Acidosis: Diagnosis and Treatment

6

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6.1 Introduction

Acidosis is characterized by a decrease in plasma pH. The first chapter will focus on the pathophysiological principles responsible for the development of an acidosis. Clinical signs of an acidosis are not specific, and the diagnosis is based on the context, on the history, and finally on the biological abnormalities. Metabolic acidosis (MA) must be distinguished from respiratory acidosis (RA) because causes and treatment are totally different. The treatment of acidosis will be developed in the last chapter.

6.2 Pathophysiology of Acidosis

Stricto sensu, the term "acidemia" refers to a low plasma pH (<7.38 ± 2) [1]. On the other hand, acidosis defines a pathophysiological process which induces an increase in plasma proton concentration ($[H^+]$) (expressed by a decrease in pH) [1–5]. Indeed, a complex acid-base disorder can associate both acidosis and alkalosis, the final resulting value of pH depending on the severity of each disorder. In practical, both acidemia and acidosis are routinely merged and only acidosis is routinely used.

The pathophysiology of MA differs according to the concept used for their interpretation. In the traditional Henderson-Hasselbalch approach, the decrease in pH is caused by an excess of plasma protons issued from an organic or a mineral acid or

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by a loss of plasma bicarbonates [1, 2, 4]. The Stewart concept which considers all of the involved parameters but not only bicarbonates attributes the decline in pH to a greater dissociation of plasma water leading to elevate plasma proton concentration according to the following relation: $H_2O \Leftrightarrow H^+ + OH^-$. Two independent major parameters may impact this degree of dissociation and in turn the plasma pH: the strong ion difference (SID) which is the difference between the strong cations and anions and the amount of weak acids (cf Chap. 5). Any decrease in plasma SID, whether resulting from a decreased strong cations (Na^+) or an increased strong anions (Cl^-, lactate$^-$, ketone bodies$^-$), induces a decrease in pH and bicarbonate concentration. Any increase in weak acids (albuminate) will lead to comparable consequences [6–8]. Finally, irrespective of its mechanism, MA is characterized by a low pH and plasma bicarbonates concentration and can be calculated by the mathematical Henderson-Hasselbalch equation: $pH = 6{,}10 + \log [HCO_3^-]/0.03 \times PaCO_2$ (6.1 being the constant half-dissociation pKa of plasma bicarbonate, 0.03 being the solubility coefficient of CO_2). The secondary adaptative respiratory response (inappropriately called "compensation") consists in hyperventilation for increasing CO_2 removal, aiming to attenuate the decrease in plasma pH. In simple MA (isolated disorder), the magnitude of the secondary respiratory response can be calculated and is considered as the expected (or predictable) $PaCO_2$ (Table 6.1). However, it must be underlined that such an answer never enables to normalize completely the pH.

Regardless the pathophysiological approach, RA is always initiated by an elevation of $PaCO_2$ [6–9]. The normal daily endogenous production of CO_2 represents 15–20,000 meq/d, which comes essentially from protein metabolism. The lung is the major organ that enables to remove CO_2 (volatile anion). Therefore, an efficient alveolar ventilation associated with an appropriate hemodynamic status is needed to maintain a constant level of $PaCO_2$. It is important to distinguish acute from chronic RA which conducts to different clinical, biological signs and has different causes. Acute RA is associated with a slight to a moderate secondary renal response due to the short delay for the kidney to develop and exert it completely; in this situation, the predictable response can be evaluated as follows: any increase of $PaCO_2$ by 10 mmHg induces a 1 meq/L increase of HCO_3^- (Table 6.1). In chronic RA, the

Table 6.1 Characteristics of predictable responses in case of simple metabolic and respiratory acidosis

Primary acidosis	Level of response	Delay	Limits
Metabolic disorders			
– Acidosis ($\searrow HCO_3^-$)	– $\searrow PaCO_2 = 1.3 \times \searrow HCO_3^-$	– 12–24 h	– $PaCO_2$ = 10 mmHg
Respiratory disorders			
– Acidosis ($\nearrow PaCO_2$)			
• Acute	– $\nearrow$ 10 mmHg $PaCO_2$ =	– 5–10 min	– HCO_3^- = 30 meq/L
	$\nearrow$ 1 meq.L^{-1} HCO_3^-		
• Chronic	– $\nearrow$ 10 mmHg $PaCO_2$ =	– 72–96 h	– HCO_3^- = 45 meq/L
	$\nearrow$ 3.5 meq.L^{-1} HCO_3^-		

secondary renal response can develop completely to reach a steady-state level, and an increase of 10 mmHg of $PaCO_2$ induces a 3.5 meq/L elevation of HCO_3^- (Table 6.1). This increase in plasma bicarbonate concentration is usually associated with a simultaneous urinary excretion of chloride which induces an alkalosis: this is the classical metabolic alkalosis associated with chronic RA. In all cases, the sole expected renal response cannot normalize totally the decrease in pH. A normal plasma pH in the presence of an abnormal value of $PaCO_2$ or HCO_3^- has to make evoke a mixed acid-base disorder (association of 2–3 disorders).

6.3 Diagnosis of Metabolic Acidosis

The diagnosis of MA can only be confirmed with certainty using biological data. However, questioning on the history and on the underlying comorbidities associated with a clinical exam remains an essential step for the diagnosis.

6.3.1 Questioning: Clinical Signs

The first step of acidosis diagnosis consists in a careful clinical evaluation. Questions must precise the context and the possible absorption of toxic or drugs that may orientate the diagnosis. Clinical signs are not specific and present only in severe MA [1, 4, 6, 9]. Cardiovascular manifestations include arrhythmias, collapse, or shock. Neurological signs can be slight to severe: headache, obtundation, confusion, seizures, or coma. A skeletal muscle weakness can be present due to the reduction in intracytoplasmic ionized calcium. Acidosis can also manifest by gastrointestinal symptoms such as nausea, vomitings, and diarrhea. Hyperventilation as the secondary response to MA manifests as regular, wide, and deep respiratory cycles. Patients with controlled ventilation can become unsynchronized from the ventilator. Acidosis causes pulmonary vasoconstriction and a shift of the hemoglobin dissociation curve on the right, favoring in turn tissues O_2 delivery. Prolonged MA (as in chronic renal insufficiency) has metabolic consequences: increased protein catabolism, insulin resistance, modifications of calcium metabolism, hyperparathyroidism with osteodystrophy, abnormal secretion of thyroid, and growth hormones.

6.3.2 Biological Signs

The diagnosis with certainty is based on measured and calculated parameters issued from arterial samples to perform simultaneously blood gas analysis and electrolytes measurements. The absolute criteria for diagnosing MA are the association of both a low pH and bicarbonate concentration (and a negative standard base excess, SBE) and a decrease in $PaCO_2$ (respiratory response) [1, 3, 6]. MA is the sole disorder (pure or simple MA) if the measured $PaCO_2$ is equal to the predictable one and if no additional metabolic alkalosis is associated. MA is a part of a mixed acid-base

disorder when the secondary renal response differs from what would be expected [1]. RA is associated with a primary MA when actual $PaCO_2$ exceeds predictable $PaCO_2$; respiratory alkalosis is associated with a primary MA when actual $PaCO_2$ is lower than the predictable one.

6.3.3 Etiologic Diagnosis

MA is commonly classified according to the value of the anion gap (AG) and of serum chloride concentration [1, 3]. The AG is based on plasma electroneutrality which indicates that the sum of cations is equal to that of anions. The AG reflects the presence of unmeasured anions and is calculated according to the following formula: $AG = Na^+ - (Cl^- + HCO_3^-) = 8–12$ meq/L [5, 8]. Therefore, there are two groups of MA, those with an elevated AG and those with a normal AG and hyperchloremia (Tables 6.2 and 6.3, Fig. 6.1). The elevated unmeasured anion concentration is responsible for the increase in AG which is associated with the decrease in pH and bicarbonates. MA caused by hyperchloremia (classical mineral acidosis) or by bicarbonate loss does not induce any changes in the AG value. However, the AG tool may be imprecise and inaccurate, especially in critically ill patients with complex acid-base disorders. Indeed, the weak anion albuminate represents a major component of the AG; therefore, its variation may lead to misinterpretation of acid-base disorders [1, 2, 10, 11]. For a constant pH, a 10 g/L variation of albumin modifies the AG of approximately 2.5 meq/L. To minimize this problem, Figge et al. [10] have proposed to calculate the corrected AG according to the following formula: cAG (meq/L) = AG + 0.25 (40 − actual Alb). However, this correction is not always sufficient to avoid this pitfall because nonproportional between variations of strong cations (Na^+) and strong anions (Cl^-) can also modify AG values [11, 12].

Table 6.2 Classification of acidosis according to the Henderson-Hasselbalch and Stewart concepts

Metabolic acidosis		Respiratory acidosis
Henderson-Hasselbalch concept		
pH	HCO_3^-	$PaCO_2$
↘	↘	↗
• High anion gap		
• Hyperchloremia		
Stewart concept		
SID	Weak acids	$PaCO_2$
↘	↗	↗
• Hyperchloremia	• ↗ Albuminate	
• Hyponatremia	• ↗ Phosphate	
• ↗ XA^- (± ↗ SIG)		

SID strong ion difference, *XA^-* unmeasured strong acids, *SIG* strong ion gap

Table 6.3 Classification of metabolic acidosis according to the anion gap (AG)

High AG metabolic acidosis
– *Caused by organic acid production*
• Hyperlactatemia
• Ketone bodies: diabetic ketoacidosis, fast ketoacidosis
– *Caused by a decreased renal excretion of organic acids: acute renal failure*
• Hyperphosphatemia, hypersulfatemia
– *Caused by an exogenous toxic anion poisoning*
• Salicylates
• Methanol, ethylene glycol
• Paraldehyde
Normal AG metabolic acidosis
– *Renal origin*
• Renal tubular acidosis
• Hyperparathyroidism
• Hypoaldosteronism
• Neoplasia
– *Gastrointestinal origin*
• Diarrhea
• Grelic/pancreatic draining or fistula drainage
– *Dilutional acidosis = hyponatremia*
– *Exogenous intake (iatrogenic or overdoses)*
• NH_4Cl, $CaCl_2$, $MgCl_2$
• Parenteral nutrition
• Inhibitors of carbonic anhydrase
• Bile acid sequestrant (cholestyramine)

Based on the Stewart approach, MA can be caused by a decreased SID or by an increased amount of weak acids (Table 6.2). The decrease in SID can be the consequence of three abnormalities [7]:

– A decrease of the difference between the major nonorganic (nonmetabolizable) extracellular strong cation (Na^+) and strong anion (Cl^-). Due to their low plasma concentration, magnesium (Mg^{++}), calcium (Ca^{++}), and potassium (K^+) cannot induce relevant modifications of SID and in turn of pH [1, 2].
– An increase of organic strong anions (lactate, ketone bodies).
– The presence of abnormal exogenous strong anions such as toxic or drugs.

The presence of organic (exogenous or endogenous) strong anions will be detected by calculating the "strong ion gap" (SIG) given by the following formula: SIG (meq/L) = apparent SID − effective SID (Table 6.4). It is not unusual to observe some associations between these abnormalities [7, 13]. The sole slight or moderate increase in weak anions (sulfate, phosphate) cannot really modify the pH because as compared to previous parameters, this absolute amount is negligeable [2]. All calculations needed for the diagnosis are summarized in Table 6.5 and Fig. 6.2.

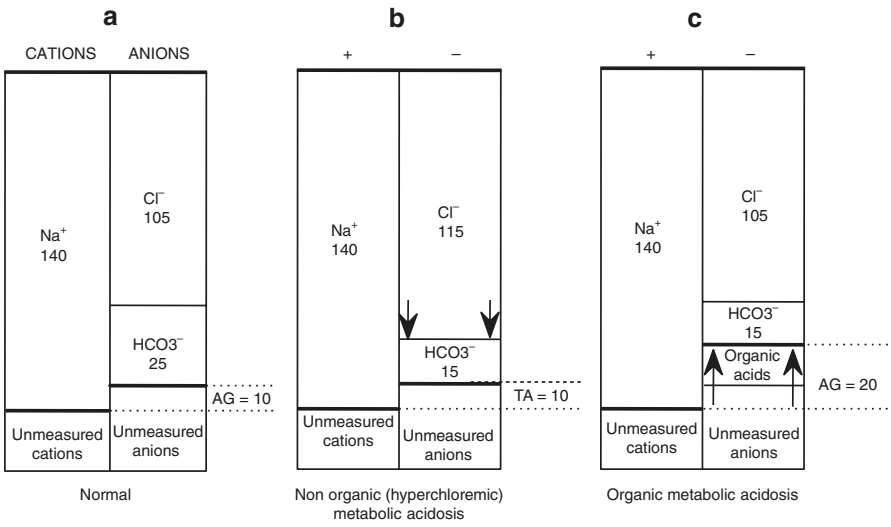

Fig. 6.1 Schematic representation of the two categories of metabolic acidosis according to the variation in anion gap (AG). (**a**) Normal situation: AG represents the difference between all unmeasured anions and cations present in plasma. (**b**) Mineral hyperchloremic metabolic acidosis: each excessive molecule Cl^- releases a proton H^+ which is buffered by one HCO_3^- to maintain electroneutrality; chloride Cl^- is elevated, and as it enters in the calculation of AG, this latter remains normal <12 mmol/L. (**c**) Organic metabolic acidosis: each excessive strong anion releases a proton H^+ which is buffered by one HCO_3^- to maintain electroneutrality; the remaining strong dissociated anion does not enter in the calculation of AG leading to a high AG >12 mmol/L

Table 6.4 Classification of metabolic acidosis according to plasma strong ion gap (SIG) and urinary strong ion difference (SID)

High SIG metabolic acidosis	Normal SIG metabolic acidosis
Endogenous anions	*Urinary SID > 0 = renal causes*
• Lactate • Ketone bodies	• Renal tubular acidosis
Exogenous anions	*Urinary SID < 0 = extrarenal causes*
• Salicylate • Methanol, ethylene glycol, paraldehyde	• Gastrointestinal losses: diarrhea, grelic/pancreatic draining, uretero-digestive anastomosis, neobladder • Iatrogenic: parenteral nutrition, unbalanced solutions infusion • Anion exchange resins (bile acid sequestrant)
Unmeasured anions	
• Intermediate substrates of the Krebs cycle (produced during sepsis, renal or liver insufficiency/failure): pyroglutamate, formate, oxalate, glycolate, etc.	

Several studies have reported that the Stewart method allows to identify more acid-base disorders, especially in case of mixed disorders and more precisely their mechanisms in intensive care unit when compared with the traditional approach [14–16]. Indeed, an acid-base disorder has been identified in 14% additional patients with the Stewart approach as compared to the Henderson-Hasselbalch one [16].

Table 6.5 Formulas required for the etiologic diagnosis of metabolic acidosis

– AG = $Na^+ - (Cl^- + HCO_3^-)$ = 8–12 mEq/L or = $(Na^+ + K^+) - (Cl^- + HCO_3^-)$ = 8–17 mEq/L
– Corrected AG = calculated AG + 0.25 × (40 − measured albumin [g/L])
• Standard base excess = $0.9287 \times [HCO_3^- - 24.4 + 14.83 \times (pH - 7.4)]$ = 0 mEq/L
– SIDa = $(Na^+ + K^+ + Ca^{++} + Mg^{++}) - (Cl^- + lactate^-)$ = 40 ± 2 mEq/L
– SIDe = $[HCO_3^-]$ + [albumin (g/L) × (0.123 × pH − 0.631)] + phosphate (mEq/L) × (0.309 × pH − 0.469)] = 40 ± 2 mEq/L
– SIG = SIDa − SIDe = 2–6 mEq/L
– Urinary SID = (urinary Na + urinary K) − urinary Cl

AG plasma anion gap, *SIDa* apparent strong ion difference, *SIDe* effective strong ion difference, *SIG* strong ion gap

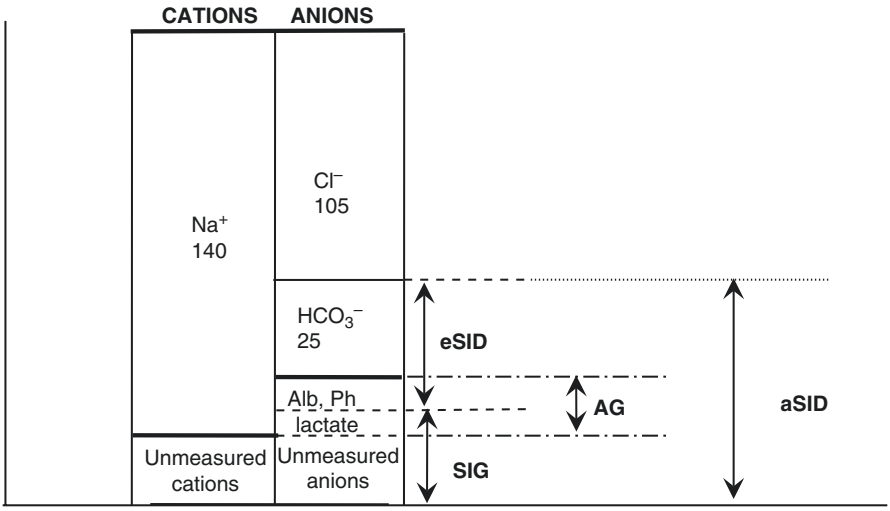

Fig. 6.2 Representation of plasma positive and negative charges. Unmeasured cations include Ca^{++} and Mg^{++}; SID is always positive, with a normal value of 40 meq/L. The normal difference between eSID and aSID (SIG) is of 0–5 meq/L, but increases if unmeasured strong anions accumulate. AG is also composed by unmeasured strong anions by also of weak acids such as albuminate and phosphate. Normal AG value is approximately 12 meq/L; it elevates in case of accumulation of organic acids (lactate, ketone bodies). *AG* plasma anion gap, *aSID* apparent strong ion difference, *eSID* effective strong ion difference, *SIG* strong ion gap, *Alb* albuminate, *Ph* phosphates

Recently, Szrama et al. [14] confirmed that critically ill patients with sepsis suffered from mixed acid-base disorders. Hypoalbuminemia was present in 100% of patients, and despite a normal standard base excess, patients presented acid-base abnormalities: hyperlactatemia, hyperchloremia, and a high SIG were observed in 21.3%, 98.4%, and 13.9%, respectively. On the other hand, acidosis (SBE < −2) was associated with hyperlactatemia in 35% and hyperchloremia in 96.9% of cases, and alkalosis (SBE > +2) was associated with hyperlactatemia in 18.4% and hyperchloremia in 88% of cases.

6.3.3.1 High SIG Metabolic Acidosis

Metabolic Acidosis Caused by Hyperlactatemia (see Chap. 8)

This represents one of the major causes of MA in intensive care unit, as it is observed in approximately 2/3 of patients [7, 11, 17]. Lactic acidosis is commonly defined as a metabolic acidosis associated with an elevated serum lactate concentration ≥ 5 mmol/L. However, hyperlactatemia is not obligatory associated with acidosis [12, 18]. Lactate is a strong organic (metabolizable) anion and is included in the group of MA with an elevated AG and cAG. However, the low precision of these two parameters forces us to measure lactatemia to confirm the diagnosis [7, 12]. According to the Stewart concept, an acidosis with hyperlactatemia is characterized by a low SID associated with a high SIG. In 1976, Cohen and Wood classified MA with hyperlactatemia into two groups according to the presence or not of an impairment of tissue oxygenation. Nevertheless, this classification proves to be inaccurate, as hyperlactatemia is caused by various disorders which associates aerobic and anaerobic metabolism such as observed during sepsis [1, 7]. In these situations, an increased lactate/pyruvate ratio can only confirm that hyperlactatemia is caused by an anaerobic metabolism [7]. But in clinical practice, the measurement of serum pyruvate concentration is difficult and not routinely available because such a measurement is long and requires to be performed rapidly as pyruvate is very labile.

Metabolic Acidosis Caused by Ketoacidosis

Diabetic ketoacidosis (DKA) is one of the acute metabolic complications of diabetes. Since more than 15 years, the mortality rate reaches less than 5%, thanks to an improved medical management [11, 19–21]. DKA is related to the accumulation in plasma of ketone bodies (acetone, acetoacetate, ß-hydroxybutyrate), all strong organic anions which are issued from an enhanced ß-oxidation of free fatty acids due to insulin deficiency and excessive concentration in counter-regulatory hormones. DKA is classically described as a pure MA with an elevated AG associated with hyperglycemia. However, it is preferred to characterize it by a decreased SID and an increased SIG which reflects the presence of excessive amount of strong organic anions (in this case ketone bodies). The determination of serum ketone bodies (ketonemia) is long and leads to perform an indirect but rapid detection in urines (ketonuria). Usually, polyuria caused by hyperglycemia induces an acute renal failure which is responsible for an accumulation of weak acids (sulfate, phosphate) that worsen MA. In the early period, the decrease in renal excretion of ketone bodies is associated with a concomitant increase in urinary chloride excretion in order to maintain urine electroneutrality. This phenomenon may cause a slight metabolic alkalosis associated with the MA. This hypochloremic metabolic alkalosis is aggravated by frequent vomitings [21]. Therefore, acid-base disorders of DKA are rarely a simple isolated organic MA. During the treatment of DKA, the development of hyperchloremia is frequently observed and is caused by two phenomenons: a high exogenous intake of chloride related to unbalanced crystalloids infused for vascular expansion and the improvement of renal function which allows to eliminate ketone bodies in urines in return to chloride reuptake. Therefore, during the improvement

of DKA, the early organic MA is progressively replaced by a hyperchloremic MA. The diagnosis of DKA is usually easy, based on the history, the context, and the classical Küssmaul polypnea. The efficacy of treatment is based on the decreased rate of hyperglycemia and on the decrease of ketone body production which is monitored by ketonuria. It must be underlined that ketone body determination by urine dipsticks uses a nitroprusside reagent which reacts only with acetoacetate (and acetone). When ketonemia is strongly high, the thermodynamic reaction favors the production of ß-hydroxybutyrate from acetoacetate and conversely [22]. This explains the discordant results between ketonuria and ketonemia (and the evaluation of DKA severity). When the patient's condition improves and ketonemia decreases, the common trap is to observe a paradoxical re-increase of ketonuria which simply indicates the inverse preferential thermodynamic metabolism of ß-hydroxybutyrate in acetoacetate. Capillary measurement of ketonemia has been advocated, using point of care devices, which presents the advantage to be rapid, in real time and available at bedside. However, values from these devices, even with the most recent generation, remain not precise and dependent on the staff training. Finally, recommendations on the method for measuring ketone body production (in plasma, capillary, or urine) for the diagnosis of DKA and its severity and monitoring its resolution remain debated [22].

The prolonged fast which is physiologically accompanied by insulinopenia and hyperglucagonemia can also stimulate ketone body production leading to the classical fast ketoacidosis, with comparable acid-base disorders as in diabetic patients.

Metabolic Acidosis Caused by Toxic Intake

In these situations, MA is also caused by the accumulation of strong anions and is characterized by a high AG or a decreased SID with an increased SIG. These strong anions are usually issued from drug or toxic catabolism (salicylate, pyroglutamate, formate, oxalate, and glycolate) [23].

Acetylsalicylate overdose associates MA with a predominant respiratory alkalosis due to the stimulation of respiratory centers by salicylate. Therefore, pH is frequently alkaline, especially within the first hours and in less severe situations [1, 2]. The association of consciousness disorders with MA with high AG/SIG in the context of poisoning must orientate to an intake of methanol or ethylene glycol. This diagnosis is strongly evoked in case of an elevated osmolar gap (measured plasma osmolarity − calculated plasma osmolarity [>10 mosm/L]). A direct measurement of serum concentration of these two toxics can confirm the diagnosis. The oxidation of methylene in formate and formaldehyde may cause blindness due to a direct toxicity on the optic nerve. The ethylene glycol poisoning can manifest by neurological disorders, cardiovascular collapse, and liver and renal failures. Its catabolism in oxalate and formate is responsible for the decreased SID and the increased SIG.

In critically ill patients, SIG is frequently elevated, independently of any abnormal excessive amount of lactate, ketone bodies, or toxics. The elevated SIG indicates the presence of unknown strong anions which seems to be intermediate substrates issued from the Krebs cycle [23].

Metabolic Acidosis Caused by Renal Insufficiency

MA during renal insufficiency has been classically attributed to an abnormal excretion of protons and bicarbonates reabsorption [1, 2]. But this pathophysiological point of view ignores totally the dependency of bicarbonates and protons and the role of other factors implicated in acid-base equilibrium. The kidney plays a major role in this equilibrium because of its involvement in plasma-urine electrolytes exchanges which modulate plasma and urine SIDs [2, 7]. The three strong ions mostly implicated in these phenomenons are Na^+ cation (and secondarily K^+) and Cl^- anion. Therefore, if Na^+ losses are superior to Cl^- ones, urinary SID and pH will increase while plasma SID and pH will decrease [7]. The excretion of Cl^- would be the principal mechanism of plasma pH regulation by the kidney. The kidney must excreted chloride anions without excreting concomitantly Na^+ or K^+, leading to acidify urines and in turn, to alkalinize plasma pH. For preserving electroneutrality, the cation that accompanies Cl^- in urines is ammoniac NH_4^+ which comes from nitrogenous metabolism.

During renal insufficiency, the mechanisms of MA are complex, multiple, and depending on the length of the disease [3, 4, 7, 24]. At the early phase of renal insufficiency, hyperchloremia is the major cause of the decreased SID and thus of the decreased pH [25]. Acidosis is therefore a MA with a low SID but a normal SIG (and a normal AG). In severe, end-stage, and terminal renal insufficiency, renal excretion of strong anions is impaired and may be responsible for more than 50% of MA with a low SID and a high SIG (and AG). In acute renal failure, the accumulation of sulfates and phosphates in plasma associated with hypocalcemia can be implicated in the development of MA with an elevated SIG. On the other hand, all these acidifying factors are frequently counterbalanced by hypoalbuminemia and hyperkalemia which cause alkalinization, leading finally to a slight-to-moderate MA.

6.3.3.2 Normal SIG Metabolic Acidosis

They are caused by solely changes in electrolyte concentrations which induce a decrease in plasma SID, due to a decrease in cations or an increase in anions or the association of both. Therefore, these MA are characterized by an increase in chloride/sodium ratio (>0.75) because of an absolute excess of chloride or a relative excess caused by a loss of sodium while SIG is normal. A recent retrospective study has evaluated the participation of chloride in MA associated with a low SID using three parameters: Na/Cl ratio, the base excess chloride ($BEcl = Na^+ - Cl^- - 32$), and the nonlactate SID (nlSID) [$(Na^+ + K^+ + Ca^{++} + Mg^{++}) - Cl^-$] [20]. One thousand sixty-nine critically ill patients were included; a high nlSID was present in 16.3% of patients and was independently associated with an increased mortality. The classification between a renal and a nonrenal cause is confirmed by the calculation of urinary SIG according to the following formula: $uSIG\ (meq/L) = (uNa^+ - uK^+) - uCl^-$ (Table 6.5) [7].

Metabolic Acidosis Caused by Renal Tubular Acidosis

These disorders are due to tubular function abnormalities while glomerular filtration rate is not impaired [6, 7, 26, 27]. Irrespective of the type of the tubular acidosis,

MA is caused by hyperchloremia with a decrease in SID, but a normal SIG associated with a positive urinary SIG. All tubular acidosis are characterized by abnormalities of electrolytes channels or transporters that induce finally a greater renal reabsorption of chloride and sodium reabsorption, leading to an elevation of the urine SID and a reduction of the plasma SID and pH.

In the renal distal tubular acidosis (type 1), disorders are essentially caused by abnormalities of intercalated cells of the collecting tube. Abnormalities are located on cells of proximal convoluted tubule in proximal tubular acidosis (type 2). Type 4 renal tubular acidosis (pseudohypoaldosteronism type 2) induces various metabolic abnormalities which are characterized by a hyperchloremic MA associated with arterial hypertension and hyperkalemia [6, 7]. This acidosis is due to multiple abnormalities of channels which are located on cells of distal convoluted tubule and collecting tube and which are involved in Na^+, K^+, and Cl^- movements and in kinase transporters.

Metabolic Acidosis Caused by Digestive Losses

The intestinal losses due to diarrhea or grelic/pancreatic draining induce MA because the gastrointestinal tube reuptakes sodium and chloride in an equal amount, leading finally to decrease plasma SID. This is a hyperchloremic MA with a low SID and a normal SIG, but the urinary SIG is negative indicating an appropriate response of the kidney (Table 6.5). Patients with a new bladder issued from the digestive tube develop a similar type of acidosis because accumulated urines in the colon undergo a comparable reuptake of both Na^+ and Cl^-.

Metabolic Acidosis Caused by Fluids

The infusion of large volume of solutions for vascular expansion can induce complex acid-base disorders which are different according to their composition. The composition, i.e., concentration in cations and anions of most solutions, is summarized in Table 6.6. One of the most common acid-base disorders is hyperchloremic MA [28]. Considering the Henderson-Hasselbalch approach, these hyperchloremic acidoses are induced by a decrease in plasma bicarbonates, leading to a dilutional acidosis. However, several studies failed to confirm the presence of any change in plasma volume or of hemodilution [29]. The accurate explanation of the mechanism of this disorder is given by the Stewart method which attributes acidosis to a decrease in SID by two phenomenons. First, the infusion of hypotonic solution induces a reduction of Na^+ which is proportionally greater than that of Cl^-, leading to a decrease in SID and in turn in pH: the classical dilutional acidosis is finally an acidosis caused by hyponatremia (not proportional to hypochloremia). But the most frequent and severe disorder is an inorganic MA due to hyperchloremia which is provoked by the infusion of solutions rich in chloride, called "unbalanced" solutions [4, 7, 8, 14, 25, 30, 31]. The best "balanced" solutions are those with a SID of approximately 24 meq/L [32–34]. Crystalloids such as saline ("normal" 0.9% NaCl or hypertonic) are characterized by a SID equal to zero, as sodium concentration equals chloride concentration, explaining their acidifying effect [35]. In the same time, they have also an alkalinizing effect because they induce a dilutional

Table 6.6 Classification of intravenous solutions in "unbalanced" and "balanced" according to their qualitative and quantitative composition

Solutions	Na^+ (meq/L)	K^+ (meq/L)	Cl^- (meq/L)	Other anions (meq/L)	Osmolarity (mosm/L)	In vivo SID (meq/L)
Crystalloids						
• *Unbalanced*						
NaCl 0.9%	154	0	154	–	308	–
NaCl 3%	510	0	510	–	1026	–
NaCl 7.5%	1275	0	1275	–	2395	–
• *Balanced*						
Ringer's lactate	130	4	108	Lactate (27.6)	277	27
Ringer's acetate	132	4	110	Acetate [28]	277	27
Acetate gluconate (Plasma-Lyte®)	140	5	98	Acetate [26] Gluconate [22]	294	50
Acetate malate (Isofundin®)	145	4	127	Acetate [23] Malate [5]	304	27
Colloids						
• *Unbalanced*						
Hydroxyethyl starch (Voluven®)	154	0	154	–	308	–
Albumin	154	0	154	–	308	–
• *Balanced*						
Hydroxyethyl starch (Tetraspan®)	140	4	118	Acetate [23] Malate [5]	297	29
Hydroxyethyl starch (Hextend®)	143	3	124	–	307	28
Gelatins 4% (Plasmion®)	154	0	120	–	307	32
Gelatins 3% (Gelofusine®)	150	0	100	–	284	56

albuminemia (they do not contain albumin). The resulting effect is still an acidification related to hyperchloremia. Balanced solution must add some strong anions to reach electroneutrality. Various anions are present in such commercialized solutions, depending on the laboratory: lactate, acetate, malate, gluconate, and citrate. The metabolization of these anions can then induce an alkalotic rebound due to a re-increase of SID. The impact of colloids such as hydroxyethyl starch or dextrans on the acid-base status depends on the SID of the solvent. Gelatins and albumin are proteins and weak acids and induce a slight acidosis [36]. But the negative charges of these proteins must conduct to increase the solvent SID, leading to minimize the acidifying effect. The "SAFE" study has shown that in clinical practice, vascular expansion with 0.9% NaCl or 4% albumin induces the same degree of MA, with a

progressive normalization within the 5 following days [37]. Red blood cell transfusion has an alkalinizing effect which is caused by both the dilution of plasma albumin and the presence of sodium citrate. Indeed when citrate is metabolized, sodium cation remains in plasma and requires an elevation of bicarbonates to reach electroneutrality. At last the SID increases and the plasma too. However, in case of liver failure, citrate anion accumulates and produces MA with an increased SIG (and AG) in association with ionized hypocalcemia.

Numerous studies conducted in the perioperative period confirm the relationship between the infusion of unbalanced solutions and hyperchloremic MA [30, 35, 38, 39]. In an experimental model of mice with hemorrhagic shock, vascular expansion was performed using iso- or hypertonic saline. All animals developed hyperchloremic MA within the first 5 min, but MA was more pronounced with hypertonic saline crystalloids [38]. Scheingraber et al. [29] compared isotonic saline versus Ringer's lactate aiming to perform vascular expansion during gynecologic surgery. These authors found that only patients receiving isotonic saline developed hyperchloremic MA. An observational prospective study including various types of surgery has shown that patients developed MA with a decrease in SID without increase in AG, which confirms the role of chloride in the development of such a disorder [35]. On the other hand, no change in plasma volume was detected within the study period, leading to eliminate any dilution to explain the decrease in plasma bicarbonates. A double-blind randomized controlled study has compared the effect of two solutions used for the priming of extracorporeal circuit during cardiac surgery: one group received unbalanced solutions vs one group receiving balanced solutions containing acetate and gluconate [36]. While plasma bicarbonates and albumin decreased initially in the same proportion in both groups, a sustained hyperchloremic MA with a decreased SID was observed only in the group receiving unbalanced solutions. In the balanced group, chloremia and SID remained normal, but the pH and bicarbonates decreased initially as indicated by the increase in AG and SIG. These results are explained by the presence of strong anions contained in the balanced solution (acetate, gluconate). The acid-base equilibrium normalizes further when these strong anions are metabolized. Globally, the severity of acidosis is correlated to the excessive level of chloride, the volume, and the speed of infusion. When renal function is normal, hyperchloremic acidosis is often transitory. In intensive care unit, hyperchloremic acidosis is frequent, present in 60–98% of patients [3, 14]. In a canine model of endotoxinic shock, Kellum et al. [30] have shown that vascular expansion with isotonic saline was associated with MA due in 1/3 of cases to hyperchloremia.

All these data questioned on the real clinical risk and the risk of inappropriate treatment in case of hyperchloremic MA. During the intraoperative period, acidosis might be interpreted as a persisting hemodynamic instability due to hypovolemia, leading to an additional inappropriate vascular expansion with unbalanced crystalloids with a worsening hyperchloremic acidosis. Therefore, it is essential to distinguish iatrogenic hyperchloremic acidosis from hyperlactatemic acidosis caused by cell deficit energy. Moreover, hypoalbuminemia secondary to dilution can blunt the usual biological markers of acidosis by minimizing the decrease in plasma pH and bicarbonates.

The second question is the real clinical impact of such disorders. Until now, there is no double-blind randomized controlled study that confirms definitively the deleterious effect of hyperchloremic acidosis. Nevertheless, since several years, some data report real deleterious effects of hyperchloremia on numerous organ functions [40]. Hyperchloremic MA has been reported to induce renal dysfunction in healthy volunteers. The experimental infusion of chloride in the renal artery induced a sustained vasoconstriction [41]. These effects are due to a tubular reabsorption of chloride and are aggravated by a previous depletion in sodium. These effects would be closely correlated to the amount of chloride delivered to the kidney but independent from that of sodium. Clinical studies are still contradictory [35, 42–44]. Some of them have found that 0.9% NaCl infusion was associated with decrease and delayed urine output as compared with balanced solutions [44]. In a recent randomized, double-blind crossover study, the infusion of 0.9% NaCl in healthy volunteers was associated with a decrease in urine output and a decrease in mean renal artery flow velocity and in renal cortical perfusion as compared with Plasma-Lyte® infusion [42]. A randomized controlled study in patients with kidney graft has reported that isotonic saline infusion was associated with hyperchloremic MA and hyperkalemia as compared with Ringer's lactate infusion [45]. Some data underline the relationship between hyperchloremia and hematological and coagulation abnormalities during elective abdominal aortic surgery [35]. The dilution of blood with 0.9% NaCl induces coagulation impairment with platelet dysfunction and thromboelastogram abnormalities in the perioperative period [46]. Hyperchloremia is also associated with some impairment in digestive functions leading to an increase in postoperative nausea and vomitings and an increase in feeding intolerance in critically ill patients with enteral nutrition [44, 47, 48]. Some experimental studies report also that hyperchloremic acidosis increases proinflammatory phenomenons by stimulating IL6, IL10, and TNF release [49]. These effects seem to be independent from the pH as for a comparable pH; MA caused by hyperlactatemia does produce inverse effects, i.e., anti-inflammatory effects [50]. In the septic rats, the infusion of balanced solutions prevents the development of MA and prolonged their survival compared with NaCl infusion [39]. A recent large randomized trial designed in crossover has compared the effects of balanced (Plasma-Lyte®) vs unbalanced (0.9% saline) solutions in critically ill patients. More than 100 patients were included in each group, and there was no difference in term of both risk of acute kidney injury and mortality rate between groups. However, these results must be interpreted cautiously, as various patients were included and not severe (ICU mortality rate was 6–7%), the mean volume of infusion was very low (approximately 2 L in 4 days), and chloremia was not measured [43]. Therefore, despite the large number of patients, in nonsevere critically ill patients requiring low volume of vascular expansion, balanced crystalloids do not reduce the risk of acute kidney injury nor the mortality rate as compared with unbalanced crystalloids. Based on two recent studies, potential beneficial effects of large volume of fluid resuscitation by balanced crystalloids must be still considered. In a retrospective propensity-matched cohort study analyzing 53,448 critically ill adults with sepsis, Raghunathan et al. [51] have reported that in-hospital rate was lower in the group receiving balanced solutions as compared to the group receiving saline, while the rate of acute renal failure was similar in both groups. A

recent meta-analysis included 21 studies (observational and randomized) and 6253 patients [52]. The results show that high-chloride fluids did not modify mortality but was weakly associated with a higher risk of acute kidney injury.

6.4 Diagnosis of Respiratory Acidosis

6.4.1 Clinical Signs [1, 9]

Acute hypercapnia induces arterial hypertension with an increased cardiac output and cerebral blood flow. Acute RA is associated with an elevated release of catecholamines, glucocorticoids, renin, aldosterone, and antidiuretic hormones leading to water and sodium retention. The more the development of hypercapnia is rapid, the more the neurological signs are severe: nausea, vomitings, confusion, obtundation, coma, seizures, etc.

Clinical manifestations of chronic hypercapnia are those of a chronic pulmonary heart with arterial hypertension. Ventricular and supraventricular arrhythmias are essentially caused by hypoxia and electrolytes abnormalities and not really related to a cardiomyopathy. Except in case of an acute worsening, chronic RA induces few central neurologic symptoms.

6.4.2 Biological Signs

Hypercapnia is the cause of the low pH. The expected secondary renal response depends on the speed of hypercapnia development, acute or chronic (Table 6.1). Hypoxemia is due to alveolar hypoventilation. During acute RA, serum concentrations of $Na^{+,}$ K^{+}, and AG do no modify, except in case of the presence of an additional disorder such as MA. During chronic RA, serum concentrations of $Na^{+,}$ K^{+}, and AG are normal because the increase in HCO_3^- is counterbalanced by a proportional decrease in Cl^- ($\Delta HCO_3^- = \Delta\ Cl^-$).

6.4.3 Etiologic Diagnosis [1, 9]

6.4.3.1 Acute Respiratory Acidosis

Most frequent causes of acute RA in anesthesia and intensive care unit are a decompensation of a preexisting chronic pulmonary disease, an airway obstruction, and a severe bronchospasm (Table 6.7). Only severe pulmonary edema is accompanied by acute RA. During anesthesia, RA is possible if minute ventilation on the ventilator is not sufficient or in case of airway obstruction, of pneumothorax or an abnormality in the ventilator circuit. Permissive hypercapnia is particular and decided as one of measures included in the therapeutic strategy of acute respiratory distress syndrome. Such a disorder does not induce deleterious effects until $PaCO_2$ is $\leq$60 mmHg [9].

Table 6.7 Major causes of respiratory acidosis (nonexhaustive list)

Acute respiratory acidosis	Acute respiratory acidosis
Airway obstruction	
Aspiration pneumonia, laryngospasm, severe bronchospasm, obstruction of superior airway	Chronic obstructive bronchopneumopathy
Inhibition of respiratory centers	
General anesthesia, sedative drugs, traumatic brain injury, stroke	Sedative drug chronic overdose, Pickwickian syndrome, brain tumor
Cardiovascular failure	
Cardiac arrest, severe pulmonary edema	
Neuromuscular deficits	
Botulism, tetanus, hypokalemia, Guillain-Barré syndrome, myasthenia crisis, toxics (neuromuscular blockers, organophosphorus)	Poliomyelitis, amyotrophic lateral sclerosis, multiple sclerosis, myopathies, diaphragmatic paralysis, myxedema
Thoracopulmonary injuries	
Pneumothorax, hemothorax, severe pneumonia, acute respiratory distress syndrome	Kyphoscoliosis, pulmonary fibrosis, obesity, hydrothorax, ascitis, diaphragmatic function impairment
Controlled ventilation	
Iatrogenic hypoventilation, permissive hypercapnia	

6.4.3.2 Chronic Respiratory Acidosis

They are observed mostly in patients with obstructive pulmonary disease, rarely in restrictive pathologies (Table 6.7). In clinical practice, it may be difficult to determine the part of acute from chronic RA. The clinical history only enables to precise this point.

6.5 Treatment of Acidosis

The treatment of the cause is necessary and frequently sufficient, but will not be detailed in this chapter. The symptomatic treatment which consists to alkalinize the pH is still strongly debated due to contradictory data.

6.5.1 The Buffer Solutions

6.5.1.1 Sodium Bicarbonate (SB)

Due to its reaction $NaHCO_3^- + H^+ \Leftrightarrow Na^+ + H_2O + CO_2$, SB is eliminated finally into CO_2 and leaves only the strong cation Na^+ in plasma. The consequence is an elevation of SID which induces in turn an increase in plasma pH. Therefore, SB is really an efficient alkalinizing solution [53, 54]. In many experimental and observational clinical studies, such an effect is accompanied by an improvement in hemodynamic parameters. However, the causality between this benefit and the correction of

acidosis is not clearly established, and this effect might be the consequence of an improvement in vascular expansion due to the sole sodium of the solution. In this point of view, SB appears as an interesting solution for vascular expansion. Indeed, BS infusion in septic pigs [55] and in patients with severe sepsis [56] improved significantly hemodynamics.

6.5.1.2 Carbicarb®

This solution is an equimolar association of bicarbonate and sodium carbonate which reacts with water as follow: $Na_2HCO_3^- + H_2O + CO_2 \Leftrightarrow 2HCO_3^- + 2Na^-$ [50]. This composition allows to produce less CO_2 than SB. However, this theoretical advantage has never been demonstrated in experimental nor in clinical studies. This solution is not available in France.

6.5.1.3 Tham® (Tris(hydroxymethyl)aminomethane)

This is also a synthetic buffer which allows to alkalinize with a lower production of CO_2 than SB, according to the following reaction: Tham + H_2O + CO_2 ⇔ HCO_3^- + Tham-Na^+. Its theoretical advantage is to cross easily cell membranes, to enter the cell, and to exert an intracellular buffering effect. But, it has also numerous side effects such as vasodilation, hyperkalemia, hypoglycemia, and vascular necrosis. As underlined for Carbicarb®, it has never been demonstrated that Tham® is a better buffer than SB, and clinical data remain limited.

6.5.1.4 Renal Removal Therapy

Renal removal therapy using SB as a buffer remains the most elegant method to increase pH, especially in case of renal failure. Such a technic allows to increase plasma pH by reducing SID by several mechanisms: removal of organic and inorganic anions (sulfate, phosphate), increased serum sodium concentration caused by SB contained in dialysate, and filtration solutions [57, 58].

6.5.2 Which Arguments to Treat Acidosis?

The treatment of acidosis using SB remains strongly debated: is severity of acidosis due to the low level of pH or to its underlying cause? Does any alkalinizing treatment using SB improve the patient's prognosis?

6.5.2.1 Acidosis: Friend or Foe?

The impact of a low pH on the prognosis of patients is clearly more dependent on the underlying cause of acidosis than on the level of pH. In a retrospective study, Gunnerson et al. [59] have shown that in critically ill patients, in-hospital mortality was higher in acidosis caused by hyperlactatemia than in those induced by other excessive strong anions or hyperchloremia. In this study, hyperphosphatemia and hyperlactatemia were independent parameters of a poor prognosis, while the pH value did not. A recent study supports such results showing that mortality rate was less than the expected one and was dependent on the

reason of acidosis in patients presenting severe acidosis (pH <7) on admission [60]. These data strongly support that the alkalinization to normalize a low pH is not logical.

Data concerning the administration of SB are contradictory and stimulate the debate. Nevertheless, considering the pathophysiological mechanisms allows to explain these contradictions. Indeed, it is not surprising to observe different effects in metabolic and respiratory acidosis or between MA as a consequence of cell energy failure and as cell suffering of hyperchloremia.

Acidosis: A Foe

Numerous deleterious effects have been attributed to acute MA. Cardiovascular disorders and myocardial depression are the most frequently described in experimental model of isolated heart or in animals [61]. In these studies, these effects were reversed by the infusion of SB. Other studies report arrhythmias, vasodilation counterbalanced by a stimulation of the sympathetic system, and an impaired response to catecholamines [62, 63]. However, the interpretation of these data must be careful due to numerous methodological bias (no control group, extreme level of acidosis pH <7 in normal conditions of oxygenation). On the other hand, myocardial depression with pH >7 was not confirmed [63]. During hemorrhagic shock, MA is classically considered to worsen shock and coagulation abnormalities by decreasing fibrinogen and platelets. But, alkalization using SB is not able to normalize coagulation [64]. The consequences of acute RA remain debated [65–67]. Jaber et al. [65] showed in a porcine model that hypercapnia enables to reduce diaphragm contractility in a sustained manner with a delayed recovery. In ventilated rats with hypercapnia, Caples et al. [66] have found that SB or Tham® administration decreased pulmonary injury. In a model of myocardial ischemia-reperfusion, preconditioning with hypercapnia reduced the volume of infarction [67].

Chronic acidosis (metabolic and respiratory) can cause hormonal abnormalities, osteodystrophy with ionized hypocalcemia, or muscle weakness.

Acidosis: A Friend

Acidosis brakes glycolysis by an inhibition of phosphofructokinase (PFK). It is also responsible for a shift on the right of the dissociation hemoglobin curve, which facilitates the release of O_2 from hemoglobin for tissues. Such modifications can easily be considered as an adaptative goal aiming to facilitate cell functions in case of energy failure. Indeed, acidosis facilitates oxygen supply to hypoxic cells, and by braking glycolysis, it allows to fight against early energy storage exhaustion.

The beneficial effects of acidosis in hypoxic conditions or ischemia-reperfusion are largely reported on various experimental models. During ischemia-reperfusion, myocardial, endothelial cells and cerebral function are improved in acidotic conditions [68–71]. In similar conditions, acidosis protects cells from necrosis and apoptosis, regardless, the tissue (myocardium, hepatocytes, or neurons) [69–71]. The most likely mechanism of these protective effects would be an intracellular acidification (pHi) which could trigger a preconditioning [69] or a postconditioning

process [70]. On contrary, other authors have reported proapoptotic effects on ex vivo myocytes but out of hypoxic conditions [72].

Sodium Bicarbonate: Balance Benefit/Risk

Most randomized controlled studies failed to demonstrate any benefit of the administration of SB in organic MA. During DKA, even in case of severe-extreme low pH, the alkalinization using SB increases pH, but does not normalize more rapidly glycemia or ketonemia nor improve myocardial function and mortality [19]. Indeed, some studies describe even deleterious effects such as a reduction in tissue oxygenation [73]. No beneficial effect has been demonstrated in randomized controlled studies in patients with shock and lactic acidosis despite the correction of acidosis by SB [53]. No benefit of SB administration has been demonstrated also for cardiac arrest, except if prolonged for more than 10 min [74, 75]. This result seems to be logical as acidosis in the early period following cardiac arrest is essentially a respiratory acidosis, and, therefore, the best treatment is to improve ventilation and to restore a spontaneous circulation.

To our knowledge, no randomized study has been performed to evaluate the efficiency of SB in patients presenting hyperchloremic MA. Treat these acidosis when chronic (as observed in chronic renal insufficiency) might be logical to fight against some side effects related to acidosis such as muscle weakness, osteodystrophia, and hormonal abnormalities. In this case, renal removal therapy remains the best treatment. The alkalinization of acute inorganic MA caused by digestive diseases is a matter of convictions because no objective data exists. If considering the Henderson-Hasselbalch pathophysiology among which acidosis is caused by bicarbonate losses, an exogenous replacement of these losses by SB seems appropriate. If referring to the Stewart approach, the treatment of acidosis should aim to correct plasma SID. Therefore, SB may reach this objective, thanks to the administration of Na^+ without Cl^-, but other balanced crystalloids such as sodium lactate will have similar alkalinizing effects [76].

Some experimental data found that hyperchloremia independently from acidosis, induces deleterious effects, which may represent an argument to prevent hyperchloremia. Indeed, for a long time, numerous pathological processes such as cell edema and arterial hypertension were attributed exclusively to an excess of sodium. However, recent data confirm the deleterious effects of high concentration of chloride which were underestimated. For example, the classical sodium-dependent arterial hypertension induced in uninephrectomized rats does not develop with the exclusive administration of sodium without chloride (bicarbonate or citrate sodium) or with the exclusive administration of chloride without sodium (ammonium chloride) [77]. Chloride channels which are membrane proteins allow to underline the major role of chloride in numerous pathophysiological processes, including the regulation of cell volume, transepithelial exchanges of fluids, muscle contraction, and neuroexcitability [78]. Nowadays, five groups of chloride channels are described in mammals. Among them, some are cyclic-AMP-dependent phosphorylation, while others are activated by calcium-, GABA-, or glycine-activating chloride channels. The most studied are the volume-regulatory channels (VRC) which depend on

the membrane potential and the voltage-gated chloride channel (CIC). The distribution, the nature, and the role of each are summarized in a review [78]. Chloride exchanges are performed by cotransporters with other anions or cations. Most studied are the Na^+/Cl^- (NCC), K^+/Cl^- (KCC), and $Na^+/K^+/Cl^-$ (NKCC) [79, 80]. NCC and NKCC facilitate the entry of sodium, potassium, and chloride in cells and are inhibited by the increase in intracellular chloride concentration. KCC favors the extrusion of potassium and chloride from cells and are stimulated by the reduction in intracellular chloride concentration. Voltage-dependent channels, type CIC-3, seem to be preferentially involved in volume cell regulation, cell multiplication, and apoptosis [81]. The role of chloride cotransporters has been particularly highlighted in the central nervous system and its disorders. Neurons intracellular concentration of chloride regulates neuronal excitability by mediating the GABAergic neurotransmission, thanks to GABA-activating gated chloride channels. This parameter is also involved in the regulation of cell volume caused by osmolar variations or ischemic injury [82]. Plasma hypertonicity activates NKCC 1 cotransporter which enhances the cell concentration in Na^+, K^+, and Cl^- (active osmotic molecules) leading to the regulatory volume increase (RVI). Indeed, cerebral shrinkage caused by plasma hypertonicity is reduced. Plasma hypotonicity activates KCC 3 which extrudes K^+ and Cl^- from the cell; this represents the well-known regulatory volume decrease (RVD) which minimizes cerebral edema [82, 83]. Cerebral ischemia induces cell changes in electrolyte concentrations and metabolism that are characterized by an accumulation of Na^+, Ca^{++}, and Cl^- inside and of K^+ outside cells. These phenomenons are observed in brain cells (neurons, astrocytes, and endothelial cells of the cerebrospinal barrier) and conduct to the development of cerebral edema which may cause brain death [79, 80, 84]. Pond et al. [80] have shown that the inhibition of NKCC 1 and KCC 2 cotransporters by furosemide or bumetanide enabled to restore ATP storage and to reduce neurons injury in human undergoing ischemia-reperfusion without glucose supply. In a model of focal ischemia-reperfusion, NKCC $1^{-/-}$ knockout mice presented with a 30–45% decrease in cerebral infarction area and edema compared with the wild NKCC $1^{+/+}$ control ones [84]. Neuronal cultures issued from NKCC $1^{-/-}$ mice showed a significant reduction of both cell death rate and Na^+ entry in the cell compared with NKCC $1^{+/+}$ cultures. The inhibition of NKCC 1 transporter by bumetanide is responsible for protective phenomenon on neurons and astrocytes: cerebral edema is associated with an intracellular accumulation of Na^+ and Cl^- while K^+ extracellular concentration is high. NKCC 1 transporter activation is also closely linked with neuronal and astrocyte excitotoxicity [79, 85]. All neurological injury (stroke, traumatic brain injury, epilepsy) triggers cerebral excitotoxicity which manifests by glutamate release and cerebral edema [83, 86]. The activation of N-Methyl-D-Aspartate (NMDA) receptors by glutamate favors the entry of chloride in the cells by opening both GABA-gated and volume-sensitive chloride channels. In case of persistent activation, cerebral edema develops followed by cell necrosis. On contrary, glutamate reuptake and disappearance facilitates chloride and potassium extrusion from the cell by activating same volume-sensitive chloride and potassium channels [85]. These data underline inverse effects of these channels according to the presence or not of excitotoxicity.

Considering these data, preventing hyperchloremia seems to be justified and suggests to favor the infusion of balanced solutions for large volume expansion. However, such a benefit has to be further demonstrated in clinical practice

Beside potential beneficial effects, SB may induce deleterious effects. Among them, intracellular hypercapnic acidosis is commonly reported. Due to its high solubility, CO_2 which is produced by SB metabolism enters the cell and is responsible for a "paradoxical" acidosis. This phenomenon has been shown experimentally in vitro [70] and in patients too [53]. But, this phenomenon depends on conditions; intracellular acidosis does not occur in opened systems, i.e., if CO_2 can be eliminated by the lung or cells are in a fluid which contains buffers [87, 92]. In practical, most relevant side effects are a decrease in ionized calcium, hypernatremia, hyperosmolarity, sodium and water overload, and hypokalemia. Using iso- or hypotonic SB by continuous slow infusion without bolus enables to minimize or prevent these complications.

6.5.3 Which Clinical Indications of BS Alkalinization?

MA caused by the accumulation of strong anions must be distinguished from that caused by inorganic anions (Cl, Na). Organic MA requires essentially the treatment of the underlying cause; the metabolism of organic anions conducts to normalize concomitantly plasma SID and pH without any need of SB infusion. Therefore, DKA does not require BS alkalinization; even acidosis is severe [19]. The etiologic treatment by hydration and insulin restores the metabolism of carbon hydrates. Ketone body metabolization and urinary excretion induced by rehydration manifest by the simultaneous disappearance of ketonemia and acidosis. For the same reasons, it is not logical to alkalinize acidosis caused hyperlactatemia during shock [88]. In this situation, acidosis caused by changes in cell metabolism reflects energy impairment which may be considered as an adaptative response and in this view probably not treated, at least when transitory. The best treatment remains to restore an appropriate hemodynamic and oxygenation of tissues. Lactate metabolism conducts to correct spontaneously pH without need for any alkalinization. During septic shock, the indication of BS alkalinization remains debated due to controversial data. In a retrospective uncontrolled trial, El-Solh et al. [89] reported that BS infusion (0.2 mmol/kg/h) in 72 patients in septic shock with a pH <7.3 shortened time for respiratory weaning and for in-ICU length of stay. Nevertheless, such a treatment failed to restore shortly hemodynamics or to decrease the mortality rate. Based on two clinical randomized studies [53], the Surviving Sepsis Campaign does recommend to perform BS alkalinization only in case of severe acidosis with a pH <7.15; in septic shock with a pH ≥7.15, BS administration is not recommended [90]. Other authors advocate BS alkalinization only for lower pH <7 [88].

BS alkalinization is only recommended during cardiac arrest prolonged over 10 min or in case of associated hyperkalemia or of tricyclic antidepressant overdose or of preexisting acidosis. In this situation, normalization of pH requires before all to restore an efficient ventilation and circulation as acidosis is mostly a respiratory

one. When cardiac arrest is prolonged and if spontaneous circulation activity is not restored, BS administration is possible [91].

During inorganic MA, the indication of BS infusion remains debated. In this case, acidosis is the primary disorder which is imposed to the cell caused by electrolyte modifications of the SID and which might exert potential deleterious effects on cell functions. Therefore, in these situations, BS administration is suggested if the pH is <7.20 [75]. But this strategy remains only symptomatic and the treatment of the cause is still the most appropriate. If considering the possible deleterious effects of hyperchloremia, a preventive attitude based on a preferential infusion of balanced solutions in case of large volume expansion appears to be the favorite.

Acute RA does not justify any exogenous administration of SB, especially if ventilation or circulation is impaired. In this situation, SB would worsen CO_2 release and accumulation in tissues and blood. Nevertheless, some studies report that BS infusion during acidosis caused by permissive hypercapnia decreases alveolar injury and improves systemic and regional circulations [66]. In practice, the threshold tolerated of acidosis induced by permissive hypercapnia is of 7.15–7.20 pH below which BS administration might be justified.

The reasons for alkalinizing chronic acidosis are completely different. As chronic renal insufficiency represents the major cause of chronic acidosis, BS is supplied with dialysis sessions. Chronic RA is usually not severe due to a complete secondary renal response that increases plasma bicarbonates and creates metabolic alkalosis. In this context, BS infusion is not justified. In case of artificial ventilation, acetazolamide might facilitate the reduction of plasma bicarbonates and the respiratory weaning.

Conclusion

Metabolic acidoses are frequent in intensive care units. They can be caused by an elevation in strong anions (lactate, ketone bodies) which represents the organic metabolic acidosis. Those resulting from disequilibrium between strong nonorganic cations and anions (mostly sodium and chloride) are called mineral or nonorganic metabolic acidosis. The diagnosis of metabolic acidosis is essentially based on arterial blood gases and electrolyte concentrations. It is essential to determine the cause in order to administer the etiologic treatment which is clearly the most appropriate. The benefit of a symptomatic alkalinization with sodium bicarbonate remains strongly debated and depends on both severity and cause of the trouble. Among respiratory acidosis, it is important to distinguish acute from chronic disorders, because causes and treatment are fundamentally different.

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