Med Chem 535P – Diagnostic Medicinal Chemistry

Blood Chemistry ~ Electrolytes Buffers and Blood Gases

A. Electrolytes

B. Buffers and Blood Gases

C. ABGs Acidosis and Alkalosis

1. Respiratory
2. Metabolic

D. Alkalosis

1. Respiratory
2. Metabolic

E. Step-Method to Interpret ABGs

Some introductory items:

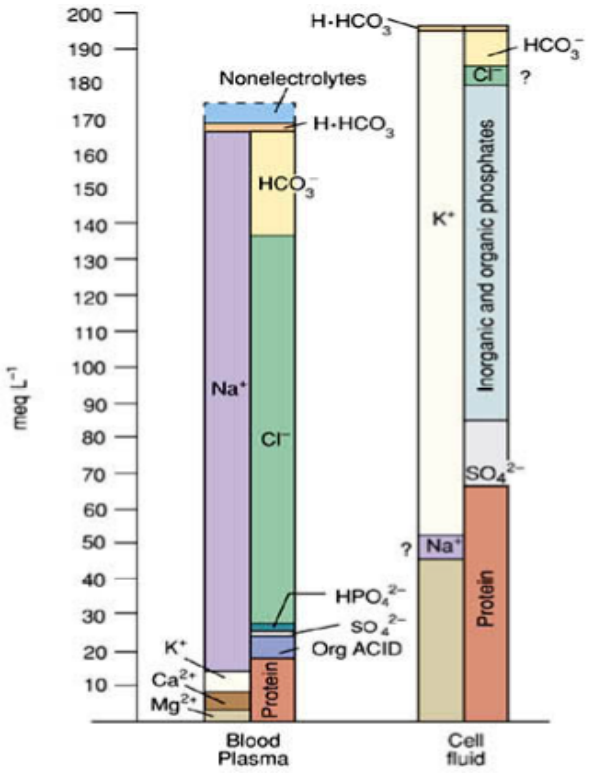
The concentrations of electrolytes in venous blood serum are measured however blood volume is only 8% of total body water.

Chem 7 Panel

Na 135-145 mEq/L	Cl 95-105 mEq/L	BUN 8-18 mg/dL	Glucose 70-110 mg/dL 3.9-6.1 mM
K 3.5-5 mEq/L	HCO_3 22-28 mEq/L	SCr 0.6-1.2 mg/dL	

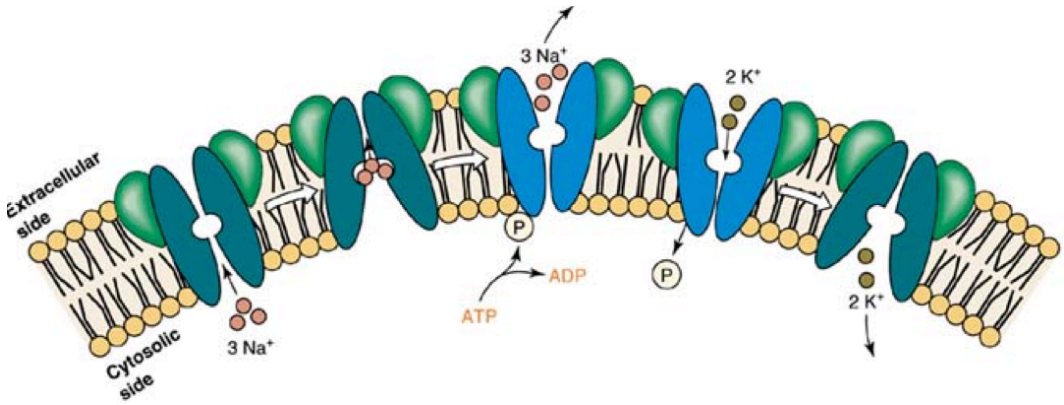
The Chem 10 also includes

Calcium	8.8-10.2 mg/dL
Mg	1.6-2.4 mEq/L
Phosphate	2.5-5.0 mg/dL



Where is the water?

1. Intracellular (ICFV) 66%
2. Extracellular (ECFV)
    a. Interstitial 25%
    b. Plasma 8%



Some Useful Rules for Electrolytes

1. Water passes freely through membranes so all compartments have equal osmolalities irrespective of the identity of the solutes. The body focuses on controlling cation concentrations using active transporters or co-transporters. Water follows net transport of solutes like Na and glucose. All of the electrolytes do not pass through membranes in the absence of a transporter. In the case of bicarbonate some CO_2 will pass membranes. Multiply charged cations (Ca^{+2}, Mg^{+2}, exist in mixtures of free and variously-complexed forms as does the phosphate and polyphosphate anions.

2. ECF: The electrolyte composition in serum and interstitial fluids are highly similar. The major extracellular cation is Na^+ and the major anion is Cl^-. The major serum buffer is bicarbonate.

3. ICF: The electrolyte composition in cells is very different. The major intracellular cation is K^+ and the major anion is a mixture of organic and inorganic phosphate $P0_4^{-2}$. The major buffer are the phosphates.

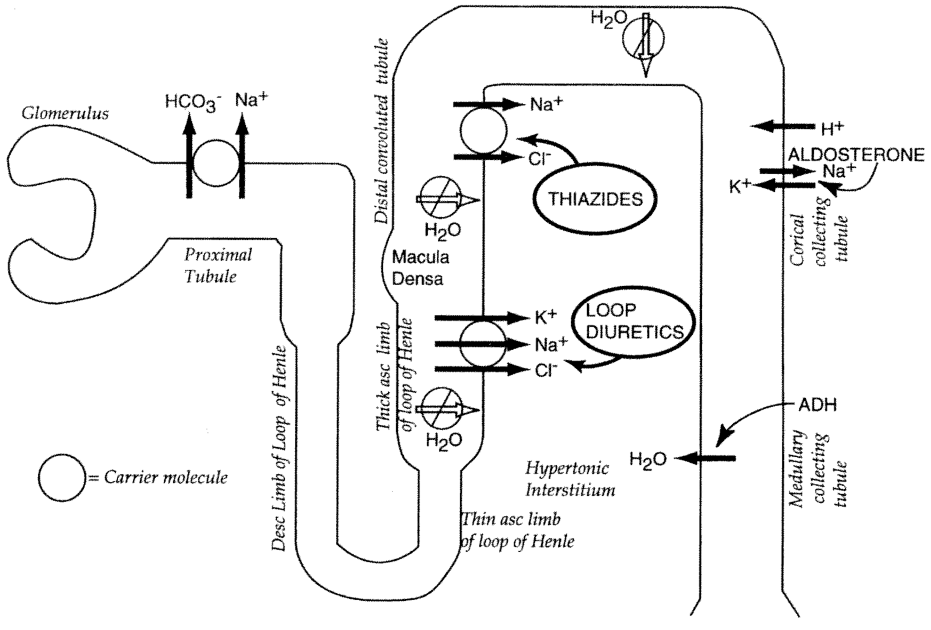
4. The Na^+ concentration in serum does not tell us the total sodium in the ECF or the size of the ECF. Thus Na^+ does not report on edema (interstitial volume) directly. The volume of the ECF is determined by the total amount of sodium. Abnormalities in Na^+ concentrations tells us that there is poor regulation of the amount of water in the ECF.

5. Three main systems control total body sodium and by extension the ECFV. These systems control sodium retention or excretion by the kidney. Here we think about only sodium, not total water in the urine.

    a. Renin-angiotension-aldesterone (increase sodium retention).

    b. Volume receptors that control atrial natriuretic factor (ANF promotes Na^+ excretion) and ECFV contraction.

    c. Pressure receptors that increase Na^+ retention when ECFV declines.



6. The brain is particularly sensitive to ECF Na^+ concentration since it is the main component of ECF tonicity. Hypernatremia leads to brain cell shrinkage while hyponatremia leads to brain cell swelling.

7. Total body water is mainly controlled by thirst (availability of water) and urine volume. The kidney reabsorbs water in the collecting tubules. The hypothalamus has osmoreceptors that control release of the hormone ADH (anti-diuretic hormone; vasopressin) to the blood. High levels of ADH cause the reabsorption of water by opening water channels. The net effect is to decrease the tonicity of the ECF and to decrease urine volume.

8. As a reminder the kidney receives 20% of cardiac output or 1.2 L/min. Approximately 180 L of blood is filtered per day and the kidney output is 2 L/day. Normal Glomerular Filtration Rate (GFR) is 90 mL/min or greater. Solutes in the filtrate include proteins less than 30K MW, amino acids, free fatty acids, electrolytes and glucose. Small proteins are endocytosed, hydrolyzed and returned as amino acids to the blood. Electrolytes, amino acids and glucose are transported into the blood. Fatty acids and lipophilic drugs are reabsorbed. The final volume, pH and concentrations of the electrolytes in urine is largely under hormonal control except when there is an overload of a solute.

BLOOD CHEMISTRY ~ ELECTROLYTES AND BLOOD GASES

A. *Serum Electrolytes* include sodium, potassium, chloride, magnesium, etc. They are among the most commonly used lab tests**.**

Serum electrolytes are typically measured with ion-specific electrodes:

1. Sodium (Na^+). *Reference Range: 135 – 145 mEq/L*

   This is the major cation in the *extra*cellular fluid (ECF). Na^+ is important in determining water balance and it's concentration is highly controlled. It is also important in maintaining cellular membrane potential. Na/water imbalances are often marked by neurological symptoms. The term volemic below refers to the volume of the ECF compartment however many think of the ECF as the blood or vascular volume.

   a. Hyponatremia (Na^+ < 135 mEq/L). Serum sodium and water are linked and hyponatremia can occur in the presence of low, normal, or elevated total body sodium. In most cases, hyponatremia is the result of free water excess. Na is the major positive electrolyte and hyponatremia can lead to confusion and seizures.

   Euvolemic hyponatremia is a dilutional form of hyponatremia. Total sodium in the ECF is normal but water retention and ECF volume is high. Seen with syndrome of inappropriate anti-diuretic hormone (SIADH) and excess uncompensated water intake. SIADH has many causes including CNS disorders (trauma, infection), cancers, pulmonary disease (cystic fibrosis) as well as a host of drugs that either stimulate ADH release or increase renal response to ADH (agnonists and sensitizers.

   Hypervolemic hyponatremia is also a dilutional form of hyponatremia. There is an increase in total sodium but an even larger increase in total body water. This condition is seen with CHF (congestive heart failure), cirrhosis of the liver, and renal disease.

   Hypovolemic hyponatremia is associated with low total body sodium and water. This can occur with prolonged sweating, vomiting, diarrhea, burn injury (loss of Na^+ and water to tissues), and renal failure. This can also occur with thiazide diuretics.

b. Hypernatremia (Na^+ > 145 mEq/L). Most often the result of a free water deficit, i.e., dehydration. As above, hypernatremia can occur in the presence of low, normal, or elevated total body sodium. Hypernatremia can lead to confusion, lethargy, weakness, seizures, and coma.

Euvolemic hypernatremia is associated with normal total body sodium. This is observed with excessive renal water excretion in patients with diabetes insipidis (large quantities of dilute urine), in ventilated patients, and with high fevers.

Hypovolemic hypernatremia is associated with low total body sodium. This can occur from renal losses (osmotic diuresis, glycosuria), severe diarrhea, and skin losses (extreme sweating, burns). Even a modest increase in serum sodium causes a thirst response (polydipsia). This type occurs commonly in the elderly, the mentally impaired, and infants who do not respond with water intake.

Hypervolemic hypernatremia is the least common. This state is seen with excessive sodium intake (sea water near drowning, inappropriate IV fluids), and metabolically: patients with Cushing's syndrome that have too much aldosterone which promotes renal Na^+ conservation.

c. How do you tell whether a patient is hyper-, eu-or hypo-volemic? Clinical judgement dominates here and dictates the overall strategy for therapy which we will not venture into.

Hypovolemia signs include orthostatic hypotension, poor skin turgor, dry skin. Also a BUN/SCr (blood urea nitrogen/serum creatinine) ratio greater than 20 indicates dehydration as urea can be reabsorbed in the kidney while creatinine cannot.

Hypervolemia signs are easier to spot and include pulmonary rales, edema, ascites and a distended jugular vein.

2. Potassium (K^+). *Reference Range: 3.5 – 5.0 mEq/L*

This is the major cation in the *intra*cellular space. Its primary role is in membrane physiology, nerve transmission and maintainence of intracellular tonicity. The most serious manifestations of potassium imbalance involve the cardiovascular system, especially the heart.

The primary regulatory organ is the kidney where K is secreted in the distal tubule after being almost completely absorbed earlier in the kidney., The colon becomes more important with advanced renal failure.

a. Hypokalemia (K^+ < 3.5 mEq/L). Hypokalemia can lead to muscle paralysis, but we usually observe muscle weakness, cramps and myalgias.

Transient hypokalemia without a true loss of potassium can occur with metabolic alkalosis (increased serum pH). H^+ is released from cells in exchange for K^+ and this can result in a transient hypokalemia. Insulin and large doses of β_2-adrenergic

agonists activate the Na^+/K^+ ATPase, which moves K^+ into cells (and out of the serum), which can result in hypokalemia.

Hypokalemia also results from systemic loss of potassium in the kidney and GI tract. This is observed with thiazide diuretics and furosemide administration, diarrhea, and severe vomiting (why?)

Amphotericin B can cause renal damage and loss of K^+, Mg^{2+}, and HCO_3^-. Note that magnesium is required for the Na/K ATPase pump that facilitates renal potassium uptake and hypomagnesemia must be corrected for efficient potassium replacement therapy.

Hypokalemia can affect multiple physiological systems, but the effect on cardiac function is the most serious. This can be especially severe in patients taking digoxin, which competes with K^+ for the Na^+/K^+ pump and can lead to arrhythmias. Skeletal muscle weakness can occur and death can ensue from respiratory muscle paralysis.

b. Hyperkalemia ($K^+ > 5$ mEq/L). Transient hyperkalemia can be seen in severe metabolic acidosis when cells exchange K^+ for H^+. However, it is most commonly observed in patients with decreased kidney function or when large numbers of cells are destroyed in a tissue or organ (rhabdomyolysis, severe burns, crush injuries, post-op, hemolysis).

True hyperkalemia can also result from (i) elderly who often have decreased renal function and who are taking K^+-sparing diuretics (spironolactone, amiloride) which inhibit renal K^+ secretion, (ii) high dose NSAID therapy which can decrease renin secretion -> potassium retention, (iii) ACE inhibitors and angiotensin II blockers do the same, (iv) trimethoprim blocks sodium channels in the distal nephron -> potassium retention, (v) β-blockers inhibit Na^+/K^+ ATPase and decrease K^+ uptake by cells, (vi) increased uptake (salt substitutes, IVs with K^+, etc.).

Hyperkalemia can lead to malaise, muscle weakness, cardiac arrhythmias which can be observed in electrocardiograms.

3. Chloride (Cl^-). *Reference Range: 95 – 105 mEq/L*

This is the major *extra*cellular anion and serves as a counter ion for Na^+ and K^+. For the most part Cl^- passively follows sodium and water across membranes and has it's own set of transporters and co-transporters. HCO_3^-/Cl^- exchange in the renal proximal tubules is used to maintain serum pH and can affect Cl^- concentration. We will look at this when we talk about pH and bicarbonate.

Alteration of chloride concentration is primarily used to confirm an alteration in fluid balance and/or acid/base balance (anion gap). Hyperchloridemia can be observed in patients with iv lines of saline.

4. Magnesium (Mg^{2+}). *Reference Range: 1.5 – 2.2 mEq/L.*

Magnesium has widespread physiological roles in neuromuscular and enzymatic function (virtually all ATPases and polymerases require Mg^{2+}).

About 50% of body Mg^{2+} is found in the bone. Generally Mg^{2+} movement follows that of phosphate and is usually opposite to that of Ca^{2+}.

Approximately 50% of the filtered Mg^{2+} is reabsorbed in the Loop of Henle so loop diuretics are magnesium wasting; thiazide diuretics do not affect Mg^{2+} status and K-sparing diuretics are also Mg-sparing.

a. Hypomagnesemia (Mg^{2+} < 1.5 mEq/L) is the more common condition and can lead to neuromuscular symptoms including weakness, muscle fasciculation, and increased reflexes (low Mg^{2+} -> increased ACh release). CNS effects (stupor, coma) and cardiac effects (arrhythmias) are potentially serious outcomes. Usually cause by excessive loss from the GI track (NG suction, diarrhea) or the kidney (diuresis).

b. Hypermagnesemia (Mg^{2+} > 2.7 mEq/L) is usually not a problem. It is usually caused by excessive intake (magnesium-containing antacids or laxatives, dietary supplements). High doses of magnesium are used to stop contractions in pre-eclampsia (4-7 mEq/L therapeutic range) and side effects are notable.

Levels greater than 5 mEq/L can result in lethargy, mental confusion, hypotension, and, at levels >10 mEq/L, flacid paralysis, respiratory and cardiac arrest.

Non-magnesium antacids and metamucil or dulcolax as laxatives should be recommended to patients who have renal problems.

5. Calcium (Ca^{2+}). *Reference Range: 8.5 – 10.5 mg/dL*

Calcium and phosphate levels are commonly monitored in the context of the endocrine system, specifically with respect to vitamin D and parathyroid hormone.

a. Hypercalcemia ~ Ca^{2+} > 10.8 mg/dL. Hypercalcemia can lead to symptoms such as confusion, constipation, heart irregularities, as well as an increased risk of kidney stones (mostly calcium oxalate). Calcium in the blood is found in 3 major forms: complexed with proteins particularly albumin (40%); complexed with phosphates, citrates and bicarbonate (6%), ionized free fraction (54%). The concentration of the free fraction (called $Ca_{(corr)}$) is usually considered to be the important relative to physiological function and can be estimated from the total albumin and Ca^{+2} concentrations. This will be important in therapeutics when albumin levels are low and Ca supplementation is contemplated. For instance hypoalbuminemia and hypocalcemia is often observed in renal failure so while total calcium may be low available free calcium may be normal.

Most common causes of hypercalcemia are (i) breast, lung, and bone tumors; (ii) kidney damage; (iii) hyperparathyroidism; (iv) consumption of foods rich in calcium (e.g., an ulcer patient who drinks a lot of milk along with calcium-containing antacids, aggressive intake of calcium supplements and vitamin D supplements).

Note – tamoxifen and calcium channel blockers can augment an established hypercalcemia.

Hypercalcemia increases heart sensitivity to digoxin leading to arrhythmias.

b. Hypocalcemia ~ Ca^{2+} *< 8.5 mg/dL*.

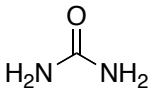
Can lead to tetany. Usual causes are poor diets, alcoholism, hypoparathyroidism, and too much phosphate in IVs.

6. Phosphate status. *Reference Range: 2.6 – 4.5 mg/dL*. Phosphate and calcium levels are usually considered together as their concentrations can be either linked or de-linked depending on a number of clinically relevant diseases, uptake and Vitamin D status. There is no simple relationship so here we look at common causes and major consequences. Most of the phosphate in the body is intracellular and is found in a number of organic and inorganic states.

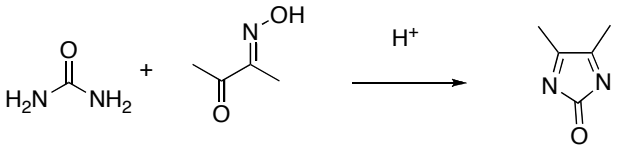
   a. Hyperphosphatemia. Phosphate > 4.5 mg/dL. Most common causes are renal insufficiency (GFR<25 ml/min), shifting of phosphate from intracellular stores, certain malignancies and increased intake of Vitamin D. Often hyperphosphatemia is associated with hypocalcemia. For instance in renal failure (GFR<25 ml/min) one usually observes hypocalcemia, hyperphosphatemia and compensatory hyperparathyroidism.

   b. Hypophosphatemia. Phosphate < 2.6 mg/dL. Occurs with alcoholism, excess use of aluminum and magnesium containing antacids, long term use of thiazide and loop diuretics leading to renal losses of phosphate. Severe hypophosphatemia (<1 mg/dL) can occur during severe diabetic ketoacidosis. Symptoms are many including muscle weakness, encephalopathy, seizures and coma due to decreased glucose utilization in the brain.

7. BUN (Blood Urea Nitrogen) Reference Range 8-18 mg/dL Urea is the end product of amino acid catabolism. Urea is produced in the liver by the urea cycle. Urea is excreted by the kidneys. Because urea is a neutral compound the excretion of urea has no effect on blood or urine pH. High levels of urea are referred to as uremia. This tests for urea in serum. The normal kidney reabsorbs approximately 50% of the filtered urea and excretes the rest into the urine.

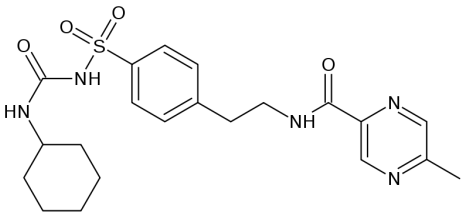


a. Direct Test in Automated Analyzers – Diacetylmonoxime Method is a colormetric test



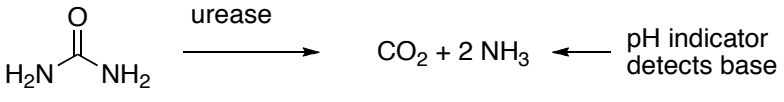
a diazene
yellow

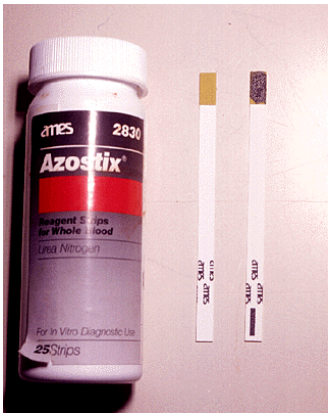
Urea containing drugs such as the sulfonoureas and biguanides may interfer by causing high values.



Glipizide (a sulfonourea)

b. Indirect Semiquantitative Test of a drop of blood with Azostix. Useful for quick diagnosis of urea > 20 mg/dL.





c. High BUN/Uremia (also called azotemia) is a marker for kidney disease.

(1) Acute kidney failure secondary to nephrotoxic drugs, hypertension, glomularnephritis and tubular necrosis.

(2) Chronic kidney dysfunction caused by diabetes, arteriosclerosis, pyelonephritis, amyloidosis.

(3) Low renal blood supply due to shock, dehydration (Some 12% of hospitalized patients with high BUN) and congestive heart failure (Some 36% of hospitalized patients with high BUN).

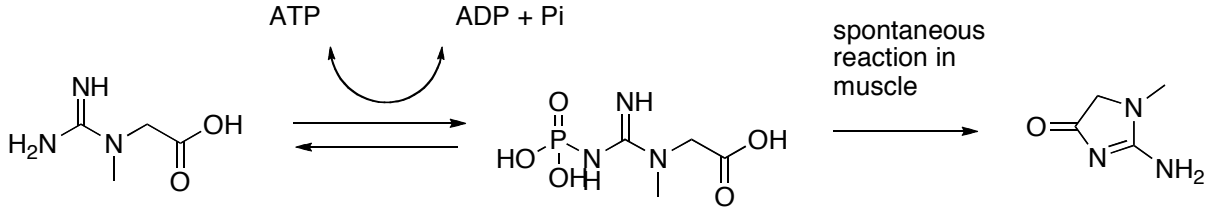
(4) High protein diets and upper GI bleeding.

d. Low BUN

(1) Severe liver disease

(2) Hypervolemia.

8. Serum Creatinine (SCr) Reference Range (0.6-1.2 mg/dL). Creatinine is produced by the non-enzymatic degradation of creatine phosphate in muscle. Creatinine is filtered by the kidney but not reabsorbed (there can be minor amounts of secretion). The primary use of serum creatinine (SCr) is in the early diagnosis of kidney disease and determination of Glomerular Filtration Rate (GFR). Creatinine is uncharged at physiological pH (pKa of conjugate acid is 3).



Creatine Creatine Phosphate Creatinine

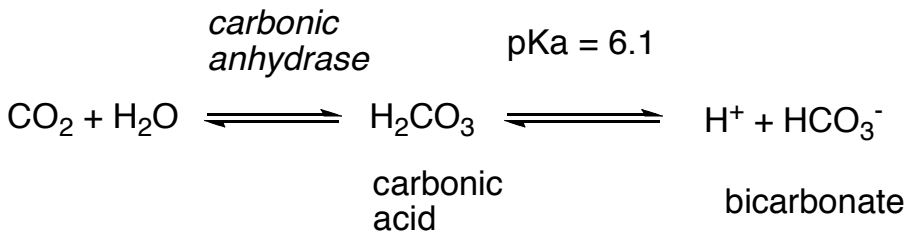
a. The commonly used test for creatinine in automated analyzers is called the Jaffe reaction. Creatinine forms a red colored complex with picric acid in a basic solution. There are some interferences with this test most notably high concentrations of glucose, ascorbic acid and the cephalosporin antibiotics. More selective HPLC methods and enzymatic assays are becoming more available.

b. Kidney dysfunction leads to high SCr. Usually BUN levels are elevated as well. Normal BUN/SCr ratios are approximately 10:1 and similar ratios are preserved in renal dysfunction.

c. High BUN but normal SCr to ratios of 20:1indicates a non-renal uremia due to dehydration, severe burns or crushing injuries.

9. Bicarbonate (HCO_3) *Reference Range 22-28 mEq/L* Bicarbonate (Bicarb) is routinely determined in electrolyte and blood gas panels. Bicarbonate is the major extracellular buffer. The pH of the blood is normally maintained in a narrow range (7.35-7.45) by controlling expiration of CO_2 in the lungs and secretion of H^+ by the kidney. Bicarbonate is filtered and completely reabsorbed in the proximal tubule by conversion to CO2 by carbonic anhydrase in the brush border region where it is taken up by the kidney cells. However some urinary excretion of bicarbonate occurs at blood levels in excess of 28 mEq/L.

a. Bicarbonate is the conjugate base of carbonic acid. Carbonic acid is a weak acid with a pKa of 6.1. From the scheme below we can see that addition of CO_2 will shift the equilibrium to the right and the pH of the solution will fall (become more acidic). This is what happens in the blood as oxygen is exchanged for CO_2 in actively respiring tissues like muscle. When CO_2 is expired in the lungs the equilibrium shifts to the left, bicarbonate concentrations fall and the pH of the blood rises.



b. The ratio of CO_2 to H_2CO_3 is approximately 600 to 1 and the interconversion between the species is slow. Carbonic anhydrase speeds up the interconversion to rates approaching the limits of diffusion but it does not change the equilibrium concentration of reactants and products. The interconversion rates for the right hand equilibrium are very fast. The net of this exercise is that the major species in solution are CO_2 and HCO_3^-.

c. Using the Henderson Hasselbalch equation and some approximations. One useful conversion when you work through this relates the partial pressure of CO_2 (pCO_2) in mm Hg to total concentration of CO_2 in mM or mEq/L. At a pH of 7.4 the ratio of bicarbonate to total CO_2 is approximately 20:1. Below we calculate the pH of the blood when bicarbonate is 44 mEq/L and pCO_2 is 48 mm Hg. We use the conversion factor $[CO_2]$ (mM or mEq/L) = pCO_2 x 0.03 in our calculations.

$$pH = pKa + \log \frac{HCO_3^-}{CO_2} \Longrightarrow 20/1$$

$$pH = 6.1 + \log \frac{22}{48 \times 0.03} = 7.28$$

9. Anion Gap Reference Range (3-16 mM or mEq/L). The total number of positive and negatively charged ions in the blood must be equal. The true anion gap then would be zero when all ions are taken into account. The anion gap is readily calculated as:

$$\text{Anion Gap} = [Na^+] - (Cl^- + HCO_3^-)$$

a. A number of cations and anions are not included in the calculation. These are called unmeasured ions. The anion gap is a positive number meaning that the number of unmeasured anions is normally greater than the number of unmeasured cations.

b. Some institutions and labs include K in the calculation which raises the reference range so it is important to keep this in mind.

c. High anion gaps signify that one or more of the unmeasured anions are unusually high. These can include metabolic ketoacidosis (high ketone bodies), renal failure (high sulfate and phosphate), lactic acidosis and salicylate poisoning.

d. Low anion gaps can signify hyponatremia, hypoalbuminemia (albumin is negatively charged) and others.

10. Blood Gases can be determined from arterial or venous blood samples. For most purposes in the hospital arterial blood gases are used. Turnaround time is usually fast. Sample handling is important as the gases will diffuse away. Sample reference ranges are given below. Note the difference between arterial and venous and the effect of altitude.

	Sea Level		1 Mile
	Arterial	Venous	Arterial
pO_2 (mm Hg)	80-100	30-50	65-75
pCO_2 (mm Hg)	35-45	40-52	34-38
O_2 Saturation	>95%	60-85 %	
HCO_3 (mEq/L)	22-28	22-26	

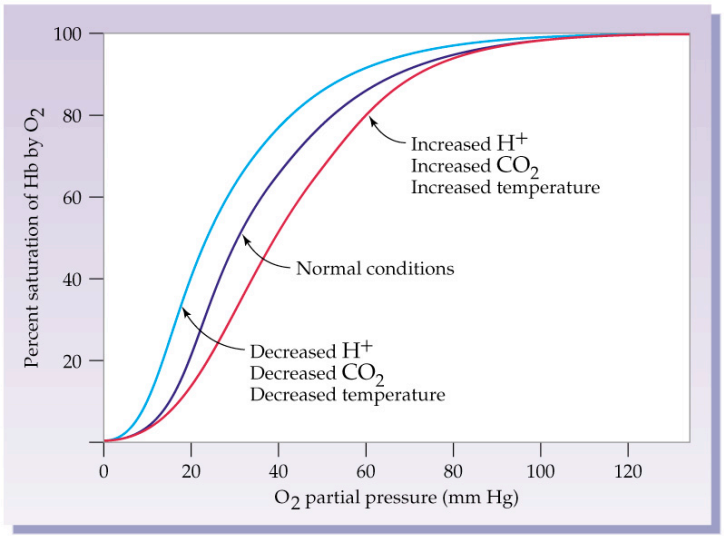
a. Blood gases are measured regularly in the hospital when a patient is on a ventilator.

b. Blood gases are also used to diagnose disease and to evaluate metabolic status.

c. O_2 saturation can be measured continuously using a pulse oximeter. These are also available for home use for patients on home oxygen and monitors for sleep apnea.

d. Some hospitals are using sophisticated and expensive point of care devices.

A simple pulse oximeter for home use and Hb saturation curve.



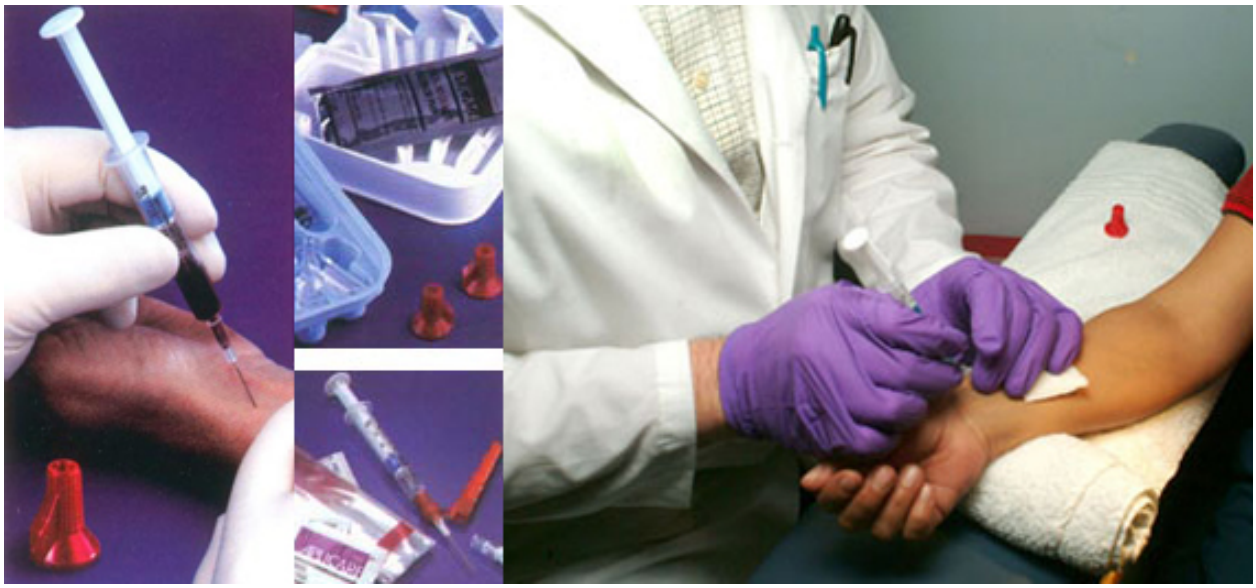
A point of care analyzer that can be used on the wards (expensive to use)

Overview

The i-STAT portable clinical analyser is a true Point Of Care analyser designed to be used at the patients bedside for critical care tests such as blood gases, electrolytes, metabolites and coagulation. There are a number of cartridges testing different combinations of analytes therefore eliminating the need for different analysers.

Only a few drops of whole blood are required for testing, between 65 and 95 µl. Samples are processed immediately and provide lab-quality results in 2 minutes making the i-STAT quick and easy to use.

B. <u>Acid-Base Disorders: Arterial Blood Gases and pH</u> (ABGs also include Hb saturation, base excess (delta base) and total CO_2). Given a pCO_2 and pH you should be able to calculate bicarbonate (see below) which is what the analyzers do.



1. An acid base disorder occurs when (1) renal or (2) respiratory function is abnormal or (3) when an acid or base load overwhelms excretory capacity. These disorders cause the extracellular pH to rise or fall.

a. Here we look at the normal acid base reference ranges and ideal values. We also note that the ratio of bicarbonate to CO2 provides the pH.

	pH	pCO_2 (mm Hg)	HCO_3^- (mEq/L)
Reference Range	7.35- 7.45	36-44	22-26
Average Value	7.40	40	24

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

$$pH = 6.1 + \log \frac{HCO_3^-}{CO_2} \Longleftarrow \text{H.H. relationship for bicarbonate}$$

$$7.4 = 6.1 + \log \frac{24\ mEq/L}{1.2\ mEq/L} \qquad \text{where } CO_2\ (mEq/L) = 0.03 \times pCO_2\ (mm\ Hg)$$

b. Acid base status refers to the plasma pH relative to the normal values.

Acidemia - decrease in the blood pH below normal range of 7.35 -7.45

Alkalemia - Elevation in blood pH above the normal range of 7.35 – 7.45

c. Clinically significant disturbances of acid base metabolism are defined in terms of the effects on the bicarbonate buffer system.

Acidosis – a process that increases $[H^+]$ by increasing pCO_2 or by reducing $[HCO_3^-]$

Alkalosis – process that reduces $[H^+]$ by reducing pCO_2 or by increasing $[HCO_3^-]$

d. Primary reasons to measure ABG in the hospital/clinic

(1) Mechanical ventilation- Patients are kept at a pCO_2 of 35-40 mm Hg. ABGs daily or when ventilator is changed.

(2) Diagnosis of acidemia/alkalemia in chronic and acute care.

(3) Code Blue (shock): ABGs vital as used to reverse shock. At Swedish handheld devices are routinely used in Intensive Care and emergency rooms.

2. Acidosis and alkalosis are further subdivided into categories that reflect the process or cause.

Anion gap analysis, additional analysis of blood and knowledge of a disease state (chronic vs acute) or event can be important in the analysis, diagnosis and treatment.

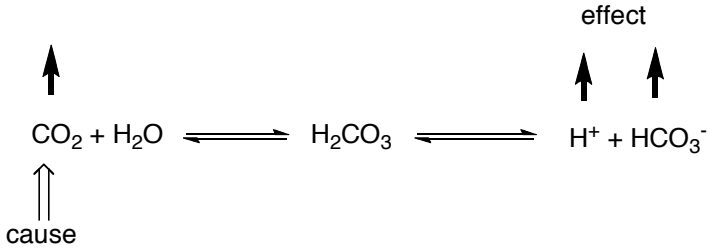
It is important to remember that the body will attempt to compensate for the event that produces the disturbance. For instance in respiratory acidosis when carbon dioxide removal is impaired by pulmonary disease the pCO_2 will rise as the primary alteration. Compensation will include a rise in bicarbonate as the body seeks to maintain pH by keeping the bicarb/CO_2 ratio as close to ideal as possible.

Compensations can also include shift of protons into or out of cells in exchange usually with potassium.

The kidney can selectively secrete protons which serves to acidify or basify the urine with the opposite effect on blood pH.

We will use the most common approach to the problems of acid/base which is to divide into 4 categories and conquer.

a. Respiratory Acidosis: ↑ pCO_2 -> ↑ HCO_3 and ↓ pH. Respiratory acidosis is usually caused by chronic pulmonary disease where oxygen and carbon dioxide exchange is compromised.



The direct ABG result of poor exchange is ↓ pO_2 and ↑ pCO_2. The increase in pCO_2 causes an increase in bicarbonate and a decrease in pH.

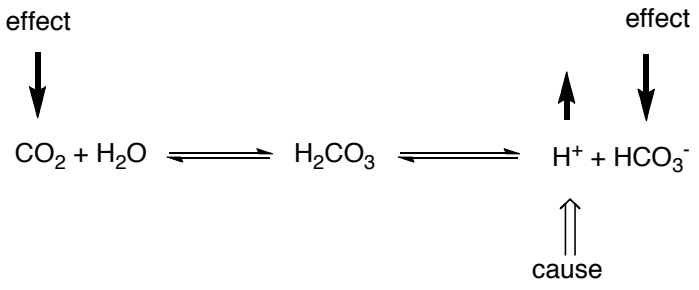
(1) Chronic conditions include emphysema, chronic obstructive pulmonary disease (COPD), pulmonary edema, congestive heart failure, chronic bronchitis, pneumonia, stroke victims neuromuscular disorders and oversedation.

(2) Hypercapnia: While supplementary oxygen can be used to increase pO_2 there is little that can be done to decrease pCO_2. Elevated pCO_2 is called hypercapnia. Symptoms of mild hypercapnia (pCO_2 = 50-60) include headache, confusion and lethargy. Severe hypercapnia is defined as pCO_2 > 75 mm Hg and is eventually fatal.

(3) Potassium levels: The increase in H^+ is compensated by cellular uptake of protons which release K to the blood in exchange leading to elevated serum K and potassium loss in the kidney so potassium levels are important to watch.

(4) Compensation: The reabsorption of filtered bicarbonate by the kidney is saturated and some bicarbonate is lost to the urine which basifies the blood. Renal excretion of H+ is also increased.

b. Metabolic Acidosis: ↓ pH -> ↓ HCO_3 and eventually ↓ pCO_2 The most common cause of metabolic acidosis is the presence of other weak acids in the blood. Note that this will often show up as an elevated anion gap. The buffer system responds by increasing CO2 and decreasing bicarbonate by mass balance. The body responds by compensating via hyperventilation to increase expiration of CO2. This pulls the equilibrium to the left and causes a compensatory fall in H+ leading to a compensatory rise in pH.



Major causes of metabolic acidosis accompanied by a high anion gap are

(1) Ketoacidosis resulting from diabetes and starvation (check ketone bodies)

(2) Lactic acidosis resulting from liver disease, metformin overdose, septic shock, heart attack (check lactate), HIV NRTIs

(3) Renal failure

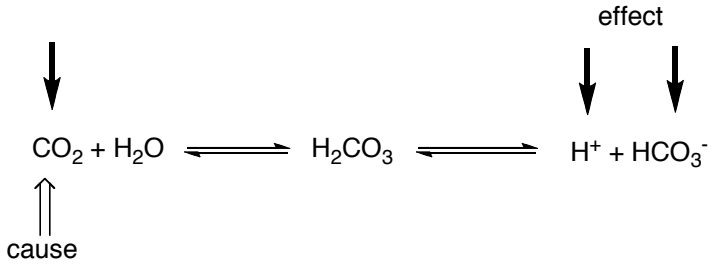
Major causes of metabolic acidosis accompanied by a normal anion gap are

(1) Diarrhea (bicarb loss and see hyperchloridemia to fill the gap)

(2) Renal tubular acidosis (hyperchloridemia)

(3) Carbonic anhydrase inhibitiors (Diamox; amphotericin B

c. Respiratory alkalosis: $\downarrow pCO_2$ -> $\downarrow HCO_3$ and $\uparrow$ pH. The most common cause of respiratory alkalosis is hyperventilation which leads to expiration of carbon dioxide. pCO_2 falls and the buffer system reacts by decreasing bicarbonate and H^+. Symptoms are usually mild and readily reversed (breathing into a bag for instance). Compensation includes cells exchanging H^+ for K^+ to decrease blood pH. This hypokalemia is transitory and does not require new potassium.



Major causes of respiratory alkalosis

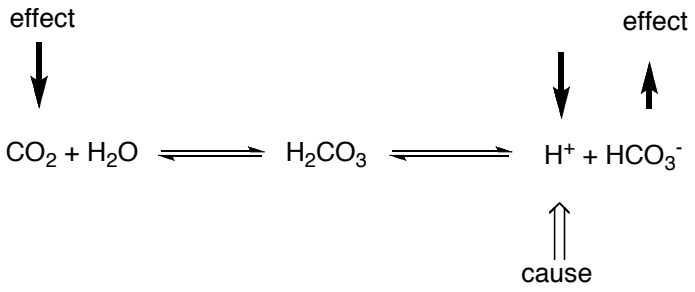
(1) Anxiety-hyperventilation (often observed during finals week?)

(2) Pregnancy

(3) Fever

(4) Pneumonia or pulmonary embolism which causes hypoxemia and rapid breathing.

d. Metabolic alkalosis ↑ pH -> ↑ HCO_3 and ↑ pCO_2 The primary cause of metabolic alkalosis is a decrease in the circulating fixed acids. A high pH and high bicarbonate are unique to metabolic alkalosis. There is a hypoventilation response to reduce expiration of carbon dioxide so the expected drop in carbon dioxide is transitory.



Major causes of metabolic alkalosis

(1) Loss of gastric acid (vomiting, nasogastric suction). This can also lead to loss of Na, K and Cl (Hypochloremic Metabolic Alkalosis) and requires electrolyte replacement.

(2) Hyperaldosteronism (Cushings) or mineralocorticoid drugs (prednisone).

(3) Hypokalemia (body excretes potassium to spare H^+: also thiazide diuretics)

(4) Alkali administration (overdose of acetate in iv; overdose of bicarbonate to treat metabolic acidosis.

C. Step by Step Program for Diagnosis:

1. The pattern of acid base abnormalities

	pH	pCO_2 (mm Hg)	HCO_3^- (mEq/L)
Reference Range	7.35-7.45	36-44	22-26
Respiratory Acidosis	⇓	⇑	⇑ (secondary)
Metabolic Acidosis	⇓	⇓ (secondary)	⇓
Respiratory Alkalosis	⇑	⇓	⇓ (secondary)
Metabolic Alkalosis	⇑	⇑ (secondary)	⇑

2. Checklist order:

a. Check pH:

pH < 7.35 = acidosis

pH > 7.45 = alkalosis

b. Check pCO_2

Change in pCO_2 in same direction as pH then it is metabolic

Change in pCO_2 in opposite direction as pH then it is respiratory.

3. In compensated respiratory cases if pH is in normal range but either pCO_2 and/or HCO_3^- are not then you have a compensated acid/base situation which we will not cover.

Use pH 7.4 as the cut-off value

Compensated acidotic if pH < 7.4

Compensated alkalotic if pH >7.4

4. Base excess (Delta Base) is another value that is related to diagnosis and treatment for disorders particularly in the ICU and emergency room. We won't cover this here either.

5. References to Acid/Base and/or Electrolytes

Acid-Base, Fluids and Electrolytes made ridiculously simple Richard Preston MD (a book at $23. Also covers how to diagnose in more detail and how to treat.

Basic Skills in Interpreting Laboratory Data Mary Lee Used quite a bit as a reference in the Therapeutics Sequence. A new edition is due soon so I would wait.

Website that walks you through acid base from U Conn Med Center
http://fitsweb.uchc.edu/student/selectives/TimurGraham/Welcome.html

Compilation of Lab Values and other goodies:
http://www.bloodindex.org/normal_laboratory_values.php