Understanding Strong Ion Difference

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Physicochemical Approach

Everything you always wanted to know about strong ion difference but were afraid to ask because of the calculations

Acid-base Strong Ion Difference

- Acid buffering – why and where
- Define cations, anions, strong ions
- Determinants of Acid/Base Status

  Weak ion buffer base, Strong ion difference
- Base Excess
- Anion Gap
- Strong Ion Gap
- Treatment Guidelines

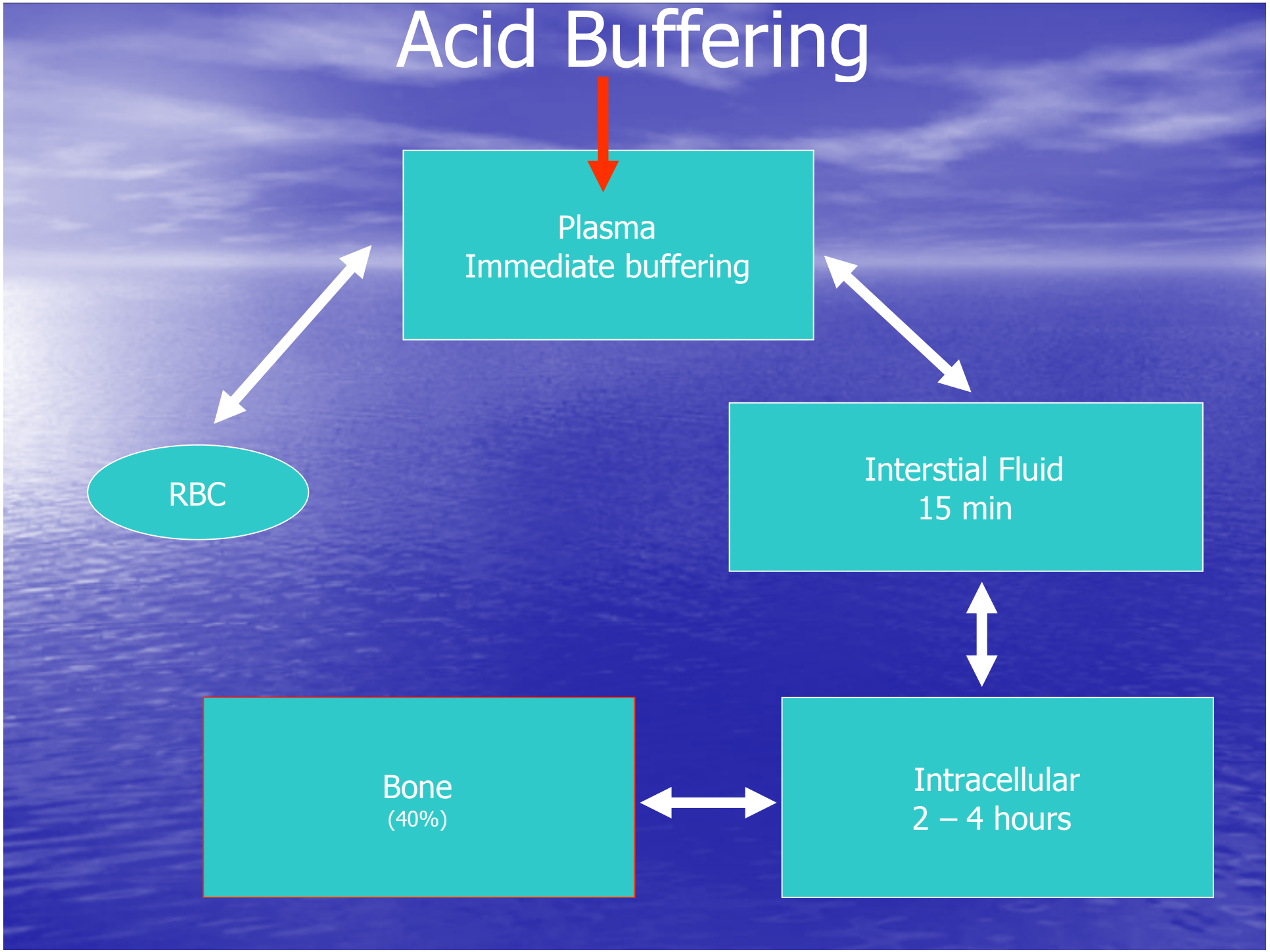
Abnormal Acid/Base Balance

- Predicts outcome
- Often not a direct cause the fatality
  - Epiphenomenon
- Acid base homeostasis is defended like
  - O_2 transport
  - Perfusion pressure

Acid/Base Balance

- $[H^+]$ maintained within nmol/l range
  - Other electrolytes mmol/l range
  - 99.99% $[H^+]$ is buffered
    - The 0.01% not buffered determines the pH
- $[H^+]$ effects
  - H-bonds
  - Protein configuration
  - Receptor binding
  - Enzyme activity
    - Rate of glycolysis varies inversely with $[H^+]$
- Water is an endless supply of H^+

Acid Buffering

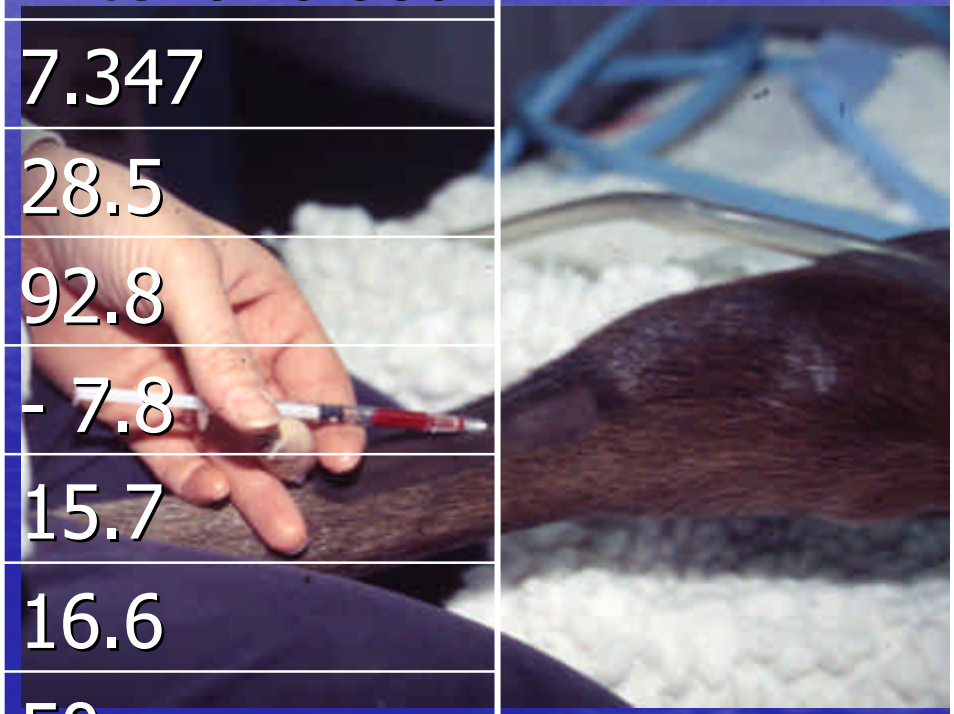


Acid/Base Balance

- Intracellular pH primary importance
  - pH varies between different cell types
  - pH varies within cellular compartments
- ECF pH is important physiologically
  - Conduit for O_2/nutrients to cell
  - It is the fluid that is sensed
    - It is the acid-base regulated by the body
  - pH varies transcellular fluid and interstitial fluid
- Plasma pH/electrolytes measured
- Plasma pH/electrolytes predict intracellular levels
  - Directly related

Acid Base measurements Arterial vs. Venous sample

Source	Venous blood	Arterial blood
pH	7.162	7.347
P_{CO2}	59.8	28.5
P_{O2}	28.4	92.8
BE-B	- 7.3	- 7.8
HCO_3	21.5	15.7
TCO_2	23.4	16.6
Dextrose	18	50



Physicochemical Approach

- Conservation of mass

  But can have metabolism – e.g. lactate

- Electroneutrality

  Charges always balance

- To balance charge

  H^+ produced or donated from weak acid – changes pH

Cations and Anions

- Cations

  Na^+ , K^+ , Ca^{++} , Mg^{++}, H^+
- Anions

  Cl^-, Lac^-

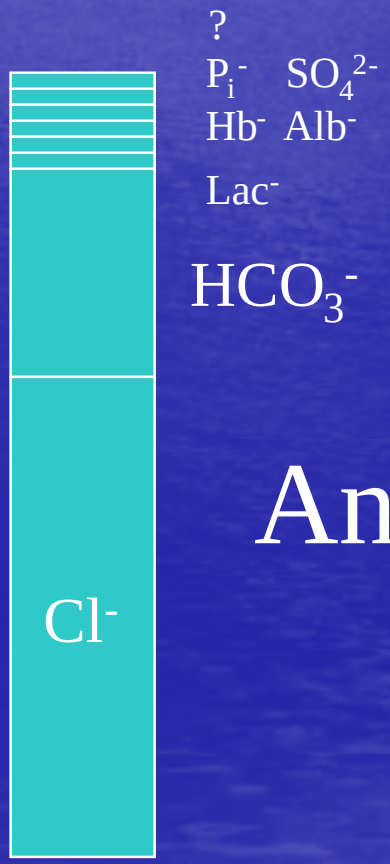
  Hgb, Alb, P_i,

  Ketones, SO_4^{2-}

  Fatty acids, aspirate, glutamate

  $HCO3^-$

Cations/Anions



Cations

Anions

Strong Ions

- Any ion which cannot combine with other ions
  - It is always free
  - Disassociated at physiologic pH
  - Always contributes a charge
- Na^+, K^+, Cl^-
- Not $HCO3^-$
  - Weak ion
  - $HCO_3^- + H^+ \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$
  - Loses its charge
- Lactate is a strong ion
  - Completely disassociated at physiologic pH

Determinants of Acid/Base Status

- CO_2 (Pco_2)
- Nonvolatile weak ion acid buffer (A_{TOT})
- Strong Ion Difference (SID)

CO_2

- Quantitated as Pco_2
- CO_2 is in equilibrium with HCO_3^-

  Can calculate HCO_3^-

  Which is related to SID

Weak Ion Acid Buffer (Buffer Base)

- Buffer takes up or releases H^+
  - in physiologic range of pH changes
- Weak acid buffer
  - Volatile
  - Nonvolatile
- Volatile buffer HCO_3^-
  - Weak ion - can take a H^+
  - Cannot buffer CO_2 (itself)
    - Not prevent acid-base changes caused by CO_2
    - HCO_3^- is not independent

Nonvolatile Weak Ion Acid Buffer

- $A_{Total} = A^- + AH$
  - Hemoglobin
  - Albumin
  - Inorganic phosphates
- A^- changes with SID & Pco_2 – dependent
- A_{Total} not change – independent
- Good buffers
  - Even at extremes of concentrations
- There's no single dissociation constant
  - Large number of buffering sites
  - Most effective near normal pH

Nonvolatile Weak Acid Buffer

- AH =
  - In plasma – Albumin + P_i^- + SO_4^{2-}
  - In RBC – Hb + P^-
- Estimate A^-
  - Using only total protein
  - Using albumin & PO_4^{2-}
    - A^- = 2 (albumin) + 0.5 (Pi)

      pH < 7.35
    - A^- = pH [(1.16 X albumin) + (0.42 X Pi)] – (5.83 X albumin) – (1.28 X Pi)

Cations/Anions
Weak Ion Acid Buffer

Cations

P_i^- SO_4^{2-}
Alb^- Hb^-

Anions

Acid/Base Balance

- As independent factors change

  CO_2, SID, A_{Total}

- "+" = "-"

  Charges must remain balanced

- Dependent factors adjust

  To keep charge balanced and maintain pH

  $A^- + H^+ \longleftrightarrow AH$

  $H^+ + HCO_3^- \longleftrightarrow CO_2 + H_2O$

SID (Strong Ion Difference)

- Old concept - new name

  Change from normal = BE

- Strong ions

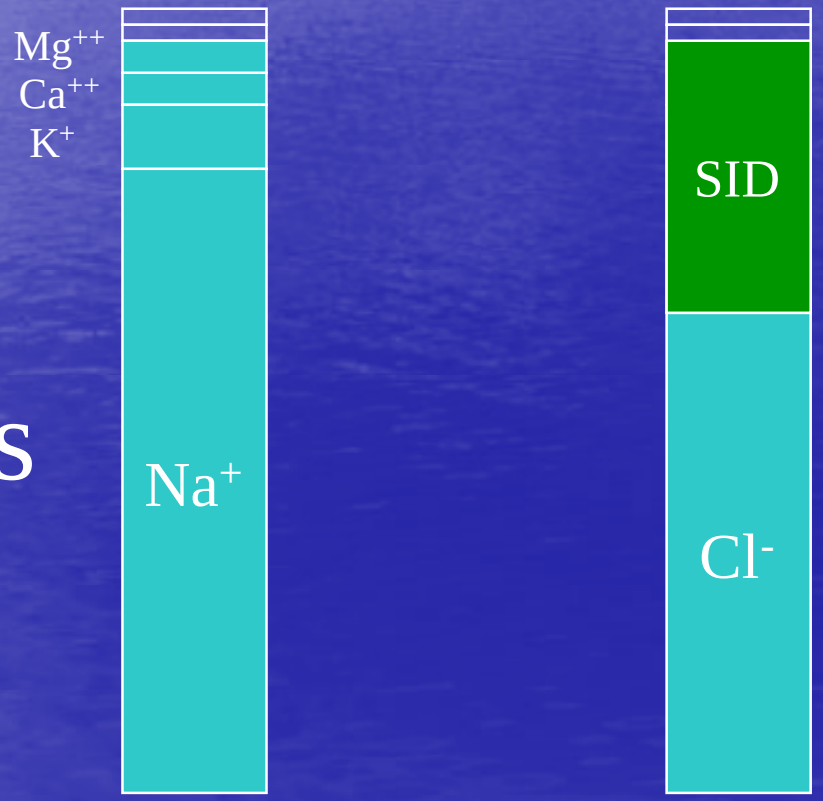
  Lactate, Hydroxybutyrate, SO_4^{2-} , Na^+, K^+, Cl^-

  SID = (Na+ + K+ + Ca++ + Mg++) – Cl

  SID = $HCO3^-$ + A^-

  SID = 40-42 (ICU patients = 30)

Cations/Anions
SID



Cations

Anions

Base Excess

- Definition

  Blood gas measured pH and P_{co2}

  If adjust P_{co2} = 40

  - pH will change

  If adjusted pH ≠ 7.40

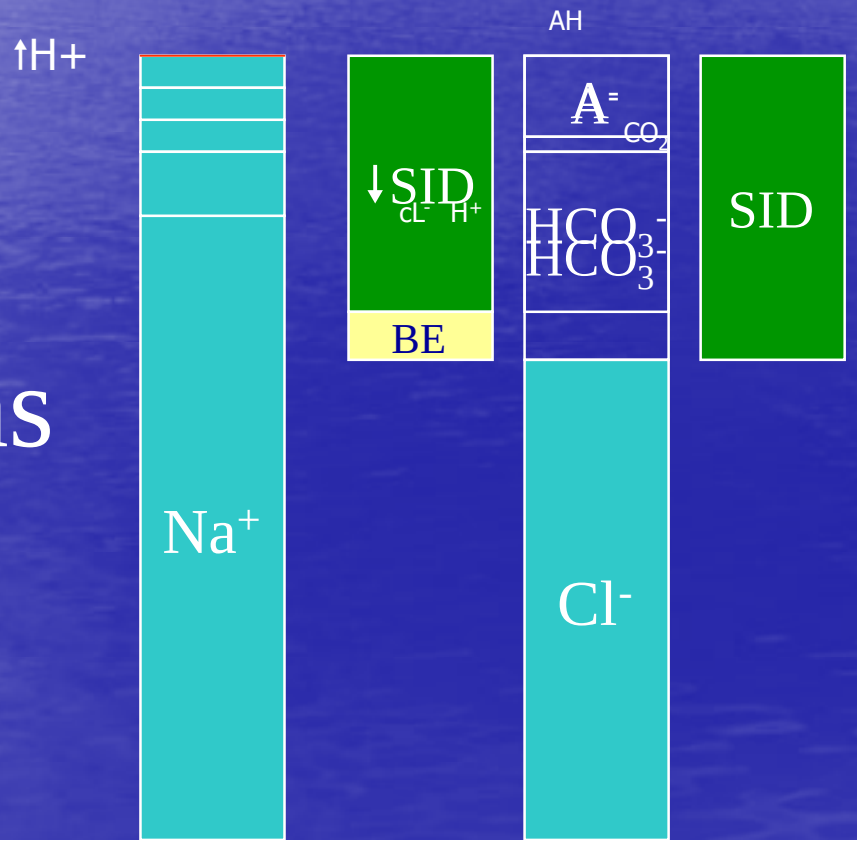
  - Amount of added base needed to pH = 7.40
- It eliminates the respiratory component
- It defines the metabolic derangement

  Causing the abnormal pH

Base Excess

- Base excess =
  Change in A^- + HCO_3^- from normal
  Change in SID from normal
- + BE = metabolic alkalosis
- - BE = metabolic acidosis
- BE = SIDex
- BE from ABG machine
  Calculation assumes
  - A_{TOT} = blood with Hb of 5 g/dl and P_{co2} = 40

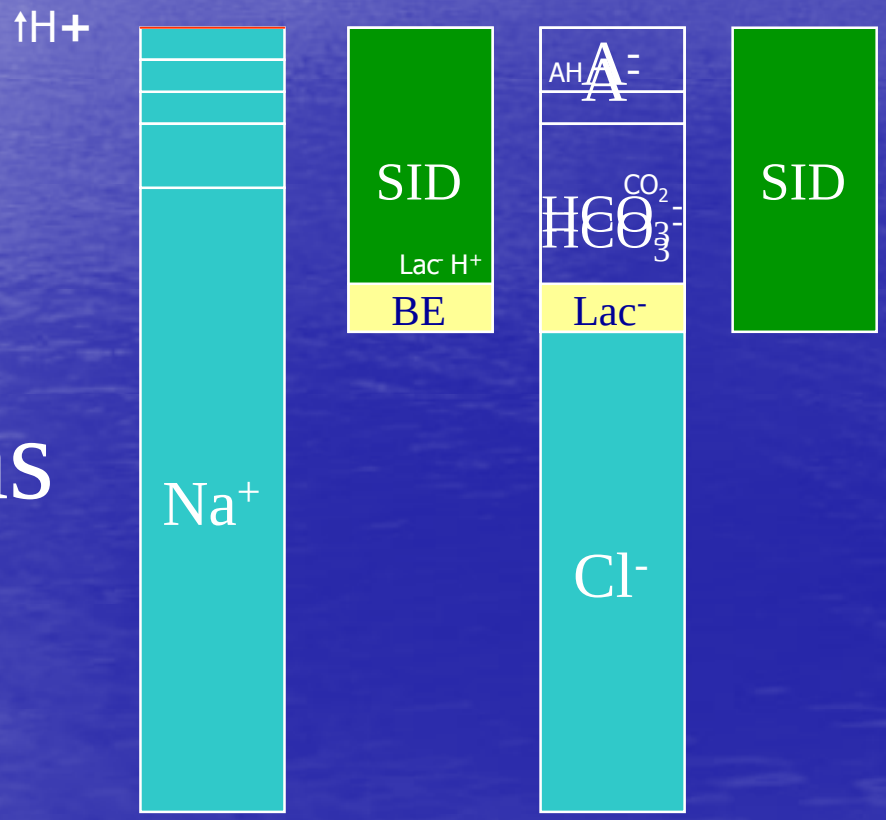
BE
Hyperchloremic Acidosis



Cations

Anions

BE
Lactic Acidosis



Cations

Anions

Anion Gap

- $Na^+ + K^+ = Cl^- + HCO3^- + A^-$
- $AG = (Na^+ + K^+) - (Cl^- + HCO3^-)$

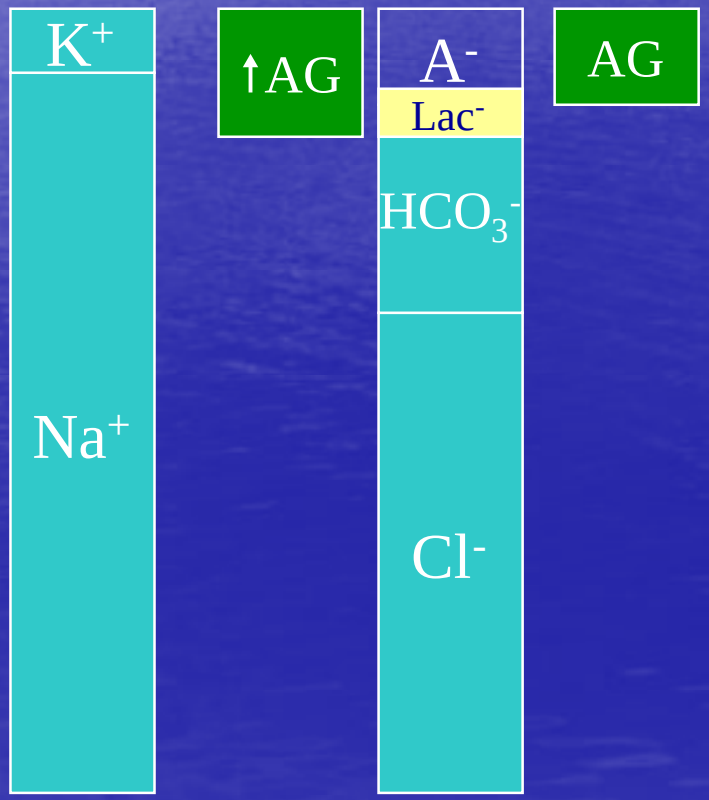
  $AG = A^-$ = ionized albumin + P_i^-
- Normal AG range is large

  Because albumin + P_i range large

  Hypoproteinemia - normal AG with lactic acidosis
- Usually measured in venous blood

  With Tco_2 used to estimated HCO_3

Cations/Anions
Anion Gap



Cations

Anions

Anion Gap Acidosis Artifacts

- Dehydration
  - Concentrating all ions
- Na salts
  - High doses Na penicillin (beta lactams)
  - Na lactate
  - Na acetate
- Decreased unmeasured cations
  - ↓Mg
  - ↓Ca
- Hypoalbuminemia
  - Severe
  - ↓AG by 2.5-3 mEq/l for each 1 g/dl decrease

Anion Gap Acidosis Artifacts

- Respiratory and metabolic alkalosis
  - ↑3-10 mEq/liter in apparent AG
- Parenteral nutrition
  - Formulas with acetate
- Multiple blood transfusions
  - Increased citrate
  - Large volumes
- Unidentified cations

Corrected Anion Gap

- ICU patient

  Albumin and P_i not normal

  Unmeasured anions which make normal gap

- As long as pH < 7.35

  "Normal" AG

  - = 2 (albumin g/dl) + 0.5 (P_i mg/dl)

    ± 5 at best

Strong Ion Difference vs. Anion Gap

- Strong Ion Difference

$$SID = (Na^{+} + K^{+} + Ca^{++} + Mg^{++}) - (Cl^{-} + Lac^{-})$$

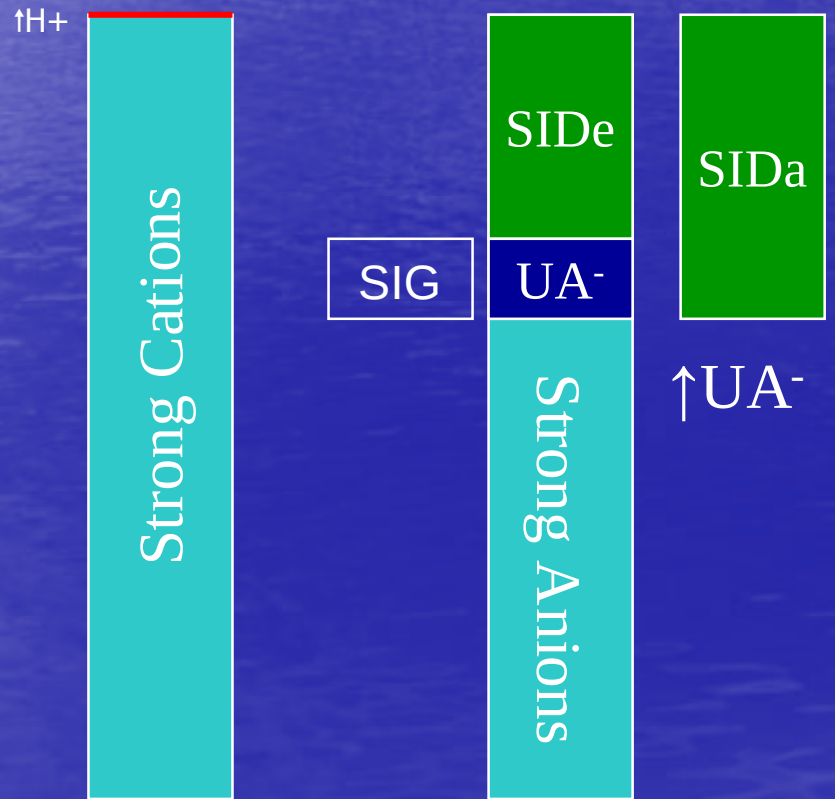
- Anion Gap

$$AG = (Na^{+} + K^{+}) - (Cl^{-} + HCO3^{-})$$

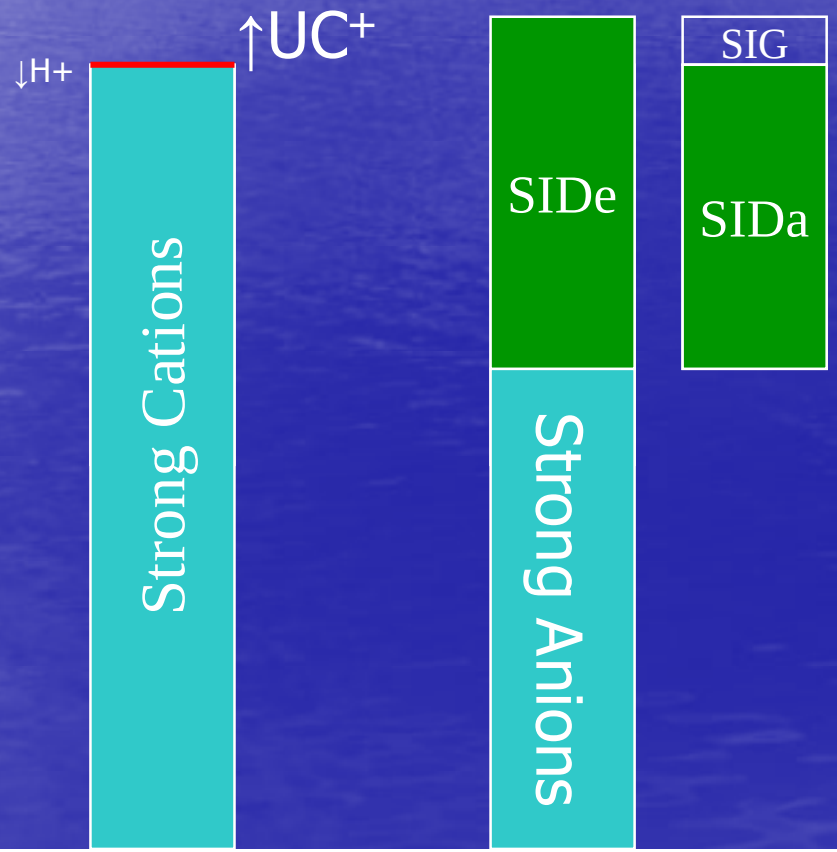
Strong Ion Gap (SIG)

- SID effective
  = A^- + HCO_3^-
  = SIDe
- SID apparent
  = $(Na^+ + K^+ + Ca^{++} + Mg^{++}) - (Cl^- + Lac^-)$
  = SIDa
  = 40-42 (healthy human)
- SIDe = SIDa
  If not there are unmeasured ions
  Difference is SIG

Metabolic Acidosis
Increase in Unidentified Anions
SIG < 0

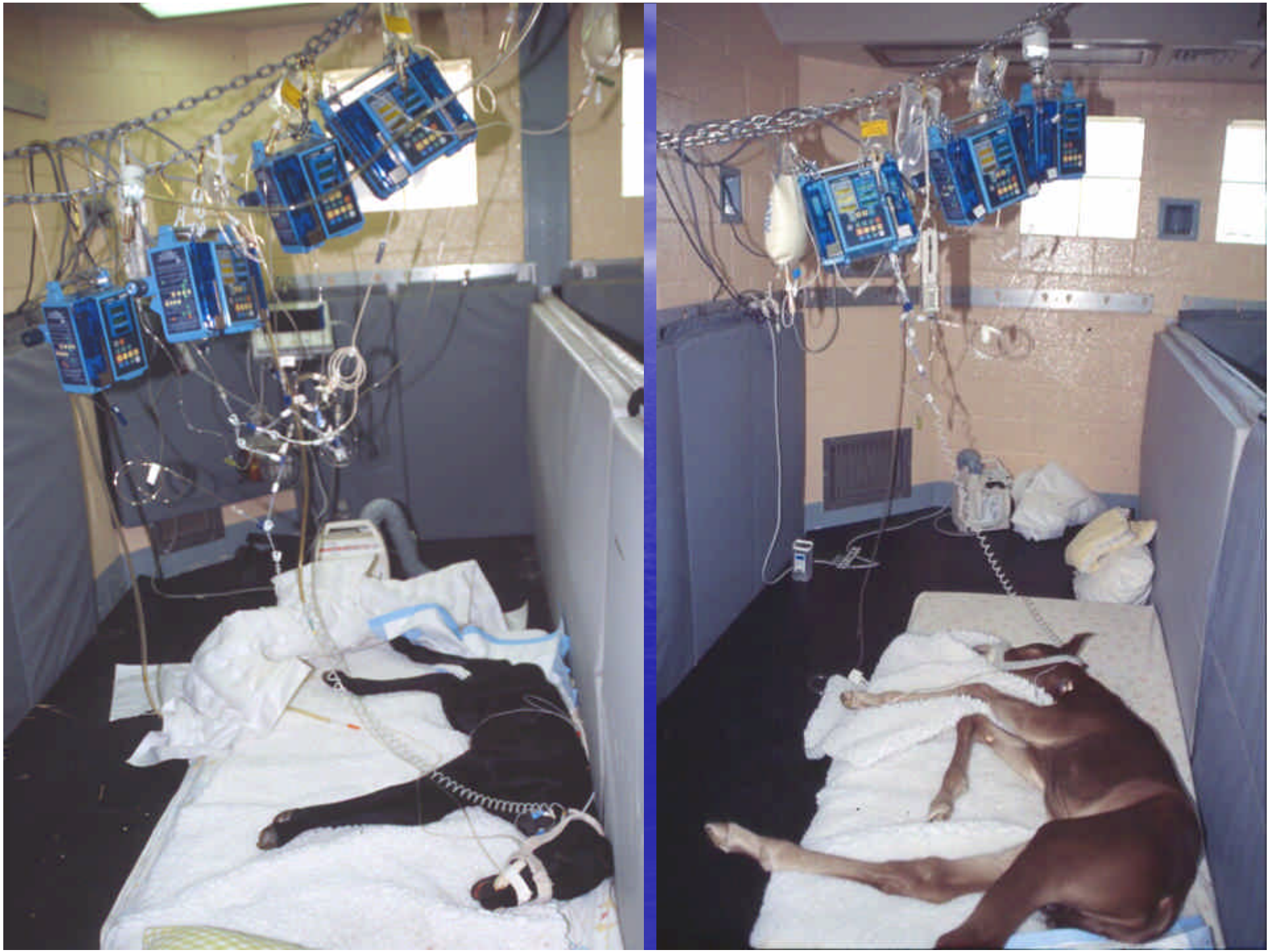


Metabolic Alkalosis
Unidentified Cation Alkalosis
SIG > 0



Strong Ion Gap (SIG)

- SIG = SIDe – SIDa
- SIG < 0 – unmeasured anions
  - Sepsis
  - Liver disease
    - liver clears unmeasured anions
    - with sepsis, failure → liver releases anions
  - If lactate is not part of SIDa
    - Most common cause of SIG > 0
    - Lactate mmol/l = SIG
- SIG does not change with
  - pH changes
  - Changes in albumin



Treatment Guidelines

- Normalize pH
- If SIG ≠0

  Investigate unmeasured ions
  - Treat underlying cause
- If SIG = 0, with acidosis

  ↓SID
  - ↑ SID – give fluids Na > Cl

    $NaHCO_3$

  ↑ SID
  - Compensation already occurring

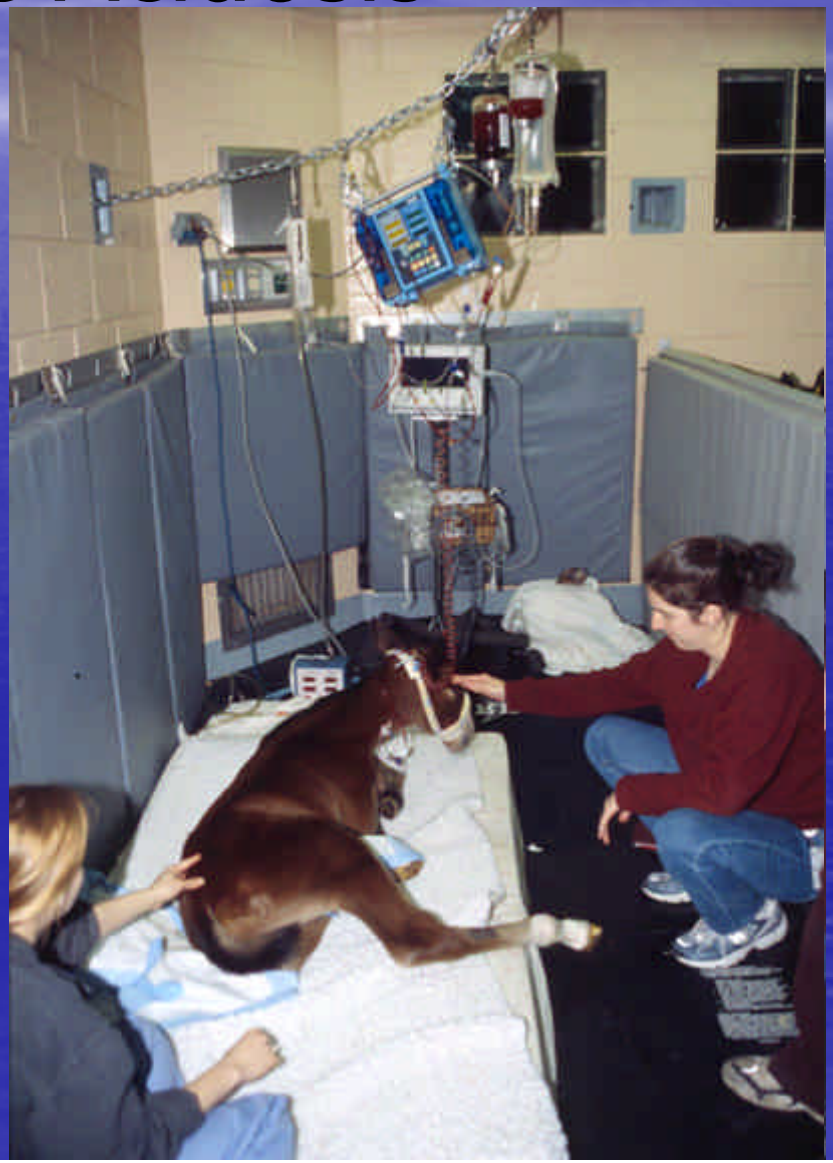
Treatment Guidelines

- If SIG = 0, with alkalosis
  - ↑ SID
    - ↓ SID – give fluids low SID (NaCl)
    - Will expand ECF
  - ↓SID
    - Compensation already occurring
- Lactate special case
  - Don't treat with NaHCO3
    - Lactate clears rapidly
    - Overshoot alkalosis and Na overload
  - Severe acidosis interferes with Lactate metabolism
    - pH < 7.20
  - Treat cause of ↑ lactate

Cases

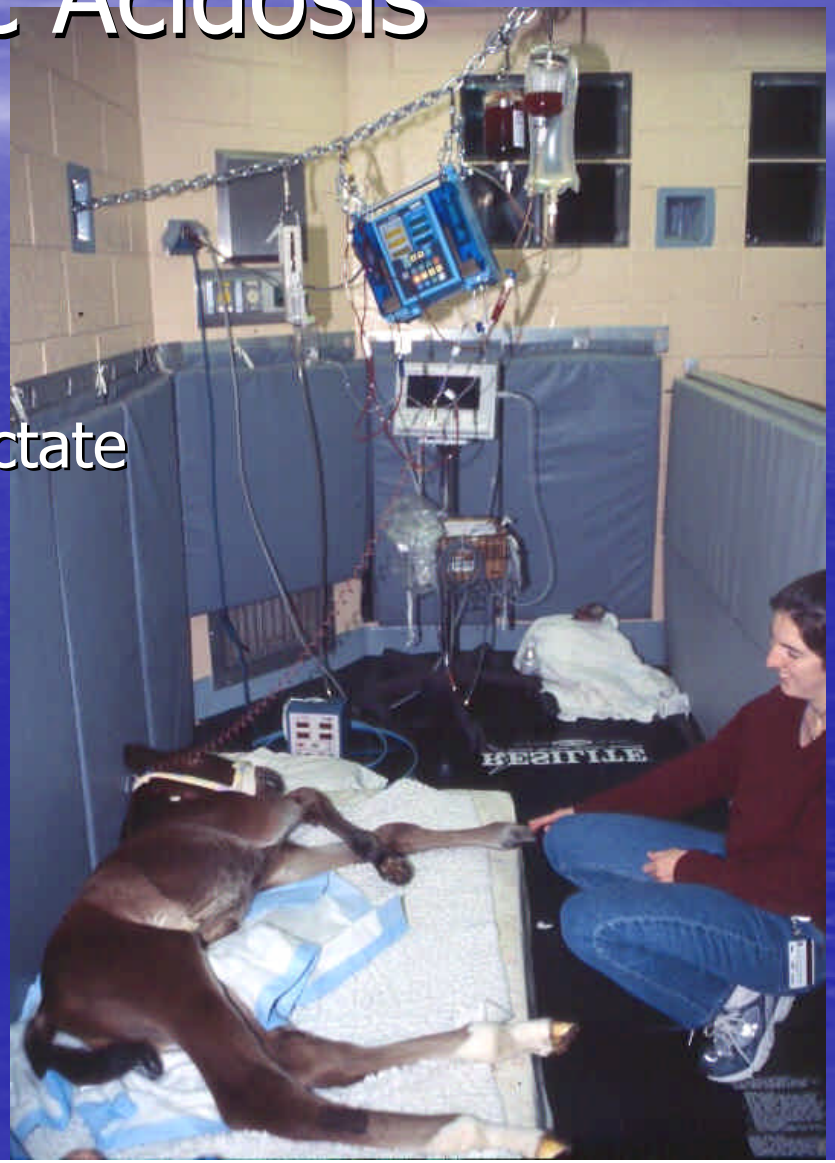
Case 1
Lactic Acidosis

- NI foal
- Present 12 hrs old
  - PCV 5%
  - TP 6.1
  - Glu <10
  - Temp 97.7
  - HR 140
  - RR 35



Case 1
Lactic Acidosis

- Lactate out of range
- SIG = -20.8
  - Lactate not in SIDa
  - Unidentified anion = lactate



Understanding Strong Ion Difference

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A strong ion is any ion which cannot combine with other ions so it is always free (disassociated). Na^+, K^+, Cl^- are strong ions but HCO_3^- is a weak ion since it can combine forming H_2CO_3, CO_2, H_2O and lose its charge. The strong ion indifference (SID) is the net charge difference between strong ions. The SID dictates the net charge of weak ions so that $SID = HCO_3^- + A^-$.

Three independent determinants of acid-base status: $[H^+]$

1. CO_2 (Pco_2): Since CO_2 is in equilibrium with HCO_3^- if Pco_2 is known, can calculate HCO_3^- which is in turn = SID.
2. Nonvolatile weak acid buffer: Hemoglobin, albumin, inorganic phosphates (A_{TOT}).
3. SID: $SID = HCO_3^- + A^- = (Na^+ + K^+ + Ca^{++} + Mg^{++}) – (Cl^- + Lac^-)$

Kidney regulation of acid-base status can be thought of in terms of H^+ and HCO_3^- or SID, which are mirror images of each other. Treatment with $NaHCO_3$ will result in excretion of HCO_3 and retention of Cl relative to Na and K resulting in decreased SID. Increased urine SID will force HCO_3 excretion to preserve electrical neutrality of the urine.

Gastrointestinal shifts in acid and base can also be thought of in terms of strong ions rather than H^+ and HCO_3^-. In the stomach, parietal cells secrete Cl^- which is a strong cation forcing H+ secretion. Since gastric mucosa and mucus layer can support a large pH gradient (lumen to cells), the lumen maintains high a H^+ concentration. When gastric fluid moves to the small intestine the Cl^- is neutralized by secreted $NaHCO_3$ and NaCl is resorb together. In the colon, reabsorbed of K^+ and Na^+, which was secreted higher in the tract will maintain the SID. With diarrhea K^+ and Na^+, which are trapped in the lumen, are lost decreasing SID which can result in a hyperchloremic acidosis.

Anion Gap

The anion gap is another way of looking at the mix of strong and weak ions. Traditionally it has been used to detect lactic acidosis, ketoacidosis and the presence of certain poisons. Anion gap is usually measured in venous blood with HCO3 estimated as total CO2. The derivation of the anion gap comes from the relationship of conservation of charges of anions and cations:

$$Na^+ + K^+ = Cl^- + HCO3^- + A^-$$

$$AG = Na^+ + K^+ - Cl^- - HCO3^-$$

So the anion gap really is A^- which usually consists of ionized albumin and P_i (inorganic phosphates). Plasma proteins other than albumin have mixed charges that in aggregate are neutral. The normal anion gap is between 3 and 11 mM in plasma. The normal range is large because

normal albumin and inorganic phosphors levels can vary a large amount. This causes a problem in interpreting AG in the face of hypoproteinemia which is a common finding in neonates. With hypoproteinemia the patient may have a normal AG in the face of lactic acidosis. Because of its dependence on albumin and phosphorus levels, the normal anion gap for a patient can be estimated if the albumin and phosphorus levels are known using the following formulas (as long as pH < 7.35):

Normal AG = 2 (albumin) + 0.5 (P_i)

AG = A^- = pH [(1.16 X albumin) + (0.42 X P_i)] - 5.83 X albumin - 1.28 X P_i

Deviations from what is calculated using albumin and phosphorus represents the presence of unmeasured anions which are contributing to the acid-base imbalance. Unmeasured anions occur in sepsis and liver disease and experimentally in endotoxemia.

Although an increase in AG is usually interpreted to suggest the presence of sepsis, ketosis, lactic acidosis, poisoning or renal failure there can be artifacts caused by a number of factors. Dehydration will cause a false increase in AG by concentrating all ions. Severe hypoalbuminemia will cause a decrease in AG by 2.5-3 mEq/liter for each 1 g/dl decrease. Respiratory and metabolic alkalosis will cause an increase by 3-10 mEq/liter in apparent AG because of increased lactate production from increased phosphofructokinase activity, decreased A^- and dehydration effect. Administration of large amounts of Na or K salts of beta lactams will also increase apparent AG. Parenteral nutrition formulas with acetate will increase apparent AG. Large volu me blood transfusions (increased citrate transfused) will increase apparent AG. Most of these situations can be readily identified and will not change AG much.

Strong Ion Gap (SIG)

Another way to predict the presence of unmeasured strong ions which may be affecting pH is to calculate the strong ion gap (SIG). This is the gap between the apparent SID [SIDa = ($Na^+ + K^+ + Ca^{++} + Mg^{++}$) – ($Cl^- + Lac^-$)] and the effective SID [SIDe = $A^- + Tco_2$]. If SIDe ≠ SIDa there are unmeasured strong ions or a SIG. If SIDa > SIDe there are unmeasured anions present as occurs in sepsis or liver disease. Usually the liver clears unmeasured anions but with sepsis the liver releases such anions. If SIDa < SIDe there are unmeasured cations. Unlike AG, SIG does not change with pH or changes in albumin and normally SIG = 0 thus eliminating the variability of the AG normal range.