MANAGEMENT OF LIFE-THREATENING ACID–BASE DISORDERS

Second of Two Parts
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ADVERSE CONSEQUENCES OF SEVERE ALKALEMIA

Severe alkalemia (blood pH greater than 7.60) can compromise cerebral and myocardial perfusion by causing arteriolar constriction, an effect that is more pronounced in respiratory than in metabolic alkalosis (Table 2).69–71 Neurologic abnormalities may ensue, including headache, tetany, seizures, lethargy, delirium, and stupor. The associated reduction in the plasma concentration of ionized calcium probably contributes to these manifestations. Although it exerts a moderate positive inotropic effect on the isolated heart, alkalemia reduces the anginal threshold and predisposes the patient to refractory supraventricular and ventricular arrhythmias. This arrhythmogenic action is more pronounced in patients with underlying heart disease. Alkalemia depresses respiration, causing hypercapnia and hypoxemia. Such effects are of little consequence in patients with adequate ventilatory reserve, but they can be consequential in patients with compromised ventilation. Even mild alkalemia can frustrate efforts to wean patients from mechanical ventilation.

Hypokalemia is an almost constant feature of alkalemic disorders, but it is more prominent in those of metabolic origin. Translocation of potassium into cells and renal and extrarenal losses contribute in varying degrees to its generation.7,69–71 In turn, hypokalemia can have several adverse effects, including neuromuscular weakness; sensitization to digitalis-induced arrhythmias; polyuria; and increased ammonia production, which can heighten the risk of hepatic encephalopathy. Alkalemia stimulates anaerobic glycolysis and increases the production of lactic acid and ketoacids.6,17 Along with the alkalemic titration of plasma proteins and the hyperproteinemia accompanying chloride-responsive metabolic alkalosis, this effect contributes to the characteristic moderate elevation in the plasma anion gap.41,72 Although acute alkalemia can reduce the release of oxygen to the tissues by tightening the binding of oxygen to hemoglobin, chronic alkalemia negates this effect by increasing the concentration of 2,3-diphosphoglyceric acid in red cells.69–71

MANAGEMENT OF LIFE-THREATENING ALKALOSES

Metabolic Alkalosis

In the presence of an appropriate ventilatory response, severe alkalemia of metabolic origin requires that the plasma bicarbonate concentration exceed 45 mmol per liter.12 Just as in severe metabolic acidemia, the immediate goal of therapy is moderation but not full correction of the alkalemia. Reducing plasma bicarbonate to less than 40 mmol per liter is an appropriate short-term goal, since the corresponding pH is on the order of 7.55 or lower. Most severe metabolic alkalosis is of the chloride-responsive form, the most common causes being loss of gastric acid and the administration of loop or thiazide diuretics.69,71 The characteristic hypochloremic hyperbicarbonatemia results from the loss of hydrochloric acid in gastric secretions or from urinary excretion of excess ammonium chloride caused by these chloruretic diuretics.

Substantial contraction of the volume of extracellular fluid as a result of diuretic-induced losses of sodium chloride can further amplify the resulting hyperbicarbonatemia by limiting the space of distribution of bicarbonate. Such a “contraction alkalosis” is particularly likely in patients with massive edema treated with combination regimens of diuretics (such as furosemide and metolazone). Maintenance of chloride-responsive metabolic alkalosis is then effected by heightened renal bicarbonate reabsorption, frequently coupled with a reduced glomerular filtration rate, changes that are mediated by chloride depletion itself, contraction of extracellular-fluid volume, and the associated potassium deficit.
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ameliorating the existing hyperbicarbonatemia. Pa-
vate the alkalosis, the clinician must then focus on
pounds, are being administered, their indication and
fludrocortisone and various glucocorticoid com-
If drugs with mineralocorticoid activity, such as
cation-exchange resins with aluminum hydroxide in
renal impairment can occur. Coadministration of
absorbable alkali and milk; severe metabolic alkalosis
be discontinued. At times, absorbable alkali is not a
complicating factor but the very cause of the meta-
bolic alkalosis, as in patients ingesting inordinate
amounts of calcium carbonate or large quantities of
abсорbable alkali and milk; severe metabolic alkalosis
coupled with variable degrees of hypercalcemia and
renal impairment can occur. Coadministration of
cation-exchange resins with aluminum hydroxide in
effect renders the nonabsorbable alkali absorbable.73
If drugs with mineralocorticoid activity, such as
fluorocortisone and various glucocorticoid com-
pounds, are being administered, their indication and
dose should be reassessed.

Having addressed the factors that cause or aggra-
vate the alkalosis, the clinician must then focus on
ameliorating the existing hyperbicarbonatemia. Pa-
tients with volume depletion require provision of
both sodium chloride and potassium chloride. Re-
pair of the prevailing sodium, potassium, and chlor-ide deficits and of the often-present functional
azotemia will promote bicarbonaturia heralded by
alkalinization of the urine. Administration of acetaz-
olamide (250 to 375 mg once or twice daily) fos-
ters bicarbonaturia but requires consideration of the
associated kaliuresis and phosphaturia.

If the pace of correction of the alkalosis must be
accelerated, alkali stores can be titrated by infusing
hydrochloric acid. Hydrochloric acid administered
intravenously as a 0.1 to 0.2 N solution (that is, one
containing 100 to 200 mmol of hydrogen per liter) is
safe and effective for the management of severe
metabolic alkalosis. The acid can be infused as such
or can be added to amino acid and dextrose solu-
tions containing electrolytes and vitamins without
causing adverse chemical reactions.74,75 Because of
its sclerosing properties, hydrochloric acid must be
administered through a central venous line at an
infusion rate of no more than 0.2 mmol per kilogram
of body weight per hour. However, it can also be ad-
ministered through a peripheral vein if it is added to
an amino acid solution and mixed with a fat emul-
sion.74

Calculation of the amount of hydrochloric acid
solution to be infused is based on a bicarbonate
space of 50 percent of body weight.15 Thus, to re-
duce plasma bicarbonate from 50 to 40 mmol per
liter in a 70-kg patient, the estimated amount of hy-
drochloric acid required is 10×70×0.5, or 350
mmol. Precursors of hydrochloric acid, such as am-
monium chloride (20 g per liter, with 374 mmol of
hydrogen per liter) and arginine monohydrochloride
(100 g per liter, with 475 mmol of hydrogen per li-
ter), can substitute for hydrochloric acid, but they
tail substantial risks and are used less commonly.
Both of these preparations are hyperosmotic solu-
tions; to avoid local tissue injury, they must be
infused through a central catheter. In addition, am-
monium chloride can raise serum ammonia concen-
trations in patients with liver failure, and arginine
monohydrochloride can induce serious hyperkale-
mia in patients with renal failure, especially when
there is coexisting liver disease.69,71,76

Treatment of severe chloride-responsive metabolic
alkalosis is considerably more challenging in patients
with cardiac or renal dysfunction.69,71 Expansion of
the extracellular-fluid volume may either accompany
alkalemia or develop as a result of treatment. Potas-
sium chloride can induce hyperkalemia in patients
with renal failure. In certain cases, downgrading the
diuretic regimen, adding acetazolamide, and cau-
tiously administering sodium chloride and potassium
chloride may suffice. In many other cases, how-
ever, cardiac and renal failure pose such limitations
that the physician must resort to more aggressive
measures. Infusion of hydrochloric acid can be effi-
cacious, but the associated fluid load is often prob-

### Table 2. Major Adverse Consequences of Severe Alkalemia.

| Cardiovascular | \( \text{H}^+ / \text{K}^+ \)–ATPase. Notably, these treatments substi-
| Arteriolar constriction | tute loss of sodium chloride for loss of hydrochloric
| Reduction in coronary blood flow | acid production
| Reduction in anginal threshold | Hypokalemia
| Predominantly to refractory supraventricular and ventricular arrhythmias |
| Respiratory | Hyperventilation with attendant hypercapnia and hypoaxemia
| Metabolic | Stimulation of anaerobic glycolysis and organic acid production
| Decreased plasma ionized calcium concentration | Hypomagnesemia and hypophosphatemia
| Cerebral | Hypotension
| Reduction in cerebral blood flow | Tetany, seizures, lethargy, delirium, and stupor

If the processes that generate metabolic alkalosis
are still ongoing, every effort should be made to
moderate or stop them, even if only temporarily.
Vomiting should be countered with antiemetics. If
continuation of gastric drainage is required, the loss
of gastric acid can be reduced by administering
H₂⁻receptor blockers or inhibitors of the gastric
H⁺/K⁺–ATPase. Notably, these treatments substi-
tute loss of sodium chloride for loss of hydrochloric
acid. Decreasing the dose of loop and thiazide di-
uretics can be coupled with the addition of potassi-
um-sparing diuretics (spironolactone, amiloride, or
triamterene), drugs that decrease distal acidification and curtail potassium excretion.

Prompt attention should be given to additional
factors that might compound the alkalosis. Admin-
istration of bicarbonate or its precursors, such as lac-
tate, citrate, and acetate (the latter being a common
ingredient of parenteral-nutrition solutions), should
be discontinued. At times, absorbable alkali is not a
complicating factor but the very cause of the meta-
bolic alkalosis, as in patients ingesting inordinate
amounts of calcium carbonate or large quantities of
absorbable alkali and milk; severe metabolic alkalosis
coupled with variable degrees of hypercalcemia and
renal impairment can occur. Coadministration of
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If drugs with mineralocorticoid activity, such as
fluorocortisone and various glucocorticoid com-
pounds, are being administered, their indication and
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Having addressed the factors that cause or aggra-
vate the alkalosis, the clinician must then focus on
ameliorating the existing hyperbicarbonatemia. Pa-
tients with volume depletion require provision of
both sodium chloride and potassium chloride. Re-

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lematic. Under these circumstances, use of an extracorporeal device is advisable. Hemodialysis and ultrafiltration can rapidly correct severe alkalemia and volume overload, especially if the bicarbonate concentration of the standard dialysate is reduced. In patients with unstable hemodynamics, the same goals can be achieved by continuous arteriovenous or venovenous hemofiltration with sodium chloride as the replacement solution.

Life-threatening alkalemia is a very rare occurrence in chloride-resistant metabolic alkalosis. Disorders of mineralocorticoid excess, severe potassium depletion, and Bartter’s or Gitelman’s syndrome are the causes of this form of alkalosis. Aggressive potassium repletion will correct or ameliorate chloride-resistant alkalosis, but the thrust of the therapy should be directed at reversing the underlying disorder, if possible. When the cause of the mineralocorticoid excess cannot be reversed, potassium-sparing diuretics coupled with moderate restriction of sodium chloride can provide symptomatic relief. Identifying laxative abuse as the culprit may prevent recurrence of the problem. Potassium-sparing diuretics, nonsteroidal antiinflammatory drugs, or angiotensin-converting–enzyme inhibitors can ameliorate Bartter’s or Gitelman’s syndrome.

Respiratory Alkalosis

Respiratory alkalosis is the most frequently encountered acid–base disorder, since it occurs in normal pregnancy and with high-altitude residence. The pathologic causes of respiratory alkalosis include various hypoxic conditions, pulmonary disorders, central nervous system diseases, salicylate intoxication, hepatic failure, sepsis, and the anxiety–hyperventilation syndrome. Respiratory alkalosis is particularly prevalent among the critically ill; in these patients, its presence is a bad prognostic sign, because mortality increases in direct proportion to the severity of the hypocapnia.

Hypocapnia elicits a secondary change in plasma bicarbonate that, as in hypercapnia, has two components. A moderate acute decrease in plasma bicarbonate originates from tissue buffering. A larger decrease accompanies chronic hypcapnia as a result of down-regulation of renal acidification and requires two to three days to reach completion. Because blood pH does not exceed 7.55 in most cases of respiratory alkalosis, severe manifestations of alkalemia are usually absent. Marked alkalemia can be observed, however, in certain circumstances, such as with inappropriately set ventilators, some psychiatric conditions, and lesions of the central nervous system. Obviously, clinical manifestations of severe alkalemia are more likely to occur in the acute, rather than the chronic, phase of respiratory alkalosis.

Management of respiratory alkalosis must be directed toward correcting the underlying cause, whenever possible. Because most cases of respiratory alkalosis, especially chronic cases, pose little risk to health and produce few or no symptoms, measures to treat the deranged acid–base composition are not required. The anxiety–hyperventilation syndrome is an exception. An active therapeutic approach that provides reassurance, sedation, and ultimately psychotherapy is most helpful in these cases. Rebreathing into a paper bag or any other closed system provides prompt, but unfortunately short-lived, symptomatic relief. If hypocapnia-induced alkalemia is severe and persistent, sedation may be required.

Pseudorespiratory Alkalosis

Arterial hypocapnia does not necessarily imply respiratory alkalosis or the secondary response to metabolic acidosis but can be observed in an idio typic form of respiratory acidosis. This entity, which we have termed pseudorespiratory alkalosis, occurs in patients with profound depression of cardiac function and pulmonary perfusion but with relative preservation of alveolar ventilation, including patients undergoing cardiopulmonary resuscitation. The severely reduced pulmonary blood flow limits the carbon dioxide delivered to the lungs for excretion, thereby increasing the mixed venous partial pressure of carbon dioxide. By contrast, the increased ventilation-perfusion ratio causes the removal of a larger-than-normal amount of carbon dioxide per unit of blood traversing the pulmonary circulation, thereby creating arterial eucapnia or frank hypocapnia (Fig. 3). Nonetheless, the absolute excretion of carbon dioxide is decreased and the carbon dioxide balance of the body is positive — the hallmark of respiratory acidosis. Such patients may have severe venous acidemia (often due to mixed respiratory and metabolic acidosis) accompanied by an arterial pH that ranges from the mildly acidic to the frankly alkaline. Furthermore, the extreme oxygen deprivation prevailing in the tissues may be completely disguised by the reasonably preserved values of arterial oxygen (Fig. 3). To rule out pseudorespiratory alkalosis in a patient with circulatory failure, blood gas monitoring must include sampling of mixed (or central) venous blood. The management of pseudorespiratory alkalosis must be directed toward optimizing systemic hemodynamics.

Mixed Alkaloses

Extreme alkalemia can occur in patients with metabolic and respiratory alkalosis, even in the presence of only moderate changes in plasma bicarbonate and the partial pressure of arterial carbon dioxide. This disorder can occur in various settings, including among patients with primary hypocapnia associated with chronic liver disease, in whom metabolic alkalosis develops because of vomiting, nasogastric
drainage, diuretics, profound hypokalemia, or alkali administration, especially in the context of renal insufficiency. Mixed alkalosis is also observed in patients with end-stage renal disease in whom primary hypocapnia develops; the inappropriately high plasma bicarbonate level reflects the absence of the renal response to the prevailing hypocapnia and the dialysis-induced alkali load. Patients undergoing peritoneal dialysis are more vulnerable than those undergoing hemodialysis, because peritoneal dialysis maintains plasma bicarbonate at a higher level (25 to 26 mmol per liter, as compared with a value of 20 to 21 mmol per liter before hemodialysis). Reducing the base concentration of the dialysate or switching the patient from peritoneal dialysis to hemodialysis will ameliorate the situation.

**REFERENCES**