DM SEMINAR
APRIL 02, 2004

ARTERIAL BLOOD GAS: INTERPRETATION AND CLINICAL IMPLICATIONS

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Conditions Invalidating or Modifying ABG Results

- DELAYED ANALYSIS

Consumptiom of O_2 & Production of CO_2 continues after blood drawn into syringe

Iced Sample maintains values for 1-2 hours

Uniced sample quickly becomes invalid

$PaCO_2$ ↑ 3-10 mmHg/hour

PaO_2 ↓ at a rate related to initial value & dependant on Hb Sat

EFFECT OF TEMP ON RATE OF CHANGE IN ABG VALUES

Parameter	37 C (Change every 10 min)	4 C (Change every 10 min)
↓ pH	0.01	0.001
↑ PCO2	1 mm Hg	0.1 mm Hg
↓ PO2	0.1 vol %	0.01 vol %

- EXCESSIVE HEPARIN

Dilutional effect on results ↓ HCO_3^- & PaCO2

Syringe be emptied of heparin after flushing

Risk of alteration of results ↑ with:

1.↑ size of syringe/needle

2.↓ vol of sample

25% lower values if 1ml sample taken in 10 ml syringe (0.25 ml heparin in needle)

Syringes must be > 50% full with blood sample

- HYPERVENTILATION OR BREATH HOLDING

May lead to erroneous lab results

- AIR BUBBLES

1. PO_2 ~150 mmHg & PCO_2 ~0 mm Hg in air bubble(R.A.)
2. Mixing with sample lead to ↑ PaO_2 & ↓ $PaCO_2$
3. Mixing/Agitation ↑ S.A. for diffusion → more erroneous results
4. Discard sample if excessive air bubbles
5. Seal with cork/cap imm after taking sample

- FEVER OR HYPOTHERMIA

1. Most ABG analyzers report data at N body temp
2. If severe hyper/hypothermia, values of pH & PCO_2 at 37 C can be significantly diff from pt's actual values
3. Changes in PO_2 values with temp predictable

4. No significant change of HCO_3^-, O_2 Sat, O_2 capacity/content, CO_2 content values with temp
5. No consensus regarding reporting of ABG values esp pH & PCO_2 after doing 'temp correction'
6. ? Interpret values measured at 37 C:
    - Most clinicians do not remember normal values of pH & PCO_2 at temp other than 37C
    - In pts with hypo/hyperthermia, body temp usually changes with time (per se/effect of rewarming/cooling strategies) – hence if all calculations done at 37 C easier to compare
    - Values other than pH & PCO_2 do not change with temp

Hansen JE, Clinics in Chest Med 10(2), 1989 227-237

7. ? Use Nomogram to convert values at 37C to pt's temp
8. Some analysers calculate values at both 37C and pt's temp automatically if entered
9. Pt's temp should be mentioned while sending sample & lab should mention whether values being given in report at 37 C/pts actual temp

- <u>WBC COUNT</u>

  0.1 ml of O2 consumed/dL of blood in 10 min in pts with N TLC

  Marked increase in pts with very high TLC/plt counts – hence imm chilling/analysis essential

- TYPE OF SYRINGE

1. pH & PCO_2 values unaffected
2. PO_2 values drop more rapidly in plastic syringes (ONLY if PO_2 > 400 mm Hg)
3. Other adv of glass syringes:
   - Min friction of barrel with syringe wall
   - Usually no need to 'pull back' barrel – less chance of air bubbles entering syringe
   - Small air bubbles adhere to sides of plastic syringes – difficult to expel

Though glass syringes preferred, differences usually not of clinical significance → plastic syringes can be and continue to be used

- QUALITY CONTROL & CALIBRATION

Mechanism of Measurement & Electronic Drift in electrodes

1. Measurement of voltages (potentiometric) – Balance Drift (Shifting of calibration points from baseline though maintain same slope)

   Sanz (pH) electrode

   Severinghaus/Stow (PCO_2) electrode

2. Measurement of amperage (amperometric) – Slope Drift (Angle of calibration points changes though baseline remains same)

   Clark (PO_2) electrode

   Recommendations for calibration of each electrode –

   2 point calibration every 8 hrs

   1 point calibration every 4 hrs

Approach to ABG Interpretation

- Assessment of the type of acid base disorder requires at a minimum 2 of the following:

1) Arterial pH
2) pCO2
3) plasma HCO_3^-

- Complete analysis of an ABG requires:

1. pH
2. pO2
3. pCO2
4. HCO_3^-
5. O2 Sat
6. BE/BD
7. Anion Gap (AG)
8. Δ AG
9. Δ HCO_3^-

Assessment of Oxygenation Status

Arterial Oxygen Tension (PaO2)

- Normal value in healthy adult breathing room air at sea level ~ 97 mm Hg.
- ↓ progressively with ↑ age
- Dependant upon
    1. FiO2
    2. P_{atm}
- Hypoxemia is PaO2 < 80 mm Hg at RA
- Most pts who need ABG usually req O2 therapy
- O2 therapy should not be withheld/interrupted ‘to determine PaO2 on RA’

Acceptable PaO2 Values on Room Air

Age Group	Accepable PaO2 (mm Hg)
Adults upto 60 yrs & Children	> 80
Newborn	40-70
70 yrs	> 70
80 yrs	> 60
90 yrs	> 50

60 yrs ~ 80 mm Hg → ↓ 1mm Hg/yr

Inspired O2 – PaO2 Relationship

FIO2 (%)	Predicted Min PaO2 (mm Hg)
30	150
40	200
50	250
80	400
100	500

If PaO2 < FIO2 x 5, pt probably hypoxemic at RA

Hypoxemia on O2 therapy

- Uncorrected: PaO2 < 80 mm Hg
  (< expected on RA & FIO2)
- Corrected: PaO2 = 80-100 mm Hg
  (= expected on RA but < expected for FIO2)
- Excessively Corrected: PaO2 > 100 mm Hg
  (> expected on RA but < expected for FIO2)
- PaO2 > expected for FIO2:
  1. Error in sample/analyzer
  2. Pt's O2 consumption reduced
  3. Pt does not req O2 therapy (if 1 & 2 NA)

Assessment of Acid-Base Status

Bicarbonate (HCO_3^-)

- **Std HCO_3^-:** HCO_3^- levels measured in lab after equilibration of blood PCO2 to 40 mm Hg (~ routine measurement of other serum electrolytes)
- **Actual HCO_3^-:** HCO_3^- levels calculated from pH & PCO2 directly
- Reflection of non respiratory (metabolic) acid-base status.
- Does not quantify degree of abnormality of buffer base/actual buffering capacity of blood.

Base Excess/Base Deficit

- Calculated from pH, $PaCO_2$ and HCT
- Expressed as meq/L of base above N buffer base range
- Negative BE also referred to as Base Deficit
- True reflection of non respiratory (metabolic) acid base status

DEFINITIONS AND TERMINOLOGY

3 Component Terminology –

1. Compensated/Uncompensated
2. Respiratory/Metabolic
3. Acidosis/Alkalosis

- **ACIDEMIA** – reduction in arterial pH (pH<7.35)
- **ALKALEMIA** – increase in arterial pH (pH>7.45)
- **ACIDOSIS** – presence of a process which tends to ↓ pH by virtue of gain of H^+ or loss of HCO_3^-
- **ALKALOSIS** – presence of a process which tends to ↑ pH by virtue of loss of H^+ or gain of HCO_3^-

RESPIRATORY VS METABOLIC

- Respiratory – processes which lead to acidosis or alkalosis through a primary alteration in ventilation and resultant excessive elimination or retention of CO2

- Metabolic – processes which lead to acidosis or alkalosis through their effects on kidneys and the consequent disruption of H^+ and HCO_3^- control

COMPENSATION – The normal response of the respiratory system or kidneys to change in pH induced by a primary acid-base disorder

SIMPLE VS. MIXED ACID-BASE DISORDER

Simple acid-base disorder – a single primary process of acidosis or alkalosis

Mixed acid-base disorder – presence of more than one acid base disorder simultaneously

Characteristics of 1° acid–base disorders

DISORDER	PRIMARY RESPONSES			COMPENSATORY RESPONSE
Metabolic acidosis	↑ $[H^+]$	↓ PH	↓ HCO_3^-	↓ pCO2
Metabolic alkalosis	↓ $[H^+]$	↑ PH	↑ HCO_3^-	↑ pCO2
Respiratory acidosis	↑ $[H^+]$	↓ PH	↑ pCO2	↑ HCO_3^-
Respiratory alkalosis	↓ $[H^+]$	↑ PH	↓ pCO2	↓ HCO_3^-

Compensation

- In the presence of acidosis or alkalosis, regulatory mechanisms occur which attempt to maintain the arterial pH in the physiologic range. These processes result in the return of pH towards, but generally just outside the normal range
- Disturbances in HCO_3^- (metabolic acidosis or alkalosis) result in respiratory compensation while changes in CO_2 (respiratory acidosis/alkalosis) are counteracted by renal compensation

  a. **Renal compensation** – kidneys adapt to alterations in pH by changing the amount of HCO_3^- generated/excreted. Full renal compensation takes 2-5 days

  b. **Respiratory compensation** – alteration in ventilation allow immediate compensation for metabolic acid-base disorders

RENAL & RESPIRATORY COMPENSATIONS TO 1° ACID–BASE DISTURBANCES

Disorder	**Compensatory response**
Metabolic acidosis	$PCO_2 \downarrow$ 1.2 mmHg per 1.0 meq/L $\downarrow HCO_3^-$
Metabolic alkalosis	$PCO_2 \uparrow$ 0.7 mmHg per 1.0 meq/L $\uparrow HCO_3^-$
Respiratory acidosis	$[HCO_3^-] \uparrow$
Acute	1.0 meq/L per 10 mmHg $\uparrow Pco_2$
Chronic	3.5 meq/L per 10 mmHg $\uparrow Pco_2$
Respiratory alkalosis	$[HCO_3^-] \downarrow$
Acute	2.0 meq/L per 10 mmHg $\downarrow Pco_2$
Chronic	4.0 meq/L per 10 mmHg $\downarrow Pco_2$

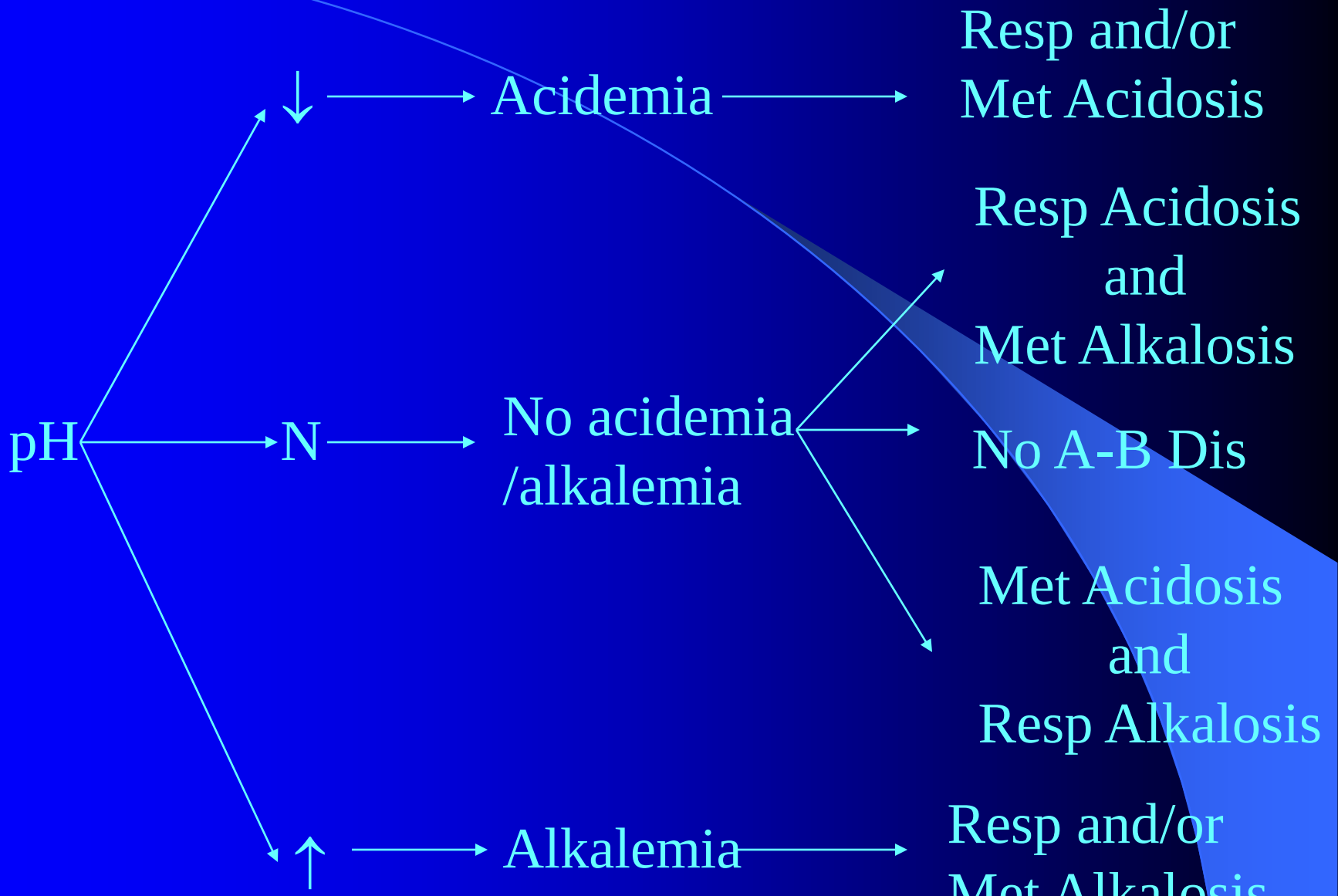
Stepwise approach to ABG Analysis

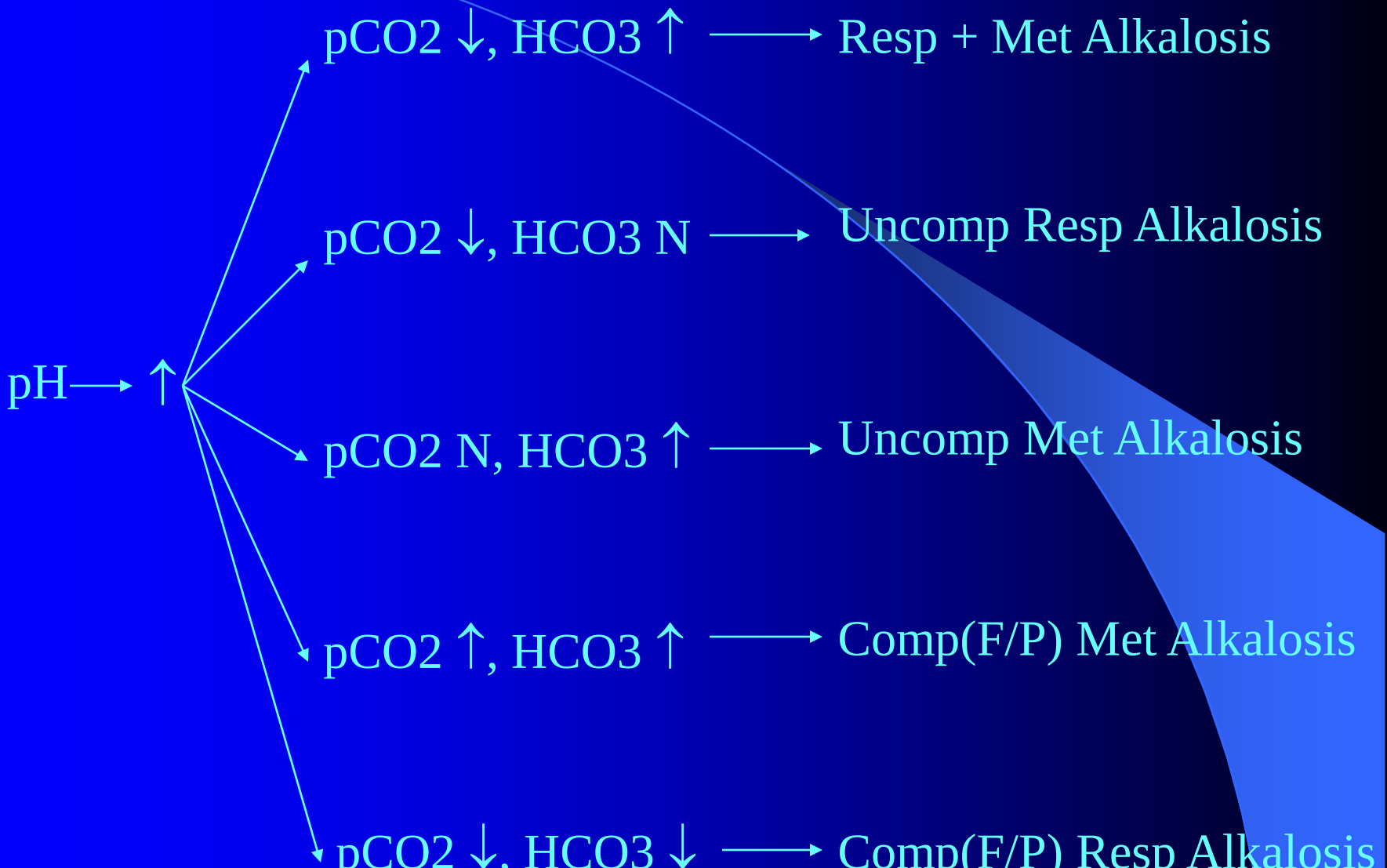
- Determine whether patient is alkalemic or acidemic using the arterial pH measurement
- Determine whether the acid-base disorder is a primary respiratory or metabolic disturbance based on the pCO2 and serum HCO_3^- level
- If a primary respiratory disorder is present, determine whether it is chronic or acute
- In metabolic disorders, determine if there is adequate compensation of the respiratory system
- In respiratory disorders, determine if there is adequate compensation of the metabolic system

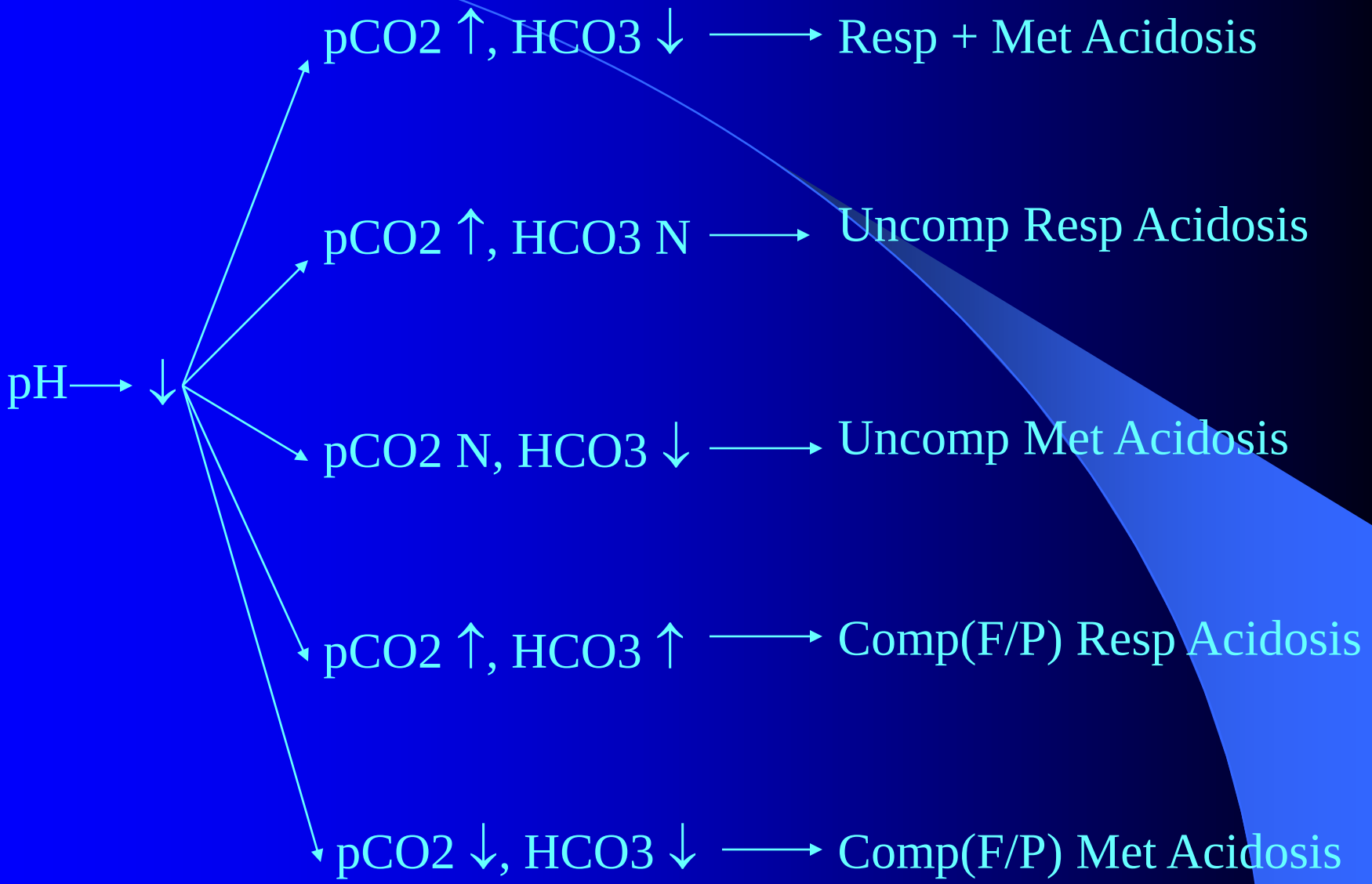
- Determine pt's oxygenation status (PaO2 & SaO2) – hypoxemic or not
- If a metabolic acidosis is present, determine the anion gap and osmolar gap
- In high anion gap acidosis, determine the change in anion gap (Δ AG) & Δ HCO_3^- in order to assess for the presence of coexisting metabolic disturbances
- In normal (non) anion gap acidosis, determine the urinary anion gap - helpful to distinguish renal from non renal causes

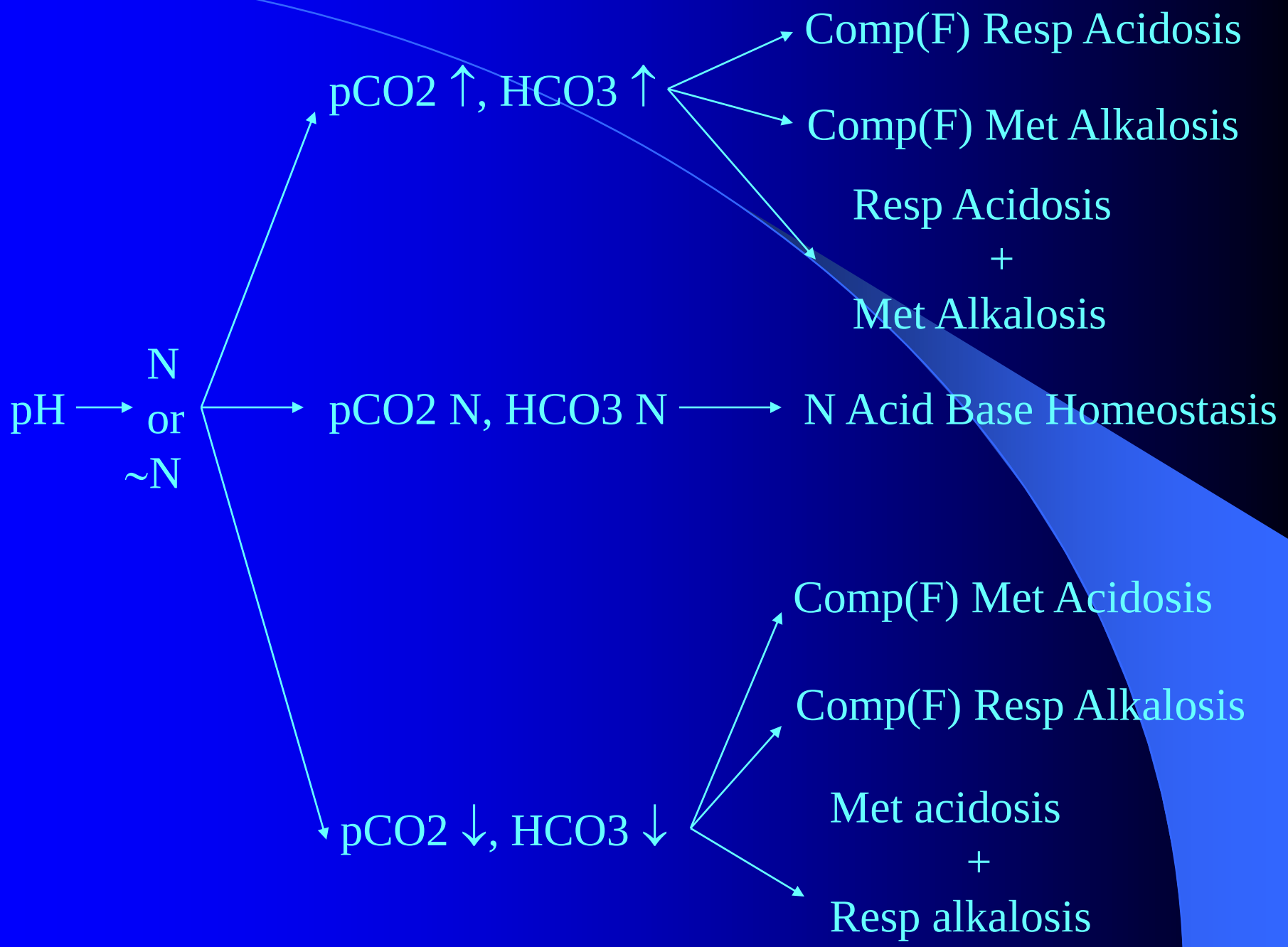
Interpretation: pH

- Normal arterial pH = 7.36 to 7.44
- Determine Acidosis versus Akalosis
  - 1. pH <7.35: Acidosis
  - 2. pH >7.45: Alkalosis
- Metabolic Conditions are suggested if
  - pH changes in the same direction as pCO2/HCO3-
  - pH is abnormal but pCO2 remains unchanged
- Respiratory Conditions are suggested if:
  - pH changes in the opp direction as pCO2/HCO3-
  - pH is abnormal but HCO3- remains unchanged


pH
↓
Acidemia
Resp and/or
Met Acidosis
N
No acidemia
/alkalemia
Resp Acidosis
and
Met Alkalosis
No A-B Dis
Met Acidosis
and
Resp Alkalosis
↑
Alkalemia
Resp and/or
Met Alkalosis


pH ↑
pCO2 ↓, HCO3 ↑
Resp + Met Alkalosis
pCO2 ↓, HCO3 N
Uncomp Resp Alkalosis
pCO2 N, HCO3 ↑
Uncomp Met Alkalosis
pCO2 ↑, HCO3 ↑
Comp(F/P) Met Alkalosis
pCO2 ↓, HCO3 ↓
Comp(F/P) Resp Alkalosis


pH ↓
pCO2 ↑, HCO3 ↓
Resp + Met Acidosis
pCO2 ↑, HCO3 N
Uncomp Resp Acidosis
pCO2 N, HCO3 ↓
Uncomp Met Acidosis
pCO2 ↑, HCO3 ↑
Comp(F/P) Resp Acidosis
pCO2 ↓, HCO3 ↓
Comp(F/P) Met Acidosis


pH
N
or
~N
pCO2 ↑, HCO3 ↑
Comp(F) Resp Acidosis
Comp(F) Met Alkalosis
Resp Acidosis
+
Met Alkalosis
pCO2 N, HCO3 N
N Acid Base Homeostasis
pCO2 ↓, HCO3 ↓
Comp(F) Met Acidosis
Comp(F) Resp Alkalosis
Met acidosis
+
Resp alkalosis

Respiratory Acid Base Disorders

- Respiratory alkalosis most common of all the 4 acid base disorders (23-46%) -followed by met alkalosis - review of 8289 ABG analysis in ICU pts

  Kaehny WD, MCNA 67(4), 1983 p 915-928
- Resp acidosis seen in 14-22% of pts
- Attention to possibility of hypoxemia and its correction always assumes priority in analysis of pts with a possible respiratory acid-base disorder

RESPIRATORY ALKALOSIS

Causes of Respiratory Alkalosis

CENTRAL RESPIRATORY STIMULATION

(Direct Stimulation of Resp Center):

Structural Causes

- Head trauma
- Brain tumor
- CVA
-

Non Structural Causes

Pain

Anxiety

Fever

Voluntary

PERIPHERAL RESPIRATORY STIMULATION

(Hypoxemia → Reflex Stimulation of Resp Center via Peripheral Chemoreceptors)

- Pul V/Q imbalance
- Pul Diffusion Defects
- Pul Shunts

Hypotension

High Altitude

- INTRATHORACIC STRUCTURAL CAUSES:

1. Reduced movement of chest wall & diaphragm
2. Reduced compliance of lungs
3. Irritative lesions of conducting airways

- MIXED/UNKNOWN MECHANISMS:

1. Drugs – Salicylates Nicotine
   Progesterone Thyroid hormone
   Catecholamines
   Xanthines (Aminophylline & related compounds)
2. Cirrhosis
3. Gram –ve Sepsis
4. Pregnancy
5. Heat exposure
6. Mechanical Ventilation

Manifestations of Resp Alkalosis

- NEUROMUSCULAR: Related to cerebral A vasoconstriction & ↓ Cerebral BF

1. Lightheadedness
2. Confusion
3. Decreased intellectual function
4. Syncope
5. Seizures
6. Paraesthesias (circumoral, extremities)
7. Muscle twitching, cramps, tetany
8. Hyperreflexia
9. Strokes in pts with sickle cell disease

- CARDIOVASCULAR: Related to coronary vasoconstriction

1. Tachycardia with ~ N BP
2. Angina
3. ECG changes (ST depression)
4. Ventricular arrythmias

- GASTROINTESTINAL: Nausea & Vomitting (cerebral hypoxia)

- BIOCHEMICAL ABNORMALITIES:

↓ tCO2 ↓PO_4^{3-}

↑Cl^- ↓ Ca^{2+}

Homeostatic Response to Resp Alkalosis

- In ac resp alkalosis, imm response to fall in CO_2 (& H_2CO_3) → release of H^+ by blood and tissue buffers → react with HCO_3^- → fall in HCO_3^- (usually not less than 18) and fall in pH
- Cellular uptake of HCO_3^- in exchange for Cl^-
- Steady state in 15 min - persists for 6 hrs
- After 6 hrs kidneys increase excretion of HCO_3^- (usually not less than 12-14)
- Steady state reached in $1_{1/2}$ to 3 days.
- Timing of onset of hypocapnia usually not known except for pts on MV. Hence progression to subac and ch resp alkalosis indistinct in clinical practice

Treatment of Respiratory Alkalosis

- Resp alkalosis by itself not a cause of resp failure unless work of increased breathing not sustained by resp muscles
- Rx underlying cause
- Usually extent of alkalemia produced not dangerous.
- Admn of O2 if hypoxaemia
- If pH>7.55 pt may be sedated/anesthetised/ paralysed and/or put on MV.

Pseudorespiratory Alkalosis

- Arterial hypocapnia can be observed in an idiotypic form of respiratory acidosis.
- Occurs in patients with profound depression of cardiac function and pulmonary perfusion but with relative preservation of alveolar ventilation (incl pts undergoing CPR).
- Severely reduced pul BF limits CO_2 delivered to lungs for excretion → ↑$PvCO_2$.
- Increased V/Q ratio causes removal of a larger-than-normal amount of CO_2 per unit of blood traversing the pulmonary circulation →arterial eucapnia or frank hypocapnia.

- Absolute excretion of CO2 decreased and CO2 balance of body +ve — the hallmark of respiratory acidosis.
- Pts may have severe venous acidemia (often due to mixed respiratory and metabolic acidosis) accompanied by an arterial pH that ranges from mildly acidic to the frankly alkaline.
- Extreme oxygen deprivation prevailing in the tissues may be completely disguised by the reasonably preserved values of arterial oxygen.
- To rule out pseudorespiratory alkalosis in a patient with circulatory failure, blood gas monitoring must include sampling of mixed (or central) venous blood.
- Mx must be directed toward optimizing systemic hemodynamics.

RESPIRATORY ACIDOSIS

Causes of Acute Respiratory Acidosis

- **EXCRETORY COMPONENT PROBLEMS:**

1. Perfusion:
   - Massive PTE
   - Cardiac Arrest
2. Ventilation:
   - Severe pul edema
   - Severe pneumonia
   - ARDS
   - Airway obstruction
     - Bronchospasm (severe)
     - Aspiration
     - Laryngospasm
     - OSA
3. Restriction of lung/thorax:
   - Flail chest
   - Pneumothorax
   - Hemothorax

4. Muscular defects:
   - Severe hypokalemia
   - Myasthenic crisis
5. Failure of Mechanical Ventilator

CONTROL COMPONENT PROBLEMS:

1. CNS:
   - CSA
   - Drugs (Anesthetics, Sedatives)
   - Trauma
   - Stroke
2. Spinal Cord & Peripheral Nerves:
   - Cervical Cord injury
   - Neurotoxins (Botulism, Tetanus, OPC)
   - Drugs causing Sk. m.paralysis (SCh, Curare, Pancuronium & allied drugs, aminoglycosides)

LGBS

Causes of Chronic Respiratory Acidosis

- **EXCRETORY COMPONENT PROBLEMS:**

1. Ventilation:
   - COPD
   - Advanced ILD
- Restriction of thorax/chest wall:
   - Kyphoscoliosis, Arthritis
   - Fibrothorax
   - Hydrothorax
   - Muscular dystrophy
   - Polymyositis

- **CONTROL COMPONENT PROBLEMS:**

1. CNS: Obesity Hypoventilation Syndrome
   Tumours
   Brainstem infarcts
   Myxedema
   Ch sedative abuse
   Bulbar Poliomyelitis
2. Spinal Cord & Peripheral Nerves:
   Poliomyelitis
   Multiple Sclerosis
   ALS
   Diaphragmatic paralysis

Manifestations of Resp Acidosis

- NEUROMUSCULAR: Related to cerebral A vasodilatation & ↑ Cerebral BF

1. Anxiety
2. Asterixis
3. Lethargy, Stupor, Coma
4. Delirium
5. Seizures
6. Headache
7. Papilledema
8. Focal Paresis
9. Tremors, myoclonus

- CARDIOVASCULAR: Related to coronary vasodilation

1. Tachycardia with ~ N BP
2. Ventricular arrythmias (related to hypoxemia and not hypercapnia per se)
3. Senstivity to digitalis

- BIOCHEMICAL ABNORMALITIES:

↑ tCO_2

↓ Cl^-

↑ PO_4^{3-}

Homeostatic Response to Respiratory Acidosis

- Imm response to rise in CO_2 (& H_2CO_3) → blood and tissue buffers take up H^+ ions, H_2CO_3 dissociates and HCO_3^- increases with rise in pH.
- Steady state reached in 10 min & lasts for 8 hours.
- PCO_2 of CSF changes rapidly to match $PaCO_2$.
- Hypercapnia that persists > few hours induces an increase in CSF HCO_3^- that reaches max by 24 hr and partly restores the CSF pH.
- After 8 hrs, kidneys generate HCO_3^-
- Steady state reached in 3-5 d

- Alveolar-gas equation predicts rise in $PaCO_2$ → obligatory hypoxemia in pts breathing R.A.
- Resultant fall in PaO_2 limits hypercapnia to ~ 80 to 90 mm Hg
- Higher $PaCO_2$ leads to PaO_2 incompatible with life.
- Hypoxemia, not hypercapnia or acidemia, that poses the principal threat to life.
- Consequently, oxygen administration represents a critical element in the management

Treatment of Respiratory Acidosis

- Ensure adequate oxygenation - care to avoid inadequate oxygenation while preventing worsening of hypercapnia due to supression of hypoxemic resp drive
- Correct underlying disorder if possible
- Avoid rapid decrease in ch elevated PCO2 to avoid post hypercapnic met alkalosis (arrythmias, seizures → adequate intake of Cl-)

- Alkali (HCO3) therapy rarely in ac and never in ch resp acidosis → only if acidemia directly inhibiting cardiac functions
- Problems with alkali therapy:

1. Decreased alv ventilation by decrease in pH mediated ventilatory drive
2. Enhanced carbon dioxide production from bicarbonate decomposition
3. Volume expansion.

- COPD pts on diuretics who develop met alkalosis often benfefited by acetazolamide

DM SEMINAR
APRIL 16, 2004

ABG II: METABOLIC ACID BASE DISORDERS

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HEADINGS

- INTRODUCTION TO ACID-BASE PHYSIOLOGY
- METABOLIC ACIDOSIS
- METABOILIC ALKALOSIS

Overview of Acid-Base Physiology

ACID PRODUCTION

- **Volatile Acids** – metabolism produces 15,000-20,000 mmol of CO2 per day.

Henderson Hasselbach Equation

$$pH = pK + \log \frac{base}{acid}$$

$$pH = 6.1 + \log \frac{HCO_3^-}{H_2CO_3}$$

$$pH = 6.1 + \log \frac{HCO_3^-}{0.03\ pCO_2}$$

$$H^+ = 24 \times \frac{pCO_2}{HCO_3^-}$$

Free H+ will be produced if the CO2 is not eliminated.

- **Non-Volatile Acids** – 50-100 meq/day of non-volatile acids produced daily.

1. The primary source is from metabolism of sulfur containing amino acids (cystine, methionine) and resultant formation of sulfuric acid.
2. Other sources are non metabolized organic acids, phosphoric acid and other acids

Range of ECF [H+] variation very small

pH Vs. [H+]

pH		nanoeq [H+]/L
7.00-7.38	Acidemia	100-44
7.38-7.44	Normal	44-36
7.44-7.80	Alkalemia	36-16

Relationship between pH and [H] at physiologic pH

pH	7.00	7.10	7.20	7.30	7.40	7.50	7.60	7.70
[H+] (nM)	100	79	63	50	40	32	25	20

Importance of pH Control

- pH (intracellular and ECF incl blood) maintained in narrow range to preserve N cell, tissue and organ f_x

Intracellular pH (pH_i)

- Maintanined at ~ 7.2:

1. To keep imp metabolic intermediates in ionized state and limit tendency to move out of cell
2. Most intracellular enzymes taking part in cellular metabolism have pH optimum close to this value
3. DNA, RNA & Protein synthesis ↑ at slightly higher pH

- Maintained with help of plasma memb H+/base transporters (activated in response to acidemia)

Blood pH

- Maintanined at ~ 7.4:

1. To keep pH_i in optimal range
2. Enable optimal binding of hormones to receptors
3. Enable optimal activity of enzymes present in blood

Kraut et al AJKD 2001; 38(4): 703-727

Regulation of arterial pH

1. **BUFFERS** – presence of buffer systems minimize the change in pH resulting from production of acid and provide imm protection from acid load. Main buffer system in humans is HCO3-

$$HCO_3\text{-} + H^+ \Leftrightarrow H2CO_3 \Leftrightarrow H_2O + CO_2$$

2. **ROLE OF THE RESPIRATORY SYSTEM** – elimination of volatile acid -- CO2.

a. Respiratory centers in the brain respond to changes in pH of CSF and blood to affect ventilatory rate.

b. Ventilation directly controls the elimination of CO2.

3. **ROLE OF THE KIDNEY -** To retain and regenerate HCO3- thereby regenerating the body buffer with the net effect of eliminating the non-volatile acid load

a. **H+ secretion**
   1. Free urinary H+ - minimal contribution
   2. Ammonia
   3. Phosphorus

b. **HCO3- reabsorption**
   1. Proximal tubule – 90%
   2. Distal tubule

Factors affecting H+ secretion/reabsorption HCO3-

a. CO2 concentration, pH
b. Aldosterone
c. ECF volume
d. Potassium concentration
e. Chloride

Anion Gap

- AG traditionally used to assess acid-base status esp in D/D of met acidosis
- Δ AG & Δ HCO_3^- used to assess mixed acid-base disorders

AG based on principle of electroneutrality:

- Total Serum Cations = Total Serum Anions
- Na + (K + Ca + Mg) = HCO3 + Cl + (PO4 + SO4 + Protein + Organic Acids)
- Na + UC = HCO3 + Cl + UA
- Na – (HCO3 + Cl) = UA – UC
- Na – (HCO3 + Cl) = AG

Unmeasured Anions	vs	Unmeasured Cations
Proteins, mostly albumin 15 mEq/L		Calcium 5 mEq/L
Organic acids 5 mEq/L		Potassium 4.5 mEq/L
Phosphates 2 mEq/L		Magnesium 1.5 mEq/L
Sulfates 1 mEq/L		
Totals: 23 mEq/L		11 mEq/L

- Normal value of AG = 12 +/- 4 meq/L
- Revised N value AG = 8 +/- 4 meq/L
- Changes in methods of measurement of Na, Cl & HCO3 and resultant shift of Cl value to higher range.

Limiting factors for AG

- **LABORATORY VARIATIONS** – Variations in normal reference range of components of AG to be taken into consideration. Each institution should assign a normal range for AG based on these values.

- **INHERENT ERRORS IN CALCULATION** – All limits of components valid for 95% of N population.

  Probability of false +ve determination for each variable (Na/Cl/HCO3) = 0.05

  Probability of false +ve determination for AG

  = 3 x 0.05 = 0.15

- **HYPOALBUMINEMIA** - Pts with lowS. albumin can have high AG acidosis, but measured AG may be N becuase albumin has many -ve surface charges & accounts for a significant proportion of AG. Severe hypoalbuminemia may exhibit N AG as low as 4. Therefore in severe hypoalbuminemia if AG is normal, one must suspect an additional metabolic cause for increased AG

- **ALKALOSIS**-Alkalemic patients with pH > 7.5, AG may be ↑ due to met alkalosis per se & not because of additional met acidosis. Reasons proposed for the same include:

1. Surface charges on albumin become more -ve in alkalemic conditions (due to loss of protons) --> ↑ unmeasured anions
2. Assoc vol contraction --> hyperproteinemia
3. Induction of glycolysis and resultant hyperlactatemia

- **HYPERCALCEMIA -** Fall in AG as expected (↑ UC) except in paraneoplastic hypercalcemia for unknown reasons

Oster et al. Nephron 1990; 55:164-169.

- **DRUGS -** Lithium and polymyxin cause fall in AG (↑ UC) while carbenicillin cause ↑ in AG (act as UA)

- **CLEARANCE OF ANIONS** - Pts with expected ↑ AG acidosis may have N AG because of clearance of added anions e.g. DKA pts in early stage with adequate clearance of ketones may have a normal AG as also those in recovey phase

- **Δ AG - Δ HCO_3^- RELATIONSHIP** - used to assess mixed acid-base disorders in setting of high AG Met Acidosis:

Δ AG/Δ HCO_3^- = 1 → Pure High AG Met Acidosis

Δ AG/Δ HCO_3^- > 1 → Assoc Metabolic Alkalosis

Δ AG/Δ HCO_3^- < 1 → Assoc N AG Met Acidosis

- Based on assumption that for each 1 meq/L increase in AG, HCO3 will fall by 1 meq/L

- However:

1. Non HCO3 buffers esp intracellular buffers also contribute to buffering response on addition of H+. Becomes more pronounced as duration of acidosis increases.

   Hence Δ AG/Δ HCO_3^- > 1 even in absence of Met Alkalosis

2. All added anions may not stay in EC comp and those that diffuse inside cells could lead to a lesser rise in AG than expected

   Hence Δ AG/Δ HCO_3^- < 1 even in states expected to have high AG Met Acidosis

Salem et al, Arch Int Med 1992; 152: 1625-1629

- Strict use of AG to classify met acidosis & of ΔAG/ΔHCO3 to detect mixed/occult met acid-base disorders can be assoc with errors because of the possibility of change of AG by factors other than metabolic acid-base disturbances.

- Use of sequential AG determinations and observation of temporal profile of AG more imp than single value.

Modifications/Alternatives for AG

Δ AG/Δ HCO_3^- = 1-2 → Pure High AG Met Acidosis

Δ AG/Δ HCO_3^- > 2 → Assoc Met Alkalosis

Δ AG/Δ HCO_3^- < 1 → Assoc N AG Met Acidosis

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Use of Corrected AG

Corrected AG = Calculated AG + 2(Albumin gm/dL)
+ 0.5 ($PO4_3^-$ mg/dL)

Kellum JA et al. Chest 1996; 110: 18S

METABOLIC ACIDOSIS

Pathophysiology

1. HCO3 loss
    a. Renal
    b. GIT
2. Decreased renal acid secretion –
3. Increased production of non-volatile acids
    a. Ketoacids
    b. Lactate
    c. Poisons
    d. Exogenous acids

Causes of High AG Met Acidosis

1. Ketoacidosis:
   - Diabetic
   - Alcoholic
   - Starvation
2. Lactic Acidosis:
   - Type A (Inadequate O2 Delivery to Cells)
   - Type B (Inability of Cells to utilise O2)
   - Type D (Abn bowel anatomy)
3. Toxicity:
   - Salicylates
   - Paraldehyde
   - Methanol
   - Toluene
   - Ethylene Glycol

4. Renal Failure
5. Rhabdomyolsis

Causes of N AG Met Acidosis

1. HCO_3 loss:

GIT	Diarrhoea
	Pancreatic or biliary drainage
	Urinary diversions (ureterosigmoidostomy)
Renal	Proximal (type 2) RTA
	Ketoacidosis (during therapy)
	Post-chronic hypocapnia

2. Impaired renal acid excretion:
    - Distal (type 1) RTA
    - Hyperkalemia (type 4) RTA
    - Hypoaldosteronism
    - Renal Failure
3. Misc:
    - Acid Administration (NH4Cl)
    - Hyperalimentation (HCl containing AA sol)
    - Cholestyramine Cl
    - HCl therapy (Rx of severe met alkalosis)

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Manifestations of Met Acidosis

- Cardiovascular
  - Impaired cardiac contractility
  - Arteriolar dilatation, venoconstriction, and centralization of blood volume
  - Increased pul vascular resistance
  - Fall in C.O., ABP & hepatic and renal BF
  - Sensitization to reentrant arrhythmias & reduction in threshold of VFib
  - Attenuation of cardiovascular responsiveness to catecholamines

Adrogue et al, NEJM 1998; 338(1): 26-34

- Respiratory
  - Hyperventilation
  - ↓ strength of respiratory muscles & muscle fatigue
  - Dyspnea
- Metabolic
  - Increased metabolic demands
  - Insulin resistance
  - Inhibition of anaerobic glycolysis
  - Reduction in ATP synthesis
  - Hyperkalemia (secondary to cellular shifts)
  - Increased protein degradation
- Cerebral
  - Inhibition of metabolism and cell vol regulation
  - Mental status changes (somnolence, obtundation & coma)

Adrogue et al, NEJM 1998; 338(1): 26-34

Evaluation of Met Acidosis

- **SERUM AG**
- **URINARY AG**

Total Urine Cations	= Total Urine Anions
Na + K + (NH4 and other UC)	= Cl + UA
(Na + K) + UC	= Cl + UA
(Na + K) – Cl	= UA – UC
(Na + K) – Cl	= AG

- Helps to distinguish GI from renal causes of loss of HCO3 by estimating Urinary NH4+ (elevated in GI HCO3 loss but low in distal RTA). Hence a -ve UAG (av -20 meq/L) seen in former while +ve value (av +23 meq/L) seen in latter.

Kaehny WD. Manual of Nephrology 2000; 48-62

- **PLASMA OSMOLAL GAP** –

  Calc P Osm = 2[Na+] + [Gluc]/18 + [BUN]/2.8

N Meas P Osm > Calc P Osm (upto 10 mOsm/kg)

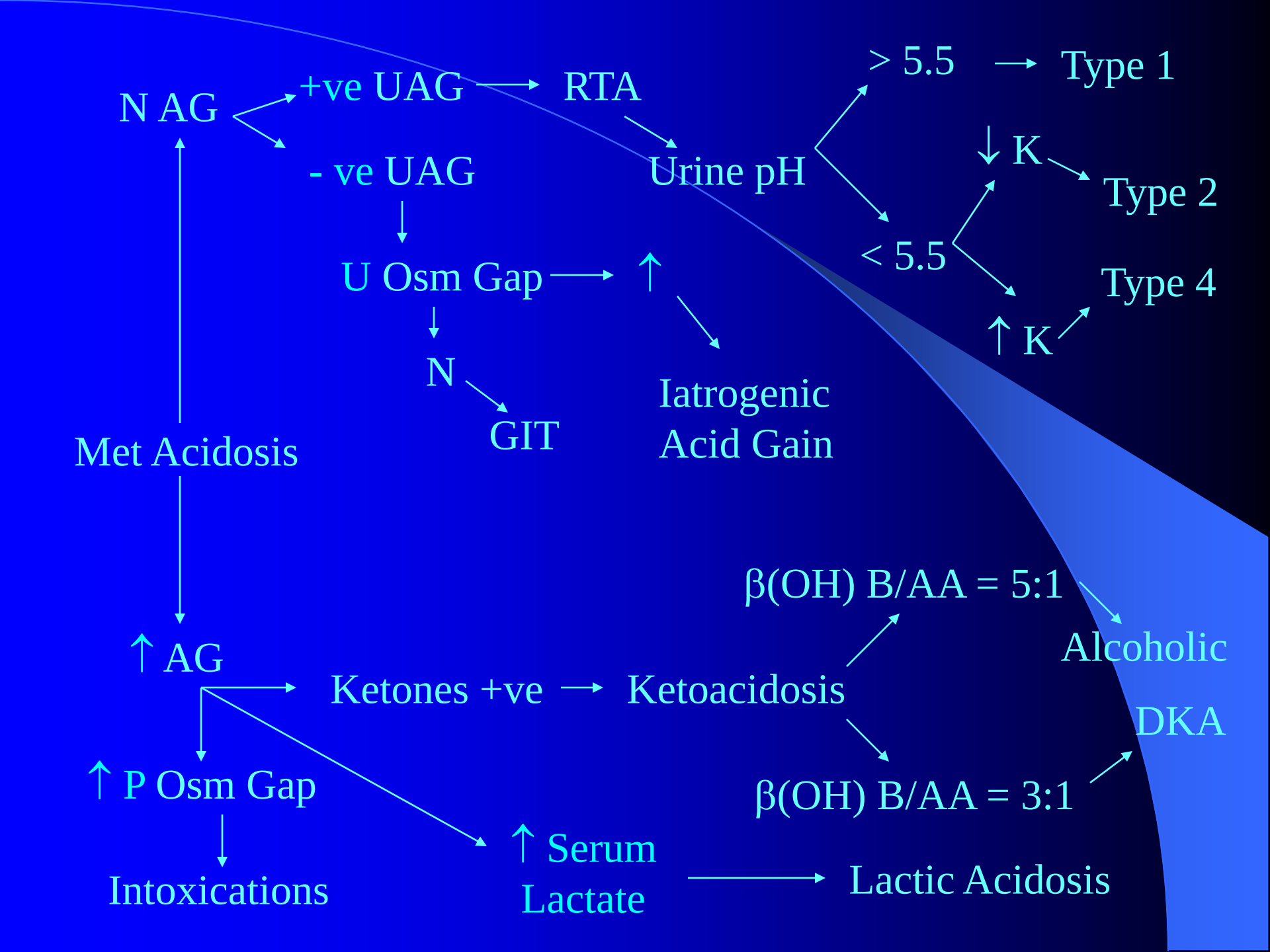
Meas P Osm - Calc P Osm > 15-20 mOsm/kg → presence of abn osmotically active substances (usually an alcohol)

- **URINE OSMOLAL GAP** - similar to P. Osm gap

  Calc U Osm = $2[(Na+_u) + (K+_u)] + [Gluc_u]/18 + [UUN]/2.8$

Meas P Osm > Calc P Osm → excretion of NH4+ with non Cl- anion (e.g.hippurate)

$[NH4+_u]$ usually ~ 50% of osmolal gap


N AG
+ve UAG
RTA
- ve UAG
Urine pH
> 5.5
Type 1
↓ K
Type 2
< 5.5
Type 4
↑ K
U Osm Gap
↑
N
GIT
Iatrogenic
Acid Gain
Met Acidosis
↑ AG
Ketones +ve
Ketoacidosis
β(OH) B/AA = 5:1
Alcoholic
DKA
β(OH) B/AA = 3:1
↑ P Osm Gap
Intoxications
↑ Serum
Lactate
Lactic Acidosis

Treatment of Met Acidosis

When to treat?

- Severe acidemia → Effect on Cardiac function most imp factor for pt survival since rarely lethal in absence of cardiac dysfunction.
- Contractile force of LV ↑ as pH ↓ from 7.4 to 7.2
- However when pH < 7.2, profound reduction in cardiac function occurs and LV pressure falls by 15-30%
- Most recommendations favour use of base when pH < 7.15-7.2 or HCO_3 < 8-10 meq/L.

How to treat?

Rx Undelying Cause

HCO3- Therapy

- Aim to bring up pH to ~7.2 & HCO3- ~ 10 meq/L
- Qty of HCO3 admn calculated:

  0.5 x LBW (kg) x HCO3 Deficity (meq/L)
- Vd of HCO3 ~50% in N adults.
- However in severe met acidosis can ↑ to 70-80% in view of intracellular shift of H+ and buffering of H+ by bone and cellular buffers.

Why not to treat?

- Considered cornerstone of therapy of severe acidemia for >100 yrs
- Based on assumption that HCO3- admn would normalize ECF & ICF pH and reverse deleterious effects of acidemia on organ function
- However later studies contradicted above observations and showed little or no benefit from rapid and complete/over correction of acidemia with HCO3.

Adverse Effects of HCO3- Therapy

- ↑ CO2 production from HCO3 decomposition → Hypercarbia (V>A) esp when pul ventilation impaired
- Myocardial Hypercarbia → Myocardial acidosis
  Impaired myocardial contractility & ↓ C.O.
  ↓ SVR and Cor A perfusion pressure →
  Myocardial Ischemia esp in pts with HF
- Hypernatremia & Hyperosmolarity → Vol expansion → Fluid overload esp in pts with HF
- Intracellular (paradoxical) acidosis esp in liver & CNS (↑ CSF CO2)

- ↑ gut lactate production, ↓ hepatic lactate extraction and thus ↑ S. lactate
- ↓ ionized Ca
- ↓ VO2, ↓ PaO2, ↓ P_{50}O2

CORRECTION OF ACIDEMIA WITH OTHER BUFFERS:

- **Carbicarb**
  - not been studied extensively in humans
  - used in Rx of met acidosis after cardiac arrest and during surgery
  - data on efficacy limited

THAM

- THAM (Trometamol/Tris-(OH)-CH3-NH2-CH3) - biologically inert amino alcohol of low toxicity.
- Capacity to buffer CO2 & acids *in vivo* as well as *in vitro*
- pK at 37 C = 7.8 (HCO3 has pK of 6.1)
- More effective buffer in physiological range of blood pH
- Accepts H+/CO2 and generates HCO3/↓ PaCO2

$$R\text{-}NH_2 + H_2O + CO_2 \Leftrightarrow R\text{-}NH_3^+ + HCO_3^-$$

$$R\text{-}NH_2 + H^+ + La^- \Leftrightarrow R\text{-}NH_3^+ + La^-$$

- Rapidly distributed in ECF except RBCs & liver cells --> excreted by kidneys in the protonated form (NH_3^+)
- Effective as buffer in closed or semiclosed system (unlike HCO_3^- which req an open system to eliminate CO_2)
- Effective in states of hypothermia
- Side Effects:

    1. Tissue irritation and venous thrombosis if admn through peripheral vein - seen withTHAM base (pH = 10.4) THAM acetate (pH = 8.6) well tolerated - does not cause tissue or venous irritation

2. Large doses can cause resp depression

3. Hypoglycemia

- Initial loading dose of THAM acetate (0.3 ml/L sol) calculated:

Lean BW (kg) x Base Deficit (meq/L)

Max daily dose ~15 mmol/kg

- Use in severe acidemia (pH < 7.2):

1. Resp failure:

a) Induced Acute Hypercapia - Apnoeic oxygenation during bronchoscopy and organ collection from organ donors

b) ARDS with permissive hypercapnia

c) Acute Severe Asthma with severe respiratory acidosis

2. DKA
3. Renal failue
4. Salicylate or Barbiturate intoxication
5. Raised ICT due to cerebral trauma
6 Cardioplegia during Open heart surgery
7. CPR (after restoration of cardiac function)
8. During liver transplantation
7. Chemolysis of renal calculi
8. Severe burns

Nahas et al, Drugs 1998; 55(2):191-224

METABOLIC ALKALOSIS

Introduction

- Met alkalosis common (upto 50% of all disorders)
- Severe met alkalosis assoc with significant mortality

1. Arterial Blood pH of 7.55 → Mortality rate of 45%
2. Arterial Blood pH of 7.65 → Mortality rate of 80%

(Anderson et al. South Med J 80: 729–733, 1987)

- Metabolic alkalosis has been classified by the response to therapy or underlying pathophysiology

Pathophysiology

1. **INITIATING EVENT**
    a. HCO3- gain
    b. H+ loss
        1) Renal
        2) GIT
    c. H+ shift
    d. Contraction/chloride depletion

2. **MAINTENANCE**

- Alkaline loads generally excreted quickly and easily by the kidney.
- Significant metabolic alkalosis can thus only occur in the setting of impaired HCO_3^- excretion
- Causes of impaired HCO_3^- excretion

    1) Decreased GFR – volume depletion
    2) Increased reabsorption –

        volume/chloride depletion

        hyperaldosteronism

Pathophysiological Classification of Causes of Metabolic Alkalosis

1. H+ loss:

GIT	Chloride Losing Diarrhoeal Diseases
	Removal of Gastric Secretions (Vomitting, NG suction)
Renal	Diuretics (Loop/Thiazide)
	Mineralocorticoid excess
	Post-chronic hypercapnia
	Hypercalcemia
	High dose i/v penicillin
	Bartter's syndrome

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2. HCO_3^- Retention:
   - Massive Blood Transfusion
   - Ingestion (Milk-Alkali Syndrome)
   - Admn of large amounts of HCO_3^-

3. Contraction alkalosis
   - Diuretics
   - Loss of high Cl^-/low HCO_3^- GI secretions (vomitting and some diarrhoeal states)

4. H^+ movement into cells
   - Hypokalemia
   - Refeeding

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Classification of Causes of Metabolic Alkalosis acc to response to therapy

VOLUME/SALINE RESPONIVE (Vol/Cl- Depletion)

- Gastric losses: vomiting, mechanical drainage, bulimia, gastrocystoplasty
- Chloruretic diuretics: bumetanide, chlorothiazide, metolazone etc.
- Diarrheal states: villous adenoma, congenital chloridorrhea
- Posthypercapneic state
- Dietary chloride deprivation with base loading: chloride deficient infant formulas
- Cystic fibrosis (high sweat chloride)

Gall JH. J Am Soc Nephrol 2000; 11: 369–375.

VOLUME REPLETE/SALINE UNRESPONIVE

1. K+ DEPLETION/MINERALOCORTICOID EXCESS

- Primary aldosteronism:

Adenoma	Renin-responsive
Idiopathic	Glucocorticoid-suppressible
Hyperplasia	Carcinoma

- Apparent mineralocorticoid excess:
  - Primary deoxycorticosterone excess: 11 β- & 17 α-hydroxylase deficiencies
  - Drugs: licorice (glycyrrhizic acid) as a confection or flavoring, carbenoxolone
  - Liddle syndrome

Gall JH. J Am Soc Nephrol 2000; 11: 369–375.

- Secondary aldosteronism
  - Adrenal corticosteroid excess: primary, secondary, exogenous
  - Severe hypertension: malignant/accelerated renovascular
  - Hemangiopericytoma, nephroblastoma, RCC
- Bartter and Gitelman syndromes and their variants
- Laxative Abuse, Clay Ingestion

2. HYPERCALCEMIC STATES (↑ HCO3- reabsorption)

- Hypercalcemia of malignancy

Gall JH. J Am Soc Nephrol 2000; 11: 369–375.

- Ac or Ch milk-alkali syndrome (both HCO3- & Ca ingested → additional mechanisms for alkalosis incl vomiting & ↓ GFR

3. MISC

- Carbenicillin/ampicillin/penicillin.
- HCO3- ingestion: massive or with renal insufficiency
- Recovery from starvation
- Hypoalbuminemia (Alkalosis usually mild and due to diminution of -ve charge normally contributed by albumin towards AG & shift in buffering curve for plasma).

Gall JH. J Am Soc Nephrol 2000; 11: 369–375.

Manifestations of Met Alkalosis

Symp of met alkalosis *per se* difficult to separate from those of Cl-/K+/Vol depletion → latter usually more apparent than those directly attributable to alkalosis.

- Cardiovascular
  - Arteriolar constriction
  - Reduction in Coronary BF/Anginal threshold
  - Predisposition to refractory SV & V arrhythmias (esp if pH > 7.6)
- Respiratory - Hypoventilation (Compensatory) → Hypercapnia/Hypoxemia

Adrogue et al, NEJM 1998; 338(2): 107-111

- Metabolic
  - Stimulation of anaerobic glycolysis & organic acid production
  - Reduction plasma ionized Calcium conc
  - Hypokalemia (secondary to cellular shifts)
  - Hypomagnesemia & Hypophosphatemia
- Cerebral
  - Reduction in Cerebral BF → mental status changes (stupor, lethargy & delirium)
  - N-M irritability (related to low ionized plasma Ca)
    - → Tetany, Hyperreflexia, Seizures

Adrogue et al, NEJM 1998; 338(2): 107-111

Evaluation of Met Alkalosis

- Urinary Cl- & K+ measurements before therapy useful diagnostically.
- Low urinary chloride (<10 mEq/L) seen in alkalotic states where Cl- depletion predominates (except cause is use of chloruretic diuretic) → Remains low until Cl- repletion nearly complete.
- Urinary K+ conc of >30 mEq/L with ↓ S. K+ suggests renal K+ wasting due to:
    1. Intrinsic renal defect
    2. Diuretics
    3. High circulating aldosterone
- Urinary K+ conc of <20 mEq/L with ↓ S. K+ suggests extrarenal K+ loss.

Treatment of Metabolic Alkalosis

- Although relationship between alkalemia and mortality not proven to be causal, severe alkalosis should be viewed with concern, and correction by the appropriate intervention should be undertaken when the arterial blood pH exceeds 7.55
- Imm goal of therapy is moderation & not full correction of the alkalemia. Reducing plasma HCO_3^- to <40 meq/L short-term goal, since the corresponding pH ~ 7.55 or lower.
- Most severe metabolic alkalosis is of Cl^- responsive type

Treatment of Vol Depleted/Saline Responsive Metabolic Alkalosis

- Rx underlying cause resp for vol/Cl- depletion
- While replacing Cl- deficit, selection of accompanying cation (Na/K/H) dependent on:
  - Assessment of ECF vol status
  - Presence & degree of associated K depletion,
  - Presence, degree & reversibility of ↓ of GFR.
- Pts with vol depletion usually require replacement of both NaCl & KCl.

DEPLETION OF BOTH CL- & ECF VOL (most common):

- Isotonic NaCl appropriate therapy → simultaneously corrects both deficits.
- In patients with overt signs of vol contraction, admn of min of 3 - 5 L of 150 mEq/L NaCl usually reqd to correct vol deficits & metabolic alkalosis.
- When ECF vol is assessed as normal, total body Cl- deficit can be estimated as:

0.2 x BW (kg) x Desired [Cl-] – Measured [Cl-] (mEq/L)

- Replace continuing losses of fluid & electrolytes
- Correction of Na, K & Cl deficits & assoc prerenal azotemia promotes HCO3 excretion and alkaline diuresis with a ↓ in plasma HCO3 towards normal.

DEPLETION OF CL- & ↑ ECF VOL

- Admn of NaCl is inadvisable for obvious reasons.
- Chloride should be repleted as KCl unless hyperkalemia present or concomitant ↓ GFR where ability to excrete K+ load is hampered.
- Administration of acetazolamide accelerates bicarbonaturia esp:
  - If natriuresis with a high Na excretion rate req simultaneously
  - If high serum K+ present
- Monitoring needed to detect associated kaliuresis and phosphaturia.
- GFR must be adequate (C/I if S. creat >4 mg/dl)

CL- DEPLETION with ↑ ECF VOL & HYPERKALEMIA (Use of NaCl/KCl C/I)

Hydrochloric Acid

- I/v HCl indicated if correction reqd imm
- Amount of HCl given as 0.1 or 0.2 M sol needed to correct alkalosis estimated as:

0.5 x BW (kg) x Desired [Cl-] – Measured [Cl-] (mEq/L)

- Continuing losses must also be replaced.
- Use of 50% of BW as V_d of infused protons done so that infused protons act to correct alkalosis in both ICF and ECF & restore buffers at both sites
- ½ correction given since imm goal of therapy is correction of severe & not full correction of alkalemia.

- HCl has sclerosing properties → must be admn through a central venous catheter (placement confirmed radiologically to prevent leakage of HCl → sloughing of perivascular tissue)
- Infusion rates N < 0.2 mmol/kg BW/hr with max rate of 25 mEq/h.
- HCl can also be infused after adding it to AA sol, fat emulsion or dextrose sol containing electrolytes & vit without causing adverse chemical RX - can also be admn through a peripheral vein
- Req frequent measurement of ABG and electrolytes.

Ammonium Chloride

- Can be given into a peripheral vein
- Rate of infusion should not exceed 300 mEq/24 h.
- C/I in presence of renal or hepatic insufficiency (worsening of azotemia & ppt of acute ammonia intoxication with coma respectively).

Dialysis

- In presence of renal failure or severe fluid overload state in CHF, dialysis +/- UF may be reqd to exchange HCO3 for Cl & correct metabolic alkalosis.
- Usual dialysates for both HD/PD contain high [HCO3-] or its metabolic precursors & their conc must be reduced.
- In pts with unstable hemodynamics, CAVH/CVVH using NaCl as replacement sol can be done.

Adjunct Therapy

- PPI can be admn to ↓ gastric acid production in cases of Cl-depletion met alkalosis resulting from loss of gastric H+/Cl- (e.g. pernicious vomiting, req for continual removal of gastric secretions, gastrocystoplasty
- Met alkalosis likely to persist & replacement of preexisting deficits hampered by ongoing losses

Treatment of Vol Replete/Saline Unresponsive Metabolic Alkalosis

MINERALOCORTICOID EXCESS

- Therapy should be directed at either removal of the source or its blockade.
- K-sparing diuretics, esp spironolactone helpful in reversing adverse effects of mineralocorticoid excess on Na, K and HCO3excretion.
- Restriction of Na and addition of K to diet also helpful both in Rx of alkalosis as well as HTN.
- Correction of K deficit reverses alkalinizing effects but elimination of aldosterone excess essential to achieve permanent correction.

MILK-ALKALI SYNDROME & OTHER HYPERCALCEMIC STATES

- Cessation of alkali ingestion & Ca sources (often milk and calcium carbonate)
- Treatment of underlying cause of hypercalcemia
- Cl- and Vol repletion for commonly associated vomiting

SUMMARY

SERIAL ABGs

CLINICAL PROFILE

SUPPORTING LAB DATA/
INVESTIGATIONAL TOOLS

CLINICIAN'S JUDGEMENT

CORRECT INTERPRETATION

SIMPLE DISORDER
(DEG OF COMPENSATION)

MIXED DISORDER
(ORDER OF PRIMARY &
SUBSEQUENT DISORDERS)

OXYGENATION /VENTILATORY STATUS

THANK YOU