Acid-Base Physiology: I

A practical approach to the diagnosis of metabolic acidosis

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Disclosures

- Consultant for Lungpacer® Medical Inc.
- Dry subject!
- Requires repetition and some memorization

Outline of the lectures

- Part I (04/16/18):
  - An approach to the diagnosis of acid base disorders (with a particular focus on metabolic acidosis)
  - Practice exercises
  - A primer on lactic acidosis
  - A (very brief) look at the Stewart method
- Part II (04/23/18):
  - Treating acid-base disorders: when, how, and does it matter?
  - A brief overview of alpha stat and pH stat

Part I: Objectives

- Why focus on metabolic acidosis?
- Outline of approaches to acid-base disorders
- A practical approach to diagnosing acid-base disorders
- Acidosis problems to work through
- A quick review of lactic acidosis
- Stewart – pros and cons

WHY METABOLIC ACIDOSIS?

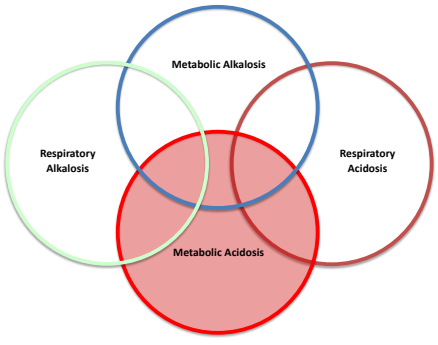


TABLE 1. MAJOR ADVERSE CONSEQUENCES OF SEVERE ACIDEMIA.

Cardiovascular
Impairment of cardiac contractility
Arteriolar dilatation, venoconstriction, and centralization of blood volume
Increased pulmonary vascular resistance
Reductions in cardiac output, arterial blood pressure, and hepatic and renal blood flow
Sensitization to reentrant arrhythmias and reduction in threshold of ventricular fibrillation
Attenuation of cardiovascular responsiveness to catecholamines
Respiratory
Hyperventilation
Decreased strength of respiratory muscles and promotion of muscle fatigue
Dyspnea
Metabolic
Increased metabolic demands
Insulin resistance
Inhibition of anaerobic glycolysis
Reduction in ATP synthesis
Hyperkalemia
Increased protein degradation
Cerebral
Inhibition of metabolism and cell-volume regulation
Obtundation and coma

Adrogue and Madias, NEJM 1998

APPROACHES TO ACID-BASE DISORDERS

Definitions

- Acid:
  - Arrhenius: Any substance delivering a H^+ ion into a solution
  - Brønsted-Lowry: Proton donor
- pH=pKa + log $[A^-]/[HA]$ (Henderson-Hasselbach eq)
- Strong Acid: Low pKa, completely dissociated at physiologic pH
- Weak Acid: High pKa, incompletely dissociated at physiologic pH

Approaches to understanding acid-base physiology

Descriptive	Semi-quantitative	Quantitative	
Henderson-Hasselbalch	Base Excess	Physical Chemical	
pCO_2 "Fixed acids" H^+	pCO_2 Buffer Base	pCO_2 SID A_{TOT}	**Affecters**
HCO_3^- Anion Gap	SBE	SIG	**Markers & Derived Variables**

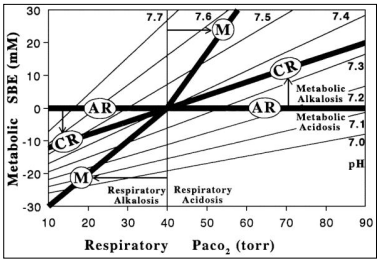
Kellum JA. *Critical Care*, 2005

A quick question:

- Is the Base Excess value reported in our ABG results influenced by the $PaCO_2$?
- Consider the following blood gas result:

  pH=7.02; $PaCO_2$=80; BE= -7
- This ABG shows:
  a) Acute respiratory acidosis only (the BE is due to the high $PaCO_2$)
  b) Respiratory acidosis + metabolic acidosis

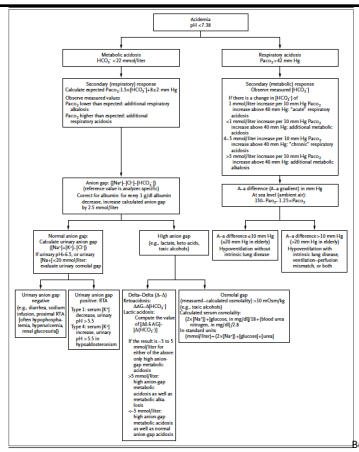
Base Excess vs. Standardized Base Excess



Human PaCO2 and standard base excess compensation for acid-base imbalance.
Schlichtig, Robert; Grogono, Alan; Severinghaus, John
Critical Care Medicine. 26(7):1173-1179, July 1998.

Figure 5 . A clinical map of the average or typical human compensations for acid base imbalances. SBE, standard base excess; M, metabolic acidosis or alkalosis; AR, acute respiratory acidosis or alkalosis; CR, chronic respiratory acidosis or alkalosis. Arrows show direction of compensatory changes from uncompensated acid base imbalances. Linear pH isopleths permit location of a patient data set on the diagram when only a pH and PaCO2 are known. Solid lines have these slopes: (Table 3)

A PRACTICAL APPROACH TO METABOLIC ACIDOSIS BASED ON THE PHYSIOLOGIC METHOD

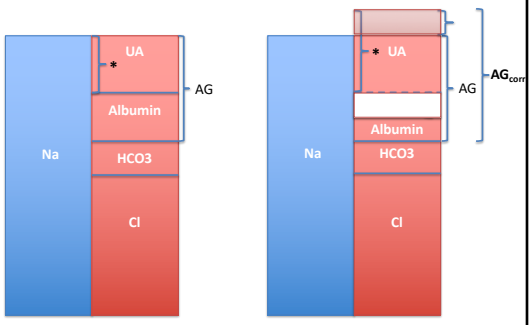


Berend K, et al. NEJM 2014

Two modifications to the 'physiologic method'

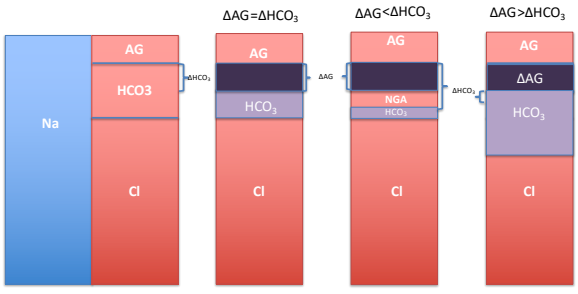
- Correction of the Anion Gap (AG) for hypoalbuminemia
  - AG = $[Na^+]$ – ($[Cl^-]$ + $[HCO3^-]$) = Unmeasured Anions (Albumin + bad stuff)
  - In other words, AG is a surrogate for UA
  - Critically ill patients often have low albumin levels
- Calculating the delta-delta (Δ/Δ)

Hypoalbuminemia and the AG



AG_{corr} = AG + (2.5 X ($[Albumin_R]$ – $[Albumin_M]$), where concentration is in gm/dL

Mixed metabolic acidosis/alkalosis



$\Delta AG-\Delta HCO_3$: 0+/-5 (pure AG acidosis); <-5(AG + Non-gap acidosis); >5(AG + Metabolic Alkalosis)

Urinary AG/Osm Gap

- Normal response to metabolic acidosis is to increase urinary H^+ excretion (as NH_4^+)
- NH_4^+ is usually excreted with Cl^- (Na+K+NH_4-Cl=0)
- Therefore the UAG is an indirect estimate of NH_4^+ excretion
- A more negative UAG suggests HCO_3 losses (GI or renal (ptoximal RTA))
- A positive UAG suggests impaired urinary acid excretion (distal RTA (1 and 4), hypoaldesteronism)
- A high urinary osm gap in non-gap acidosis suggests normal NH_4 excretion, while a low (<40) gap suggests impaired acid excretion
- Use U Osm gap (instead of UAG) when U Na <20 or pH>6.5

A relatively simple approach to evaluating metabolic acidosis

1. pH -> Acidemia/Alkalemia
2. SBE/HCO_3 -> Metabolic Acidosis/Alkalosis
3. Expected $PaCO_2$ [=(1.5 X [HCO_3^-]) + 8)+/- 2] for met. acidosis; $\Delta PaCO_2 = 0.7 \text{ X } \Delta HCO_3$ for met. alkalosis-> Superimposed respiratory acidosis/alkalosis/neither
4. AG and AG_{corr}
5. If AG_{corr} is high -> Δ/Δ
6. If Ag_{corr} wnl -> Urinary AG ([Na] + [K] – [Cl])/ Urinary Osmolal Gap (2x [Na] + 2x [K] + [UUN/2.8] + [U Gl/18)
7. Plasma Osmolal Gap

A word on secondary (compensatory) responses

- Complete compensation in chronic respiratory alkalosis and (perhaps) chronic respiratory acidosis
- Multiple formulae exist – it is difficult to remember them all – here is what I remember:
  - $\Delta pH/\Delta PaCO_2$ (acute): 0.08/10
  - Expected $PaCO_2 = (HCO_3 \text{ X } 1.5) + 8$ (acidosis)
  - Expected $PaCO_2 = (0.7 \text{ X } [HCO_3 - 24]) + 40$ (alkalosis)
  - Expected $PaCO_2 = HCO_3 + 15$ (both acidosis and alkalosis)

A 67 year old patient has acute cholangitis. She is on 30 mcg/min levo, 0.04 vasopressin, with a MAP of 67 mm Hg. Her Labs are as follows:

pH :7.12, Lactate 18, Serum HCO_3: 6

She is tachypneic but not in distress.

Does she need to be intubated because of her high lactate?

- If so, why?
- If not, what would prompt intubation, assuming she does not get worse from a hemodynamic perspective?

Practice Examples

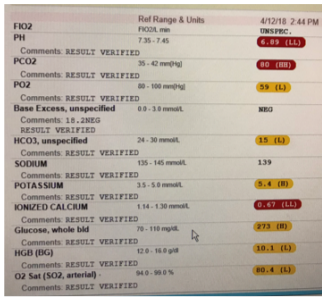
- To get a reasonably detailed picture, you need to order 3 labs, simultaneously:
  - ABG
  - Chem7
  - Albumin
- A way to cross-verify ABG and bicarb:
  - The Henderson eq ([H] X [HCO_3]) = K X $PaCO_2$, where K = 24 and [H] is molar concentration of H^+ ions (determined by pH)

Table 1 pH values and equivalent [H^+] for water. [H^+] is the physical chemistry expression of molar concentration H^+.

pH value	[H^+]; nmol.l^{-1}
7.6	25
7.5	32
7.4	40
7.3	50
7.2	60
7.1	80
7.0	100
6.9	125
6.8	160

Morris and Low. *Anaesthesia* 2008

Define the acid-base abnormalities



Case 1

Answer
- Primary Respiratory alkalosis
- High AG metabolic acidosis

TEMP	36.4
FIO2	0.97
aPO2	77(L)
aPCO2	16(L,T)
aPH	7.50(H)

NA	130(L)
K	3.7
CL	91(L)
CO2	14(L)
BUN	36(H)
CRE	5.01(HT)
EGFR	see detail
GLU	141(H)
ANION	25(H)

CA			8.0(L)		8.4(L)
IC					
PHOS			3.1		3.8
MG			1.5(L,T)		2.0(T)
URIC		14.3(H)			
TBILI			7.3(H)		2.0(H)
DBILI			3.1(H)		0.3
TP			7.0		7.4
ALB			3.5		4.1
GLOB			3.5		3.3
LDH		693(H)		737(H)	
LACT	6.5(H)				
AMY			23		
LIPS			8(L)		

Case 2-3

Patient 88
- High AG metabolic acidosis
- Metabolic alkalosis

Patient 59
- High AG metabolic acidosis

Table 3 Measured and calculated values for two representative patients with acid–base disorders and for nine controls

	Patient 88	Patient 59	Controls (n = 9)
Measured values			
pH	7.40	7.33	7.42
p_aCO_2 (mm Hg)	39	30	38
$[Na^+]$ (mEq/l)	137	117	142
$[K^+]$ (mEq/l)	4.9	3.9	4.1
$[Cl^-]$ (mEq/l)	102	92	106
$[Mg^{2+}]$ (mEq/l)	1.6	1.4	0.8
$[Ca^{2+}]$ (mEq/l)	3.2	3.0	2.3
Albumin (g/l)	6	6	44
P_i (mmol/l)	0.3	0.6	1.0
Calculated values			
$[HCO_3^-]$ (mEq/l)	24	15	24.5
$[Cl^-]_{corr}$ (mEq/l)	106	112	106
ΔAG_{corr} (mEq/l)	13	11	3
SIG (mEq/l)	19	18	8
BE_{lab} (mEq/l)	0	−10	0.3

Modified from Fencl et al.[9]

Fidkowski and Helstrom, *CJA* 2009

Case 4

A female patient with fever, vomiting, and postrenal failure

Hemoglobin; g/dL	Na+ meq/L	K+ meq/L	Cl- meq/L	HCO3- meq//L	Anion gap; meq/L	Albumin g/dl	pH	PCO2 mm Hg	Lactate, meq/L	Osm/osm gap	Creatinine, mg/dl
11	140	4.3	89	6	45	2.4	7.32	12	<2	306/1	7.3

This 47 year-old woman has an invasive cervical cancer causing complete obstruction of urinary flow, renal failure with concomitant volume depletion from vomiting and watery diarrhea ongoing for weeks after radiotherapy . There is evidence of C. difficile in the stool and E. Coli in the urine with an inflammatory systemic response. Potentially toxic medications in this setting include opiates and acetaminophen.

- High AG metabolic acidosis (Renal failure and **acquired 5-oxoprolinurea**, a byproduct of impaired tylenol metabolism)
- Respiratory alkalosis
- Metabolic alkalosis

Seifter JL. NEJM 2014

Case 5

A patient with alcohol abuse and coma

Hemoglobin; g/dL	Na+ meq/L	K+ meq/L	Cl- meq/L	HCO3- meq//L	Anion gap; meq/L	Albumin g/dl	pH	PCO2 mm Hg	Lactate, meq/L	Osm/osm gap	Creatinine, mg/dl
9.3	132	4.2	92	3.6	36.4	3	7.07	12.6	14	338/34.6	2.7

- High AG metabolic acidosis Appropriate respiratory compensation
- Metabolic alkalosis
- Possible ingestion given high osmolal gap

Case 6

Patient 1, a 22-year-old woman who had been injured in an accident, received 6 liters of isotonic saline, after which the level of sodium was 135 mmol per liter, potassium 3.8 mmol per liter, chloride 115 mmol per liter, and bicarbonate 18 mmol per liter. The arterial blood pH was 7.28, and the $Paco_2$ was 39 mm Hg. The urinary sodium level was 65 mmol per liter, potassium 15 mmol per liter, and chloride 110 mmol per liter.

Answer
- Non-gap (hyperchloremic) acidosis
- Respiratory acidosis

Berend K, et al. NEJM 2014

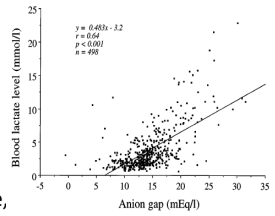
A REVIEW OF LACTATE IN SEPSIS

Lactic acidosis and the critically ill patient

- Does a high anion gap/base deficit accurately predict a high lactate?
- Do all patients with an elevated lactate have tissue hypoxia?
- What is the data on lactic acidosis and outcomes? Is there a 'critical threshold' that we should worry about?
- Is lactic acidosis in non-hypotensive patients a concerning sign?
- Should we incorporate lactate clearance into our resuscitation strategies?

Do the anion gap and base deficit predict high lactate?

- Not necessarily
- A high AG (corrected) is sensitive, not specific
- Some patients may actually have a normal base deficit in spite of high lactate levels (Tuhay G, et al. Crit Care, 2008)



Levraut J, et al. Intensive Care Med. 1997;23:417

Is lactate = tissue hypoxia?

TABLE 1. Causes of Elevated Lactate Levels

- Shock
  - Distributive
  - Cardiogenic
  - Hypovolemic
  - Obstructive
- Post–cardiac arrest
- Regional tissue ischemia
  - Mesenteric ischemia
  - Limb ischemia
- Burns
- Trauma
- Compartment syndrome
- Necrotizing soft-tissue infections
- Diabetic ketoacidosis
- Drugs/toxins
  - Alcohols
  - Cocaine
  - Carbon monoxide
  - Cyanide
- Pharmacological agents
  - Linezolid
  - Nucleoside reverse transcriptase inhibitors
  - Metformin
  - Epinephrine
  - Propofol
  - Acetaminophen
  - β_2-Agonists
  - Theophylline
- Anaerobic muscle activity
  - Seizures
  - Heavy exercise
  - Excessive work of breathing
- Thiamine deficiency
- Malignancy
- Liver failure
- Mitochondrial disease

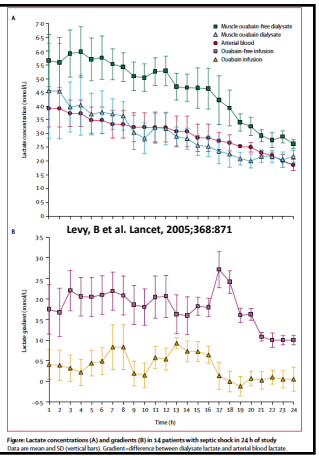
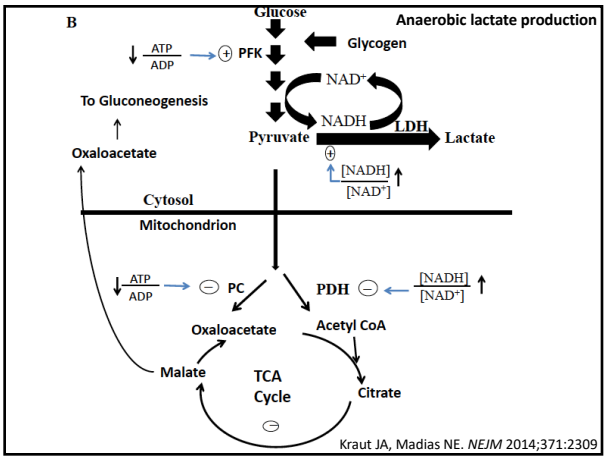
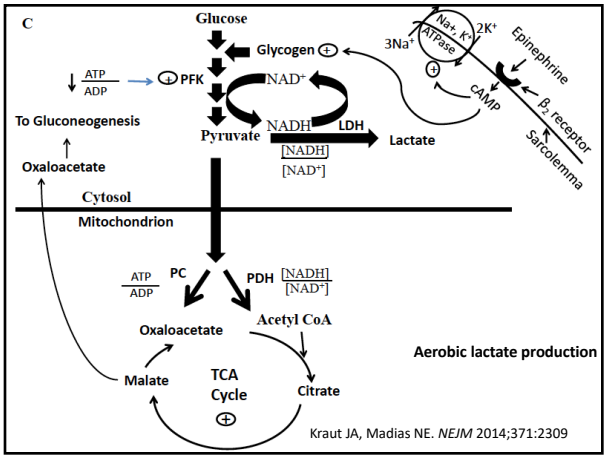


Figure: Lactate concentrations (A) and gradients (B) in 14 patients with septic shock in 24 h of study
Data are mean and SD (vertical bars). Gradient=difference between dialysate lactate and arterial blood lactate.



Kraut JA, Madias NE. *NEJM* 2014;371:2309



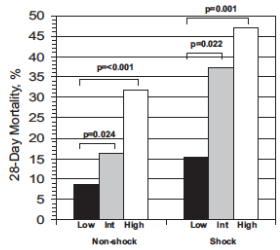
Kraut JA, Madias NE. *NEJM* 2014;371:2309

Lactate and outcomes

- Lactic acidosis is a poor prognostic sign in multiple settings (septic shock, post-cardiac arrest, trauma)[1,2,3]
- Higher lactates correlate with worse prognosis[1]
- Even high-normal values may be a signal for poor outcomes in critical illness[4,5]
- An elevated lactate portends poor prognosis even in the **absence** of hypotension[5,6]
- A generally accepted threshold for severe lactate level is >4 mmol/L

1. Trzeciak S, et al. *Int Care Med* 2007;33: 970; **2.** Kliegel A, et al. *Medicine* 2004;83:274; **3.** Abramson D, et al. *J Trauma* 1993;35:584; **4.** Nichol AD, et al. *Crit Care* 2010;14:R25; **5**. Mikkelsen ME, et al. *CCM* 2009;37:1670; **6**. Casserly B, et al. *CCM* 2015;43:567

Lactate and mortality



Mikkelsen ME, et al. Crit Care Med 2009;37:1670

Should lactate clearance be a resuscitation end-point?

- Opinions differ
- A study found that lactate clearance was non-inferior to $ScVO_2$ as an end point[1]
- However, $ScVO_2$ use has been called into question by recent studies (ProCESS[2], ARISE[3])
- Surviving sepsis guidelines recommend lactate clearance (grade 2C)[4]
- I would suggest using both $ScVO_2$ and lactate, but in context, and keeping our knowledge of physiology in mind

1. Jones AE, et al. *JAMA* 2010;303: 739; **2.** Yealy DM, et al. *NEJM* 2014;370:1683; **3.** Peake SL, et al. *NEJM* 2014;371:1496; **4.** Dellinger RP, et al. *CCM* 2013;41:580

The Stewart Method

Which of the following is NOT an independent variable in determining the pH of a solution according to the Stewart method?

A. Strong Ion Difference (SID)

B. Total weak acid concentration (A_{TOT})

C. $[HCO_3^-]$

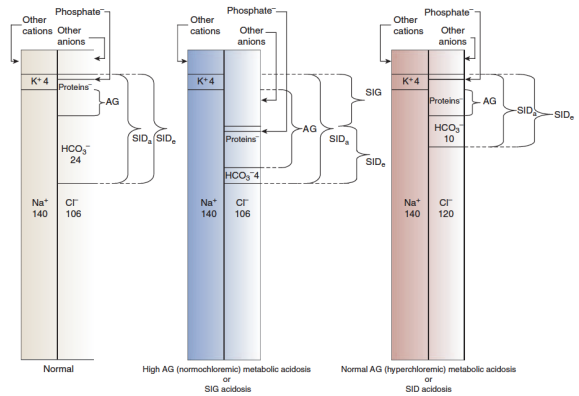
D. P_aCO_2

Answer: C

- $SID = ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) – ([Cl^-] + [SO_4^{2-}] + [A^-]) = 40\text{-}44$ mEq/L
- $[A_{TOT}]$ = Total weak acid concentration (proteins and phosphate)

Variables in the Stewart Method

- Apparent Strong Ion Difference (SID_A)
- Effective Strong Ion Difference (SID_E)
- Strong Ion Gap ($SID_A – SID_E$) = SIG
- $PaCO_2$



Adrogue HJ, et al. *Kidney International*, 2009

Table 1 | Assessment of the metabolic component of acid-base status

Approach	Variable	Determination	Remarks
Physiological	Plasma [HCO_3^-]	Measured pH and PCO_2	Interpretation complemented by evaluation of plasma anion gap, [Na^+]−[(Cl^-]+[Total CO_2])
Base excess	Blood base excess (BE)	CO_2 equilibration method or calculated from measured pH and PCO_2	BE is a measure of the metabolic component of acid-base status as reflected in whole blood Interpretation complemented by evaluation of plasma anion gap
	Standard BE (SBE)	Calculated from measured pH, PCO_2, and hemoglobin	SBE is a measure of the metabolic component of acid-base status as reflected in the extracellular compartment. It is usually calculated automatically from arterial blood gas results, but it can also be obtained using the blood acid-base nomogram with the hemoglobin set at 5 g/dl[62] Interpretation complemented by evaluation of plasma anion gap
Physicochemical	SID_a (apparent strong ion difference)	([Na^+]+[K^+]+[Ca^{++}]+[Mg^{++}])−([Cl^-]+[lactate$^-$])	These three formulas for SID_a, as well as additional variants, are currently in use. SID_a is mathematically equivalent to the plasma buffer base of Singer and Hastings[64]
		([Na^+]+[K^+])−[Cl^-]+[lactate$^-$]+[other strong anions])	
		([Na^+]+[K^+])−[Cl^-]	
	SID_e (effective strong ion difference)	[HCO_3^-]+[Alb^-]+[P^{i-}] where: [Alb^-]=[Alb, g/l] × [(0.123 × pH)−0.631] [P^{i-}]=[P_i, mmol/l] × [(0.309 × pH)−0.469]	Represents the sum of plasma [HCO_3^-] and non-bicarbonate buffers (anionic equivalency of albumin and phosphate)
	SIG (strong ion gap)	$SID_a - SID_e$	An estimate of the concentration of unmeasured anions in plasma that resembles the plasma anion gap Value depends upon the variant of SID_a used
	A_{tot} (total concentration of weak acids in plasma)	2.43 × [total protein, g/dl]	Primarily related to albumin concentration For clinical purposes, approximated by the concentration of total protein

All variables and electrolytes listed are expressed in mEq/l, unless otherwise indicated.

Adrogue HJ, et al. *Kidney International*, 2009

Which of the following is NOT consistent with a non-gap (hyperchloremic) acidosis?

A. Normal corrected anion gap
B. Elevated strong ion gap (SIG)
C. Decreased strong ion difference (SID)
D. Normal to low [Cl^-] concentration

Answer

B

Drawbacks of the Stewart Method

- Complex, requiring many variables
- Mathematically, it is possible to show that the Stewart Method is equivalent to the physiologic method (Krutz I, et al. *Am j Physiol Renal Physiol* 2008)
- Does not provide a sense of the ***physiology***, as opposed to the ***chemistry***
- Cannot be used to determine degree of compensatory changes
- Most importantly, essentially NO clinical advantage

Evidence?

- Gunnerson et al – 851 patient records analyzed. Strongest association of mortality with lactic acidosis (56%) and SIG acidosis (39%) was significantly higher than hyperchloremic (29%) or no acidosis (25%)[1]
- Rocktaeschel et al in 300 patients showed that only unmeasured anions (UA) had a correlation with mortality. Also showed strong correlation between AG_{corr} and SIG[2].
- 3 studies[3, 4], among them a prospective study in >900 patients[5] showed a tight correlation between AG_{corr} and SIG (R^2>0.97)
- Taken together: Unmeasured anions and lactate are correlated with mortality, and AGcorr is as accurate as the SIG in detecting UA

To summarize…

- Frequent repetition helps proficiency
- There is no gold standard method – use the system you are comfortable with
- Use as many data points as you can to help support your judgment
- The time to send a lactate is when you first think about it!

Questions?

References

1. Gunnerson et al. *Critical Care*, 2006. 10;R22-30.
2. Balasubramanyan et al. *Crit Care Med*, 1999: 27: 1577-81
3. Dubin , et al. *Crit Care Med*, 2000: 35; 1264-70.
4. Kellum et al. *J Crit Care* 1995: 10; 50-55
5. Moviat et al. *Crit Care Med* 2003:7; R41-45

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