Management of acid-base disorders

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Premise

A brief premise. The treatment of acid-base disorders cannot be improvised and does not need to be implemented. Do not start the navigation without a route drawn on the relatively precise coordinates of the pathophysiology and without a goal to reach. Do not feel obliged to take off: the compulsion to act that often takes possession of the doctor can be very dangerous, especially if it pushes him or her uncritically to the normalization of the parameters. There is always time to think. Good navigation.

Treatment of respiratory acidosis

Introduction

Unlike metabolic acidosis which can be caused by different acidogenic mechanisms, respiratory acidosis is always determined by CO_2 accumulation due to reduced alveolar ventilation.

There is therefore always at the base a picture of type 2 respiratory insufficiency (hypoxic-hypercapnic) which can be acute, chronic or acute on chronic. The rationale of therapy is therefore to improve ventilation by increasing CO_2 pulmonary clearance.

Acute respiratory acidosis treatment

Patients with acute respiratory acidosis are usually critically ill patients with acute reduction of alveolar ventilation.

In the emergency approach it is essential on one hand to identify the underlying causes and the pathophysiological mechanisms [reduction of respiratory rate (RR), reduction of tidal volume (Vt), increase of the dead space volume (Vd)] and set a targeted etiological treatment. On the other hand it is important to assess the need for mechanical ventilation support (invasive or non-invasive) based on the severity of respiratory failure, the underlying disease and the patient's functional reserve. Unlike the two ventilation options, there is "palliative" support in selected patients who would not benefit from conventional treatment.

Among the causes that can produce a depression of the respiratory drive, some substances with central action (sedatives and opioids for pharmacological or recreational use) can be neutralized with the specific antidote; similarly, the modification of excessive oxygen therapy may be sufficient to gradually restore a normal respiratory drive in patients with chronic obstructive pulmonary disease (COPD) with hypercapnic response to oxygen (see Chapter 4).

It should be remembered that, in any case, the depression of respiratory centers induced by O_2 therapy at high flows is only partly responsible for the accumulation of CO_2.

The most significant causes are the effect of oxygen in displacing the hemoglobin linked to CO_2 and therefore increasing its circulating share (Haldane effect) and the opening of vessels that involve unventilated alveoli, followed by alteration of the ventilation/perfusion ratio.

The rapid unblocking of the upper airways with aspiration and extraction of foreign bodies and the prompt treatment of laryngeal spasms are often decisive maneuvers, as well as the drainage of pneumothorax and pleural effusions.

In case of an acute asthma attack or exacerbation of COPD, on the other hand, therapy with bronchodilators and steroids, reducing the lower airways ob-

struction and consequently the alveolar air trapping, can reduce the airway resistance portion and improve the $\dot{V}a/\dot{Q}$ ratio and the pulmonary compliance. The genesis of acute respiratory acidosis is more complex, often accompanying a picture of acute cardiogenic pulmonary edema. In this case the presence of a low pulmonary compliance due to the diffuse alveolar transudate, determines a distribution of ventilation mostly in areas where the alveolar pressure is dominated by the intrathoracic pressure (respiration that occurs below the residual functional capacity). Therefore, the resultant is a prevalence of areas with low ventilation/perfusion ratio and therefore hypercapnia.

Treatment, for example, with positive airway pressure (CPAP – continuous positive airway pressure or BPAP – bilevel positive airway pressure) determines an immediate, dramatic, hemodynamic effect (reduction of the left ventricular pre- and after load) with consequent unloading of the small circle congestion and increasing pulmonary compliance. This effect translates into a rapid improvement in gas exchange (the oxygenation increases and the hypercapnia decreases) as well as in respiratory rate reduction.

The use of mechanical ventilation is often useful and sometimes unavoidable in hypercapnic respiratory failure treatment, especially in cases where the cause cannot be quickly resolved.

The inspiration pressure delivered by the ventilator supports or replaces the patient's respiratory musculature in conditions where, due to increased respiratory work (compliance deterioration and resistive forces increase) and/or due to muscle exhaustion, the latter is not able alone to perform adequate alveolar ventilation; the muscular work reduction also allows to decrease CO_2 metabolic production. The delivery of a positive end expiratory pressure (PEEP), on the other hand, determines alveolar recruitment, counterbalances the intrinsic PEEP typical of bronchial obstruction clinical conditions and stabilizes the peripheral airways by moving the point of equal pressure more proximally, thus reducing the early bronchiolar collapse at high lung volumes.

Non-invasive mechanical ventilation (NIMV) due to its practicality and lower complications is increasingly an alternative to invasive ventilation.

Ventilation treatment is now the first choice in respiratory failure due to exacerbated COPD and acute cardiogenic pulmonary edema (ACPE) (level of evidence A).

In COPD the presence of respiratory distress (with increased RR, use of accessory respiratory musculature and thoracoabdominal dyskinesia), a persistent pH < 7.35 and/or a $PaCO_2 > 50$ after bronchodilator therapy and O_2, are an indication for ventilatory support. In the ACPE, the NIMV, due to its effect on alveolar recruitment and hemodynamics, is instead indicated during respiratory distress and $P/F < 250$.

NIMV is also indicated in the acute respiratory failure treatment in patients with neuromuscular disease, when an infectious episode or an exacerbation of the disease can reduce patient's functional capacity, increase the elastic load imposed on the respiratory muscles and produce an increase in the RR (> 20) which may precede an initial muscular fatigue.

In pneumonia respiratory failure, the presence of a respiratory acidosis is always an alarm sign and an indication not to further delay invasive ventilation (pneumonia in COPD patients is an exception).

While in cases of acute respiratory acidosis the therapeutic goal is to normalize $PaCO_2$ and therefore pH, in acute on chronic acidosis the goal remains the acute component resolution, with pH increase and a $PaCO_2$ reduction, as close as possible to patient's baseline values, so as to prevent the onset of post-hypercapnic alkalosis.

In correcting respiratory acidosis, alkalizing substances (i.e., THAM – tromethamine) are no longer indicated. Bicarbonate use also contraindicated: dissociating to buffer H^+ ions can aggravate hypercapnia, increase the risk of post-hypercapnic alkalosis in the case of effective ventilation and has a negligible protective effect on the central nervous system (CNS) pH due to its poor diffusion through the blood-brain barrier.

Chronic respiratory acidosis treatment

Chronic respiratory acidosis can count on an effective renal compensation mechanism that can bring pH back to acceptable values.

Therapeutic approach must aim primarily to prevent

exacerbations and the onset of an acute over a chronic acidosis, and in the event of an appearance to treat it quickly. It is therefore essential to optimize chronic therapies of the underlying disease and favor an adequate patient compliance. In COPD patients, chronic therapy optimized with bronchodilators reduces the exacerbations number and their rapid treatment avoids the onset of an acute respiratory acidosis picture over a chronic one.

In patients with obesity-hypoventilation syndrome (OHS), characterized by chronic day and night hypercapnia, the weight loss, lifestyle changes and CPAP-BPAP would be sufficient to progressively improve ventilation.

NIMV use in the chronic hypercapnia treatment is strongly indicated only in patients with OHS; even in that small share without a concomitant nocturnal obstructive apnea syndrome (< 30%), chronic NIMV cycles improve blood gas analysis parameters, symptoms, quality of life and sleep.

In patients with COPD, although certainly indicated in cases of overlap with obstructive sleep apnea syndrome (OSAS), some recent studies on selected populations (GOLD IV stage patients with $PaCO_2$ persistence > 52-53 mmHg at 2-4 weeks after discharge for bronchitis exacerbation) have shown that NIMV cycles alternated with O_2 therapy can reduce the exacerbations number and mortality at 12 months.

Respiratory alkalosis treatment

Respiratory alkalosis rarely, in both acute and chronic forms, generates pH variations requiring urgent action. An urgent correction is necessary if the pH increase is followed by a reduction in the ionized proportion of Ca^{++} and Mg^{++} and a reduction in serum potassium such as to induce electrocardiographic alterations or muscular symptoms (spasms, paresthesia), or if the sharp CO_2 drop causes symptomatic cerebral vasoconstriction (drowsiness, coma, seizure).

Treatment almost always aims to correct the underlying disease, especially when hyperventilation is caused by hypoxia, fever, low flow state, hyperthyroidism.

It is appropriate to differentiate the respiratory alkalosis according to the shunt presence (pulmonary embolism, pneumonia, contusion, atelectasis) or shunt absence typically during pulmonary interstitial diseases, where oxygen therapy plays a fundamental role unlike pathologies causing intrapulmonary shunt (see Chapter 4).

A special case is represented by the anxiety-hyperventilation syndrome in which hypocapnia can arise abruptly and be critical and symptomatic. In these cases a mild sedation (usually with low doses of benzodiazepines) may be indicated to reduce the action of the respiratory drive; "rebreathing" techniques to increase CO_2 in the inhaled air and reduce hypocapnia (for example, breathing into a paper bag), are generally not recommended because of risk of generating important and sometimes symptomatic hypoxemia.

Metabolic acidosis: principles of treatment

Metabolic acidosis includes an extremely heterogeneous group of disorders, with therapeutic indications that, in most cases, differ in relation to etiology and severity.

However, it is possible to identify four general points to which every therapeutic decision must refer. Priority:

- identify emergency situations, potentially life-threatening, requiring immediate measures and eventually intensive care;
- identify the determining cause of acidosis;
- evaluate whether is indicated an alkali administration (intravenously or orally);
- estimate possible changes in potassium before starting the acidemia correction.

- **Identify emergency situations.** In emergency contexts, before the results of laboratory tests are available (including arterial blood gas), patients must always be approached according to the ABC scheme, to evaluate and maintain airway patency, ventilation and perfusion.
- **Identify the determining cause of acidosis.** Causes identification is important for at least three reasons. It allows, first of all, to start specific and etiopath-

ogenic therapeutic measures, which we will describe in detail below; but it also allows to intervene promptly on those conditions, which regardless of patient's state, represent by themselves a danger to life. In intoxications, for example, rapid diagnosis allows to implement immediately measures to counteract the toxic substance (gastric lavage, antidotes and urine alkalinization) even before the development of significant metabolic alterations.

Finally, identifying the cause, allows us to estimate the rate of hydrogen ion production, which in some cases can be particularly high (type A lactic acidosis) and sometimes rather restrained (alcoholic ketoacidosis and prolonged fasting, chronic renal failure, intoxication from toxic alcohols). In forms with a high production rate it is essential to quickly block the production of H^+ (restoration of perfusion in the case of lactic acidosis type A) in order to avoid a rapid decline in blood pH.

- **Evaluate whether there is an indication for alkali administration.** The indication for the use of alkali (sodium bicarbonate) in the metabolic acidosis treatment depends on the pathophysiological mechanism underlying the acidosis and should be evaluated in parallel with the potential adverse reactions of the alkalizing solutions. Oral alkali therapy in hyperchloremic metabolic acidosis with normal anion gap (renal insufficiency, renal tubular acidosis, diarrhea) is a consolidated treatment of undoubted benefit, because the primum movens (cause) of these conditions is bicarbonate loss, accompanied by the inability of the nephron to regenerate it. In particular, in chronic forms of renal origin (chronic renal failure, renal tubular acidosis), oral bicarbonate limits long-term complications: bone demineralization, growth retardation and perhaps even renal disease progression.

  The use of intravenous bicarbonate solutions in the acute acidemia treatment is extremely controversial. In vitro and animal model studies have shown, on several occasions, the negative effects on the cellular function of the rapid lowering of arterial and intracellular pH. Enzyme activity and proteins three-dimensional structure are in fact both pH-dependent processes. pH drop in the extracellular fluid influences the binding of hormones to their receptors, increases the ionized calcium concentration and alters the flow through the potassium channels in the conduction tissues (heart, vascular musculature, nervous system).

  The most susceptible tissue to rapid pH reduction is with no doubt the cardiac tissue: acute acidemia reduces cardiac contractility and catecholamine sensitivity, increases venous congestion and therefore the risk of pulmonary edema and has vasoplegic effects. Acute acidemia also has profound effects on oxygen transport; it shifts the dissociation curve of oxyhemoglobin (P50) to the right, increasing the oxygen transfer to the tissues, but this effect, potentially positive in hypoperfused patients or those with respiratory failure, can be reset by the concomitant reduction of erythrocyte 2, 3-diphosphoglycerate levels, which on the contrary moves the curve to the left. Although the experimental data, which show how damaging effects of acute acidemia are solid, it remains difficult to prove that the rapid therapeutic inversion of a low pH is really advantageous. First of all because the blood pH does not always correlate with intracellular pH, but above all because the therapy with intravenous bicarbonate solutions is not free from potentially dangerous adverse events, especially when used in bolus and high osmotic formulations (8.4% sodium bicarbonate solution).

  The disadvantageous effects of bicarbonate solutions (summarized in **Table 6.1**) often nullify the

TABLE 6.1 Main side effects of sodium bicarbonate infusion.

Hypokalemia
Hypocalcemia
Prolonged Q-T interval
Hypercapnia
Hemodynamic instability

potential positive effects induced by blood pH normalization. For details, refer to the treatment of the individual forms of metabolic acidosis listed below in this chapter.

These considerations highlight the limits of sodium bicarbonate therapy, especially in the metabolic acidosis with high anion gap (ketoacidosis and lactic acidosis, in particular).

In fact, in these forms, acidosis is only one of the manifestations of a complex pathological process, but it does not in itself represent the disease. Therapy goal should therefore be to reverse the pathophysiological process, treating determinant and triggering causes. The effective treatment of the cause leads to a reduction in the production of organic acids (lactates and ketoacids), improves their clearance and regenerates bicarbonate within a few hours. Supplying the extracellular buffers is unlikely to provide the same benefit.

The situation is different in severe toxic alcohols intoxications (ethylene glycol and methanol).

These patients could benefit from therapy with exogenous alkali, because due to the same effect of the toxic substance retention, endogenous (renal) regeneration of bicarbonate occurs only slowly over several days.

NOTE

In common clinical practice when one decides to administer a bicarbonate solution, the following formula is often referred to, to calculate the bicarbonate deficit:

ΔHCO_3^- = 0.5 (target serum bicarbonate – actual serum bicarbonate) x total body weight (Kg)

This formula underestimates the actual deficit, because blood bicarbonate is not directly proportional to the total amount of body bicarbonate.

- **Estimate possible changes of potassium.** It must never be forgotten that quickly correcting acidemia can mean reducing potassium just as quickly.

  In fact, in order to mantain intracellular electroneutrality, the cell membranes exchange the hydrogen ion with potassium and, by the same principle, acidemia correction moves potassium from the extracellular fluid (ECF) to the intracellular fluid (ICF), with consequent hypokalemia. The increased renal potassium excretion induced by acidosis participates in the genesis of hypokalemia. Since the relationship between the intracellular and extracellular potassium concentration (K^+_{in}/k^+_{out}) is mainly responsible for the resting membrane potential (for details see the Nernst equation), it follows that any abrupt kalemia modification alters excitability in the conduction tissues. Rapidly established hypokalemia has two serious clinical consequences: malignant arrhythmia and respiratory failure due to muscular weakness.

  The problem is particularly relevant in metabolic acidosis forms that accompany a deficit of the intracellular potassium pool (diabetic ketoacidosis and metabolic acidosis due to diarrhea). In these cases administering potassium becomes a priority and it can be extremely dangerous to administer alkali or insulin before having corrected the kalemia (see below).

Treatment of anion gap metabolic acidosis

Lactic acidosis

Introduction

Lactic acidosis and hyperlactatemia are traditionally considered to be biological and prognostic markers of tissue hypoxia. However, this view is too simplistic and does not take into account the numerous causes of lactate increase, which may occur in absence of tissue hypoxia or in addition to hypoxia itself. Lactate is not just a metabolic “waste” deriving from anaerobic glycolysis; rather, it is

an important energy "shuttle" whose production involves different metabolic pathways, activated in conditions of exalted cellular metabolism (sepsis in the first place). Identifying and controlling the triggering conditions of hyperlactatemia is currently the only meaningful therapeutic device.

Lactate is produced from pyruvate in the last stage of anaerobic glycolysis.

In physiological conditions blood lactate/pyruvate ratio is 10:1, but it can increase significantly in hypoperfusion contexts. Lactate is produced in all tissues, but the main ones are skeletal muscle and red blood cells. Its catabolism occurs mainly in the liver (around 70%) and only a small part in the kidney. In these organs lactate is a substrate of neoglucogenesis. The whole process that converts lactate into glucose is called the "Cori cycle" (**Figure 6.1**).

The renal excretion threshold for lactate is very high (around 6-10 mEq/L), therefore the kidney directly eliminates lactate only during severe hyperlactatemia. As already mentioned in the premise, establishing the pathogenetic mechanism underlying hyperlactatemia is a necessary condition to face therapy. Cohen and Woods have historically classified lactic acidosis into two types: type A from tissue hypoxia and type B from mechanisms other than hypoxic.

Type B hyperlactatemia is further subdivided into B1, if associated with an underlying disease (i.e., liver failure); B2, when it is induced by drugs or toxic substances; B3, if caused by congenital defects of metabolism (**Table 6.2**).

Tissue hypoxia (global or district) occurs whenever there is a mismatch between oxygen supply (oxygen delivery – DO_2) and its use (oxygen consumption – VO_2). In this context, anaerobic glycolysis and therefore lactate production reach their maximum expression.

In type B forms the main pathophysiological mechanism is the exalted aerobic glycolysis.

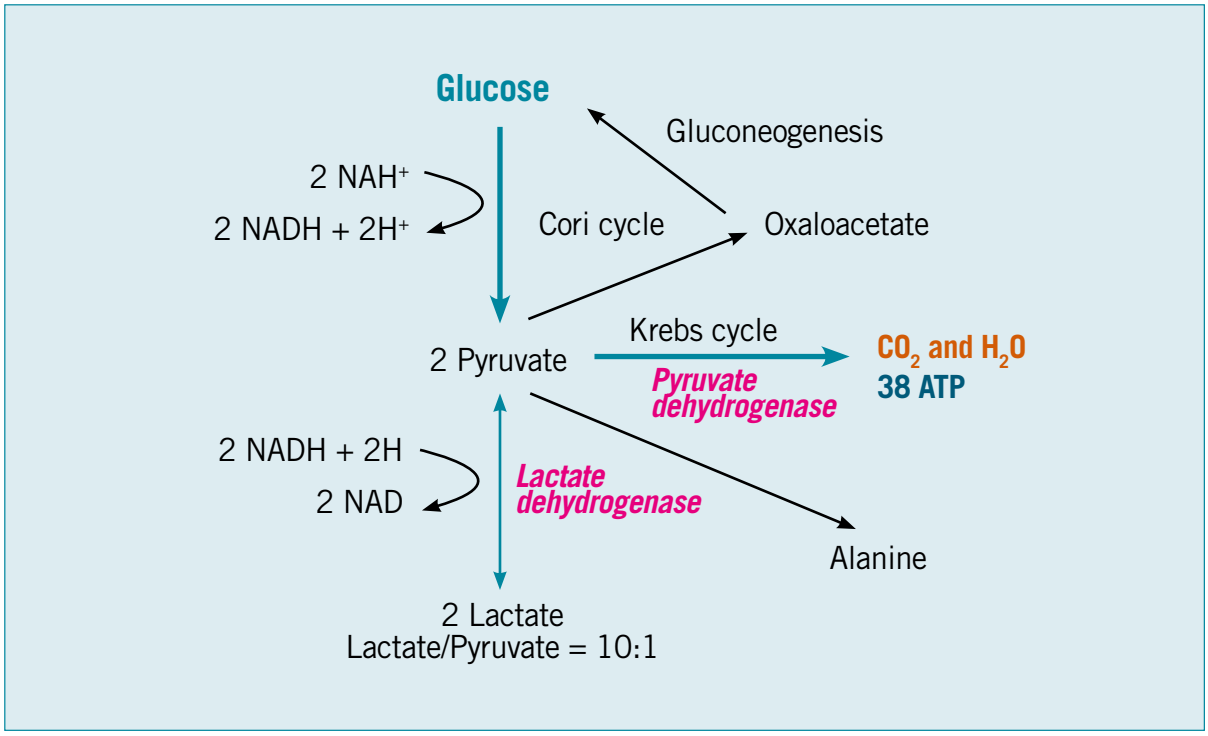

Figure 6.1 Lactate production.

In this scenario, glucose metabolism exceeds the oxidizing capacity of mitochondria and the increase in pyruvate concentration supports lactate production. Adrenergic (β_2) and cytokine hyperstimulation are most often the cause. This explains hyperlactatemia in the hyperdynamic state of sepsis, acute asthma attack, trauma, pheochromocytoma, diabetic ketoacidosis and AIDS.

Some drugs and toxic substances cause type B hyperlactatemia because they inhibit mitochondrial oxidative phosphorylation: it is the case of antiretrovirals, propofol, metformin and toxic alcohols.

NOTE

The mechanism that links liver failure to lactate production is complex. Cirrhosis, even severe, rarely generates significant hyperlactatemia and never acidosis. In contrast, in acute (fulminant) hepatitis, hyperlactatemia is common and reflects its prognosis. In septic patients (including hemodynamically stable) reduced hepatic metabolism (from pyruvate -dehydrogenase inhibition) participates together with the exalted production to the genesis of hyperlactatemia.

TABLE 6.2 Causes and classification of lactic acidosis. From Seheult J, Fitzpatrick G, Boran G. Lactic acidosis: an update. Clin Chem Lab Med. 2017; 55 (3): 322-33 (modified).

Type A Tissue hypoxia	Type B Mechanisms other than hypoxic
Shock (systemic hypoperfusion) • Hypovolemic • Cardiogenic • Maldistributive	**B1: associated with underlying diseases** • Diabetic ketoacidosis (DKA) • Leukemia/Lymphoma • Acquired immunodeficiency syndrome (AIDS) • Severe liver disease • Sepsis • Thiamine deficiency • Pheochromocytoma
Local hypoperfusion • Splanchnic ischemia • Aortic thromboembolism	**B2: associated with drugs and toxins** • Acetaminophen • β-agonists (including cocaine and adrenaline) • Cyanide • Insulin • Nitroprusside • Nucleoside reverse - transcriptase inhibitors • Phenformin • Propofol • Salicylates • Toxic alcohols: methanol, ethanol, ethylene glycol, diethylene glycol, propylene glycol
Other causes of tissue hypoxia • Severe hypoxemia (PaO_2 < 30-40 mmHg) • Severe euvolemic anemia • Carbon monoxide toxicity **Increased glycolysis** • Excessive muscle activity • Exercise • Trembling **Seizure**	**B3: associated with inborn errors of metabolism** • Mitochondrial myopathy • Pyruvate dehydrogenase deficiency **Miscellaneous** • Alkalosis/Hyperventilation • Hypoglycemia

General therapeutic approach

A high level of lactate should, for first instance, suggest an assessment of the causes of oxygen supply reduction (DO_2).

DO_2 is expressed by the product between cardiac output (CO) and arterial oxygen content (CaO_2). The content of arterial oxygen depends, in turn, on the quantity of hemoglobin (Hb), on its saturation in arterial blood (SaO_2) and on a minimal amount of oxygen dissolved in the blood (0.003 x PaO_2). All summarized in the following formula:

$$\mathbf{DO_2 = CO \times CaO_2}$$
$$\mathbf{CaO_2 = (1.34 \times Hb \times SaO_2) + (0.003 \times PaO_2)}$$

Therefore the causes of DO_2 reduction and hyperlactatemia due to tissue hypoxia (type A) are: systemic hypoperfusion status caused by reduced cardiac output (CO), severe anemia, respiratory failure with severe hypoxemia and regionally reduced perfusion (i.e., limb ischemia or mesenteric ischemia). In these forms the treatment consists in optimizing oxygen supply to the tissues.

Hemodynamics must be restored by administering the right amount of fluids and in selected cases with vasopressors and inotropes. Ventilation should be sustained (in an invasive or non-invasive manner) only when the oxygen saturation is less than 92%, due to the known vasoconstrictor effect that oxygen has on the cerebral and coronary circulation. Finally, in the case of severe anemia, recent evidence indicates the need to transfuse for hemoglobin concentrations below 7 g/dL.

If tissue hypoxia is excluded, after an exhaustive examination, the physician must consider the possibility of causes of hyperlactatemia without concomitant tissue hypoxia (type B forms).

Therapeutic approach in type A lactic acidosis

The basic principles of therapeutic treatment of type A lactic acidosis are: circulatory support, treatment of causes and, in some cases, containment of acidosis.

Circulatory support

Fluids – The fluids administration, aiming to cardiac output, remains the cornerstone of initial therapy for most hypoperfusion states. Regarding the choice of the solution to be administered, the dispute between colloids and crystalloids has enthralled intensivists for over twenty years (see Chapter 11).

Many studies (2012) (CHEST, CRYSTAL, 6S) have shown that colloids and in particular hydroxyethyl starch are not superior to crystalloids, indeed they are potentially dangerous especially in terms of developing acute renal failure; the only colloid that has any indication is albumin; two studies (SAFE – 2004 and ALBIOS – 2014) suggest the hemodynamic advantages (and potentially over the mortality) in patients with severe sepsis (according to the old definition) or septic shock. However, the role of albumin in patients with septic shock requires further study.

But even the crystalloids are not all the same. Normal saline solution, when used in large quantities, can generate or exacerbate hyperchloremic metabolic acidosis and cause renal vasoconstriction.

Crystalloids containing bicarbonate or its precursors (balanced saline solutions), such as Ringer's solutions with lactate and acetate, do not cause hyperchloremic metabolic acidosis, but may occasionally determine metabolic alkalosis.

Two recent (2018) RCTs (SMART and SALT-ED) have shown a significant superiority of balanced solutions (Ringer lactate and Plasma-Lyte A) in critically ill patients in intensive care and emergency areas, both in terms of mortality and acute kidney damage.

With regard to the method of administration, in recent years, the potential risk of fluid overload has been highlighted several times, with negative consequences also on septic patients mortality.

The pathophysiological assumption is the damage that the excess of liquids creates to endothelial glycocalyx which results in capillary rarefaction, interstitial edema and impairment of capillary-cell exchanges. Therefore, caution is advised on the amount of liquid to be administered.

Vasopressors and inotropes – In the case of septic patients in a state of hypoperfusion, unresponsive to fluids, there is an indication for the vasopressors administration.

Regarding the choice, a Cochrane meta-analysis (2016) on the use of vasopressors in shock, which compared six molecules (epinephrine, norepinephrine, dopamine, terlipressin, phenylephrine and vasopressin), did not show significant differences on mortality. However, the levels of evidence are low, except in the comparison between norepinephrine and epinephrine.
The expert opinion is to consider norepinephrine as the first choice drug. Norepinephrine is above all an α-agonist, with mild beta-stimulating properties, for this reason it is above all a vasoconstrictor, with little effect on the heart rate; a low dose is recommended (0.1-2 μg/Kg/min), to act only on the vasoplegic component of the shock.
At these dosages norepinephrine can be used safely even in peripheral vein.
Dopamine, used so much in the past, is associated with a greater risk of arrhythmias, has no protective effect on the splanchnic and renal circulation, if administered at low doses (study SOAP II – 2010) and seems to have immunosuppressive properties, therefore completely inappropriate in a septic context. Its only niche use is in patients in states of hypoperfusion and bradycardia.

NOTE

Recall that there is a complex relationship between catecholamines and lactic acidosis. Acidemia attenuates the catecholamines response, thus increasing the dose required. High doses of catecholamines can aggravate hyperlactatemia by reducing tissue perfusion and over stimulating β_2-receptors; therefore the doses must be regulated carefully.

The second vasopressor of choice is considered vasopressin, especially after the results of the VASST study (2008), which showed that adding vasopressin to norepinephrine in patients with septic shock is safe and effective, particularly in moderate forms and in patients using glucocorticoids; the recommended dosage is 0.03-0.04 U/min.
Inotrope drugs play a very limited role in the treatment of hyperlactatemia and lactic acidosis.
In extremely selected cases, the only indication drug is dobutamine. Its role is limited to transient use, in case of left ventricular dysfunction (acute heart failure and sepsis); however, the evidence is rather weak and the risk of ischemic cardiac complications are instead relevant.
Greater benefits are not obtained even with the other inotropes (phosphodiesterase III inhibitors, e.g. milrinone and levosimendan); these drugs are in fact potent vasodilators and therefore potentially hypotensive, they also have a strong proarrhythmic action and a long duration of action, in particular the levosimendan (LEOPARDS study – 2017).

Containment of acidosis
Role of bicarbonate and bases – Given the potentially harmful effects of an acid environment, some clinicians recommend intravenous sodium bicarbonate therapy in severe acidemia (pH < 7.2).
However, the role of bicarbonate therapy in reducing mortality or improving hemodynamics remains without evidence.
Bicarbonate in fact determines two main adverse events that compromise its effectiveness even at very low pH: the intracellular acidification due to the enzymatic transformation of bicarbonate into carbon dioxide and the reduction of ionized calcium levels, which depress cardiac contractility much more than acidosis itself. Intracellular acidification is assumed to be more frequent and severe, when large amounts of bicarbonate are rapidly administered in patients with severe hypoperfusion, because hypoperfusion prevents CO_2 removal first from the tissues and then from the lungs.
The results of the recent BICAR-ICU study (2018) seem to be in line with these assumptions. The study evaluated the effects of bicarbonate administration in intensive care patients for severe non-ketoacidotic metabolic acidosis (pH < 7.2). In these patients bicarbonate infusion reduces neither the mortality nor the organ dysfunction, with the sole exception of those with severe renal failure (stage 2 and 3 according to AKIN classification).

Dialysis can provide bicarbonate, countering the potential complications: decrease in ionized calcium, volume overload and hyperosmolality. Dialysis can also directly remove some substances responsible for lactic acidosis, such as metformin.
Continuous dialysis is often favored over intermittent dialysis, since it provides bicarbonate at a slower rate and is associated with fewer adverse events in patients with hemodynamic instability.
Other non-bicarbonate buffers have been developed to minimize carbon dioxide generation.
THAM alone (tris-hydroxymethylaminomethane) is currently available for clinical use, but there is little evidence of its real effectiveness.

Therapeutic approach in type B lactic acidosis
The treatment of type B lactic acidosis is very different because the goal is not to correct the mismatch between DO_2 (oxygen delivery) and VO_2 (oxygen consumption).
Since most cases are due to neoplastic conditions, drugs or toxic substances, treatment must focus on eliminating the determining cause.
The treatment main objective is to limit the harmful effects of acidosis, in particular the inhibition of myocardial contractility. Sodium bicarbonate, dichloroacetate, carbicarb and tromethamine have been studied for the management of type B lactic acidosis, but with little success.
In contrast, hemodialysis and continuous dialysis techniques play an important role in drug-induced lactic acidosis and in particular the one caused by metformin.
L-carnitine has shown promising results in the patients with AIDS treatment, since the latter often develop carnitine deficiency and the molecule plays an important role in mitochondrial function.
Thiamine and biotin deficiencies are common in patients with lactic acidosis due to total parenteral nutrition and chronic alcoholism. These nutrients should be integrated accordingly.
Mitochondrial disorders treatment involves the use of antioxidant molecules (coenzyme Q10, vitamin C, vitamin E) and amino acids (L-arginine), although there is not a good level of evidence.

Ketoacidosis

Introduction
Clinically relevant ketoacidosis includes:
– diabetic ketoacidosis;
– alcoholic ketoacidosis;
– prolonged fasting ketoacidosis.
The common denominator of the three forms is the establishment of a "hepatic ketogenic state", sustained from a bio-humoral point of view by low levels of insulin as opposed to enhanced secretion of counter-regulatory hormones (glucagon, epinephrine, cortisol, growth hormone). This peculiar hormonal arrangement generates uncontrolled lipolysis in the adipose tissue; the fatty acids thus released arrive in large quantities to the liver and by the mitochondria are oxidized into ketone bodies (acetoacetate and beta-hydroxybutyrate). The ketone bodies are strong acids, therefore they consume bicarbonate, determining metabolic acidosis and increase of the anion gap.

Diabetic ketoacidosis
DKA (Diabetic Ketoacidosis) is one of the acute complications of diabetes mellitus, in which insulin deficiency and elevated glucagon levels create a metabolic paradox: a large glucose availability is opposed to an almost impossible utilization.
The body, therefore, to get alternative fuel to glucose, uses other metabolic pathways, overlapping those activated in fasting, first of all lipolysis with consequent ketogenesis. Ketone bodies, it is worth remembering, are the only energy substrate of the neuron in the absence of glucose (**Figure 6.2**).

Identification and treatment of triggering causes
The DKA is in some cases the initial clinical presentation of an unknown diabetes, but more frequently it occurs in conjunction with physiological or pathological stressful events (pregnancy, infections, ischemia, trauma, inadequate compliance with insulin therapy, glucocorticoid therapy).
Regardless of the context, the identification and treatment of triggering factors is an integral part of the diabetic ketoacidosis therapy.

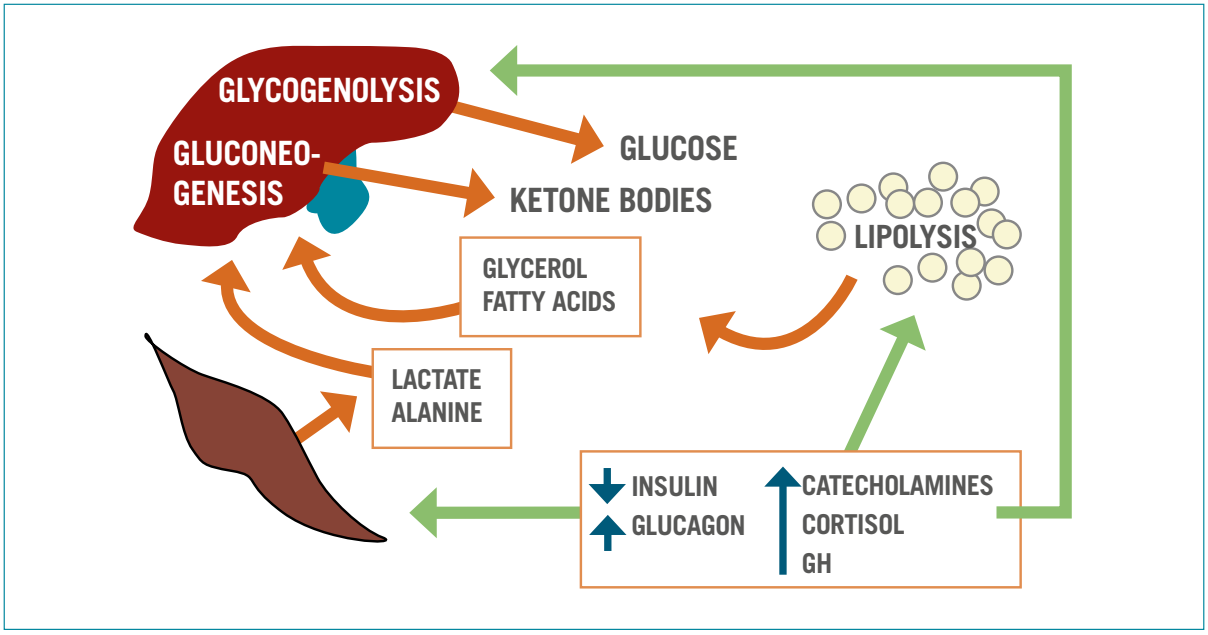

Figure 6.2 Diabetic ketoacidosis pathogenesis.

NOTE

About 10% of patients with DKA are surprisingly euglycemic (blood glucose level < 200 mg/dL). The euglycemic DKA (EDKA) occurs when one of the causes triggering ketoacidosis acts in the presence of reduced caloric intake. In these cases prolonged fasting and concomitant insulin therapy end up depleting glycogen storages and therefore also glucose, while lipolysis continues to support ketogenesis. The most common EDKA causes reported in literature are pregnancy, pancreatitis, cocaine overdose, prolonged vomiting or diarrhea, insulin pump malfunction and a new class of oral hypoglycemic agents, the sodium-glucose cotransporter 2 inhibitors (SGLT2) empagliflozin, canagliflozin.

The three phases of DKA and therapeutic implications

It is very important to remember, for therapeutic implications, that in diabetic ketoacidosis the anion gap is not increased at all stages of the disorder. There are in fact at least two phases in which the anion gap is normal and the acidosis has the characteristics of a hyperchloremic form: the "early phase" in which the circulating blood volume is still preserved and the "late phase" in which the blood volume was restored by saline solution administration.

In the "early phase", in fact, most of the ketone bodies are not held in plasma, but buffered and eliminated by the kidney in the form of sodium and potassium salts. Net this condition generates an indirect bicarbonate loss and therefore a hyperchloremic metabolic acidosis.

When the ketogenic process accelerates and volume depletion becomes more severe, the generated ketoacids concentrate to a greater extent in plasma and increase the anion gap. It is at this stage that ketoacidosis usually becomes symptomatic.

In the course of treatment ("late phase"), the metabolic acidosis is transformed once again into a hyperchloremic form. In fact, by ceasing ketoacids and restoring the extracellular volume, a structure very similar to the

early one is recreated, in which the remaining ketoacids resume their urinary elimination. Fluids administered in this phase participate in the genesis of the disorder. The solutions containing chloride and in particular the normal saline solution, acidify when administered in large volumes (see Chapter 11) and potassium and sodium ions that accompany the chloride enter the cells in exchange to hydrogen ions.

Therapeutic approach

The order of priority in diabetic ketoacidosis treatment is as follows: volume restoration, potassium deficiency correction, insulin administration.

Although these three cornerstones (volume, electrolytes, insulin) are very clear, there are few randomized studies able to guide doctors towards the best management of the disorder; in particular the questions on "quantity" and "rate" of liquids and insulin to be administered remain open.

NOTE

Once the appropriate treatment has been started, the average resolution time for acidosis is 10-18 hours. During treatment, vital signs, diuresis, water-electrolyte balance and the dose of insulin administered should be monitored. After the initial arterial blood gas analysis, a venous blood gas with glucose and electrolytes should be performed every 2-4 hours. Patients with severe forms or potentially dangerous triggers (pH < 7.0, serum bicarbonate < 10 mEq/L, altered mental status, sepsis, gastrointestinal bleeding, myocardial infarction) should be admitted to an intensive care unit.

Fluid replacement

In DKA the osmotic diuresis induced by hyperglycemia is the cause of intracellular dehydration and ECF (extracellular fluid) reduction.

Water deficit can be considerable, up to 10% of the total body weight. Rapid replacement with fluids is essential to maintain tissue perfusion and eliminate ketone bodies.

Regardless of insulin therapy, fluid intake alone improves glycemic control, corrects acidosis and electrolyte imbalances, and reduces the level of counter-regulatory hormones.

Crystalloids are the fluids to be used even if among these it is not yet clear which is the best choice.

Normal saline solution, when used in large volumes, may worsen the hyperchloremic metabolic acidosis, which marks the terminal phase of diabetic ketoacidosis. Balanced solutions have less impact on hyperchloremic acidosis although this does not result in a reduction in mortality or outcomes.

Furthermore, the use of lactated Ringer's solution is associated with a significant delay in hyperglycemia correction. In summary, it is the experts opinion that the normal saline solution, economic and familiar, premixed with potassium, still remains the fluid of choice in the initial therapy of DKA.

The American Diabetes Association (ADA) guidelines suggest a dosage of 15-20 mL/Kg in the first hour. Once the hemodynamics has been restored, the choice of the infused solution depends on the natremia: the NaCl 0.9% saline solution in case of hyponatremia, the hypotonic (NaCl 0.45%) in the case of normal or hypernatremia at a rate of 250-500 mL/h. As soon as the glycemia levels have reached 200 mg/dL, the recommendation is to start 5-10% dextrose solution, to prevent hypoglycemia from occurring before the final correction of blood ketosis. The British guidelines [Joint British Diabetes Societies (JBDS), 2013] merely suggest the use of isotonic NaCl at a "not too rapid" rate with the sole exception of hypoperfusioned patients.

However, half of the water deficit should be corrected in the first 12 hours.

Another open question is the infusion rate for fluids after the first volume recovery phase; physicians have always been warned about the need to limit the infusion rate in this phase, to avoid a too rapid reduction in effective plasma osmolality (tonicity).

The risk is in fact the onset of the most threated ketoacidosis complication: cerebral edema. Cerebral edema develops in approximately 0.5-1% of patients with di-

abetic ketoacidosis during volume recovery. It is quite typical in childhood, very rare in adults.
The risk of death and sequelae is quite high, between 30% and 50%.

NOTE

Although there are studies (PERCAN DKA FLUID – 2013) suggesting that the rapid correction of plasma tonicity can only play a marginal role in determining neurological damage, giving more credit to alternative pathogenetic hypotheses, such as ischemia-reperfusion and neuroinflammatory damage, both correlated to the severity of underlying disease, rather than to the aggressiveness of reperfusion, it is still good practice to use hypotonic solutions only in strictly selected cases of high plasma tonicity, in conditions of restored perfusion.

Correction of potassium deficiency
DKA is characterized by a significant potassium deficiency (up to 3-5 mEq/Kg of body weight). Osmotic diuresis, elimination of ketoacids that bind opposite charge ions, metabolic acidosis and losses with vomiting are responsible.
However, despite the deficit, many patients with DKA appear with normal or even high levels of serum potassium, because the concentration of serum potassium does not reflect the total body content of the ion, due to its prevalent intracellular distribution (only 2% of the total potassium is found in circulating form in the blood).
During DKA the dehydration increases the concentration of serum potassium, despite the total deficit, and the acidosis favors the potassium passage from the intracellular to the extracellular space for the electroneutrality maintenance.
The presence of normal and reduced kalemia during DKA is a sign of a significant potassium loss and its administration, prior to any other therapeutic intervention, becomes a priority to avoid severe arrhythmic complications.
Insulin therapy and acidosis correction, in fact, favor potassium passage inside the cell, contributing to the kalemia reduction and increasing the risk of arrhythmias. For this reason in all hypokalemic patients the insulin administration should not be started before the correction of the electrolyte disorder.
The infusion rate should range between 10 and 40 mEq/h, because according to the experts opinion, at this rate, adverse cardiovascular and muscular events are minimal.
For pragmatic purposes we report the following indications from ADA:

- if kalemia > 5.2 mEq/L do not administer intravenous potassium, start insulin infusion and monitor the kalemia every 2 hours;
- if kalemia < 3.3 mEq/L do not administer insulin, start potassium infusion at 20-30 mEq/h until a value greater than 3.3 mEq/L is reached;
- if kalemia is between 3.3 and 5.2 mEq/L, add 20-30 mEq of potassium to each liter of infused fluid, with the aim of maintaining a kalemia between 4 and 5 mEq/L.

Insulin administration
Once the hypokalemia is corrected and the administration of fluids has begun, it is necessary to administer rapid acting insulin, aiming to correct the hyperglycemia, but above all to stop the lipolysis and consequently the ketogenesis.
Continuous intravenous infusion is preferred due to short latency and easy dose titration.
The main protocols (ADA and JBDS) suggest an insuline infusion rate of 0.1 IU/Kg/h until a blood glucose of 200 mg/dL is reached; at this point the dose should be halved (0.05 IU/Kg/h), parallel to the glucose infusion.

NOTE

For practical purpose we suggest to dilute 50 UI of rapid acting insulin in 500 mL of normal saline solution and infuse at a rate in mL/h equal to the patient's estimated body weight.

For non-severe forms in a non-monitored environment, subcutaneous administration is feasible.
In these cases it is recommended to perform a subcutaneous bolus of rapid acting insulin at a dose of 0.2-0.3 UI/Kg (twice or triple the recommended intravenous doses), followed by 0.1-0.2 UI/Kg every 1-2 hours until upon reaching a blood glucose of 250 mg/dL.

NOTE

Patients with type 1 diabetes mellitus often use continuous subcutaneous infusion pumps and it is well known that their malfunction can be the cause of DKA; in these cases, although not supported by any evidence, the current recommendations suggest the interruption of the subcutaneous infusion and the transition to intravenous infusion.

Controversies in the DKA treatment

Sodium bicarbonate administration
The current guidelines trend is to recommend the administration of sodium bicarbonate for arterial pH < 6.9.
Small randomized controlled studies show that administering bicarbonate for pH between 6.9 and 7.1, improves blood pH rapidly, albeit transiently. However, the effect on pH does not translate into a reduction in mortality or a faster resolution of ketosis and hyperglycemia, nor does it reduce the risk of neurological and cardiac damage.
On the contrary, complications from bicarbonate solutions in patients with acidemia are now well known (see also section on lactic acidosis): intracellular acidosis and paradoxical respiratory acidosis, increased plasma tonicity (especially when the 1 molar at 8.4% solution is used), worsening of kalemia and calcemia. At these blood pH values, therefore, bicarbonate would have only a cosmetic effect and its use is not recommended.

NOTE

Some experts (Kamel S, Halperin M, NEJM 2015) propose not to use pH as a parameter to assess bicarbonate indication, but rather to identify those subgroups of patients that would benefit the most. The first category is made up of subjects who are unable to adequately remove ketone bodies. Since the oxidative catabolism of ketone bodies occurs mainly in the cerebral glia and at renal level, patients with altered state of consciousness (diabetic coma, pharmacological sedation) or with severe renal failure (glomerular filtrate less than 30 mL/min) could benefit from the early administration of bicarbonate. A second category of patients are those that develop hyperchloremic acidosis after the first fluid replacement phase. The latter in fact may have insufficient circulating anions to metabolize and produce bicarbonate ions and the acidemia may rapidly deteriorate with a rapid infusion of normal saline solution, which, as written before, acidifies if infused at large volume.

Bolus insulin administration
The ADA suggests administering a bolus of intravenous insulin, at a dosage of 0.1 UI/kg, before starting the continuous infusion.
Numerous studies have shown that with an infusion regimen of at least 0.1 UI/Kg/h there is no advantage in terms of ketosis resolution, in a hospital lenght of stay and mortality.
It is also the experts opinion that bolus should be avoided in children to prevent a sharp reduction in plasma tonicity resulting in an increased risk of cerebral edema.

Subcutaneous insulin administration
One of the most difficult problems to solve in the DKA treatment is the transition to subcutaneous insulin administration once the ketoacidosis has resolved and the patient has resumed eating.
In fact, once intravenous administration of insulin is interrupted, its effect ends in a few minutes, while the

latency period of a basal (long-acting) insulin can be 1-2 hours: it follows that overlapping of the two administrations is absolutely necessary. There is currently solid evidence to recommend an insulin glargine dose of 80% of the insulin requirement at least two hours before discontinuing intravenous administration.

Potassium phosphate administration

As for potassium, in DKA, serum phosphate often appears normal or even increased, although there is a total body phosphate deficiency, generally up to 1.0 mmol/Kg of body weight. Phosphate levels further decrease with insulin therapy. Randomized prospective studies have shown that phosphate replacement offers no improvement in outcomes.

Nevertheless, the ADA suggests the administration of potassium phosphate (20-30 mmol) in patients with cardiac dysfunction, anemia, respiratory failure or with phosphate levels < 3.2 mmol/L.

Alcoholic ketoacidosis

Chronic alcoholism is accompanied by a variety of acid-base and water-electrolyte disorders. Isolated alcoholic ketoacidosis is rare, most often it occurs together with other acid-base alterations (up to 78% of cases according to one study). Metabolic acidosis (lactic acidosis and ketoacidosis) can coexist with metabolic alkalosis (vomiting) and respiratory alkalosis (liver failure).

Acid pH is found in about half of the cases. AKA (Alcoholic Ketoacidosis) is more frequent in subjects with discontinuous alcohol abuse, who experience dyspepsia, abdominal pain or vomiting induced by another alcohol related pathology (gastritis and pancreatitis, for example).

Reduced food intake indeed determines the characteristic hormonal structure (low levels of insulin, high levels of counter-regulatory hormones) that activates hepatic ketogenesis.

The ketogenesis is also supported by the same hepatic metabolism of ethanol: conversion of ethanol to acetaldehyde and acetate increases NADH/NAD ratio favoring the preferential formation of beta hydroxybutyrate. The high NADH/NAD ratio also explains the lactate increased synthesis, which however is always rather limited; on the contrary, severe lactic acidosis should lead to suspect thiamine deficiency or hypoperfusion (**Figure 6.3**).

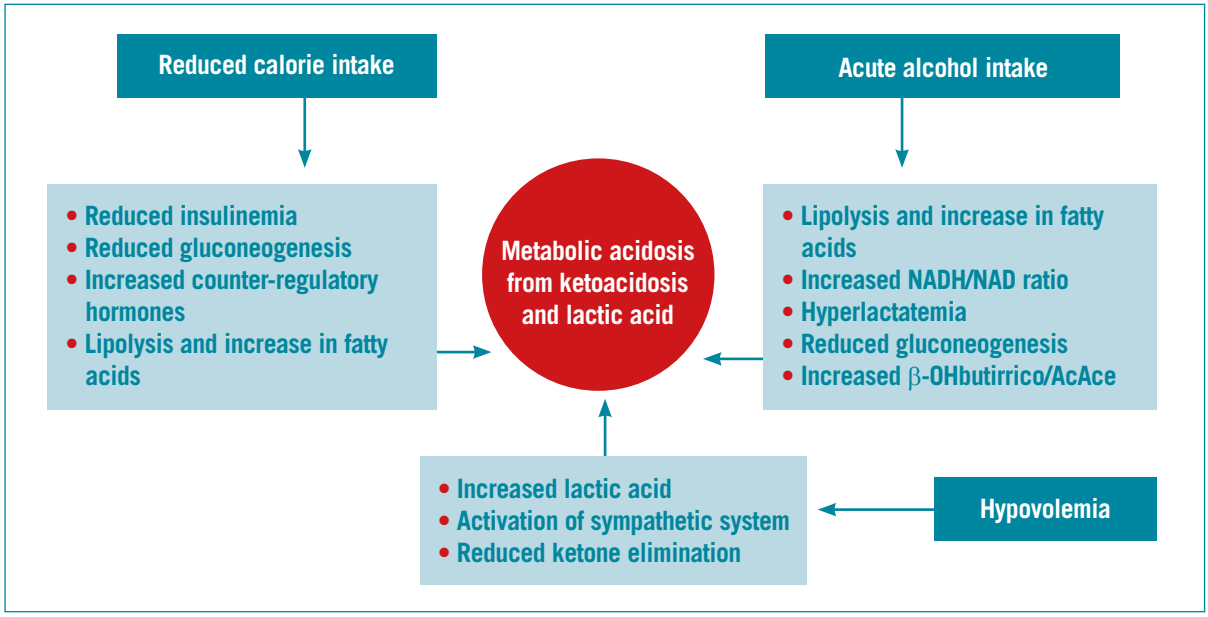

Figure 6.3 Alcoholic ketoacidosis pathogenesis.

Hypoglycemia accompanies AKA in about a quarter of cases and usually occurs after 14-24 hours of fasting, because the metabolism of ethyl alcohol inhibits the glucose synthesis (neoglucogenesis), but has no effect on the glucose mobilization by glycogen deposits (glycogenolysis).
Hypoglycemia is a potentially fatal event, because the transition from the alcoholic drowsiness to a hypoglycemic coma can be imperceptible and may escape to the physician evaluating the patient.

NOTE

Test stripes measuring urine ketones are sensitive to acetoacetate and not to hydroxybutyrate, with high risk of false negatives.

Therapy principles
The therapeutic goals in the treatment of AKA are:
- supporting hemodynamics and blocking ketogenesis;
- prevent neurological damage;
- control the symptoms of alcohol withdrawal;
- correct associated water and electrolyte disorders.

The first objective is pursued by administering crystalloids (normal saline solution) and dextrose 5-10% solution. The glucose administered, in fact, increases the insulin release and blocks the glucagon one, while volume recovery decreases the levels of circulating catecholamines. Intravenous glucose administered at a rate between 7.0 and 7.5 g/h usually reverses acidosis in 12-24 hours. Thiamine administration is very important to avoid the development of acute Wernike-type encephalopathy.
Traditionally it was believed that administering glucose before thiamine could increase the risk of neurological damage. According to some studies, this fear is unfounded and, on the contrary, it is essential not to delay of hypoglycemia correction.
Finally, benzodiazepine administration controls the symptoms of alcohol dependence.There is no indication for bicarbonate administration, due to the potential harmful effects, already mentioned in the paragraph on DKA, but above all because the kidney maintains unchanged the ability to "regenerate" bicarbonates. Attention should also be paid to the correction of electrolyte alterations, which are very frequent in these patients, in particular hypomagnesemia. Finally, remember that chronic alcoholics look for other alcohols to satisfy their dependence, in particular isopropyl alcohol (used as a skin disinfectant and as a detergent). Doctors must therefore be aware of the clinical effects and treatment following their voluntary ingestion (see below).

Starvation ketoacidosis
Starvation ketoacidosis is nothing but the extreme phase of a physiological process.
In fact, hepatic ketogenesis is essential for the production of alternative energy sources, when glucose is no longer available.
It usually begins after at least two or three days of fasting, but in patients with increased caloric needs (pregnancy, lactation) or depletion of the muscular mass (dystrophies) the process appears more rapid and severe.
Treatment involves fluid replacement and administration of 5-10% dextrose solution, in relation to the same pathophysiological assumptions already described for the AKA.
Caloric intake is then gradually reintroduced to avoid the so-called refeeding syndrome (hyperalimentation syndrome). The rapid transition from a catabolic metabolism to an anabolic one can in fact have several negative consequences.
The glucose increased synthesis and the resumption of protein synthesis consumes ATP and reduces the levels of different ions, in particular phosphate, magnesium and potassium with the risk of organ complications and severe arrhythmias.

Toxic alcohols

Introduction
Toxic alcohols are intoxicating psychotropic substances, but they are not directly responsible for metabolic acidosis. The effects on the acid-base balance derive from their hepatic metabolism. The two key enzymes

are alcohol-dehydrogenase and aldehyde-dehydrogenase (the same as in ethanol metabolism); the first enzyme catalyzes the alcohol oxidation into aldehyde while the second aldehyde oxidation into carboxylic acid which is then responsible for hig anion gap metabolic acidosis. Specifically, methanol is oxidized into formic acid and ethylene glycol into glycolic acid and oxalic acid.

Alcohol-dehydrogenase represents the main target on which antidotes act.

Toxic alcohol intoxications are characterized, not only by an anion gap increase but also by an osmolal gap increase because alcohols are small (low molecular weight) molecules and therefore able to significantly increase plasma osmolality.

During intoxication the anion gap and the osmolal gap do not change in parallel, but tend to have opposite trends. Both are then influenced by the start time of antidote therapy.

A high osmolal gap and a low anion gap are in fact characteristic of the first phase of intoxication, when the alcohol level is high and the carboxylic acid level is low. With the gradual transformation of alcohol into acid, the relationships are reversed. Antidotes block the alcohols metabolism, slowing the formation of toxic acids.

NOTE

It is worth remembering, in order to avoid misunderstanding, that many forms of metabolic acidosis caused by organic acids are accompanied by an osmolal gap increase (lactic acidosis, ketoacidosis, chronic renal failure). Therefore, the only increase of the osmolal gap in the presence of a high anion gap metabolic acidosis is not sufficient to diagnose alcohol intoxication without a history of ingestion.

Methanol and ethylene glycol intoxication

The two most frequent forms of alcohol intoxication are those from methanol and ethylene glycol.

Methanol is currently used in windshield detergents and fuels and as a solvent in chemical industry. It causes depression of the central nervous system, abdominal pain, reduction of visual acuity up to blindness and parkinsonism.

Ethylene glycol is used widely, as an engine coolant, in antifreeze and in brake fluid. Because of its sweet taste, accidental ingestion it is often in children and animals: the reason why products containing it are most often added with bitter agents.

Ethylene glycol toxicity typically evolves in three stages. A first stage (first 12 hours) in which neurological symptoms prevail (from intoxication to coma); a second stage (from 12 to 48 hours) characterized by cardiac toxicity (arrhythmia, acute pulmonary edema) and lung damage (ARDS); a third stage called “renal” (after 48 hours) in which acute renal failure develops, from tubular-interstitial damage, induced by the deposition of calcium oxalate.

Treatment principles

The treatment includes:

- inhibition of metabolism of the two alcohols with the use of antidotes;
- removal of alcohol and its metabolites.

The gastrointestinal absorption of methanol or ethylene glycol is fast, so the gastric lavage is worthless.

In accordance with the American Academy of Clinical Toxicology (AACT) guidelines, antidote treatment is indicated for:

- concentration of methanol or ethylene glycol greater than 20 mg/dL;
- documented ingestion of toxic quantities of methanol or ethylene glycol and an osmolal gap > 10 mOsm/Kg;
- strong clinical suspicion of poisoning and at least two of the following criteria: arterial pH < 7.3; $[HCO_3^-]$ < 20 mEq/L; osmolal gap > 10 mOsm/Kg.

The first choice antidote (absolute choice in children) is fomepizole (or 4-methylpyrazole), a strong alcohol dehydrogenase inhibitor (with an affinity 8,000 times

higher than that of ethanol), which has received FDA approval for poisoning treatment with methanol and ethylene glycol, but it is not approved for the treatment of other poisonings with toxic alcohols. Fomepizole is effective at low concentrations, has minimal side effects and does not require monitoring in intensive care units. For patients who are not on dialysis, the loading dose is 15 mg/Kg, followed by a maintenance dose of 10 mg/Kg administered every 12 hours.

Since fomepizole is an inducer of its own metabolism by cytochrome P-450 enzymes, after 48 hours the maintenance dose should be increased to 15 mg/Kg every 12 hours.

The drug is removed by dialysis, so it should be administered immediately after the dialysis session. An alternative antidote to fomepizole, although not approved by the FDA, is ethanol.

Ethanol is in fact an alcohol with greater affinity for alcohol dehydrogenase (about 10 times higher than others) and when administered together with another alcohol it competitively blocks the enzyme, preventing its metabolism. The inhibitory effect is obtained with serum ethanol concentrations of at least 100 mg/dL.

The advantages of ethanol are its easy availability and low cost.

The disadvantages include the need to monitor serum concentrations, its effect on the sensory (which overlaps that of the alcohol taken), the risk of adverse reactions from ethanol administration (hypoglycemia, ion imbalances) and the need for hospitalization in intensive or intermediate care unit.

Ethanol can be administered intravenously in a 10% dilution or alternatively orally or by a nasogastric tube.

Toxic alcohols and their metabolites are small and water-soluble molecules, therefore easily removable by hemodialysis.

The indications for hemodialysis are well defined in the guidelines (AACT – American Academy of Clinical Toxicology and EXTRIP – EXtracorporeal TReatments In Poisoning); in general there is absolute indication in case of severe metabolic acidosis, concentrations of methanol and ethylene glycol greater than 50 mg/dL, deterioration of vital signs despite supportive care, visual disturbances or acute kidney damage. Intermittent hemodialysis removes toxic alcohols more rapidly than the continuous forms (CVVH – continuous veno-venous hemofiltration and CVVHD – continuous veno-venous hemodiafiltration).

Many experts promote the use of dialysis in association with antidotes, beyond the stringent indications dictated by the guidelines, because the use of antidotes alone greatly increases the elimination half-life of toxic substances, consequently increasing hospitalization duration.

There is indication for intravenous administration of sodium bicarbonate in methanol intoxication. Bicarbonate, in fact, increases the transformation of formic acid into formate, facilitating urinary excretion and preventing its diffusion into the optic nerve. In methanol poisoning, 1 mg per kilogram of folic acid every 4-6 hours promotes the conversion of formic acid to carbon dioxide and water.

In poisoning with ethylene glycol, pyridoxine and thiamine promote the metabolism of glycolic acid in less toxic compounds.

Salicylates intoxication

Acetylsalicylic acid is rapidly transformed in the body into salicylic acid. Although there is no correlation between plasma salicylates concentration and symptoms, most patients show signs of intoxication when plasma levels are above 40-50 mg/dL. A fatal overdose can occur with doses of 10-30 grams in adults and even only 3 grams in children.

The first symptoms, into which intoxication is suspected, are oto-vestibular (vertigo, dizziness, tinnitus) and neurovegetative (nausea, vomiting, diarrhea). More severe intoxications determine alterations in the state of consciousness (from headedness to coma), non cardiogenic pulmonary edema, hypoglycemia. During salicylates intoxication various acid-base disorders may occur.

The most common is respiratory alkalosis, due to the salicylates ability to directly stimulate the breath center. Metabolic acidosis is more frequent in children: the smaller they are, the more probable and serious the disorder is.

Metabolic acidosis is only minimally linked to the pres-

ence in the circulation of salicylic acid, but it is mainly sustained by accumulation of other organic acids: ketoacids (salicylates activate hepatic ketogenesis) and lactic acid (salicylates inhibit oxidative phosphorylation and the concomitant respiratory alkalosis increases the pH-dependent activity of 6-phosphofructokinase enzyme).
Metabolic acidosis is often accompanied by hypouricemia, due to the salicylates uricosuric effect.

Treatment principles
Gastric lavage represents an emergency procedure and it is often necessary to resort to decontaminative endoscopy to remove individual tablets or bezoars that can be formed.
In case of severe intoxication, with acetylsalicylic acid concentrations above 60 mg/dL, hemodialysis should be considered. The choice becomes mandatory for concentrations above 90 mg/dL. There is absolute indication for dialysis even in patients in coma, with renal failure or water overload.
For lower plasma concentrations the therapeutic goal is to alkalize plasma and urine.
Neurological effects and death during salicylates intoxication are related to the concentration of salicylic acid (HS) in brain tissue.
Salicylic acid, in fact, lacking an electrical charge, is fat-soluble and passes through cell membranes very easily, on the contrary the salicylate anion (S^-) remains confined in the extracellular fluid. Maintaining a blood pH of between 7.45 and 7.50 favors the conversion of salicylic acid (HS) to salicylate (S^-) thus reducing intracellular toxic effects. In a similar way an alkaline urinary pH (higher than 6.5) favors the drug urinary elimination. It follows that during metabolic acidosis there is room for the use of bicarbonate solutions.
However, if respiratory alkalosis is the predominant disorder, it is not necessary to induce further alkalinization.
The use of acetazolamide is controversial.
The drug is able to alkalize the urine and therefore promote the salicylates excretion, but with the same mechanism it acidifies the plasma and above all increases free salicylate blood levels because it competes with its binding to albumin. In case of severe intoxication (Reye's syndrome), glucose may also be indicated to prevent neuroglycopenia.

Treatment of hyperchloremic metabolic acidosis

Introduction
Hyperchloremic metabolic acidosis is caused by loss of bicarbonate in the form of Na^+ or K^+ salts, followed by Cl^- retention.
The bicarbonates loss may be due to:
- direct loss: gastrointestinal route (diarrhea, pancreatic, biliary and intestinal fistulas) or renal (proximal tubular acidosis);
- indirect loss: kidney reduced capacity to regenerate bicarbonates due to deficit of net urinary excretion of H^+ (acute or chronic renal failure, distal tubular acidosis).

The common therapeutic denominator of these forms is the indication for the exogenous alkali (use sodium bicarbonate or citrate).
In the chronic forms (chronic diarrhea, renal tubular acidosis, chronic renal failure) an aggressive approach is not necessary and the alkali are most often administered orally, which minimizes the risks of intravenous administration.

Gastrointestinal losses
Fuids in the alimentary tract below the stomach, including biliary and pancreatic secretions, are relatively alkaline.
The basic compounds of these liquids can reach a total concentration of 50-70 mEq/L and consist mainly of bicarbonate and organic anions. The result is that diarrhea, abuse of laxatives, removal of pancreatic, biliary or intestinal secretions (through drainage tubes, fistulas, vomiting due to small bowel obstruction), can all lead to metabolic acidosis. Treating the underlying cause (i.e. antibiotic therapy in the case of infectious diarrhea) and volume recovery are the two main therapeutic aids; maintaining an ad-

equate "effective" volume means restoring renal perfusion and tubular secretion of H^+ which regenerates bicarbonate. For this purpose, normal saline solution and Ringer lactate are the best solutions.

In severe diarrhea (with the exception of cholera) oral rehydration solutions are strongly recommended. The rehydrating solution of the World Health Organization has a total osmolality of 311 mOsm/L and contains: sodium 90 mEq/L, chloride 80 mEq/L, potassium 20 mEq/L, glucose 111 mmol/L (about 20 g/L) and citrate 10 mEq/L; there is evidence that solutions with lower osmolality reduce stool volume and duration of diarrheal phenomenon.

In the case of acute diarrhea, with severe acidemia, intravenous bicarbonate solutions are indicated, to be preferred those with low osmolality (1.4% and 5%), to increase the water load in case of severe dehydration. In these cases, the 1 molar solution (8.4% sodium bicarbonate solution) could cause excessive increases in plasma tone and natremia.

It is always essential to ensure that there is no hypokalemia before administering bicarbonate intravenously; in this case (as for the DKA) the kalemia correction is mandatary to avoid severe arrhythmic complications.

Renal losses

Chronic renal failure

In chronic renal failure the metabolic acidosis has different characteristics in relation to the degree of filtrate compromise. For filtrates greater than 15-20 mL/min, a hyperchloremic metabolic acidosis prevails, due to the impairment of ammoniagenesis; at lower filtrate values, on the other hand, the high anion gap metabolic acidosis, from the retention of inorganic acids (sulphates, phosphates) and organic (urate) is more characteristic.

Classical uremic acidosis is characterized by a reduced rate of production and excretion of NH_4^+, caused by renal mass decrease. In general, acidosis does not occur until the nephron population falls below 75%. In this initial phase, due to secondary hyperaldosteronism, the urinary excretion of phosphates and therefore the kidney ability to buffer the hydrogen ion through urinary phosphates (so-called titratable acidity) is not compromised.

As renal failure progresses, the retention of inorganic and organic anions produces a high anionic gap acidosis.

The anion gap increase is rarely greater than 4-6 mEq/L and HCO_3^- usually stabilizes between 12 and 20 mEq/L, probably due to some degree of buffering caused by bone buffers.

Both forms of metabolic acidosis require the administration of oral alkali (sodium bicarbonate or citrate) to maintain the plasma bicarbonate concentration above 22 mEq/L (recommended by the National Kidney Foundation). Alkalinizing therapy is necessary to avoid bone demineralization. To achieve this, 0.5 mEq/Kg/day of sodium bicarbonate is often sufficient. For practical purposes, we remind you that 1 g sodium bicarbonate tablets contain 11.9 mEq.

For a 70 Kg subject it will therefore be necessary to administer about 35 mEq/day, the equivalent of 3 tablets.

Sodium citrate increases the aluminum salts absorption from the gastrointestinal tract, so it should never be taken together with antacids containing aluminum oxide, due to the risk of intoxication.

When hyperkalemia is present, the alkali should be administered together with furosemide (60-80 mg/day). For some patients, chronic administration of sodium polystyrene sulfate (kayexalate) or other resins may be necessary (see Chapter 13).

Finally, remember that in patients on dialysis the best way to correct metabolic acidosis in case of acidemia is to use bicarbonates in dialysis fluid; bicarbonate has completely replaced acetate as the buffer of choice in dialysis, because it offers better hemodynamic stability.

Tubular acidosis

The cornerstone in the treatment of type 1 and type 2 tubular acidosis is the alkali administration. In the type 2 (proximal) form, bicarbonate deficiency is very consistent and dosages up to 10-30 mEq/Kg/day of HCO_3^- may be required; in the distal forms the requirement is limited to 1-3 mEq/Kg/day. In children it is recommended to bring blood bicarbonate concentration close to normal values (24 mEq/L) to ensure adequate

growth. Acidemia is in fact a powerful inhibitor of protein synthesis and the use of bone buffers, at this age, causes osteomalacia. Only in proximal tubular acidosis (type 2), to reduce the bicarbonate need, it is useful to administer a thiazide diuretic which, by reducing the extracellular volume, increases the HCO_3^- reabsorption in the proximal tubule. It is often necessary (especially in the proximal forms) to supplement with potassium salts. Amiloride, a potassium-sparing diuretic, inhibitor of sodium channels, has also been used successfully for the kalemia correction.

Type 4 tubular acidosis, due to aldosterone deficiency or resistance, requires special attention.

The main disorder in these cases is not acidosis, which is always marginal, but rather hyperkalemia. Therapy involves the administration of the deficient mineralocorticoid hormone. However, the associated sodium retention is potentially dangerous in case of hypertensive or edematous patients. These can effectively be treated with loop diuretics and low potassium diet. The diuretic loop also has positive effects on the kalemia correction and on acidosis. These drugs, in fact, by increasing the amount of sodium reaching the distal nephron, create an increase in the electro-negativity of the lumen, which favors the excretion of the hydrogen ion and potassium.

Metabolic alkalosis treatment

Introduction

As explained in Chapter 4, for diagnostic and therapeutic purposes it is very useful to differentiate metabolic alkalosis in chloride-responsive forms (urinary chloride less than 15 mEq/L) and chloride-resistant ones (urinary chloride greater than 20 mEq/L). The latter, in turn, include the forms due to mineralocorticoids excess, severe potassium and magnesium depletion and Bartter and Gitelman syndromes (see Chapter 4).

Chloride-responsive metabolic alkalosis

The treatment goal in these forms is to restore a correct bicarbonate urinary excretion and correct the so-called paradoxical aciduria, which is the basis for maintaining the disorder.

To achieve this goal we should intervene on the three conditions that determine this phenomenon: depletion of the effective blood volume (and the consequent activation of renin-angiotensin-aldosterone axis), chloride ion deficit and the potassium deficiency. The mainstay of therapy is the administration of normal saline solution intravenously. This therapeutic regimen is in fact able to restore the HCO_3^- urinary excretion through three mechanisms:

1) correction of circulating blood volume;
2) elimination of urinary sodium retention stimulus;
3) increase in Cl^- portion reaching the distal nephron.

The therapy effectiveness can be verified by checking urinary pH and urinary chloride. Paradoxical aciduria usually takes the urinary pH below 5.5; once the effective blood volume and chloride levels have been restored, the nephron reduces the H^+ excretion and the pH begins to rise up to 7.0 and in rare cases will reach 8.0.

At the same time there is an increase in urinary chloride.

Even if adequate NaCl administration is able to correct the alkalosis, in some cases it may not be sufficient to solve potassium depletion when present; in such cases it is essential to integrate the ion orally or intravenously. In this regard, it is important to remember that only potassium chloride is effective, because the administration of potassium together with any other anion, other than chloride, causes an increase in the H^+ excretion, preventing the alkalosis correction.

Balanced solutions (Ringer's lactate and acetate) are contraindicated in metabolic alkalosis treatment, because lactate and acetate are converted to bicarbonate and the low chloride content hinders the correction of the disorder.

In cases of vomiting or prolonged use of a nasogastric tube it is recommended to use proton pump inhibitors or H_2 blockers in order to minimize gastric chloride secretion.

However, it is not always possible, in the chloride-responsive forms, to administer intravenous NaCl. This is the case of patients with edematous syndromes (cir-

rhosis, nephrotic syndrome, congestive heart failure, chronic pulmonary heart disease, chronic renal failure) who use loop diuretics or thiazides. In these cases, metabolic alkalosis is supported by the reduction of effective blood volume, despite the significant increase in extracellular water. In these cases, normal saline solution increases the edema degree and places the patient at risk of acute pulmonary edema due to fluid overload. The correct therapy includes, when possible, the suspension of the diuretic and the possible administration of acetazolamide. During renal failure a valid alternative is dialysis with a dialysis bath solution at lower HCO_3^- concentrations.

Acetazolamide (250 mg two or three times a day) is indicated in patients with metabolic alkalosis, water overload and preserved renal function. It is an inhibitor of carbonic anhydrase and is the only diuretic not causing metabolic alkalosis, therefore its use allows to reach the double purpose of intervening both on edema and alkalosis. As in the case of normal saline solution, the efficacy of acetazolamide can also be assessed by monitoring urinary pH, which should remain above 7.0. Acetazolamide, however, may worsen hypokalemia, already induced by loop diuretics and thiazides.

Acetazolamide is often used in the treatment of post-hypercapnic metabolic alkalosis, especially in patients with chronic pulmonary heart disease weaned from ventilation (invasive and non-invasive). In these contexts, the pH normalization is very important, because the alkalemia depresses the ventilation and makes the oxygen binding to hemoglobin more greedy (hemoglobin dissociation curve moves to the right), worsening tissue hypoxia. However, acetazolamide may also cause a transient increase in PCO_2 (approximately 3-7 mmHg), due to the inhibition of carbonic anhydrase of red blood cells, which is essential for the gas transport from the tissues to the lungs. Recent studies and a meta-analysis seem to support the acetazolamide use with this indication, which however still remains *off-label*.

Another frequent condition in which a prudent use of acetazolamide is functional in the patient with respiratory acidosis and severe metabolic alkalosis capable of strongly conditioning ventilation and where normal saline solution is not indicated due to concomitant heart failure. In such cases bicarbonate concentration must not be normalized but brought at the appropriate level of ongoing hypercapnia. The treatment of severe metabolic alkalosis, in patients with an edematous state due to chronic renal failure, represents a real challenge. In patients not yet on dialysis, acetazolamide at a reduced dose (250 mg or 500 mg/day given as a single dose) remains a viable option and may assist in the loop diuretics effect on edema. However, attention must be paid to the synergistic effects on the reduction of kalemia. In patients on dialysis there is no alternative to dialysis itself, however, the characteristics of dialysis bath should be modified. Continuous modalities represent more adequate solutions than conventional hemodialysis. The evolution of dialysis techniques has in fact made obsolete therapies with intravenous HCl and its oral precursors (ammonium chloride and arginine hydrochloride).

Chloride-resistant metabolic alkalosis

The therapy of these forms involves two common interventions: correction of basic disease and supplementation with potassium salts.

Excess of mineralocorticoids

The most appropriate treatment is to remove the cause of the persistent mineralocorticoid activity. In neoplastic forms (adrenal adenomas, renin-secreting tumors, ACTH-secreting pituitary adenomas) the therapy of choice is surgical.

When this approach is not possible, the therapeutic goal is to reduce the kidney mineralocorticoid action. One way is the administration of aldosterone antagonists (spironolactone and potassium canrenoate), which act by directly blocking the mineralocorticoid renal receptor.

The only form resistant to aldosterone antagonists is Liddle syndrome, in which the defect is post-receptorial. Drugs that are equally effective (and can also be used in Liddle syndrome) are sodium channel inhibitors (amiloride and triamterene). The direct bond to sodium channel, expressed on the luminal membrane of distal nephron, allows these molecules to re-

duce intraluminal electroneutrality and consequently inhibit the excretion of hydrogen ion and potassium. Hypokalemia is characteristic of all the conditions in which there is an excess of mineralocorticoids, on the contrary water retention is rather modest. This is because the increased absorption of sodium in distal nephron is compensated by an almost equal reduction in the other tubule segments (aldosterone escaping phenomenon). Correction of hypokalemia contributes to the alkalosis correction with two mechanisms: intracellular exchange between potassium and hydrogen ion to maintain electroneutrality and increased tubular bicarbonate excretion.

Severe hypokalemia

In patients with hypovolemia and severe hypokalemia (less than 2 mEq/L), the correction of volume depletion alone may not be sufficient to resolve alkalosis and surprisingly the urinary chloride appears high (above 20 mEq/L), despite the sodium retention. This phenomenon is the consequence of an increased excretion of chloride induced by severe potassium deficiency. In these cases an aggressive kalemia correction is necessary to resolve the alkalosis.

Bartter syndrome and Gitelman syndrome

Nephrologists know very well that, among all the metabolic alkalosis causes, these two syndromes represent the greatest therapeutic challenge. As with all other forms of chloride-resistant metabolic alkalosis, the treatment mainstay, for both disorders, is the administration of potassium chloride. Being chronic forms, they should be administered orally at extremely high doses (sometimes up to 500 mEq/day) and magnesium should always be associated with potassium supplementation. Although potassium and magnesium supplements reduce the severity of the respective deficits (thus avoiding the most severe arrhythmic complications), unfortunately they almost never completely correct hypokalemia and metabolic alkalosis. Prostaglandin inhibitors (NSAIDs) are therefore often used in combination, acting with a dual mechanism: lowering renin levels and reducing the glomerular filtrate, thus limiting the losses of different ions (chloride, potassium and sodium) by glomerular-tubular feedback. Less frequently, potassium-sparing agents (aldosterone antagonists and inhibitors of potassium channels) and ACE inhibitors are used. These latter treatments have limited usefulness due to their hypotensive effects and reduction in the extracellular volume; the consequence is that, unfortunately, patients continue to have hypokalemia and metabolic alkalosis, despite all these interventions.

Mixed acid-base disorders treatment

Introduction

The mixed disorders of acid-base balance are extremely frequent and in some contexts they are much more frequent than simple disorders.

Most of the time they are found in critically ill patients arriving in the emergency department or in those admitted to intensive care units. It is not infrequent, however, to find mixed disorders even in the elderly multipathological population (diabetic patients, patients with liver disease, kidney disease, or bronchial pulmonary disease), which mainly occupies ordinary hospitalizations in medical or specialized departments. For example, in sepsis as in hepatic failure hyperventilating respiratory alkalosis is frequent at onset; as the underlying disease progresses, lactic acidosis may develop due to hypoperfusion (type A) or hyperactivation of aerobic glycolysis (type B).

Similarly, the post-hypercapnic metabolic alkalosis is a typical example of a mixed disorder in the elderly with bronchial pulmonary disease and with chronic pulmonary heart disease.

Formally, mixed disorders can be divided into two categories: additives, if they determine pH changes in the same direction (double acidosis or double alkalosis), and counterbalancing, if they cause pH changes in the opposite direction (acidosis with alkalosis); it is evident that additive disorders are responsible for important clinical consequences, due to the greater impact that profound alterations of blood pH have on cellular function. As a result, pH extremes impose ap-

propriate therapeutic interventions. The approach to mixed disorders necessarily requires a more in-depth pathophysiological knowledge and a further diagnostic effort, which is never an end in itself. To use the previous example (post-hypercapnic metabolic alkalosis), not recognizing a metabolic alkalosis overlapped on a chronic respiratory acidosis can aggravate hypoxia, because both disorders increase PCO_2 and at the same time, a vigorous administration of a saline solution could improve the metabolic disorder, but also bring blood pH back to too low levels. To avoid such consequences, it is extremely important to recognize both disorders, clarify which of the two is the dominant one and treat them simultaneously, paying particular attention to the consequences of pH changes.

Treatment of the main mixed disorders

Counterbalancing disorders

Respiratory acidosis and metabolic alkalosis

This combination is common in COPD complicated by chronic pulmonary heart disease and congestive heart failure during treatment with loop diuretics and thiazides or, more rarely, during vomiting or NGT use. Occasionally patients with metabolic alkalosis at onset may develop respiratory acidosis if airway infections occur. Post-hypercapnic metabolic alkalosis has already been extensively discussed in the paragraph on metabolic alkalosis.

In this disorder, alkalosis tends to reduce the acidemia degree, which would seem apparently advantageous; but as already mentioned in the introduction, clinical studies have shown that the overlap of metabolic alkalosis on a stable respiratory acidosis can worsen the CO_2 retention degree, because these patients use mild acidemia as a respiratory drive. For this reason, it is essential to also correct the metabolic alkalosis to obtain a benefit on lung function. Since the forms of metabolic alkalosis from diuretics and vomiting are chloride-responsive, administration of NaCl and KCl is effective in reducing plasma bicarbonate levels and lowering blood pH.

In plethoric patients with congestive heart failure or chronic renal failure, in whom the administration of sodium chloride is not indicated and it is not possible to reduce the diuretic dosage, the administration of carbonic anhydrase inhibitors (acetazolamide) will increase renal bicarbonate excretion. Another option is dialysis with a low bicarbonate bath.

Metabolic acidosis and respiratory alkalosis

This mixed disorder occurs in septic patients who develop renal failure, lactic acidosis or ketoacidosis, in hypotensive patients with decompensated cirrhosis, in salicylates intoxication, and in high-risk pulmonary embolism (with unstable hemodynamics).

In all conditions the onset disorder is respiratory alkalosis, induced by cytokines (in the case of sepsis and hepatic failure), by metabolites in salicylates intoxication, by hypoxemia and by direct receptor stimulation in the case of pulmonary embolism. However, the dominant disorder is almost always metabolic acidosis. All these conditions require first and foremost immediate interventions on the pathological basis.

Skipping the specific actions to be taken during sepsis or pulmonary embolism, we recall that in the salicylates intoxication, there is indication to use bases only if the dominant disorder is metabolic acidosis. In the most severe forms, with a concentration of salicylates greater than 60 mEq/L, hemodialysis should be considered.

More generally, since respiratory alkalosis can cause a significant increase in intracellular pH, the clinician should always be very cautious in administering bases to patients with this combination of acid-base disorders. Similarly, some patients may benefit from hypocapnia induced by metabolic acidosis. In fact, some studies have shown that in intubated patients, in whom hypocapnia had been reduced by the sodium bicarbonate infusion, an important exacerbation of respiratory acidosis was often observed.

Metabolic acidosis and metabolic alkalosis

The condition that most frequently causes this disorder is diabetic ketoacidosis complicated by protracted vomiting.

In general, there are two contexts in which this disorder can occur:

- a metabolic acidosis with high anion gap (ketoacidosis, lactic acidosis, advanced chronic renal failure) with overlapping metabolic alkalosis induced by vomiting or by the placement of a nasogastric tube;
- a metabolic alkalosis from loop diuretics or thiazides, to which a renal failure caused by dehydration or a lactic acidosis due to hypoperfusion overlaps.

Adequate volume recovery with normal saline solution and possible supplementation with potassium chloride are able to correct both disorders.

Additive disorders

Mixed acidosis (metabolic acidosis and respiratory acidosis)

Mixed acidosis is the typical disorder of patients with cardio-respiratory failure who have previously undergone cardio-pulmonary resuscitation, but it is also very frequent in critically ill patients admitted to intensive care units, in whom lactic acidosis is accompanied by respiratory failure.

At other times it is accompanied by advanced heart failure. The mixed acidosis poses first of all a diagnostic problem: it is not always easy to distinguish an acute respiratory acidosis on chronic respiratory acidosis from a chronic respiratory acidosis with overlapped metabolic acidosis being the anion gap a very specific but not very sensitive parameter. A correct anamnesis that allows to determine the chronology of the events is essential to correctly classify the disorder.

The combination of metabolic and respiratory acidosis produces the most severe degree of acidemia and intracellular acidosis.

Studies conducted both in vitro and in vivo have shown that both alterations are the main cause of cellular dysfunction.

Although to a lesser extent also changes in plasma CO_2, regardless of their effects on pH, can have negative effects on the cellular function. Therefore, it appears evident that during severe acidemia the main therapeutic goal remains to quickly correct blood and intracellular pH.

The optimal value of blood pH to be reached is still the subject of discussion among experts. Maintaining the pH around 7.2 seems a reasonable goal, because in animal models, below these values, there is a significant reduction of cardiac contractility and cardiac output.

Unfortunately, short-term human studies have not shown these beneficial effects, probably due to the adverse effects of administering bicarbonate solutions.

In particular, intravenous bicarbonate is rapidly converted into CO_2, which crosses cell membranes and exacerbates intracellular acidosis (phenomenon of intracellular paradoxical acidosis).

This complication appears to be more likely when sodium bicarbonate is administered as a bolus, in the presence of tissue hypoperfusion or respiratory dysfunction.

Plasma alkalinization also reduces the amount of ionized calcium, with a negative inotrope effect greater than that of mild acidemia.

Finally, the increase in plasma osmolality, with consequent volume overload, induced by the more concentrated solutions (8.4% sodium bicarbonate), can further aggravate respiratory failure.

For all these reasons, some clinicians avoid the administration of bicarbonate in patients with metabolic acidosis, especially in the presence of respiratory failure.

The most consistent advantages in mixed acidosis treatment come however from dialysis; today, different dialysis methods are available to stabilize the extracellular ionized calcium and to prevent the volume overload induced by hypertonic solutions. Large but uncontrolled studies have shown benefits on mortality in patients with lactic and respiratory acidosis when treated with ultra filtration (CVVH).

$PaCO_2$ lowering in patients with combined metabolic and respiratory acidosis attenuates acidemia and presumably also decreases the degree of intracellular acidosis.

On the basis of this pathophysiological assumption, controlled hyperventilation is proposed.

Mixed alkalosis (metabolic alkalosis and respiratory alkalosis)

The combination of respiratory and metabolic alkalosis is often present in patients with chronic infections or

liver disease (responsible for respiratory alkalosis) who use diuretics, who have vomiting or a nasogastric tube, or if they are poly-transfused (all factors responsible for metabolic alkalosis).

Another category at risk are pregnant women. Progesterone is able to stimulate the breath centers and gravidic emesis are often the cause of metabolic alkalosis. It is the acid-base disorder with the worst prognosis. In a study of more than 300 patients, the overall mortality reached 44%, with a direct correlation between the magnitude of alkalemia and mortality: mortality approaches 49% when the pH exceeds 7.60.

These data justify the aggressive treatment.

In principle, the intervention on the metabolic component is easier to carry out and foresees the same measures already mentioned in the simple disorder discussion (saline solution, KCl, dialysis with a bath at low bicarbonate concentrations).

In intubated patients, increasing the dead space or reducing the respiratory rate can increase the CO_2 to bring the pH below 7.5, a value considered safe.

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