Metabolic alkalosis in the Intensive Care Unit

N Shah1, C Shaw1, LG Forni2

1 Department of Renal Medicine, Worthing Hospital, Worthing, West Sussex, United Kingdom
2 Department of Critical Care, Worthing Hospital and Brighton & Sussex Medical School, University of Sussex, Brighton, United Kingdom

Abstract. Metabolic alkalosis is a relatively common finding in the critically ill and has a varied aetiology. We outline the fundamental principles that govern both the generation and maintenance of a metabolic alkalosis. Causes are discussed with particular attention to those which predominate in the critically ill. Signs and symptoms of metabolic alkalosis are described together with both general and specific treatments for this relatively common disturbance in acid-base homeostasis.

Introduction
As an acid-base disturbance, metabolic alkalosis fails to attract the attention that its acidic counterpart receives but, despite this, it is still a relatively common metabolic derangement encountered in the critically ill [1,2]. Manifest as an alkalaemia with a pH>7.45 it can be defined simply as an acid-base disturbance initiated by a primary increase in plasma bicarbonate concentration ([HCO₃⁻]) either as a consequence of H⁺ losses or through an increase or retention in HCO₃⁻ [3,4]. Clinically, metabolic alkalosis is often induced through the loss of gastric secretions or secondary to diuretic therapy. In the intensive care unit the consequences of a metabolic alkalosis may be evident through a decrease in cardiac output, depression of central ventilation and its effects on the oxyhaemoglobin saturation curve. From a practical point of view, the presence of a metabolic alkalosis may cause disturbances in the balance of other important ions including worsening of hypokalaemia and hypophosphataemia and may also affect the ability to wean patients from mechanical ventilation [5-7]. Furthermore, the mortality associated with severe metabolic alkalosis is considerable with mortality rates of 45% being observed in patients with an arterial blood pH of 7.55 and rising to 80% when the pH was greater than 7.65 [8,9].

Pathophysiology
Metabolic alkalosis occurs through the development of an alkalaemia through an increase in the concentration of plasma bicarbonate together with a decrease in the overall bicarbonate excretion in order to sustain this metabolic abnormality. In order to understand both the genesis and maintenance of a metabolic alkalosis the fundamental principles involved are outlined in brief below.

i) The normal response
The normal renal response to a plasma bicarbonate over 24mmol/l is prompt and effective bicarbonate excretion in the urine. This ability of the kidney to rapidly excrete supranormal levels of bicarbonate contrasts to the response to a low plasma bicarbonate where almost all the filtered load is reabsorbed. A useful analogy is that of filling a bucket with water. No water is lost until the bucket is full, but after

that, all additional water is lost. This is sometimes referred to as the ‘waterfall effect’. Renal secretion of bicarbonate by the kidney is schematically outlined in Figure 1.

Development of a metabolic alkalosis in a non-ventilated individual results in a compensatory alveolar hypoventilation leading to a rise in the arterial carbon dioxide tension (PaCO₂) which attenuates any rise in pH. This compensatory response is rapid and arterial PaCO₂ increases by 0.5 to 0.7 mm Hg for every 1 mmol/l increase in plasma bicarbonate concentration. The expected PaCO₂ due to appropriate hypoventilation in a simple metabolic alkalosis can be estimated from the following formula:

Expected PaCO₂ = 0.7 [HCO₃⁻]⁻¹ + 20 mm Hg ±/+ 5 (i)

This response is somewhat variable in the clinical setting due to factors affecting minute ventilation such as pain, pulmonary congestion, hypoxaemia and in the intensive care unit, mechanical ventilation.
metabolic alkalosis. In turn, is accompanied by H+ ions. This results in enhanced excretion of H+ excess aldosterone which in turn stimulates reabsorption of sodium in the tubule when distal delivery of sodium increases in the presence of aldosterone. Furthermore, renal loss of H+ tubule is linked to Cl- charged sodium and potassium ions. Na+ and hydrogen ions (to buffer the generated bicarbonate ion) into the circulation. Reduced acid load into the gut thereby reduces pancreatic secretion of H+ into the circulation which results in no buffering of the HCO3- formed from HCl secretion and K+ exchange with CO2. The bicarbonate anion is then resorbed into the systemic circulation through Cl-/HCO3- exchangers in the luminal membrane principally combining with ammonia to form the ammonium ion.

ii) Development of alkalosis
The pathogenesis of metabolic alkalosis depends on the source of the excess alkali, which is the primary event responsible for generation of the hyperbicarbonataemia. This may result through several potential mechanisms including hydrogen ion losses, shift of hydrogen ions or volume depletion:

i) Gastrointestinal hydrogen ion loss
Excessive loss of gastric contents leads to a loss of hydrogen ions (H+) as well as potassium and chloride ions. This, together with volume losses, leads to the development of a hypochloraemic hyperbicarbonataemia metabolic alkalosis. The formation of gastric acid together with its effective ‘neutralization’ are shown in Figure 2 where it is seen that bicarbonate generated during the production of gastric acid returns to the circulation. Under normal conditions the excretion of acidic gastric contents into the duodenum stimulates pancreatic secretion of both bicarbonate ions into the gut (to neutralise the HCl) and hydrogen ions (to buffer the generated bicarbonate ion) into the circulation. It follows that excessive vomiting or gastrointestinal losses by other routes such as large nasogastric aspirates, reduces the acid load entering the gut. This, in turn, results in systemic accumulation of bicarbonate ion and hence a metabolic alkalosis.

ii) Renal hydrogen ion loss
Ionic equilibrium is maintained by the kidney through balance of the negatively charged bicarbonate and chloride ions with the positively charged sodium and potassium ions. Na+ reabsorption by the renal tubule is linked to Cl- reabsorption, H+ secretion and K+ exchange (Figures 1 and 3). Furthermore, renal loss of H+ occurs in the distal tubule when distal delivery of sodium increases in the presence of excess aldosterone which in turn stimulates reabsorption of sodium ions. This results in enhanced excretion of H+ and K+. A fall in the filtered chloride load leads to reduced sodium resorption which, in turn, is accompanied by H+ or K+ secretion and generation of a metabolic alkalosis.

iii) Hydrogen ion shift into cells
In the presence of hypokalaemia, potassium ions move from the intracellular to the extracellular space. To maintain neutrality, H+ shift from the extracellular to intracellular space, leading to a decrease in plasma H+ concentration and hence alkalemia.

iv) Bicarbonate/alkali administration
Administration of alkali over and above that of the kidneys’ ability to excrete this excess alkali load may result in a metabolic alkalosis. The renal capacity for excretion of bicarbonate is reduced in renal failure or when enhanced tubular absorption occurs, such as in volume depleted states.

v) Volume depletion where the extracellular bicarbonate concentration is constant (so-called ‘contraction alkalosis’).
This phenomenon is observed when there is loss of relatively large volumes of chloride-rich and bicarbonate-poor extracellular fluid such as with diuretic therapy or profuse gastro-intestinal losses. Under such conditions there is ‘contraction’ of the extracellular volume but the total extracellular bicarbonate is relatively unchanged and thus the observed plasma bicarbonate concentration rises. However, this observed increase rarely exceeds 2-4 mmol/l as it is minimized by intracellular buffering [10,11].

iii) Maintenance of alkalosis
As outlined, renal excretion of bicarbonate is an efficient process therefore, for metabolic alkalosis to ensue there must be either:
- a concomitant decrease in renal bicarbonate excretion
- enhanced renal reabsorption of bicarbonate
- or a combination of both processes.

In the intensive care unit this often reflects renal injury, however, in the patient with normal renal function the hyperbicarbonataemia is sustained by one, or more often, several other factors. The predominant factors responsible for this include:
- hypokalaemia,
- chloride depletion
- effective circulating volume depletion.
Table 1. Main causes of metabolic alkalosis

<table>
<thead>
<tr>
<th>Hypo/Hyperkalaemia</th>
<th>Vomiting</th>
<th>NG suction</th>
<th>High output fistula</th>
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<tbody>
<tr>
<td>Renal H+ loss</td>
<td>Mineralocorticoid loss (Primary)</td>
<td>Diuretic usage (Thiazide or Loop)</td>
<td>Post hypercapnic alkalosis</td>
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<td>Hypercalcaemia</td>
<td>Milk-Alkali Syndrome</td>
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<td>Apparent H+ loss</td>
<td>Hypokalaemia</td>
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<td>through intracellular shift</td>
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<td>Alkali administration</td>
<td>Citrate</td>
<td>Cocaine abuse</td>
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<td>'Contraction' alkalosis</td>
<td>Over-diuresis</td>
<td>Villous adenoma</td>
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<td>Rare genetic causes</td>
<td>Factitious diarrhoea</td>
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<td>Other</td>
<td>Bartter's Syndrome</td>
<td>Gitelman's Syndrome</td>
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<td></td>
<td>Substance abuse</td>
<td>Antibiotics</td>
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Causes of metabolic alkalosis

i) General causes:
As pointed out metabolic alkalosis is a relatively common clinical problem with the commonest causes being diuretic treatment or the loss of gastric secretions. Table 1 shows the commonly encountered causes of metabolic alkalosis. Also listed are the rarer, principally inherited conditions which will not be explored further here and are discussed in detail elsewhere [16].

With regard to ICU practice, perhaps the most common causes are the loss of gastric secretions coupled with hypokalaemia. These factors are intimately linked because the major causes of metabolic alkalosis (vomiting, diuretics, mineralocorticoid excess), directly cause both potassium ion and hydrogen ion loss. Although renal acid loss is a well recognized cause of metabolic alkalosis, in the intensive care unit it is uncommon apart from that following chronic respiratory acidosis.

Any condition that leads to primary mineralocorticoid hypersecretion can lead to a metabolic alkalosis although this is often in the presence of hypertension. In contrast, untreated secondary hyperaldosteronism such as that found with congestive heart failure or cirrhosis do not present with metabolic alkalosis or hypokalaemia. Under these conditions the decreased distal renal tubular sodium delivery negates the stimulatory effect of aldosterone. In thiazide or loop diuretic therapy adequate distal renal tubular sodium delivery persists together with an increased of aldosterone secretion. This leads to an increase in urinary hydrogen secretion coupled with further volume contraction thereby leading to a metabolic alkalosis [17].

Generation of a metabolic alkalosis through alkalai ingestion in the presence of normal renal function is rare due to the efficiency with which bicarbonate is excreted. However, acute administration in large quantities to correct a metabolic acidosis such as lactic acidosis or diabetic ketoacidosis may lead to a metabolic alkalosis. Under such conditions correction of the underlying condition driving the acidosis will result in eventual metabolism of the organic acids to bicarbonate. Therefore the administered alkali is effectively ‘excess’ and an alkalosis may ensue. However, the beneficial effects of correction of an underlying metabolic acidosis should not be underestimated [18]. Other rarer causes include drug abuse and metabolic alkalosis with hypomagnesaemia has also been reported with aminoglycoside therapy [19].

ii) Causes of metabolic alkalosis found in the ICU population
There are several causes of metabolic alkalosis that are almost entirely encountered in the intensive care setting. These include respiratory acidosis, complications of renal replacement therapy and therapeutic plasma exchange as well as that associated with hypoalbuminaemia.

a) Chronic respiratory acidosis
Chronic respiratory acidosis may be seen in the intensive care setting either as an acute exacerbation of an underlying respiratory condition or following a prolonged period of hypercapnic ventilation. Under conditions of chronic respiratory acidosis there is a loss of protons from the kidney and this excretion of hydrogen ion is an entirely appropriate physiological response. This will lead to, as highlighted above, a rise in the plasma bicarbonate concentration and hence restoration of the normal pH. Consequently any rapid correction of a chronically elevated PaCO₂ through over-zealous mechanical ventilation will lead to a metabolic alkalosis due to the subsequent...
The development of a metabolic alkalosis in this patient group does not only occur in massive blood transfusion where the banked blood is anticoagulated with acid citrate dextran and in therapeutic plasma citrate anticoagulation also has the theoretical benefit of exclusively anticoagulating the extracorporeal circuit thereby avoiding systemic adverse effects principally those of hypernatraemia, hypocalcaemia and metabolic alkalosis. The generation of the observed metabolic alkalosis is through the metabolism of citrate itself. This occurs principally in the mitochondria via the tricarboxylic acid pathway to generate bicarbonate and eventually CO$_2$. Stochiometrically this leads to three bicarbonate molecules generated for each one of citrate used anticoagulant but is associated with several disadvantages, not least those associated with bleeding [24]. An alternative approach is the use of regional anticoagulation with trisodium citrate particularly in individuals at increased risk of bleeding or those with suspected heparin-induced thrombocytopenia [25]. This technique has recently gained much popularity despite the fact that it was first described in haemodialysis over 20 years ago and was being used in continuous techniques over 15 years ago [26]. The anticoagulant effect of citrate is mediated through chelation of ionized calcium which is directly involved in platelet activation and interaction of platelets with clotting factors and other calcium-dependant enzyme systems. Regional anticoagulation also has the theoretical benefit of exclusively anticoagulating the extracorporeal circuit thereby avoiding systemic complications [27]. However the use of citrate is not without adverse effects principally those of hypernatraemia, hypocalcaemia and metabolic alkalosis. The generation of the observed metabolic alkalosis is through the metabolism of citrate itself. This occurs principally in the mitochondria via the tricarboxylic acid pathway to generate bicarbonate and eventually CO$_2$. Stochiometrically this leads to three bicarbonate molecules generated for each one of citrate c

b) Complications of renal replacement therapy
Renal replacement therapy for the patient with multi-organ failure has various guises but the commonest remains continuous veno-venous haemofiltration techniques [22,23]. As this utilizes an extracorporeal circuit then anticoagulation is often, but not always, required. Heparin and its derivatives, remains the most frequently used anticoagulant but is associated with several disadvantages, not least those associated with bleeding [24]. An alternative approach is the use of regional anticoagulation with trisodium citrate particularly in individuals at increased risk of bleeding or those with suspected heparin-induced thrombocytopenia [25]. This technique has recently gained much popularity despite the fact that it was first described in haemodialysis over 20 years ago and was being used in continuous techniques over 15 years ago [26]. The anticoagulant effect of citrate is mediated through chelation of ionized calcium which is directly involved in platelet activation and interaction of platelets with clotting factors and other calcium-dependant enzyme systems. Regional anticoagulation also has the theoretical benefit of exclusively anticoagulating the extracorporeal circuit thereby avoiding systemic complications [27]. However the use of citrate is not without adverse effects principally those of hypernatraemia, hypocalcaemia and metabolic alkalosis. The generation of the observed metabolic alkalosis is through the metabolism of citrate itself. This occurs principally in the mitochondria via the tricarboxylic acid pathway to generate bicarbonate and eventually CO$_2$. Stochiometrically this leads to three bicarbonate molecules generated for each one of citrate

c) Liver transplantation
Orthotopic liver transplantation is often associated with a metabolic alkalosis in the early postoperative period with up to 50% of patients exhibiting such an acid-base disturbance. Interestingly, the development of a metabolic alkalosis in this patient group does not appear to be associated with an adverse outcome, unlike that seen in the intensive care population [30]. The exact mechanism of this observed alkalosis is still far from clear although it appears to be a temporary acid-base disturbance principally involving the early recovery period [31]. Various causes have been considered including gain of base from blood products, improvement in renal function and hence increased removal of filtered acids, and excessive gastrointestinal losses but it is likely a multifactorial process [32].

d) Hypoalbuminaemia
Hypoalbuminaemia is almost a ubiquitous finding in the critically ill. Unlike other serum globulins which do not carry a significant net electric charge at pH values prevailing in plasma, albumin has a variable net negative charge at physiological pH. As a consequence much work has focused on its role in acid-base balance particularly in the critically ill [33]. Hypoproteinaemia itself is a well recognized cause of metabolic alkalosis. This is principally due to loss of the normal buffering plasma proteins which can act as weak acids under physiological conditions. It follows that any loss of such non-volatile weak acids will result in alkalaeemia. This has been demonstrated in vitro where the acid-base effects of altering the concentration of plasma proteins have been quantified under controlled conditions [34].

The anion gap
This phenomenon has particular relevance to calculations of the anion gap, one of the earliest tools for addressing the potential aetiology of metabolic acidosis, which even in its simplest form helps to characterize many cases of metabolic acidosis. The normal value is approximately 15 mmol/l calculated from:

$$(\text{\([Na^+\]) + (\text{\([K^+\])}) - (\text{\([Cl^-\]) + (\text{\([HCO_3^-\])}) = AG})$$

When some additional “unidentified anions” are present (in addition to the normal unidentified anions that correspond to the net negative charges on the proteins), the gap is increased [35]. Therefore the value of the ‘normal’ anion gap should depend on the concentration of plasma proteins and indeed, low values of the anion gap with hypoproteinaemia and high values attributable to hyperproteininaemia have been observed in patients. This effect is significant given that for every 10 g/l fall in the plasma albumin concentration, the reference range for the anion gap falls by 2.5 mmol/l. It follows that if hypoproteininaemia is present and the usual normal numerical value of the anion gap is found, one has to suspect that some unidentified anions (lactate, ketoacids) are present, which will be missed if information on plasma protein concentration is not sought for evaluation of the acid-base status. This has lead to the various refinements of the equation over the years with possibly the simplest shown below [36]:

$$(\text{\([Na^+\]) + (\text{\([K^+\])}) - (\text{\([Cl^-\]) + (\text{\([HCO_3^-\])} + (0.25 \times (40-\text{albumin})) = AG_c})$$

Clinical presentation of metabolic alkalosis
i) Signs and symptoms
These are non-specific and in the ventilated sedated patient will be missed. Mild to moderate metabolic alkalosis may be asymptomatic unless hypokalaemia is significant, in which case neuromuscular signs and symptoms predominate including weakness and myalgia. Hypokalaemia also increases myocardial irritability and
may precipitate cardiac arrhythmia and potentiate digitalis toxicity for example. Associated decreased ionised calcium concentration contributes to peri-oral paraesthesia, tingling, numbness and muscle spasms and in extreme metabolic alkalosis signs of tetany manifest. The compensatory hypoventilation which develops due to the depression of the medullary respiratory centre may lead to hypercapnia and hypoxaemia, and in severe cases this is followed by headache, lethargy, stupor, delirium and seizures.

**ii) History**

The history is very important as it may point to the underlying etiology of the metabolic alkalosis. For example, a history of excess ingestion of alkali, calcium supplements or potassium containing resins may be found. A history of renal failure, gastro-intestinal losses through whatever cause (diarrhoea, vomiting, gastric suction and bulimia) or diuretic use (loop or thiazide) can point the clinician toward an underlying mechanism for the maintenance of metabolic alkalosis. An important factor to consider is also signs and symptoms suggestive of glucocorticoid excess (Cushing’s syndrome) or mineralocorticoid excess which may be present and can be easily missed. In practice, on the intensive care most cases are due to disturbances in volume status or through compensation of a respiratory acidosis and rarely through exogenous agents.

**Diagnosis**

Diagnosis of a metabolic alkalosis in the intensive care unit is rarely a problem given the regularity of blood tests, particularly arterial blood gas analyses, that our patients are exposed to. As indicated, metabolic alkalosis may be suspected based on symptoms, but often may not be noticeable. A pH on arterial blood gas greater than 7.45 confirms the diagnosis. Levels of other electrolytes like potassium, sodium, and chloride are also often outside the normal range for the reasons described. The level of bicarbonate in the blood will be high, usually greater than 29 mmol/l and in the presence of normal renal function, urinary pH may rise to about 7.0.

In patients with normal renal function, the analysis of renal electrolytes particularly chloride may be of diagnostic help. As with all measurements of urinary electrolytes they should be interpreted with caution. The presence of renal dysfunction may render the urinary chloride levels misleading and indeed, the presence of profound hypokalaemia (which may well be present) will prevent maximal tubular chloride conservation from being achieved even in the presence of a low serum chloride. However, in individuals with normal renal function measuring the urinary chloride can aid the clinician in distinguishing between chloride responsive (urine chloride <10 mEq/L) and chloride resistant (urine chloride >20 mEq/L) metabolic alkalosis.

**Treatment**

There are several potential benefits to be achieved by correcting a metabolic alkalosis and in severe cases this is a medical emergency. Of particular relevance to those practicing in intensive care is that correction of a metabolic alkalosis increases both minute ventilation and PaO₂, potentially allowing patients to be weaned more rapidly from mechanical ventilation [37,38]. The fundamental principles in treating metabolic alkalosis are:

- Correct volume depletion
- Correct chloride depletion
- Correct potassium depletion

**i) Correction of volume depletion**

Where the presumed aetiology is volume depletion through whatever mechanism, the alkalosis can be corrected through administration of saline replacement. This will result in both increased bicarbonate secretion and decreased reabsorption of bicarbonate by the kidney. Restoration of the circulating volume removes the drive to retain sodium which in turn, reduces the amount of bicarbonate reabsorbed. Furthermore, the resulting increase in chloride delivery to the distal tubule will promote chloride passage intracellularly, hence leading to increased bicarbonate secretion in the cortical collecting tubule and a significant rise in urinary bicarbonate excretion.

**ii) Correction of chloride depletion**

The importance of chloride replacement has been demonstrated in studies of both acute and chronic chloride depletion [15]. Chloride-depletion alkalosis has been completely corrected by administration of several non-sodium chloride salts even in circumstances that would maintain or generate an alkalosis. However, alkalosis was not corrected without chloride replacement [39]. Chloride depletion appears to decrease GFR through tubuloglomerular feedback which may be a protective mechanism to prevent excessive fluid and sodium losses [40]. Normal functioning of the proximal tubule is essential to permit appropriate bicarbonate reabsorption but during metabolic alkalosis the collecting duct appears to play a major role in electrolyte and proton transport. During the maintenance of metabolic alkalosis, bicarbonate secretion does not occur because insufficient chloride is available for bicarbonate exchange but following chloride administration luminal or cellular chloride concentration increases and bicarbonate is promptly excreted and alkalosis is corrected. Where volume depletion is present, isotonic saline should be given which corrects both volume status and chloride deficiency. In severe volume contraction the administration of a minimum of 3-5L of 150 mmol/l NaCl is usually necessary to correct volume deficits and metabolic alkalosis. If the volume status is normal then the total body chloride deficit can be estimated from equation (4) with the caveat that ongoing losses of fluid and electrolytes must also be accounted for [3]:

\[ 0.2 \times \text{body weight (kg)} \times \text{desired increase in plasma chloride (mmol/l)} \]

As the chloride deficit is corrected, a brisk alkaline diuresis will occur with a decrease in plasma bicarbonate toward normal.

**iii) Correction of potassium depletion**

The correction of potassium depletion is also of vital importance in the treatment of metabolic alkalosis. Correction of potassium results in a movement of potassium ion into the cells together with a movement of hydrogen ions into the extracellular compartment through a transcellular cation exchange mechanism. This increase in extracellular proton concentration buffers the excess extracellular bicarbonate and the resultant rise in intracellular pH in renal tubular cells reduces hydrogen secretion and consequently bicarbonate reabsorption [12]. Because nephropathy due to potassium depletion may impair free water excretion, plasma sodium should be monitored closely during treatment, particularly if hypotonic fluids are administered.
Other treatment strategies for correction of metabolic alkalosis

In certain cases alternative approaches to treatment may be needed which including the use of hydrochloric acid, acetazolamide and renal replacement.

i) Hydrochloric acid

In the clinical setting of volume overload such as in congestive heart failure, the administration of large volumes of saline is clearly inadvisable. Although the use of KCl may be used this may also be limited where an increased plasma potassium is present. Under such conditions and where the alkalosis is severe (e.g. arterial pH is greater than 7.55) hydrochloric acid can be used usually as an isotonic solution (150 mmol/l) over 8 to 24 h. The amount of HCl needed to correct alkalosis is calculated by the formula and again continuing losses must also be replaced [3]:

\[ \text{0.5 x body weight (kg) x desired reduction in plasma bicarbonate (mmol/l)} \]

The treatment aim is to rescue the patient from severe alkalosis thus it is recommended that initially the plasma bicarbonate concentration is restored to approximately halfway to normal. Needless to say hydrochloric acid solutions must be given through a catheter placed in a large central vein after radiographic confirmation that the catheter is correctly sited. Clearly frequent measurement of arterial blood gases and electrolytes should ensue. An alternative agent is ammonium chloride but this is contraindicated in renal or hepatic insufficiency due to a potential worsening of uraemia and acute ammonia intoxication. Minimizing continuing acid loss in this setting with either a H2-blocker or proton pump inhibitor may also be beneficial [41].

ii) Acetazolamide therapy

The potential toxicity of ammonium chloride and hydrochloric acid tend to limit their usage and most intensivists tend to use acetazolamide as the first line of therapy to correct a metabolic alkalosis after volume and electrolyte replacement. Acetazolamide is a carbonic anhydrase inhibitor which preferentially inhibits proximal sodium bicarbonate reabsorption by up to 80%, thereby correcting both metabolic alkalosis and where present, volume overload [42]. In several studies acetazolamide has been shown to significantly decrease serum HCO₃⁻ and restore pH to normal within 24 hrs [43,44], however the use of acetazolamide is not without its pitfalls particularly when multiple doses are used. This is manifest as an overcorrection of the metabolic alkalosis potentially resulting in a hyperchloraemic, hypokalaemic metabolic acidosis [45]. Acetazolamide enhances potassium secretion and therefore patients should be relatively normokalaemic before commencement of therapy. Also, carbonic anhydrase inhibition in patients with chronic respiratory acidoses may cause a small, transient, rise in the PCO₂. This effect is due to inhibition of carbonic anhydrase in red cells impairing CO₂ transport by the red cell and the subsequent elimination of CO₂ by the lungs. Although this is a theoretical problem, it is of little clinical significance. Although several dosing schedules have been used with acetazolamide one randomized double-blind trial on a medical ICU compared the use of a single dose of acetazolamide to multiple dosing [46]. This study concluded that a single dose of 500 mg of acetazolamide effectively reverses metabolic alkalosis for a prolonged period in mechanically ventilated asthma/COPD patients. However, in patients with severe metabolic alkalosis due to high output losses this may not be sufficient.

iii) Renal replacement

Where severe, life-threatening metabolic alkalosis coexists with acute renal failure this presents additional problems. The dialysates and replacement fluids used for both haemodialysis and haemofiltration contain high concentrations of bicarbonate or its metabolic precursors and therefore must be modified in these circumstances. An alternative approach is to correct the alkalosis with acid, as noted above, in tandem with renal replacement therapy. This requires careful consideration of fluid and electrolyte balance. In milder cases, renal replacement with CVVHD for example can be performed as the replacement fluid will have a lower bicarbonate concentration than the blood bicarbonate. In this case the filter will act as a ‘metabolic clamp’ with eventual equilibrium being reached between plasma and replacement fluid bicarbonate concentrations. Continual renal replacement also has the advantage that the volume balance desired can be easily achieved and electrolyte disturbances are readily corrected.

Conclusions

There are many causes of metabolic alkalosis which may present in the critically ill. In most cases the cause will be apparent and may well be iatrogenic. Careful attention to electrolyte and volume balance should correct the problem. In more severe cases further aggressive treatment may be needed including acetazolamide therapy, hydrochloric acid infusion or renal replacement therapy.


