Malnutrition in a patient with chronic alcoholism

A 62-year-old man presented to the orthopaedic clinic with a proximal **femoral fracture**. He had been drinking **750 ml of wine daily for the last 8 years** and was found to have signs of **malnutrition (BMI 17.9 kg/m^2)** and **osteoporosis**. Postoperatively, he was given **high-energy drinks.** On the **second postoperative day**, he developed **ophthalmoplegia**, **diplopia, ataxia, confusion** and **hypotension**. Initial labs show **falls in serum K** (2.2 mmol/l), **PO_4** (0.53 mmol/l) and **Mg** (0.61 mmol/l).

What is the most likely diagnosis?
What is the best initial treatment?

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What is the most likely diagnosis? **Refeeding syndrome with Wernicke-Korsakoff syndrome**
What is the best initial treatment? **IV thiamine** supplementation (200 mg/day for 5 days) , **IV correction of electrolyte abnormalities** (PO_4 20 mmol/day, K 40 mmol/day, Mg 10 mmol/day), re**stricted refeeding regime** (5→10 kcal/kd/day for the first 4 days)

Hunger striker

Protesting against a deportation order, a 27-year-old asylum seeker, with no previous medical history, went on hunger strike over a period of 4 months, refusing all nourishment apart from tea and coffee with sugar. At this time, he was admitted to hospital and, over the subsequent 2 weeks, lost a further 10 kg in weight (to 49 kg, body mass index (BMI) 14.7 kg/m2). He became progressively weaker, more inactive and apathetic. At this point, he was treated by enteral and parenteral nutrition with a total intake of 1600 kcal/day. He was also given a daily infusion of 500 ml 0.9% saline with 20mmol KCl and vitamins and trace elements according to the dietary reference intakes (DRI). After 3 days, his condition had deteriorated. He had gained 5 kg in weight, due to salt and water retention, and developed hypokalaemia (2.8 mmol/l, normal range: 3.5–4.7 mmol/l), hypomagnesaemia (0.49 mmol/l, normal range: 0.7–1.0 mmol/l) and hypophosphataemia (0.05 mmol/l, normal range: 0.74–1.55 mmol/l). He showed neurological symptoms and signs with vertigo and vertical nystagmus. A single dose of thiamine 200mg was given intravenously (i.v.). Artificial nutritional support was decreased to 5 kcal/kg/day for 2 days then to 10 kcal/kg/day. Potassium phosphate 40mmol was infused daily for 3 days. He also received a single i.v. dose of magnesium sulphate 20 mmol. After 3 days his electrolyte and mineral concentrations had risen into the normal range (K 4.2 mmol/l, Mg 0.77 mmol/l and PO4 1.16 mmol/l). Three days later, oral nutrition (1600 kcal/day) was started and micronutrients were given i.v. according to the DRI (one ampoule each of Soluvit, Vitalipid and Addamel). After 37 days, his vertigo resolved. His mood and physical strength gradually improved and he was discharged after 57 days in hospital with a weight of 64.4 kg (gain of 15.4 kg) and a BMI of 19.2 kg/m2. Unfortunately, the vertical nystagmus continued, preventing him from reading or watching television.

Refeeding Syndrome

Symptoms of refeeding syndrome occur from fluid and electrolyte imbalances resulting from nutritional supplementation via oral, enteral, or parenteral routes following a period of adaption to a prolonged starvation or malnourishment.

Gerontology
International Journal of Experimental, Clinical Behavioural, Regenerative and Technological Gerontology
2009;55:393-397

Mortality after Nasogastric Tube Feeding Initiation in Long-Term Care Elderly with Oropharyngeal Dysphagia – The Contribution of Refeeding Syndrome

Emilia Lubart, Arthur Leibovitz, Yosef Dror, Elena Katz, Refael Segal

CRITICAL CARE *Critical Care*, 2010, **14**:R172

Refeeding syndrome influences outcome of anorexia nervosa patients in intensive care unit: an observational study

Marie Vignaud[1,2], Jean-Michel Constantin[1,2*], Marc Ruivard[2,3], Michele Villemeyre-Plane[4,2], Emmanuel Futier[1], Jean-Etienne Bazin[1], Djillali Annane[5], for the AZUREA group (AnorexieRea Study Group)[1]

Patients at high risk of refeeding syndrome

- Patients with anorexia nervosa
- Patients with chronic alcoholism
- Oncology patients
- Postoperative patients
- Elderly patients (comorbidities, decreased physiological reserve)
- Patients with uncontrolled diabetes mellitus (electrolyte depletion, diuresis)
- Patients with chronic malnutrition:

  -Marasmus

  -Prolonged fasting or low energy diet

  -Morbid obesity with profound weight loss

  - High stress patient unfed for >7 days

  -Malabsorptive syndrome (such as inflammatory bowel disease, chronic pancreatitis, cystic fibrosis, short bowel syndrome)
- Long term users of antacids (magnesium and aluminium salts bind phosphate)
- Long term users of diuretics (loss of electrolytes)

Criteria from the guidelines of the National Institute for Health and Clinical Excellence for identifying patients at high risk of refeeding problems (level D recommendations*)[3]

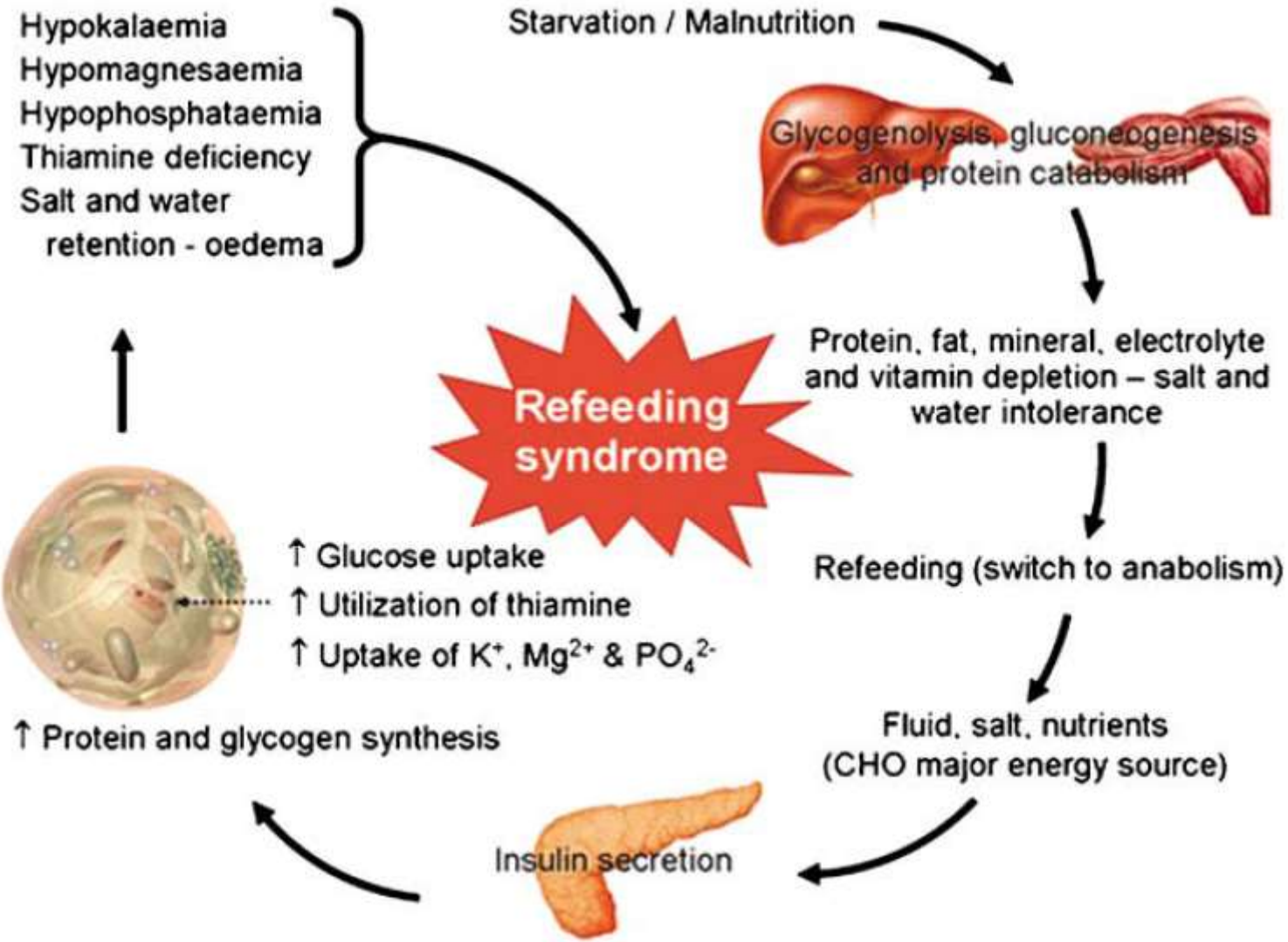
Either the patient has one or more of the following:

- Body mass index (kg/m^2) <16
- Unintentional weight loss >15% in the past three to six months
- Little or no nutritional intake for >10 days
- Low levels of potassium, phosphate, or magnesium before feeding

Or the patient has two or more of the following:

- Body mass index <18.5
- Unintentional weight loss >10% in the past three to six months
- Little or no nutritional intake for >5 days
- History of alcohol misuse or drugs, including insulin, chemotherapy, antacids, or diuretics

*Recommendations derived from low grade evidence—mainly cohort and case series studies—and from consensus expert opinion



European Journal of Clinical Nutrition (2008) 62, 687–694;

Table 1 Some groups of malnourished patients at particular risk of developing the refeeding syndrome

Unintentional weight loss
Loss of >5% of body weight in 1 month
Loss of >7.5% of body weight in 3 months
Loss of >10% of body weight in 6 months
Low nutrient intake
Patients starved for >7 days
Prolonged hypocaloric feeding or fasting
Chronic swallowing problems and other neurological disorders
Anorexia nervosa
Chronic alcoholism
Depression in the elderly
Patients with cancer
Chronic infectious diseases (AIDS, tuberculosis)
During convalescence from catabolic illness
Postoperative patients
Diabetic hyperosmolar states
Morbid obesity with profound weight loss
Homelessness, social deprivation
Idiosyncratic/eccentric diets
Hunger strikers
Increased nutrient losses/decreased nutrient absorption
Significant vomiting and/or diarrhoea
Dysfunction or inflammation of the gastrointestinal tract
Chronic pancreatitis
Chronic antacid users (these bind minerals)
Chronic high-dose diuretic users
After bariatric surgery

The Effect of Insulin on Renal Handling of Sodium, Potassium, Calcium, and Phosphate in Man

RALPH A. DEFRONZO, C. ROBERT COOKE, REUBIN ANDRES, GERALD R. FALOONA, and PAUL J. DAVIS

The Journal of Clinical Investigation Volume 55 April 1975·845–855

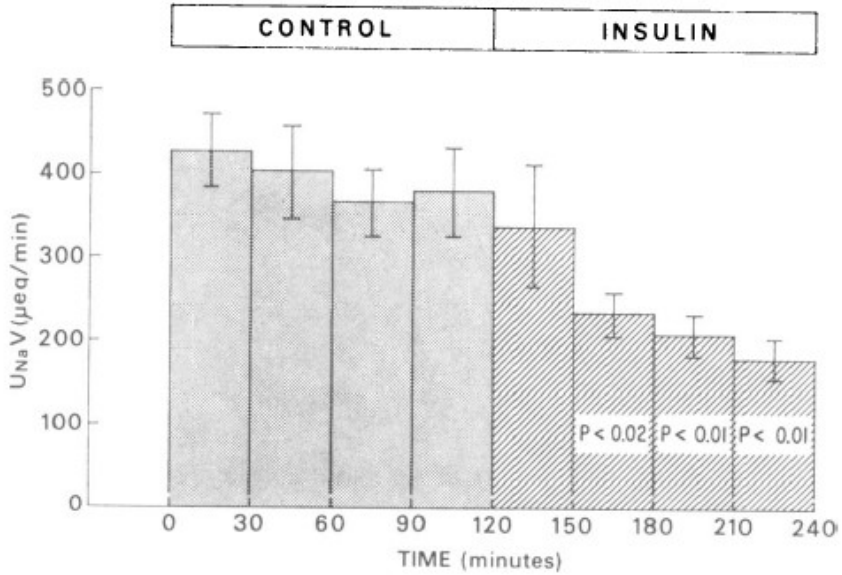


FIGURE 1 Time-course of fall in urinary sodium excretion ($U_{Na}V$) during insulin administration in man. Data represent mean values of six subjects. Plasma insulin concentrations during insulin infusion were constant for each subject (range for the group was 98–193 μU/ml). Steady-state water diuresis was maintained throughout control and insulin administration periods.

Metabolism of CHO

- **Thiamin Pyrophosphate** is a coenzyme for **pyruvate dehydrogenase** complex and **alpha-ketogluterate dehyrgoenase** complex which is required in the Citric Acid Cycle.

- In this process TPP acts as a dehydrogenase and removes CO2

- **Pyruvate - -> Acetyl CoA + CO2**
- ***alpha*-ketoglutarate - -> succinyl CoA + CO2**

A new model of acute liver steatosis induced in rats by fasting followed by refeeding a high carbohydrate-fat free diet. Biochemical and morphological analysis

Journal of Hepatology 1997; **26**: 880–885

Nathalie M. Delzenne, Nancy A. Hernaux and Henryk. S. Taper

Unité de Biochimie Toxicologique et Cancérologique, Département des Sciences Pharmaceutiques, Université Catholique de Louvain, Brussels, Belgium

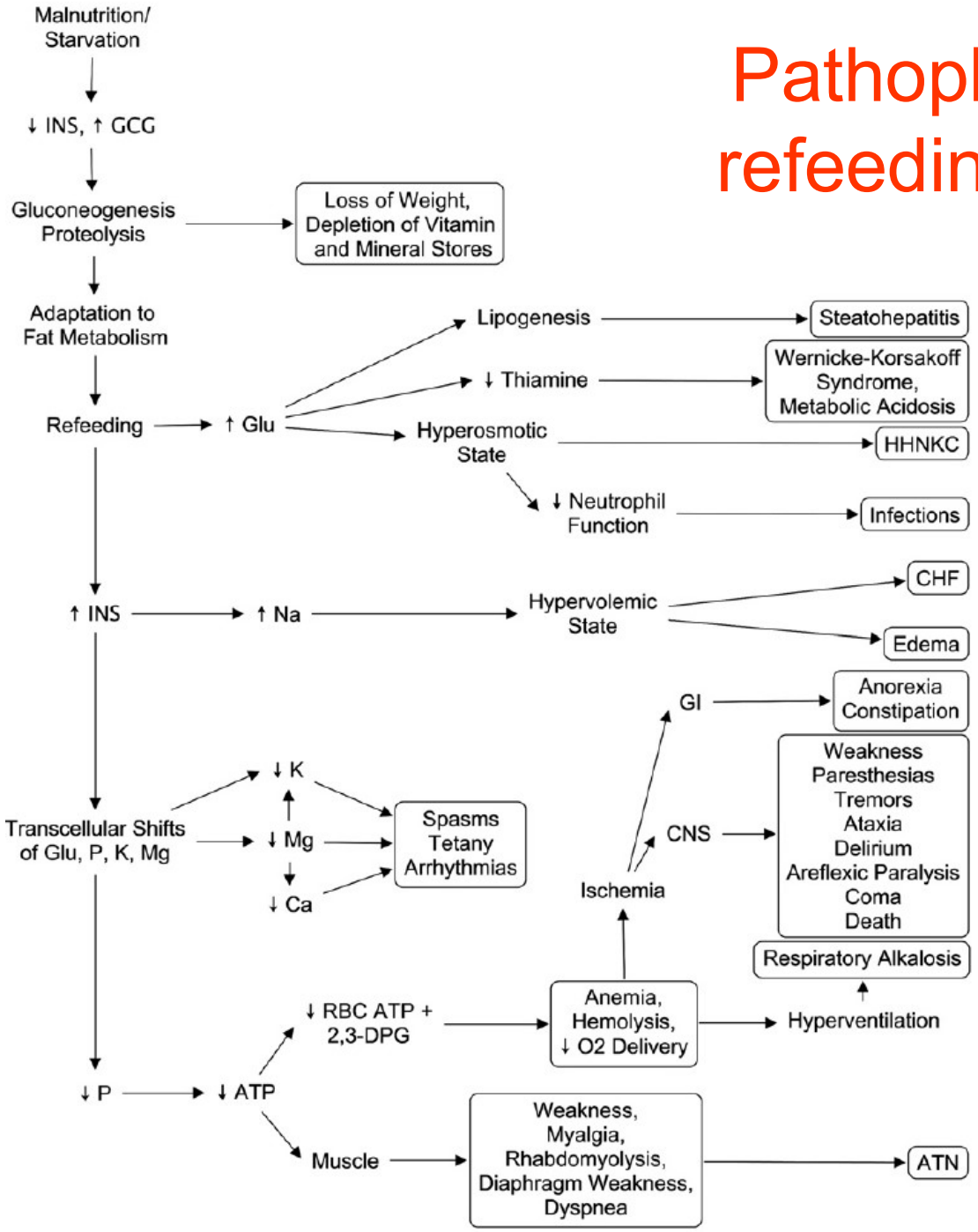
Modulation of lipid homeostasis by starvation, followed by refeeding a hyperglucidic-fat free diet in rats

	Control	Starved 48 h	Refed hcff1 diet		
			6 h	24 h	48 h
Serum					
TG (mM)	1.52±0.07	0.67±0.03**	0.43±0.05**	1.62±0.21	1.82±0.22*
PL (mM)	1.87±0.07	1.13±0.03**	1.14±0.11**	1.38±0.08**	2.10±0.08*
NEFA (mM)	0.34±0.03	1.37±0.15**	0.09±0.02**	0.25±0.02*	0.57±0.14*
Liver					
TG (nmol/mg prot.)	31.28±2.33	29.75±4.28	39.31±2.40	128.56±11.01**	403.01±23.45**
PL (nmol/mg prot.)	120.61±5.26	122.76±6.97	120.47±3.39	121.94±12.48	159.29±8.33**
FAS activity (UI/mg prot.)	25.66±2.67	3.65±0.44**	4.13±1.40**	151.74±11.85**	149.38±5.06**
VLDL-TG secretion ($mmol \cdot l^{-1} \cdot h^{-1}$)	2.45±0,06	0.95±0.06**	nd	3.7±0,24*	7.13±0.71**

Results are expressed as mean±SEM. Measurements were performed in rats: a) fed *ad libitum* with the standard AO4 diet (CONTROLS, $n=7$); b) starved for 48 h ($n=9$); c) starved for 48 h, then refed the HCFF1 diet (the composition of which is given in Material and Methods) for 6 h ($n=5$), 24 h ($n=9$), or 48 h ($n=10$).
VLDL-TG secretion was calculated from the increase in serum TG concentration measured 1 h after Triton WR 1339 to inhibit lipoprotein lipase.
nd=non-determined. Results were statistically compared to control.
Student's *t*-test: *=$p<0,05$, **=$p<0,01$.

fatty acid synthase (FAS) activity, (marker of lipogenic enzyme induction); phospholipids (PL),

Pathophysiology of refeeding syndrome



INS, insulin;
GCG, glucagon; Glu, glucose;
P, phosphorus;
K, potassium;
Na, sodium;
Ca, calcium;
ATP, adenosine triphosphate;
RBC, red blood cell;
CHF, congestive heart failure;
ATN, acute tubular necrosis;
HHNKC, hyperosmolar hyperglycemic nonketotic coma; GI, gastrointestinal system;
CNS, central nervous system.

Alcoholic patients with chronic thiamine deficiency also may have central nervous system (CNS) manifestations known as *Wernicke's encephalopathy*, which consists of horizontal nystagmus, ophthalmoplegia (due to weakness of one or more extraocular muscles), cerebellar ataxia, and mental impairment When there is an additional loss of memory and a confabulatory psychosis, the syndrome is known as *Wernicke-Korsakoff syndrome*. Despite the typical clinical picture and history, Wernicke-Korsakoff syndrome is underdiagnosed.

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Gastroenterology Research and Practice
Volume 2011, Article ID 410971, 6 pages
doi:10.1155/2011/410971

Review Article

Refeeding Syndrome: A Literature Review

L. U. R. Khan, J. Ahmed, S. Khan, and J. MacFie

Table 4: Refeeding regime for patients at risk of RFS [5, 29].

Day	Calorie intake (All feeding routes)	Supplements
Day 1	10 kcal/kg/day For extreme cases (BMI < 14 kg/m^2 or no food >15 days) 5 kcal/kg/day Carbohydrate: 50–60% Fat: 30–40% Protein: 15–20%	Prophylactic supplement PO_4^{2-}: 0.5–0.8 mmol/kg/day K^+: 1–3 mmol/kg/day Mg^{2+}: 0.3-0.4 mmmol/kg/day Na^+: <1 mmol/kg/day (restricted) IV fluids-Restricted, maintain "zero" balance IV Thiamine + vitamin B complex 30 minutes prior to feeding
Day 2–4	Increase by 5 kcal/kg/day If low or no tolerance stop or keep minimal feeding regime	Check all biochemistry and correct any abnormality Thiamine + vitamin B complex orally or IV till day 3 Monitoring as required (Table 3)
Day 5–7	20–30 kcal/kg/day	Check electrolytes, renal and liver functions and minerals Fluid: maintain zero balance Consider iron supplement from day 7
Day 8–10	30 kcal/kg/day or increase to full requirement	Monitor as required (Table 3)

If RFS is suspected based on clinical and biochemical assessment or the patient develops intolerance to artificial nutritional support, the energetic intake should be reduced or stopped.
Feeding rate should be increased to meet full requirements for fluid, electrolytes, vitamins, and minerals if the patient is clinically and biochemically stable.

Nausea and vomiting after a prolonged drinking binge

A 45-year-old man with a **history of alcohol abuse** is brought to the emergency room complaining of **nausea and vomiting and mild abdominal pain**. He had been on a **5-day drinking binge** until the onset of these symptoms. He has no other medical history and was taking no other drugs and no medications. On examination, he is **sleeping** on the stretcher but is easily **arousable**. He is afebrile with a pulse rate of 115 bpm, blood pressure 122/72 mm Hg, and respiratory rate of 18 breaths per minute. His **breath has a strong odor of alcohol**. His eyes are bloodshot but anicteric, his chest is clear to auscultation, and his heart is tachycardic but regular in rhythm, and no murmurs are appreciated. His abdominal examination is significant for mild epigastric tenderness with hypoactive bowel sounds, but no guarding or tenderness is noted. He has no focal neurologic deficits. Initial labs show **sodium 145 mEq/L**, **potassium 5 mEq/L**, **chloride 102 mEq/L**, and **bicarbonate 14 mEq/L**, with BUN 20 mg/dL, and **creatinine 1.5 mg/dL**. Serum glucose is 142 mg/dL. A serum Acetest is weakly positive for ketones. Urinalysis shows **ketonuria** but **no glycosuria** and no cells, casts, or crystals. Urine drug screen is negative, and abdominal x-rays show a normal bowel gas pattern with no signs of obstruction.

What is the most likely diagnosis?
What is the best initial diagnostic test?
What is the best initial treatment?

CFIM n° 23

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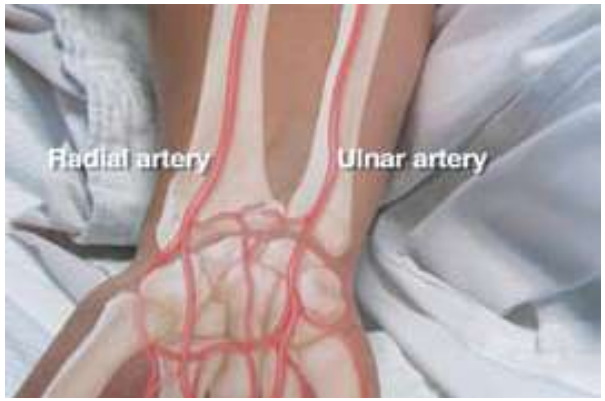
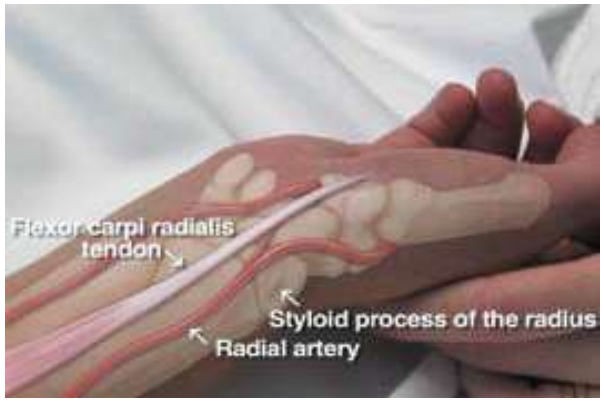
What is the most likely diagnosis? **Alcoholic ketoacidosis**
What is the best initial diagnostic test? **Hemogasanalysis** with **phosphate**, **magnesium** and **calcium** determination
What is the best initial treatment? **IV thiamine supplementation (200 mg/day for 5 days), infusion of 5% dextrose with 0.9% saline, restricted feeding regime, follow serum electrolyte levels and correct any abnormalities.**

CFIM n° 23





LOCATION OF THE RADIAL ARTERY

Extend the patient's wrist to bring the radial artery to a more superficial position. First, palpate the styloid process of the radius. Next, palpate the flexor carpi radialis tendon located medial to the styloid process of the radius. The radial artery is located between the styloid process of the radius and the flexor carpi radialis tendon

The syringe should be held at a 45° angle or less in your opposite hand, much like you would hold a pencil or a dart. This near-parallel insertion of the needle will minimize trauma to the artery and allow the smooth muscle fibers to seal the puncture hole after you withdraw the needle.

Arterial Puncture for Blood Gas Analysis

N Engl J Med 2011;364:e7

EMOGASANALISI ARTERIOSA

pH	7.350 - 7.450	
pCO_2	35.0 - 45.0	mm Hg
pO_2	80.0 - 90.0	mm Hg
HCO_{3-}	22.0 - 26.0	mmol/L
HCO_3 st	22.0 - 26.0	mmol/L
CO_2 tot	23.0 - 27.0	mmol/L
BE st	-4	mmol/L
BE	-4	mmol/L
O_2 sat.	96.00 - 97.00	%

Standard bicarbonate is the bicarbonate concentration of a sample when the pCO2 has been adjusted (or 'standardised') to 40 mmHg at a temperature of 37C. This would remove the influence of changes in pCO2 by seeing what the [HCO3] would be if the respiratory component was made the same for all measurements.

Base excess is the commonest parameter used to express non-respiratory pH disturbances.
Base excess is the quantity of base (HCO3-, in mEq/L) that is above or below the normal range of buffer base in the body (22 -28 mEq/L).
Severe metabolic acidosis is associated with a base deficit of -10 mEq/L
A **positive number** is called a base excess and indicates a **metabolic alkalosis**.
A **negative number** is called a base deficit and indicates a **metabolic acidosis**.

EMOGASANALISI ARTERIOSA

pH	7.350 - 7.450	
pCO_2	35.0 - 45.0	mm Hg
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HCO_3 st	22.0 - 26.0	mmol/L
CO_2 tot	23.0 - 27.0	mmol/L
BE st	-4	mmol/L
BE	-4	mmol/L
O_2 sat.	96.00 - 97.00	%

EMOGASANALISI VENOSA

pH	7.320 - 7.420
pCO_2	41.0 - 51.0
pO_2	20.0 - 40.0
HCO_{3-}	24.0 - 28.0
CO_2 tot	25.0 - 29.0
O_2 sat.	40.0 - 70.0

Venous blood gases can provide useful information for acid–base assessment since the arteriovenous differences in pH and Pco_2 are small and relatively constant. Venous blood pH is usually 0.03–0.04 units lower than arterial blood pH, and venous blood Pco_2 is 7 or 8 mm Hg higher than arterial blood Pco_2. Calculated HCO_3^- concentration in venous blood is at most 2 mEq/L higher than arterial blood HCO_3^-. Arterial and venous blood gases will not be equivalent during a cardiopulmonary arrest; arterial samples should be obtained for the most accurate measurements of pH and Pco_2.

Acid–base balance

Arterial blood pH is closely regulated in health to 7.40 ± 0.05 by various mechanisms including bicarbonate, other plasma buffers such as deoxygenated haemoglobin, and the kidney. Acid–base disorders needlessly confuse many people, but if a few simple rules are applied, then interpretation and diagnosis are easy. The key principle is that primary changes in HCO_3^- are *metabolic* and in CO_2 *respiratory*. See fig 1.

A simple method

1 *Look at the pH:* is there an acidosis or alkalosis?
- pH <7.35 is an acidosis; pH >7.45 is an alkalosis.

2 *Is the CO_2 abnormal?* (Normal concentration 4.7–6.0kPa) **35-45mm Hg**
If so, is the change in keeping with the pH?
- CO_2 is an acidic gas—is CO_2 raised with an acidosis, lowered with an alkalosis? If so, it is in keeping with the pH and thus caused by a *respiratory* problem. If there is no change, or an opposite one, then the change is compensatory.

3 *Is the HCO_3^- abnormal?* (Normal concentration 22–28mmol/L)
If so, is the change in keeping with the pH?
- HCO_3^- is alkaline—is HCO_3^- raised with an alkalosis, lowered with an acidosis? If so, the problem is a *metabolic* one.

Table 21–12. Primary acid-base disorders

Disorder	Primary Defect	Compensatory Response
Respiratory acidosis		
Acute	↑Pco_2	↑HCO_3^-
Chronic	↑Pco_2	↑HCO_3^-
Respiratory alkalosis		
Acute	↓Pco_2	↓HCO_3^-
Chronic	↓Pco_2	↓HCO_3^-
Metabolic acidosis	↓HCO_3^-	↓Pco_2
Metabolic alkalosis	↑HCO_3^-	↑ Pco_2

An example

15mm Hg

Your patient's blood gas shows: pH 7.05, CO_2 2.0kPa, HCO_3^- 8.0mmol/L. There is an *acidosis*. The CO_2 is low, and thus it is a compensatory change. The HCO_3^- is low and is thus the primary change, ie a *metabolic* acidosis.

In order to recognize 'compensation' look for a change in the buffering system that was not involved in the 'primary' problem.

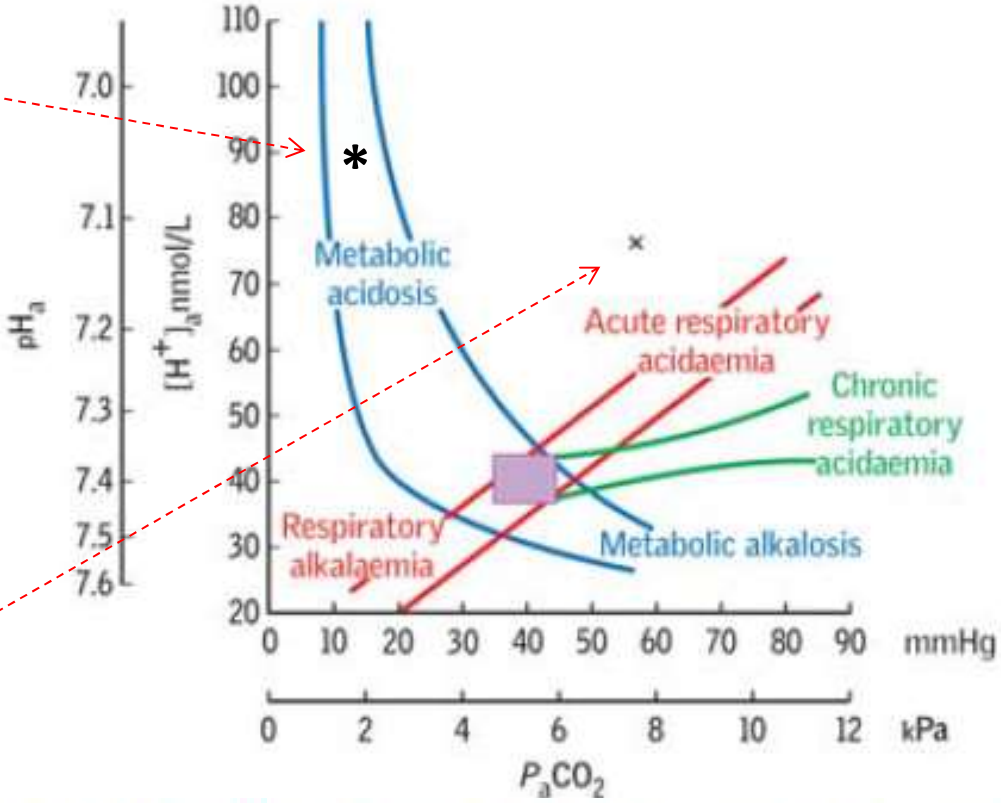


Fig 1. The shaded area represents normality. This method is very powerful. The result represented by point x, for example, indicates that the acidosis is in part respiratory and in part metabolic. Seek a cause for each.

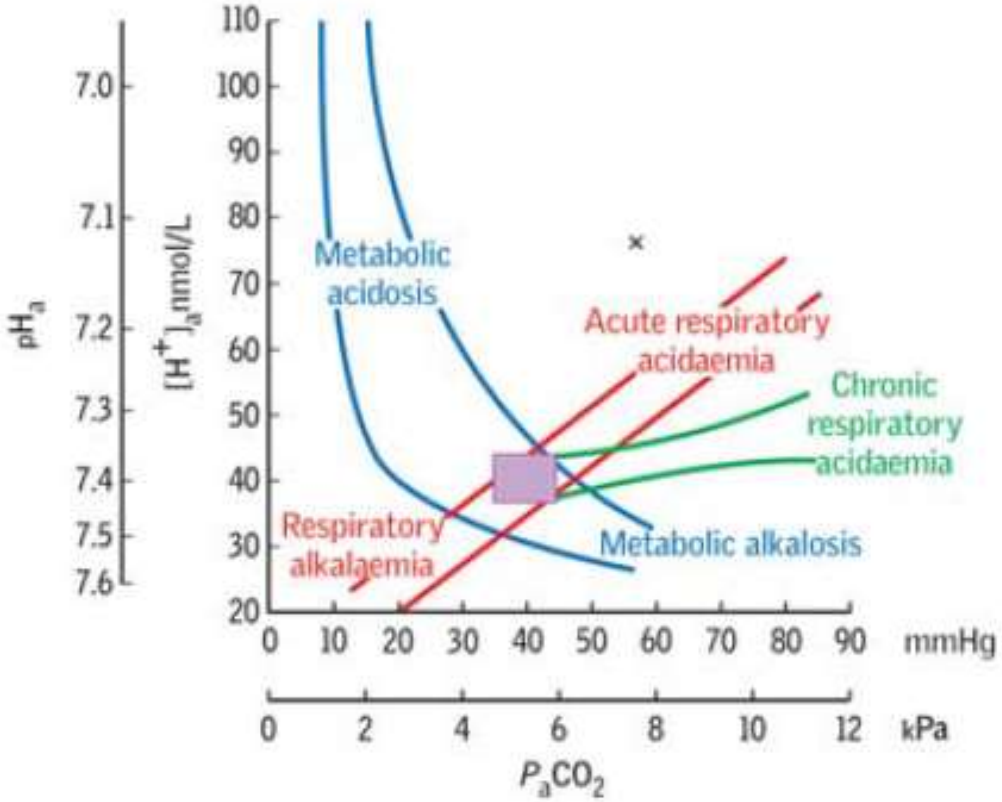
Compensatory Responses: summary and take home points

- **Compensatory response to respiratory disorders** is two-fold; a fast response due to cell buffering and a significantly slower response due to renal adaptation.
- **Compensatory response to metabolic disorders** involves only an alteration in alveolar ventilation.
- Metabolic responses cannot be defined as acute or chronic in terms of respiratory compensation because the extent of compensation is the same in each case.

Primary disorder	Initial chemical change	Compensatory response	Compensatory Mechanism	Expected level of compensation
Metabolic Acidosis	↓HCO3-	↓PCO2	Hyperventilation	PCO2 = (1.5 × [HCO3-]) + 8 ± 2 ↓PCO2 = 1.2 ×Δ [HCO3-] PCO2 = last 2 digits of pH
Metabolic Alkalosis	↑HCO3-	↑PCO2	Hypoventilation	PCO2 = (0.9 × [HCO3-]) + 16 ± 2 ↑PCO2 = 0.7 × Δ [HCO3-]
Respiratory Acidosis	↑PCO2	↑HCO3-		
Acute			Intracellular Buffering (hemoglobin, intracellular proteins)	↑[HCO3-] = 1 mEq/L for every 10 mm Hg ΔPCO2
Chronic			Generation of new HCO3- due to the increased excretion of ammonium.	↑[HCO3-] = 3.5 mEq/L for every 10 mm Hg ΔPCO2
Respiratory Alkalosis	↓PCO2	↓HCO3-		
Acute			Intracellular Buffering	↓[HCO3-] = 2 mEq/L for every 10 mm Hg ΔPCO2
Chronic			Decreased reabsorption of HCO3-, decreased excretion of ammonium	↓[HCO3-] =4 mEq/L for every 10 mm Hg ΔPCO2

Table 21–12. Primary acid-base disorders and expected compensation.

Disorder	Primary Defect	Compensatory Response	Magnitude of Compensation
Respiratory acidosis			
Acute	↑Pco_2	↑HCO_3^-	↑ HCO_3^- 1 mEq/L per 10 mm Hg ↑ Pco_2
Chronic	↑Pco_2	↑HCO_3^-	↑ HCO_3^- 3.5 mEq/L per 10 mm Hg ↑ Pco_2
Respiratory alkalosis			
Acute	↓Pco_2	↓HCO_3^-	↓HCO_3^- 2 mEq/L per 10 mm Hg ↓Pco_2
Chronic	↓Pco_2	↓HCO_3^-	↓HCO_3^- 5 mEq/L per 10 mm Hg ↓Pco_2
Metabolic acidosis	↓HCO_3^-	↓Pco_2	↓Pco_2 1.3 mm Hg per 1 mEq/L ↓HCO_3^-
Metabolic alkalosis	↑HCO_3^-	↑ Pco_2	↑Pco_2 0.7 mm Hg per 1 mEq/L ↑HCO_3^-



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Respiratory alkalosis			
Acute	↓Pco_2	↓HCO_3^-	↓HCO_3^- 2 mEq/L per 10 mm Hg ↓Pco_2
Chronic	↓Pco_2	↓HCO_3^-	↓HCO_3^- 5 mEq/L per 10 mm Hg ↓Pco_2
Metabolic acidosis	↓HCO_3^-	↓Pco_2	↓Pco_2 1.3 mm Hg per 1 mEq/L ↓HCO_3^-
Metabolic alkalosis	↑HCO_3^-	↓Pco_2	↑Pco_2 0.7 mm Hg per 1 mEq/L ↑HCO_3^-

Table 21–12. Primary acid-base disorders

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Respiratory acidosis		
Acute	$\uparrow P_{CO_2}$	$\uparrow HCO_3^-$
Chronic	$\uparrow P_{CO_2}$	$\uparrow HCO_3^-$
Respiratory alkalosis		
Acute	$\downarrow P_{CO_2}$	$\downarrow HCO_3^-$
Chronic	$\downarrow P_{CO_2}$	$\downarrow HCO_3^-$
Metabolic acidosis	$\downarrow HCO_3^-$	$\downarrow P_{CO_2}$
Metabolic alkalosis	$\uparrow HCO_3^-$	$\uparrow P_{CO_2}$

The anion gap estimates unmeasured plasma anions ('fixed' or organic acids such as phosphate, ketones, and lactate, which are hard to measure directly). It is calculated as the difference between plasma cations (Na^+ and K^+) and anions (Cl^- and HCO_3^-). It is helpful in determining the cause of a metabolic acidosis.

Anion gap = $Na^+ – (HCO_3^- + Cl^-)$
Normal range 6-12 mmol/L

When serum potassium is included in the anion gap measurement, the normal range is approximately 4 meq/L higher than the number calculated without including potassium.

Metabolic acidosis pH↓, HCO_3^- ↓

Causes of metabolic acidosis and an increased anion gap: **>12 mEq**

Due to increased production, or reduced excretion, of fixed/organic acids. HCO_3^- falls and unmeasured anions associated with the acids accumulate.

- Lactic acid (shock, infection, tissue ischaemia)
- Urate (renal failure)
- Ketones (diabetes mellitus, alcohol)
- Drugs/toxins (salicylates, biguanides, ethylene glycol, methanol)

Causes of metabolic acidosis and a normal anion gap: **6-12 mEq** **Hyperchloremic**

Due to loss of bicarbonate or ingestion of H^+ ions (Cl^- is retained).

- Renal tubular acidosis
- Diarrhoea
- Drugs (acetazolamide)
- Addison's disease
- Pancreatic fistula
- Ammonium chloride ingestion

Na^+ = 135-145 mEq/L
K^+ = 3.5-5.0 mEq/L
HCO_3^- = 22-26 mmol/L
Cl^- = 98-110 mEq/L

Table 21–13. Anion gap in metabolic acidosis.[1]

Decreased (< 6 mEq)
Hypoalbuminemia (decreased unmeasured anion)
Plasma cell dyscrasias
Monoclonal protein (cationic paraprotein) (accompanied by chloride and bicarbonate)
Bromide intoxication
Increased (> 12 mEq)
Metabolic anion
Diabetic ketoacidosis
Alcoholic ketoacidosis
Lactic acidosis
Chronic kidney disease (advanced stages) (PO_4^{3-}, SO_4^{2-})
Starvation
Metabolic alkalosis (increased number of negative charges on protein)
5-oxoproline acidosis from acetaminophen toxicity
Drug or chemical anion
Salicylate intoxication
Sodium carbenicillin therapy
Methanol (formic acid)
Ethylene glycol (oxalic acid)
Normal (6–12 mEq)
Loss of HCO_3
Diarrhea
Recovery from diabetic ketoacidosis
Pancreatic fluid loss, ileostomy (unadapted)
Carbonic anhydrase inhibitors
Chloride retention
Renal tubular acidosis
Ileal loop bladder
Administration of HCl equivalent or NH_4Cl
Arginine and lysine in parenteral nutrition

[1]Reference ranges for anion gap may vary based on differing laboratory methods.

Anion gap = $Na^+ – (HCO_3^- + Cl^-)$
Normal range 6-12 mmol/L

Anion gap = $(Na^+ + K^+) – (HCO_3^- + Cl^-)$
Normal range - +4mmol/L

Na^+ = 135-145 mEq/L
K^+ = 3.5-5.0 mEq/L
HCO_3^- = 22-26 mmol/L
Cl^- = 98-110 mEq/L

Na^+ = 135-145 mEq/L
K^+ = 3.5-5.0 mEq/L
HCO_3^- = 22-26 mmol/L
Cl^- = 98-110 mEq/L

Metabolic alkalosis pH↑, HCO_3^-↑

- Vomiting
- K^+ depletion (diuretics)
- Burns
- Ingestion of base

Control of potassium Most K^+ is intracellular, and thus serum K^+ levels are a poor reflection of total body potassium. The concentrations of K^+ and H^+ in extracellular fluid tend to vary together. This is because these ions compete with each other in the exchange with Na^+ that occurs across most cell membranes and in the distal convoluted tubule of the kidney, where Na^+ is reabsorbed from the urine. Thus, if the H^+ concentration is high, less K^+ will be excreted into the urine. Similarly K^+ will compete with H^+ for exchange across cell membranes and extracellular K^+ will accumulate. Insulin and catecholamines both stimulate K^+ uptake into cells by stimulating the Na^+/K^+ pump.

Respiratory acidosis pH↓, CO_2↑

- Type 2 respiratory failure due to any lung, neuromuscular, or physical cause (p180).
- Most commonly chronic obstructive pulmonary disease (COPD). Look at the P_aO_2. It will probably be low. Is oxygen therapy required? Use controlled O_2 (Venturi connector) if COPD is the underlying cause, as too much oxygen may make matters worse (p181).

►► Beware exhaustion in asthma, pneumonia and pulmonary oedema, which can present with this picture when close to respiratory arrest. These patients require urgent ITU review for ventilatory support.

Arterial blood gas (ABG) analysis Heparinized blood is usually taken from the radial or femoral artery (see p785), and pH, P_aO_2, and P_aCO_2 are measured using an automated analyser. Remember to note FiO_2 (fraction or percentage of inspired O_2).

- Normal pH is 7.35–7.45. A pH <7.35 indicates *acidosis* and a pH >7.45 indicates *alkalosis*. For interpretation of abnormalities, see p684.
- Normal P_aO_2 is 10.5–13.5kPa. Hypoxia is caused by one or more of the following reasons: ventilation/perfusion (V/Q) mismatch, hypoventilation, abnormal diffusion, right to left cardiac shunts. Of these, V/Q mismatch is the commonest cause. Severe hypoxia is defined as a P_aO_2 <8kPa (see p180). **80-100 mm Hg**
- Normal P_aCO_2 is 4.5–6.0kPa. P_aCO_2 is directly related to alveolar ventilation. A P_aCO_2 <4.5kPa indicates *hyperventilation* and a P_aCO_2 >6.0kPa indicates *hypoventilation*. **35-45mm Hg**

< 60 mm Hg **< 45 mm Hg**

Type 1 respiratory failure is defined as P_aO_2 <8kPa and P_aCO_2 <6.0kPa.

Type 2 respiratory failure is defined as P_aO_2 <8kPa and P_aCO_2 >6.0kPa.

< 60 mm Hg **> 45 mm Hg**

Respiratory alkalosis pH↑, CO_2↓

A result of hyperventilation of any cause. *CNS causes:* Stroke; subarachnoid bleed; meningitis. *Others:* Mild/moderate asthma, anxiety; altitude; T°↑; pregnancy; pulmonary emboli (reflex hyperventilation); drugs, eg salicylates.

MIXED ACID–BASE DISORDERS

Two or three simultaneous disorders can be present in a mixed acid-base disorder, but there can never be two primary respiratory disorders. Uncovering a mixed acid-base disorder is clinically important, but requires a methodical approach to acid-base analysis (see box, Step-by-Step Analysis of Acid-Base Status). Once the primary disturbance has been determined, the clinician should assess whether the compensatory response is appropriate (Table 21–12). An inadequate or an exaggerated response indicates the presence of another primary acid-base disturbance.

The anion gap should always be calculated for two reasons. First, it is possible to have an abnormal anion gap even if the sodium, chloride, and bicarbonate levels are normal. Second, a large anion gap (> 20 mEq/L) suggests a primary metabolic acid-base disturbance regardless of the pH or serum bicarbonate level because a markedly abnormal anion gap is never a compensatory response to a respiratory disorder. In patients with an increased anion gap metabolic acidosis, clinicians should calculate the corrected bicarbonate. In increased anion gap acidoses, there should be a mole for mole decrease in HCO_3^- as the anion gap increases. A corrected HCO_3^- value higher or lower than normal (24 mEq/L) indicates the concomitant presence of metabolic alkalosis or normal anion gap metabolic acidosis, respectively.

In **alcoholic ketoacidosis,** decreased carbohydrate intake reduces insulin secretion, and alcohol-induced inhibition of gluconeogenesis leads to stimulation of lipolysis and contributes to increased ketoacid formation, predominantly β-hydroxybutyrate. The nitroprusside reaction test to detect serum ketones (Acetest) can detect acetoacetate, but not β-hydroxybutyrate, so the nitroprusside reaction may only be weakly positive, and can lead one to underestimate the degree of ketosis. With treatment, as the patient improves, the formation of acetoacetate is favored, so the degree of measured ketosis may appear to paradoxically worsen. In contrast to the markedly elevated glucose levels in DKA, the plasma glucose concentration in alcoholic ketoacidosis may be low, normal, or somewhat elevated. In alcoholic or fasting ketoacidosis, the primary treatment is administration of dextrose and saline solutions; the dextrose will increase insulin secretion and reduce lipolysis, along with saline to replenish fluid deficits. Electrolyte deficiencies such as hypophosphatemia, hypokalemia, or hypomagnesemia are also common, and should be corrected. **In alcoholics, thiamine 100 mg should be administered prior to any glucose-containing solution to decrease the risk of precipitating Wernicke encephalopathy or Korsakoff syndrome.**

Alcoholic patients with chronic thiamine deficiency also may have central nervous system (CNS) manifestations known as *Wernicke's encephalopathy*, which consists of horizontal nystagmus, ophthalmoplegia (due to weakness of one or more extraocular muscles), cerebellar ataxia, and mental impairment When there is an additional loss of memory and a confabulatory psychosis, the syndrome is known as *Wernicke-Korsakoff syndrome*. Despite the typical clinical picture and history, Wernicke-Korsakoff syndrome is underdiagnosed.

23.1 A 34-year-old woman presents to your office for a checkup. Her only medical history is recurrent kidney stones. She is currently asymptomatic. Her labs show Na 136, K 3.0, Cl 110, HCO_3 16, creatinine 1.0, and glucose 110. Her urine pH is 6.5. What is the most likely diagnosis?

A. Bulimia with chronic hypokalemia

B. Ethylene glycol ingestion with calcium oxalate stones

C. Type 1 distal RTA

D. Type 4 RTA due to diabetic kidney disease

23.2 Which of the following urine electrolytes is most useful in estimating the ECF volume status of a patient with metabolic alkalosis?

A. Urine Na

B. Urine Cl

C. Urine urea

D. Urine anion gap

23.3 A 59-year-old man is brought to the emergency room obtunded and unable to give a history. He is afebrile and normotensive. He has edema of the optic disc, and his neurologic examination does not reveal any focal neurologic deficits. His labs include pH 7.25, $Paco_2$ 23, Na 145, K 5.3, Cl 105, HCO_3 10, BUN 25, creatinine 1.3, and glucose 80. His measured serum osmolality is 335 mOsm, and his blood alcohol level is 0. Urinalysis shows no crystals. What is the most likely cause of his mental status and acidemia?

A. Ethanol intoxication

B. Acute stroke with hypoventilation

C. Methanol intoxication

D. Ethylene glycol intoxication

23.1 **C.** She has a non-AG acidosis with alkaline urine, suggestive of RTA. Patients with type 1 RTA tend toward hypokalemia, whereas type 4 RTA has hyperkalemia. With alkaline urine and hypercalciuria, patients are predisposed to recurrent calcium phosphate stones. Vomiting from bulimia might cause metabolic alkalosis. Ethylene glycol would cause AG acidosis.

23.2 **B.** Urine chloride is useful for judging the volume status of patients with metabolic alkalosis, and is used to classify them as either volume depleted (low urine Cl) or volume repleted (high urine Cl). If low urine chloride, they are considered chloride responsive, and the alkalosis can be corrected with the infusion of saline. Urine Na is not a good indicator of volume status, since urinary HCO_3 losses will force a certain amount of Na with it.

23.3 **C.** The patient has a high AG metabolic acidosis. He has a high osmolal gap, but his ethanol level is undetectable. The most likely intoxication is methanol, which is metabolized to formic acid. This toxic metabolite causes mental status depression, papilledema, optic neuritis, and metabolic acidosis. Hypoventilation would cause respiratory acidosis. Ethylene glycol may cause the formation of calcium oxalate crystals in the urine.

In **alcoholic ketoacidosis,** decreased carbohydrate intake reduces insulin secretion, and alcohol-induced inhibition of gluconeogenesis leads to stimulation of lipolysis and contributes to increased ketoacid formation, predominantly β-hydroxybutyrate. The nitroprusside reaction test to detect serum ketones (Acetest) can detect acetoacetate, but not β-hydroxybutyrate, so the nitroprusside reaction may only be weakly positive, and can lead one to underestimate the degree of ketosis. With treatment, as the patient improves, the formation of acetoacetate is favored, so the degree of measured ketosis may appear to paradoxically worsen. In contrast to the markedly elevated glucose levels in DKA, the plasma glucose concentration in alcoholic ketoacidosis may be low, normal, or somewhat elevated. In alcoholic or fasting ketoacidosis, the primary treatment is administration of dextrose and saline solutions; the dextrose will increase insulin secretion and reduce lipolysis, along with saline to replenish fluid deficits. Electrolyte deficiencies such as hypophosphatemia, hypokalemia, or hypomagnesemia are also common, and should be corrected. **In alcoholics, thiamine 100 mg should be administered prior to any glucose-containing solution to decrease the risk of precipitating Wernicke encephalopathy or Korsakoff syndrome.**

In a patient with an elevated AG acidosis and a suggestive social history, one must also consider the possibility of other ingestions, such as methanol or ethylene glycol. Methanol and ethylene glycol are frequently found in high concentration in automotive antifreeze and deicing solutions, windshield wiper fluid, and other solvents. They may be ingested as a substitute for ethanol, by accident, or intentionally, for example, in a suicide attempt. **Methanol** is metabolized via the alcohol dehydrogenase (ADH) enzyme to formaldehyde and formic acid, causing **optic nerve and CNS injury.** **Ethylene glycol** is metabolized by ADH to glycolate, glyoxylate, and oxalate and can cause acute renal failure due to glycolate-induced damage to tubules, and tubular obstruction from precipitated oxalate crystals. If either of these ingestions is suspected,

Table 23–3 • CAUSES OF NON-ANION GAP ACIDOSIS

Gastrointestinal bicarbonate loss

- Diarrhea
- External pancreatic or small bowel drainage
- Ureterosigmoidostomy, jejunal loop, ileal loop

Renal acidosis

A. Hypokalemia
   - Proximal RTA (type 2)
   - Distal (classic) RTA (type 1)

B. Hyperkalemia
   1. Generalized distal nephron dysfunction (type 4 RTA)
      - Mineralocorticoid deficiency
      - Mineralocorticoid resistance

Drug-induced hyperkalemia (with renal insufficiency)

- Potassium-sparing diuretics (amiloride, triamterene, spironolactone)
- Trimethoprim
- ACE inhibitors and ARBs
- NSAIDs

Other causes

- Acid loads (ammonium chloride, hyperalimentation)
- Expansion acidosis (rapid saline administration)

Non-AG metabolic acidosis: Causes of non-AG metabolic acidosis are listed in Table 23–3. With bicarbonate losses from the GI tract or kidney, there is a rise in chloride concentration that approximates the fall in bicarbonate concentration (hyperchloremic metabolic acidosis), so the AG remains normal. Most GI causes can be elicited by the clinical history (diarrhea, external pancreatic, biliary, or small bowel drainage). In patients with diarrhea and hypokalemia, renal synthesis and secretion of ammonia is stimulated, causing a buffering of the urine with a pH greater than 5.5 (higher than expected in acidosis). Acidosis with high urine pH due to GI losses (has high urinary NH_4^+) can be differentiated from RTA (has low urinary NH_4^+) by assessing urinary NH_4^+ excretion. Urine NH_4^+ cannot be directly measured, but it can be estimated with the urine anion gap (UAG).

When **[Na + K] − [Cl] is negative** (usually −20 to −50 mEq/L), then urinary NH_4^+ is appropriately increased, suggesting a **GI or extrarenal cause of acidosis.**

When the **UAG is positive**, it suggests **impaired NH_4^+ excretion**. Causes include **distal (type 1) RTA**, hypoaldosteronism, or **type 4 RTA**. In patients with advanced chronic kidney disease, decline in functional renal mass also causes a proportional reduction in renal NH_4^+ excretion.

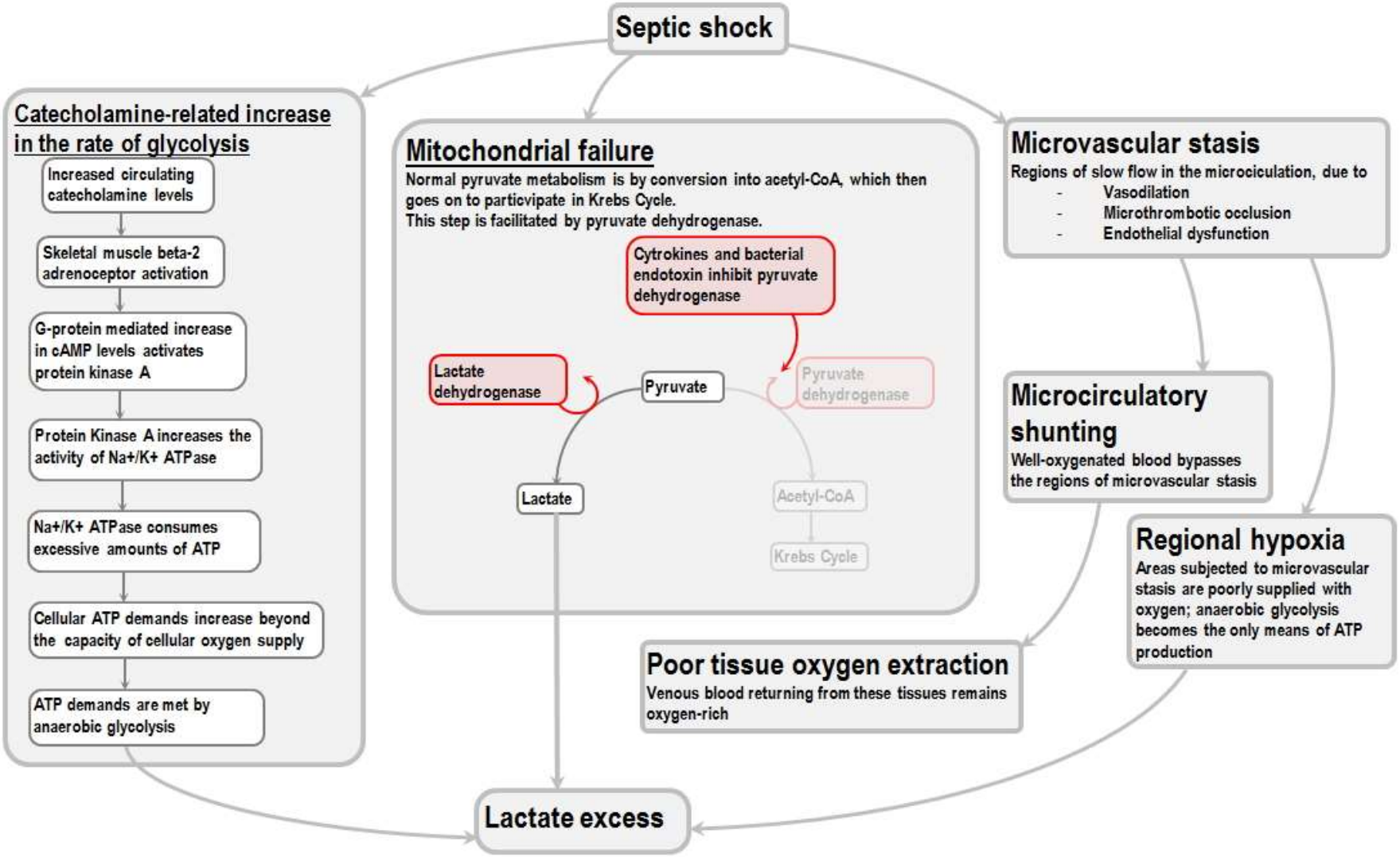
Distal or type 1 RTA in adults is most commonly caused by autoimmune diseases such as **Sjogren syndrome** or rheumatoid arthritis. Patients have a high urine pH, and often have **hypokalemia.** Most patients have hypocitraturia and hypercalciuria, so **kidney stones** and nephrocalcinosis commonly occur. Treatment usually involves alkalinization and citrate supplementation with sodium or potassium citrate to normalize pH and prevent stone formation.

Type 4 RTA is due to generalized distal nephron dysfunction, and is commonly seen in patients with **diabetic nephropathy**. Low plasma renin activity is common in diabetic patients, leading to hyporeninemic hypoaldosteronism. Patients typically present with **hyperkalemia** and a mild hyperchloremic metabolic acidosis. The hyperkalemia is usually managed with a low potassium diet and use of loop or thiazide diuretics.

Diabetic ketoacidosis (DKA)[42]

Mechanism Normally the body metabolizes carbohydrates, leading to efficient energy production. Ketoacidosis is an alternative metabolic pathway, normally used in starvation states, it is far less efficient, and produces acetone as a by product (hence the fruity breath of patients in ketosis). In acute diabetic ketoacidosis, there is excessive glucose, but because of the lack of insulin, this cannot be taken up into cells to be metabolized, so pushing the body into a starvation-like state where ketoacidosis is the only mechanism of energy production. The combination of severe acidosis and hyperglycaemia can be deadly, so early recognition and treatment is important.

Typical picture Gradual drowsiness, vomiting and dehydration in type 1 diabetic (very rarely type 2) ►Do glucose in *all* those with unexplained vomiting, abdo pain, polyuria, polydipsia, lethargy, anorexia, ketotic breath, dehydration, coma, or deep breathing (sighing 'Kussmaul' hyperventilation). *Triggers:* Infection, eg UTI; surgery; MI; pancreatitis; chemotherapy; antipsychotics;[43] wrong insulin dose/non-compliance.


Septic shock
Catecholamine-related increase in the rate of glycolysis
Increased circulating catecholamine levels
Skeletal muscle beta-2 adrenoceptor activation
G-protein mediated increase in cAMP levels activates protein kinase A
Protein Kinase A increases the activity of Na+/K+ ATPase
Na+/K+ ATPase consumes excessive amounts of ATP
Cellular ATP demands increase beyond the capacity of cellular oxygen supply
ATP demands are met by anaerobic glycolysis
Mitochondrial failure
Normal pyruvate metabolism is by conversion into acetyl-CoA, which then goes on to particvipate in Krebs Cycle.
This step is facilitated by pyruvate dehydrogenase.
Cytrokines and bacterial endotoxin inhibit pyruvate dehydrogenase
Lactate dehydrogenase
Pyruvate
Pyruvate dehydrogenase
Lactate
Acetyl-CoA
Krebs Cycle
Microvascular stasis
Regions of slow flow in the microciculation, due to
- Vasodilation
- Microthrombotic occlusion
- Endothelial dysfunction
Microcirculatory shunting
Well-oxygenated blood bypasses the regions of microvascular stasis
Regional hypoxia
Areas subjected to microvascular stasis are poorly supplied with oxygen; anaerobic glycolysis becomes the only means of ATP production
Poor tissue oxygen extraction
Venous blood returning from these tissues remains oxygen-rich
Lactate excess

Causes of Lactic Acidosis.

Cause	Presumed Mechanism or Mechanisms	Comments
Cardiogenic or hypovolemic shock, advanced heart failure, or severe trauma	Decreased O_2 delivery to tissues; epinephrine-induced β_2-adrenoceptor stimulation can be a contributory factor	With sepsis, these causes account for the majority of cases of lactic acidosis
Sepsis	Epinephrine-induced β_2-adrenoceptor stimulation with or without decreased O_2 delivery to tissues; reduced clearance of lactate even in hemodynamically stable patients	Evidence of decreased O_2 delivery can be subtle; even in the absence of macrocirculatory impairment, dysfunction of microcirculation can be present
Severe hypoxemia	Decreased O_2 delivery to tissues	Requires Pao_2 <30 mm Hg
Carbon monoxide poisoning	Decreased O_2 delivery to tissues, interference with oxidative phosphorylation	Hyperbaric O_2 therapy is recommended if pH <7.1
Severe anemia	Decreased O_2 delivery to tissues	Requires hemoglobin level <5 g/dl
Vigorous exercise, seizures, or shivering	Increased O_2 requirements	The decrease in pH and hyperlactatemia is transient; lactic acidosis can impair exercise performance
Diabetes mellitus	Mechanism unclear	The risk of death in patients with ketoacidosis can be increased by coexisting lactic acidosis
Cancer	Increased glycolytic activity of tumor (Warburg effect), tumor tissue hypoxia, decreased clearance of lactate with severe liver metastases	Lactic acidosis can be seen in association with lymphomas, leukemias, and solid tumors; HCO_3^- administration may increase lactic acid production; acidic microenvironment is critical for tumorigenesis, angiogenesis, and metastasis
Liver disease	Lactate clearance decreased	Fulminant liver disease can cause substantial hyperlactatemia; hyperlactatemia is usually mild with chronic liver disease alone; lactate clearance can also be decreased when liver function is normal, in association with sepsis

Pheochromocytoma	Decreased O_2 delivery to tissues and epinephrine-induced β_2-adrenoceptor stimulation	In rare cases, lactic acidosis is a presenting feature of pheochromocytoma
Metformin	Interference with oxidative phosphorylation, suppression of hepatic gluconeogenesis	This is usually seen in association with high plasma metformin levels; treatment with dialysis is beneficial
Nucleoside reverse-transcriptase inhibitors	Interference with oxidative phosphorylation	Marked hyperlactatemia is uncommon in the absence of other predisposing factors
Cocaine	Decreased O_2 delivery to tissues and epinephrine-induced β_2-adrenoceptor stimulation	Marked hyperlactatemia is seen in some patients having seizures or being restrained
Toxic alcohols, methanol, ethylene glycol, diethylene glycol	Interference with oxidative phosphorylation	The increase in lactate is small; a small increase in the osmolal gap (usually <20 mOsm/kg H_2O) can be seen in some cases of lactic acidosis without toxic alcohols
Propylene glycol	D-Lactate and L-lactate are normal products of metabolism	Lactic acidosis can occur in the absence of impaired oxidative phosphorylation
Salicylates	Interference with oxidative phosphorylation	Hyperlactatemia is usually minimal
Cyanide	Interference with oxidative phosphorylation	Lactic acidosis is an important manifestation of poisoning
β_2 agonists	Stimulation of aerobic glycolysis	This is most common with treatment of acute asthma; hypokalemia can result from enhanced cellular uptake of potassium
Propofol	Interference with oxidative phosphorylation	Lactic acidosis can be seen with prolonged high-dose infusion
Thiamine deficiency	Impairment of pyruvate dehydrogenase activity	This is most common in children or adults receiving parenteral nutrition or those with fulminant beriberi

- Causes of AG metabolic acidosis include: lactic acidosis, ketoacidosis, toxic ingestion, and renal failure.
- In AG acidosis, a large osmolal gap (>10) can be caused by ingestion of methanol or ethylene glycol.
- In non-AG acidosis, positive urine anion gap is suggestive of RTA, and negative urine anion gap is consistent with extrarenal (GI) cause of acidosis.
- Patients with respiratory alkalosis may experience symptoms of cerebral vasoconstriction (dizziness) and transient hypocalcemia (perioral numbness and paresthesias).
- In metabolic alkalosis, low urine chloride can determine that the alkalosis can be corrected by saline infusion (chloride responsive).