Blood Gas Analysis and Acid-Base Disorders

9

Nitin Rai and Dalim Kumar Baidya

Human body maintain homeostasis by many physiological processes which keep a fine tuning of pH between 7.35 to 7.45. This pH enables various essential processes like oxygen delivery to tissue, maintaining protein structure in the proper configuration and helps in carrying out various biochemical reactions smoothly. Two types of acids contribute to daily acid load—respiratory (or volatile) acids and metabolic (or fixed) acids. Respiratory acid is carbon dioxide produced by complete oxidation of carbohydrates and fatty acids [1]. Although CO_2 itself is not an acid as per Bronsted-Lowry system as it does not contain a hydrogen, instead it has a potential to create an equivalent amount of carbonic acid (H_2CO_3). Daily basal CO_2 production is 12,000 to 13,000 mmols/day. All acids other then H_2CO_3 are fixed acids as those are not eliminated by lungs. These acids are produced due to incomplete metabolism of carbohydrates (e.g. lactate), fats (e.g. acetoacetate or b-hydroxybutyrate) and protein (e.g. sulphate, phosphate) and are eliminated by kidneys. Daily production is about 70 to 100 mmoles of H^+ per day in an adult.

9.1 Buffers

Any acid base disturbance is compensated by buffers system in the body, respiratory response by alteration in arterial pCO_2 or renal response by alteration in HCO_3^- elimination [1, 2]. Buffering is a rapid physico-chemical phenomenon carried out by various buffers like-intracellular (proteins, phosphates), blood (bicarbonates,

N. Rai
Department of Critical Care Medicine, King George Medical University, Lucknow, India

D. K. Baidya (✉)
Department of Anaesthesiology, Pain Medicine and Critical Care, All India Institute of Medical Sciences, New Delhi, India

V. Kumar et al. (eds.), *Onco-critical Care*,
https://doi.org/10.1007/978-981-16-9929-0_9

haemoglobin, plasma proteins), interstitial fluids (bicarbonates protein), urine (phosphate, ammonia) and bone buffer [3]. Extracellular buffers contributes to 43% of total buffering (by bicarbonate & protein buffers) and remaining 57% is contributed by intracellular buffers [4]. Respiratory response to acid base perturbation occurs rapidly within minutes to hours by alteration in ventilation. Being able to cross cell membranes easily, respiratory response mainatains intracellular pH as well as extracellular pH. Renal response is much slower process (several days to reach maximum capacity) and involves adjustment of bicarbonate excretion by the kidney.

9.2 Respiratory Regulation of Acid Base Disorders

Respiratory regulation involves adjustment of pH due to pCO_2 changes from adaptation in ventilation. This is an inherently rapid process by virtue of CO_2 being lipid soluble and crossing cell membrane rapidly [5]. The quantification of respiratory variation can be estimated by two equations which provide the connection between alveolar ventilation, pCO_2 and pH. These are

$$\text{First}, \text{pa}CO_2 \text{ is proportional to} [V_{CO2}/V_A] \tag{9.1}$$

where:

- $paCO_2$ = Arterial partial pressure of CO_2
- V_{CO2} = Carbon dioxide production by the body
- V_A = Alveolar ventilation

Second, Henderson Hasselbach Equation

$$\text{pH} = 6.1 + \log HCO_3 - 0.03\, pCO_2 \tag{9.2}$$

Where:

- HCO_{3-}: in millimoles per litre
- $PaCO_2$: partial pressure of arterial CO2 in mmHg
- pK: Acid dissociation constant
- 0.03 the solubility of CO_2 in blood

9.3 Renal Regulation of Acid Base Disorders

Kidneys are responsible for excretion of the fixed acids and this is also a critical role even though the amounts involved (70–100 mmols/day). This action is mediated by 2 processes—Excretion of the fixed acids (1 mmol/kg/day) and Reabsorption of filtered bicarbonate at proximal convoluted tubules [5].

9.4 Technicalities of Blood-Gas Analysis

9.4.1 Site Selection

Common sites for arterial sampling includes radial, brachial, axillary femoral or dorsalis pedis artery. There is no evidence that any site is superior to the others. However, being more accessible and comfortable for the patients radial artery is used most often. Allen's test or modified Allen's test can be performed prior to sampling the radial artery to demonstrate collateral flow from the ulnar artery through the superficial palmar arch [6, 7].

9.4.2 Transport and Analysis

Analysis of the sample should be done immediately after sampling. In the event of any delay, arterial blood sample should be placed on ice. Delayed analysis results in increased potassium, phosphates, proteins and LDH. Ongoing metabolism during the delay results in reduced bicarbonate, decreased glucose and increased lactate [8]. Properly timed sample reduces oxygen consumption by leukocytes or platelets (i.e., leukocyte or platelet larceny), which can cause a factitiously low partial pressure of arterial oxygen (PaO_2). Delayed analysis result in falsely low PaO_2 and high $PaCO_2$ (increases at the rate of 3–10 mmHg/hour). [9].

9.4.3 Sources of Errors

Presence of air bubble in an ABG sample can significantly affect $PaCO_2$ and PaO_2 values. $PaCO_2$ and PaO_2 values move towards that of room air (PaO_2 room air is about 150 mm Hg, $PaCO_2$ room air is approximately zero) [10].

Heparin acts as another source of preanalytical error. It can decrease the pH (as heparin and extreme anionic charge and near-total dissociation at physiologic pH) and dilute the $PaCO_2$, resulting in a falsely low value. N+, K+, Cl−, Ca++, glucose, and lactate values also decrease by dilution with liquid heparin.[11] Dead space volume of a standard 5 ml syringe with 1 inch 22 guage needle is 0.2 ml, filling the syringe dead space with heparin provides sufficient volume to anticoagulate a 4 ml blood sample.

Types of syringes also affect the results. O_2 diffuses out at higher PaO_2 from plastic syringes. Glass syringes are less pervious to O_2. Though glass syringes may be preferred, differences are usually not of clinical significance. pH & pCO_2 values unaffected by types of syringes.

Solubility of CO_2 and O_2 is increased in hypothermia [12]. This principle is utilized in temperature based interpretation of blood gases values—*pH stat and alpha stat*. During pH-stat acid-base management, the patient's pH is maintained at a constant level by managing pH at the patient's temperature. pH-stat pH management is temperature-corrected. Compared to alpha-stat, pH stat (which aims for a pCO_2 of

40 and pH of 7.40 at the patient's actual temperature) leads to higher pCO_2 (respiratory acidosis), and increased cerebral blood flow. While, during alpha-stat acid-base management, the ionization state of histidine is maintained by managing a standardized pH (measured at 37C). Alpha-stat pH management is not temperature-corrected—as the patient's temperature falls, the partial pressure of CO_2 decreases (and solubility increases), thus a hypothermic patient with a pH of 7.40 and a pCO_2 of 40 (measured at 37C) will, in reality, have a lower pCO_2 (because partial pressure of CO_2 is lower), and this will manifest as a relative respiratory alkalosis coupled with decreased cerebral blood flow [13, 14].

Clotted sample, haemolysis by inappropriately small needle, haemolysis by syringe vacuum and poorly calibrated ABG analyser are another sources of error.

9.5 Various Models of Acid-Base Interpretation

Three common interpretation models for blood gas analysis are

1. Boston/Physiological approach
2. Copenhagen/Base excess approach
3. Stewart/Physicochemical approach

9.5.1 Boston/Physiological Approach

This approach was developed by Schwartz and colleagues at Tufts University in Boston. Based on Henderson Hasselbach Equation, the Boston approach adapts carbonic acid–bicarbonate buffer system. A primary change in the partial pressure of carbon dioxide (pCO_2) causes a secondary "adaptive" response in the bicarbonate concentration and vice versa and further changes in carbon dioxide or bicarbonate reflect additional changes in acid–base status. The six primary acid–base disorders has been described—two metabolic disorders (acidosis and alkalosis) and four respiratory disorders—acute respiratory acidosis and alkalosis, and chronic respiratory acidosis and alkalosis. Patients with known acid-base disturbances evaluated and using acid–base maps mathematic relationship between $PaCO_2$ and HCO_3- is established.[15].

Boston approach is the most frequently used approach for bed side ABG analysis. The details are presented later in the chapter.

Corrected anion gap is used to account for UMAs (unmeasured anions like albumin), in presence of which uncorrected anion gap may be normal [16]. It is calculated as

$$\text{Anion gap corrected}\left(\text{for albumin}\right) = \text{Calculated anion gap} + 2.5\,\text{x}\left(\text{Normal albumin g / dL} - \text{Observed albumin g / dL}\right)$$

Anion gap assessment in Boston approach evaluates mixed acid-base disorders using delta ratio method. Delta ratio delta identify if the presence of high anion gap

metabolic acidosis 'pure' or if there is coexistant normal anion gap metabolic acidosis (NAGMA) or metabolic alkalosis [17]. Delta ratio is

Increase in AG or AG-12/Decrease in HCO_3^- or 24-HCO_3^-
- Interpretation, 0.4—Normal AG metabolic acidosis
- 0.4–1.0—High AG+ Normal AG metabolic acidosis
- 1–2—Pure high AG metabolic acidosis
- >2—High AG metabolic acidosis + Metabolic alkalosis

The advantages of Boston approach is that it is a physiological, simplest, most rigorous and most serviceable of all the approaches. Drawbacks include-Assumption that pCO_2 & HCO_3 are independent, all buffering of metabolic acids are mediated by HCO_3^-, buffering by intracellular buffers is ignored and does ot many complex acid-base abnormalities like acute acidosis in setting of hypoalbuminemia, hyperchloremic acidosis and lactic acidosis [18].

9.5.2 Copenhagen/Base Excess Approach

The Copenhagen method involves the use of standard base excess (SBE) to distinguish between respiratory and metabolic influences on acid base balance. SBE, also known as the **base excess of extracellular fluid** (BEECF), is a calculated variable from pH, $PaCO_2$ and haematocrit. ABG machine calculates SBE for anaemic blood, with a Hb of 50 g/L using algorithms based on Van Slyke equation, to account for whole blood buffering [19]. Copenhagen approach uses three steps for acid base disorders-

- First step: To evaluate standard base excess in relation to pH and PCO_2
- Second step: To determine secondary response
- Third step: Partition of standard base excess (to consider mixed metabolic acid–base disorders)

The advantages of base excess approach are—SBE value is readily available from most blood gas machines, useful for evaluating acid–base disorders, four calculations of $PaCO_2$ and SBE to evaluate secondary response and easier to remember and perform.

9.5.3 Stewart/Physicochemical Approach

This approach was introduced by Peter Stewart in 1978 [20]. It is based on two main principles-electroneutrality (Sum of all positively charged ions = sum of all negatively charged ions in aqueous solutions) and Conservation of mass (Total concentration = Dissociated + Undissociated forms). pH or $[H^+]$ concentration in the body is determined by two variables, independent and dependent. The independent variables are $PaCO_2$ (controlled by respiratory system), strong ion difference/SID (controlled by kidney) and weak acid/Atot-include serum albumin, phosphate and

globulins (controlled by liver and metabolic state). Dependent variables are [H+], [OH−], [HCO_3−].

Normal value of SID ranges between 38–44 mmol/L. (value less than 38 mmmol/L is interpreted as SID acidosis and higher than 44 mmol/L is SID alkalosis) [21].

Stewart approach identifies 6 acid base disorders-Respiratory acidosis and alkalosis, SID acidosis and alkalosis, Increased Atot acidosis and decreased Atot alkalosis.

$$SID_a = \left(\left[Na+\right]+\left[K+\right]+\left[Mg++\right]+\left[Ca++\right]\right)-\left(\left[Cl-\right]+\left[\text{lactate}\right]\right)$$

$$SID_e = \left[HCO_3-\right]+\left[\text{albumin}\right]+\left[\text{phosphates}\right]$$

Where, SID_a is strong ion difference apparenrent and SID_e is strong ion difference effective. The difference between SID_a and SID_e is stong ion gap (SIG) and SIG is close to zero in normal situations. SIG Quantifies amount of unmeasured anions present in the plasma. [20, 21].

Advantages of Stewart approach are quantitative mathematical explanation of acid-base disorders, a more scientific approach which apply concepts of physical chemistry to traditional acid-base concepts and a logical framework for design of resuscitation fluids. Disadvantages are complex, complicated, and difficult to apply approach at bedside, substantially different to well-validated classical Boston approach, numerous variables creates confusion and no evidence that this approach has any influence on mortality.

9.6 What to Correct, How Much to Correct and How to Correct?

Being the most commonly used approach, physiological/Boston approach is selected here as a primary method for correction of acid base disorders.

9.7 Approach to Patient with Metabolic Derangements

Bedside approach to patient with metabolic acid base disorders involve

- Identification of presence of metabolic acidosis (pH < 7.30, serum [HCO_3^-] < 24 mEq/l)/metabolic alkalosis (pH > 7.40, serum [HCO_3^-] > 24 mEq/l)
- Respiratory compensation-adequate or inadequate
- Estimation of AG (anion gap) in the presence of metabolic acidosis
- Acknowledge presence of mixed disorders using delta ratio

9.7.1 Expected Respiratory Compensation to Metabolic Acidosis [15]

Rule 1: for Metabolic Acidosis

$$\text{Expected pCO2} = 1.5\left[\text{HCO}_3\right] + 8\left(\text{Range} : +/-2\right)$$

9.7.2 Anion Gap

Anion gap (AG) is used for evaluation of metabolic acidosis. The sum of the positive and negative ion charges in plasma are equal in vivo: [Na+] + [K+] + [Ca2+] + [Mg2+] + [H+] + unmeasured cations = [Cl−] + [HCO_3−] + [CO_3^{2-}] + [OH−] + albumin+phosphate+sulfate+lactate+unmeasured anions (e.g., inorganic anions) [22–24]. Other ions being in extremely low concentration, following formulas are used to estimate AG [25]:

$$\text{AG}\left(\text{simple}\right) = \left(\left[\text{Na} + -\left(\left[\text{Cl}-\right] + \left[\text{HCO3}-\right]\right)\right) = 12 - 14\,\text{mEq / L}$$

$$\text{AG}\left(\text{conventional}\right) = \left(\left[\text{Na} =\right] + \left[\text{K} +\right] - \left(\left[\text{Cl}-\right] + \left[\text{HCO3}-\right]\right) = 14\,\text{to}\,18\,\text{mEq / L}\right.$$

$$\text{AG}\left(\text{modern}\right) = \left(\left[\text{Na} =\right] + \left[\text{K} +\right] - \left(\left[\text{Cl}-\right] + \left[\text{HCO3}-\right] + \left[\text{Lactate}\right]\right) = 14\,\text{to}\,18\,\text{mEq / L}\right.$$

Corrected anion gap is used to account for UMAs (unmeasured anions like albumin), in presence of which uncorrected anion gap may be normal.[16] It is calculated as

$$\text{Anion gap corrected}\left(\text{for albumin}\right) = \text{Calculated anion gap} + 2.5\,\text{x}\left(\text{Normal albumin g / dL} - \text{Observed albumin g / dL}\right)$$

9.8 Causes and Treatment of High Anion Gap Metabolic Acidosis

L-Lactic acidosis	Correction of underlying disorder, correction of shock, improving oxygenation, removing offending drugs, treatment of seizures, Hemodialysis may be indicated in resistant cases
Diabetic ketoacidosis	Fluids and insulin
Methanol toxicity	Oral charcoal, soda bicarbonate, fomepizole
Salicylate toxicity	Alkalinization of urine, Haemodialysis
Ethylene glycol	Ethanol or fomepizole
Propylene glycol toxicity	Stop the drug infusion
Impaired lactate clearance in liver failure	Supportive management, NAC
D-Lactic acidosis	sodium bicarbonate and antimicrobial agents

9.9 Nonanion Gap Acidosis

Bicarbonate loss is the primary pathophysiology for nonanion gap acidosis. Cl^- is raised maintaining the anion gap to normal. Gastrointestinal losses and renal etiology are the primary causes of nonanion gap acidosis and urine anion gap (UAG) is used to distinguish between them.

$$\mathrm{UAG} = \left(\mathrm{Urine}\left[\mathrm{Na}+\right] + \mathrm{Urine}\left[\mathrm{K}+\right]\right) - \left(\mathrm{Urine}\left[\mathrm{Cl}-\right]\right)$$

The UAG is normally zero or slightly positive. In the setting of a nonanion gap acidosis, the appropriate renal response would be to increase ammonium excretion, as NH4Clcausing the UAG to become negative, usually ranging from −20 to −50 mEq/L. This is seen in nonrenal causes of.

nonanion gap acidosis, such as severe diarrhea. In renal derangements, like chronic kidney disease (CKD) and distal renal tubular acidosis (RTA), the UAG will remain positive or become only slightly negative.

Normal anion gap metabolic acidosis
1. Loss of bicarbonate
• Gastrointestinal conditions (diarrhea, ureteral diversions, biliary or pancreatic fistulas)
2.Renal tubular acidosis-Type 1, 2 and 4
3. Other causes: fluid resuscitation with saline, hyperalimentation (lysine, histidine, or arginine hydrochloride), administration of hydrochloride, ammonium chloride, cholestyramine, hippuric acid, sulfuric acid

9.10 Metabolic Alkalosis

The diagnosis of metabolic alkalosis is sometimes a clinical one, but it is often found incidentally of laboratory work. A higher serum bicarbonate level in association with hypokalemia is highly suggestive of metabolic alkalosis.

Rule 2: Respiratory compensation for a Metabolic Alkalosis [15]

$$\mathrm{Expected\ pCO2} = 0.7\left[\mathrm{HCO_3}\right] + 20\left(\mathrm{Range}: +/-2\right)$$

9.11 Causes of Metabolic Alkalosis

Urine chloride concentration (U_{Cl}) a useful tool in the diagnosis and management of metabolic alkalosis [26].

Chloride Responsive ($U_{Cl} \leq 25$ mEq/L)	Chloride Resistant (UC > 25 mEq/L)
Gastrointestinal losses-vomiting, Nasogastric suction – Post hypercapnia – Cystic fibrosis – Prior loop/thiazide diuretics use – Chloride losing diarrhoea-villous adenoma, laxative abuse **Treatment**—administration of 0.9% or 0.45% NaCl, potassium repletion	**With high B.P** – Primary/secondary hyperaldosteronism, Cushing's syndrome, recent diuretics use, renal artery stenosis, rennin secreting tumor, hydroxylase deficiencies, licorice intake **With normal B.P** – Bartter syndrome, Gitelman syndrome **Other causes** – Alkali intake or administration Milk alkali syndrome – Severe potassium depletion **Treatment—**Treat the underlying cause, potassium repletion, Acetazolamide (metabolic alkalosis associated with volume overload complicated by the need for continued attempts at diuresis), intermittent hemodialysis with the bicarbonate bath decreased to the lowest allowable value or a continuous hemofiltration modality using primarily a nonbicarbonate, noncitrate replacement fluid.

9.12 Approach to Respiratory Acid–Base Disorders [27, 28]

Bedside approach to patient with respiratory acid base disorders involve

- Identification of presence of respiratory acidosis (pH < 7.30, $PaCO_2$ > 45 mm Hg)/respiratory alkalosis (pH > 7.40, $PaCO_2$ < 45 mm Hg)
- Metabolic compensation-adequate or inadequate
- Determine if mixed acid base disorder is present
- Treat the underlying causes

9.13 Expected Metabolic Compensation to Respiratory Derangements [15]

Rule 3: Acute Respiratory Acidosis

$$\text{Expected}\left[HCO_3\right] = 24 + \left\{\left(\text{Actual}\, pCO_2 - 40\right)/10\right\}$$

Rule 4: Chronic Respiratory Acidosis

$$\text{Expected}\left[HCO3\right] = 24 + 4\left\{\left(\text{Actual}\, pCO2 - 40\right)/10\right\}$$

Rule 5: Acute Respiratory Alkalosis

$$\text{Expected}\left[\text{HCO3}\right] = 24 - 2\left\{\left(40 - \text{Actual pCO2}\right)/10\right\}$$

Rule 6: Chronic Respiratory Alkalosis

$$\text{Expected}\left[\text{HCO3}\right] = 24 - 5\{\left(40 - \text{Actual pCO2}\right))/10\}\left(\text{range} : +/-2\right)$$

The 0.008 rule: The pH change in response to an acute respiratory acid-base disturbance

$$\text{pH} = 7.40 - \left(\left(\text{PaCO}_2 - 40\right)\text{x}\,0.008\right))$$

The 0.003 rule: The pH change in response to a chronic respiratory acid-base disturbance

$$\text{pH} = 7.40 - \left(\left(\text{PaCO}_2 - 40\right)\text{x}\,0.003\right))$$

9.14 Causes of Respiratory Derangements

Respiratory acidosis	Respiratory alkalosis
Decreased alveolar ventilation – Central respiratory depression e.g. by drugs or post-ictally – Neuromuscular disorders resulting in weakness – Lung or chest wall defects resulting in restriction – Airway obstruction, e.g. after a seizure – Inadequate mechanical ventilation	Respiratory control centre – Head injury, stroke – Anxiety, fear, stress, pain – Salicylates – Pregnancy – Chronic liver disease – Hypoxia
Increased inspired fraction of CO_2 – Rebreathing of CO_2-containing expired gas – Addition of CO_2 to inspired gas – Insufflation of CO_2 into body cavity (eg for laparoscopic surgery)	Pulmonary receptors – Pulmonary embolism – Pneumonia – Asthma – Pulmonary oedema
Increased metabolic CO_2 production – Malignant hyperthermia – Thyrotoxicosis – Phaeochromocytoma – Sepsis – Liver failure	
Treatment – Addressing the underlying etiology (bronchodilators for patients with asthma and chronic obstructive pulmonary disease, reversal of medication/drug effects, treatment of pulmonary edema, treatment of neuromuscular diseases, and mechanical ventilation	Treatment – Addressing the underlying etiology (Decreasing minute ventilation in mechanically ventilated patients, reassurance and anxiolytics for psychogenic hyperventilation, acetazolamide to induce a metabolic acidosis to compensate for the respiratory alkalosis caused by high altitudes)

References

1. Adrogue HE, Adrogue HJ. Acid-base physiology. Respir Care. 2001 Apr;46(4):328–41.
2. Johnston DG, Alberti KG. Acid-base balance in metabolic acidoses. Clin Endocrinol Metab. 1983 Jul;12(2):267–85.
3. Hasan A. Buffer systems. In: Handbook of blood gas/acid-base interpretation. London: Springer; 2013. https://doi.org/10.1007/978-1-4471-4315-4_4.
4. Worthley LI. Hydrogen ion metabolism. Anaesth Intensive Care. 1977 Nov;5(4):347–60. pmid:23014.
5. Hamm LL, Nakhoul N, Hering-Smith KS. Acid-base homeostasis. Clin J Am Soc Nephrol. 2015;10(12):2232–42.
6. Bartella AK, Flick N, Kamal M, Steegmann J, Kloss-Brandstätter A, Teichmann J, Hölzle F, Lethaus B. Hand perfusion in patients with physiological or pathological Allen's tests. J Reconstr Microsurg. 2019 Mar;35(3):182–8.
7. Romeu-Bordas Ó, Ballesteros-Peña S. Reliability and validity of the modified Allen test: a systematic review and metanalysis. AbrEmergencias. 2017;29(2):126–35.
8. Tanner M, Kent N, Smith B, Fletcher S, Lewer M. Stability of common biochemical analytes in serum gel tubes subjected to various storage temperatures and times pre-centrifugation. Ann Clin Biochem. 2008;45(4):375–9.
9. Hess CE, Nichols AB, Hunt WB, Suratt PM. Pseudohypoxemia secondary to leukemia and thrombocytosis. N Engl J Med. 1979;301:361.
10. Biswas CK, Ramos JM, Agroyannis B, Kerr DN. Blood gas analysis: effect of air bubbles in syringe and delay in estimation. Br Med J (Clin Res Ed). 1982;284(6320):923–7. https://doi.org/10.1136/bmj.284.6320.923.
11. Bageant RA. Variations in arterial blood gas measurements due to sampling techniques. Respir Care. 1975;20:565.
12. Ashwood ER, Kost G, Kenny M. Temperature correction of blood-gas and pH measurements. Clin Chem. 1983;29(11):1877–85.
13. Tarik Kiziltan H, Baltali M, Bilen A, Seydaoglu G, Incesoz M, Tasdelen A, Aslamaci S. Comparison of alpha-stat and pH-stat cardiopulmonary bypass in relation to jugular venous oxygen saturation and cerebral glucose-oxygen utilization. Anesth Analg. 2003;96(3):644–50.
14. Sakamoto T, Kurosawa H, Shin'oka T, Aoki M, Isomatsu Y. The influence of pH strategy on cerebral and collateral circulation during hypothermic cardiopulmonary bypass in cyanotic patients with heart disease: results of a randomized trial and real-time monitoring. J Thorac Cardiovasc Surg. 2004;127(1):12–9.
15. Berend K, de Vries APJ, Gans ROB. Physiological approach to assessment of acid–base disturbances. N Engl J Med. 2014;371:1434–45.
16. Figge J, et al. Crit Care Med. 1998;26:1807.
17. Tsapenko MV. Modified delta gap equation for quick evaluation of mixed metabolic Acid-base disorders. Oman Med J. 2013;28(1):73–4. https://doi.org/10.5001/omj.2013.18.
18. Adrogué HJ, Gennari FJ, Galla JH, Madias NE. Assessing acid-base disorders. Kidney Int. 2009;
19. Kofstad J. Base excess. Clin Chim Acta. 2001.
20. Stewart PA. Independent and dependent variables of acidbase control. Resp Physiol. 1978;33:9–26.
21. Stewart PA. How to understand acid-base: a quantitative acid-base primer for biology and medicine. New York: Elsevier; 1981.
22. Feldman M, Soni N, Dickson B. Influence of hypoalbuminemia or hyperalbuminemia on the serum anion gap. J Lab Clin Med. 2005;146:317–20.
23. Moe OW, Fuster D. Clinical acid-base pathophysiology: disorders of plasma anion gap. Best Pract Res Clin Endocrinol Metab. 2003;17:559–74.

24. Kellum JA. Making strong ion difference the “Euro” for bedside acid-base analysis. In: Vincent JL, editor. Yearbook of intensive care and emergency medicine. Berlin: Springer; 2005. p. 675–85.
25. Emmett M, Narins RG. Medicine (Baltimore). 1977;56:38.
26. Soifer JT, Kim HT. Approach to metabolic alkalosis. Emerg Med Clin North Am. 2014;32(2):453–63.
27. Epstein SK, Singh N. Respiratory acidosis. Respir Care. 2001;46(4):366–83.
28. Foster GT, Vaziri ND, Sassoon CS. Respiratory alkalosis. Respir Care. 2001;46(4):384–91.