
بسم الله الرحمن الرحيم

Pathophysiology and Diagnosis of acute metabolic acidosis

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- Metabolic acidosis is a frequent acid-base disturbance in daily clinical medicine.

- Metabolic acidosis:
- Increase in hydrogen ion concentration = Hco3 < 24 meq/lit

- Definition: if acidosis or acidemia evolves within minutes to days.

- Exact epidemiological data are difficult to provide, since many diseases/circumstances can induce AMA.

- It is not a benign condition
- Needs to be corrected to minimize mortality and morbidity.

- Metabolic acidosis occurs if an increase in extracellular hydrogen ion concentration does not result from net accumulation of carbon dioxide.

- Both the pH and serum bicarbonate decrease.

- Two mechanisms account for the generation of metabolic acidosis:

- The net accumulation of organic acids or the net loss of bicarbonate.

Organic acids may accumulate due to:

- Endogenous overproduction
- Exogenous ingestion
- Impaired excretion.

- Acetoacetate and beta hydroxybutyrate in DKA, lactic acid in shock/ sepsis,
- Formic acid after ingestion of methanol,
- Renal dysfunction.

- Net loss of bicarbonate :
- Upper gastrointestinal tract disease,
- Impaired reabsorption of bicarbonate containing pancreas secretion.
- Renal tubular acidosis
- Acetazolamide
- The loss of bicarbonate results in increased de novo bicarbonate synthesis, which also increases the production of hydrogen ions.

Lactic Acidosis

- Lactate is the anion of lactic acid.
- Two enantiomers exist, L- and D-lactate.
- In most situations, lactic acidosis evolves as the result of L-lactate accumulation.
- Two types of L-lactic acidosis :
- Type A, in which accumulation of lactic acid results from impaired oxygen supply,
- Type B, which does not necessarily run parallel with tissue hypoxia.

- Main causes of hyperlactatemia Type A:
- Severe anemia
- Septic, hemorrhagic, cardiogenic shock
- CO poisoning
- Organ ischemia
- Convulsions
- Intense physical exercise

- **Type B**
- Sub-type B1 (Underlying primary diseases)

- Cancer and hemopathy
- Decompensated diabetes
- HIV infection
- Liver failure
- Sepsis
- Severe malaria attack

Sub-type B2 (Medication and toxins)

- Alcohol
- Beta-adrenergic agents
- Cyanide and cyanogenic compounds
- Diethyl ether
- Fluorouracil (5-FU)
- Halothane
- Iron
- Isoniazid
- Linezolid
- Metformin
- Nalidixic acid
- Niacin (vitamin B3 or nicotinic acid)
- Nucleoside reverse transcriptase inhibitors

- Paracetamol
- Propofol
- Psychostimulants: cocaine, amphetamines, cathinones
- Salicylates
- Strychnine
- Sugars: fructose, sorbitol, xylitol
- Sulfasalazine
- Total parenteral nutrition
- Valproic acid
- Vitamin defciency: thiamine (vitamin B1) and biotin (vitamin B8)

- Sub-type B3 (Inborn errors of metabolism):
- Fructose-1,6-diphosphatase defciency
- Glucose-6-phosphatase defciency (von Gierke disease)
- Kearns–Sayre syndrome
- MELAS syndrome
- MERRF syndrome
- Methylmalonic acidemia (methylmalonyl-CoA mutase defciency)
- Pearson syndrome
- Pyruvate carboxylase defciency
- Pyruvate dehydrogenase defciency

- Serum L-lactate is a predictor of mortality, particularly in septic individuals.

- Serum lactate in sepsis should be lowered as effectively as possible, the exact target level is still a matter of debate.

- Hematological and solid malignancies can induce L-lactic acidosis .
- The acid-base disorder predominantly results from acid overproduction by malignant cells.

- Muscular Hyperactivity: L-Lactate levels often increase in patients with seizures or severe asthma.
- Lactic acidosis can result from both lack and accumulation of certain substances.

- Thiamine and pyridoxine deficiency

- Severe ethanol and methanol intoxication,
- Antiretroviral drugs, linezolid, or propofol.

Metformin-Associated Acidosis

- lowers systemic glucose concentrations through inhibiting gluconeogenesis in the liver.

- In addition, peripheral glucose utilization is stimulated because metformin increases insulin sensitivity.

- The risk of metformin-induced lactic acidosis has most likely been overestimated in recent years.

- It has been reported at 0.03–0.06 per 1,000 patient-years.
- Increase in the following situations:

- systemic hypoxia , liver insufficiency and impaired excretory kidney function.

- Expanding the extracellular chloride load results in higher glomerular filtration and tubular elimination of bicarbonate, and in reduced proton net excretion by the kidney.

- Thus, hyperchloremic metabolic acidosis ensues, where the anion gap remains unchanged.

- The chloride content in 0.9% saline solution is above the range of the human extracellular fluid (154 vs. 95 mmol/L).

- The fact that these preparations can induce aMA has been discussed for many years.

- animal experiments indicated that unbalanced
- (chloride-enriched) crystalloids might affect kidney function in an unfavorable manner.

- Meanwhile, this concept has partly been confirmed by clinical observations.

- In a study Administration of saline worsened almost all outcome variables including mortality, rate of postoperative infection, and AKI incidence.

- Updated recommendation for the prevention of acute kidney injury in critically ill patients from 2018 favored balanced crystalloids.

Metabolic Acidosis and Compensatory Respiratory Response

- Metabolic acidosis also triggers a hyperventilatory compensatory response.
- The normal PaCO2 is 35-45 mm Hg.
- The compensatory hyperventilatory response to metabolic acidosis is fully developed within

12 to 24 hours

- **Paco2 = 1.5× HCO +8 ±2**

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

- More severe metabolic acidosis ([HCO3 less than
- 5-7 mEq/L), should reduce the PaCO2 maximally to the 8 to 12 mm Hg range.

- Alternatively, adding 15 to the [HCO3] generates a number that should approximate the PaCO2 in mild to moderate metabolic acidosis.

- If metabolic acidosis exists and the PaCO2 is not in the predicted range, a second, respiratory, acid-base disturbance probably exists.

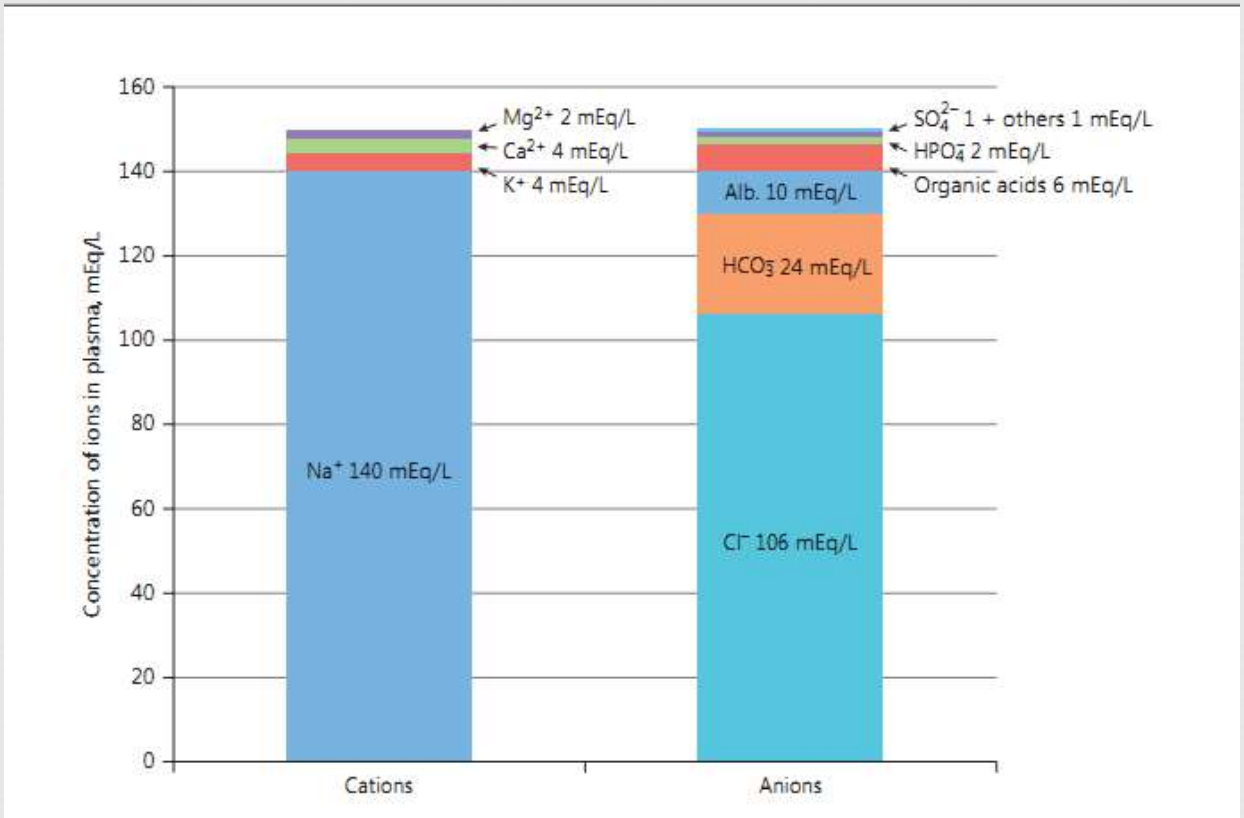
Anion Gap

The concept of the AG was introduced in

1936 by James Gamble

Not popular until the rapid availability of serum electrolyte measurements in the 1950s and 1960s.

- In any solution, the total charge concentration (measured in units of mEq/L) of dissolved cations must equal the total charge concentration of dissolved anions.
- if the sum of [Cl and HCO3] is subtracted from [Na+], an AG is noted.
- The normal [AG] is generally 8 to 12 mEq/L.


Concentration of ions in plasma, mEq/L
160
140
120
100
80
60
40
20
0
Mg2+ 2 mEq/L
Ca2+ 4 mEq/L
K+ 4 mEq/L
Na+ 140 mEq/L
SO4 2− 1 + others 1 mEq/L
HPO4− 2 mEq/L
Organic acids 6 mEq/L
Alb. 10 mEq/L
HCO3− 24 mEq/L
Cl− 106 mEq/L
Cations
Anions

- Normal electrolyte values can vary from laboratory to laboratory so each laboratory should determine their own normal [AG] range.

- It would be ideal to know each patient's own baseline. However, when that value is not known, we then suggest using a value of 10 mEq/L, with the adjustments for abnormal albumin concentrations.

- The correction factor for albumin is 2.3–2.5 [albumin].
- Each g/dL albumin decline will decrease the AG with about 2.5 mEq/L.

Normal AG Metabolic Acidosis

- In normal AG metabolic acidosis, bicarbonate loss is replaced by chloride and the AG equation will, therefore, remain the same, or "normal."

- If bicarbonate drops 10 mEq/L and chloride raises 10 mEq/L, the sum of the anions remains the same.

- This exchange of bicarbonate and chloride
- occurs in diseases of the gastrointestinal tract and the kidneys.
- Gastrointestinal Causes:
- Severe diarrhea, ileostomy
- Ureteral diversion
- Cholestyramine

Renal Tubular Acidosis

- There are three major forms of RTA:
- Proximal RTA (type 2)
- Distal RTA (type 1)
- Hyperkalemic RTA (type 4)
- RTA type 3 is a mixed RTA form of type 1 and type 2

Proximal Tubule Dysfunction

- The proximal tubule absorbs approximately 85–90% of the filtered bicarbonate and 60% of the filtered sodium along with water, phosphate, amino acids, and glucose.

- The loop of Henle reabsorbs around 10% of the filtered bicarbonate and the remaining 5–10% is reabsorbed in the collecting tubules.

- The process of bicarbonate reabsorption in the distal tubule involves an HCO3 /Cl exchanger.

Isolated Carbonic Anhydrase Defect

- Failing of the enzyme carbonic anhydrase (CA) IV by enzyme blockers like acetazolamide and topiramate.

- CA II is cytoplasmic and found in the proximal and distal tubule. CA IV is located in the apical membrane of the proximal tubule.

- filtered bicarbonate reacts with hydrogen ions to form carbonic acid (H 2 CO 3) that splits into CO 2 and H2O by the action of luminal enzyme CA IV.
- CO2 diffuses back into the cells where it reacts with H2O in the presence of cytoplasmic CA II and generates HCO 3 and H +.
- HCO 3 is transported into the blood, in exchange of chloride, while H + is secreted into the lumen.

- Bicarbonate absorption by this mechanism is saturable.
- whenever the normal level of 24 mmol/L is reached, loss of bicarbonate in the urine develops.
- Under normal conditions, however, there is virtually no bicarbonate in the urine.

- The plasma bicarbonate concentration usually does not fall below 12 mEq/L in patients with proximal RTA as distal renal tubules have substantial bicarbonate reabsorptive capacity.

Fanconi Syndrome

- A generalized proximal tubular dysfunction may cause the so-called Fanconi syndrome characterized by a complex transport defect of the proximal tubule.

- Decreased reabsorption of glucose, amino acids, bicarbonate, uric acid, and phosphate.

Distal Tubular Dysfunction

- In the distal tubules, (H+)secretion is counterbalanced by K retention, by H + /K + ATPase.
- A defect in this exchange leading to hypokalemia and metabolic acidosis .
- Another defect may be an increased permeability of the luminal membranes to secreted protons. This results in back diffusion of H+.
- This is the only type of classic RTA with high urine pCO 2 levels

(> 65 mm Hg) and corresponding high urine-blood pCO2 difference (>25 mm Hg).

- A small number of patients with distal RTA have a voltage defect in the distal tubules leading to hyperkalemia rather than hypokalemia.

- The necessary transepithelial voltage gradient for the exchange of H+/K+ cannot be maintained, forcing retention of both K + and H+ in exchange for Na+ as can be seen in aldosterone-related RTA type 4.

- Patients with RTA type 4 maintain their ability to acidify urine in response to acidemia in contrast with distal RTA due to a voltage defect.

RTA Type 4

- Aldosterone plays an essential role in the maintenance
- of fluid and electrolyte homeostasis in the collecting duct where Na+ is exchanged for H + and K .

- The kidney accounts for about 90% of excreted potassium, primarily governed by plasma aldosterone and delivery of sodium and water to the distal secretory site.

Normal AG Acidosis due to Saline Infusion

- Numerous severely ill patients admitted to the hospi-tal will develop an iatrogenic normal AG metabolic acidosis caused by fluid resuscitation with normal saline
- (NaCL 0.9%)
- All patients with severe diabetic ketoacidosis treated with NaCl 0.9% will have a combined high AG and normal AG metabolic acidosis soon after admission
- Hyperchloremia develops rapidly, increasing to 50% by 4 h.

- Patients treated with therapeutic plasma exchange with a replacement solution of 4% human albumin with a high chloride concentration can also develop a normal AG metabolic acidosis.
- Another rare cause :use of NaCl 0.9% for total gut irrigation
- through the nasogastric route method as a bowel prepa-
- ration in children undergoing colorectal surgeries.

- Because of this increase in chloride, a decrease in bicarbonate follows to maintain electroneutrality.

- Serum chloride is responsible for about one third of the extracellular fluid tonicity and two thirds of all an ionic charges in plasma.
- Because of its high concentration, chloride is the most important anion to balance extracellular cations.

Diagnostic Evaluation of Normal AG Acidosis

- The first step is to exclude severe diarrhea or the use of medications that can cause RTA.
- **Urinary Ammonium/Urine AG**
- Few laboratories measure urinary ammonium routinely
- **Urinary AG** ([Na +] + [K +] – [Cl –])
- **Urinary osmolal gap** ([Na +]+ [K +] + glucose + BUN – [Cl –]

- Urine AG will have a positive value (about +20 to +90 mmol/L) in healthy individuals.
- Urinary AG must become negative in sever diarrhea (about –30 to –50 mEq/L).
- In RTA type 1 and type 4, the urine AG will become positive.

- In proximal RTA, bicarbonate resorption is defective, but the ammonium excretion remains intact, urinary AG will be negative

The Urinary Osmolal Gap

The urinary AG becomes unreliable in:

- polyuria
- urine pH exceeds 6.5
- urinary ammonium is excreted with an anion other thanchloride (e.g., keto acids, acetylsalicylic acid, D -lactic acid and large quantities of penicillin.
- Acidification of the urine requires adequate distal deliver of sodium;
- usefulness of the urinary AG is questionable when the urinary sodium level is less than 20mmol/L.
- In such cases, the urinary osmolal gap generally more reliable.

- The urinary osmolal gap determines the difference between measured and calculated
- urinary osmolality.

- The urinary osmolality is calculated as follows: (2 [Na +] + 2 [K +]) + (urine urea nitrogen/2.8) + (urine glucose/18)

- In patients without diabetes, the glucose
- concentration is often omitted from this calculation.
- Normal urine osmolal gap is approximately 10–100 mosm/kg, with urinary ammonium excretion being approximately one half of this value (5–50 mmol/L).

- A high urine osmolal gap >200 mmol/L suggests a high urine ammonium concentration, and a nonrenal cause for the acidosis like diarrhea is more likely than RTA.

- Urinary osmolal gap below 40 mmol per liter in normal anion-gap acidosis indicates impairment in urinary ammonium excretion.

Urine pH

- The urine pH reflects the hydrogen ion concentration and the degree of acidification of the urine.
- The gold standard of measurement is with a pH electrode, dipsticks offer the convenience of cost and ease of use.
- Using dipsticks : significant deviations from the true pH are observed for values below 5.5 and above 7.5

- The pH of urine is dependent on the time of day, the prandial state, diet, health status, and medications.
- In metabolic acidosis and acidemia, the urine pH should decrease below 5.3 when the kidney function is intact.
- It may be challenging to differentiate be-
- tween diarrhea and distal RTA as a cause of normal AG acidosis and an elevated urine pH.
- Hypokalemia due to diarrhea can result in a inappropriately elevated urine pH .

Ammonium Chloride Load

- Administration of NH 4 Cl to induce metabolic acidosis with assessment of the renal response by serial measurement of urine pH has been often utilized in the past.
- NH 4 Cl test is poorly tolerated since it induces nausea and vomiting.
- The ability to acidify the urine may be assessed with less aggressive explorations.

Furosemide and Fludrocortisone

- The combination of both increased distal Na
- delivery, and the mineralocorticoid effect will stimulate distal H secretion.

- Normal subjects will lower urine pH to values below 5.5 with either maneuver.

The Urine-Blood pCO2 during NaHCO 3 Loading

- In the NaHCO 3 loading test, 2.75% NaHCO 3 solution should be infused intravenously at a rate of 4 mL/kg/h.
- Urine and blood samples are taken at 2-h intervals until the plasma bicarbonate concentration reaches 24 mmol/L.
- Urine and blood pCO 2 are measured then using a blood gas analyzer.
- The urine-blood pCO 2 is ≤ 30 mm Hg in patients with distal RTA and a H -ATPase defect but >30 mm Hg in health.

Bicarbonate Load

$$\text{Fractional } HCO_3 \text{ excretion} = \frac{(\text{urine } HCO_3^-) \times (\text{plasma creatinine})}{(\text{plasma } HCO_3^-) \times (\text{urine creatinine})} \times 100.$$

- When patients are in a steady state and there is no hypokalemia, sodium bicarbonate 0.5–1.0 mEq/kg/h can be infused until the plasma HCO3 increases to the threshold and bicarbonaturia ensues resulting in a high urine pH and high fractional HCO3 excretion.

- A urine pH >7.5 or fractional excretion of HCO3 >15% is diagnostic of proximal RTA after bicarbonate loading.

- Urine pH will be unchanged in normal patients or those with distal RTA.

- A fractional excretion of HCO_3 <5% excludes proximal RTA, and a value of 5–15% is indeterminate.

Table 1. Characteristics of normal anion gap (AG) metabolic acidosis diseases

	Serum bicarbonate, mEq/L	Plasma K^+	Ca^{2+} excretion	Urine AG mEq/L	Urine osmolol gap,mosm/kg in metabolic acidosis	Urinary NH_4^+, mEq/day	Minimal urine pH	Ability to acidify urine in response to acidemia	Urine-blood pCO_2, mm Hg	Comment
Health	Normal	Normal	Normal	+20 to +90	10–100	30–40	4.5–6	Yes	>30	
Severe diarrhea	<24	Low	Normal	−20 to −50	>200	High	>5.5	Yes		
Toluene/hippurate	<24	Low	Normal	Positive	>200	High		Yes		
Defective CA II activity/proximal RTA (type 2)	12–20	Low/ normal	Normal	Negative −20 to −50	>150	Normal	<5.5	Yes		Urine pH >6.5 during early phase with bicarbonaturia
Fanconi syndrome/ proximal RTA (type 2)	12–18	Low	↑	Negative −20 to −50	>150	Normal	<5.5	Yes		Hypophosphatemia/ phosphaturia, hypouricemia/ hyperuricosuria renal glucosuria (glucosuria with a normal serum glucose concentration), aminoaciduria

Hypokalemic distal RTA (type 1)	10–20	Low	↑	Positive	<150 (usually <50–100)	Low	>5.5 (often >6.5)	No	<30	
Back diffusion	8–15	Low	?	Positive	?	Low		No		
Hyperkalemic distal RTA (voltage-dependent RTA)	8–15	High	Normal or ↑	Positive	<150 (usually <50–100)	Low	>5.5 (often >6.5)	No		
RTA type 3	Low	Low	↑			Low	>5.5	No		
RTA type 4	16–22	High	Normal	Positive	<150 (usually <50–100)	Low	<5.5	Yes		Often increased creatinine

Delta anion gap/ ratio

When metabolic acidosis is generated by extracellular fluid (ECF) accumulation of relatively strong acids (such as lactic acid, β-hydroxybutyric, or acetoacetic acids (but not hydrochloric acid), [HCO3] falls and the [AG] increases reciprocally.

the Δ[AG]/Δ[HCO3 ratio is generally about 1.

- Several factors may disrupt this 1:1 relationship.
- They include different distribution spaces for bicarbonate and the accumulating acid anions, intracellular proton buffering.
- Variable rates of kidney excretion of the protons and acid anions.
- Mixed acid-base disorders

- If the [AG] is increased but the [HCO3−] is not reciprocally reduced, consider mixed AG metabolic acidosis and metabolic alkalosis (or AG metabolic acidosis and chronic respiratory acidosis—the arterial blood pH will differentiate).

- Marked increases or decreases in "unmeasured" anion and/or cation concentrations will impact the [AG] calculated value.

- Hypoalbuminemia, Marked hyperphosphatemia, hypercalcemia, hypermagnesemia, will also increase or reduce the [AG].

- Electrolyte measurement artifacts can occur

- These [AG] and [HCO3 relationships are very useful concepts, they are not quantitatively exact.

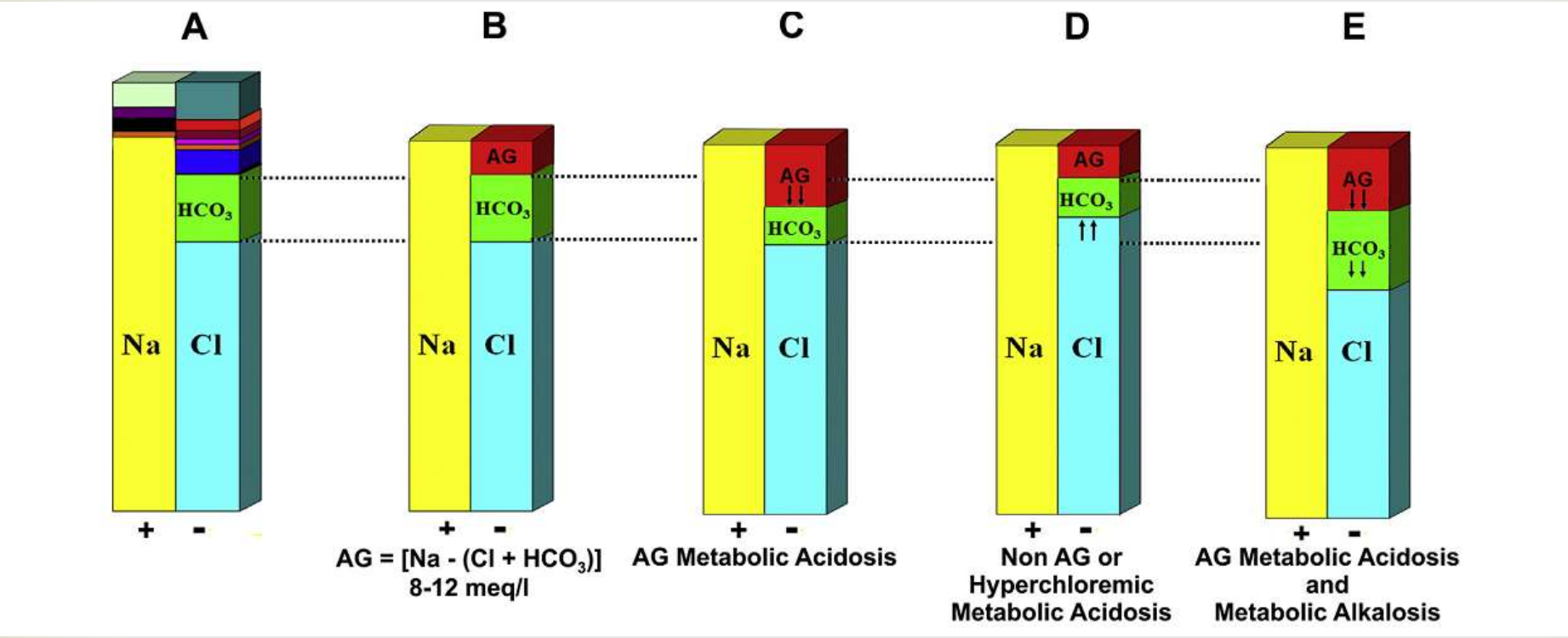

A
B
C
D
E
Na
Cl
HCO3
AG
+
-
AG = [Na - (Cl + HCO3)]
8-12 meq/l
AG Metabolic Acidosis
Non AG or
Hyperchloremic
Metabolic Acidosis
AG Metabolic Acidosis
and
Metabolic Alkalosis

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.

Organic acidemia

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

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با تشکر از توجه شما

Case 1: A six month old boy with a history of PUVD presents to the emergency department (ED) with 3 days of fever, poor feeding and letahargy. His vital signs are temperature 39.5 C; mm Hg; and pulse,130/min

The physical examination is notable for dry mucous membranes and lethargy.

Na= 138 mEq/L; K= 3.1 mEq/L; Cl =111 mEq/L; HCO3= 17 mEq/L, (BUN) = 26 mg/dL; creatinine = 0.8 mg/dL; glucose= 126 mg/100 mL; albumin, 2.0 g/dL.

ABG: pH 7.25; pCO2=32mmHg; HCO3= 15 mEq/L and pO2 =72mmHg.

What is the acid-base abnormality in this patient?