Chapter 14

Electrolytes and Acid-Base Analysis

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Educational Objectives

1. Understand physiologic regulation of serum electrolytes and describe common abnormalities
2. Understand the importance of acid base regulation in clinical practice
3. Describe the determinants of pH according to both the Stewart and traditional approach
4. Understand physiologic regulation of pH
5. Understand the causes of both metabolic and respiratory acid base disturbances
6. Understand risks and benefits of treatment options available for metabolic acidosis

Introduction to Serum Electrolyte Composition

While blood components contain electrolytes in physiologic concentrations, this is not true for all crystalloids and colloids. As such, this chapter will give the reader more insight into the use of fluids in the perioperative period and how this relates to electrolyte and acid-base physiology. In physiology, electrolytes are defined as compounds that contain an electrical charge when dissolved in a solution such as water and as such are able to conduct electricity. These charged compounds are referred to as ions, and their charge may be either positive (cations) or negative (anions). Tight regulation of electrolytes in both the intracellular and extracellular spaces is essential for normal cellular function in every organ system. The body will seek to maintain serum electrochemical

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neutrality; that is, a balance of all positive and negative charges. In addition to this, the body seeks to maintain acid-base regulation within a very narrow range. These two forces, electrochemical neutrality and acid-base balance, are tightly coupled in order to maintain normal homeostasis. Disruption of this balance leads to cellular dysfunction and can cause fatal pathologic processes such as renal dysfunction, dysrythmias, seizures, and coma.

Physiologic Regulation of Electrolytes

The major serum cations are sodium and potassium, with calcium, and magnesium also being present in lower concentrations. The major serum anions are chloride and bicarbonate, with phosphate and lactate also being present in lower concentrations. Intracellular concentration of these ions is determined by active transmembrane pumps, and to a lesser extent by passive ion-specific channels. Extracellular – including serum – concentration of electrolytes is regulated primarily by the renal system with significant input from the hypothalamic-pituitary-adrenal (HPA) axis.

Sodium

Sodium is the most abundant serum cation, and is a major determinant of serum osmolality. Serum osmolality is tightly regulated between 275 and 290 mOsm/kg.

Serum osmlality is estimated by the following equation:

$$\text{Serum Osmolality} = \left(\text{Serum } Na^{+} \times 2\right) + \left(\text{Serum glucose} / 18\right) + \left(\text{Serum BUN} / 2.8\right)$$

The HPA axis is one of the major organ systems regulating sodium balance and serum osmolality. Serum osmolality is sensed by osmoreceptors in the organum vasculosum of the lamina terminalis (OVLT), located in the portion of the hypothalamus outside of the blood-brain barrier. Changes in osmolality of as little as 1 % are sensed by the osmoreceptors, which send projections to the supra-optic (SON) and para-ventricular (PVN) hypothalamic nuclei. The SON and PVN synthesize anti-diuretic hormone (ADH) and send projections to the posterior pituitary. These projections in the posterior pituitary release ADH into systemic circulation. ADH acts on the medullary collecting duct of the nephron, and causes increased water absorption. This increase in water absorption leads to a subsequent decrease in serum sodium concentration, thus driving down serum osmolality.

The other major system regulating sodium balance is the renin-angiotensin system (RAS). Decreased sodium delivery to the macula densa triggers the synthesis and release of renin from the juxtaglomerular apparatus. Renin converts angiotensinogen to angiotensin I, which is then rapidly converted into angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II acts directly on the vasculature to increase systemic vascular resistance (SVR), increase ADH release, and stimulate the release of aldosterone from the zona golmerulosa of the adrenal cortex. Aldosterone acts on the distal tubules and collecting ducts of the nephron to increase the reabsorption of water and sodium, and increase the secretion of potassium. Abnormalities in either of these systems – HPA or RAS – can lead to disorders of sodium homeostasis.

Hyponatremia

Given that sodium and serum osmolality are tightly linked, and that osmolality is influenced by relative volume status, disorders of sodium homeostasis are categorized by intravascular volume status. Hyponatremia can occur in the context of intravascular hyper-, hypo-, or euvolemia, and patients' intravascular volume status must be evaluated in order to diagnose the underlying cause of the hyponatremia.

Hypovolemic causes are due to the loss of both sodium and total body water as occurs with profuse sweating, prolonged vomiting or diuretic use. A rare cause of hypovolemic hyponatremia is cerebral salt wasting syndrome (CSW). CSW is typically seen in the context of head trauma, or intracranial lesion, and is characterized by decreased renal sodium retention, polyuria, and dysautonomia. Treatment of hypovolemic hyponatremia is mainly supportive and aimed at fluid and electrolyte replacement. Fludrocortisone can be used to increase renal sodium reabsorption. Most cases typically resolve spontaneously within 2–4 weeks, although a few persist longer.

Hypervolemic hyponatremia is due to increased total body water, and typically occurs in the context of decreased effective serum osmolality, and is often associated with peripheral edema. Common etiologies include heart failure, nephrotic syndrome, and liver disease with associated ascites. In these states, plasma osmolality is decreased and oncotic pressure is unable to retain volume in the intravascular space. This leads to decreased effective circulating volume and the body responds by increasing water reabsorption, further decreasing serum osmolality. Treatment for these causes is aimed at the underlying etiology, and usually includes fluid restriction. A new class of medication, the

vaptans, act as vasopressin antagonists and may find clinical use in some of these disease states.

Euvolemic hyponatremia is typically caused by either presence of osmotically active molecules (pseduohyponatremia) or excess secretion of ADH. Pseudohyponatremia occurs when hyperosmolarity from non-sodium osmotically active agents (glucose, triglycerides, immunoglobulins) draws water from the intracellular compartment into the intravascular space with subsequent dilution of sodium content. Syndrome of Inappropriate Anti-Diurectic Hormone (SIADH) is the paradigm for euvolemic hyponatremia, and is seen in a wide array of clinical conditions ranging from intracranial abnormalities to various tumors. SIADH is characterized by inappropriately elevated levels of ADH in the absence of a physiologically appropriate stimulus (i.e. hypotension or hypotonicity). The hallmark of SIADH is inappropriately concentrated urine relative to plasma osmolality. As discussed, one of the physiologic effects of ADH is water retention and these patients develop a pure water excess. Water is not confined to one fluid compartment, it distributes equally throughout all of them, thus these patients appear clinically euvolemic. Classically, water restriction has been the mainstay of SIADH treatment. In cases where water restriction is poorly tolerated, demeclocycline has been used. Demeclocycline is a tetracycline analogue that inhibits vasopressin mediated water reabsorption in the collecting duct. The new class of vasopressin inhibitors, the Vaptans, promises to radically alter the treatment of SIADH.

The deleterious physiologic effects of hyponatremia develop when sodium levels drop enough to significantly lower plasma tonicity, leading to a shift of water into the intracellular space. This leads to cellular dysfunction, particularly in the CNS and accounts for the clinical manifestations of confusion, coma and seizures. In cases of symptomatic hyponatremia, sodium repletion maybe given either orally, or in the form of concentrated 3 % saline. Correction must be gradual, so as to avoid neurologic devastation through central pontine myelinosis, which results from the rapid shift of water out of the intracellular space in the CNS. Plasma sodium concentration should not be raised by more than 0.5 mmol/L/h, and no more than 10 mmol/L in 24 h.

Hypernatremia

Hypernatremia leads to an increase in serum osmolality, with a subsequent shift of water out of the intracellular compartment and cellular dysfunction. As with hyponatremia, the CNS is particularly sensitive to these shifts and patients with symptomatic hypernatremia typically present with weakness, confusion and lethargy. In contrast to hyponatremia, hypernatremia is almost always a result of water loss in excess of sodium loss rather than excess sodium intake relative to water intake. As such, these patients are typically hypovolemic.

Most commonly, hypernatremia occurs via either evaporative losses or by excretion of large volumes of very dilute urine. Evaporative, or insensible losses result from evaporation of pure water from the respiratory tract or other exposed mucosal surfaces. These losses are highly variable and are increased by patients who are febrile, tachypnic, or in warm environments. Surgical procedures that expose large body cavities to room air greatly increase the surface area for evaporative loss, and can cause losses triple to those under normal environmental conditions. The loss of large volumes of dilute urine is characteristic of diabetes insipidus (DI). DI results from either a lack of vasopressin release from the posterior pituitary, or lack of renal response to circulating vasopressin. Patients with DI who are able to regulate their water intake typically do not develop hypernatremia, as their input matches their output. However, patients who are unable to do so can rapidly develop hypernatremia and dehydration.

Treatment of hypernatremia depends on the underlying cause. In patients with central DI, a synthetic vasopressin analogue, desmopressin or DDAVP, is the treatment of choice. DDAVP lacks the hypertensive effects of vasopressin and can be given nasally, intravenously, or orally. In patients with nephrogenic DI, thiazide diuretics have a paradoxic anti-diuretic effect and are the treatment of choice if the underlying cause cannot be reversed. In patients who are hypernatremic secondary to free water loss, the correction of the free water deficit results in correction of the hypernatremia. Free water deficit can be calculated from the following equation:

$$\begin{aligned}\text{Deficit} = \text{TBW}\left(1 - \left[140 / \text{Plasma Na} + \right]\right) &\text{where TBW} \\ &\text{is total body water}\left(\text{L}\right)\text{estimated at} 0.5\times \\ &\text{lean body weight for women and} \\ &0.6\times\text{lean body weight for men.}\end{aligned}$$

Rapid correction of hypernatremia can lead to cerebral edema, therefore no more than half of the deficit should be replaced in the first 24 h of treatment. The remainder can be corrected in the following 24–48 h. Chronic hypernatremia is remarkably well tolerated secondary to compensatory changes which occur at the cellular level. These changes involve intracellular production of osmotically active substances to offset the extracellular hypertonicity.

Potassium

Potassium is the second most common cation in the body following sodium. Ninety-eight percent of the total body potassium content is contained intracellularly. The significant gradient in potassium concentration across the cell membrane leads to a negative electric charge in the intracellular space. This charge, known as a resting membrane potential, is necessary for the proper functioning of excitable tissues such as muscle and nerve. This gradient is maintained by active ion transport pumps located in the cellular membrane, which can account for up to 2/3 of a cell's total energy expenditure. Small changes in extracellular potassium concentration can lead to dysfunction of excitable tissue with potentially catastrophic consequences. Maintenance of potassium homeostasis is accomplished at both the cellular and organ system level; shifts of potassium into and out of cells buffers against acute changes in extracellular potassium, while the renal system maintains a balance between potassium intake and excretion. Multiple disease states affect these systems and can lead to disorders of potassium regulation.

Hyperkalemia

Hyperkalemia maybe classified by duration of the insult as either acute (<48 h) or chronic. Acute hyperkalemia is almost always caused by a shift of potassium out of cells, but rarely can be caused by an excessive intake of potassium. A transcellular shift of only 2 % of intracellular K+ would cause serum K+ levels to double. Dramatic transcellular shifts of potassium are often associated with cell death, such as tumor lysis syndrome or rhabdomyolysis. A metabolic acidosis also results in a transcellular shift of potassium, as H+ displaces K+ from the intracellular compartment. Certain medications are also associated with transcellular shifts of potassium, notably digitalis and succinylcholine. Under normal circumstances, succhinycholine induced fasculations cause a small amount of K+ to leak from muscle. This small leak causes an increase in serum K+ by about 0.5 mmol/L. However, in patients

with prolonged immobilization or paralysis, severe burns, or muscle inflammation this K+ leak can be significantly larger, with potentially fatal consequences. These diseases are associated with proliferation of immature forms of the AchR outside of the motor end plate. These extra receptors are activated by succinylcholine, resulting in more potassium being release from the cells than under normal circumstances. Excessive potassium intake is almost always iatrogenic, as can occur with overly aggressive oral or IV potassium replacement therapy. Banked blood contains a small amount of potassium, however massive transfusions can lead to accumulation of large amounts of potassium and cause symptomatic hyperkalemia. Causes of chronic hyperkalemia include renal failure, Addison's disease, and both aldosterone deficiency and tubular unresponsiveness to aldosterone. Hyperkalemia causes depolarization of cardiac myocytes resulting in dysrhythmias and impaired conduction disorders. Classic EKG changes associated with progressive hyperkalemia include (in order of their appearance): peaked T waves, prolongation of the PR interval, widening of the QRS complex, loss of P wave, "sine wave" appearing ventricular fibrillation, and finally asystole. Hyperkalemia is also associated with paresthesias and skeletal muscle weakness progressing to a flaccid paralysis. Therapy for hyperkalemia is aimed primarily at stabilizing the cell membranes of excitable tissues. Once this has been achieved, therapy is guided towards redistribution of K^+ into cells and enhanced elimination of K^+ from the body. Calcium directly antagonizes the myocardial effects of hyperkalemia and is the treatment of choice for membrane stabilization. Redistribution of potassium into cells can be accomplished by both insulin and albuterol. A dextrose infusion should be started to counteract the hypoglycemic effects of insulin therapy in these patients. Increased elimination of potassium from the body can occur via either the renal or GI route. Renal elimination of potassium is increased by increased flow through the distal nephron, typically accomplished by administration of saline, and is enhanced by loop diuretics. GI losses of potassium are increased by the administration of sodium polystyrene sulfonate (SPS). SPS is a cation exchange resin that exchanges sodium for secreted potassium in the colon. SPS causes constipation and should be given with a cathartic. Cases of colonic necrosis have been reported following administration of SPS, with an estimated incidence of 1.8 % in post-operative patients according to a retrospective analysis. Hemodialysis can also be used to enhance potassium elimination.

Hypokalemia

As with hyperkalemia, hypokalemia may be classified according to duration as either acute (<48 h) or chronic. Acute changes are almost always caused by transcellular shifts of potassium into cells. This inward shift is often seen with treatment of DKA secondary to insulin therapy, and can also be seen in re-feeding syndrome due to increased endogenous insulin production. Other medications, such as β2-agonists, also cause a shift of potassium into cells and can cause acute hypokalemia. Chronic hypokalemia is usually the result of either decreased intake or increased elimination. Elimination can occur from either the GI or renal route. Renal losses of potassium are increased by diuretics, various antibiotics, and mineralcorticoids. Hypomagnesemia is also associated with renal K+ wasting, and often must be repleted along with potassium. Various inborn tubular transport abnormalities, such as Barter, and Gitelman's syndromes are also associated with increased renal losses of K+ and hypokalemia. Hypokalemia leads to cell membrane hyperpolarization, and can cause cardiac arrhythmias and conduction defects. Non specific EKG changes include ST segment depression, T wave flattening and prominent U waves. Neuromuscular signs include weakness, muscle fatigue and myalgias. Treatment of hypokalemia involves replacement of the body deficit and correction of underlying cause when able. Potassium may be given either orally or IV. If given IV, potassium should be administered over 1–2 h to avoid causing a hyperkalemia. Serum potassium levels peak immediately following an infusion, and over the next 2–3 h decrease to the new steady state. Repeat measurements of serum potassium should be taken after the new steady state has been achieved to further guide therapy.

Chloride

Chloride is the predominant anion in the extracellular fluid. As mentioned above, electroneutrality is maintained at all times; that is, the concentration of cations and anions is equal and charges offset. As such, changes in chloride concentration significantly effect the concentration of other anions such as bicarbonate, lactate and other organic acids. Many of these other anions take part in the buffering of serum H+ concentration and help determine plasma pH. Due to the interplay of chloride and other serum anions, chloride physiology and acid base balance are closely related and interdependent.

An example of this sort of interdependence can be seen in patients who have been resuscitated with large volumes of normal saline. 0.9 % normal

saline contains 154 meq of sodium and 154 meq of chloride compared to a normal serum chloride concentration of approximately 100 meq. This increase in serum chloride causes a reciprocal decrease in other serum anions, notably bicarbonate. As serum bicarbonate levels decrease, there is a concomitant increase in unbuffered serum H+ concentration and serum pH decreases resulting in an acidosis. The role of chloride physiology and acid-base balance will be further discussed in the next section.

Introduction to Acid Base Physiology

The tight control of extracellular hydrogen ion concentration is of paramount importance to the function of trans-membrane ion transport pumps and intracellular biochemical reactions. As such the body has developed numerous weak acid buffer systems to maintain a homeostatic pH between 7.35 and 7.45. Deviations in pH beyond this zone are termed acidemia (pH <7.35) and alkalemia (pH >7.45). The presence of acidemia or alkalemia indicates gross metabolic or respiratory abnormalities, which if uncorrected, may lead to end organ dysfunction and death.

Acid-Base balance is a complex physiochemical process. Two different approaches can be used to explain acid-base interaction: anion gap/base excess and strong ion difference (Stewart approach). The Stewart approach introduced by Peter Stewart in 1981 emphasizes two important elements of physical chemistry as the driving forces for acid base balance: electroneutrality and conservation of mass. The primary tenant of Stewart's approach is that serum bicarbonate does not alter blood pH. According to Stewart's theory, pH is the result of the interplay of three variables: Strong Ion Difference (SID), $PaCO_2$, and plasma concentration of weak non-volatile acids such as albumin and phosphate (Atot). The SID equals the difference between completely dissociated cations and anions in plasma. The equation for SID consists of the most abundant ions in plasma and is calculated as such:

$$\begin{aligned} SID = &\left(\left[Na^+\right]+\left[K^+\right]+\left[Ca^{2+}\right]+\left[Mg^{2+}\right]\right) \\ &-\left(\left[Cl^-\right]+\left[Lactate^-\right]\right) = 40-44\ \text{mEq} \end{aligned}$$

Processes that increase the SID cause an alkalemia, whereas processes that reduce it cause acidemia. For example, the loss of gastric fluid, which has a high concentration of Cl^-, increases the SID and thus leads to alkalemia; by comparison, infusion of sodium chloride, a solution with equal parts Na^+ and Cl^- thus an SID of zero, reduces the SID and causes an acidemia.

The anion gap approach is based on the Bronsted–Lowry definition of an acid in which the primary extracellular buffer system is the equilibrium of carbonic acid and bicarbonate represented by the equation below.

$$H_20 + CO_2 <--> H_2CO_3 <--> H^+ + HCO3^-$$

The Henderson–Hasselbach equation describes the relationship between this equilibrium equation and pH as such:

$$pH = pK + \log_{10}\left(HCO_3^- / \alpha_{CO2} \times pCO_2\right)$$

In this equation α_{CO2} represents the solubility coefficient of CO_2 (0.03) and pK represents the equilibrium constant (6.1). A derivative of this equation, known as the Henderson equation, simplifies matters as such:

$$H^+ = 24 \times pCO_2 / HCO_{3^-}$$

From this equation, it is evident that changes in pH may be either the result of a change in pCO_2 (referred to as respiratory) or HCO_3^- (referred to as metabolic). There is much emerging evidence of the likely clinical utility of the Stewart approach and while understanding both approaches is ultimately important, due to its simplicity and widespread use, the anion gap approach will be discussed in this chapter.

Maintenance of homeostatic concentrations of CO_2 and HCO_3^-, including compensatory responses to insult, is a result of the interplay of the pulmonary and renal systems. Consequently, metabolic disturbances are accompanied by a respiratory compensation and visa versa. Compensation results in normalization of pH and can give some indication as to the duration of the insult, with chronic processes being better compensated. Attention must be paid to compensation, as multiple acid-base abnormalities can co-exist in the same patient, which are diagnosed by comparison of anticipated and actual compensatory changes. More than one metabolic abnormality may be present in a patient at one time, however, only one respiratory disturbance is possible at any given moment.

The introduction of blood-gas analysis in the 1950s allowed for the diagnosis and categorization of acid-base derangements and their subsequent treatment. The relatively low cost and ease of collection have led to the use of blood gas analysis in everyday anesthetic practice. Typical blood gas values include pH, pO_2, pCO_2, HCO_3^-, and base excess. Base excess is defined as the amount

Table 14.1 Acid-base disturbances and the expected compensation

Primary disorder	Primary change	Compensatory change	Expected compensation
Metabolic acidosis	↓ HCO_3	↓ $PaCO_2$	$\Delta PaCO_2 = 1.2 * \Delta HCO_3$
Metabolic alkalosis	↑ HCO_3	↑ $PaCO_2$	$\Delta PaCO_2 = 0.9 * \Delta HCO_3$
Respiratory acidosis	↑ $PaCO_2$	↑ HCO_3	*Acute:* $\Delta HCO_3 = 0.1 * \Delta PaCO_2$ *Chronic:* $\Delta HCO_3 = 0.35 * \Delta PaCO_2$
Respiratory alkalosis	↓ $PaCO_2$	↓ HCO_3	*Acute:* $\Delta HCO_3 = 0.2 * \Delta PaCO_2$ *Chronic:* $\Delta HCO_3 = 0.5 * \Delta PaCO_2$

of strong acid (if BE >0) or strong base (if BE <0) which is required to return 1 L of whole blood at a pCO_2 of 40 mmHg to a pH of 7.4. In theory, the base excess represents the metabolic component of an acid base disorder with positive values indicative of a metabolic alkalosis and negative values indicative of a metabolic acidosis. The deviation of BE from 0 can be used as a surrogate measure of severity of the metabolic derangement, with more severe disturbances resulting in values further from zero. Classical blood gas measurements allow for diagnosis of acidemia and alkalemia with levels of compensation as seen in Table 14.1. Further diagnosis and classification necessitates serum electrolytes, hemoglobin and serum lactate concentrations, which are available on most modern blood gas machines.

Metabolic Abnormalities

Metabolic Acidosis

Any process that causes a reduction in the extracellular bicarbonate concentration, via increased loss of bicarbonate or via accumulation of excess acid, is termed a metabolic acidosis. Multiple abnormalities can lead to a metabolic acidosis, and these are grouped according to whether or not they lead to an associated increase in the serum anion gap. The serum anion gap is calculated by the following equation:

$$AG = \left(\text{Serum } Na^+ + \text{Serum } K^+\right) - \left(\text{Serum } HCO_{3^-} + \text{Serum } Cl^-\right)$$

A normal value for anion gap is between 8 and 12 mmol/L and represents the concentration of anions normally unmeasured by a basic metabolic panel

Table 14.2 Causes of non-anion gap metabolic acidosis: HARD-UP

Hyperalimentation
Acetazolamide administration
Renal tubular acidosis
Diarrhea
Ureteroenteric fistula
Pancreaticoduodenal fistula

Table 14.3 Causes of high anion gap metabolic acidosis: MUD PILES

Methanol intoxication
Uremia
Diabetic ketoacidosis
Propylene glycol toxicity
Isoniazid toxicity
Lactic acidosis
Ethylene glycol intoxication
Salicylate toxicity

such as albumin, phosphates, sulfates and organic anions. Due to the large contribution of albumin, the anion gap varies significantly with serum concentration of albumin. Each 1.0 g/dL decrease or increase in serum albumin from 4.4 g/dL results in a corresponding increase or decrease in the anion gap approximately 2.3–2.5 meq/L. Consequently, hypo- or hyper- albuminemia must be considered when calculating anion gap. In a metabolic acidosis with decreased serum bicarbonate, serum electroneutrality is maintained by a compensatory increase in either serum chloride or unmeasured anions present in the anion gap. If electroneutrality is maintained by increasing chloride concentrations, the anion gap remains normal and we refer to the process as a "non anion gap metabolic acidosis" or "hyperchloremic metabolic acidosis". Causes of a non-anion gap metabolic acidosis are outlined in Table 14.2. If, however, electroneutrality is maintained by increasing unmeasured serum anions, the anion gap increases. We refer to this process as a "high anion gap metabolic acidosis" or "hypochloremic metabolic acidosis". Causes of a high anion gap metabolic acidosis are outlined in Table 14.3. It should be noted that

the terms "hypochloremic" and "hyperchloremic" are not in relation to normal laboratory values, but rather in relation to relative ionic composition of the plasma. It is possible to see a non-anion gap metabolic acidosis with a normal serum chloride.

Acidemia leads to cellular and enzymatic dysfunction with multiple deleterious effects including a decrease in cardiac output, hypotension and decreased binding of epinephrine to adrenergic receptors. Several physiologic mechanisms have developed which serve to correct plasma pH. The increase in plasma H^+ is sensed by the carotid bodies, which in turn stimulate the medullary respiratory center to increase minute ventilation and decrease pCO_2. The decreased plasma pH is also sensed by the kidneys, which respond by increasing H^+ secretion in the distal nephron. These compensatory changes take approximately 12–24 h to complete, and can be estimated by Winter's formula:

$$\text{Compensated}\, pCO_2 = 1.5 \times \left[HCO_3^- \right] + 8$$

If the pCO_2 is less than that predicted by Winter's formula, a secondary respiratory alkalosis is present. Similarly, a secondary respiratory acidosis would be indicated by a pCO_2 higher than that predicted by Winter's formula.

Treatment of metabolic acidosis is aimed at correction of the underlying cause. As such, accurate diagnosis of cause is essential. Debate exists as to whether or not correcting the acidemia is necessary. Current guidelines suggest correction of pH less than 7.10 until the underlying process can be corrected. Classically this has been done with sodium bicarbonate to replace the whole body deficit of bicarbonate. However, the volume of distribution for bicarbonate varies significantly with the degree of acidemia from between 50 % and 100 % total body water volume, which makes accurate dosing difficult. Recently the use of sodium bicarbonate as an alkalinizing agent has come under scrutiny. Several studies have demonstrated a lack of benefit, and in some populations increased mortality with the use of sodium bicarbonate to treat acidosis. Numerous adverse physiologic effects can occur from infusing sodium bicarbonate, although no single cause seems to be at fault. Sodium Bicarbonate is usually infused as a hypertonic solution. A 50 mL ampule containing 50 meq of sodium bicarbonate (1000 mmol/L) will raise the serum sodium concentration of a 70 kg person by about 1 meq/L and expand the ECF volume by about 250 mL. In addition, the infused bicarbonate will combine with plasma H+ and dissociate into CO2 and H_2O. In patients with impaired ventilatory

function this will lead to a respiratory acidosis. Alternative alkalinizing agents exist, such as the amino alcohol THAM. The buffering action of THAM does not generate CO_2, and has been used successfully for the treatment of various metabolic acidosis. It is excreted by the kidneys and should be dosed with caution in patients with renal insufficiency. Reported toxicities of THAM include hyperkalemia, hepatic necrosis in neonates, and respiratory depression secondary to an increase in pH and subsequent decrease in CNS CO_2.

Metabolic Alkalosis

Any process that leads to an accumulation of extracellular bicarbonate, via either decreased excretion of bicarbonate or increased loss of non-volatile acid, is termed a metabolic alkalosis. Non-volatile acids are lost either via the upper GI tract (vomiting, naso- or oro-gastric suctioning) or via increased urinary excretion. The kidney is able to excrete large amounts of bicarbonate in response to an alkalosis, thus maintenance of an alkalosis is due to an underlying disease state. These disease states can be grouped into either volume expanded or volume contracted states Table 14.4. Volume contraction reduces cardiac output and subsequently GFR. The reduced GFR leads to decreased chloride delivery to the distal nephron, therefore the $Cl–/HCO_3–$ counter-exchange pumps are unable to excrete $HCO_3–$. Furthermore, in response to the hypovolemia, aldosterone levels are increased which causes increased urinary H+ secretion.

Alkalemia is associated with a variety of negative physiologic effects. The affinity of hemoglobin for oxygen is acutely increased, resulting in a right shift of the oxygen-hemoglobin dissociation curve. This leads to impaired oxygen delivery to peripheral tissues. The increased pH causes a decrease in the

Table 14.4 Causes of metabolic alkalosis

Volume contracted state
Loss of gastric secretions: excessive NGT suctioning or vomiting
Loss of intestinal secretions: villous adenoma, congenital secretory diarrheas
Loop or thiazide diuretics
Sweat losses in cystic fibrosis
Volume expanded states
Primary mineralcorticoid excess
Liddle's syndrome

ionized concentration of calcium. This relative hypocalcemia can cause some of the classic clinical manifestations such as paresthesias and tetany. Other electrolyte abnormalities are seen, such as hypokalemia and hypomagnesemia. The compensation for a metabolic alkalosis is a decrease in ventilation with subsequent rise in pCO_2. Appropriate compensation can be calculated by the following equation:

$$pCO_2 = 0.9 \times \left[HCO_{3^-} \right] + 9$$

Once the underlying mechanism responsible for the alkalosis has been identified, treatment is aimed at correction of the metabolic abnormalities. Treatment of choice for the hypovolemic causes is IV rehydration, preferably with normal saline. Attention must be paid to potassium and calcium hemostasis so as not to worsen existing electrolyte abnormalities. If upper GI losses cannot be controlled, starting an H2 blocker or PPI may be warranted to decrease acid loss. In patients with decreased effective circulating volume, or volume overload, saline resuscitation is not warranted and could be catastrophic. In some cases, acetazolamide can be used to increase renal bicarbonate wasting. Attention must be paid to serum potassium concentrations if acetazolamide is used, as renal potassium wasting also increases. In states of mineralcorticoid excess, spironolactone can be used to antagonize the effects of aldosterone until surgical correction can be obtained. Spironolactone is considered a potassium sparing diuretic, and the potential for hypokalemia is less than with acetazolamide. Infusions of HCl have been used successfully to correct pH in cases of severe, refractory metabolic alkalosis. These infusions must be given slowly via central line with frequent lab measurements to avoid creating an iatrogenic metabolic acidosis.

Respiratory Abnormalities

Respiratory Acidosis

Any process that leads to an increase in pCO_2 due to an imbalance in alveolar minute ventilation and carbon dioxide production is termed respiratory acidosis. A respiratory acidosis may be caused by increased production of CO_2 with insufficient respiratory compensation, or decreased minute ventilation with normal production of CO_2. A third cause unique to the ventilated patient is rebreathing of exhaled CO_2 in the ventilator circuit. Respiratory acidosis is classified as either acute or chronic which can be determined by a large extend

by the degree of compensation. As previously stated, respiratory abnormalities are compensated via metabolic mechanisms. In the case of a respiratory acidosis, the compensation is by increased renal HCO_3^- reabsorption. During the acute phase of a respiratory acidosis, the kidneys are able to raise serum HCO_3– by approximately 1 meq/L for each 10 mmHg rise in pCO_2 above 40. Over time, the kidneys are better able to compensate and can raise plasma HCO_3– by approximately 3.5 meq/L for every 10 mmHg rise in pCO_2. Serum HCO_3– levels not consistent with expected levels of compensation indicate concurrent metabolic abnormalities.

Elevated CO_2 is associated with numerous systemic effects across multiple organ systems. Carbon dioxide is a direct myocardial depressant and acts directly on the vasculature to decrease overall tone. This is offset by increased sympathetic output, which results in elevated heart rate and net increase in cardiac output. Hypercapnia results in a rightward shift of the oxygen-hemoglobin dissociation curve and facilitates oxygen unloading in peripheral tissues. In the central nervous system, hypercapnia results in cerebral vasodilation, which increases cerebral blood flow and ICP. This can be an important consideration in patients with pre-existing elevated ICP or space occupying lesions. In the lungs, hypercapnia results in vasoconstriction and dilation of the small airways. In cases of severe hypercapnia (pCO_2 >90 mmHg), carbon dioxide displaces oxygen in the alveoli resulting in hypoxia, which can be fatal unless FiO_2 is increased.

As with the metabolic abnormalities, treatment of a respiratory acidosis should be aimed at the underlying cause. Occasionally intubation and mechanical ventilation are necessary as temporizing measures until the underlying cause has been reversed. Care must be exercised in patients with long standing respiratory acidosis with metabolic compensation. Increased ventilation and CO_2 elimination in these patients may lead to a relative hypocapnea and resultant metabolic alkalosis.

Respiratory Alkalosis

Any process that leads to a reduction in pCO_2, from increased alveolar minute ventilation relative to production, will result in a respiratory alkalosis. Most often this is secondary to increased alveolar minute ventilation but rarely may be due to decreased production of carbon dioxide with unchanged minute ventilation, such as the hypothermic mechanically ventilated patient. Similarly to a respiratory acidosis, a respiratory alkalosis can be classified as either acute or

chronic given the degree of metabolic compensation. In an acute respiratory alkalosis, every 10 mmHg drop in pCO_2 from 40 is accompanied by a 2 meq/L decrease in serum bicarbonate. A chronic respiratory alkalosis is expected to be compensated by a 5 meq/L decrease in serum bicarbonate for every 10 mmHg drop in pCO_2 from 40. This metabolic compensation is accomplished by decreased renal reabsorption of bicarbonate from the proximal renal tubule and an increase in ammonia excretion. This renal compensation begins within 2 h of a prolonged alkalosis, but is not maximally effective for 2–3 days.

The physiologic effects of decreased pCO_2 inversely correlate to those of an increase in pCO_2. Perhaps the most clinically significant effect of decreased pCO_2 is its effect on cerebral vascular tone. A decrease in pCO_2 results in cerebral vasoconstriction and a subsequent reduction in cerebral blood volume and ICP. In patients with TBI, CBF changes approximately by 3 % for each millimeter of mercury change in $PaCO_2$ over the range of 20–60 mmHg. This can cause a significant reduction in ICP, as a 0.5 mL change in CBF is associated with a 1 mmHg change in ICP. This effect is transient, though, as cerebral vasculature resets to the elevated CO_2. Current consensus does not recommend iatrogenic lowering of $paCO_2$ lower than 30 mmHg due to the increased risk of cerebral ischemia and lack of demonstrable clinical benefit. In addition to changes in CBF, other metabolic derangements occur as well. The decreased serum H+ leads to translocation of H+ from the intracellular to the extracellular space with a concurrent translocation of K+ from extracellular to intracellular space. This relative intracellular alkalosis causes activation of the enzyme phosophofructokinase and increase in glycolysis with generation of H+.

Treatment of the alkalosis is aimed at reversal of the underlying cause. In rare cases intubation and controlled mechanical ventilation may be necessary. However, in cases of chronic metabolic alkalosis correction must be done in a controlled manner allowing for renal compensation, lest a metabolic acidosis result from too rapid of correction.

Evaluating Multiple Disorders

It is not uncommon for multiple acid-base abnormalities to co-exist in the same patient. Diagnosis of these occult disorders requires knowledge of not only the expected direction, but also the expected magnitude of compensatory responses. The interplay of these complex interactions can be explained numerically as follows: in the absence of other metabolic derangements, the fall in the serum HCO_3 should equal the rise in the serum anion gap. We refer

to the difference between changes in serum anion gap and serum HCO_3 as the "Delta Gap." There have been multiple ways to approach this calculation, but one simple way is as follows:

$$\text{Delta Gap} = (\text{Anion Gap}) - (\text{Serum } HCO_3),$$
$$\text{where Anion Gap} = AG_{\text{measured}} - AG_{\text{normal(12)}}$$
$$\text{and Serum } HCO_3 = 24 - HCO_{3\text{measured}}.$$

If the Delta Gap is significantly positive (> +6), a concurrent metabolic alkalosis is usually present because the rise in anion gap is more than the fall in HCO_3. Conversely, if the Delta Gap is significantly negative (< −6), then a second acidosis is present because the rise in anion gap is less than the fall in HCO_3. This is usually a hyperchloremic metabolic acidosis. For example, 3 h into the operation, a blood gas shows an anion gap of 25 and a serum HCO_3 of 18. The Δ Anion Gap is 13 (25−12 = 13) and the Δ Serum HCO_3 is 6 (24−18 = 6), thus the delta gap is 7 (13−6 = 7). Therefore, for this patient we know in addition to the high anion gap metabolic acidosis, a concurrent metabolic alkalosis exists, as the serum HCO_3 would be expected to be lower if the alkalosis were not present.

In conclusion, an in-depth understanding of electrochemical and acid-base homeostasis is very important in the care of the surgical patient. The application of these principles ranges from acute resuscitation of a patient in various forms of shock to perioperative planning for an otherwise healthy patient undergoing major surgery.

Case Study

A 34-year-old man is scheduled to come to your OR for emergent exploratory laparotomy. He presented to the emergency department complaining of abdominal pain for the past 18 h following a 1-day history of diarrhea. His past medical history is significant for insulin-dependent (Type 1) diabetes, ethanol abuse, and poor medical adherence. On physical exam he has dry mucous membranes, a fruity odor to his breath, and has slurred speech. He is guarding his abdomen. Vital signs are: HR: 120, BP: 101/74, RR: 20, SpO2: 99 % on room air, Temp: 101.4 F

What laboratory evaluation would you order preoperatively? Why?
Given the history of diabetes, poor medical adherence, and 2 days of fluid losses and likely little or no oral intake, it is likely that he has some metabolic derangements. You should order a metabolic panel, a complete blood count, and probably a serum or urine ketone test. If you suspect an acid/base disturbance, a blood gas is also needed.

Laboratory values are returned and are shown below. What metabolic disturbance is likely responsible for these values?

Sodium: 134 mmol/L
Chloride: 110 mmol/L
Potassium: 4 mmol/L
Bicarbonate: 13 mmol/L
BUN: 36 mg/dL
Creatinine: 1.10 mg/dL
Glucose: 284 mg/dL

WBC: 21 × 103/mcL
Hemoglobin: 16 g/dL
PCV: 48 %
Platelet: 200 × 103/mcL
MCV: 104 fL
RDW: 16 %

Serum Beta-hydroxybutyrate: 4 mg/dL

ABG: pH 7.21/pCO2 28 mmHg/pO2 99 mmHg/HCO2 13 mmol/L

This patient is in diabetic ketoacidosis (DKA) as confirmed by his hyperglycemia, serum ketones, and acidemia present on ABG. DKA usually presents in patients with IDDM who have a concurrent illness and/or poor insulin regimen adherence.

What acid base abnormalities are present? Is there more than one? Are they appropriately compensated?
The low pH, low bicarbonate and low pCO_2 point to a metabolic acidosis with respiratory compensation. To evaluate the etiology of the metabolic acidosis, we must first calculate the ion gap.

$$\left(\text{Serum Na}^{+} + \text{Serum K}^{+}\right) - \left(\text{Serum HCO}_{3^{-}} + \text{Serum Cl}^{-}\right)$$
$$= (134 + 4) - (13 + 110) = 15$$

As the normal anion gap is 8–12, there is a high anion gap metabolic acidosis present. To determine whether or not we have appropriate compensation, we will use Winter's formula to calculate what his pCO_2 should be.

$$pCO_2 = 1.5 \times \left[\text{HCO}_{3^{-}}\right] + 8 = (1.5 \times 13) + 8 = 27.5$$

This is very close to the measured value of 28, so appropriate respiratory compensation has occurred. To determine whether or not multiple acid base abnormalities are present, we must calculate the delta-gap for this patient.

$$\text{Delta Gap} = (\text{Anion Gap}) - (\text{Serum HCO}_3)$$

$$\text{Anion Gap} = \text{AG}_{\text{measured}} - \text{AG}_{\text{normal(12)}}$$
$$\text{and} \quad \text{Serum HCO}_3 = 24 - \text{HCO}_{3\text{measured}}$$

$$\text{DG} = (15 - 12) - (24 - 13) = -8$$

If a single acid base disturbance is present, the delta gap should be 0+/−6. The delta gap in this case is significantly negative, which is to say we would expect the change in the anion gap to be larger given the change in the serum bicarbonate. Consequently, in addition to a high-anion gap metabolic acidosis, we can also conclude that a non-anion gap metabolic acidosis is present.

What is the likely etiology of the second metabolic acidosis?
The patient demonstrates a combined high-anion gap and non-anion gap metabolic acidosis with appropriate respiratory compensation. His high anion gap acidosis is likely secondary to his DKA, and his non-anion gap acidosis is likely secondary to his diarrhea. In diarrhea, bicarbonate is lost and acidemia occurs; depending on the fluids administered subsequently, chloride may also increase ("hyperchloremic acidosis").

He is started on an insulin infusion and taken to the OR. 15 min into the case he has received 500 mL of normal saline, and the operation is under way. You look up at the ECG and notice ST-segment depression and flattening of the T wave. What is the most likely diagnosis and appropriate treatment?

The patient has most likely developed hypokalemia, which has manifest as ST segment depression and T wave flattening. U waves may also be seen in cases of severe hypokalemia. Patients with DKA may present with normal serum potassium, however they often have a total body potassium deficit. This is due to the transcellular shift of potassium caused by the acidosis and resultant osmotic diuresis from the elevated plasma glucose. This deficit is revealed with the re-introduction of insulin, which stimulates the membrane bound Na^+/K^+-ATPase and causes an intracellular shift of potassium. Treatment is hydration (ideally prior to insulin administration) and repletion of potassium; in severe cases it may be necessary to temporarily pause the insulin infusion.

Halfway through the case, a serum osmolality value is reported by the lab at 340 mosmol/kg. How do you interpret this result? Is this consistent with the calculated serum osmolality?

Calculated serum osmolality is given by the equation:

$$\text{Serum Osmolality} = \left(\text{Serum } Na^+ \times 2\right) + \left(\text{Serum glucose} / 18\right) + \left(\text{Serum BUN} / 2.8\right)$$

In this case: $\left(134 * 2\right) + \left(284 / 18\right) + \left(36 / 2.8\right) = 297$.

Therefore, we can say that an osmolal gap exists in the amount of 43 mosm/kg. An osmolar gap can occur by one of two mechanisms: either an osmotically active solute other than electrolytes, glucose or urea is present, or pseudohyponatremia. In the case of an unmeasured osmotically active solute, the serum osmolality is actually increased and the measured value is the correct value. In the case of pseudohyponatremia, the measured osmolality is spuriously reduced by the presence of increased lipids or proteins (such as triglycerides or immunoglobulins), which reduce the fraction of serum that is water. This represents a measurement artifact and the calculated serum osmolality is the correct osmolality. Osmolar gaps are

important to calculate, particularly in the case of high anion gap metabolic acidosis, as potential causes include toxic alcohols and glycols, which will cause a serum osmolar gap. The most common cause is acute ethanol ingestion, the contribution of which can be estimated by dividing the serum ethanol concentration by 3.7.

You recall that the patient has a history of ethanol abuse and had slurred speech on initial presentation. Using the osmolality you calculated and measured, how would you estimate his blood alcohol concentration?
Assuming the osmolar gap is caused by ethanol, we would multiple the gap by the contribution of ethanol to the osmolality, or 3.7: 43 * 3.7 = 159 mg/dL, or in layman's terms, 0.16 (which is roughly twice the U.S. legal limit for drivers).

A colonic perforation is found, and a subtotal colectomy is performed with end colostomy placement. The abdomen is closed and the patient is transported to the surgical ICU. On arrival to the ICU, your most recent BMP is as follows:

Sodium: 140 mmol/L
Chloride: 108 mmol/L
Potassium: 3.5 mmol/L
Bicarbonate: 21 mmol/L
BUN: 42 mg/dL
Creatinine: 1.3 mg/dL
Glucose: 120 mg/dL

Noting the glucose of 120, the nurse asks if she can discontinue the insulin infusion. What should your response be?
No! When treating DKA insulin administration should be continued until the anion gap is normal, which represents a resolution of ketoacidosis. In this case the anion gap is still 14.5, so insulin therapy should be continued, with IV dextrose administration to prevent hypoglycemia.

Suggested Readings

1. Wrenn K (1990) The delta (delta) gap: an approach to mixed acid-base disorders. Ann Emerg Med 19(11):1310–1313

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3. Gerstman BB, Kirkman R, Platt R (1992) Intestinal necrosis associated with postoperative orally administered sodium polystyrene sulfonate in sorbitol. Am J Kidney Dis 20:159–161

4. Gehlbach BK, Schmidt GA (2004) Bench-to-bedside review: treating acid-base abnormalities in the intensive care unit—the role of buffers. Crit Care 8:259–265

5. Williamson JC (1995) Acid-base disorders: classification and management strategies. Am Fam Physician 52(2):584–590

6. Gauthier PM, Szerlip HM (2002) Metabolic acidosis in the intensive care unit. Crit Care Clin 18(2):289–308

7. Wooten EW (2004) Science review: quantitative acid-base physiology using the Stewart model. Crit Care 8(6):448–452

8. Sabatini S, Kurtzman NA (2009) Bicarbonate therapy severe metabolic acidosis. JASN 20(4):692–695