Chapter 12: Fluids and Acid-Base Management

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INTRODUCTION

FOCUS POINTS

1. The Holliday-Segar formula, known as the "4-2-1" rule, is used to calculate the rate of maintenance fluids.
2. There is a wide variety of intravenous fluids that can be used as maintenance fluids and it is important to know their composition to select the adequate one depending on the patient's comorbid condition and the surgical procedure.
3. Important formulas to remember when taking care of pediatric patients include the estimated blood volume and allowable blood loss formulas.
4. Adverse reactions to blood transfusions include non-immune-mediated and immune-mediated reactions.
5. The acid-base balance in the body is regulated by the lungs and the kidneys, via buffer systems.
6. It is essential to be able to interpret the results of an arterial blood gas to diagnose acidosis or alkalosis and differentiate between a metabolic or respiratory etiology.

Fluid management in the operating room is as important as the medications administered to achieve anesthesia and analgesia. Fasting times can significantly affect infants and toddlers, and subsequently lead to hemodynamic instability under general anesthesia. Furthermore, in the pediatric population, physiological buffer systems are still immature making the patient more prone to acid-base disturbances. This chapter will review the main principles of fluid management, the different strategies for fluid repletion, including the transfusion of blood products, the physiology behind acid-base homeostasis, and the diagnostic approach to acid-base disturbances.

FLUID MANAGEMENT

One of the first considerations when evaluating a pediatric patient who presents to the preoperative area is to inquire about fasting times. This allows the anesthesiologist to calculate the fluid deficit already present prior to induction. The Holliday-Segar formula, developed in the 1950s,[1] is used to calculate the rate of maintenance fluids; it is more commonly known as the "4-2-1" rule. For the first 10 kg of a patient's weight, the patient requires 4 mL/kg/h. For the next 10 kg, the patient should receive an additional 2 mL/kg/h. Lastly, for each kilogram thereafter, 1 mL/kg/h should be administered in addition to the 60 mL/h calculated for the first 20 kg. This holds true for an otherwise healthy patient, or even a patient with comorbid conditions that are medically optimized, presenting for an elective procedure. In a patient who is acutely sick and likely dehydrated, other clinical signs can guide fluid resuscitation perioperatively. There are several criteria obtained from a physical examination that can help classify a patient's status into mild, moderate, or severe dehydration (Table 12-1). Fluid resuscitation can then be carried out accordingly prior to induction, then continued intraoperatively to achieve hemodynamic stability.

Table 12-1

Clinical Criteria to Classify Dehydration[2]

	Mild (3% - 5%)	Moderate (6% - 9%)	Severe (> 10%)
Mental status	Well-appearing	Ill-appearing, nontoxic	Lethargic, toxic
Heart rate	Normal to increased	Tachycardia	Marked tachycardia
Breathing	Normal	Increased	Increased, deep
Pulse	Normal quality	Normal to decreased quality	Poor quality
Capillary refill	Normal (<2 sec)	Normal to slightly prolonged (2–4 sec)	Markedly prolonged
Perfusion	Warm	Cool	Cool, mottled
Blood pressure	Normal	Normal	Hypotensive
Eyes	Normal	Slightly sunken	Very sunken
Tears	Normal	Decreased	Absent
Mucous membranes	Moist	Sticky	Very dry
Skin turgor (recoil)	Instant recoil	Delayed (2 sec)	Very prolonged
Urine output	Normal to slightly decreased	Decreased	Minimal

Source: Used with permission of EB Medicine. Mark A. Hostetler. Gastroenteritis: an evidence-based approach to typical vomiting, diarrhea, and dehydation. *Pediatric Emergency Medicine Practice*. 2004;1(5):1-20 © 2004 EB Medicine. www.ebmedicine.net.

There is a wide variety of intravenous fluids that are used as maintenance fluids perioperatively depending on the patient's comorbid conditions and the indicated surgical procedure. The difference between these fluids lies in the osmolarity of the fluid and content of electrolytes.

CRYSTALLOIDS VERSUS COLLOIDS

Lactated Ringer's

The most common type of intravenous fluid used in the operating room for the pediatric population is lactated Ringer's. The osmolarity of lactated Ringer's, at 273 milliOsmoles per liter (mOsm/L), is similar to plasma osmolarity, which ranges from 275 to 290 mOsm/L (Table 12-2). The concentration of electrolytes is also comparable to physiologic plasma concentrations, making it an ideal fluid to achieve euvolemia perioperatively. However, one must keep in mind that lactated Ringer's contains lactate and must be avoided in conditions where lactate metabolism may be compromised or the administration of lactate itself may be detrimental. Such conditions include severe liver disease, anoxic states, and severe metabolic acidosis or alkalosis. A common misconception is that the patient in renal failure may develop life-threatening hyperkalemia due to the concentration of potassium present in lactated Ringer's. O'Malley has conducted a prospective, randomized, double-blind trial comparing lactated Ringer's to normal saline in the setting of renal transplantation. The group who received Lactated Ringer's had a lower incidence of hyperkalemia requiring treatment (defined as a potassium level greater than 6 mEq/L) and metabolic acidosis.[3] Lactated Ringer's also contains calcium and should not be used during the transfusion of blood products due to the presence of citrate. It is incompatible with ceftriaxone because precipitates can form with calcium leading to significant morbidity and mortality.

Table 12-2

Composition of Commonly Used Crystalloid Solutions

Fluid	pH	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	Ca^{2+} (mEq/L)	Other	Osmolality (mOsm/L)
Lactated Ringer's	6.5	130	4	109	3	Lactate 28 mEq/L	273
Normal saline	5.6	154	–	154	–	–	308
Plasma-Lyte®	5.5	140	5	98	–	Magnesium 3 mEq/L Acetate 27 mEq/L Gluconate 23 mEq/L	294
5% Dextrose and 0.9% sodium chloride	4.3	154	–	154	–	Dextrose 50 g/L	560
5% Dextrose and 0.45% sodium chloride	4.4	77	–	77	–	Dextrose 50 g/L	405

0.9% Sodium Chloride

The second most common intravenous fluid used in the pediatric population is 0.9% sodium chloride solution, or normal saline. This fluid is favored during neurosurgical cases because infusion of a large amount of lactated Ringer's can result in cerebral edema due to its hypo-osmolarity compared to plasma osmolarity. Normal saline has an osmolarity of 309 mOsm/L and contains equal but supraphysiologic concentrations of sodium and chloride, at 154 mEq/L. Therefore, when infused in large quantities, it can lead to a hyperchloremic metabolic acidosis. Another important consideration to keep in mind when usi ng normal saline is the lack of electrolytes such as potassium, magnesium, calcium, or glucose, because a prolonged infusion can result in electrolyte imbalances or hypoglycemia.

Plasma-Lyte®

Plasma-Lyte has emerged as an alternative for fluid maintenance, especially in the critical care population, and during the transfusion of blood products. Each liter of Plasma-Lyte has an osmolarity of 294 mOsm and contains 140 mEq of sodium, 5 mEq of potassium, 98 mEq of chloride, 3 mEq of magnesium, 27 mEq of acetate, and 23 mEq of gluconate. The acetate and gluconate ions inside the solution are metabolized to carbon dioxide and water through the consumption of hydrogen ions, thus leading to an overall metabolic alkalosis. Therefore, it may not be ideal in patients already in respiratory or metabolic alkalosis. Similarly, to lactated Ringer's, it must be used with caution in patients with hyperkalemia or renal failure due to its potassium content.[4]

Albumin 5%

When to transition from crystalloids to colloids? There is a concern when crystalloids are used exclusively for fluid resuscitation or in the setting of excessive blood loss. Over time, only a transient response will be appreciated because only 30% of the crystalloid solution stays in the intravascular

space. Alternatively, an infusion of colloids will remain mostly in the intravascular space, instead of expanding the interstitial fluid space. The rule-of-thumb during fluid resuscitation is to replace the estimated volume of blood lost in a 3 to 1 ratio when using crystalloids, but a 1 to 1 ratio when using colloids. The most common colloid solution used intraoperatively is albumin 5%. It is dispensed in a sterile glass bottle as a slightly yellow and viscous liquid. Large pools of human plasma are used to manufacture this colloid solution. Other components of albumin 5% include sodium, potassium, *N*-acetyl-*DL*-tryptophan, and caprylic acid. Sodium levels should be monitored if large volumes of albumin 5% are administered. The United States Food and Drug Administration (US FDA) issued a warning regarding the use of this solution because it is derived from human plasma and thus may contain infectious agents that can be transmitted to the recipient and cause disease. However, it is pasteurized at 60°C and there are no reported cases of viral hepatitis from an infusion of albumin 5%. It is classified as Category C for use in pregnant women. Lastly, using a large volume of albumin 5% after significant blood loss can lead to hemodilution, dilution of coagulation factors, and electrolyte disturbances.[5]

TRANSFUSION OF BLOOD PRODUCTS

During invasive surgeries where significant blood loss is anticipated, it is important to calculate a patient's estimated blood volume and the allowable blood loss (Table 12-3). Assuming that the patient has a hematocrit within normal limits preoperatively, the calculated allowable blood loss can serve as a guide to determine the necessity for transfusion of blood products. It is very important to monitor the ongoing blood loss during a surgical procedure. This can be done by keeping track of the amount of fluids collected in the suction canister, the number of sponges used on the field, and the amount of blood absorbed into the drapes. The three most common sponges used in the operating room are as follows: a 4 × 4 piece of gauze that holds 10 mL of blood, a Ray-Tec® sponge that holds up to 20 mL of blood, a pediatric lap sponge that holds 50 mL of blood, and an adult lap sponge that holds 100 mL of blood. Irrigation fluids are also often used to irrigate wounds or body cavities to assist during procedures such as a cystoscopy or arthroscopy, and when certain instruments are used such as coblation wands. The total amount of irrigation fluids used during the operation must be subtracted to ensure a correct estimation of blood loss.

Table 12-3

Estimated Blood Volume and Allowable Blood Loss Formulas

Patient's Age	Estimated Blood Volume (mL/kg)
Preterm neonate	100
Full-term neonate	90
Infant	80
Child	75
Teenager/Adult	70

Allowable blood loss = Estimated blood volume × $(Hct_{initial} - Hct_{allowable})/Hct_{initial}$

If a transfusion is highly likely during the surgical procedure, a type and crossmatch must be obtained preoperatively to ensure that the appropriate blood products will be readily available. Blood type is classified into four major groups: A, B, AB, and O. For instance, a person with blood group A carries the A antigen and will mount an immune response with anti-B antibodies when exposed to blood group B or blood group AB, which both carry the B antigen. Furthermore, blood types are further subclassified into Rh D antigen positive or negative. To avoid detrimental effects from a blood transfusion, compatibility between the donor's blood and the recipient's blood must be verified. The first step involves determining the patient's blood type, meaning his or her ABO type and Rh D status. A crossmatch is then performed to rule out possible adverse reactions to other antigens. This involves mixing a small volume of the recipient's serum with a small volume of red blood cells from the donor's blood. Examination under a microscope will reveal if antibodies from the recipient cause agglutination of the donor red blood cells. If agglutination occurs, the transfusion is deemed incompatible and the recipient will not receive that specific unit of blood. On the other hand, a type and screen can also be performed. This is only recommended if the possibility of transfusion is low. The test determines the patient's blood type and screens for the most commonly found

unexpected antibodies. However, because there is no actual compatibility test between the recipient's and the donor's blood samples, a transfusion reaction can still occur. A type and crossmatch can take between 45 and 60 minutes. Therefore, results must be obtained prior to transferring a patient to the operating room. This is especially crucial in a patient who has received multiple blood transfusions in the past, such as an oncology patient, or one with known rare antigens. In those cases, it might take longer before a compatible unit of blood can be identified. For the transfusion of other blood products such as platelets, fresh frozen plasma, or cryoprecipitate, a type and crossmatch are not necessary because they contain minimal amounts of red blood cells.[6]

ADVERSE REACTIONS TO BLOOD TRANSFUSION

There are several considerations to keep in mind when initiating the transfusion of blood products in the pediatric population. Adverse reactions can range from mild to severe; can be acute or delayed reactions; and can be categorized as immune- or non-immune-mediated events.

Non-Immune-Mediated Reactions

Hypothermia

Blood products, except for platelets, are kept in coolers once they are released from the blood bank. Therefore, it is important to use a fluid warmer to administer them to prevent contributing to hypothermia in the pediatric patient. Hypothermia may lead to cardiac arrhythmias, platelet and clotting factors dysfunction, and increase in bleeding time.[7] Platelets, on the other hand, are stored at room temperature.[8] A common misconception is that platelets cannot be transfused through a fluid warmer because it will affect their function. Konig et al have conducted a small-scale study that has refuted that belief. Their results "do not support the prohibition against mechanical platelet warming." However, they also state that further studies should be performed to investigate platelet activation.[9] Fluid warmers will warm fluids up to 42°C. Rao et al have demonstrated that warming platelets above 43 to 45°C has an adverse effect on platelet aggregation. Heat also affects the cytoskeletal proteins of platelets and surface membrane receptors, leading to altered function. The biochemical systems involved in activation events are however not impacted.[10] Blood products should be administered through a standard filter, usually a 170 to 260 µm filter.[8] The most common solution used as a priming fluid when administering blood products is normal saline. Plasma-Lyte is also a great alternative: it is compatible with blood products[4] and will not lead to a hyperchloremic metabolic acidosis compared to normal saline.

Volume Overload

The quantity of blood transfused should be determined meticulously to avoid volume overload and possible respiratory complications. A useful rule of thumb is that the transfusion of 4 to 5 mL/kg of packed red blood cells will increase the hemoglobin level by 1 g/dL. The transfusion of 5 mL/kg of platelets will increase the platelet count by 15,000 per microliter. Fresh frozen plasma is usually transfused 10 to 20 mL/kg at a time until bleeding improves clinically. One unit of cryoprecipitate per 7 kg of body weight will increase the fibrinogen level by 100 mg/dL. Once the decision has been made to start transfusing red blood cells, it is important to remember that coagulopathy can be associated with transfusions. To prevent this, it might be necessary to also transfuse fresh frozen plasma and platelets. More research is needed to determine the optimal ratio for a balanced transfusion strategy. In the meanwhile, most guidelines recommend transfusing in a PRBC:FFP:platelet ratio of 2:1:1.[11]

Electrolyte Disturbances

The two most common types of electrolyte disturbances from a blood transfusion involve potassium and calcium. Potassium is released from older, damaged red blood cells into the circulation during the transfusion process. The most serious complication from acute hyperkalemia is the development of cardiac arrhythmias.[6] This occurs rarely due to rapid dilution, redistribution into the cells, and excretion of excess potassium by the kidneys. Interestingly, hypokalemia is more common than hyperkalemia after a transfusion. The proposed mechanism is inward movement of potassium intracellularly into donor red blood cells. Citrate metabolism enhances this migration of potassium. During a massive transfusion, the release of catecholamines and loss of aldosterone in the urine also contribute to the development of hypokalemia.[7] Furthermore, citrate is the major anticoagulant used during the collection and storage process of packed red blood cells. Unfortunately, transfusion of large volumes of red blood cells can lead to hypocalcemia due to chelation by citrate. This would manifest clinically with muscle spasms, seizures, and cardiac arrhythmias.[6]

Transfusion-Associated Circulatory Overload

Another significant acute adverse reaction is transfusion-associated circulatory overload, or TACO. It is rare but is associated with considerable morbidity and mortality. The clinical symptoms are related to fluid overload, such as dyspnea, tachycardia, jugular venous distention, and edema. A hallmark sign is hypertension with a widened pulse pressure. Management consists mainly of treating the underlying etiology, mechanical ventilation, fluid restriction, and diuretic therapy.[7]

Infectious Diseases

Concern in the general population when faced with a possible transfusion is the risk of transmission of infectious diseases. Since the 1960s, blood banks have started universally screening donor's blood before it reaches the patient. Eligibility criteria are strict and anyone with a history of hepatitis or transfusions in the six preceding months is excluded from donating blood. The thorough evaluation of the donor, laboratory screening tests (including serologic testing and viral nucleic acid testing), and procedures to inactivate pathogens are the three main processes that serve to significantly decrease, but unfortunately cannot eradicate, the risk of transfusion-transmitted infections. The relative risk of transmission of the most frequent viruses has significantly decreased with time (Table 12-4). This has led to the risk of bacterial contamination being greater than the risk of a viral infection, at 1 in less than 40,000 when transfusing packed red blood cells and as high as 1 in 5000 when platelets are transfused. This can be explained by the storage conditions of platelets at room temperature where bacteria thrive better compared to the cold temperatures of 1 to 6°C that red blood cells require for storage.[12]

Table 12-4

Relative Risk of Transfusion-Transmitted Viral Disease in the United States[1,2]

Virus	Relative Risk of Transmission
Human immunodeficiency virus	1 in <2.2 million
Hepatitis C virus	1 in <2 million
Hepatitis B virus	1 in <300,000
West Nile virus	1 in 350,000
Human T cell lymphotrophic virus	1 in <3 million

Source: Data from Bihl F, Castelli D, Marincola F, Dodd RY, Brander C. Transfusion-transmitted infections. *J Transl Med.* 2007;5:25. https://translational-medicine.biomedcentral.com/.

Immune-Mediated Reactions

Hemolytic Reactions

Immune-mediated blood transfusion reactions are defined by the substance that generates the immune response. Hemolytic transfusion reactions can be acute or delayed in onset. The acute reactions are further separated into intravascular or extravascular processes. Antigens present on the donor red blood cells are recognized by the recipient's immune system as foreign. This triggers antibody-medicated detection and destruction of the donor red blood cells. This can happen inside the blood vessels, or in the spleen and liver if the destruction is carried out by macrophages. Clinical signs include fever, chills, and back and flank pain. Unfortunately, the most common cause of this transfusion reaction is ABO incompatibility, most likely caused by human error. A hemolytic transfusion reaction can occur the day following the transfusion or 14 days later resulting in a delayed reaction. The reason for this "delay" is the low quantities of antibodies present in the circulation. The immune system will then produce more antibodies once the antigens are encountered, leading to extravascular hemolysis.[6,7]

Febrile Nonhemolytic Reactions

Febrile nonhemolytic reactions are acute in onset and are caused by the recipient's antibodies attacking HLA antigens on donor white blood cells. This is usually a mild reaction that presents as a rise in temperature of at least 1°C, chills, and rigors. Leukodepletion is a process that removes white blood cells from donated blood prior to storage and can prevent this reaction. Antipyretics can also be administered prophylactically before the transfusion occurs.[6,7]

Post-Transfusion Purpura

Post-transfusion purpura occurs when the recipient's platelet-specific antibody reacts with donor platelets leading to thrombocytopenia. It is a delayed reaction with an onset of 5 to 10 days and leads to the formation of purpura as well as an increased risk of bleeding. Unfortunately, during this process, the antibodies also attack the recipient's own platelets and the patient becomes thrombocytopenic. Treatment includes the infusion of intravenous immunoglobulins or plasmapheresis.[6,7]

Allergic Reactions

Allergic reactions can occur due to IgE or IgA antibodies. Urticaria, or hives, is caused by recipient or donor IgE antibodies that bind to a certain antigen leading to the activation of mast cells and basophils resulting in histamine release. This is more likely to happen in atopic patients such as those with seasonal allergies. Treatment is simple and consists of discontinuing the transfusion and administering antihistamines. In the case of a more severe reaction such as angioedema, steroids such as methylprednisolone or prednisone can be used. The transfusion can usually be resumed once the symptoms have resolved. If IgA antiplasma protein antibodies are involved, a life-threatening allergic reaction will develop, known as anaphylaxis. This reaction is more common in patients with IgA deficiency. Clinical symptoms include dyspnea, wheezing, coughing, nausea, or vomiting. This can rapidly progress to hypotension, loss of consciousness, respiratory arrest, and circulatory shock. Depending on the hemodynamic status of the patient, treatment includes discontinuing the transfusion, administering epinephrine, and even performing cardiopulmonary resuscitation.[6,7]

Transfusion-Associated Lung Injury

TRALI, or transfusion-associated lung injury, is among one of the most serious adverse reactions from the transfusion of blood products. It is rare but can become fatal. Donor antileukocyte antibodies attack the recipient's white blood cells leading to aggregation in the pulmonary vasculature. Inflammatory mediators are released and increase the permeability of the lung capillaries, resulting in pulmonary edema. It is a clinical diagnosis that manifests with the acute onset of shortness of breath within 6 hours of transfusion in the absence of preexisting lung pathology. A chest radiograph shows findings consistent with bilateral pulmonary edema and an echocardiogram should be obtained to rule out the presence of left atrial hypertension. An arterial blood gas reveals hypoxemia with a Pao_2 to Fio_2 ratio less than or equal to 300 or an oxygen saturation less than 90% on room air by pulse oximeter. In 80% of the cases, oxygenation improves within 48 to 96 hours and the lung injury resolves. Treatment is supportive and given the normal findings on echocardiogram, diuretics are not indicated.[6,7]

Transfusion-Associated Graft-Versus-Host Disease

The last important immune-mediated adverse reaction is TA-GVHD, or transfusion-associated graft-versus-host disease. This delayed adverse reaction occurs approximately 1 week after the transfusion due to donor T lymphocytes attacking the recipient's own cells that have the HLA antigen. Clinically, the patient will present with a fever, characteristic maculopapular rash that progresses to hemorrhagic bullae, and enterocolitis with diarrhea. Further evaluation reveals elevated liver function tests and pancytopenia indicating bone marrow failure. Unfortunately, the prognosis is grim with TA-GVHD and death occurs within a few weeks in 90% of the cases. High-risk patients include immunocompromised patients where the immune system is unable to eliminate the T cells in question. In that population, it is essential to limit blood transfusions when possible and use irradiated blood products if necessary.[6,7]

ACID-BASE MANAGEMENT

Homeostasis is defined as "a self-regulating process by which biological systems tend to maintain stability while adjusting to conditions that are

optimal for survival."[13] In the human body, acid-base balance is achieved through buffer systems, excretion of carbon dioxide through ventilation, and elimination of acid by the kidneys.

Definitions

The Brønsted-Lowry definition of acids and bases states that an acid is a proton (or hydrogen ion) donor, and a base is a proton acceptor. A substance can be a strong or a weak acid or base, depending on how readily it donates or accepts a hydrogen ion, respectively. The Henderson-Hasselbalch equation can then be used to determine the acidity of a solution. The pK_a is the intrinsic value of a substance defined as the pH where it can be found in both its protonated and deprotonated forms in a 1:1 ratio.

$pH = pK_a + \log([A^-]/[HA])$, where pK_a represents the dissociation ionization constant, A^- the base, and HA the conjugate acid.

Regulation of Acid-Base Balance

The two main organs that allow regulation of acid-base balance are the lungs and the kidneys. The lungs allow elimination of carbon dioxide through alveolar ventilation to maintain arterial P_{CO_2} around 40 mm Hg. Two types of chemoreceptors help regulate the rate of alveolar ventilation. Central chemoreceptors are located on the anterolateral surface of the medulla oblongata. When carbon dioxide diffuses across the blood-brain barrier, the concentration of hydrogen ions in the cerebrospinal fluid increases leading to a decrease in pH. The chemoreceptors are sensitive to the change in pH and respond by increasing alveolar ventilation.[14] This relationship is linear except at the extremes of arterial $Paco_2$. Carbon dioxide narcosis occurs at very high arterial $Paco_2$ where alveolar ventilation no longer increases. On the other end of the spectrum, at very low arterial $Paco_2$, the apneic threshold is reached, and alveolar ventilation can no longer decrease. There are two groups of peripheral chemoreceptors: the carotid bodies at the bifurcation of the common carotid arteries in the carotid sinus, and the aortic bodies around the aortic arch. They are most sensitive to variation in Pao_2 but will also respond to changes in $Paco_2$, pH, and arterial perfusion pressure. A decrease in Pao_2, increase in $Paco_2$, or decrease in pH stimulates the carotid body chemoreceptors to send a signal via the glossopharyngeal nerves to the respiratory centers in the brainstem. A signal that originates from the aortic bodies travels via the vagus nerves to the cardiovascular centers in the brainstem. However, alveolar ventilation can only decrease to a certain extent because without supplemental oxygenation, hypoxia will inevitably ensue in response to significant hypoventilation. The decrease in Pao_2 stimulates chemoreceptors and limits the respiratory compensation to metabolic alkalosis.[15]

The kidneys also serve to preserve homeostasis, but these effects may take hours to days before they are observed clinically. There is an important chemical reaction necessary to understand the purpose of bicarbonate in the body:

$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$CO2+H2O↔H2CO3↔HCO3−+H+

This reaction is catalyzed by the enzyme carbonic anhydrase, which is located on the luminal side and inside the tubular cell. In the proximal tubule, bicarbonate is reabsorbed mainly through secretion of protons via the Na^+,H^+ antiporter. This exchange requires energy that is provided by the Na^+,K^+-ATPase. The reaction between carbon dioxide and water leads to the formation of bicarbonate and a hydrogen ion. Bicarbonate enters the bloodstream to be reabsorbed. The hydrogen ion is eliminated into the urine in exchange for sodium entering the tubular cell. It reacts with filtered bicarbonate present in the tubular lumen to form carbon dioxide and water. Carbon dioxide then reenters the tubular cell to start the cycle again. A third of bicarbonate reabsorption occurs via the H^+-ATPase. In the distal tubule, secretion of acid via the H^+-ATPase and H^+,K^+-ATPase serves to regenerate bicarbonate. Phosphate is the most abundant buffer present in the urine. It combines with a hydrogen ion to form phosphorous acid, which is excreted into the urine. Phosphate is thus considered a titratable acid because it is a weak acid anion present in the urine and used to maintain acid-base balance. Finally, ammonium excretion represents another mechanism that occurs in the kidneys. Inside the renal cell, glutamine is used to form NH_3, or ammonia, which is allowed to diffuse into the tubular lumen because it does not possess a charge. NH_3 in turn combines with a hydrogen ion to form NH^{4+}, or ammonium. Ammonium is then eliminated into the urine. There are a few factors that affect the amount of acid excreted in the distal tubule. Distal acidification is decreased in the setting of hyponatremia because the active transport of sodium creates a negative potential difference in the tubule, thus increasing the rate of proton excretion into the tubular lumen. Aldosterone modulates multiple processes occurring in the kidneys: it augments the rate of sodium reabsorption, stimulates Na^+,K^+-ATPase and H^+-ATPase, and enhances the production of ammonia. Therefore, an excess of aldosterone will significantly increase the quantity of acid excreted.[16]

Buffer Systems

A buffer system is defined as the presence of a weak base and its conjugate acid that serves to resist any extreme changes in the pH of the solution. This is important because a significant amount of acid is produced in the body, but it is essential to maintain the pH of body fluids within a narrow range for optimal conditions. There are four important buffer systems.

The bicarbonate–carbonic acid buffer system operates in the extracellular fluid. It starts with carbon dioxide reacting with water to form carbonic acid, with the help of the enzyme carbonic anhydrase as a catalyst. Since carbonic acid is a weak acid, it readily dissociates into bicarbonate and a hydrogen ion.

The hemoglobin buffer system is located in the red blood cells, a site that is abundant in carbonic anhydrase. This is important because the mechanism by which carbon dioxide travels to the lungs depends on the cooperation between the bicarbonate–carbonic acid and hemoglobin buffer systems. Carbon dioxide from tissues diffuses into the bloodstream to enter the red blood cells. Inside the cell, carbonic anhydrase catalyzes the chemical reaction to form bicarbonate and a hydrogen ion. The hydrogen ion combines with amino acid side chains in hemoglobin, while bicarbonate leaves the red blood cell in exchange for a chloride anion to maintain electroneutrality. The reverse occurs as the red blood cells travel toward the lungs, thus allowing for release of carbon dioxide into the alveoli to be eliminated through ventilation.

The last two buffer systems in the body, phosphate anions and proteins, exert their effect mainly in the intracellular fluid. Proteins are able to accept protons in a similar fashion to hemoglobin.[17]

Arterial Blood Gas Analysis

To apply the principles described above, it is essential to be able to interpret results of an arterial blood gas. However, if an arterial line is not warranted to monitor the patient during the surgical procedure, a venous blood gas can be acceptable in some circumstances. It is important to remember that a venous Pco_2 will be about 4 mm Hg higher than an arterial Pco_2 while the pH will be approximately 0.03 lower. This does not apply to a critical or hemodynamically unstable patient, and an arterial blood gas should be obtained for greater accuracy. A meta-analysis by Byrne et al found that venous Pco_2 does not consistently correlate with arterial Pco_2 and is not always greater as expected.[18] Furthermore, only the pH, Po_2, and Pco_2 are directly measured from the blood sample, while the concentration of bicarbonate and base excess are mathematically derived. The method used to obtain the arterial blood sample is critical. Depending on the size of the patient, it can be challenging to ensure that the blood sample is arterial, and not venous. Ideally, the sample should be analyzed within 30 minutes, or it should be collected in a glass syringe and placed in ice. Any delay could lead to erroneous results, especially in the setting of a shunt, elevated white blood cell, or platelet counts. Air bubbles present in the sample can also interfere with the accuracy of the results. Depending on the patient's oxygenation status when the sample was obtained, if the partial pressures of oxygen and carbon dioxide in the air bubble equilibrate with those in the blood sample, the values obtained could be falsely high or low.[19] Lastly, the patient's temperature affects the partial pressure of oxygen and carbon dioxide in blood, and therefore the pH of the blood sample. Hypothermia leads to increased solubility and therefore decreased partial pressures of oxygen and carbon dioxide.[20]

Once the results of an arterial or venous blood gas have been obtained, the next step is to diagnose the acid-base disturbance present. The disorder (acidosis or alkalosis) can be metabolic, respiratory, or mixed in etiology; acute or chronic in nature; and compensated or uncompensated. The first step is to look at the pH of the arterial or venous blood gas. Physiologic pH is maintained between 7.35 and 7.45. Acidosis is defined as a blood pH less than 7.35 and alkalosis is a blood pH above 7.45.

Metabolic Acidosis and Strong Ion Difference

Metabolic acidosis is differentiated from respiratory acidosis by the value of Pco_2. When the pH is below 7.35, the concentration of bicarbonate is below 24 mEq/L, and Pco_2 is normal or below normal, the diagnosis is a metabolic acidosis resulting from the accumulation of acid in the body. The body attempts to maintain homeostasis by increasing ventilation to eliminate carbon dioxide and attempts to bring the pH closer to a normal value. There are two main categories of metabolic acidosis differentiated by the presence of an anion gap. The anion gap measures the difference between the concentration of cations (sodium) and anions (chloride and bicarbonate) in the serum. A normal anion gap is 12 ± 4 mEq/L. It is important to note that alterations in the concentration of unmeasured anions affect the anion gap. The concentration of plasma albumin has been shown to correlate linearly with plasma pH. Therefore, in the setting of hypoalbuminemia, the anion gap would be falsely lowered. The following formula can be used to possibly

unmask a metabolic acidosis in a patient with hypoalbuminemia:

$$AG_{corrected} = AG + 0.25([albumin]_{reference} - [albumin]_{measured})$$AGcorrected=AG+0.25([albumin]reference−[albumin]measured)

The mnemonic MUDPILES is commonly used to identify the underlying pathology causing an anion gap metabolic acidosis (Table 12-5). On the other hand, metabolic acidosis in the setting of a normal anion gap can be explained by the loss of bicarbonate and replacement by chloride. Gastrointestinal pathologies are a common etiology because gastrointestinal fluids are alkaline with a high concentration of bicarbonate. Renal disorders such as renal tubular acidosis result in the inability to acidify the urine and decreased excretion of acid. Another etiology is the use of normal saline for aggressive fluid resuscitation because a significant chloride burden will lead to impaired renal bicarbonate reabsorption. Table 12-5 describes the possible causes of metabolic acidosis.[21]

Table 12-5

Causes of Metabolic Acidosis

Anion Gap Metabolic Acidosis	Non-Anion Gap Metabolic Acidosis
Methanol **U**remia, chronic renal failure **D**iabetic, alcoholic, or starvation ketoacidosis **P**araldehyde, propylene glycol **I**nfection/sepsis, isoniazide, inborn errors of metabolism **L**actic acidosis: congestive heart failure, cyanide toxicity **E**thanol, ethylene glycol **S**alicylates	Infusion of normal saline, TPN Gastrointestinal losses: diarrhea, vomiting, ileostomy, biliary or pancreatic fistula, ureteral diversion Renal losses: renal tubular acidosis, Addison's disease Drugs: potassium sparing diuretics, carbonic anhydrase inhibitors

An alternative way of evaluating a metabolic acidosis is to calculate the strong ion difference, or SID. In the early 1980s, Peter Stewart developed a new method to evaluate acid-base disorders. He emphasized the importance of the water dissociation equation as the main determinant of the pH of any fluid, with the influence of several modifiers such as P_{CO_2}, weak acids, and electrolytes. He defined a new term, A_{TOT}, which represents the total concentration of nonvolatile weak acids. A_{TOT} is the sum of the concentration of a weak acid and its conjugate base, or $A_{TOT} = [HA] + [A^-]$. Therefore, it is a constant and is not affected by pH. A decrease or increase in pH reflects a shift toward an increase or a decrease in the concentration of the weak acid, respectively. He also characterized the strong ion difference as the difference between strong cations and strong anions present in body fluids. The normal value for SID is 42 mEq/L, reflecting excess of strong cations in the body. Stewart's method highlights the concept of electroneutrality in any body fluids. Strong cations in the body include sodium, potassium, magnesium, and calcium. Strong anions include chloride, lactate, and unidentified strong anions such as ketoacids and lactate. Urate is usually present at a concentration less than 0.2 mEq/L and is usually omitted from the equation. This leads to the following:

$$SID = [Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-] - [lactate]$$SID=[Na+]+[K+]+[Ca2+]+[Mg2+]−[Cl−]−[lactate]

The simplified SID equation is as follows:

$$SID = [Na^+] + [K^+] - [Cl^-] - [lactate]$$SID=[Na+]+[K+]−[Cl−]−[lactate]

The significant deviation from traditional teaching that arises with Stewart's method is that there are only three independent variables: SID, A_{TOT}, and P_{CO_2}. These can in turn affect the dependent variables: pH and concentration of bicarbonate, carbonate anion, and hydroxide. A metabolic alkalosis is represented by an increase in SID or a decrease in A_{TOT}, while a decrease in SID or an increase in A_{TOT} reflects a metabolic acidosis.[22]

Metabolic Alkalosis

Metabolic alkalosis is characterized by a pH greater than 7.45. It can be separated into two groups based on its response to chloride repletion. The

underlying pathophysiology that causes a metabolic alkalosis is a gain of bicarbonate or a loss of nonvolatile acid. Acid can be lost from the gastrointestinal tract, such as in vomiting or nasogastric tube suctioning; from the kidneys, for example, primary aldosteronism and use of diuretics; or via intracellular shifts to compensate for hypokalemia. The body can experience excessive bicarbonate loads from alkali administration. Examples include milk alkali syndrome, lactate in intravenous fluids, acetate in total parenteral nutrition, and citrate during the transfusion of blood products.[16]

Respiratory Disorders

Respiratory disorders can be diagnosed when the change in pH can be explained by the deviation of $Paco_2$ from normal and the concentration of bicarbonate remains within normal limits. There is a mismatch between alveolar minute ventilation and carbon dioxide production leading to the acid-base disturbance. In the operating room, the patient is often mechanically ventilated and respiratory disorders can be corrected with simple changes of the ventilator settings. It is important to remember that the normal gradient between $Paco_2$ and end tidal CO_2 is around 5 mm Hg. Unless an arterial catheter is present, it is difficult to obtain $Paco_2$ values and readings from capnometry are used to estimate $Paco_2$. Furthermore, when a respiratory acid-base disorder has been diagnosed, it is important to determine whether it is an acute or a chronic process. If the disturbance occurred acutely, there will be a change in pH of 0.08 for every 10 mm Hg deviation from the normal value of 40 mm Hg. On the other hand, with a chronic process, the change in pH is decreased to 0.03.

Respiratory Acidosis

Respiratory acidosis occurs when the lungs are not able to eliminate enough carbon dioxide to match the amount produced by the body. This can be due to a decrease in elimination or an increase in production or both. This results in an increase in $Paco_2$ leading to a decrease in pH.

Circumstances where excess carbon dioxide is produced include exercise, fever, sepsis, burns, thyrotoxicosis, multi-organ failure, and overfeeding. Decreased elimination of carbon dioxide can be caused by a decrease in alveolar ventilation or ventilatory drive, or abnormal chest wall or respiratory muscles. General anesthesia with the administration of sedatives and opioids can lead to both alveolar and central hypoventilation. Mismatch between pulmonary perfusion and ventilation, such as in the presence of a pulmonary embolus, will also lead to alveolar hypoventilation. Other etiologies of central hypoventilation are as follows: central sleep apnea, obesity hypoventilation syndrome, central nervous system infection or trauma, and brainstem lesions. Disorders of the chest wall such as obesity and kyphoscoliosis, or respiratory muscle weakness can also cause respiratory acidosis. The three main categories of the latter include spinal cord injuries, neuromuscular junction disorders, and myopathies. Intraoperatively, respiratory muscle weakness can be caused by inadequate reversal of neuromuscular blockers.[23] Lastly, respiratory acidosis can also occur iatrogenically. During laparoscopic surgery, carbon dioxide is often used for insufflation and absorption will increase end-tidal and arterial CO_2 concentrations. Rebreathing can also cause an increase in carbon dioxide in the body and can be observed if the soda lime absorber is exhausted or the breathing machine has an incompetent one-way valve.

Respiratory Alkalosis

The reverse stands true for respiratory alkalosis: it is caused by increased minute ventilation or decreased production of carbon dioxide. There is a wide variety of pathologic states leading to hyperventilation. A few examples include hypoxia, intrinsic lung disease (parenchymal or bronchial), drugs, mechanical ventilation, pain, fever, hepatic disease, and diseases of the central nervous system. Hypoxia leads to stimulation of the chemoreceptors located on the carotid bodies resulting in hyperventilation.[24] It is also important to remember that end-tidal carbon dioxide levels can reflect cardiac output. An unanticipated decrease in end-tidal carbon dioxide with no recent change in ventilation should alert the anesthesiologist to possible cardiovascular compromise.

Compensatory Mechanisms

Compensation can occur in a chronic setting, where the lungs compensate for a metabolic disturbance or the kidneys compensate for a metabolic or respiratory disturbance. Winter's formula can be used to determine whether compensation or a mixed acid-base disorder is present. In the setting of a metabolic acidosis, the measured Pco_2 should be close to:

$Pco_2 = (1.5 \times [HCO_3^-]) + 9$Pco2=(1.5×[HCO3−])+9

If it is greater, then there is both a respiratory and a metabolic acidosis. If it is less, the metabolic acidosis is compensated by a respiratory alkalosis. If

the underlying disorder has been identified as a metabolic alkalosis, the following equation is used to estimate P_{CO_2}:

$P_{CO_2} = (0.7 \times [HCO_3^-]) + 21$Pco2=(0.7×[HCO3−])+21

If it is greater than the measured P_{CO_2}, there is a compensatory respiratory acidosis. If it is less, there is both a respiratory and a metabolic alkalosis.

It is ideal but not realistic to expect the pH to remain within normal limits when a patient with multiple comorbidities undergoes a prolonged and invasive surgical procedure. While it is important to correctly identify the acid-base disturbance and treat the underlying etiology, electrolyte disturbances may occur before treatment can be completed. One of the most important electrolyte abnormalities is hyperkalemia. The body attempts to compensate for the metabolic acidosis by buffering the excess of hydrogen ions in the cells. However, to maintain electroneutrality, an exchange has to occur. Potassium ions are released into the extracellular fluid in exchange for hydrogen ions being reabsorbed into the cells. The main concern then becomes myocardial stability in the setting of hyperkalemia. Calcium supplementation is administered to stabilize myocardial cells and avoid any cardiac rhythm disturbances. This is not a long-term solution but simply serves to maintain the patient hemodynamically stable while the underlying acid-base disturbance and resulting electrolyte abnormalities are resolved.

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