INTRODUCTION — Like ketoacidosis, lactic acidosis replaces bicarbonate with an organic anion. Removing the stimulus to lactic acid production by treating the underlying disease enables oxidative processes to metabolize the accumulated lactate, resulting in the regeneration of bicarbonate and correction of the acidosis. Thus, treatment with sodium bicarbonate is indicated only for acute control of the acidemia. It has been suggested, for example, that severe acidemia may contribute to continued tissue hypoperfusion by decreasing cardiac contractility via a reduction in myocardial cell pH \[1,2\]. To the degree that this occurs, the administration of sodium bicarbonate may raise the extracellular pH both directly and by improving oxygen delivery to the tissues.

EFFECTS OF BICARBONATE THERAPY — The infusion of sodium bicarbonate, however, can lead to a variety of problems in patients with lactic acidosis, including fluid overload, a postrecovery metabolic alkalosis (as the excess lactate is converted back to bicarbonate), and hypernatremia. Furthermore, studies in both animals and humans suggest that alkali therapy may only transiently raise the plasma bicarbonate concentration \[3,4\]. This finding appears to be related in part to the carbon dioxide generated as the administered bicarbonate buffers excess hydrogen ions. This carbon dioxide is normally eliminated via the lungs. However, patients with severe circulatory failure or cardiac arrest often have a marked reduction in pulmonary blood flow. As a result, the newly formed carbon dioxide accumulates in the venous system \[5,6\]. Mixed venous PCO2 will continue to rise until the product of the greater than normal mixed venous PCO2 and the less than normal pulmonary blood flow is sufficient to eliminate the CO2 that is produced. (See "Arterial and mixed venous blood gases in lactic acidosis".)
It has been proposed that the rise in PCO2 in the venous blood that is perfusing the tissues may then exacerbate the intracellular acidosis, leading to an impairment in both hepatic lactate utilization and cardiac contractility [3,7]. However, careful biochemical analysis suggests that a further reduction in intracellular pH with bicarbonate administration should not occur. Conversion of bicarbonate to CO2 requires that each meq of bicarbonate combine with a meq of proton. The amount of protons carried by blood buffers (proteins, phosphate, hemoglobin) is insufficient to buffer all of the exogenous bicarbonate. Thus, the induced rise in venous CO2 (and fall in venous pH) must be secondary to buffering by intracellular buffers, a process that restores the intracellular pH and the chemical structure of intracellular proteins.

The administration of bicarbonate can also prevent an improvement in cardiac function by inducing a fall in the plasma ionized (unbound) calcium concentration due to increased protein binding [8], since calcium is required for normal cardiac contractility [9]. Cautious administration of calcium may become necessary in some patients.

It is at present unclear if the disparity in mixed venous and arterial PCO2 and pH occurs in septic shock in which the cardiac output is typically above normal but still too low to meet tissue needs. There is, however, no evidence that sodium bicarbonate improves circulatory hemodynamics in this setting [8].

**ALTERNATIVES TO BICARBONATE** — The limitations and potential deleterious effects of bicarbonate therapy have prompted investigation into the use of alternative buffering agents, such as carbicarb and THAM, and agents which may decrease the formation of lactic acid.

**Tromethamine** — Tromethamine (tris-hydroxymethyl aminomethane; THAM; trometamol) is an inert amino alcohol which buffers acids and CO2 by virtue of its amine (-NH2) moiety via the following reactions [10]:

\[
\text{THAM-NH}_2 + \text{H}^+ = \text{THAM-NH}_3^+ \\
\text{THAM-NH}_2 + \text{H}_2\text{O} + \text{CO}_2 = \text{THAM-NH}_3^+ + \text{HCO}_3^-
\]
Protonated THAM is excreted in the urine at a slightly higher rate than creatinine clearance in conjunction with either chloride or bicarbonate. Thus, THAM supplements the buffering capacity of blood without generating carbon dioxide but is less effective in anuric patients. Reported toxicities include hyperkalemia, hypoglycemia, and respiratory depression; the last complication probably results from the ability of THAM to rapidly increase the pH and decrease the PCO2 in the central nervous system. (See "Control of ventilation".)

Published clinical experience with THAM is limited, but the drug has been used to treat severe acidemia due to sepsis, hypercapnia, diabetic ketoacidosis, renal tubular acidosis, gastroenteritis, and drug intoxications [10]. One study compared one hour infusions of THAM versus sodium bicarbonate in 18 patients with mild lactic acidosis (mean blood pH 7.34; mean serum bicarbonate 18 mEq/L) [11]. Although the infusion of THAM was associated with less of an increase in arterial PCO2, it also resulted in less of an increase in serum bicarbonate concentration. Hemodynamic consequences of these therapies were not reported.

Thus, the clinical efficacy compared to sodium bicarbonate remains unproven in the treatment of severe metabolic acidosis, and THAM is of uncertain safety.

**Carbicarb** — It has been proposed that a more effective alternative to sodium bicarbonate may be the administration of carbicarb, which is an equimolar mixture of sodium carbonate (Na2CO3) and sodium bicarbonate [3,7]. Sodium carbonate uses carbonic acid (H2CO3) to generate bicarbonate via the following reaction [12]:

\[
\text{CO3}^{2-} + \text{H2CO3} = 2 \text{HCO3}^-
\]

Thus, the carbonate component of carbicarb will diminish the tendency toward venous hypercapnia and worsening intracellular acidosis [12]. However, the risks of hypernatremia and hypervolemia are similar to those of sodium bicarbonate [13].
Carbicarb has yet to be evaluated in humans, but it is not likely to be effective in lactic acidosis due to cardiopulmonary arrest. Studies in animals with ventricular fibrillation have demonstrated a progressive reduction in the myocardial cell pH and an increase in coronary venous PCO2, neither of which is ameliorated by carbicarb or sodium bicarbonate [14,15]. In this setting, the excess CO2 is generated locally by the metabolic activity of the fibrillating ventricular muscle.

**Dichloroacetate** — Dichloroacetate is another investigational modality that represents an alternative to buffer therapy. It increases the activity of pyruvate dehydrogenase, which allows pyruvate to be oxidized rather than being converted to lactate [16]. Although dichloroacetate may lower lactate levels and raise the arterial pH, one controlled study demonstrated that these effects were modest and that there was no improvement in systemic hemodynamics or patient survival [16]. This observation again illustrates the primary importance of correcting the underlying cause of tissue hypoperfusion.

**VASOPRESSORS** — Vasopressors can raise the blood pressure in patients with septic shock but it is unclear if they affect the prognosis. (See "Use of vasopressors and inotropes" and "Management of severe sepsis and septic shock in adults".) One report compared the effect of dopamine and epinephrine in 23 patients with lactic acidosis and shock due to sepsis or malaria [17]. Epinephrine had the following deleterious effects:

- It raised serum lactate levels (3.2 meq/L versus a fall of 1.0 meq/L with dopamine)
- It further lowered the arterial pH (0.05 units versus no change with dopamine)

Why this occurred is not clear. One possibility is that it may worsen tissue hypoxia by causing maldistribution of blood flow.
The American Thoracic Society (ATS) statement on the detection, correction, and prevention of tissue hypoxia, as well as other ATS guidelines, can be accessed through the ATS web site at www.thoracic.org/sections/publications/statements/index.html.

**RECOMMENDATIONS** — In summary, the efficacy of and indications for alkali administration in hypoperfusion-induced lactic acidosis remains unresolved [18]. The primary aim of therapy must be reversal of the underlying disease. At best, raising the extracellular pH will only be of benefit if there is a parallel rise in intracellular pH [15]. This goal does not appear to be achieved with bicarbonate administration during cardiopulmonary resuscitation (CPR) [14,15]. (See "Therapies of uncertain benefit in basic and advanced cardiac life support".)

Preliminary studies in patients with shock-induced lactic acidosis have not demonstrated any improvement in cardiac output or systemic blood pressure with the acute administration of sodium bicarbonate (when compared to an infusion of an equivalent amount of sodium chloride) [8]. Because acidemia is only one of many factors affecting the mortality of these critically ill patients, very large numbers will have to be assessed to determine if there is a therapeutic role for alkali.

Partial elevations in both extracellular and intracellular pH can be achieved in patients being ventilated by increasing the rate of ventilation, thereby lowering the PCO2 [15]. Most physicians would limit the use of sodium bicarbonate to patients with severe metabolic acidemia (arterial pH below 7.10 to 7.15), with the aim being to maintain the pH above 7.15 until the primary process can be reversed. There is at present no evidence that alkali therapy is beneficial during CPR [15].

It is possible that the concerns about bicarbonate therapy may not apply to lactic acidosis associated with metformin therapy. In reports of patients with concurrent renal failure, bicarbonate hemodialysis can both correct the acidosis and remove metformin [19,20]. (See
REFERENCES


