Acid-Base Balance: Part II. Pathophysiology

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ABSTRACT

Objective: *To review the normal human acid-base physiology and the pathophysiology and management of acid-base disturbances in a two-part presentation.*

Data sources: *Articles and published peer-review abstracts and a review of studies reported from 1990 to 2000 and identified through a MEDLINE search of the English language literature on acid-base balance.*

Summary of review: *Acid-base disorders are usually classified as metabolic (non-respiratory) or respiratory, depending on whether the primary change occurs in the plasma bicarbonate or the carbonic acid (i.e. carbon dioxide) concentrations, respectively. Respiratory or renal compensatory changes usually occur to minimise the effect of the primary disturbance. A metabolic acidosis arises from an abnormal process that generates non-carbonic acid or an abnormal loss of HCO_3^- and may be identified by an increase or normal anion gap, respectively. The arterial blood gas usually reveals a pH < 7.36, PCO_2 < 35 mmHg and 'calculated' HCO_3^- < 18 mmol/L. In general, a high anion gap acidosis is managed by treating the disorder generating the acid (thereby ceasing the acid production) and enhancing the clearance of the acid anion (e.g. by metabolism or excretion) thereby regenerating the HCO_3^- reduced by buffering.*

A metabolic alkalosis arises from an abnormal process generating excess HCO_3^-. The arterial blood gas usually reveals a pH > 7.44, PCO_2 > 45 mmHg and 'calculated' HCO_3^- > 32 mmol/L. As the kidney has a large capacity to excrete HCO_3^-, management usually requires treatment of the processes that are generating as well maintaining the alkalosis.

Respiratory acidosis and alkalosis are usually caused by a primary disorder of carbon-dioxide excretion, and correction of the pH disorder only occurs with correction of the primary disease process.

Conclusions: *In man, acid-base disturbances are usually classified as either metabolic or respiratory. Correction of the underlying disorder is often all that is required to allow the body to metabolise or excrete the acid or alkali and return the buffer pair (HCO_3^- and PCO_2) to normal.* (**Critical Care and Resuscitation 2001; 3: 188-201**)

Key words: Acid-base balance, metabolic acidosis, metabolic alkalosis, anion gap, strong ion difference, renal tubular acidosis

Classification of an acid-base defect

The primary defect in an acid-base disorder is usually defined by its initiating process (e.g. lactic acidosis, ketoacidosis or renal tubular acidosis). A broader classification, however, divides them into metabolic or respiratory, with the latter relating to changes in arterial blood carbonic acid (i.e. carbon dioxide) only.

A compensatory response describes the secondary physiological response to the primary disturbance and is by definition not designated as an acidosis or an alkalosis.[1] The responses are described as secondary or compensatory responses and may be broadly quantified, for example:

- Chronic respiratory acidosis with partial renal compensation,
- Lactic acidosis with respiratory compensation, or
- Metabolic alkalosis without respiratory compensation

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Biochemical description of an acid-base defect

Three arterial blood values are necessary to describe an acid-base defect:

1. pH or H^+ nmol/L, i.e. a measure of the acidity or alkalinity,
2. $PaCO_2$ (mmHg or kPa), i.e. a measure of the respiratory component, and
3. HCO_3^- (mmol/L), i.e. a measure of the metabolic component.

Although pH and $PaCO_2$ may be measured directly, there is no direct method to measure the plasma HCO_3^- concentration. Also HCO_3^- concentrations may vary with changes in $PaCO_2$.

To separate the respiratory from the non-respiratory HCO_3^- components, derived indices of standard bicarbonate (i.e. the plasma bicarbonate concentration in fully oxygenated blood which has been equilibrated to a PCO_2 of 40 mmHg at 37°C), buffer base (i.e. the sum of the concentrations of all the buffer anions in the blood, which includes haemoglobin, bicarbonate, protein, and phosphate), "strong ion difference" (similar to plasma buffer base which is the sum of the concentrations of all the buffer anions in the blood, excluding haemoglobin), base excess or deficit (i.e. the titratable base or acid, in mmol/L, needed to titrate blood *in vitro* to a pH of 7.4, at a PCO_2 of 40 mmHg and temperature of 37°C),[2] and standard base excess (or *in vivo* base excess where correction factors, e.g. 0.3 x the Hb value, are used to approximate the buffering effect of the extracellular fluid),[3] have been proposed.

Although many believe that from all of the above derived indices, standard base excess reflects the metabolic component of an acid-base disorder most accurately, the correction does not differentiate a metabolic alkalosis or acidosis from a compensatory renal response.[3]

For clinical purposes, in addition to the history and physical examination, the HCO_3^- concentration calculated from the Henderson equation (i.e. the 'actual' or 'calculated' bicarbonate), with the $PaCO_2$ and pH, are all that are required to interpret the acid-base disorder.[2,4]

Diagnosis of an acid-base defect

Here one seeks to define the primary attack upon H^+ homeostasis, the duration and severity of the pH defect and assess the body's compensatory response. Clinical features (e.g. Kussmaul breathing, tachypnoea, cyanosis, tracheal 'tug', hypotension, shock, ketotic breath) and biochemical data (e.g. arterial blood gas analysis, anion gap, renal and hepatic plasma 'profiles' and urinary electrolytes) should all be taken into account. The acid-base defects, however, are usually identified from:

1. *The arterial blood pH, pCO_2 and HCO_3^-*. These values are used to detect the major acid-base defect, the likely compensatory response and the presence of a mixed disorder.
2. *The anion gap.* This is used to detect a high anion gap metabolic acidosis (e.g. keto-acidosis or lactic acidosis) and a mixed metabolic acidosis. For example, if the decrease in HCO_3^- is greater than the increase in anion gap, then both a high anion and normal anion gap (i.e. HCO_3^- losing) metabolic acidosis may coexist, whereas if the decrease in HCO_3^- is less than the increase in the anion gap, the patient may have both a high anion gap metabolic acidosis and a metabolic alkalosis.
3. *An acid base diagram.* This may be used as an aid to the diagnostic process.[5] However, diagrams are not mandatory, as various 'rules of thumb' are easily used at the bedside to facilitate the diagnosis.[6] For example:
   a. A primary metabolic acidosis is associated with a compensatory decrease in $PaCO_2$, the numerical value of which (in mmHg) is usually within $\pm$ 5 mmHg of the number denoted by the two digits after the decimal point of the pH value, down to a pH of 7.15 - 7.10 (i.e. the $PaCO_2$ usually goes no lower than 10 mmHg, even with a profound metabolic acidosis).[7]

      Also in a primary metabolic acidosis as the calculated HCO_3^- halves, the pH decreases by approximately 0.1.
   b. A primary metabolic alkalosis may be associated with a compensatory increase in $PaCO_2$, the numerical value of which (in mmHg) is usually up to the number denoted by the two digits after the decimal point of the pH value, until the pH value reaches 7.55 - 7.60 (i.e. the $PaCO_2$ usually goes no higher than 60 mmHg, even with a profound metabolic alkalosis). However, compensatory changes in $PaCO_2$ are not immediate (c.f. metabolic acidosis) and usually do not occur in the presence of hypoxia.
   c. In a primary acute respiratory acidosis the calculated HCO_3^- value rises 1 mmol/L for each 10 mmHg (1.3 kPa) rise in $PaCO_2$, up to a HCO_3^- value of 30 mmol/L.

      Also in a primary respiratory acidosis the pH decreases by approximately 0.1 for each 20 mmHg increase in the $PaCO_2$.
   d. In a primary respiratory alkalosis (both acute and chronic) the calculated HCO_3^- decreases 2.5 mmol/L for each 10 mmHg (1.3 kPa) reduction in $PaCO_2$, down to a HCO_3^- value of 18 mmol/L.

Also, in a primary respiratory alkalosis the pH increases by approximately 0.1 for each 10 mmHg decrease in $PaCO_2$.

e. In chronic respiratory acidosis (due to renal compensation) the calculated HCO_3^- increases by 4 mmol/L for each 10 mmHg (1.3 kPa) rise in $PaCO_2$, up to a HCO_3^- value of 36 mmol/L.

Also in chronic respiratory acidosis the pH decreases by approximately 0.05 for each 20 mmHg increase in $PaCO_2$.

CLINICAL ACID-BASE DISORDERS

Metabolic (nonrespiratory) acidosis

This arises from an abnormal process generating excess non-carbonic acid or an abnormal loss of HCO_3^-, which may be identified by an increased anion gap (the anion in question approximating the 'gap' increase[8]) or normal anion gap, respectively (Table 1). Characteristically, the arterial blood gas analysis reveals a pH < 7.36 (H^+ > 44 nmol/L), PCO_2 < 35 mmHg (4.7 kPa), and calculated HCO_3^- < 18 mmol/L.

Although an arterial pH of less than 6.8 is often associated with death, pH values of 6.78, 6.57, 6.49 and 6.46 have been reported in patients who have survived poisoning with ammonium chloride, strychnine, isoniazid and ethylene glycol, respectively,[9] and a pH of 6.33 (due largely to a lactic acidosis) has been reported in a patient who survived near drowning.[10]

High anion gap metabolic acidosis (HAGMA)

Ketoacidosis

This may be found in starvation, insulin-dependent diabetes and alcoholism. The elevated plasma levels of acetoacetate and β-hydroxybutyrate are due to:[11]

a. an increased hepatic synthesis of the ketoacids (i.e. acetoacetate and β-hydroxybutyrate) caused by an increase in free fatty acid (FFA) liberation from adipose tissue (due to reduced insulin and increased catecholamine levels),
b. an altered hepatic metabolism (i.e. a reduction in insulin and increased glucagon levels, promoting ketogenesis rather than triglyceride synthesis), and
c. the finite capacity of peripheral tissues to metabolise ketones.

Acetoacetate, β-hydroxybutyrate and acetone are collectively known as ketone bodies. Acetoacetate undergoes spontaneous decarboxylation to yield carbon dioxide and acetone (which is not an acid) which are both excreted largely by the lungs.

Table 1. Aetiology of metabolic acidosis

Accumulation of acid (anion gap > 16 mEq/L)	
Disorder	Acid
Ketoacidosis	β-hydroxybutyrate, acetoacetate
Lactic acidosis	D or L-lactate
Methanol	Formate, lactate
Renal failure	Sulphate, phosphate
Salicylic acid	Salicylate, lactate, keto-acids
Paraldehyde	Lactate, acetate
Formaldehyde	Formate
Ethylene glycol	Glycolate, oxalate, lactate
Toluene	Hippuric acid
Paracetamol	Lactate, pyroglutamate
Intravenous	
Fructose	Lactate
Sorbitol	Lactate
Ethanol	Lactate
Xylitol	Lactate
Accumulation of HCl (anion gap < 16 mEq/L)	
Releasing HCl with metabolism	
Arginine hydrochloride, lysine hydrochloride	
NH_4Cl	
Direct administration of HCl	
Intravenous HCl	
Loss of HCO_3^- (anion gap < 16 mEq/L)	
Hypokalaemic variants	
Gastrointestinal loss	
Small bowel, biliary or pancreatic fistula	
Diarrhoea, ureteroenterostomy	
Renal loss	
Type I RTA	
Type II RTA	
Hyperkalaemic variants (Type IV RTA)	
Decreased mineralocorticoid secretion	
Addison's disease	
Hyporeninaemic hypoaldosteronism	
Decreased mineralocorticoid action	
Spironolactone, amiloride	
Interstitial nephritis, hydronephrosis	
Acute and chronic renal failure	

RTA = renal tubular acidosis

Acetoacetate and β-hydroxybutyrate are in equilibrium with each other which is controlled by the mitochondrial ratio of $NADH:NAD^+$ (i.e. the redox state). The β-hydroxybutyrate:acetoacetate ratio is normally 3:1, although it may vary from 1:1 to 10:1. The ratio increases when the hepatic mitochondrial redox state decreases (e.g. hypoxia), which is usually associated with a reduced cytosolic redox state (causing

an increase in lactate production). The fasting level of β-hydroxybutyrate is normally < 1.2 mmol/L, although with prolonged fasting, the levels may rise to 2 - 5 mmol/L. The FFA concentration in plasma normally ranges from 0.4 to 0.8 mmol/L (most of which is bound to albumin) and seldom rises to more than 1 mmol/L. In diabetic ketoacidosis, the FFA levels may increase to 2 - 4 mmol/L[11] and the keto-acid levels may increase up to 10 - 15 mmol/L. As the nitroprusside reaction of 'Ketostix' only reacts with acetoacetate, if a patient has both keto- and lactic acidosis (e.g. alcoholic ketoacidosis) the ketoacidosis may be concealed, because the majority of the keto-acid will be β-hydroxybutyrate.[11]

If diabetic ketoacidosis has been prolonged, then the continued renal loss of keto-acids produces an effective loss of HCO_3^-. Therefore, while insulin will inhibit ketone production and allow the ketones already present to be metabolised, when the ketoacidosis is finally corrected, a normal anion gap metabolic acidosis may remain.[12,13]

Lactic acidosis

This is defined as a metabolic acidosis associated with a high plasma concentration of lactate (> 5.0 mmol/L). Plasma lactate is measured in a heparinised arterial blood sample stored on ice and assayed within 1 hour,[14] or measured on blood collected in a fluoride oxalate tube normally used for glucose assay (oxalate inhibits the glycolytic enzyme enolase).

Lactic acidosis may be caused by an increased lactate production (due to hypoxia or inhibition of tissue oxidative metabolism), or a decrease in rate of lactate utilisation by liver and kidney. Normal arterial blood lactate levels are usually less than 2 mmol/L and levels between 2 - 4 mmol/L are abnormal but of uncertain clinical significance.[11] Although plasma lactate levels greater than 5 mmol/L are used to diagnose lactic acidosis, in most cases of lactic acidosis the levels are between 10 - 30 mmol/L.

The assessment of the cellular redox state by measuring blood lactate, is of limited value because the plasma lactate may also increase when there is an increase in the rate of glycolysis (e.g. respiratory alkalosis). Measurement of the lactate:pyruvate (L:P or $NADH/NAD^+$ ratio) ratio has been used to distinguish an increase in glycolysis (where the L:P ratio is normal, i.e. 10:1), from hypoxia (where the L:P ratio is increased, i.e. greater than 10:1). However, this assumes that the cytoplasmic redox potential (measured by the L:P ratio) reflects the mitochondrial redox potential, which may not be so.[15] The cytosolic and mitochondrial redox states may even be reversed.[16] Moreover, while a normal β-hydroxybutyrate:acetoacetate ratio may indicate a normal hepatic mitochondrial redox state and this may exist with an abnormal lactate:pyruvate ratio (to indicate abnormal redox state of organs other than the liver[17]), in the critically ill patient these metabolites are often not in equilibrium.[18]

Non-arterial specimens, specimens not transported 'on-ice' or a delay in measurement may also falsely elevate the L:P ratio.[19]

Lactic acidosis is often classified as either type A, in which an inadequate delivery of oxygen, for tissue requirements generates lactate faster than it can be removed, or type B, where overt tissue hypoxia does not appear to play a major role (Table 2). However, some believe that there is little utility in this division as both types often share mechanisms of over-production and underutilisation.

Table 2. Classification of lactic acidosis

Type A
Severe exercise
Seizures
Cardiac arrest
Shock
Severe Hypoxia < 35 mmHg (4.7 kPa)
Anaemia < 30 g/L
Type B
Thiamine deficiency
Diabetes
Hepatic failure
Renal failure
Infection
Leukaemia, lymphoma
Pancreatitis
Short bowel syndrome (D-lactate)
Phaeochromocytoma
Drug or toxin induced
Phenformin, metformin
Ethanol, methanol, ethylene glycol, toluene
Salicylates, paracetamol
Intravenous, fructose, xylitol or sorbitol
Nucleoside-analogue reverse-transcriptase inhibitors
Nitroprusside, cyanide
Nalidixic acid
Isoniazid
β_2-adrenergic agonists (adrenaline, isoprenaline, salbutamol)
Hereditary
Glucose 6-phosphatase deficiency
Fructose 1,6-diphosphatase deficiency
Mitochondrial myopathy

The lactic acidosis associated with an excessive β_2 adrenergic effect (e.g. salbutamol, adrenaline, isoproterenol, or the adrenaline 'surge' during injury and sepsis[20]) is caused by an increase in glycogenolysis (by activating muscle and hepatic glycogen phosphorylase) which increases both pyruvate and lactate production. However, a β_3-adrenergic effect may also be present, increasing lipolysis (by activating hormone-sensitive lipoprotein lipase) and acetylCoA and NADH production, which in turn inhibit pyruvate oxidation and cause an increase in the lactate pyruvate ratio in the absence of tissue hypoxia.[21]

An acute fulminating form of beri-beri (i.e. thiamine deficiency) which is typically seen in the alcoholic patient (known as acute pernicious beri-beri, or, to the Japanese, shoshin beri-beri; sho = acute damage and shin = heart[22]) presents clinically with shock (absent arm pulses but moderately strong femoral pulses[23]), cyanosis, dyspnoea, lactic acidosis, high cardiac output, depressed left ventricular function, high right and left atrial pressures, low systemic vascular resistance, high circulating catecholamine levels (increasing lactate production) and high mixed venous oxygen saturation.[24-27] Thiamine deficiency may be diagnosed by detecting a low erythrocyte transketolase activity which is activated, in vitro, by thiamine pyrophosphate (although the latter effect is an insensitive test as it may not occur in patients with gross thiamine deficiency[28]).

The plasma lactate measured in clinical practice is L-lactate. In patients with a blind-loop or short bowel syndrome, D-lactic acid may be produced by gastrointestinal tract microorganisms, causing a D-lactic acidosis,[29] which usually presents as a high anion gap metabolic acidosis without a measurable increase in plasma L-lactate. A chronic D-lactic acidosis may also present with a normal anion gap metabolic acidosis, as the H^+ ion is absorbed and buffered, and the acid anion is lost via the gastrointestinal tract (i.e. diarrhoea) or excreted in the urine (as D-lactate is poorly absorbed by the nephron) with the cations of potassium or sodium.[30]

Clinical features of D-lactic acidosis are largely encephalopathic (e.g. ataxia, dysarthria, confusion, memory loss, fatigue, weakness, behavioral changes, headache, visual changes, nystagmus) and occur when D-lactate levels are greater than 3 mmol/L.[31]

Renal failure

Uraemic acidosis usually occurs when the glomerular filtration rate is less than 20 mL/min. The continuous daily positive H^+ balance is then buffered by bone.[11] The increase in the anion gap is often mild (e.g. 3 - 5 mEq/L) as the plasma sulphate and phosphate which can increase up to 2 - 4 mEq/L and 3 - 6 mEq/L, respectively (increasing the anion gap by up to 8 mEq/L), is often offset by an accompanying hypoalbuminaemia which reduces the anion gap by 3 - 5 mEq/L.

Poisoning

Salicylate toxicity. Therapeutic plasma levels of salicylate can often increase up to 30 mg/100 mL (2.2 mmol/L). Toxicity usually occurs at plasma levels of 50 - 75 mg/100 mL (3.6 - 5.5 mmol/L), and levels greater than 75 mg/100 mL (5.5 mmol/L) may require haemodialysis. Even with severe toxicity the anion gap due to the salicylate anion will be no greater than 5 - 6 mmol/L; the remainder of the gap is due to other organic acid anions.

Paracetamol. Paracetamol toxicity may cause a high anion gap metabolic acidosis due to a lactic[32] or pyroglutamic acidosis.[33,34] The diagnosis of paracetamol induced pyroglutamic acidosis is made by detecting a high anion gap metabolic acidosis, not explained by L-lactate, and detecting pyroglutamate (5-oxoproline) acidaemia or aciduria. Pyroglulamate aciduria has also been described in children taking vigabatrin,[35] and in an adult patient with staphylococcal pneumonia taking flucloxacillin and netilmicin.[36]

Methanol. Methanol is metabolised by alcohol dehydrogenase to formaldehyde and formic acid. The anion gap is due largely to formate, although lactate and ketones, as well as other unmeasured acid anions, contribute.

Ethylene glycol. The acidosis accompanying ethylene glycol toxicity is due to glycolic, oxalic and lactic acids.

Toluene. Exposure to toluene (e.g. glue sniffing) may cause an acidosis due to the metabolism of toluene to benzoic acid which in turn is metabolised to hippuric acid. If renal function is preserved, the excretion of the hippurate ion with sodium and potassium may convert the high anion gap metabolic acidosis to a low anion gap metabolic acidosis (i.e. hyperchloraemic acidosis).[37]

Paraldehyde. Paraldehyde causes an acidosis by being metabolised to acetaldehyde and then to acetic acid.

Formaldehyde. Formaldehyde toxicity causes an acidosis due to an accumulation of formic acid.[38]

Normal anion gap metabolic acidosis (i.e. hyperchloraemic acidosis)

Hyperchloraemic acidosis is characterised by a low plasma bicarbonate level, a commensurate increase in the plasma chloride level and a normal anion gap. These acidoses may be conveniently divided into those

associated with hypokalaemia and those associated with hyperkalaemia (Table 1).

Hypokalaemic variants

Gastrointestinal losses. Pancreatic, small bowel or biliary fistulae and diarrhoea cause hyperchloraemic acidosis due to the gastrointestinal loss of potassium and sodium bicarbonate. These disorders may be distinguished from patients with distal renal tubular acidosis by measuring the urinary anion gap (i.e. $Na^+ + K^+ - Cl^-$). A negative urinary anion gap [i.e. $Cl^- > (Na^+ + K^+)$] suggests a large unmeasured cation (due to NH_4^+) and therefore normal distal tubule acidification mechanisms.[39] A positive urinary anion gap [i.e. $Cl^- < (Na^+ + K^+)$] suggests a low level of unmeasured cation (i.e. NH_4^+), indicating a distal RTA.[39] Ureterosigmoidostomy causes the urine chloride to be absorbed in exchange for HCO_3^-. There is also colonic reabsorption of NH_4^+ derived from urine and colonic urea-splitting bacteria.

Renal losses or renal tubular acidosis (RTA). The renal tubular acidoses consists of a group of disorders characterised by excess urinary loss of HCO_3^-, normal anion gap and an elevated plasma level of Cl^-, and, depending on the renal tubular site of the defect, is classified as proximal or distal.[40]

a. *Distal RTA (Classic RTA or type I RTA).* This arises from an inability of the distal nephron to generate (secrete) or to maintain a steep lumen to peritubular H^+ gradient, reducing the net rate of H^+ secretion and causing a renal acidification defect. With the standard acid load test (which is only needed if the plasma HCO_3^- is greater than 20 mmol/L) of 0.1 g NH_4Cl/kg body weight, the urine pH does not fall below 5.4. Nephrocalcinosis occurs in 60% of patients with distal RTA, distinguishing this from other forms of RTA.[41] Nephrolithiasis (usually calcium phosphate calculi), hypokalaemia and osteomalacia are other features of type I RTA. In adults, the disorder is usually seen as an acid excretion defect, whereas in children type I RTA (which used to be called a mixed proximal and distal RTA or RTA type III), renal bicarbonate wasting is a more important cause of acidosis than is the reduction in acid secretion itself.[42] Causes of Type I RTA are listed in Table 3.

   Glue sniffing may generate hippuric acid, although a distal RTA picture may be found due to the high fractional excretion of the hippurate anion.[43]

b. *Proximal RTA (type II RTA).* This arises from a reduced proximal tubular capacity to secrete H^+ (required to reclaim filtered HCO_3^-), causing a renal bicarbonate wasting defect. A reduced level of plasma HCO_3^- is reached at which normal urinary acidification occurs (i.e. urine pH < 5.5), reflecting normal distal acidification mechanisms. Usually, other proximal tubular defects also exist (e.g. amino aciduria, glycosuria, and phosphaturia). Osteomalacia (vitamin D resistant rickets) and hypokalaemia also exist. The hypokalaemia is caused by an increased distal delivery of sodium, promoting distal Na^+/K^+ exchange. Causes of type II RTA are listed in Table 4. Therapy with alkaline solutions is often not undertaken unless the acidosis is severe (i.e. HCO_3^- < 16 mmol/L). While carbonic anhydrase may cause hyperchloraemic acidosis, it is unusual for acetazolamide to cause the plasma bicarbonate to fall below 18 mmol/L.[11]

Table 3. Causes of type I renal tubular acidosis

Idiopathic
Immunological
Sjögren's syndrome
Systemic lupus erythematosus
Chronic active hepatitis
Hypergammaglobulinaemia
Diseases associated with nephrocalcinosis
Medullary sponge kidney
Idiopathic hypercalciuria
Primary hyperparathyroidism
Hyperthyroidism
Vitamin D intoxication
Tubulointerstitial disease
Acute renal failure (transient)
Obstructive uropathy (transient)
Renal transplantation
Chronic hydronephrosis
Drugs and toxins
Amphotericin B
Lithium
Toluene
Cyclamate
Analgesic nephropathy
Other
Hypomagnesaemia

Hyperkalaemic variants (type IV RTA)

Failure of the kidney to liberate renin, failure of the adrenal to synthesise or excrete aldosterone, or failure of the distal nephron to respond to aldosterone can cause hyperkalaemic hyperchloraemic metabolic acido-sis, due to failure of the distal Na^+/H^+ or K^+ exchange mechanism. Causes of type VI RTA are listed in Table 5. If there is a reduced distal delivery of sodium, distal

H^+ excretion is likewise reduced. Therefore, to diagnose a distal Na^+/K^+ or H^+ exchange defect, urinary sodium should be greater than 40 mmol/L.[44]

Table 4. Causes of type II renal tubular acidosis

Idiopathic
Inherited systemic disease
Fanconi-like syndromes
Disorders associated with hyperparathyroidism
Primary hyperparathyroidism
Vitamin D deficiency
Vitamin D resistance
Drugs or toxins
Cadmium, mercury, copper or lead poisoning
Acetazolamide
Streptozotocin
Miscellaneous renal diseases
Multiple myeloma, nephrotic syndrome

Table 5. Causes of type IV renal tubular acidosis

Hypoaldosteronism
Primary
Addison's disease, adrenalectomy
Hyporeninaemic
Diabetes
Interstitial nephritis
Renal tubular dysfunction
Urinary tract obstruction
SLE, medullary cystic disease, analgesic nephropathy
Drugs
Spironolactone, triamterene, amiloride
Trimethoprim, pentamidine, NSAIDs, cyclosporine

Dilution acidosis and contraction alkalosis

The addition or removal of normal saline causing dilution acidosis (by reducing plasma HCO_3^-) and contraction alkalosis (by increasing plasma HCO_3^-) respectively, are mentioned so that the pathophysiology of the resultant acidosis or alkalosis may be carefully reviewed.

In a closed system, the addition (or subtraction) of any solution containing neither acid nor alkali (e.g. saline, 5% dextrose) would dilute (or concentrate) both components of the buffer pair and thus will not alter the pH.[45] However, in man the bicarbonate buffer pair operates as an open system and any change in carbon dioxide tension caused by an increase (or decrease) in the extracellular fluid (ECF) volume, is quickly returned to normal (as there is no reduction or increase in the intracellular pH to alter respiration via chemoreceptors[46]), leaving the remaining change in HCO_3^- (due to its dilution or concentration) to provide an 'acidaemia' (or alkalaemia) before renal correction of the reduced (or excess) ECF HCO_3^- concentration occurs.

However, the *in vivo* effect of changing the ECF HCO_3^- concentration is reduced with cellular buffers providing or taking up extracellular sodium bicarbonate, yielding only a limited alteration in the ECF bicarbonate level.[45] Any change in ECF bicarbonate due to an ECF volume change is also influenced by any associated change in tonicity. For example, infusing hypotonic solutions is accompanied by enhanced ECF bicarbonate generation,[47] whereas infusing hypertonic solutions is associated with a reduction in ECF bicarbonate generation, due to an alteration of cellular membrane H^+ ion permeability,[48] or change in intracellular H^+ metabolism.[49]

In the case of isotonic change in ECF volume, if the *in vivo* experimental data are applicable to man then there would need to be the addition or removal of 6 litres of normal saline to provide a $\pm$ 10% change in bicarbonate concentration (i.e. 24 $\pm$ 2.4 mmol/L), which would lead to marked cardiovascular effects before a clinical acid base defect had occurred.[45] However, clinical cases of a reduced extracellular pH have been reported with administration of less than 6 L of 0.9% saline, indicating a lower intracellular buffer capacity in man compared with the experimental animal.[50] In one study of women undergoing a gynaecological procedure and receiving approximately 5 litres of 0.9% saline in a 2 hr period, the HCO_3^- concentration was lowered by an average of 5 mmol/L.[51] Nevertheless, this condition should be called 'dilution acidaemia' rather than 'dilutional acidosis'.[52]

In the presence of intravascular volume depletion (i.e. bicarbonate depletion), a high chloride (and low nonreabsorbable anion) intake may impair renal bicarbonate generation and increase chloride reabsorption, to produce a hyperchloraemic normal anion gap metabolic acidosis,[53] just as an increased intake of a sodium salt of a nonreabsorbable anion and a low chloride intake, may increase renal H^+ loss and renal bicarbonate generation, to produce a metabolic alkalosis.[54]

Treatment of metabolic acidosis

Acid production or bicarbonate loss is often an epiphenomenon of disease so, in acid-base disorders, treatment should always focus upon the management of the underlying disorder. For example, in an anion gap acidosis, insulin for diabetic ketoacidosis, or measures

to improve the cellular redox state in lactic acidosis, will terminate the production of H^+ and allow metabol-ism of the organic acid to return the pH towards normal. With a toxin-induced metabolic acidosis (e.g. methanol, ethylene glycol, toluene) dialysis may be required to remove the toxin rapidly and replace the acid anion with bicarbonate. A non anion gap acidosis usually requires bicarbonate replacement with sodium or potassium salts.

To maintain the intracellular pH homeostasis, while the treatment of the underlying disorder takes effect, the compensatory PCO_2 for the metabolic acidosis is often maintained.

Acid-base defects associated with cardiac arrest

Cardiac arrest produces a mixed respiratory and metabolic acid-base disorder, consisting of a respiratory acidosis (which is associated with a mixed venous hypercapnia and a low or high $PaCO_2$, depending on the patient's ventilation[55]) and lactic acidosis.[56-58] In patients with hypotension, shock or cardiac arrest, the ability of the cardiopulmonary system to excrete carbon dioxide is reduced. This is reflected by a decrease in the end-expired carbon dioxide, an increase in the mixed venous PCO_2 and (in patients who are ventilated) a widening of the arteriovenous PCO_2 and pH gradient.[59-61]

Although $NaHCO_3$ can buffer H^+, it generates carbon dioxide in the process. As 1 mol of carbon dioxide occupies 22.2 L at 0°C, then at 37°C 100 mmol of $NaHCO_3$ will produce 2.53 L of carbon dioxide when it buffers 100 mmol of H^+. In the presence of a reduced capacity to excrete carbon dioxide, $NaHCO_3$ increases the mixed venous PCO_2 causing an intracellular acidosis. Respiratory acidosis has a greater negative inotropic effect on myocardial contractility than metabolic acidosis[62,63] and severe elevation in PCO_2 may even cause pulseless electrical activity.[64]

Administration of $NaHCO_3$ does not improve the ability to defibrillate, improve left ventricular contract-ility,[65] increase the cardiovascular response to circulat-ing catecholamines,[66] or improve survival rates in cardiac arrest,[62,67-69] and is now no longer recommended. Instead, therapy is aimed at rapidly returning the patient to sinus rhythm, improving cardiac output, pulmonary blood flow and ventilation, to enhance carbon dioxide removal and correct the lactic acidosis.

Lactic acidosis

Many agents have been used to treat lactic acidosis, indicating a general dissatisfaction with any one form of treatment. For example, $NaHCO_3$,[70] sodium acetate,[71] tris-(hydroxymethyl)-aminomethane (THAM),[70] THAM with acetate,[72] THAM with acetate, bicarbonate and phosphate (i.e. Tribonat®),[73] insulin and glucose,[74] dichloroacetate,[75] haemo and peritoneal dialysis,[76] methylene blue,[77] thiamine, pantothenic acid, biotin,[6] and nitroprusside,[78] have all been tried.

Although bicarbonate therapy is often used in lactic acidosis, it is no longer recommended, as there is no evidence that it reduces mortality.[62,66,67,79-81] Further-more, it may cause hyperosmolality,[82] intracranial haemorrhage,[83] a reduction in cardiac output,[84] prolong-ed coma,[85,86] a left-shift in the oxygen dissociation curve,[87] an increase in lactate production (i.e. worsening of the acidosis),[88] peripheral vasodilation with reduction in coronary perfusion pressure,[89] hypocalcaemia and rebound alkalosis, indicating that it is not without hazard.[62,81,90] Other agents such as THAM (a carbonic acid buffer which has little practical application in the management of respiratory acidosis, as its action is usually offset by a reduction in ventilation)[91] or carbicarb (an equimolar mixture of Na_2CO_3 and $NaHCO_3$ that during buffering generates two-thirds of the amount of carbon dioxide in comparison to $NaHCO_3$) have not been shown to improve mortality when administered to patients with metabolic acido-sis,[91-93] and so cannot be recommended.

The only indications for bicarbonate therapy are normal anion gap metabolic acidosis (i.e. $NaHCO_3$ loss acidosis), tricyclic antidepressant poisoning (to increase the tricyclic protein binding and reduce the amount of circulating free drug) and to facilitate the ICF shift of K^+ during the treatment of hyperkalaemia.

Although continuous venovenous haemodiafiltrat-ion (CVVHDF) using bicarbonate buffered dialysate has been used successfully in patients with lactic acidosis,[94,95] there have been no prospective randomised clinical studies showing a reduction in mortality associated with this treatment. In one study, lactate clearance using bicarbonate buffered CVVHDF was negligible (e.g. < 3%).[96] This may mean that if the plasma lactate levels fall during CVVHDF the patient is probably improving rather than lactate is being cleared by dialysis.[97]

In all disorders in which lactic acidosis is present, cardiac dysfunction and poor peripheral perfusion are the fundamental problems. Thus, treatment should be aimed at optimising oxygen delivery, not only to reduce lactate production but to improve lactate metabolism as well.[6] If vasoactive agents are required then non-β_2 adrenergic agonists (e.g noradrenaline) or digoxin may be of greater benefit rather than adrenaline, as adrenaline may increase lactate production.

With acute pernicious (or sho-shin) beri-beri the patient usually responds rapidly to intravenous thiamine 500mg intravenously followed by 100 mg 8-hourly (up to 1000 mg i.v. 12-hourly[98]) for 24 hr, thereafter 100 mg daily for 14 days.[99] Magnesium deficiency in patients with beri-beri should also be corrected as it can lead to a

refractory response to thiamine.[100,101] While the systemic vascular resistance returns towards normal within 30 - 90 minutes of thiamine administration and clinical symptoms usually resolve after 24 hours, a normal haemodynamic status may not return until 1 - 2 weeks of treatment,[26] and digoxin may also be required.[99] Deficiencies of pantothenic acid, biotin or coenzyme Q_{10} should also be corrected, as they are important cofactors for lactate metabolism. Recently, riboflavin (50 mg daily) has been reported to reverse the lactic acidosis associated with nucleoside reverse-transcriptase inhibitors used to treat HIV-1 infected patients.[102]

Patients who have D-lactate acidosis may require fluid resuscitation if excessive diarrhoea has occurred (with added sodium bicarbonate if there is a normal anion gap metabolic acidosis), oral antibiotics (e.g. ciprofloxacin, gentamicin, metronidazole), carbohydrate restriction and yoghurt (e.g. *Lactobacillus* GG species which produces L-lactate. *Lactobacillus delbrueckii* is contraindicated as it produces D-lactate only[103]), surgical removal of infarcted gut or correction of the gastrointestinal bypass.

Diabetic ketoacidosis

Insulin, correction of fluid deficits, potassium and phosphate replacement are the principles of management for the diabetic ketoacidotic patient. As sodium bicarbonate therapy increases the production of keto-acids[88] and does not alter mortality, it is no longer recommended.[104]

Alcoholic ketoacidosis

Intravenous glucose (to inhibit ketogenesis), correction of extracellular volume loss and electrolyte abnormalities (e.g. hypophosphataemia, hypokalaemia, hypomagnesaemia, hyponatraemia) and thiamine (to facilitate lactate metabolism) are usually all that are required.[105] Insulin is only rarely required (i.e. when plasma glucose levels are 20 mmol/L or greater)[106] and sodium bicarbonate solutions should be avoided.[107]

Poisoning

In general, in severe poisoning, particularly when renal failure occurs, haemodialysis (or CVVHDF) may be required to remove the toxin (e.g. salicylate, methanol) and to replace the acid anion (e.g. formate, salicylate, pyroglutamate, hippurate) with bicarbonate to return the ECF buffer to normal. N-acetylcystine is used in paracetamol toxicity (particularly in the presence of sepsis and glutathione depletion) to reduce the formation of pyroglutamate.[108] 4-methyl-pyrazole is also used to inhibit alcohol dehydrogenase in methanol and ethylene glycol poisoning to reduce the formation of formate and glycolate, glyoxylate and oxalate, respectively.[109]

Renal failure

Dialysis will replace the acid anion (e.g. sulphate, phosphate) with bicarbonate and return the ECF buffer to normal.

Normal anion gap metabolic acidosis

Normal anion gap metabolic acidoses are caused by renal tubular acidosis or gastrointestinal bicarbonate loss. As hyperchloraemic acidosis induces renal vaso-constriction,[110] causing a reduction in glomerular filtration rate,[111] bicarbonate therapy is usually administered if the plasma bicarbonate level is 18 mmol/L or less. Intravenous sodium bicarbonate or potassium acetate (depending on the need for the associated cation of potassium or sodium) may be administered at 1 - 3 mmol/kg/day. If long term therapy is required to correct the loss of bicarbonate, sodium and potassium citrate are administered rather than bicarbonate compounds, as the latter may form excessive gastrointestinal gas, due to carbon dioxide production. Citrate therapy (usually as potassium citrate 60 - 90 mmol/day) as well as 2 - 3 litres of oral fluid daily are important in patients who have RTA type I with nephrolithiasis, as hypocitraturia and dehydration promote renal calculi formation.[112]

Metabolic (nonrespiratory) alkalosis

This condition arises from an abnormal process generating excess HCO_3^-, or an abnormal loss of non-carbonic acid. Characteristically, arterial blood gas measurements reveal a pH > 7.44 (H^+ < 36 nmol/L), PCO_2 > 45 mmHg (6.0 kPa), and HCO_3^- > 32 mmol/L.

Normally, the kidney has a large capacity to excrete HCO_3^-, therefore once metabolic alkalosis is generated, maintenance of this state requires an abnormal retention of HCO_3^- (Table 6).

Renal generation of excess bicarbonate requires persistent mineralocorticoid excess, a distal delivery of sodium and a potassium deficiency.[113]

The process of generating a metabolic alkalosis can be terminated if therapy is directed at the underlying disease. However, correction of the pH defect only occurs with renal excretion of the excess HCO_3^-, which often requires therapy to be directed at the abnormal renal HCO_3^- retention mechanisms. Renal maintenance of the metabolic alkalosis is usually caused by a proximal or a distal nephron mechanism.[113]

Proximal mechanism. In the proximal tubule there is an obligatory uptake of Na^+ controlled by the ECF volume. Normally, some of the Na^+ uptake occurs with H^+ secretion. With diminished ECF volume this Na^+/H^+ exchange mechanism is exaggerated, and if a metabolic alkalosis exists, it will be maintained.[113] Reversal of the pH defect, even in the presence of mild hypokalaemia, can be achieved with saline infusions,[114] but not with

Na^+ solutions of a non-reabsorbable anion.[54] Correction of the alkalosis can also occur with the administration of saline-free albumin solutions,[115] suggesting that nephron recognition of a diminished ECF volume is the major determinant in the maintenance of the alkalosis, and not just a chloride deficiency.[6] Nevertheless, while correction of a metabolic alkalosis may be achieved without the use of saline or potassium chloride solutions, it should not be interpreted as being desirable if saline or potassium chloride deficiencies exist. Moreover, correction of an existing hypokalaemia enhances the ability of saline solutions to correct metabolic alkalosis.[6]

Table 6. Causes of metabolic alkalosis

Generation
Loss of H^+
Renal
- ECF volume excess
  Conn's syndrome
  Renal artery stenosis
  Reninoma
  ACTH secreting tumours
  Cushing's syndrome
  Liddle's syndrome
  Drugs: corticosteroids, carbenoxolone, licorice
- ECF volume reduction
  Bartter's syndrome
  Gitelman's syndrome
  2° hyperaldosteronism with K^+ depletion and diuretics
  Post-hypercapnic alkalosis

Gastrointestinal
- Nasogastric suction, vomiting
- Villous adenoma
- Congenital alkalosis with diarrhoea

Gain of HCO_3^-
$NaHCO_3$
Metabolic conversion of citrate, acetate, lactate

Maintenance
Diminished functional extracellular fluid volume
Mineralocorticoid excess with K^+ depletion
Severe K^+ depletion (> 1000 mmol)
Renal failure

Distal mechanism. Under the influence of mineralocorticoids, distal Na^+ reabsorption promotes K^+ and H^+ excretion. In the presence of hypokalaemia, H^+ excretion is augmented. In primary hyperaldosteronism, mechanisms to generate and maintain the metabolic alkalosis exist, although to generate the alkalosis, hypokalaemia is also required.[116] In secondary hyperaldosteronism, the excess proximal Na^+ reabsorption reduces distal nephron flow, and therefore reduces K^+ and H^+ loss. Thus, while the metabolic alkalosis may be maintained, it is not generated unless there is concomitant use of diuretics, which increases the distal delivery of Na^+.

Clinical features

Severe metabolic alkalosis of greater than three days duration may cause somnolence, seizures, arrhythmias, sputum retention, prolonged weaning from a mechanical ventilator and hypoxia, which are largely caused by the alveolar hypoventilation associated with the respiratory compensation. In one study, mortality was correlated positively with the pH, reaching 48.5% when the pH reached 7.60; although, it was significantly greater in medical patients (36.6%) compared with surgical patients (12.4%), indicating that the underlying disorder may have also been important.[117]

Although an arterial pH greater than 7.8 is usually considered incompatible with life, a pH value of 7.95 has been reported in an acutely ill patient with pyloric stenosis who survived.[118]

Treatment

Treatment of metabolic alkalosis should be directed at correcting both proximal and distal mechanisms (Table 7).

Table 7. Treatment of metabolic alkalosis

Inhibition of renal mechanisms maintaining alkalosis
- Proximal mechanism
  Increase functional ECF
    Saline infusions
    Inotropic agents
  Carbonic anhydrase Inhibition
    Acetazolamide
- Distal mechanism
  KCl
  Aldosterone inhibition (e.g. spironolactone)
  Triamterene, amiloride

HCl or following metabolism to urea and HCl
Arginine or lysine hydrochloride, NH_4Cl
Intravenous HCl

In the presence of renal insufficiency, these manoeuvres may be insufficient, and treatment with NH_4Cl, arginine hydrochloride or lysine hydrochloride is sometimes recommended. However, in the presence of hepatic failure these agents cannot be metabolised to HCl and may produce hyperammonaemia. In such cases, administration of intravenous HCl (200 mmol in 1 litre of 5% dextrose) through a central venous line (one

report recommended a concentration of no greater than 100 mmol/L if it was to be given through a Swan-Ganz catheter[119]), at a maximum rate of 300 - 350 mmol/day, may be used.[120] Intravenous hydrochloric acid in patients with metabolic alkalosis will cause the hypoventilation to be corrected first, before the arterial pH changes occur.[120,121]

Respiratory acidosis

This arises from an acute or chronic excess of carbon dioxide, and depends on the rate of production as well as excretion of carbon dioxide. Therapy is often aimed at improving ventilation. In chronic respiratory acidosis there often coexists an iatrogenic metabolic alkalosis caused by concurrent corticosteroid or diuretic administration.

Respiratory alkalosis

This is caused by a reduction in carbon dioxide which often accompanies increased ventilation associated with hypoxia, hysteria, hepatic failure, shock or sepsis. If the process is chronic, there is some renal compensation with loss in HCO_3^-, which may result in a similar plasma electrolyte profile to RTA.[122,123] The increase in intracellular pH caused by the reduction in carbon dioxide stimulates phosphofructokinase which in turn increases glycolysis, lactate production and plasma lactate and pyruvate levels.[124] Therapy for respiratory alkalosis is directed at correcting the underlying abnormality causing the hyperventilation.

Received: 20 June 2001
Accepted: 24 August 2001

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