Approach to Patients With High Anion Gap Metabolic Acidosis

2024.Jan

Am J Kidney Dis. 78(4):590-600.

Metabolic Acidosis and Compensatory Respiratory Response

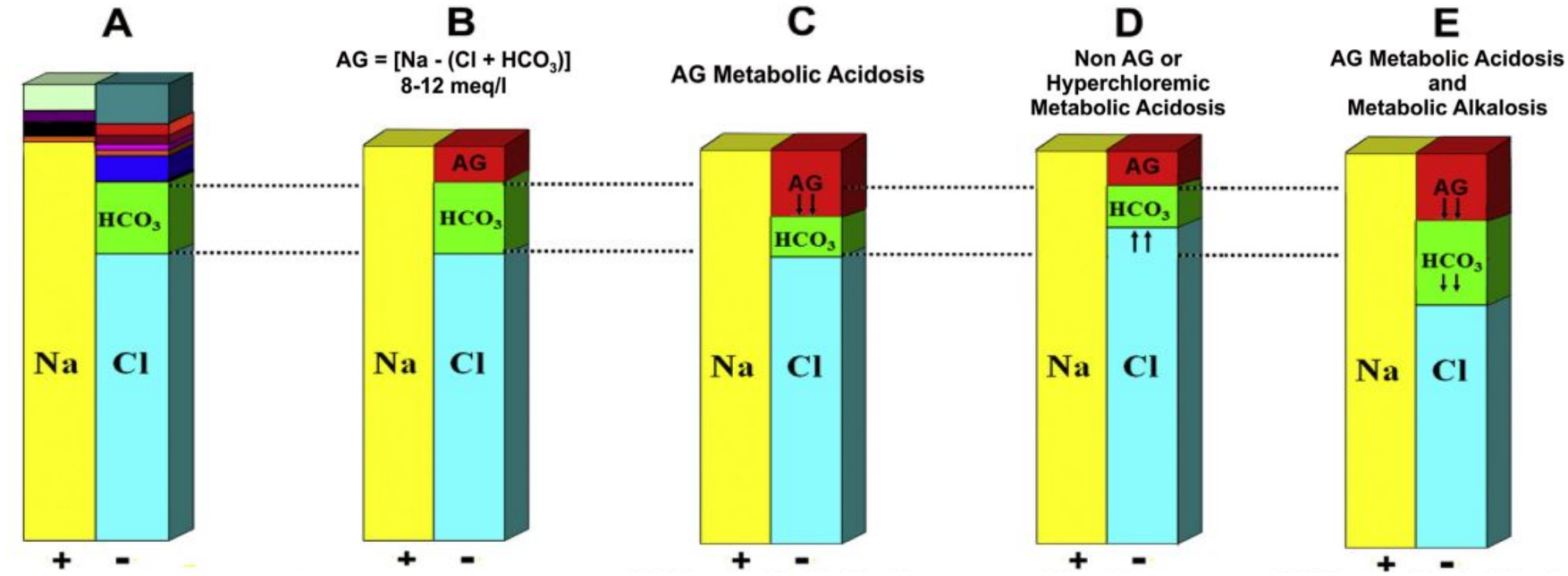
The normal $PaCO_2$ is 35-45 mm Hg. The compensatory hyperventilatory response to metabolic acidosis is fully developed **within 12 to 24** hours.

The appropriate respiratory response to metabolic acidosis is the **Winters equation**: $\mathbf{Paco2 = \{(1.5 \times \Delta HCO3) + 8\} \pm 2}$

This prediction relationship works well for mild to moderately severe metabolic acidosis ([HCO3] between **7 and 22** mEq/L).

If metabolic acidosis exists and the $PaCO_2$ is not in the predicted range, a second, respiratory, acid-base disturbance probably exists.

The Anion Gap



The total anion and total cation concentrations (measured in units of mEq/L) must be equal.

If only [Na+], [Cl−], and [HCO 3−] are considered, an anion gap (AG) normally exists

High AG metabolic acidosis reduces the [HCO 3−] w/o changing [Cl−] and thereby increases the [AG] in a reciprocal fashion.

Normal AG, or hyperchloremic acidosis, reduces the [HCO3−] and increases the [Cl−] in a reciprocal fashion

Mixed AG metabolic acidosis and metabolic alkalosis. If the [AG] is increased but the [HCO 3−] is not reciprocally reduced, consider mixed AG metabolic acidosis and metabolic alkalosis

Total charge concentration (measured in units of mEq/L) of **dissolved cation**s must **equal** the total charge concentration of **dissolved anions**.

If only the concentrations of the 3 major serum electrolytes ([Na], [Cl], and [HCO3]) are considered, then the cation concentration ([Na+]) normally exceeds the sum of the anion concentrations: **[Na+]> ([Cl−] + [HCO3−]**).

The normal [AG] is generally **8 to 12** mEq/L,

The degree of increase of the [AG] (or **Δ [AG]**) represents the plasma concentration of the **accumulating acid anions** (ie, lactate, ketoacid anions, etc). Furthermore, the Δ [AG] is generally similar to the Δ [HCO3].

Consequently, the **Δ [AG]/ Δ [HCO 3] ratio** is generally about **1**.

HAGMA - the mnemonic "**GOLDMARK**"

Table 1. GOLDMARK Mnemonic for the High Anion Gap Metabolic Acidoses

Letter	Parameter	Potential causes
G	Glycols	Ingestion/infusion of ethylene, propylene, or diethylene glycol; metabolism generates glyoxylic, oxalic, D and L lactic acid.
O	5-Oxoproline	Chronic acetaminophen use can generate 5-oxoproline (a strong acid that is also called pyroglutamic acid).
L	L-Lactic acidosis	Multiple etiologies of types A and type B lactic acidosis.
D	D-Lactic acidosis	Carbohydrate loading in patients with short gut syndromes.
M	Methanol	Metabolism generates formic acid.
A	Aspirin	Toxic levels generate multiple organic acids including keto acids.
R	Renal failure	Accumulation of multiple inorganic and organic acids including sulfuric and phosphoric acid.
K	Ketoacidosis	B-OH butyric and acetoacetic acid.

Based on mnemonic proposed in Mehta et al, *Lancet*. 2008;372(9642):892.

When metabolic acidosis is due to either the **accumulation of hydrochloric acid** or the **loss** from the body of **sodium bicarbonate** anion salts such as sodium butyrate, citrate, acetate, lactate — representing potential bicarbonate), then a normal AG, or hyperchloremic acidosis, develops.

Serum **albumin** has a net **negative charge** of about **2.5 mEq/g**, and this anion is **the largest component** of the **normal AG**. Therefore, **hypoalbuminemia will reduce the [AG]** (and **hyperalbuminemia will increase** the **[AG]**). The [AG] must be "corrected" when the albumin concentration is reduced or elevated.

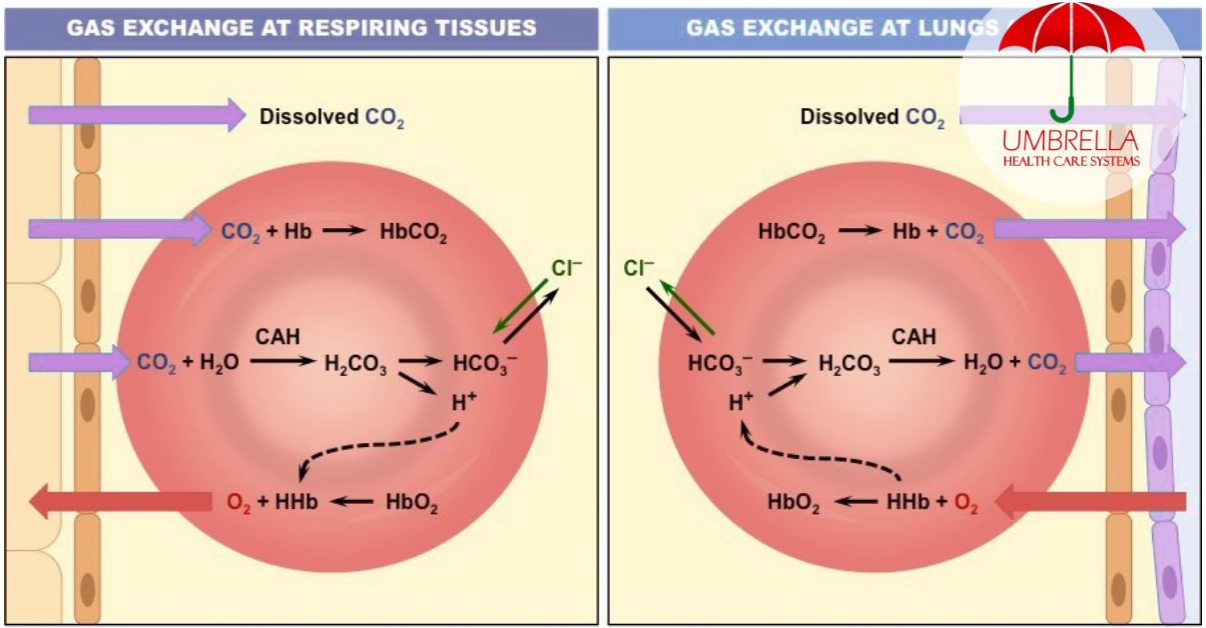
For **each 1 gram per 100 milliliters** that the albumin concentration is **reduced below a normal level of 4.5 g/100 mL**, the **[AG] falls** by about **2.5 mEq/L**. The [AG] can be corrected for hypoalbuminemia with the following formula:

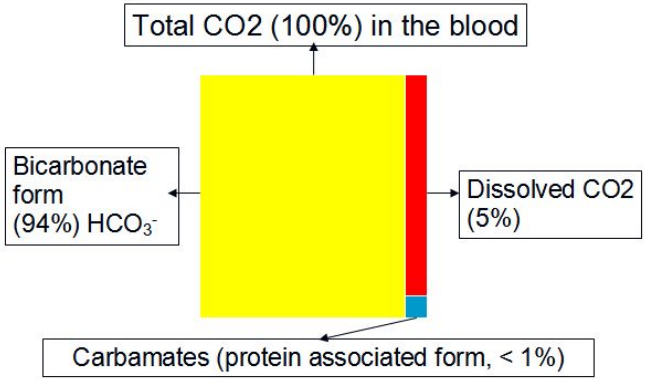
$$[\mathrm{AG}]_{(\mathrm{CORRECTED})} = [\mathrm{AG}]_{(\mathrm{UNCORRECTED})} + 2.5 \times (4.5 - [\mathrm{Albumin}])$$

Total CO2 concentration and serum bicarbonate

This number usually represents the total venous CO2 , which includes [HCO3−],[carbonic acid], and dissolved CO 2 .
The **venous [total CO2]** is typically **2-4 mEq/L** greater than the **arterial [HCO 3−]**.

Total CO2 = [HCO3-] + [H2CO3] = **[HCO3-]** + **pCO2 × 0.0307 mmol/L**





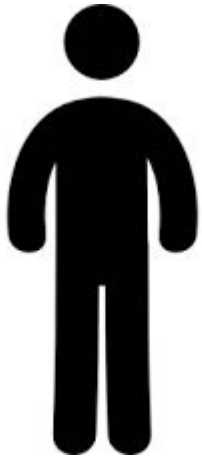
Case 1

A 68-year-old man with a history of well-controlled **hypertension** and **benign prostatic hypertrophy** presents to the emergency department (ED) with 3 days of **fever**, **dysuria**, and weakness and **1 day** of **rigors**.

His vital signs are temperature **38.6C**; blood pressure, **90/70 mm Hg**; and pulse, **110/min** and regular. The physical examination is notable for **dry mucous membranes** and lethargy.

His laboratory values are **[Na], 138 mEq/L**; potassium ([K]), 3.1 mEq/L; **[Cl], 111 mEq/L**; [HCO3], 17 mEq/L; serum urea nitrogen (SUN), 26 mg/dL; creatinine, 1.1 mg/dL; glucose, 126 mg/100 mL; **albumin, 2.0 g/dL**.

His arterial blood gas (ABG)values are **pH 7.30**; **pCO2 , 32 mm Hg**; **[HCO3], 15 mEq/L**;and pO2 72 mm Hg.



Question 1: Which of the following acid-base abnormalities exist in this patient?

a) HAGMA with appropriate respiratory compensation

b) Hyperchloremic (normal AG) metabolic acidosis

c) Mixed metabolic acidosis and respiratory alkalosis

d) Metabolic alkalosis and metabolic acidosis

Lactic Acidosis

It occurs when **lactic acid production exceeds** lactic acid **clearance** (both normally about 1 mmol/min). Usually **lactate production increases** because of **impaired tissue oxygenation**, due to either **decreased oxygen delivery** or a **defect in mitochondrial oxygen utilization**.

The generation of lactic acid from **anerobic glycolysis** primarily by **muscle** and the conversion of this lactic acid back to glucose by the liver defines the Cori cycle.

One commonly used classification system divides the clinical causes of lactic acidosis into those associated with clear **impairment in tissue oxygenation (type A)**, and those in which a systemic impairment in oxygenation is absent or is not easily apparent (type B).

The classic causes of **type A lactic acidosis** include **hypovolemia, sepsis, major gastrointestinal hemorrhage, cardiac failure**, or **cardiopulmonary arrest**.

The causes of **type B lactic acidosis** include a variety of **toxins, drugs, and vitamin deficiencies** (ie thiamine) that impair cellular and/or mitochondrial metabolism or generate **regional areas of ischemia**. One classic cause of type B lactic acidosis is **metformin toxicity**, which usually occurs in patients with acute or chronic kidney injury because of the systemic accumulation of metformin.

Other causes of type B lactic acidosis include various **malignancies**, particularly leukemia and lymphoma, **chronic severe alcohol** use disorder, and some **antiretroviral medications** used to treat patients infected with human immunodeficiency virus (HIV).

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

N Engl J Med 2014; 371:2309-2319

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

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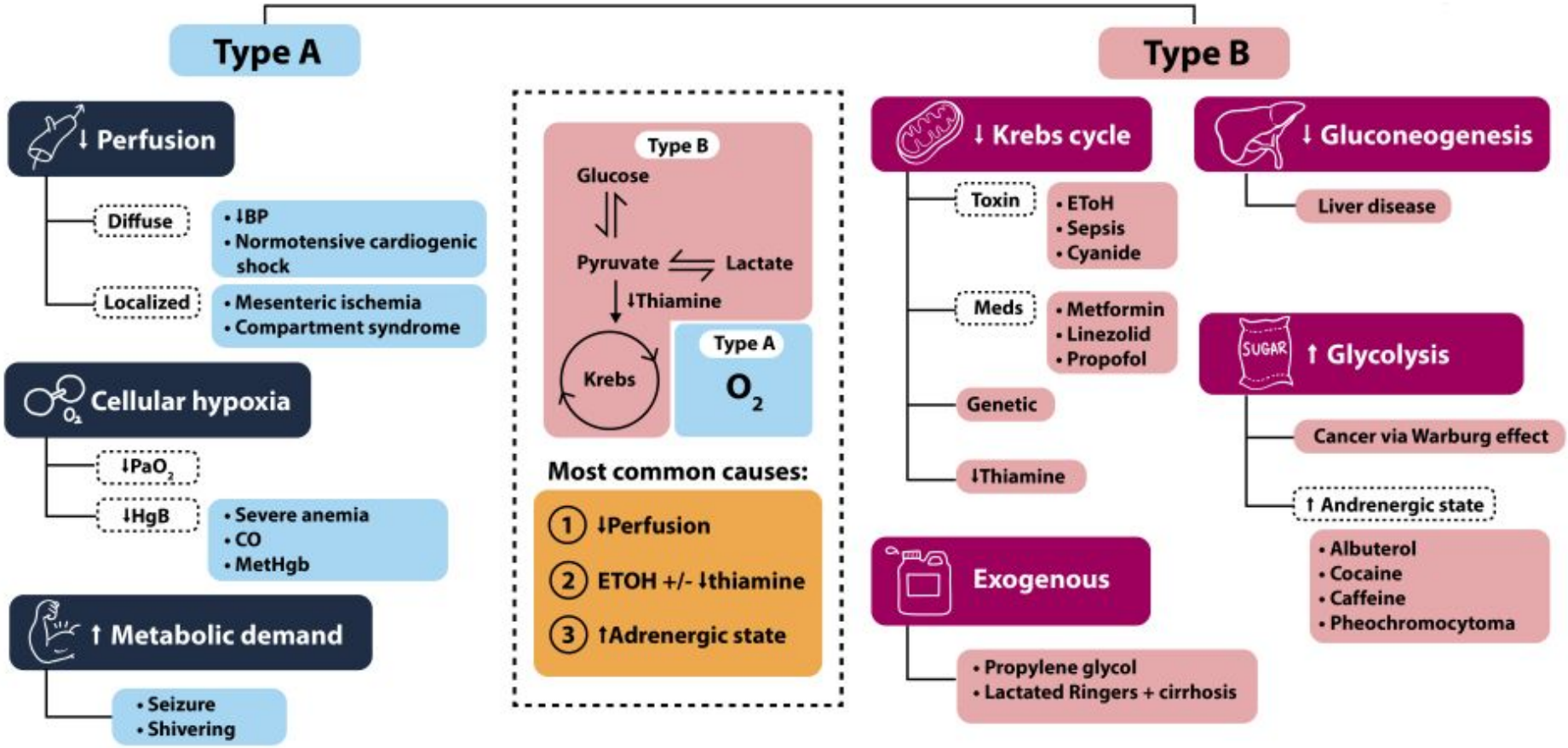
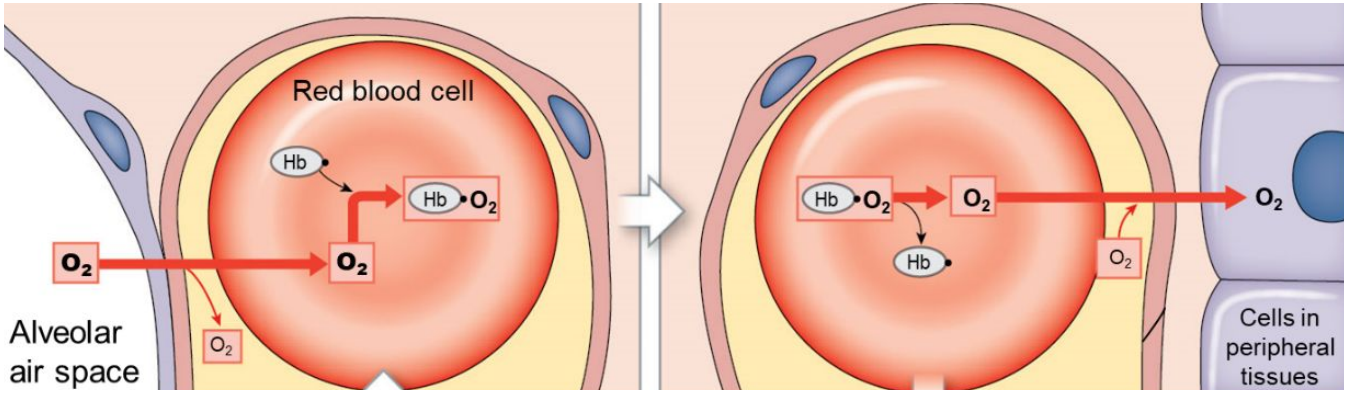

Type A
↓ Perfusion
Diffuse
• ↓BP
• Normotensive cardiogenic shock
Localized
• Mesenteric ischemia
• Compartment syndrome
Cellular hypoxia
↓PaO2
↓HgB
• Severe anemia
• CO
• MetHgb
↑ Metabolic demand
• Seizure
• Shivering
Type B
Glucose
Pyruvate
Lactate
↓Thiamine
Krebs
Type A
O2
Most common causes:
1 ↓Perfusion
2 ETOH +/- ↓thiamine
3 ↑Adrenergic state
Type B
↓ Krebs cycle
Toxin
• EToH
• Sepsis
• Cyanide
Meds
• Metformin
• Linezolid
• Propofol
Genetic
↓Thiamine
Exogenous
• Propylene glycol
• Lactated Ringers + cirrhosis
↓ Gluconeogenesis
Liver disease
SUGAR
↑ Glycolysis
Cancer via Warburg effect
↑ Andrenergic state
• Albuterol
• Cocaine
• Caffeine
• Pheochromocytoma

Oxygen delivery



Maximal oxygen-carrying capacity of the blood (ml/g of Hb): normally, 1.39ml/g

Percentage saturation of haemoglobin, expressed as a fraction (i.e. 97% would be 0.97)

$$DO_2 = CO \times \left((1.39 \times [Hb] \times SaO_2) + (PaO2 \times 0.03)\right)$$

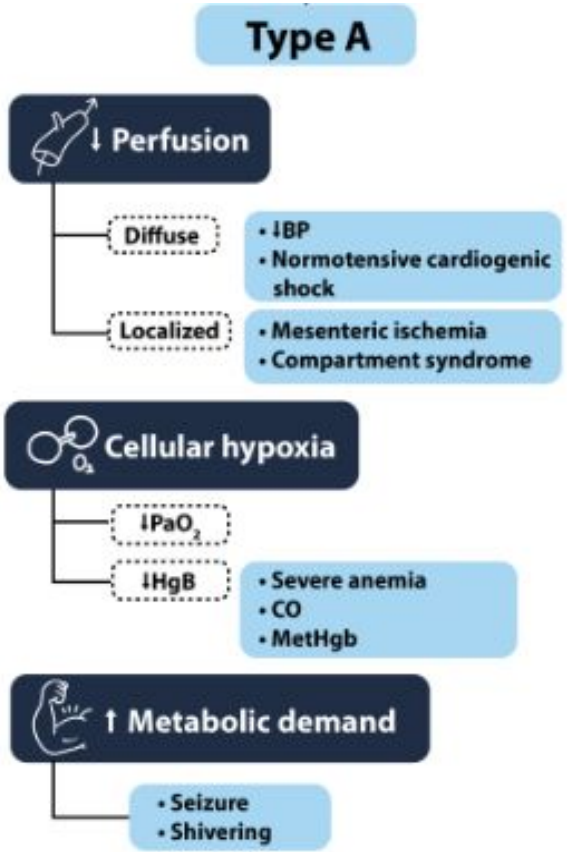
Rate of oxygen delivery in ml/min

Cardiac output in L/min

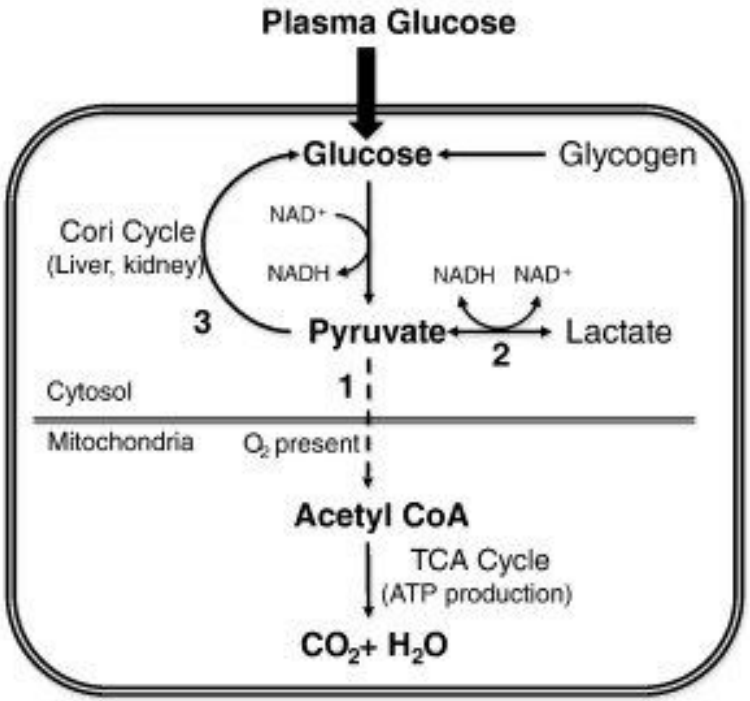
Concentration of haemoglobin in g/L

Partial pressure of oxygen, in mmHg

Solubility constant for oxygen at 37° - normally, 0.03ml/L/mmHg



Oxygen delivery

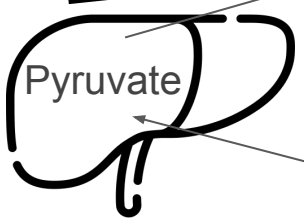


↓ Gluconeogenesis

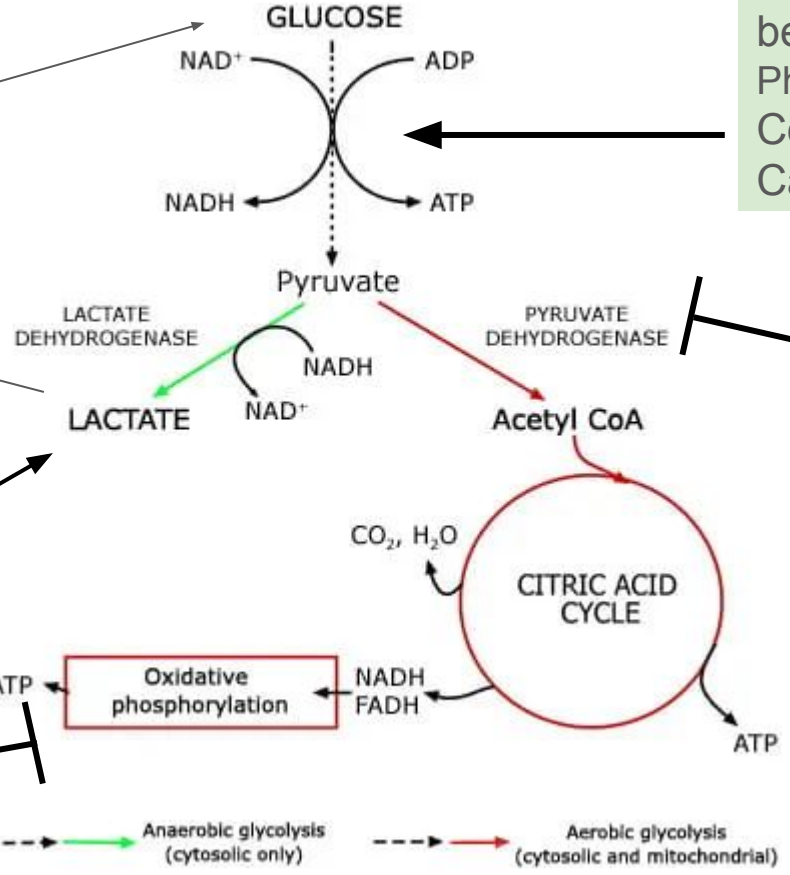
Liver failure

↑ Glycolysis

beta agonist
Pheochromacytoma
Cocaine
Cancer



Cori cycle



Exogenous

Propylene glycol

↓ Krebs cycle

Thiamine deficiency

↓ Krebs cycle

Metformin
Salicylate
Propofol
Cyanide

Diabetic ketoacidosis

Case 2: *A 25-year-old man with a 10-year history of type 1 diabetes mellitus becomes anorexic after developing gastroenteritis and reducing his insulin dose. He then develops nausea, vomiting, polyuria, and dyspnea and presents to the ED. The patient also has a long history of depression and is taking fluoxetine. He has orthostatic hypotension. His breath has a fruity odor. The initial laboratory studies reveal SUN, 40 mg/dL; creatinine, 1.5 mg/dL; glucose, 800 mg/100 mL; [Na^+], 120 mEq/L; [Cl^-], 75 mEq/L; [HCO_3^-], 12 mEq/L; K^+, 3.0 mEq/L; ([AG], 32 mEq/L); and albumin, 4.0 g/100 mL. The measured osmolality is 330 mOsm/L; serum β-hydroxybutyrate, >8 mEq/L; and urine ketones, 3+ by dipstick. Blood ethanol level is nondetectable. ABG values are pH 7.16; P_{O_2}, 90 mm Hg; p_{CO_2}, 35 mm Hg; and [HCO_3^-], 12 mEq/L.*

Question 2: What is his acid-base disorder?

a) HAGMA due to diabetic ketoacidosis (DKA)
b) HAGMA due to DKA and metabolic alkalosis
c) HAGMA due to DKA, metabolic alkalosis, and respiratory acidosis
d) HAGMA due to DKA and hyperchloremic acidosis

The [AG] was calculated using the reported [Na] of 120 mEq/L. **Hyperglycemia reduces the blood [Na]** because **ECF hypertonicity** moves water from the intracellular fluid (ICF) into the ECF and **expansion of the ECF dilutes the ECF [Na]**.

Formula for glucose in mg/dL

$$\text{Corrected}\,[Na^+] = \text{Measured}\,[Na^+] + \frac{1.6 \times (\text{glucose in mg/dL} - 100)}{100}$$

A glucose value of **800** mg/dL will reduce the [Na] by about **14** mEq/L (expect about a **2 mEq/L [Na]** decrease per **100 mg/dL glucose increase above normal**).
With treatment, as the glucose concentration falls toward normal and water shifts back into the ICF, the [Na] will increase from 120 to about 134 mEq/L. Hence, **the [Na] "corrected"** for hyperglycemia is **134** mEq/L.

Question:

To calculatedAG, which [Na] level should be use, the uncorrected [Na]: 120mEq/L or corrected [Na]: 134 mEq/L ?

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The **water shift generated by hyperglycemia** will also have **similar dilution effects** on the **ECF chloride** and **bicarbonate concentrations**.
Therefore, by convention, **the "uncorrected" (for glucose) electrolyte concentrations** are used for the **AG calculations when hyperglycemia exists**.

Question:

To calculated osmolality gap, which [Na] level should be use, the uncorrected [Na]: 120mEq/L or corrected [Na]: 134 mEq/L ?

SUN, 40 mg/dL; creatinine, 1.5 mg/dL; glucose, 800 mg/dL; [Na], 120 mEq/L. Measured osmolality is 323 mOsm/L.

This patient's measured osmolality (323 mOsm/L), which is **25 mOsm/L** greater than his calculated osmolality (2 ×[Na] + (glucose/18) + (SUN/2.8)) = 298 mOsm/L.

The "**uncorrected" [Na] of 120 mEq/L** is also used in the **osmolality equation** because this is his **"true" admission plasma [Na]**; the denominators 18 and 2.8 convert the glucose and SUN concentrations from mg/100 mL to mmol/L, or roughly mOsm/L.

Question 3: What is the most likely cause of this patient's 25 mOsm/L osmolal gap?

a) Accumulated ketoacids
b) Ingestion of an alcohol or glycol (other than ethanol, which was not detectable on admission)
c) Acetone
d) The sodium reduction generated by hyperglycemia

A **HAGMA** should **no**t directly generate an **osmolal ga**p.
The addition to the blood of **alcohols, acetone, glycerol**, and so on will **raise** the **measured osmolality** and create an "osmolal gap."
This **osmolal gap disappears** if the **alcohol/glycol/etc. is metabolized** to an acid.
Patients with **ketoacidosis** often develop an osmolal gap because of increased levels of **acetone** (and to a smaller extent glycerol).
This phenomenon also occurs commonly in patients with alcoholic ketoacidosis, so be cautious about diagnosing a toxic alcohol or glycol poisoning in that situation on the basis of a high osmolal gap.
Also, note that **acetone is not an acid** and **does not reduce the [HCO3]** or **raise the [AG]**.

Measured osmolality
vs.
Calculated osmolality
vs.
Effective osmolality

A = **Measured osmolality** = All osmotically active solutes in blood

B = **Calculated osmolarity** = Expected osmotically active solutes in blood

$$Calculated\ Osmolarity\ \left(\frac{mOsm}{L}\right) = 2Na + \frac{Gluc}{18} + \frac{BUN}{2.8} + \frac{Ethanol}{4.6}$$

A-B = **Osmol gap**: Unmeasured ("unknown") remaining solute in blood

$$Plasma\ osmolal\ gap = \left[\frac{measured}{osmolality}\right] - \left[\frac{calculated}{osmolarity}\right]$$

CORE IM

Content by Dr. Helbert Rondon (@NephroMD)

$$\text{Plasma Osmolality} = 2 \times [Na^+] + \frac{\text{Glucose}}{18} + \frac{\text{BUN}}{2.8}$$

(mOsm/kg) (mEq/L) (mg/dL) (mg/dL)

Plasma Osmolality ≠ Plasma Tonicity

INEFFECTIVE OSMOLES	EFFECTIVE OSMOLES	NOT OSMOLES
Solutes that **cross** plasma cell membrane	Solutes that do **NOT** cross plasma cell membrane	Elevated serum proteins or lipids may lead to a **lab error,** known as **pseudohyponatremia**
↑ Plasma osmolality ↔ Plasma tonicity	↑ Plasma osmolality ↑ Plasma tonicity	Normally, serum contains 7% solids by volume. Substances which alter that ratio and cause a lab error include:
Urea	Sodium	Lipids (cholesterol, triglycerides)
Ethanol	Glucose (in the absence of insulin)	Proteins and gammaglobulins
Other: Methanol, acetone, isopropanol, glycerol, ethylene glycol	Mannitol	Lipoproteins

Effective osmolality

HHS, also known as non-ketotic hyperglycaemic hyperosmolar syndrome (NKHS). Characterised by **profound hyperglycaemia** (glucose ≥30 mmol/L [≥540 mg/dL]), **hyperosmolality** (**effective serum osmolality ≥320 mOsm/kg** [≥320 mmol/kg]), and **volume depletion** in the **absence of significant ketoacidosis**.

Case 2, continued: *The patient is appropriately treated with intravenous fluids (mainly normal saline), intravenous potassium chloride, and intravenous regular insulin. The next morning, he feels much better and is hungry. His blood chemistries now show the following: SUN, 18 mg/dL; creatinine, 0.9 mg/dL; glucose, 150 mg/100 mL; [Na^+], 139 mEq/L; [Cl^-], 110 mEq/L; [HCO_3^-], 17 mEq/L; [K^+], 4.0 mEq/L; and [AG], 12 mEq/L.*

Question 4: Which of the following statements is most correct about the development of a hyperchloremic metabolic acidosis in this patient?

a) The normal saline infusion diluted his [HCO3] and thereby generated hyperchloremic metabolic acidosis.
b) This is a common measurement artifact that develops after acute treatment of DKA.
c) Different volumes of distribution of ketoacids anions and chloride generate hyperchloremic metabolic acidosis.
d) The loss of ketoacids anion salts into the urine converts a HAGMA to a hyperchloremic metabolic acidosis.

Case 3: *A 60-year-old man is brought to the ED by his wife who says he has become increasingly depressed over the past 3 months and that he may have tried to hurt himself. He is confused and uncooperative and smells of alcohol. Otherwise, his physical examination is unremarkable, and his vital signs are normal. His laboratory values on arrival are SUN, 20 mg/dL; creatinine, 1.0 mg/dL; glucose, 100 mg/100 mL; [Na^+], 138 mEq/L; [Cl^-], 105 mEq/L; [HCO_3^-], 24 mEq/L; and [K^+] 4.0 mEq/L. His ABG values are pH 7.40; pO_2, 100 mm Hg; and pCO_2, 40 mm Hg. The urine analysis is unremarkable. His ethanol level is 110 mg/100 mL, and blood osmolality is 350 mOsm/L.*

Question 5: Which of the following is most likely correct?

a) He is inebriated with a high blood ethanol level and will likely improve as the ethanol is metabolized.
b) He has ingested ethanol but also has evidence of one/or several other alcohols or glycols.
c) The absence of a high anion gap metabolic acidosis makes ingestion of methanol or ethylene glycol unlikely.
d) He has ingested a toxic dose of salicylate together with the ethanol.

Before discussing the correct answer let us assume that the ED physician incorrectly believed that answer (a) was correct: the patient is inebriated with ethanol, and he will improve. He is observed in the ED for several hours.

Case 3, continued (hypothetical scenario): *After 3 hours the patient remains confused and has become increasingly combative. His serum chemistries are repeated, and now they reveal SUN, 30 mg/dL; creatinine, 1.2 mg/dL; glucose, 120 mg/100 mL; [Na^+], 140 mEq/L; [Cl^-], 105 mEq/L; [HCO_3^-], 16 mEq/L; and [K^+], 4.5 mEq/L. His ABG values are pH 7.32; pO_2, 100 mm Hg; and pCO_2, 30 mm Hg. The blood osmolality is measured again and has fallen from 350 to 310 mOsm/L. Urine analysis is also repeated and now reveals many crystals consistent with calcium oxalate.*

Question 6: What is the most likely cause of the patient ' s change in status?

a) He has developed lactic acidosis.
b) He has developed metabolic acidosis secondary to accumulation of glyoxylic and oxalic acid.
c) He has developed ethanol withdrawal syndrome.
d) He ingested salicylate in addition to ethanol and now has a salicylate-induced HAGMA.

Ethanol level of 110 mg/dL would only have increased his serum osmolality (ie, created an osmolal gap) by about 24 mOsm/L (divide the ethanol level [in mg/100 mL] by 4.6 to estimate its osmolality contribution).

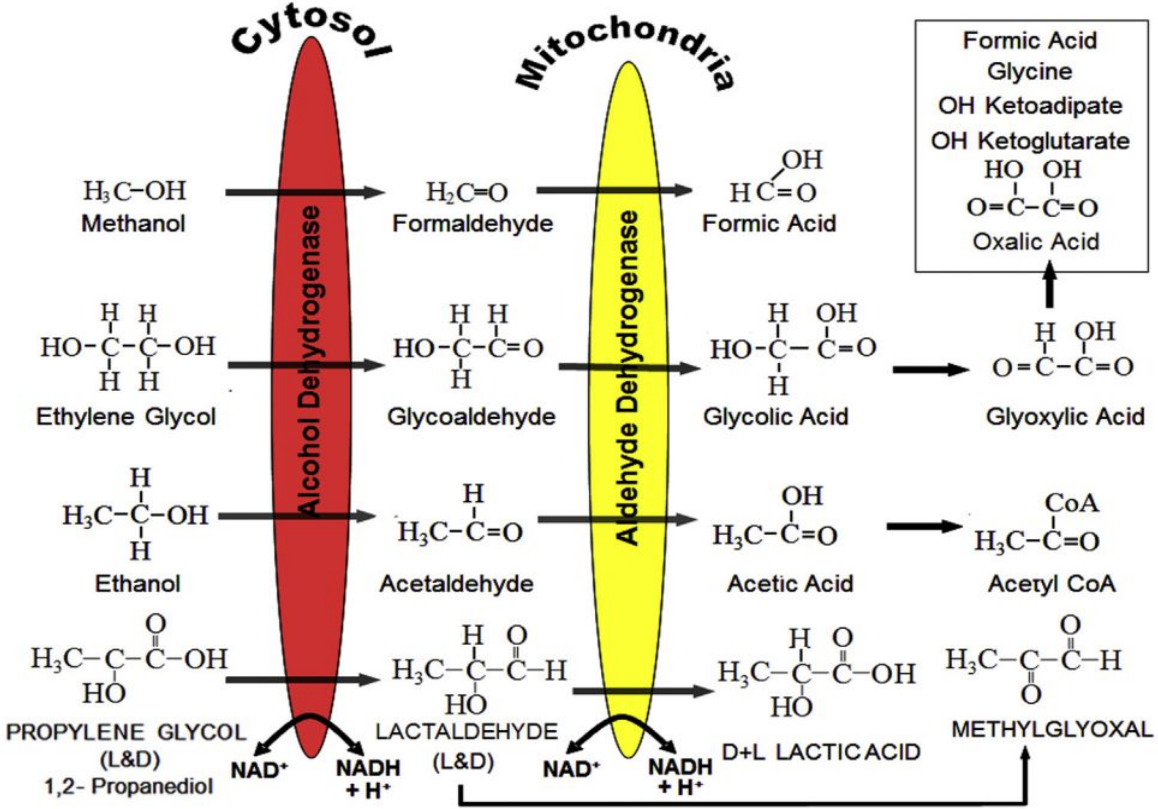
This man's osmolal gap was 57:
350 − [(138 × 2) + (30/2.8) + (120/18)] = 57.

Therefore 33 mOsm/L of the osmolal gap was not accounted for by the ethanol level in his blood.

	Molecular Weight (mg/mmol)	Osmolal Gap Produced by 100 mg%
Ethanol	46	22
Isopropanol	60	17
Acetone	58	17
Methanol	32	31
Ethylene glycol	62	16
Propylene glycol	76	13
Diethylene glycol	106	9

Ethanol 100mg/dL = 1000mg/L = 21.7mOso/L

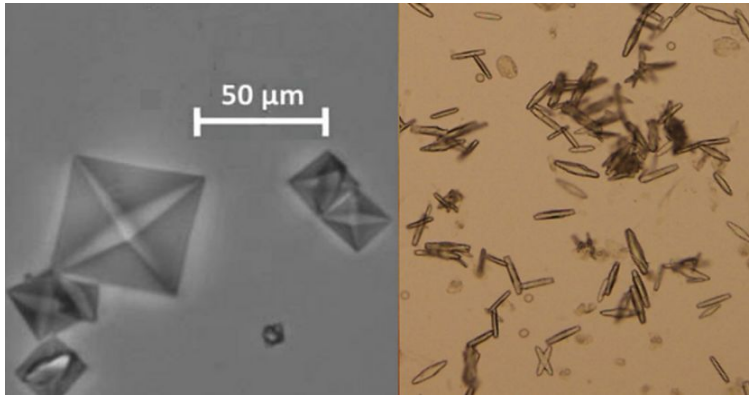
When a toxic alcohol, such as methanol, isopropanol, or ethylene glycol, is ingested, ethanol coingestion is common. Co-ingested ethanol will slow the oxidation of many toxic chemicals that are oxidized by the enzyme alcohol dehydrogenase.



The oxidation of the **ethanol** generates **acetyl CoA**, which is metabolized by the liver. As the **ethanol levels fall**, **accelerated oxidation** of the **co-ingested toxic chemical** will generate **toxic organic acids** .

This metabolic sequence can simultaneously **reduce the osmolal gap** and **generate a HAGMA**. In this particular case the finding of **calcium oxalate crystals in the urine** strongly suggested that he had ingested **ethylene glycol**. Therefore, for both questions 5 and 6, answer (b) is correct, and the accumulating organic acids are probably mainly **glyoxylic** and **oxalic acid**.

Note that one commonly ingested toxic alcohol, isopropanol (rubbing alcohol), is metabolized to acetone. Neither isopropanol nor acetone is an acid.Therefore, isopropanol ingestion will raise the osmolal gap but not generate a HAGMA.



Photomicrographs of typical calcium oxalate crystals in urine.
Left: classic-appearing “ back of envelope ” calcium oxalate crystals.
Right: less pathognomonic, but more common, thick needle-shaped calcium oxalate crystals.

Case 4: *A 20-year-old woman with a history of schizophrenia and a mood disorder has presented to the ED after taking a "small bottle full of aspirin pills," stating she had wanted to kill herself. Her psychiatrist has prescribed oral haloperidol in the past, but she denies taking any other medications and denies alcohol ingestion. She vomited several times after the aspirin ingestion and developed dyspnea and tinnitus. She has no previous history of suicide attempts. Physical examination reveals an anxious young woman who is alert and oriented × 3. Her vital signs are blood pressure, 118/70 mm Hg; pulse, 100 beats per minute and regular; respiratory rate, 26 breaths per minute; temperature 37.2 °C. The examination is only notable for deep ventilation and dry mucous membranes. The laboratory findings are [Na^+], 141 mEq/L; [K^+], 3.8 mEq/L; [Cl^-], 95 mEq/L [HCO_3^-], 25 mEq/L; [AG], 21 mEq/L; albumin, 4.0 g/dL; SUN, 10 mg/dL; creatinine, 1.06 mg/dL; and glucose, 116 mg/100 mL. Her ABG (room air) values are pH 7.63; pCO_2, 24 mm Hg; [HCO_3] 24 mEq/l and pO_2, 90 mm Hg. Her salicylate level is 71.8 mg/dL (therapeutic level is less than 20), and her urine pH was 5.5. A toxicology screen is negative except for salicylate.*

Question 7: What is this patient ' s acid-base disturbance?

a) HAGMA
b) HAGMA and respiratory alkalosis
c) HAGMA, metabolic alkalosis and respiratory alkalosis
d) Metabolic alkalosis, respiratory alkalosis, and an artifactual elevation of the anion gap (pseudohypochloremia)

The most characteristic acid-base disorder generated by **salicylate intoxication** is **mixed HAGMA** and **respiratory alkalosis**. Toxic salicylate levels directly stimulate the **medullary respiratory center**, increasing both the **rate** and **depth of respirations**; this generates the **respiratory alkalosis**. Salicylate toxicity also **uncouples oxidative phosphorylation**, **inhibits citric acid cycle dehydrogenases**, **accelerates glycolysis** (generating **lactic acid**), and stimulates **lipolysis and hepatic ketogenesis**. These actions combine to generate the **HAGMA**. A small component of the HAGMA is the salicylic acid itself.

This patient's [AG] was 21 mEq/L (Δ AG = 11), and this degree of metabolic acidosis would be expected to reduce her [HCO3] reciprocally by about 11 mEq/L.

But her [HCO3] is 23 mEq/L. These results are consistent with **HAGMA** due to the **salicylate poisoning** and **metabolic alkalosis** due to **vomiting**. The resulting normal [HCO3] of 23 mEq/L should not generate any respiratory compensatory response.

However, the ABG revealsan alkaline pH (7.63 [whenever the pCO 2 and HCO3 equal one another the pH must be 7.63]) and a markedly reduced PaCO2 (24 mm Hg).

This is due to respiratory alkalosis generated by the salicylate toxicity. Thus, the correct answer to question 7 is (c): HAGMA, metabolic alkalosis, and respiratory alkalosis.

Case 4, continued: *After 3 hours, the patient's blood chemistries are repeated and reveal [Na^+], 140 mEq/L; [K^+], 3.5 mEq/L; [Cl^-], 135 mEq/L; [HCO_3^-], 24 mEq/L; SUN, 9 mg/dL; creatinine, 0.92 mg/dL; glucose, 115 mg/100 mL; and [AG], −19 mEq/L.*

Question 8: How do you explain these electrolyte values?

a) The patient also ingested bromide salts.
b) This represents pseudohyperchloremia related to the salicylate.
c) This represents pseudohyperbicarbonatemia related to the salicylate.
d) The sodium concentration is spuriously decreased.

Several clinical conditions can **reduce the AG** to a level **near 0** or even generate a slightly **negative AG**. The 2 **most common conditions** that can cause this to occur are **hypoalbuminemia** (reduced “unmeasured” anions) and **multiple myeloma** (**increased “unmeasured” cations** with IgG myeloma, but usually not with IgA myeloma).

However, when the AG is found to be **extremely negative (more negative than − 5 mEq/L)** this is usually due to an **electrolyte measurement artifact** (pseudohyponatremia, pseudohyperchloremia, or pseudohyperbicarbonatemia).

Pseudohyperchloremia can be generated by several clinical disorders. Historically the most common cause of pseudohyperchloremia was **chronic bromide ingestion**.

Bromide ions in the specimen can generate very high artifactual chloride concentrations. More recently, it has been discovered that **salicylate** can also generate marked **pseudohyperchloremia**.

Case 5: *A 38-year-old woman with a history of severe restrictive lung disease had a bilateral lung transplant 4 months ago. She has had a complex posttransplant course with several episodes of successfully treated acute lung rejections. She also had 2 episodes of AKI, and now has a persistently reduced GFR. Her poor oral intake required placement of a gastric feeding tube. She is very depressed and reports persistent pain at the site of her G-tube. She has been taking acetaminophen, 650 mg 3 times a day, for the past 3 weeks. She denies use of any other medications and said she would not try to harm herself. Physical examination shows normal vital signs and malnutrition, with temporal wasting and diffuse muscle wasting. The G-tube exit site is erythematous but without drainage. Her serum chemistries are glucose, 90 mg/100 mL; SUN, 10 mg/dL; creatinine, 0.7 mg/dL; [Na^+], 140 mEq/L; [K^+], 4.2 mEq/L; [Cl^-], 106 mEq/L; [HCO_3^-], 12 mEq/L. Her ABG values are pH 7.21; $paCO_2$ 26 mm Hg; [HCO_3^-], 10 mEq/L. Her albumin is 3.0 g/dL, and L-lactate is 0.8 mmol/L. Her urine is negative for ketones, and her serum β-hydroxybutyrate is normal at 0.5 mEq/L. Serum osmolality (by freezing point depression) is 290 mOsm/L. Serum salicylate is undetectable. Acetaminophen level is in the therapeutic range.*

Question 9: The most likely cause of the patient ' s HAGMA is:

a) Ethylene glycol ingestion/instillation
b) 5-Oxoproline (pyroglutamic acid)
c) Starvation ketoacidosis
d) D -Lactic acidosis

This patient has a HAGMA with no readily apparent etiology. There is no biochemical evidence for lactic or keto acidosis.

Although a D -lactate level was not measured, there is no history to suggest that she would be susceptible to this disorder (**D -lactic acidosis** typically develops in patients with **short gut syndromes**). If D -lactic acidosis is suspected, a specific serum D -lactate level should be measured because D -lactate is not detected by routine “lactic acid” assays, which measures only the L optical isomer of lactate.

Her measured osmolality was normal at 290 mOsm/L and consistent with a [Na] = 140 mEq/L (which generates about 280 mOsm/L) and a normal glucose and SUN (accounting for about 9 mOsm/L).

The patient has a history of depression, but there was no history of a toxin or poison ingestion (or infusion into her feeding tube). If she had ingested/infused a toxic alcohol, such as methanol, or a glycol such as ethylene glycol, these compounds should increase her measured osmolality and would generate an osmolal gap.

Salicylate poisoning will often produce an **HAGMA** due to the combination of **salicylic acid itself** and **other endogenous intermediary organic acids** that accumulate. However, **salicylate-generated HAGMA** only occurs with **toxic salicylate levels**, and no salicylate was detected on admission. All these normal or negative laboratory results together with her clinical story strongly suggest that the most likely cause of her HAGMA is a disorder related to chronic acetaminophen ingestion.

Chronic ingestion of acetaminophen, especially by ill and malnourished women, has become increasingly recognized as a cause of HAGMA due to the accumulation of **5-oxoproline**, also called pyroglutamic acid.

Detoxification of acetaminophen is accomplished by converting the native compound to several **sulfated metabolites**, including acetaminophen sulfate, acetaminophen glutathione, and acetaminophen mercapturate, which are then excreted in the urine.

These reactions **deplete glutathione, cysteine**, and other sulfated intermediary molecules, especially when the **patient is malnourished**. The combination of **glutathione** and **cysteine deficiency** accelerates generation and accumulation of **5-oxoproline**. Thus, the correct answer to question 9 is (b).

High levels of acetaminophen can generate **acute severe liver toxicity** as well as **acute kidney injury**. That form of acute acetaminophen poisoning sometimes generates lactic acidosis.

By contrast, the HAGMA due to **chronic acetaminophen ingestion** is a result of the **accumulation of 5-oxoproline and develops in patients with therapeutic or even subtherapeutic acetaminophen** levels.

The **HAGMA due to acetaminophen related 5-oxoproline** accumulation typically **resolves quickly after acetaminophen is discontinued** and the patient's overall medical status has been improved with general supportive measures. Although the administration of N -acetyl-cysteine seems reasonable and has little apparent downside, there is **no clear evidence** that it is necessary or that it accelerates recovery.

In addition, some patients treated with the antibiotics flucloxacillin or netilmicin and others treated with the anticonvulsant vigabatrin have developed HAGMA due to 5-oxoproline. However, most often 5-oxoproline acidosis is generated by chronic use of acetaminophen, especially in malnourished women.

Case 6: *A 45-year-old man presents with increasing confusion, ataxia, and slurred speech for the prior 5 days. His past medical history is notable for an abdominal stab wound 3 years ago that required multiple abdominal surgeries with extensive small-bowel resections. Subsequently he developed chronic intermittent diarrhea, lost weight, and appeared malnourished. His family reports several prior episodes of milder confusion. His only medication is a daily multivitamin. He denies ingestion of any illicit drugs or alcohols. Physical examination reveals normal vital signs. He is lethargic, confused, has slurred speech, nystagmus, and a staggering gait. His laboratory values are* $[Na^+]$, *140 mEq/L;* K^+, *3.8 mEq/L;* $[Cl^-]$, *105 mEq/L;* $[HCO_3^-]$, *10 mEq/L; SUN, 12 mg/dL; creatinine, 0.9 mg/dL; glucose, 96 mg/100 mL; albumin, 3.9 g/dL; and serum lactate, 1.1 mEq/L. His ABG values are pH 7.20;* pCO_2, *21 mm Hg; and* pO_2, *98 mm Hg. The urine analysis is unremarkable and negative for ketones.*

Question 10: The most likely acid-base diagnosis is

a) Hyperchloremic metabolic acidosis due to chronic diarrhea
b) Ingestion of a toxic alcohol
c) D -Lactic acidosis
d) 5-Oxoproline (pyroglutamic) acidosis

D-Lactic acidosis is a rare (but likely underdiagnosed) form of metabolic acidosis that can affect some patients with **short bowel clinical syndrome** or other types of gastrointestinal malabsorption.

In these patients, **intestinal bacteria** metabolize (ferment) **unabsorbed glucose and starch** to multiple **organic acids**, including the **D-optical isomer of lactic acid**, which is metabolized very slowly by humans. Hence, when **this lactic acid isomer is systemically absorbed from the bowel**, D -lactate acidosis develops.

D - Lactic acid levels can also increase in patients who receive or ingest large amounts of **propylene glycol** and in many patients with **diabetic ketoacidosis**. In these patients, D -lactic acid is a metabolic product of lactaldehyde with propylene glycol intoxication and methylglyoxal in diabetic ketoacidosis.

In diabetic ketoacidosis, the concentration of D -lactic acid may reach the 8 to 10 mEq/L range and hence significantly contribute to the HAGMA.

Patients with short bowel syndrome may have chronic, low-grade elevations that are insufficient to generate significant acidosis or symptomatology. However, **carbohydrate loading** can lead to **severe and symptomatic D -lactic acidosi**s. In addition, if **kidney function declines**, a similar **clinical picture may emerge**.

Patients with D -lactic acidosis typically present with an **AG metabolic acidosis** and characteristic **neurological abnormalities**, such as confusion, cerebellar ataxia, slurred speech, incontinence, and nystagmus.

The renal tubule reabsorption of D -lactate is not as efficient as the reabsorption of L -lactate. Therefore, **large renal losses of D -lactate** can **convert this HAGMA to a hyperchloremic acidosis**. If **D -lactic acidosis** is strongly suspected, **measurements of urine D -lactate levels are commercially available** and may be very helpful.

Treatment for D -lactic acidosis must be tailored to each patient.

When severe metabolic acidosis develops, sodium bicarbonate can be administered. When the syndrome develops in patients with short bowel syndrome, **oral antimicrobial agents** (such as **neomycin** or **metronidazole**) can be helpful.

They probably act by **decreasing** the density of **D -lactate-producing organisms**. **Preventive strategies** include a **low-carbohydrate diet**, which **reduces colonic carbohydrate delivery** and **D -lactate production**.

Some patients with frequent episodes of D -lactic acidosis have been successfully treated with **fecal transplantation.**