorize listed above and your clinical impression to decide.

3. Is the HCO_3 buffer system available to buffer a H^+ load?

Answer: Measure the venous Pco_2 and estimate if for other organs.

4. Is the basis of respiratory acidosis due to intrinsic lung disease?

Answer: Use the A – a difference; high values suggest lung disease whereas values < 15 mm Hg suggest a neurological or muscular cause for hypoventilation with some exceptions.

III. CASE TO EVALUATE YOUR CLINICAL EXPERTISE

CASE 12-1

My Pco_2 is 40 mm Hg

The following laboratory data were being interpreted on rounds. The focus was on the Pco_2 of 40 mm Hg.

Parameters		Plasma
pH		7.20
P_{HCO3}	mmol/l	15
Pco_2 (arterial)	mm Hg	40
Anion gap	mEq/l	12

Questions

- **What is the acid base disorder?**
- **What is the leverage for therapy?**
- **Can you guess the history?**

Discussion of Case 12-1

What is the acid base disorder?

The patient has a low pH and P_{HCO3}; therefore metabolic acidosis is present. In this setting, the arterial Pco_2 should = 40 - fall in P_{HCO3} from 25 mmol/l or in this case 40 - 13 or 27 mm Hg. The arterial Pco_2 is 40 mm Hg, therefore there is also a ventilatory form of respiratory acidosis.

What is the leverage for therapy?

We do not know how quickly the Pco_2 will change so we must understand why the Pco_2 is higher than expected. If the Pco_2 were the expected 27 mm Hg, the plasma $[H^+]$ would be 50 nmol/l (pH 7.30). Therefore simply improving ventilation will remove the immediate threat of acidemia and protein-bound H^+ very quickly.

Can you guess the history?

The patient needs a cause for metabolic acidosis with a normal plasma AG and a cause for hypoventilation. There are many possibilities but in this case, the patient suffered from diarrhoea and severe hypokalemia (causing muscular weakness and hypoventilation).

IV. ALVEOLAR MINUS ARTERIAL PO_2 DIFFERENCE

1. Clinical aspects

It is beyond the scope of this text to discuss the pulmonary mechanisms, details of energy metabolism and problems with carriage of oxygen by hemoglobin. Nevertheless, some of these factors are described succinctly in the appendix to this chapter.

2. Causes for low delivery of O_2

These can be evaluated simply; a lung problem will present if there is a low arterial Po_2, a blood problem can be recognized by a low or abnormal hemoglobin and a problem where delivery is inadequate to

match needs can be identified by finding a circulatory problem and a very low mixed -venous Po_2.

3. Definition of the A-a difference

The Po_2 in alveolar air is virtually identical to the Po_2 of arterial blood in normal subjects, but it will be higher than the Po_2 of arterial blood if blood could pass from the pulmonary artery to the pulmonary vein without perfusing alveoli that have had a good exchange of air. Rarely, there might be a barrier to diffusion of oxygen from alveolar air to the capillaries in lungs.

4. Problems with the A-a difference

This section is considered succinctly here (see Halperin and Goldstein in suggested reading for a more detailed consideration).

A Consider Problems Originating in Arterial Blood

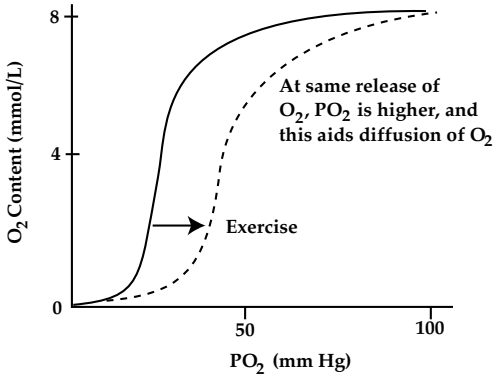
(i) Role of the Sigmoid curve

We examine the Po_2 instead of the O_2 content in blood (the sigmoid curve in Figure 12-1). A decrease in the content of O_2 in arterial blood of 0.8 mmol/l can be projected onto the Po_2 scale in two situations (Figure 12-2):

FIGURE 12-1

Hemoglobin-O_2 saturation Vs Po_2

The content of O_2/L of blood (or the saturation of hemoglobin with O_2) is depicted on the Y-axis and the Po_2 is on the x-axis.



(a) Assume that the alveolar Po_2 was 100 mm Hg

The content of O_2 bound to hemoglobin would fall by 10% (0.8/8 mmol O_2). Now if these results were expressed in Po_2 terms, the new arterial Po_2 would be ~ 70 mm Hg and cause an A-a difference of 30 mm Hg.

(b) Assume that the alveolar Po_2 was 50 mm Hg

Consider a decrease of 0.4 mmol of O_2/l of arterial blood in this second patient (Po_2 50 mm Hg, 6 mmol O_2/litre). A decrease of 0.4 mmol will cause a 13.3 Vs a 10 % reduction in O_2 content (0.8 Vs 6 mmol O_2/l), but a smaller A-a Po_2 difference (4 mm Hg) owing to the starting point on the Po_2/hemoglobin saturation curve (Figure 12-2). Thus the difference in A-a Po_2 (30 Vs 4 mm Hg) depends in part on the Po_2 in arterial blood.

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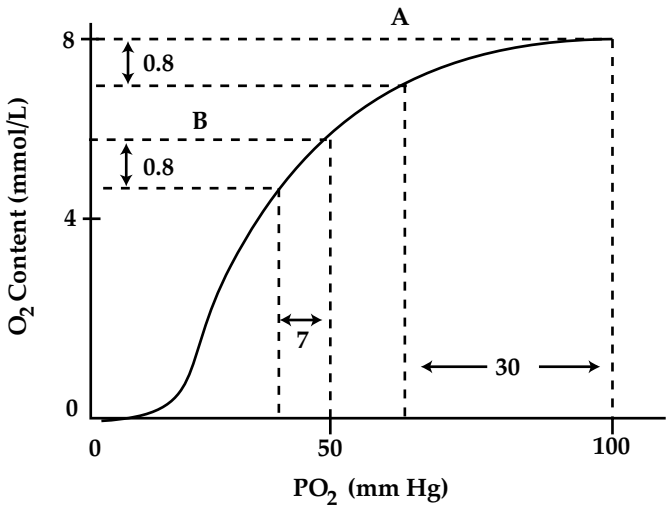
FIGURE 12-2

A-a Difference with different P_aO_2

The content of O_2/L of blood is depicted on the Y-axis in mmol/l. In both examples A and B, 0.8 mmol of O_2 is extracted per L of blood. The PO_2 in blood is shown on the X-axis in mm Hg. Because of the S-shaped curve, note that the (A-a) PO_2 difference will be much larger when the alveolar PO_2 is 100 mm Hg (A) as compared to when there is a lung problem and the alveolar PO_2 is ~ 50 mm Hg (point B).



(ii) Content of oxygen in shunted blood:

Two examples will be considered.

(a) Consider a patient in whom arterial blood has 8 mmol of O_2/l before the shunt. Now 10% of the blood in the pulmonary vein is delivered into the pulmonary artery bypassing aerated alveoli. Further, the content of O_2 in the blood in the pulmonary artery, is 60% of normal, or 4.8 mmol/l. After this 10% shunt, arterial blood would contain 7.7 mmol of O_2/l (0.9 L with 8 mmol/l + 0.1 L with 4.8 mmol/l).

(b) Assume that the blood in the pulmonary artery contains 30% of its capacity for oxygen or 2.4 mmol O_2/l. After the 10% shunt, the arterial blood has 7.4 mmol O_2/l instead of 8 mmol. Although these differences in content of O_2 seem small (7.7 Vs 7.4 mmol O_2/l), their impact on the Po_2 of arterial blood is much larger. The new Po_2 of arterial blood in the first instance would be 95 mm Hg whereas it would be 70 mm Hg in the second example (91% saturated). The corresponding A-a differences would be 5 and 30 mm Hg.

(iii) Cardiac output

Consider the volume of a shunt to be 0.1 L/min. If this were mixed with 5 L of cardiac output, the shunt would be 2% by volume. In contrast, with a very low cardiac output of 2 L/min, the same shunt would be 5% by volume. The net effect on the A-a difference would be much larger with the lower cardiac output.

B. Metabolic issues

When the A-a is calculated, assume that the RQ is 0.8 (patient is oxidizing 50% of calories from carbohydrate and 50% from fat). This in effect means that for every 4 mmol of CO_2 produced, 5 mmol of O_2 were removed from alveolar air.

You may now ask, "How much would the error in A-a difference be if a normal subject oxidized only carbohydrate or only fat Vs a mixed meal?" If one now substitutes 0.7 for 0.8 as the RQ (fat is the sole fuel oxidized, i.e., fasting or diabetes mellitus in poor control), the calculated value for the A-a difference would rise by 6 mm Hg. Similarly, if the RQ were 1.0 (oxidation of carbohydrate, i.e., after a meal rich in carbohydrate, the RQ can exceed 1.0 by an appreciable amount), the A-a Po_2 difference would now be 10 mm Hg lower than if one used the arbitrary value of 0.8 for the RQ.

C Normal values

It is dangerous to use usual or normal values as these depend on the volume of shunt, the volume of blood it is diluting and the content of oxygen in the blood that is shunted.

V. CASE TO EVALUATE YOUR CLINICAL EXPERTISE

CASE 12-2

Why has the A-a difference fallen?

An 87-year old lady with chronic obstructive lung disease (COPD) and congestive heart failure was treated with a diuretic and lost 5 L of ECF (isotonic NaCl). Her mental state deteriorated following treatment. On physical examination, she was obtunded; she had all her previous findings of COPD except that her edema disappeared. A summary of the lab results is provided below. She now has an extremely high Pco_2 on room air. There was little rise in net acid excretion with the diuresis.

Parameter		Steady State	Post Diuretic
pH		7.32	7.37
Pco_2	mm Hg	54	85
Po_2	mm Hg	50	39
A-a	mm Hg	23	5
P_{HCO3}	mmol/l	30	44
P_K	mmol/l	4.1	3.1
Creatinine	µmol/l (mg/dl)	57 (0.7)	66 (0.8)

Questions:

- **What are the acid-base disorders after diuresis?**
- **Why did the P_{HCO3} rise so markedly?**
- **Why did the A-a difference fall?**
- **What should the therapy be?**

Discussion of Case 12-2

What are the acid-base disorders after diuresis?

The major acid-base disturbance before therapy was chronic respiratory acidosis. Two major changes occurred with diuresis, a large rise in P_{HCO3} (metabolic alkalosis) and Pco_2 (acute on chronic respiratory acidosis).

Why did the P_{HCO3} rise so markedly?

The elevation in the P_{HCO3} was not due to intake of $NaHCO_3$ or excretion of net acid. Hence it may be due to an internal shift of H^+ when K exited from cells (minor) or a loss of ECF volume, (i.e., the same content of HCO_3 in a smaller ECF volume, a major effect). In fact, this is a "contraction metabolic alkalosis".

Why did the A-a difference fall?

The major problem here is the use of the Po_2 scale Vs O_2 content or saturation of hemoglobin scale (Figure 12-1). A larger fall in Po_2 of 23 mm Hg (73 to 50 mm Hg) before therapy than after diuresis of 5 mm Hg (44 to 39 mm Hg) really represents a smaller decline in content of O_2 in blood (see Figure 12-2; project values for Po_2 (X axis) onto the saturation of hemoglobin with O_2 on Y axis). Hence the Po_2 scale is misrepresenting the large A-a difference in O_2 content.

What should therapy be?

The aim of therapy is to lower the Pco_2 and P_{HCO3}. The first step was to replace the deficit of K to see if ventilation would improve (it did not). The next step was to administer 250 mg acetazolamide, a carbonic anhydrase inhibitor diuretic, to induce a degree of bicarbonaturia; losses of K in the urine were replaced. With bicarbonaturia, the Pco_2 and P_{HCO3} returned to her steady-state values within 24 hours, the patient felt better and was discharged. The other option was to administer HCl (NH_4Cl) to titrate her P_{HCO3}; since CO_2 production will rise, this mode of therapy was not selected.

VI. ADDITIONAL FACTS

Rate of consumption of O_2

Consumption of fuels in the presence of oxygen regenerates the ATP needed to perform biological work. The amount of O_2 needed by the average adult at rest is 12 mmol/min. With a P:O ratio of 3:1, and two atoms of O per molecules of O_2, 72 mmol of ATP are needed/min.

Units:

There are many units to describe O_2:

(i) Po_2: Pressure needed to dissolve a given quantity of oxygen in water.

Advantage: Critical for diffusion of O_2 in the lungs and from blood to mitochondria

Drawbacks: Only a minute amount of O_2 (< 0.1 mmol/l) is dissolved in blood (8 mmol/l). The relationship between Po_2 and content of O_2 in blood is not linear (Figure 12-1). Therefore Po_2 is not a measure of the content of O_2 in blood.

(ii) Content of O_2: The amount of oxygen in blood (or air).

Molar terms: This reveals how much O_2 is present in a given volume of blood. This value can be calculated from: Hemoglobin (Hgb) (140 g/l of blood, molecular weight ~ 70,000, or ~ 2 mmol Hgb/l).

Stoichiometry: 4 O_2 bound per hemoglobin so ~ 8 mmol O_2/l of blood.

Volume terms: The volume of O_2 in ml per volume of blood. These units were useful when older techniques (volumetric measures) were used. Molar terms are superior to think in energy metabolism terms.

Integration: Of interest, since air is 21% O_2, and the molar volume is 22.4 L at STP, there is close to 8 mmol of O_2/l of air. Further, since alveolar ventilation and cardiac output are both ~ 5 L/min at rest, delivery of O_2 by lungs and heart are 40 mmol/min at rest. This means that the extraction of O_2/l of blood and air are equal.

SECTION IV

CASES FOR REVIEW

CHAPTER 13

FLUID AND ELECTROLYTE CASES

In this chapter, I selected several cases with fluid and electrolyte problems as a central feature to emphasize important clinical points that were not highlighted in Chapters 1 – 7.

I. POLYURIA

CASE 13-1

Polyuria by Inference

The only information supplied is that the P_{Na} is 160 mmol/l.

Question

What you know for sure about a patient who has a P_{Na} of 160 mmol/l?

Suggested reading

Halperin ML, Bichet DG and Oh MS. Integrative physiology of basal water permeability in the distal nephron: implications for the syndrome of inappropriate secretion of antidiuretic hormone. *Clin Nephrol* 56: 339-345, 2001.

Discussion of the Consult

What you know for sure about a patient who has a P_{Na} of 160 mmol/l?

(i) ICF volume

Since the P_{Na} is inversely related to the ICF volume in the absence of a gain in ICF osmoles (seizure, rhabdomyolysis), a P_{Na} of 160 mmol/l indicates that the cell volume is reduced.

(ii) Thirst

The expected response to a high P_{Na} is thirst. In fact the urge to drink is so strong that hypernatremia will only occur if there is a defect in the thirst mechanism, an inability to get water, and/or a

communication problem where the patient cannot tell those around that thirst is present.

(iii) Basis for hypernatremia

As part of the story, you should expect to see a reason for a positive balance for Na and/or a negative balance for water.

Conclusion

You will not be surprised to find out that the patient is a newborn, cannot communicate that he is thirsty, his intake had an unusually high Na concentration, and that polyuria was present. There were no seizures or rhabdomyolysis. A more detailed history in Case 13-1 is provided below.

More detailed history

A 1-week old newborn weighed 4 kg at birth. He was brought to the Emergency Department because of failure to thrive. He is extremely unhappy and cries very frequently. His mother states that she has been having trouble with breast-feeding, but does not elaborate on the nature of the difficulty. She noted that the baby has had a very 'good' urine output until today; now there is little urine output. On physical examination, the baby has a contracted ECF volume. He does not have a fever and is not sweating. On laboratory examination, there were three major findings: a P_{Na} of 160 mmol/l, a $P_{Glucose}$ of 2.5 mmol/l (45 mg/dl), and his P_{urea} is 20 mmol/l (56 mg/dl). There was no urine available for analysis.

Suspecting a problem with the mother's milk, the intern sent a sample for analysis. Its Na concentration was very high (70 mmol/l instead of the usual 17 –15 mmol/l).

Questions

- **What is the major reason for his high P_{Na}, a positive balance for Na or a negative balance for water?**
- **What might the role of basal water permeability be in integrative physiology in the newborn?**
- **What are the medical emergencies and what are the most important considerations for therapy?**

Discussion of Case 13-1

What is the major reason for his high P_{Na}, a positive balance for Na or a negative balance for water?

Positive balance for Na

There is qualitative information to suggest that this patient has a positive balance for Na, namely his intake had a higher Na, but we must have quantitative information to make a clinical decision. It is clear that we will not have urine data over the first week of life, so we must use a different strategy, calculate the ECF Na content by multiplying his ECF volume (use 1 L for simple math) times the P_{Na}. At birth, his P_{Na} should be equal to the maternal P_{Na} (~ 136 mmol/l) and his ECF contained 136 mmol of Na. If there were no change in his Na content in his ECF volume, the current ECF volume would have to be 136/160 or 85 % of normal. If the ECF volume was so obviously contracted on clinical grounds, his degree of ECF volume contraction probably exceeded 15 %. In any case, a positive balance of Na is not a major cause of the hypernatremia.

Negative balance for water

From the above, the cause of the hypernatremia is a deficit of water. The cause of this deficit is water loss in the sweat and the urine because there was no history of GI loss. Sweat loss is proportional to heat dissipation and there is little sweat once the ECF volume is contracted. Moreover, there was a comment that he did not sweat profusely. We were told that he had a 'good' (translate to large) urine output. To raise the P_{Na}, this urine should be poor in Na + K. Therefore suspect a water diuresis or an osmotic diuresis due to an organic osmole.

(a) Water diuresis

Newborn infants have nephrogenic DI because they cannot excrete urine with a low flow rate and a high U_{osm} in response to ADH. In molecular terms, aquaporin 2 (AQP 2) water channels are <u>not</u> inserted into the luminal membrane of the distal nephron. Nevertheless, this water diuresis does not cause a severe degree of hypernatremia because as the ECF volume falls, distal delivery of filtrate declines abruptly. This, in turn, is due to a fall in the GFR and a rise in Na reabsorption in the PCT (Figure 13-1).

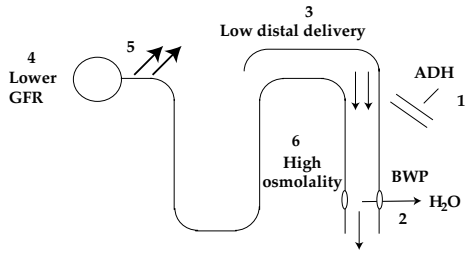
(b) Osmotic diuresis

The agent causing the water diuresis can be deduced from an examination of filtered organic osmoles. The $P_{Glucose}$ is low and therefore its filtered load will be too low to cause an osmotic diuresis. In contrast, the P_{Urea} is high enough to cause an osmotic diuresis. Nevertheless, the volume of urine cannot be too high because if distal delivery rose too much, there would be a water diuresis.

FIGURE 13-1

Water channels in the distal nephron and the excretion of electrolyte-free water

The stylized structure represents a nephron. In the newborn, ADH does not cause the insertion of AQP-2 water channels (site 1). In contrast, there are water channels in the MCD causing basal water permeability (BWP) (site 2). With a low ECF volume, distal delivery of filtrate declines (site 3), due to the contracted ECF volume and the resultant fall in the GFR (site 4) and enhanced proximal Na reabsorption with water following via aquaporin 1, ADH insensitive, water channels (site 5). In response to this contracted ECF volume water reabsorption can occur via BWP until the U_{osm} equals the interstitial osmolality (site 6).



More detailed physiology

Newborns can achieve a U_{osm} of ~ 800 mOsm/kg H_2O when their ECF volume is very contracted. You can deduce that they must have water channels in the medullary collecting duct in this setting to raise their U_{osm} so high. The water channels are called basal water channels and they have a low capacity to reabsorb water. Hence they cause a marginally lower water diuresis when distal delivery is high, but they can prevent a large water diuresis when distal delivery declines markedly (Figure 13-1).

What might the role of basal water permeability be in integrative physiology in the newborn?

Having a physiological form of nephrogenic DI early in life along with a relatively high basal water permeability could operate as a

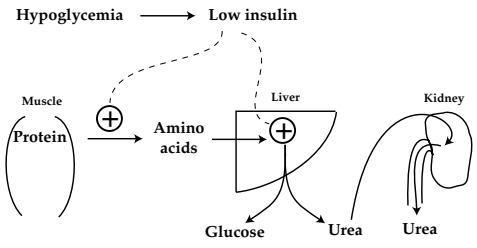
safeguard when viewed from a larger, more integrated perspective. For example, hypoglycemia poses a unique threat in the first month of life. At this time, the metabolic requirements of the brain are relatively large, the availability of circulating ketoacids is low, and the size of storage pools of glucose is limited. Hence the newborn needs a frequent exogenous supply of sugar in milk to avoid neuroglucopenia. To have the highest concentration of lactose, milk must have very low electrolyte concentrations because the osmolality of milk is similar to plasma. Once the sugar from milk is oxidized, the newborn will be faced with a large water load—about half of this water is excreted in the urine. Therefore a well-developed renal diluting mechanism is also essential.

Having a neonatal renal concentrating system that does not respond to ADH could provide several advantages. First, if the infant had a non-osmotic stimulus for the release of ADH, acute hyponatremia could develop. Second, perhaps the renal non-responsiveness to ADH helps avoid hypoglycemia. Since the source of milk sugar is the mother, the excretion of a large volume of dilute urine could lead to both thirst and a 'wet diaper' producing signals for early arousal and a 'call' for a source of sugar. Third, basal water permeability could limit the magnitude of this water diuresis by permitting a fall in the urine volume when the effects of a low ECF volume are superimposed on the low GFR of the newborn (Figure 13-2). Thus it could account for the high U_{osm} once enough water was lost, making this a safer signal system.

FIGURE 13-2

Basis for a urea-induced water diuresis

A low $P_{Glucose}$ causes a low level of insulin in plasma. This hormonal setting leads to net protein breakdown in muscle, the release of amino acids and their conversion to glucose plus urea in the liver. With a higher filtered load of urea, distal delivery of filtrate rises, increasing the excretion of a larger volume of urine with a low Na concentration because of the limited capacity to reabsorb water by BWP water channels in the MCD (see Figure 13-1).



What are the medical emergencies and what are the most important considerations for therapy?

There are three potential medical emergencies, hypoglycemia, a low effective blood volume, and the low ICF volume. You must give glucose to feed the brain and stop the catabolism. The speed with which you re-expand the ECF volume depends on a more detailed examination of the degree of ECF volume contraction. Use isotonic saline for this purpose. While it is important to re-expand his ICF volume, do not do this too quickly because of the possible danger of osmotic demyelination in a chronic setting.

CASE 13-2

Water diuresis with an emphasis on therapy

A 32-year-old healthy male was injured l and has a basal skull fracture. His urine output is ~ 4 L/day, and this is a consistent finding. It was associated with thirst, a P_{Na} 143 mmol/l, a 24-h urine osmolality of 220 mOsm/kg H_2O, and undetectable plasma ADH levels. When the patient was given dDAVP, his urine flow rate decreased to 0.5 ml/min and the U_{osm} rose to 900 mOsm/kg H_2O. Two other facts were important. First, he was thirsty. Second, his sleep was not interrupted by a need to urinate. In fact his U_{osm} was 425 mOsm/kg H_2O in overnight urines. Moreover, an infusion of hypertonic saline led to the release of ADH and the excretion of very concentrated urine.

Questions

- **Is this a water or an osmotic diuresis?**
- **What is the basis for his partial central DI?**
- **What is the best option for therapy?**

Discussion of Case 13-2

Begin by examining Flow Chart 2-1.

Step 1. What is the U_{osm}?

Since the U_{osm} was 200 mOsm/kg H_2O and the urine volume was 4 L/day, this was a water diuresis—his osmole excretion rate was 800 mosmoles/day.

Step 2. Left side. Is his P_{Na} high enough to stimulate the release of ADH?

Yes, this rules out primary polydipsia as a current diagnosis.

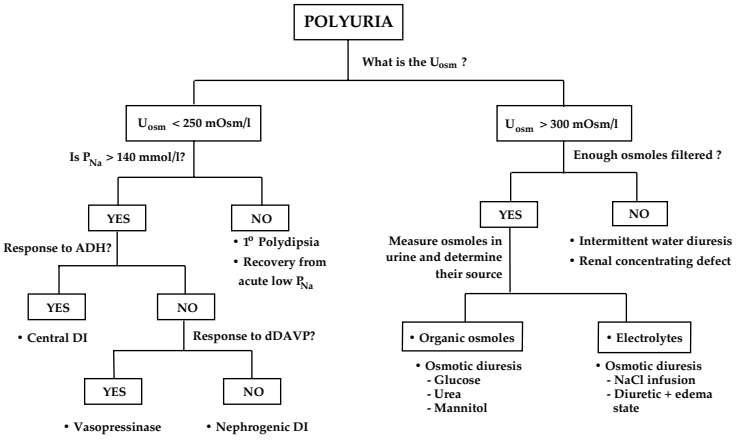
Step 3. Left side. Did he have an adequate renal response to ADH?

Yes, because when dDAVP was given, his U_{osm} rose to 900 mOsm/kg H_2O—this ruled out nephrogenic DI. This is central DI. Because his urine volume was 4 L/day, the diagnosis is 'partial central DI'. While the diagnosis of central DI was straightforward, there were two facts in the history that have not yet been interpreted.

(i) He is thirsty

Because of thirst, his osmostat and thirst center as well as the fibers connecting them appear to be functionally intact (Figure 13-3). Similarly, because he could excrete concentrated urine when his P_{Na} was 143 mmol/l overnight, his ADH release center was also functioning, but only when there was this 'stronger stimulus' for the release of ADH. Therefore a possible site for his lesion was destruction of some but not all of the fibers linking his osmostat to his ADH release center (Figure 13-3). This could also explain why polyuria was not present overnight (he stopped his oral water intake several hours prior to going to sleep). On the other hand, his U_{osm} was 90 mOsm/kg H_2O during the daytime. This suggests that primary polydipsia was present while he was awake. Its basis probably reflects a 'learned behavior' to avoid the very uncomfortable feeling of thirst. This interpretation, although speculative, provides a rationale to understand the natural history of, and treatment for his partial central DI.

FLOW CHART 2-1



(ii) He was able to sleep for 8-hr without having to void

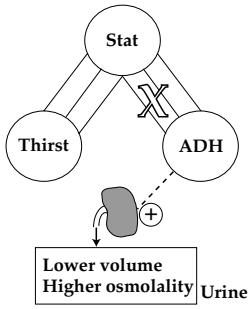
This is a surprise because 8-hr is 1/3 of a day and 1/3 of this 4 L urine volume is 1.33 L; this exceeds normal urinary bladder capacity and suggests that his urine flow was likely lower during the night, either because of a higher U_{osm} or a lower osmole excretion rate (equation below). When measured, his overnight U_{Osm} was 425 mOsm/kg H_2O. This challenged the diagnosis of partial central DI, or at least our concept of what that diagnosis really means.

Urine volume = # mosmoles excreted/U_{osm}

FIGURE 13-3

Lesion in the CNS causing central DI

The 3 circles represent areas in the hypothalamus, the top one labeled 'stat' is the sensor ('osmostat'), the circle on the lower left is the thirst centre and the circle on the lower right is the ADH release centre. The X symbol represents the hypothetical severing of some but not all of the fibres connecting the 'osmostat' to the ADH release centre.



What is the best option for therapy?

A higher P_{Na} could stimulate the release of ADH. There are 2 ways to raise the P_{Na}, Na input or a water deficit. The patient selected oral NaCl tablets to raise his P_{Na} to control his daytime polyuria because of its rapid and reproducible onset as well as the fact that there would not be a danger of acute hyponatremia if he drank an excessive quantity of water while dDAVP was acting. In contrast, he selected water deprivation to raise his P_{Na} overnight to permit him to have undisturbed sleep. He was able to tolerate the thirst that developed.

CLINICAL PEARL

- *The use of multiple spot urines with simultaneous P_{Na} values led to a more correct diagnosis of the basis of his polyuria. Of greater importance, better treatment strategies were designed that suited the patient.*

Suggested reading

Kamel KS, Bichet DG and Halperin ML. Studies to clarify the pathophysiology of partial central diabetes insipidus. *Am J Nephrol* 37: 1290-1293, 2001.

II. HYPERNATREMIA

This Case is presented to illustrate that Na gain is often present in patients with a water deficit.

CASE 13-3

Hypernatremia and a contracted ECF volume

A 34-year old patient began treatment recently with lithium for bipolar affective disorder. Thirst and polyuria soon became evident. On physical examination, the ECF volume appeared to be normal. In most 24-h periods, his urine volume is 4 L. Laboratory data are provided below.

		Plasma	Urine
Na	mmol/l	146	40
K	mmol/l	4.0 15	
Cl	mmol/l	109	40
HCO_3	mmol/l	25	0
pH		7.40	5.8
Creatinine	µmol/l (mg/dl)	95 (1.1)	-
Urea (BUN)	mmol/l (mg/dl)	3 (8)	-
Glucose	mmol/l (mg/dl)	5.0 (90)	0
Osmolality	mOsm/kg H_2O	304	200

---**Questions**

- **What is the basis for the hypernatremia?**
- **Does he have primary polydipsia?**
- **What dangers do you anticipate?**

Discussion of Case 13-3

What is the basis for the hypernatremia?

(i) Gain of Na

If I assume that the ECF volume is indeed normal, one basis of hypernatremia is a gain of Na in his ECF compartment of 90 mmol (146 – 140 mmol/l x ECF volume of 15 L). The reason for the positive balance for Na is that when a water deficit first occurred, his ECF volume was decreased. This decrease stimulated the reabsorption of Na until his ECF returned to its usual value (expansion) providing the signal to excrete his daily intake of Na and come back into balance.

(ii) Deficit of water

Separate analyses are needed for the ECF and ICF compartments. We are told that there is no change in his ECF volume, so the net balance is zero in the ECF compartment. With respect to his ICF compartment, a higher P_{Na} implies that the ICF volume is reduced. In quantitative terms, the reduction is equal to the product of his normal ICF volume (30 L in this 70-kg male) times the ratio of his normal P_{Na} (140 mmol/l) divided by his current P_{Na} (146 mmol/l) or 29 L.

Normal P_{Na} x Normal ICFV = Current P_{Na} x Current ICFV

(iii) Overall

He has a positive balance of 90 mmol Na in his ECF and a deficit of 1 L of water in his ICF compartment.

Does he have primary polydipsia?

Thirst is a very uncomfortable feeling and patients 'learn' to drink to avoid thirst. Thus during the day, they often have a lower P_{Na} due to primary polydipsia whereas they have simple nephrogenic DI overnight with a high P_{Na} in the morning. Hence, the P_{Na} is not consistently high and thus is not a good diagnostic test for this diagnosis.

What dangers do you anticipate?

The patient will be in danger of developing hypernatremia if his water intake is restricted. A common cause is when he cannot get to water or if his thirst is 'amputated'—e.g., general anaesthesia.

III. HYPONATREMIA

The first Case is presented to illustrate the value of performing a tonicity balance to understand what is actually happening. I emphasize, that there is no treatment of hyponatremia that is common for all patients.

CASE 13-4

Wrong for a number of reasons

Calculations can help to avoid errors in therapy. The following case illustrates the importance of a quantitative analysis.

A 67-year old male (60 kg, 30 L total body water (TBW)) is currently having prostate surgery (TURP, bladder irrigation with isosmolar glycine). A generalized tonic-clonic seizure developed very early after surgery began. Of note, his blood pressure had fallen suddenly to very low levels and the patient had become very agitated before the seizure.

		Before surgery	15 min later
Na	mmol/l	140	104
K	mmol/l	4.8	4.2
Cl	mmol/l	100	81
Glucose	mmol/l (mg/ml)	5.0 (90)	10 (180)
Osmolality	mOsm/kg H_2O	290	290

Questions

- **What is the basis for his hyponatremia?**
- **Should he receive hypertonic saline?**

Suggested reading

Agarwal R and Emmett M. The post-trasurethral resection of prostate syndrome: theraputic proposal. *Am J Kidney Dis* 24: 108-111, 1994.

Discussion of Case 13-4

What is the basis for his hyponatremia?

The P_{Na} can fall because of a negative balance of Na and/or a positive balance of water. Because he had an IV infusion of isotonic saline and no time for a huge deficit of Na to occur, this is water gain type of hyponatremia. You must now decide how large was the positive balance for water and where this water is located.

Water shift from the ICF

This requires the addition of hyperosmolar solute to the ECF, but only isotonic solutions were infused. He was not given hyperosmolar mannitol and he did not have a sufficiently high $P_{Glucose}$ to cause a water shift from cells. Moreover, his P_{osm} was not elevated. Isosmolar glycine does not cause a shift of water <u>out</u> of his ICF.

Water accumulated and distributed in total body water

If his P_{Na} fell by ~ 1/4 (36/140 mmol/l) due to a gain of water, the positive balance for water would have to be close to 7.5 L or 0.5 L/min—highly unlikely.

Water accumulated and was restricted to the ECF compartment

Factors influencing the degree of hyponatremia are the volume of lavage fluid absorbed (number of veins cut and the hydrostatic pressure in the bladder), the cardiac output (volume of 'diluent'), and where blood was sampled (before the capillaries so it would have a much lower P_{Na} because no mixing occurred with interstitial fluid). To lower the P_{Na} by 1/4, he would need a positive balance of close to 2.5 L (close to 167 ml/min); this is also unlikely.

Water accumulated and was restricted to the plasma volume

In this case, the positive balance would have to be 0.75 L if the original plasma volume was 3 L. You are not dealing with a steady state.

Should he receive hypertonic saline?

Hyponatremia is acute and a seizure occurred—a knee-jerk response is to treat this as an emergency requiring hypertonic saline. Before doing that, establish where the blood was drawn from. Look at the time course and the quantitative analysis. All of the latter indicate another possible cause for the seizure.

Although hyponatremia was acute and a seizure were present, a direct relationship between these two observations does not stand up to a quantitative analysis for a cause and effect link due to expansion of the ICF volume. Perhaps the seizure was due to hyperammonemia (a consequence of metabolism of glycine and the liver problem). If true, the best treatment would be to withhold glycine. This impression would be strengthened if blood were drawn from an artery.

CASE 13-5

Hyponatremia with a contracted ECF volume

This Case is presented to illustrate that at times, therapy for the patient with hyponatremia must be creative to meet the needs of that patient.

A thin, 63-year old woman (weight, ~ 40 kg) had a CVA that left her with residual paralysis. Her family cares for her at home; she is fed by stomach tube. The salt content in this diet was reduced in the past several weeks because of concern about a rise in blood pressure. Prior to this change in diet, her P_{Na} was normal. Over the past 4 weeks, she became progressively less lucid, and in the past few days, she was difficult to rouse. On physical examination, her ECF volume was markedly contracted; her blood pressure was 86/44 mm Hg. Laboratory data are provided below. The plasma cortisol level was in the mid-normal range.

		Plasma	Urine
Na	mmol/l	96	23
K	mmol/l	3.9	20
Cl	mmol/l	70	18
HCO_3	mmol/l	24	-
Albumin	g/l (g/dl)	26 (2.6)	-
Creatinine	µmol/l (mg/dl)	69 (0.6)	< 1.5 (< 15)
Urea	mmol/l (mg/dl)	13.6 (38)	-
Glucose	mmol/l (mg/dl)	6.5 (117)	0
Osmolality	mOsm/kg H_2O	223	232

Questions

- **Is this chronic hyponatremia?**
- **Is hyponatremia due primarily to Na gain or water deficit?**
- **What dangers are present as therapy begins?**

Discussion of Case 13-5

Is this chronic hyponatremia?

The possibility that some of the fall in P_{Na} was due to acute hyponatremia should be evaluated. While there could be a component of acute hyponatremia, there was no acute water intake or a noticeable deterioration in neurological status in the past 24-h. Nevertheless, this is difficult to ascertain. On one hand, she is at a higher risk of brain cell swelling with a small gain in water because of her low muscle mass. On the other hand, the number of brain cells (and volume) is probably reduced due to her age and the prior CVA.

Is hyponatremia due primarily to Na gain or water deficit?

(i) Deficit of Na

A contracted ECF volume and a low P_{Na} indicate that she has a deficit of Na. Nevertheless, there are no definitive data to estimate her ECF volume in quantitative terms (this cannot be done by clinical examination).

Quantitative estimate

Even if her ECF volume were normal (7 L in this thin woman who weighs 40 kg), she would have a deficit of 308 mmol of Na (7 L X (140-96 mmol/l)). To that, one would have to add 96 mmol of Na for each L that her ECF volume was contracted. Hence her Na deficit is probably ~ 50 % of her total ECF Na content.

Conclusion: Look for a lesion that will inhibit the reabsorption of Na in major nephron segments. Adrenal insufficiency may be playing a role because her plasma cortisol should have been much higher than observed.

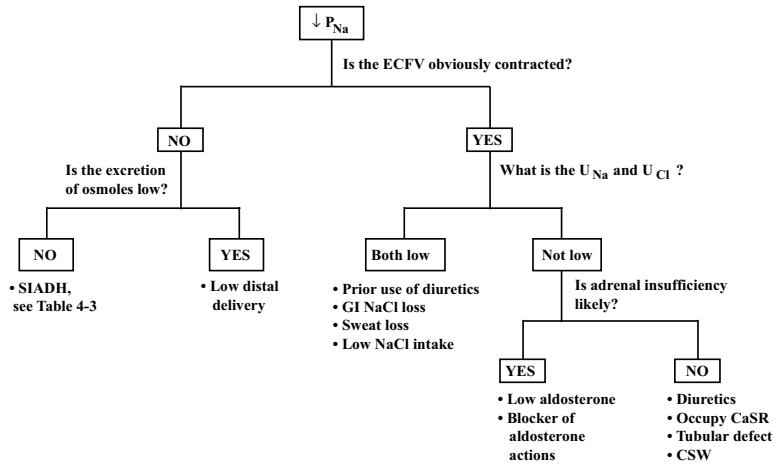
(ii) Positive balance for water

Hyponatremia indicates that there is a positive balance of water. Nevertheless, the calculation must take her very low muscle mass into account. There are insufficient data to calculate a tonicity balance so I turn to a less accurate estimate of this volume. The expected ICF volume in a 40 kg normal individual would be ~ 14 L (50 % of body weight (40 kg) = 20 L; 2/3 of which is water in the ICF compartment). Her ICF volume with a P_{Na} of 96 mmol/l would be ~ 18.4 L ((140-96 mmol/l)/140 mmol/l) X 14 L), reflecting the gain of ~ 4.4 L. There is a caveat, however, in the above estimate. Skeletal muscle accounts for ~ 50 % of total body water and she has a markedly decreased muscle mass on physical examination. If, for

simplicity, I assume that she lost 50 % of her skeletal muscle mass, her estimated ICF volume would be reduced by 5 L (50 % X 20 L of total body water). Therefore her ICF volume would be 9 L when her P_{Na} was 140 mmol/l and it would rise to only 11.8 L (9 L + 2.8 L) when her P_{Na} was 96 mmol/l ((140-96 mmol/l)/140 mmol/l) X 9 L), a gain of 2.8 L.

Conclusion: Subtracting the deficit of water from her ECF compartment (~ 2 L) yields a net gain of water of possibly < 1 L of total body water. Therefore the main reason for her low P_{Na} is a deficit of Na. Now turn to Flow Chart 4-2, which is reproduced here.

Flow Chart 4-2



Step 1. Is the ECF volume obviously contracted?

Yes, so follow the right side of this Flow Chart.

Step 2. What is the U_{Na} and U_{Cl}?

Because the patient has a very large deficit of Na, her U_{Na} and U_{Cl} should be close to nil if the renal response to the contracted ECF volume was normal; however, this was not the case. Accordingly, the reason for the salt wasting should be sought.

Step 3. Is adrenal insufficiency likely?

My initial step is to look for hyperkalemia. Although she did not have a high P_K, I am still suspicious of adrenal insufficiency because 1/3 of patients with adrenal insufficiency do not have hyperkalemia. Moreover, although her plasma cortisol level was in the normal range, the patient is under a severe stress and the plasma cortisol is low for this stimulus.

Another possible diagnosis for the large deficit of Na and Cl is occupancy of the Ca-SR by a cationic protein (notice the very low value for her anion gap in plasma). Finally, she could have a renal tubular lesion or, as a remote possibility, cerebral salt wasting.

What dangers are present as therapy begins?

(i) Marked degree of hypotension
Re-expanding her ECF volume rapidly can minimize this danger.

(ii) ODS
To prevent an initial, rapid rise in her P_{Na}, the intravenous fluids should be isotonic to her plasma. A second risk for the development of ODS is if our therapy inhibits the release of ADH and/or increases the distal delivery of filtrate. The net result would be a rapid excretion of dilute urine and thereby a rapid rise in her P_{Na}. The danger of ODS may be even more marked because she is malnourished and she may have a deficit of K.

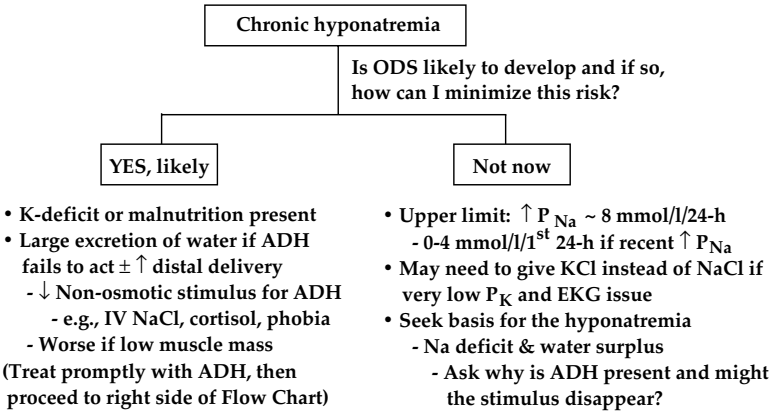
(iii) Adrenal insufficiency
It could be argued that this patient should be given cortisol on the presumption that adrenal insufficiency could not be ruled out. One should recognize that this therapy removes one stimulus for the release of ADH.

Conclusion: My initial therapy was to give ADH (has pressor effects too) or dDAVP to minimize the excretion of water because most of the emergency therapies had the danger of inducing a water diuresis if they either inhibited the release of ADH and/or increased the distal delivery of filtrate. The net result would be a rapid excretion of dilute urine and thereby a rapid rise in her P_{Na} with the danger of inducing ODS.

Flow Chart 13-1

Dangers to anticipate when therapy begins in a patient with chronic hyponatremia

For details, see text. Be careful if the patient has a condition that could predispose to the development of ODS. If present, it is safer to set a much lower upper limit for the rise in the P_{Na} and give ADH before therapy begins. A less obvious danger is if the P_{Na} might have risen in the past 24-h due to an unusual NaCl intake for example. Be cautious if a fall in ADH or a rise in distal delivery might occur because this could cause a sudden water diuresis. The risk of a sudden rise in the P_{Na} is higher if the patient has low total body water (e.g., low muscle mass). Ultimately, limit the daily water deficit by adjusting the duration between ADH doses.



CLINICAL PEARLS

- *Beware, the reason for a lack of a water diuresis can disappear. This is especially likely in a patient with negative Na balance who will be given NaCl. It is safer to begin therapy with dDAVP in this setting.*
- *Beware of the patient with a small muscle mass! These patients will have larger changes in their P_{Na} for a given change in water balance.*

CASE 13-6

Hyponatremia with a contracted ECF volume

A 9-month old developed profound diarrhoea and vomiting over several days. Upon advice from her husband, the baby was given sugar plus water. Because the baby's condition did not improve, the patient was brought to hospital. On physical findings, there was marked contraction of the ECF volume, but no other abnormalities were noted.

		Plasma
Na	mmol/l	118
K	mmol/l	3.0
Cl	mmol/l	85
HCO_3	mmol/l	20
Creatinine	μmol/l (mg/dl)	63 (0.7)
Glucose	mmol/l (mg/dl)	5 (90)

Questions

- **What dangers do you anticipate on admission?**
- **What are your options for therapy?**
- **What problems might develop during therapy?**

Discussion of Case 13-6

What dangers do you anticipate on admission?

There are three dangers on admission:

(i) Swollen brain cells.
(ii) Impending shock from loss of vascular volume.
(iii) Underlying illness (this seems to be abating at present).

What are your options for therapy

(i) Rapid re-expansion of the ECF volume.

This should be done with fluids isotonic to the patient.

(ii) Shift water out of brain cells with hypertonic saline:

This should be done rapidly **only** if the baby is seriously symptomatic (convulsions). Since water moves across cell membranes, relate administered Na to total body water. Raise the P_{Na} by less than 8 mmol/l/day. Since the baby has 4 L of water, give 32 mmol of Na, positive balance (without water) today.

What problems might develop during therapy?

The major potential danger is ODS from too rapid loss of water from brain cells. This risk can be minimized if a rapid loss of water in the urine is prevented. A water diuresis is currently being prevented by the release of ADH and/or the low distal delivery of filtrate due to the low ECF volume. Therefore ADH should be administered before a water diuresis begins (when saline is administered). Limit the P_{Na} rise to 4-8 mmol/L/day.

III. POTASSIUM

CASE 13-7

Is hypokalemia due to a Bartter's-like Syndrome?

A 27-year old female complains of weakness, but but vigorously denies vomiting, diarrhoea, and the intake of drugs. On physical examination, her blood pressure is 100/60 and there is postural drop of 15 mm Hg; JVP below the sternal angle. There is no evidence of edema. The laboratory data are provided below. Plasma aldosterone levels and renin activity are both high.

Parameter		Plasma	Urine
Na	mmol/l	133	47
K	mmol/l	2.9	36
Cl	mmol/l	87	3
HCO_3	mmol/l	33	?
pH		7.47	7.8
Glucose	mmol/l (mg/dl)	5 ((90)	0
Urea (BUN)	mmol/l (mg/dl)	10 (28)	-
Osmolality	mOsm/kg H_2O	280	420

Question

- **What is the basis for hypokalemia?**
- **What is the basis for the high U_{Na}?**

Discussion of Case 13-7

What is the basis for hypokalemia?

There could be a modest K shift into cells as judged from the pH and P_{HCO3}. In the face of hypokalemia, the U_K is too high. The high TTKG of 8.3 (36 mmol/l/(420/280)/2.9) suggests a stimulus for K secretion; the cause for aldosterone release is likely to be the contracted ECF volume.

What is the basis for the high U_{Na}?

The cause of the high U_{Na} in the face of ECF volume contraction can be deduced from the urine anion composition. The anion is not Cl; it is probably HCO_3 (high urine pH). The combination of high P_{HCO3} and bicarbonaturia (dragging Na in the urine) demands an input of HCO_3. With no renal source, suspect vomiting.

Hospital course

The hypokalemia and metabolic alkalosis were cured with KCl and NaCl therapy. When confronted with the data, the patient admitted to vomiting and psychiatric help was sought.

IV. INTEGRATIVE PHYSIOLOGY

CASE 13-8

Hypokalemia that developed in hospital

This 27-year old woman is concerned about her body image. She has been hospitalized on several occasions where hypokalemia was the major concern. She admitted to self-induced vomiting and has taken diuretics without prescription, but she vigourously denies these habits now.

Her present hospital admission was for treatment of an acute urinary tract infection; antibiotics were prescribed and there was a very good initial response. Nevertheless, after a week or so of therapy, she began to feel poorly. There are no other findings in the history. On physical examination, she has a contracted ECF volume. The laboratory data are summarized below. Her plasma renin activity was high. The urine was

obtained after several days of treatment for her urinary tract infection and while her ECF volume was still contracted.

		Plasma				Urine
		Past	Admission		Now	
Na	mmol/l	136		140	136	52
K	mmol/l	2.9		3.8	2.9	45
Cl	mmol/l	89		103	89	63
HCO_3	mmol/l	36		25	36	< 5
pH		7.48		7.40	7.48	6.1
Mg	mmol/l (mg/dl)	0.7	(1.7)	0.7	0.4 (1.0)	3.1
Ca	mmol/l (mg/dl)	2.4		2.4	2.4	6.1
Creatinine	µmol/l (mg/dl)	70	(0.8)	60	108(1.2)	5000
Urea (BUN)	mmol/l (mg/dl)	3.1	(9)	3.0	7 (20)	200
Osmolality	mOsm/kg H_2O	280		288	284	402

Questions

- **Is hypokalemia due to a shift of K into cells?**
- **Is K excretion excessive?**
- **How likely is vomiting to be the sole cause for hypokalemia and metabolic alkalosis?**
- **How would you rule out diuretics as a major cause of her hypokalemia?**
- **Which nephron segment is not functioning properly and causing her hypokalemia?**
- **What role might drugs have played in her hypokalemia?**

Discussion Case 13-8

Is hypokalemia due to a shift of K into cells?

Begin with Flow Chart 7-1 to assess whether there is a shift of K into cells.

Step 1. Is hypokalemia both severe and acute?

No, look further to see if there is a shift of K into cells.

Step 2. Is hypokalemia due to a shift of K?

There could be a shift of K into cells because metabolic alkalosis was present and there might have been an adrenergic response (β-agonist) to the contracted ECF volume.

Is K excretion excessive?

Do not compare her urine data to those in normal subjects. Rather, compare these values to the ones expected for a person with a deficit of K. The expected rate of K excretion is < 10-15 mmol/day or < 2 mmol/mmol of creatinine. Since her urine K/creatinine is 9, her K excretion rate is high. Therefore proceed to Flow Chart 6-2 to examine why she had a high rate of K excretion and consider both the flow rate in the CCD and the $[K]_{CCD}$

Step 1. Left side of flow chart. What is the flow rate in the terminal CCD?

The flow rate in the terminal CCD was not high because the rate of excretion of osmoles was less than 900 mosmoles/day (402 mOsm/l and 1.5 L of urine flow judging from her muscle mass (expect 8 mmol creatinine/day) and a urine creatinine of 5 mmol/l).

Step 1. Right side of the flow chart; What is the $[K]_{CCD}$?

The K_{CCD} was 45 mmol/l/(402/284 mOsm/l) = 32 mmol/l, and the TTKG was 11, values that are very high in the presence of hypokalemia. This reflects a high lumen-negative voltage in the CCD, due to either a faster rate of reabsorption of Na or a relatively slower rate of reabsorption of Cl. This differential diagnosis will be explored below.

Step 2. Right side of the flow chart; What is the ECF volume?

On clinical assessment, the ECF volume was contracted and the plasma renin activity was high. Therefore the increased lumen-negative voltage in her CCD was likely due to a relatively slower rate of reabsorption of Cl. The differential diagnosis is shown in Table 6-3 and Figure 6-2.

How likely is vomiting to be the sole cause for hypokalemia and metabolic alkalosis?

Key to this decision is the U_{Cl}; it should be virtually zero in vomiting, so I would not like vomiting as a sole diagnosis. She could have vomited and took a thiazide diuretic, so, given the past history, I cannot rule out vomiting with absolute certainty at present.

How would you rule out diuretics as a major cause of her hypokalemia?

There are two steps. First, frequent and unannounced random urines should be analyzed for Na and Cl. A urine that has very low concentrations of Na and Cl would make me very suspicious of diuretic abuse. Second, if you are still not sure, measure diuretic levels in a urine sample containing Na + Cl—this test for diuretics was negative.

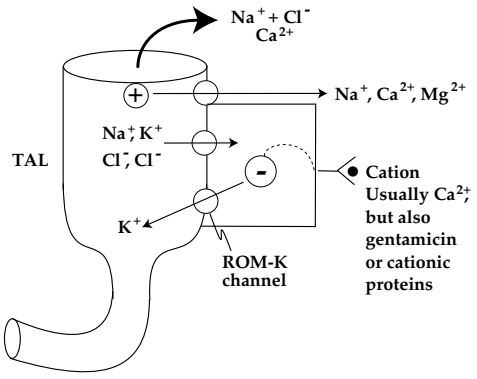
Which nephron segment is likely to be involved?

The key findings are hypokalemia, renal wasting of Na, K, and Cl, a high Ca excretion rate, and a lower than expected U_{osm} after ADH was given—it remained close to 400 mOsm/kg H_2O. All of the above add up to a lesion in the thick ascending limb of the loop of Henle.

Figure 13-4

Role of the calcium-sensing receptor in the loop of Henle

When the Ca-SR is occupied by ionized calcium or gentamicin, the ROM-K ion channel in the luminal membrane of mTAL cells becomes inhibited and the lumen lacks K as well as its usual positive voltage. As a result, there is less reabsorption of Na and Cl as well as ionized calcium in the LOH. The consequences of this reabsorption defect could lead to findings akin to actions of a loop diuretic with wasting of Na, Cl, K, and calcium in the urine, and the subsequent development of metabolic alkalosis.



What role might drugs have played in her hypokalemia?

Look for a drug that has a loop diuretic-like action, but not a loop diuretic (assay negative). Strongly suspect that the antibiotic is gentamicin because it binds to the ionized Ca sensing receptor on the basolateral aspect of

cells in the thick ascending limb of the loop of Henle (Figure 13-4). When bound, it closes the luminal membrane K ion channel (ROM-K). The net result is compromised NaCl reabsorption in the LOH (lumen lacks K), a defect in maximal concentrating ability, and excessive excretion of Ca (lumen lacks positive voltage). These findings are the same as in the ROM-K deficiency variant of Bartter's syndrome. Her prior normal K values, the absence of a family history, and the intake of gentamicin make Bartter's syndrome an unlikely diagnosis.

CASE 13-9

Polyuria in a patient with diabetes mellitus

A 16-year old female has a long history of poorly controlled type 1 diabetes mellitus because of compliance issues with insulin administration. On this occasion, she presents to hospital with a chief complaint of urinating large volumes at frequent intervals over the past 24 hours. She drank large volumes of fruit juice, but while in the Emergency Department, she drank only bottled water. On physical examination, her blood pressure was 105/66 mmHg and her heart rate was 80 beats per minute. The laboratory data are provided below.

		Admission		**0-100 min**		**100-200 min**	
		Pl	**Ur**	**Pl**	**Ur**	**Pl**	**Ur**
Glucose	mmol/l	70	325	70	325	35	325
Na	mmol/l	125	50	125	50	123	50
Osmolality	mOsm/L	320	450	320	450	281	450

Pl - Plasma; Ur - Urine
$P_{Glucose}$ of 70 mmol/l = 1260 mg/dl.

Other lab data
P_K 4.8 mmol/l/, blood pH 7.33, P_{HCO3} 28 mmol/l, plasma anion gap 16 mEq/l, $P_{Creatinine}$ 88 µmol/l (1.0 mg/dl) with a usual value of 60 µmol/l, P_{Urea} 8 mmol/l (BUN 21 mg/dl), and the urine flow rate was 10 ml/min over 300 min.

Questions

- **What is the basis of the polyuria?**
- **How can this patient have such a severe and sustained degree of hyperglycemia?**

- **In what way might this degree of hyperglycemia 'help' this patient?**
- **How can the ECF volume be defended during therapy?**
- **What is the specific plan for therapy?**
- **How can her effective P_{osm} be defended during therapy?**

Suggested reading

Davids MR, Edoute Y, Stock S and Halperin ML. Severe degree of hyperglycemia: Novel insights revealed by the use of simple principles of integrative physiology. *Quart J Med* 95: 113-124, 2002.

Davids MR, Lin S-H, Edoute Y, Cheema-Dhadli S and Halperin ML. Hyponatraemia and hyperglycaemia during laproscopic surgery. *Quart J Med* 95: 321-330, 2002.

Discussion of Case 13-9

What is the basis of the polyuria?

The U_{osm} of 450 mOsm/kg H_2O indicates that this is an osmotic diuresis. Because her GFR is modestly low and her $P_{Glucose}$ is 70 mmol/l, this is a glucose-induced osmotic diuresis (Table 13-1). This was confirmed by finding a $U_{Glucose}$ of 320 mmol/l.

TABLE 13-1

EFFECT OF HYPERGLYCEMIA AND THE GFR ON THE EXCRETION OF GLUCOSE

Very high levels of glucose excretion occur when there is both hyperglycemia (70 mmol/l) and a GFR that is ~ 1/2 normal (6 L/100 min).

Excretion of glucose = GFR (L/100 min) X ($P_{Glucose}$ – 10 mmol/l glucose reabsorbed/L GFR).

	Glucose Excreted (mmol/100 min)		
GFR (L/100 min)	**6**	**3**	**1.5**
$P_{Glucose}$ (mmol/l)			
15	30	15	7.5
30	120	60	30
70	360	180	90
100	540	270	135

Quantitative analysis

Because her GFR was somewhat reduced (high P_{Urea} and $P_{Creatinine}$), I shall assume that her ECF volume is 9 L for these calculations. Her urinary loss of 320 mmol of glucose in 1 L of urine represents ~ 1/2 of her current glucose pool size (70 mmol/l X 9 L), yet her $P_{Glucose}$ did not decline—this is a very unexpected finding! For comparison, a normal diet will supply an average of 18 g or 90 mmol of glucose per 100 min.

Comment: Patients with a similarly high $P_{Glucose}$ usually excrete little glucose because of a very low GFR, the consequence of a deficit of Na induced in the prior osmotic diuresis. On the other hand, the history of such a large urine output and the somewhat reduced GFR as reflected by the values for $P_{Creatinine}$ and P_{Urea} made a low filtered load of glucose an unlikely description of her pathophysiology.

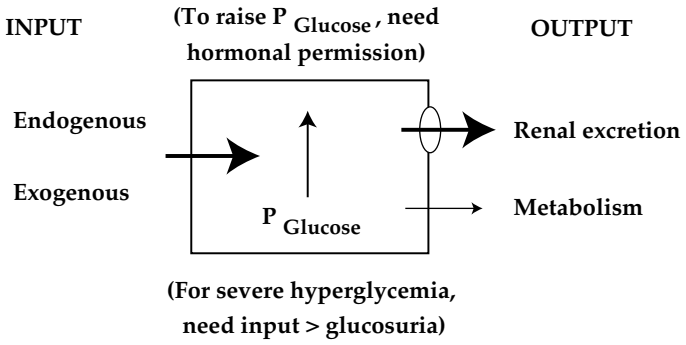
How can this patient have such a severe and sustained degree of hyperglycemia?

The patient was clearly suffering from a deficiency of insulin that was sufficient to permit a degree of hyperglycemia, but not one that is this severe enough to cause a clinically important degree of ketoacidosis. To have such a high $P_{Glucose}$, its input should be very large and exceed glucose output by a quantitatively appropriate amount (Figure 13-5).

Figure 13-5

Change in the concentration of a metabolite in plasma

To raise the $P_{Glucose}$, either glucose input must rise and/or glucose output must fall. The major path for glucose output at this very high $P_{Glucose}$ is glucosuria (large oval and bold arrow).



Comment: While glucose entry into the body can be from endogenous sources, these can be dismissed as a serious possibility because of the low rate of urea appearance and the small size of the glycogen pool. Therefore this patient needs a very rapid rate of gastric emptying to permit this high glucose input.

In what way might this degree of hyperglycemia 'help' the patient?

The usual clinical impression is that a high $P_{Glucose}$ is detrimental, but this impression is based on statistical associations rather than on pathophysiology (see quantitative analysis).

Quantitative analysis

Because her ECF volume is currently 9 L, she should have an extra 585 mmol of glucose in her ECF compartment ((70 – 5 mmol/l) x 9 L). With an effective P_{osm} of 320 mOsm/l, this degree of hyperglycemia would be responsible for maintaining ~ 1.8 L in her ECF compartment and thus could help to maintain an adequate circulatory status. Beware—this severe degree of hyperglycemia should resolve when the input of glucose declines, but the rate of stomach emptying as well as the concentration of glucose in gastric fluid will remain unknown.

How can the ECF volume be defended during therapy?

To understand how much her ECF volume will change, one needs a quantitative assessment of this volume. Notwithstanding, the physical examination does not provide quantitative information and a hematocrit and total proteins were not measured. Thus we are left with the estimate of her GFR discussed above to suggest that her ECF volume might be ~ 9 L. If we accept this value of 9 L, the Na content in her ECF compartment was reduced by 375 mmol (10 L X 140 mmol/l – 9 L X 125 mmol/l) or 750 mosomole while its content of glucose was increased by 585 mmol (9 L X (70 – 5 mmol/l)). Thus there was a small net decline in the number of effective osmoles in her ECF compartment of 165 mosmoles. In addition, polyuria will cause a further decrease in the number of effective osmoles. The goal of therapy will be to replace the majority of the losses of glucose with Na and Cl.

The same type of information can be obtained by examining the effective P_{osm} with therapy. The present high effective P_{osm} caused close to 2 L of water (10% of the ICF volume of 20 L) to enter the ECF compartment. When the P_{osm} returns to its normal value, the patient will

need to have a positive balance of ~ 300 mmol of Na plus 2 L of water to replace the 2 L of water that will shift back into her cells. In addition, there will need to be a positive balance of 1 L of isotonic saline to restore the ECF volume to 10 L. Because there is no hemodynamic emergency, there is no urgency to replace the deficit of Na quickly.

What is the specific plan for therapy?

The plan has two steps, one for water and another for effective osmoles in the first and second 100 min periods.

Water balance in the first 100 minutes

There was no infusion and 1 L of water was excreted in the urine—this should have resulted in a water deficit of 1 L.

The $P_{Glucose}$ offers an additional clue to help interpret the true water balance. There should have been a negative balance of 320 mmol of glucose and a fall in the $P_{Glucose}$ of 35 mmol/l (320 mmol lost/9 L ECF). Hence there appears to be an occult input of glucose from the GI tract. Because there was no change in the P_{Na}, there was probably an input of close to 1 L of water along with the glucose. Nevertheless, there is no easy way to monitor stomach contents or the rate of stomach emptying.

Na balance in the first 100 minute

The actual values are small and will not be discussed.

Water balance in the second 100 minutes

The patient was given 1 L of water as isotonic saline and excreted 1 L of urine. Thus there appeared to be water balance. Again, turn to the $P_{Glucose}$ for an additional clue. The fall in the $P_{Glucose}$ was consistent with the amount excreted and this suggested that there was little glucose absorbed from the GI tract in the second 100 min. Please read the next paragraph as well.

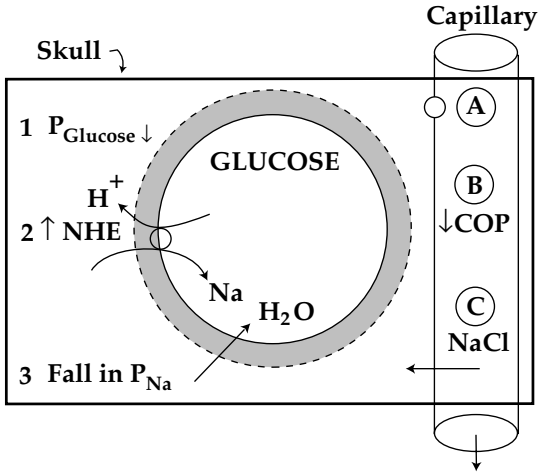
Na balance in the second 100 minutes

There was a positive balance of 100 mmol of Na (input of 150 mmol and an excretion of 50 mmol). This should have raised the P_{Na}, yet the P_{Na} actually fell by 3 mmol/l. Hence there must have been an occult gain of water to prevent the rise in the P_{Na}. Recall that the patient had changed her intake from fruit juice to bottled water in the Emergency department.

FIGURE 13-6

Risk factors for the development of cerebral edema

The solid rectangle represents the skull. The 3 risk factors for swelling of brain cells are show on the left and include a rapid fall in the $P_{Glucose}$ leading to a higher concentration difference for glucose across brain cells (site 1), activation of the $Na:H^+$ exchanger (NHE) by insulin (site 2), and/or a fall in the P_{Na} (site 3). The factors causing expansion of the ECF volume in the skull are shown on the right and include a less restrictive BBB (site A), a fall in the colloid osmotic pressure (COP) in plasma (site B), and/or a higher hydrostatic pressure across the blood-brain barrier due the excessive administration of saline (site C).



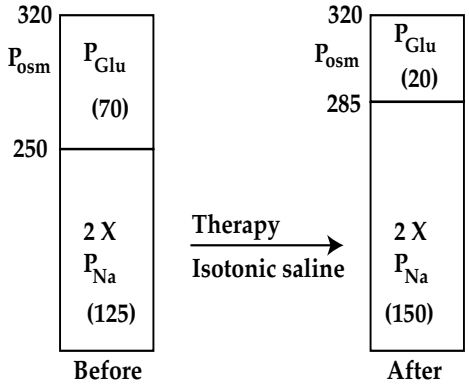
How can her effective P_{osm} be defended during therapy?

The goal is to prevent a fall in the effective P_{osm} ($P_{Glucose}$ and 2 P_{Na}) in the first 12-hours. If the fall in the $P_{Glucose}$ is 2-fold larger than the rise in P_{Na}, this will maintain a constant effective P_{osm} and thereby avoid inducing ICF volume expansion and as a result, brain cell swelling (Figure 13-7).

FIGURE 13-7

Defense of the effective osmolality of plasma

A rise in the P_{Na} is needed to prevent a fall in the effective P_{osm} when there is a fall in the $P_{Glucose}$. The P_{Na} must be > 140 mmol/l if the P_{Na} on admission is close to 140 mmol/l.



CLINICAL PEARL

Although a number of references suggest that there is a fixed relationship between changes in the $P_{Glucose}$ and the P_{Na}, these calculations are based on adding hypertonic glucose to the body, a situation different from that of our patient.

Caution! "Never apply data from one setting to a second one where the conditions are not identical".

Suggested reading

Carlotti APCP, Bohn D and Halperin ML. Importance of timing of risk factors for cerebral oedema during therapy for diabetic ketoacidosis. *Arch Dis Child* 88: 170-173, 2003.

CHAPTER 14

ACID-BASE CASES

In this chapter, I selected several cases with acid-base problems as a central feature. Please return to Chapters 8 – 12 for a review of the approaches to these disorders.

I. METABOLIC ACIDOSIS; NORMAL ANION GAP TYPE

CASE 14-1

Metabolic acidosis in a patient with cholera

A 26-year old healthy male (weight 60 kg) ingested food containing cholera bacteria. Later that day, he developed profuse watery diarrhoea; he had 24 bowel movements the next day. On physical examination, he appeared very ill. He had a contracted ECF volume—blood pressure was 90/60 mm Hg and the heart rate was 110 beats/min, jugular venous pressure was low. Data from arterial blood did not reveal the expected metabolic acidosis resulting from a deficit of $NaHCO_3$.

pH	7.37	Pco_2	mm Hg	39
P_{HCO3} mmol/l	22	Hematocrit	%	60

Questions

- **What is the best way to diagnose metabolic acidosis?**
- **What is the most accurate way to quantitate the ECF volume?**
- **What should his P_{HCO3} be if the only influence was the decrease in his ECF volume?**
- **Does this patient have respiratory acidosis?**

Suggested reading

Watten RH, Morgan FM, Songkhla YN, Vanikiati B, and Phillips RA. Water and electrolyte studies in cholera. *J Clin Invest* 38: 1879-1889, 1959.

Zalunardo N, Lemaire M, Davids MR and Halperin ML. Acidosis in a patient - with cholera: A need to redefine concepts. *Quart J Med* 97: 681-696, 2004.

Discussion Case 14-1

What is the best way to diagnose metabolic acidosis?

There are two ways to make this diagnosis, a low P_{HCO3} or a decrease in the content of HCO_3 in the ECF compartment. Even with a P_{HCO3} of 22 mmol/l, the content of HCO_3 in his ECF compartment could be low due to the loss of $NaHCO_3$ in the diarrhoeal fluid if his ECF volume is very contracted (see response to the next 2 questions).

What is the most accurate way to quantitate the ECF volume?

There best way to obtain a quantitative estimate of the ECF volume is to measure a change in the hematocrit or the total proteins in plasma. The normal hematocrit is ~ 40% (0.40) in a healthy young male and it was 0.40 on recovery. His hematocrit before therapy was 60 %, indicating that the plasma volume had decreased by 56 %. One can infer that there are similar or larger changes in the interstitial fluid volume from the Starling forces.

Hematocrit of 0.40 = 2 L RBC/(2 L RBC + 3 L plasma)
Hematocrit of 0.60 = 2 L RBC/(2 L RBC + X L plasma)
$\therefore$ Plasma volume = 1.33 L

What should his P_{HCO3} be if the only influence was the decrease in his ECF volume?

Because our patient had close to a 50 % reduction in his ECF volume, his expected P_{HCO3} should have been ~ 50 mmol/l (> 2 X 25 mmol/l) if this were the only influence. Hence this patient had two simultaneous acid-base disorders, contraction metabolic alkalosis and metabolic acidosis due to the loss of $NaHCO_3$ in diarrhoeal fluid, resulting in a P_{HCO3} in the near-normal range. This becomes very important for therapy. If $NaHCO_3$ is not added to the infusate when the ECF volume is re-expanded, metabolic acidosis will become very severe and it could have important hemodynamic consequences.

Conclusions

1. Definition of metabolic acidosis should include an assessment of both the concentration and the content of HCO_3 in the ECF compartment.

2. Interpretations of acid-base disorders based on arterial blood values may be erroneous if there is not a separate measure of the change in the ECF volume (e.g., the hematocrit).

Does this patient have respiratory acidosis?

Because the arterial blood pH, P_{HCO3} and Pco_2 were in the normal range, this patient does not have a *ventilatory form of respiratory acidosis*. In metabolic acidosis, however, the objective is to lower the Pco_2 in cells to ensure that H^+ are buffered by HCO_3 rather than intracellular proteins (see Chapter 8). The Pco_2 in tissues is controlled by factors in addition to the arterial Pco_2 such as the rate of production of CO_2 and the rate of blood flow to remove CO_2 from cells. In simplest terms, this means how much O_2 was extracted from each L of blood perfusion.

In our patient with a significant degree of ECF volume contraction, the tissue blood flow rate is very low. Hence more O_2 is extracted while almost an identical amount of CO_2 is added to capillary blood, raising the venous Pco_2. Accordingly, CO_2 accumulation may lead to intracellular respiratory acidosis (*tissue form of respiratory acidosis*). The tissue-form of respiratory acidosis can be confirmed by measuring the venous Pco_2.

Conclusion

One cannot diagnose the tissue form of respiratory acidosis from arterial blood values. Hence all methods of analysis (including the Stewart approach) fail to provide this essential information.

CASE 14-2

Metabolic acidosis due to glue sniffing

A 27-year old male is brought into the emergency department because he is confused and extremely weak. On physical examination, there was a marked degree of ECF volume contraction. On CNS examination, there was poor coordination, confusion and generalized weakness; there were no localizing lesions. The results of the laboratory tests are shown below.

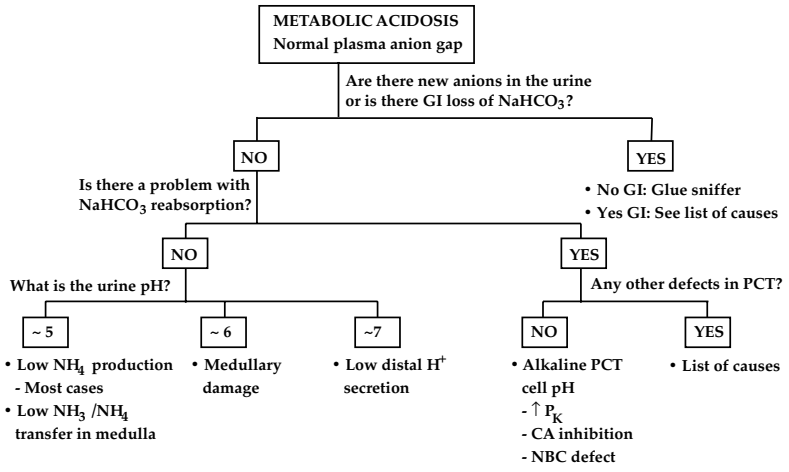
		Plasma	Urine
pH		7.05	6.1
Pco_2	mm Hg	30	-
HCO_3	mmol/l	8	1
Na	mmol/l	130	60
K	mmol/l	1.8	20
Cl	mmol/l	110	3
Glucose	mmol/l (mg/dl)	4 (72)	0
Urea (BUN)	mmol/l (mg/dl)	1.5 (4)	100
Creatinine	µmol/l (mg/dl)	90 (1.0)	8 mmol/l
Osmolality	mOsm/kg H_2O	270	566
Albumin	g/l (g/dl)	30 (3.0)	0
Volume	L/day	-	1

Discussion of Case 14-2

Because there are no unmeasured anions in plasma, proceed by following the steps outlined in Flow Chart 14-1.

Flow chart 14-1

Approach to the patient with metabolic acidosis and a normal plasma anion gap in plasma



Step 1. Are there many new anions in the urine or a GI problem?

There is no GI history, but because the $U_{Na} + U_K$ (60 + 20 mEq/l) is > the U_{Cl} (3 mEq/l) and the U_{HCO3} is low (urine pH is 6.2), there are new urine anions. To quantitate the excretion of unmeasured anions, I will need to know the U_{NH4} and the urine flow rate.

Next ask, "Is the excretion of unmeasured anions high because of a high filtered load, low renal reabsorption and/or their renal secretion?" It is likely that the high renal excretion of unmeasured anions was due to secretion because of the low value for the plasma anion gap.

To confirm that RTA is not present, ask: "Is the rate of excretion of NH_4 high?" When the basis of the metabolic acidosis is due to added acids and its duration is chronic, the expected renal response is to excrete NH_4 at its maximum rate—this should exceed 150 mmol/day. When measured during therapy, this excretion rate was 160 mmol/day.

Interpretation

Although the patient had a near-normal plasma anion gap, he had a high rate of excretion of NH_4 with many unmeasured anions in his urine. Hence there was overproduction of acids. Moreover, the accompanying anions were secreted by the kidney—this is the fate of hippuric acid.

Biochemistry

Hippuric acid is the end product of the metabolism of toluene, a constituent of glue—hence the metabolic acidosis is due primarily to glue sniffing (Figure 14-1). The excretion of more hippurate than NH_4 caused a large renal loss of Na and K. Thus the patient will need initial treatment with KCl to remove the threat of profound hypokalemia. He will also need sufficient NaCl to restore his ECF volume. $NaHCO_3$ will not be needed because his NH_4 excretion rate was high—moreover, there is a danger in giving $NaHCO_3$ to a patient with a severe degree of hypokalemia.

Two brief comments on the urine electrolytes should be made. First, despite the contracted ECF volume, the U_{Na} was high (60 mmol/l). This does not represent renal damage because the U_{Cl} was appropriately low (3 mmol/l)—the U_{Na} was high due to the excretion of more hippurate than NH_4. Second, the U_K was high (20 mmol/l) despite the low P_K (1.9 mmol/l). This is due to the actions of aldosterone released in response to the low ECF volume to open ENaC and the reabsorption of Na faster than Cl due to the very low distal delivery of Cl.

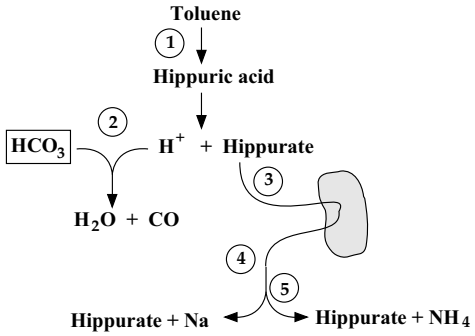
Suggested reading

Carlisle EJF, Donnelly SM, Vasuvattakul S, Kamel KS, Tobe S and Halperin ML. Glue-sniffing and distal renal tubular acidosis: sticking to the facts. *J Am Soc Nephrol* 1: 1019-1027, 1991.

FIGURE 14-1

Metabolic acidosis due to the metabolism of toluene

The metabolism of toluene occurs in the liver where benzoic acid is produced via alcohol and aldehyde dehrdrogenases. Hippuric acid is produced due to conjugation with glycine (all represented as site 1 for simplicity). The H^+ are titrated by HCO_3 for the most part (site 2). The hippurate anion is secreted by the PCT and excreted in the urine, initially with NH_4 (site 4) and then with Na and K when the capacity to excrete NH_4 is exceeded (site 5). The excretion of hippurate anions with Na and/or K (and not NH_4) is a major factor in the metabolic acidosis.



CASE 14-3

Renal tubular acidosis with a low carbonic anhydrase activity

A 7-year old male had growth retardation and multiple bone fractures. Several family members have similar findings and osteopetrosis on X-ray examination. His parents are close relatives. On physical examination, his ECF volume appears to be normal. The data from the laboratory examination are provided below.

		Plasma		Urine
pH		7.34		7.0
PCO_2	mm Hg	33		-
HCO_3	mmol/l	18		-
Na	mmol/l	139		36
K	mmol/l	3.6		32
Cl	mmol/l	110		39
Anion gap	mEq/l	11		+ 29
Albumin	g/l (g/dl)	37	(3.7)	0
Creatinine	µmol/l (mg/dl)	60	(0.7)	8.0
Urea	mmol/l (mg/dl)	3.3	(9)	200
Osmolality	mOsm/kg H_2O	288		400

Other data

The urine citrate was high and the Pco_2 in alkaline urine was consistently 80 mm Hg.

Discussion of Case 14-3

Begin by following the initial step in Flow Chart 9-1, "Are there a significant number of new unmeasured anions in plasma? The answer is no because the plasma anion gap was 11 mEq/l while the albumin concentration in plasma was 37 g/l. Therefore proceed by following the steps outlined in Flow Chart 14-1.

Step 1. Are there many new anions in the urine or a GI problem?

There is no GI history and the rate of excretion of unmeasured anions is not high. Therefore confirm that this is RTA by finding a low rate of excretion of NH_4. When measured, this excretion rate was 25 mmol/day, a very low value in a patient with chronic metabolic acidosis. Calculating the urine osmolar gap or the urine net charge would reveal the same information.

Step 2. Is there a problem with the renal reabsorption $NaHCO_3$?

Yes, there was also a defect in H^+ secretion in the PCT because the fractional excretion of HCO_3 was > 15 %. Because citraturia was present in the face of metabolic acidosis, an alkaline PCT cell might be the underlying disorder.

Step 3. What is the urine pH?

The urine pH of 7.0 suggests that the low rate of excretion of NH_4 was due to a diminished distal H^+ secretion and/or a high distal HCO_3 delivery or secretion. To test the latter, measure the urine Pco_2 in freshly voided alkaline urine (U-B Pco_2). Because the U_{PCO2} was 40 mm Hg while the blood Pco_2 was 30 mm Hg, distal H^+ secretion was low (the expected value would be 70 mm Hg with a normal distal H^+ secretion).

Interpretation:

The patient had metabolic acidosis due to a low rate of reabsorption of HCO_3 in his PCT and a low rate of excretion of NH_4 caused by a defect in H^+ secretion that involved both the proximal and distal nephron. Since the mechanisms for H^+ and HCO_3 transport are different in both these nephron segments, these are very unlikely as the site of a common

lesion. Therefore the lesion probably caused an alkaline proximal and distal cell, a defect in intracellular carbonic anhydrase (CA_{II}) activity. Since this enzyme is also present in osteoclasts where H^+ secretion mediates bone resorption, a defect in this enzyme could be the basis for osteopetrosis. This was confirmed by a direct assay of CA_{II} activity in his red blood cells.

CASE 14-4

Renal tubular acidosis in a patient with Southeast Asian ovalocytosis (SAO)

An 18-year old female is known to have SAO. Unlike other patients with this disorder, she and her family members suffer from progressive weakness, which is now very profound. On physical examination, her ECF volume is normal and there are no other important specific findings. The data from the laboratory examination are provided below.

		Plasma	Urine
pH		7.32	6.8
PCO_2	mm Hg	34	-
HCO_3	mmol/l	17	-
Na	mmol/l	139	86
K	mmol/l	2.7	32
Cl	mmol/l	111	113
Anion gap	mEq/l	11	+5
Creatinine	µmol/l (mg/dl)	60 (0.7)	6 mmol/l
Urea	mmol/l (mg/dl)	3.3(9)	200 mmol/l
Osmolality	mOsm/kg H_2O	288	450

Other data:

The urine citrate was very low and the Pco_2 in alkaline urine was consistently ~ 80 mm Hg.

Suggested reading

Kaitwatcharachai C, Vasuvattakul S, Yenchitsomanus P, Thuwajit P, Malasit P, Chuawatana D, Mingkum S, Halperin ML and Nimmannit S. Distal Renal Tubular Acidosis in a Patient with Southeast Asian Ovalocytosis: Possible interpretations of a high urine PCO_2. *Am J Kidney Dis* 33: 1147-1152, 1999

Discussion of Case 14-4

Following the initial step in Flow Chart 9-1, because there are no new unmeasured anions in plasma, proceed to the steps outlined in Flow Chart 14-1.

Step 1. Are there many new anions in the urine or a GI problem?

There is no GI history and the rate of excretion of unmeasured anions is not high. Therefore this will be RTA if the rate of excretion of NH_4 is low. When measured, this excretion rate was 25 mmol/day, a very low value in a patient with chronic metabolic acidosis. Calculating the U_{osm} gap or the urine net charge would reveal the same information.

Step 2. Is there a renal problem reabsorbing $NaHCO_3$?

No because the fractional excretion of HCO_3 was < 3 % when the P_{HCO3} and the P_K were in the normal range. The low urine citrate was suggested that the pH in her PCT cells was low.

Step 3. What is the urine pH?

The urine pH of 7.0 suggests that the low rate of excretion of NH_4 was due to a diminished distal H^+ secretion. To test this function, measure the urine Pco_2 in freshly voided alkaline urine (U-B Pco_2); surprisingly, the U_{PCO2} was 80 mm Hg.

Interpretation

The patient had a low rate of excretion of NH_4 that seemed to be due to a defect in H^+ secretion because her urine pH was persistently close to 7.0. H^+ secretion by her PCT seemed to be intact because her P_{HCO3} remained in the normal range after initial therapy and her FE_{HCO3} was < 3%. Because her U_{PCO2} was unexpectedly high, perhaps her mutant AE was mis-targeted to the luminal membrane of α-intercalated cells. The high U_{PCO2} would thus be due to distal secretion of HCO_3 by alkaline distal cells.

II. METABOLIC ACIDOSIS; HIGH ANION GAP TYPE

CASE 14-5

What happens when we feed the GI bacteria?

One week ago, diarrhoea began in a male during of a trip abroad; he was treated with an anti-motility drug and an antibiotic. However, in the past 24 hours, his diarrhoea increased; his only intake was many popsicles to satisfy his desire for cold liquids. On physical examination, he appeared very ill and was confused. He had poor balance and an abnormal gait. He did not have signs of a contracted ECF volume. Acetone was not detected on his breath or in his urine. The abdomen was distended and bowel sounds were scanty. There were no masses or enlarged organs. The laboratory results are summarized below.

Parameters		Plasma	Urine
pH		7.22	5.0
Pco_2	mm Hg	27	-
Na^+	mmol/l	138	110
K	mmol/l	3.8	10
Cl	mmol/l	101	10
HCO_3	mmol/l	11	0
Glucose	mmol/l (mg/dl)	6.0 (108)	0
Urea (BUN)	mmol/l (mg/dl)	5.0 (14)	450
Creatinine	µmol/l (mg/dl)	103 (1.2)	1400
Albumin	g/l (g/dl)	38 (3.8)	-
Osmolality	mOsm/kg H_2O	289	906

Questions

- **What is the basis for metabolic acidosis?**
- **What factors permit bacteria in the GI tract to over-produce organic acids?**

Suggested reading

Halperin ML and Kamel KS. Turning sugar into acids in the gastrointestinal tract. *Kidney Int* 49: 1-8, 1996.

Discussion of Case 14-5

What is the basis for metabolic acidosis?

It was not simply the loss of $NaHCO_3$ because the plasma AG was 26 mEq/l. L-Lactic acidosis was unlikely because there was no hemodynamic problem, liver function tests were normal, and the time period was too short for a nutritional problem. Moreover, he did not have ethanol or the intake of drugs that causes L-lactic acidosis. Of greater importance, L-lactic acidosis and ketoacidosis were ruled out because their levels were not elevated in blood or urine. Toxic alcohol ingestion was not likely from the history or the laboratory data (no P_{osm} gap). Renal failure was not present ($P_{Creatinine}$ was near-normal). Hence the most likely diagnosis is D-lactic acidosis.

What factors permit bacteria in the GI tract to over-produce organic acids?

The factors that might lead to over-production of these organic acids include a change in this GI bacterial flora due to the use of antibiotics, a slower transit time due to the drug used to treat diarrhoea, and provision of substrates to these bacteria (popsicles contain sucrose and fructose is poorly absorbed in the intestinal tract). It is also possible that a disorder involving the liver and/or the kidneys could aggravate this tendency because these organic acids are normally cleared by these organs. Nevertheless, this was not evident from the laboratory tests.

Final Diagnosis:

I suspected overproduction of D-lactic acid and possibly loss of $NaHCO_3$ via the GI tract.

CASE 14-6

Role of markedly reduced muscle mass

A 32-year old cachetic male did not eat for 3 days, but drank some ethanol several hours ago. He denied the intake of medications. On physical examination, he was alert and oriented, but severely emaciated (weight 23 kg). His heart rate was 110 bpm, blood pressure was 90/60 mm Hg, and respiratory rate was 28/min. His JVP was below the sternal angle. Acetone was detected on his breath.

Parameters		Blood	Urine
pH		7.32	5.0
Pco_2	mm Hg	14	-
HCO_3	mmol/l	7	-
Na	mmol/l	140	137
K	mmol/l	5.0	11
Cl	mmol/l	103	75
Anion gap	mEq/l	30	73
Urea (BUN)	mmol/l (mg/dl)	5.0 (14)	-
Creatinine	µmol/l (mg/dl)	90 (1.0)	-
Glucose	mmol/l (mg/dl)	2.5 (45)	0
Albumin	g/l (g/dl)	21 (2.1)	

Other values:

Ketones 4+, L-lactate 2 mmol/l, salicylates 0.22 mmol/l, ethanol 20 mmol/l (92 mg/dl). No other alcohols were detected. His liver enzymes were normal.

Questions

- **What is the basis for ketoacidosis?**
- **How might the markedly reduced muscle mass contribute to the severity of the acidosis?**
- **How could this cachectic patient be able to maintain a low arterial Pco_2?**

Suggested reading

Kamel KS, Richardson RMA, Goguen JM, Fine A, Levin A and Halperin ML. Rate of production of carbon dioxide in patients with a severe degree of metabolic acidosis. *Nephron* 64: 514-517, 1993.

Discussion of Case 14-6

What is the basis for ketoacidosis?

The most likely basis for ketoacidosis is an overproduction of ketoacids due to ethanol metabolism in the setting of prolonged fasting where insulin levels would be low due to a low $P_{Glucose}$ and a low ECF volume. There could also be low metabolism of ketoacidosis in the brain (ethanol effect) and in the kidneys (low GFR; examine his $P_{Creatinine}$ in conjunction with the low muscle mass).

How might the markedly reduced muscle mass contribute to the severity of the acidosis?

Normally, with severe metabolic acidosis, most H^+ ions are buffered in the ICF of muscle. As the patient has minimal muscle mass, much less buffering could occur in this organ. Thus, a larger proportion of buffering occurs in his ECF and this could explain why the acidosis appears to be more severe.

How could this cachectic patient be able to maintain a low arterial Pco_2?

It is difficult to imagine that this patient was able to increase alveolar ventilation appropriately. Hence his rate of production of CO_2 was probably low and might reflect inactivity, sedation, and/or cachexia. Perhaps the intoxicating effect of ethanol reduced the metabolic rate in his brain. The low GFR reduced the rate of oxidation of ketoacids in the kidneys.

III. METABOLIC ALKALOSIS

CASE 14-7

Importance of urine electrolytes

A 22-year-old ballerina has been feeling poorly for several months. She complains of weakness but denies vomiting or intake of diuretics. On physical examination, her blood pressure was 100/60 mm Hg and there was a 15 mm Hg postural drop. The jugular venous column height was below the sternal angle. Laboratory data are shown below.

Parameters		Plasma	Urine
Na	mmol/l	140	46
K	mmol/l	2.8	42
Cl	mmol/l	90	56
HCO_3	mmol/l	34	0
pH		7.48	5.0
Urea (BUN)	mmol/l (mg/dl)	10 (28)	-
Osmolality	mOsm/kg H_2O	297	450

Question

- **What is the basis for metabolic alkalosis?**

Discussion of Case 14-7

What is the basis for metabolic alkalosis?

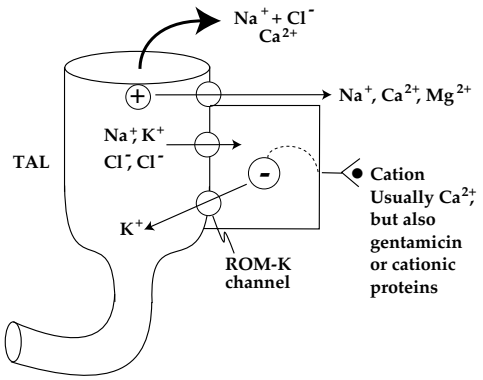
ECF volume contraction and the absence of hypertension suggest that metabolic alkalosis is due to loss of NaCl and KCl. However, the urine contains abundant Cl, not supporting this diagnosis. The blood urea is somewhat elevated. Therefore, the diagnoses to entertain are occult diuretic abuse, or the 'endogenous diuretic diseases', an occupied Ca-sensing receptor (Ca-SR) (Figure 14-2), Bartter's syndrome, or Gitelman's syndrome.

Further lab studies revealed that the urine concentrating ability was not compromised, Mg levels in plasma were low, and that the urine *consistently* contained Na and Cl while it had very little Ca. Blood and urine were negative for diuretics. Although diuretic abuse was the initial diagnosis, Gitelman's syndrome is now the most likely cause because NaCl, KCl and Mg in large amounts did not correct the abnormalities.

Figure 14-2

Role of the calcium-sensing receptor in the loop of Henle

When the Ca-SR is occupied by ionized calcium, the ROM-K ion channel in its luminal membrane becomes inhibited and the lumen lacks K as well as its usual positive voltage. As a result, there is less reabsorption of Na and Cl as well as ionized calcium in the LOH. The consequences of this reabsorption defect could lead to findings akin to actions of a loop diuretic with wasting of Na, Cl, K, and calcium in the urine and the subsequent development of metabolic alkalosis.



CASE 14-8

Metabolic alkalosis after a long run

A 26-year-old elite soldier was the only man who collapsed at the end of a forced 6-h run in a very hot environment. He sweated profusely and drank large volumes of water, as did all his mates. He did not vomit or take medications. Physical examination at the end of the march revealed that his effective blood volume was very contracted. For simplicity, assume that his ECF volume had declined from a normal value of 15 L to his current value of 12 L. Laboratory values in plasma of arterial blood are listed below.

pH		7.47	P_{Na}	mmol/l	116
P_{HCO3}	mmol/l	37	P_K	mmol/l	2.7
Pco_2	mm Hg	44	P_{Cl}	mmol/l	56

Questions

- **What are the balances for Na, and Cl in his ECF compartment?**
- **How was electroneutrality achieved in his ECF compartment?**
- **What process added the new HCO_3 to the ECF compartment?**
- **How was electroneutrality achieved in his ICF compartment?**
- **What is your therapy for this patient?**

Discussion of Case 14-8

What are the balances for Na and Cl in his ECF compartment?

Because of the contracted ECF volume, and the low P_{Na} and P_{Cl}, there were very large deficits of these ions in his ECF compartment. To calculate values, multiply the P_{Na} and the P_{Cl} by the ECF volume before and after the run. Accordingly, his deficit of Na was 708 mmol (140 mmol/l x 15 L) – (116 mmol/l x 12 L) and the deficit of Cl was 873 mmol (103 mmol/l x 15 L) – (56 mmol/l x 12 L). Therefore he had a deficit of 708 mmol of NaCl and an unexplained deficit of 165 mmol of Cl (873 – 708 mmol) with another cation.

How was electroneutrality achieved in his ECF compartment?

There are two possibilities—first, he could have lost 165 mmol of Cl with another cation if it were present in his ECF, but there are not enough non-Na ECF cations. Second, these 165 mmol of Cl were lost in conjunction

with the gain of a non-Cl anion in his ECF compartment. Because there was an insufficient gain of new anions as indicated by the plasma AG, his new anion gain had to be HCO_3. In fact, his P_{HCO3} was 44 mmol/l and his content of in the ECF compartment is currently 528 mmol (12 L x 44 mmol/l) whereas it was 375 mmol before the run (15 L X 25 mmol/l).

What process added new HCO_3 to the ECF compartment?

The source of the new HCO_3 appears to be from an endogenous source because he had no intake other that water and he did not vomit. Moreover, because of the short time, the lack of a chronic stimulus for NH_4 production, and that he had a small urine output, there was not an appreciable loss of NH_4Cl. Another source of the new HCO_3 was from CO_2 and water, but what happened to these H^+?

How was electroneutrality achieved in his ICF compartment?

Given the fact that he had hypokalemia and sweat was the major site of his electrolyte losses, the likely cation excreted with the 165 mmol of Cl in sweat was K (Figure 14-3). The driving force for the K loss in sweat is an electrical force created when Na is reabsorbed faster than Cl. The pathway for Cl reabsorption in the sweat duct is via the cystic fibrosis related Cl ion channel—this is defective in a patient with cystic fibrosis. To the extent that there are K channels in the luminal membrane of sweat ducts with an open probability, K will be lost with Cl in sweat in a patient with cystic fibrosis. A diagnosis of cystic fibrosis was confirmed later by molecular studies.

The ionic composition of his ICF compartment should also be changed. He likely had a large K deficit in his ICF compartment and this was matched by a gain of H^+ rather than Na in his ICF compartment. In fact, the gain of H^+ in the ICF compartment will lead to a higher P_{HCO3} if the source of these H^+ were derived from carbonic acid (Figure 9-14, page 130); the high tissue Pco_2 was due to his contracted ECF volume.

What is your therapy for this patient?

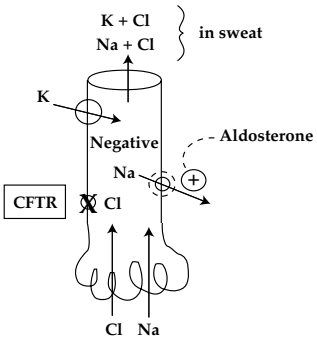
Make a list of the dangers and prioritize them. Often, considerations other than the acid-base disorder take precedence in therapy. The major dangers are a rise in the intracranial pressure due to brain cell swelling (P_{Na} 116 mmol/l) and the low effective circulating volume. Because of the former, re-expansion of his effective blood volume with saline that is isotonic to the patient is <u>not</u> the best way to reduce the threat of acute brain herniation. Accordingly, the initial mode of treatment should be with hypertonic saline to decrease the ICF volume of brain cells.

The patient will need a positive balance for KCl to return his ICF composition to normal. Even if metabolic alkalosis is due to a deficit of KCl, emergency therapy was with hypertonic NaCl because there was also acute hyponatremia with a contracted ECF volume. The KCl deficit can then be replaced later.

Figure 14-3

Loss of K + Cl in sweat

The structure represents a sweat gland. In a patient with cystic fibrosis, there is poor reabsorption of Cl in the duct of the sweat gland (low Cl ion channels (CFTR)). The reabsorption of Na via ENaC is stimulated by aldosterone released in response to a low ECF volume. Electroneutrality will be maintained if there was a loss of Na plus Cl and/or K plus Cl.



Suggested reading

Smith H, Dhatt G, Melia W and Dickinson J. Cystic fibrosis presenting as hyponatremic heat exhaustion. *Brit Med J* 310: 579-580, 1995.

CASE 14-9

Betel nuts and chronic metabolic alkalosis

A 60-year old male complained of malaise, anorexia, and constipation, which gradually increased in severity over the past several months—weight loss was 7 kg. By habit, he chewed and swallowed ~ 40 betel nuts/day. On physical examination, he was conscious, but responded slowly to questions. He had a mildly contracted ECF volume and the only other finding was a brick-red stain on his tongue, oral mucosa, and the angles of his mouth. The laboratory data on admission are provided

below. Parathyroid hormone and 1,25-dihydroxyvitamin D_3 levels in plasma were extremely low.

		Plasma	Urine
pH		7.47	7.5
HCO_3	mmol/l	36	-
Pco_2	mm Hg	50	-
K	mmol/l	3.2	21
Cl	mmol/l	91	42
Anion gap	mEq/l	10	43
Albumin	g/l (mg/dl)	39 (3.9)	-
Creatinine	µmol/l (mg/dl)	844 (9.7)	9400
Calcium	mmol/l (mg/dl)	3.2 (12.8)	5.9
Phosphate	mmol/l (mg/dl)	1.84 (5.7)	2.1

Questions

- **Why did hypercalcemia develop?**
- **What is the basis for metabolic alkalosis?**
- **How might hypercalcemia cause a contracted ECF volume, hypokalemia, and a low GFR?**
- **What is the therapy?**

Suggested reading

Lin S-H, Lin Y-F, Cheema-Dhadli S, Davids MR and Halperin ML. Hypercalcaemia and metabolic alkalosis with betel nut chewing: emphasis on its integrative pathophysiology. *Nephrol Dial Transplant* 17: 708-714, 2002.

Discussion of Case 14-9

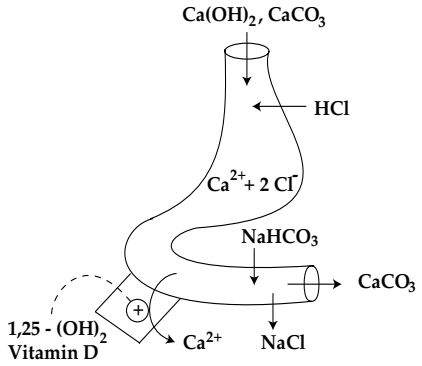
Why did hypercalcemia develop?

Because this rate of excretion of Ca was high, the basis for hypercalcemia was an increased input of Ca. There was no evidence for enhanced bone reabsorption, so increased Ca absorption form the GI tract was suspected. Once ionized Ca enters the small intestine, secretion of $NaHCO_3$ converts ionized Ca to $CaCO_3$, which is delivered downstream in the intestine (Figure 14-4). Because there was no vitamin D administration and blood levels of the active form of this vitamin were low, the excessive absorption of Ca probably occurred downstream in the intestinal tract (Figure 14-5).

FIGURE 14-4

Delivery of ionized calcium to the intestinal tract

Betel nut preparations have added $Ca(OH)_2$ to conceal the bitter taste of these nuts. $Ca(OH)_2$ and $CaCO_3$ are converted to ionized Ca by gastric HCl. There are three possible fates of ionized Ca leaving the stomach. First, while in its ionic form, Ca can be absorbed in the duodenum. Second, ionized Ca may be removed by precipitation with inorganic phosphate. Third, when sufficient $NaHCO_3$ is secreted into the duodenum, ionized Ca will be precipitated as $CaCO_3$. This $CaCO_3$ will be delivered to the colon (see Figure 14-5).

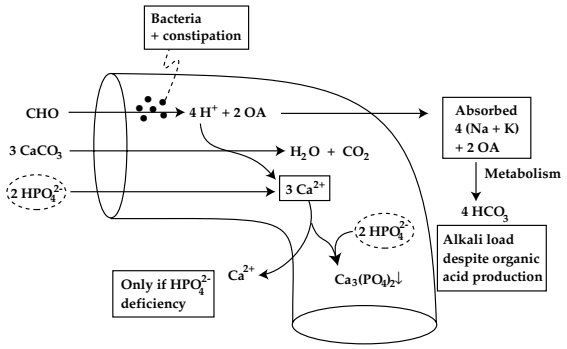


A reduced amount of inorganic phosphate is needed in the lumen of the colon to have a high concentration of ionized Ca here. This could occur if the source of dietary Ca were not of animal or vegetable origin (need for a low phosphate content)—i.e., an intake of alkaline Ca salts. Moreover, once initiated, hypercalcemia can cause a vicious cycle by causing anorexia. Now the intake of alkaline Ca salts in the betel nut preparation or as $CaCO_3$ might further exceed the dietary intake of phosphate. The net result would be increased Ca, but low phosphate absorption due to a diminished precipitation of $Ca_3(PO_4)_2$ in the lumen of the intestinal tract as was suggested by his low excretion of phosphate (2 mmol/day Vs 20-30 mmol/day normally). Due to production of H^+ by fermentation in the colon, ionized Ca and an organic anion are absorbed—the latter is converted to HCO_3 in the body, which is a component of the metabolic acidosis.

Figure 14-5

Absorption of ionized calcium in the colon

The structure represents downstream segments of the intestinal tract where Ca can be reabsorbed if it exists in an ionized form. Delivery of calcium is via $CaCO_3$; ionized calcium (Ca^{2+}) is formed when H^+ are formed by bacterial fermentation. Should the delivery of inorganic phosphate be less than required to precipitate Ca^{2+} as $Ca_3(PO_4)_2$, some Ca^{2+} could remain in the lumen and be absorbed passively. A potential HCO_3 load (organic anions (OA)) is also absorbed representing the conversion of some of the alkali in $CaCO_3$ to HCO_3 in the body when OA are metabolized to neutral end-products.



What is the basis for metabolic alkalosis?

Ingesting alkali as $NaHCO_3$ or alkaline calcium salts, even in large amounts, is not sufficient to cause the development of chronic metabolic alkalosis unless there is a very low GFR. If this were the sole cause, the ECF volume should be expanded, but this was not the observed finding. Given his very low GFR, the metabolic alkalosis could be due in part to the input of alkali and a low rate of HCO_3 excretion because of a low filtered load of this ion. Therefore the intake of $Ca(OH)_2$ could have played an important role in the development of his metabolic alkalosis.

Renal mechanisms to explain why chronic metabolic alkalosis and a low ECF volume were present in this patient will now be considered. There were two important stimulators of proximal HCO_3 reabsorption other than hypercalcemia and suppressed levels of PTH in this patient, angiotensin II and hypokalemia. Hypercalcemia can cause arteriolar vasoconstriction within the kidney and thereby a reduction in the GFR which contributes to a lower rate of excretion of HCO_3.

How might hypercalcemia cause a contracted ECF volume, hypokalemia and a low GFR?

The above findings resemble those of a pharmacologic agent that inhibits Na reabsorption in the kidney (a diuretic). In fact, hypercalcemia produces a net effect that is equivalent to actions of a *loop diuretic* (Figure 14-2). This will cause excessive excretion of NaCl (low ECF volume), renal K wasting (hypokalemia), and a low GFR (high delivery of Cl out of the LOH to the juxtaglomerular apparatus leads to a low GFR by tubuloglomerular feedback).

What is the therapy?

With the initial therapy of intravenous isotonic saline + KCl to re-expand his ECF volume, his plasma calcium concentration fell and his metabolic alkalosis and hypokalemia resolved. The key to his clinical problem is the presence of a low phosphate intake; he will need oral phosphate intake.

CLINICAL PEARLS

- *Oral $CaCO_3$ + vitamin D when phosphate intake is low is now the third-leading cause of hypercalcemia in adults. The target group is 'little old ladies' who eat little phosphate (tea & toast diet) and take $CaCO_3$ plus vitamin D for osteoporosis. Prevent this disorder by following their urine Ca/creatinine ratio—change therapy when this ratio rises, before permanent defects occur.*

- *The high U_{Cl} was a clue to look for a diuretic-like action in this case.*

CHAPTER 15

SUGGESTED READING

I. SALT AND WATER

CLASSICAL REFERENCES

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