Pathogenesis, consequences, and treatment of metabolic acidosis in chronic kidney disease

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INTRODUCTION

Most individuals produce approximately 15,000 mmol (considerably more with exercise) of carbon dioxide and 50 to 100 mEq of nonvolatile acid each day. Acid-base balance is maintained by normal elimination of carbon dioxide by the lungs (which affects the partial pressure of carbon dioxide [PCO2]) and normal excretion of nonvolatile acid by the kidneys (which affects the plasma bicarbonate concentration). The hydrogen ion concentration of the blood is determined by the ratio of the partial pressure of carbon dioxide and plasma bicarbonate concentration. (See "Simple and mixed acid-base disorders", section on 'Physiology and assessment of acid-base status'.)

Acidosis associated with chronic kidney disease (CKD) will be discussed in this topic. An overview of simple acid-base disorders and renal tubular acidosis, as well as the approach to patients with metabolic acidosis, are presented elsewhere:

- (See "Simple and mixed acid-base disorders".)
- (See "Overview and pathophysiology of renal tubular acidosis and the effect on potassium balance".)
- (See "Approach to the adult with metabolic acidosis".)
- (See "Approach to the child with metabolic acidosis".)

ACID-BASE BALANCE IN CKD

Acid-base balance is normally maintained by the renal excretion of the daily acid load (approximately 1 mEq/kg per day, derived mostly from the generation of sulfuric acid during the metabolism of sulfur-containing amino acids) [1,2]. Elimination of this acid load is achieved by the urinary excretion of hydrogen ions, both as titratable acidity and as ammonium [3]. Near-normal balance can be maintained even if the acid load is modestly increased since net acid excretion rises appropriately, primarily via increased ammonium production and excretion (figure 1) [4].

Development of metabolic acidosis — Metabolic acidosis can develop as a result of one or more of the following pathophysiologic processes [5]:

- Increased production of nonvolatile acids
- Increased loss of bicarbonate
- Decreased renal excretion of acid

Metabolic acidosis is commonly associated with chronic kidney disease (CKD) [6,7]. As the number of functioning nephrons declines in CKD, acid excretion is initially maintained by an increase in the ammonium excreted per nephron [1]. However, total ammonium excretion begins to fall when the glomerular filtration rate (GFR) is below 40 to 50 mL/min [1,2,8]. At this level of kidney function, ammonium excretion per total GFR is three to four times above normal, suggesting that the impairment in ammonium excretion is caused by too few functioning nephrons rather than impaired function in the remaining nephrons [1,9].

As a result, CKD leads to retention of hydrogen ions [1,6,8,10]. In addition to the fall in ammonium excretion, diminished excretion of titratable acid (primarily as phosphoric acid) also may play a role in the pathogenesis of metabolic acidosis in patients with advanced kidney disease. Both dietary phosphate restriction and the use of oral phosphate binders to prevent hyperphosphatemia may contribute to the fall in phosphate excretion.

The retained acid is buffered by bicarbonate in the extracellular fluid, by tissue buffers, and by bone [11]. With worsening kidney function, however, progressive metabolic acidosis and acidemia can develop. As a result, metabolic acidosis and acidemia become more common with advancing stages of CKD [12]. The prevalence of a serum bicarbonate concentration of <22 mEq/L, for example, is <5 percent in CKD stages 1 and 2 and increases linearly to approximately 25 percent in patients with nondialysis-dependent CKD stage G5 (table 1) [13]. As the patient approaches end-stage kidney disease (ESKD), the plasma bicarbonate concentration tends to stabilize between 12 and 20 mEq/L [1,8,14]. A level below 10 mEq/L is unusual since buffering of

the retained hydrogen ions prevents a progressive fall in the plasma bicarbonate concentration. Typically, the anion gap remains normal until late stages of CKD when it begins to widen due to the retention of anions such as phosphate, sulfate, urate, and hippurate [14,15]. (See "Approach to the adult with metabolic acidosis".)

Patients receiving dialysis — Initiation of kidney replacement therapy typically results in improvement in metabolic acidosis as a result of the additional base load delivered in the dialysate, although metabolic acidosis can persist in patients who have higher net acid generation, typically those whose diet contains higher amounts of animal proteins [16,17].

Some patients undergoing maintenance dialysis have spuriously low plasma bicarbonate levels. If blood samples are transported from the dialysis clinic to the clinical laboratory by air freight, delayed centrifugation of the specimen may lead to increased lactic acid production by blood cells; this can artifactually reduce the plasma bicarbonate concentration [18].

By contrast, a small number of patients with ESKD have a normal plasma bicarbonate concentration and anion gap [14]. A reduced daily acid load caused by decreased protein intake (which diminishes both acid and sulfate generation) and/or increased fruit intake (which provides citrate that is converted to bicarbonate) are the most likely explanations. For unclear reasons, most patients with ESKD who have a normal plasma bicarbonate and a normal anion gap also have diabetes mellitus [19].

A superimposed metabolic alkalosis (as occurs with vomiting or diuretic therapy) is another factor that could normalize the plasma bicarbonate concentration in advanced kidney failure. In this setting, the anion gap should still be elevated. (See "Approach to the adult with metabolic acidosis" and "The delta anion gap/delta HCO3 ratio in patients with a high anion gap metabolic acidosis".)

Kidney transplant recipients — A mild metabolic acidosis is frequently observed among kidney transplant recipients [20] even though the urinary acidification defects associated with CKD often resolve following allograft implantation [21]. The mean serum bicarbonate concentration was 22 mEq/L among 823 unselected kidney transplant patients, with nearly 60 percent having levels less than 24 mEq/L [22]. Decreased kidney function, increased parathyroid hormone (PTH) and phosphate levels, and decreased serum albumin and calcium levels were associated with lower bicarbonate levels. In another cohort of 2318 adult kidney transplant recipients, serum bicarbonate concentrations of <22 mEq/L were present in 30 to 70 percent of patients with estimated GFR (eGFR) <30 mL/min/1.73 m^2 [23].

Potential mechanisms responsible for posttransplantation metabolic acidosis include the development of renal tubular acidosis (due, for example, to calcineurin inhibitors such as

cyclosporine and tacrolimus), hyperkalemia, hypercalcemia, and disordered citrate metabolism and other tubular dysfunctions [24-28].

- (See "Potassium balance in acid-base disorders", section on 'Metabolic acidosis'.)
- (See "Clinical manifestations of hypercalcemia", section on 'Renal tubular acidosis'.)
- (See "Cyclosporine and tacrolimus nephrotoxicity", section on 'Metabolic acidosis'.)

CONSEQUENCES OF METABOLIC ACIDOSIS IN CKD

Chronic metabolic acidosis in patients with chronic kidney disease (CKD) may produce a variety of pathophysiologic changes:

- Bone resorption and osteopenia [11,29-34]
- Increased muscle protein catabolism [7,35-42]
- Aggravation of secondary hyperparathyroidism [43,44]
- Reduced respiratory reserve and exhaustion of body buffer systems, resulting in increased severity of acute intercurrent illnesses [45]
- Reduced Na^+-K^+-ATPase activity in red blood cells [46] and myocardial cells [47], which could impair myocardial contractility and produce heart failure [48]
- Endocrine disorders such as resistance to growth hormone and insulin, and hypertriglyceridemia [7,35,49]
- Systemic inflammation [50,51]
- Hypotension and malaise [6,7]
- Cognitive dysfunction [52]

Association with mortality — Most observational studies in patients with nondialysis-dependent CKD [53-57] and end-stage kidney disease (ESKD) [58-61] have described a significant association of metabolic acidosis with higher mortality. The following studies are representative:

- In a study of 1240 military veterans with nondialysis-dependent CKD, those whose serum bicarbonate was <22 mEq/L had a significantly higher risk of mortality as compared with

those whose bicarbonate was 26 to 29 mEq/L (adjusted hazard ratio 1.43, 95% CI 1.10-1.87) [54].

- In 3939 patients from the Chronic Renal Insufficiency Cohort (CRIC) with CKD stages 2 to 4, the four-year mortality rate was higher among those with a serum bicarbonate less than or equal to 22 as compared with greater than 26 mEq/L (approximately 3 versus 2 percent) [56]. However, this association was not significant after controlling for other risk factors.

- In a cohort of 2318 kidney transplant recipients, a serum bicarbonate <22 mEq/L was associated with a threefold higher multivariable adjusted risk of all-cause mortality [23].

- In a study of 56,385 patients on maintenance hemodialysis, the two-year mortality rate was lowest among those whose serum bicarbonate was 17 to 19 mEq/L [60]. However, as noted above, most patients receiving dialysis have a low serum bicarbonate; normal bicarbonate concentrations usually reflect reduced protein intake and malnutrition. After controlling their analysis for markers of poor nutrition, the authors found that patients who had a serum bicarbonate <22 mEq/L had a significantly greater mortality risk as compared with patients who had higher values.

Association with cardiovascular outcomes — The association of metabolic alkalosis with mortality may be explained at least in part by effects on cardiovascular disease. Some, but not all, observational studies support this hypothesis [56,62,63]. The following represent the range of findings:

- In the Systolic Blood Pressure Reduction Intervention Trial (SPRINT), a serum bicarbonate <22 mEq/L was associated with a 54 percent higher relative risk of a composite cardiovascular outcome (including acute coronary syndrome, stroke, acute heart failure, and cardiovascular death) [63]. Data from a large administrative database produced similar conclusions [62].

- Although there was no association between metabolic acidosis and cardiovascular disease in the CRIC cohort [56], these findings may have been confounded by an association of heart failure with higher serum bicarbonate [64].

Association with progression of CKD — Observational studies in patients with nondialysis-dependent chronic kidney disease (CKD) have found that lower serum bicarbonate concentrations, higher anion gap, higher net endogenous acid production, high dietary acid load, and inability to excrete acid are all associated with a higher risk of progressive kidney function loss [54,55,57,65-76]. The following examples illustrate the range of findings:

- Among 1094 patients with CKD participating in the African American Study of Kidney Disease (AASK) trial, kidney event rates (defined as ESKD, a 50 percent decline in glomerular filtration rate [GFR], or a 25 mL/min decline in GFR from baseline) were approximately three times higher in patients whose serum bicarbonate was <20 as compared with >25 mEq/L [55]. After controlling for other factors, a serum bicarbonate of 28 to 30 mEq/L was associated with the lowest risk for kidney events.

- Among 5422 patients followed in an urban medical clinic, those whose serum bicarbonate was ≤22 as compared with 25 to 26 mEq/L had a significantly increased risk for progression of kidney disease (defined as a 50 percent reduction in estimated GFR [eGFR] or reaching an eGFR less than 15 mL/min/1.73 m^2; adjusted hazard ratio 1.54, 95% CI 1.13-2.09) [65].

- Among 3939 patients in the CRIC study mentioned above, lower serum bicarbonate was significantly associated with a higher risk of developing ESKD or having a 50 percent decline in eGFR (adjusted hazard ratio 0.97 for every 1 mEq/L lower serum bicarbonate, 95% CI 0.94-0.99) [56].

- Among 632 patients enrolled in the AASK trial, higher net endogenous acid production was associated with a faster annual decline of measured GFR [69].

- In two large cohorts of children with CKD, lower serum bicarbonate was associated with a higher risk of CKD progression [77,78]; in addition, patients whose bicarbonate was corrected had a slower rate of progression than those who had persistently low serum bicarbonate [78].

Lower serum bicarbonate is also associated with progressive loss of kidney function among individuals **without** CKD [79,80]. As an example, in a multiethnic population of 5810 individuals with a baseline eGFR ≥60 mL/min/1.73 m^2, those whose serum bicarbonate was <21 mEq/L had a significantly increased risk for having rapid kidney function decline (ie, eGFR loss of more than 5 percent per year) compared with those whose serum bicarbonate was 23 to 24 mEq/L (adjusted hazard ratio 1.35, 95% CI 1.05-1.73) [79].

Potential mechanisms for progression of CKD — The reason for the association between metabolic acidosis and more rapid progression of chronic kidney disease (CKD) is not clear and may not be causal. If causal, however, it may be due at least in part to the adaptive response of surviving nephrons to the loss of their neighboring nephrons [81-88]. Metabolic acidosis promotes an adaptive increase in ammonium excreted per nephron, which is associated with activation of the complement system, activation of the renin-angiotensin system, and increased renal production of endothelin-1, all of which may produce tubulointerstitial inflammation and

chronic damage to the kidney [89]. (See 'Development of metabolic acidosis' above and "Secondary factors and progression of chronic kidney disease".)

Endothelin-1 may play an important role in the nephrotoxicity associated with metabolic acidosis. In rats, for example, metabolic acidosis induced through either partial nephrectomy or dietary supplementation increases renal endothelin-1 and promotes progressive kidney functional decline in the rat [86,90]. Both endothelin receptor antagonists and bicarbonate supplementation ameliorated the nephrotoxicity of the acidosis. However, the benefit was greater with bicarbonate supplementation, suggesting that other factors in addition to endothelin-1 contribute to the kidney injury.

Another potential mechanism involves activation of the renin-angiotensin system, which is important for urinary acidification but can also result in proteinuria [82], kidney damage, and progressive CKD [82,90].

TREATMENT OF METABOLIC ACIDOSIS IN CKD

Children with acidemia are treated with bicarbonate therapy because acidemia impairs normal growth [91]. Traditionally, however, exogenous alkali has not been used to treat the generally mild acidemia (arterial pH generally above 7.25) in asymptomatic adults with kidney disease. Reluctance to treat adults with sodium bicarbonate may reflect concerns that the increased sodium intake will exacerbate the volume expansion and hypertension that are commonly present in chronic kidney disease (CKD), or that raising the pH can precipitate tetany in patients with hypocalcemia.

However, sodium bicarbonate produces less sodium retention and blood pressure elevation than comparable doses of sodium chloride [92,93], and may have little if any effect on blood pressure compared with no alkali therapy [94,95]. The factors responsible for this difference between bicarbonate and chloride are incompletely understood, although a similar phenomenon can be demonstrated in patients with salt-sensitive hypertension who have normal kidney function. (See "Salt intake and hypertension".)

Therapeutic approach — We broadly agree with 2013 Kidney Disease Improving Global Outcomes (KDIGO) and the 2020 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines that, in patients with CKD and metabolic acidosis, alkali therapy (usually with sodium bicarbonate) be used to maintain the serum bicarbonate concentration in the normal range (23 to 29 mEq/L or 24 to 26 mEq/L, respectively) [96-99]. The upper bound of this target range is

less clear than the lower bound, especially since the association between serum bicarbonate and mortality appears to be U shaped [54]. (See 'Association with mortality' above.)

Alkali therapy usually consists of sodium bicarbonate or sodium citrate (citrate is rapidly metabolized to bicarbonate), typically in a dose of 0.5 to 1 mEq/kg per day. Sodium citrate should be avoided in patients also taking aluminum-containing antacids.

Evidence supporting bicarbonate therapy — In addition to the adverse physiologic consequences linked to metabolic acidosis in CKD and the observational studies showing an association of metabolic acidosis with mortality and CKD progression, the rationale behind our approach is based upon randomized trials showing benefits of alkali therapy on:

- Progression of CKD
- Bone health
- Nutritional status

Additional benefits of metabolic acidosis therapy may also include improvement in insulin sensitivity and a reduction in atherogenic lipid levels [100,101], although further research is needed to corroborate these findings.

Slowing of CKD progression — Bicarbonate supplementation appears to slow the progression of CKD [102-110]. In a two-year, single-center, open-label trial of 134 patients with stage 4 CKD (creatinine clearance 15 to 30 mL/min/1.73 m^2) and metabolic acidosis (baseline serum bicarbonate 16 to 20 mEq/L) randomly assigned to oral sodium bicarbonate, beginning with a dose of 600 mg three times daily and increased as needed to achieve a serum bicarbonate ≥23 mEq/L, or to no treatment, the following significant benefits of bicarbonate supplementation were observed [102]:

- A lower risk of end-stage kidney disease (ESKD) – 6.5 versus 33 percent
- A lower mean rate of decline of creatinine clearance – 1.88 versus 5.93 mL/min/1.73 m^2 per year
- A lower risk of having an annual decline in creatinine clearance of at least 3 mL/min/1.73 m^2 – 9 versus 45 percent

Patients in the bicarbonate group were more likely to develop edema and worsened hypertension requiring intensification of therapy, although this difference was not statistically significant.

These results were confirmed by a larger, open-label trial of 740 patients with stage 3, 4, or 5 CKD (mean creatinine clearance of 30 mL/min) and a mean baseline serum bicarbonate of 21.5 mmol/L [108]. Patients were assigned to oral sodium bicarbonate or no treatment. At three years, the following significant benefits of bicarbonate therapy were observed:

- A lower all-cause mortality – 3.1 versus 6.8 percent
- A lower risk of requiring kidney replacement therapy – 6.9 versus 12.3 percent
- A lower risk of a doubling of serum creatinine – 6.6 versus 17 percent

Sodium bicarbonate therapy was not associated with higher blood pressure, increase in body weight, or increase in hospitalization rates.

While the results of these trials are compelling, the number of ESKD events was relatively small, the beneficial effects of bicarbonate were considerably larger than the effects of most rigorously studied interventions, and both trials had open-label designs; these considerations limit the credibility of the findings. However, provided that bicarbonate therapy does not substantially increase the rate of uncontrolled hypertension nor impair compliance with other therapies in patients with CKD, there seems to be little downside to its use while awaiting additional data to confirm the clinical benefit.

Two other trials suggested a benefit from alkali therapy in patients with mild CKD who did not have metabolic acidosis (serum bicarbonate 22 to 24 mEq/L). The first trial randomly assigned 120 patients with a mean estimated glomerular filtration rate (eGFR) of 75 mL/min/1.73 m^2 and an albumin-to-creatinine ratio >300 mg/g to sodium bicarbonate, sodium chloride (each at 0.5 mEq/kg per day), or matching placebo [103]. At five years, the annual rate of decline in eGFR was slightly but significantly smaller in the sodium bicarbonate group (-1.5 min/min/1.73 m^2) as compared with the sodium chloride and placebo groups (-2.0 and -2.1 mL/min/1.73 m^2, respectively). The second trial randomly assigned 108 patients with stage 3 CKD (eGFR 30 to 59 mL/min/1.73 m^2) to usual care or to alkali therapy achieved with sodium bicarbonate supplements or base-producing fruits and vegetables. At three years, eGFR decreased to a lesser extent in the high alkali group [106].

In a meta-analysis of 15 trials, including 2445 patients with CKD, alkali therapy resulted in improvement in a slower decline in eGFR (mean difference -2.6 mL/min/1.73 m^2, 95% CI -4.6 to -0.7) and a lower risk of ESKD (relative risk 0.53, 95% CI 0.32-0.89) [110]. The evidence was judged to be of low quality.

Prevention of bone buffering — Bone buffering of some of the excess hydrogen ions is associated with the release of calcium and phosphate from bone [11,97,111]. Hypocalciuria is one of the earliest findings in kidney failure; therefore, calcium released from bone is probably lost in stool. Preventing this change may minimize the degree of negative calcium balance and prevent or delay the progression both of osteopenia and of hyperparathyroid bone disease [11,112-114]. (See "Overview of chronic kidney disease-mineral and bone disorder (CKD-MBD)".)

A study of 21 patients on maintenance hemodialysis suggested that correction of metabolic acidosis improves metabolic bone disease. Patients were randomly assigned to therapy with a standard bath or a bicarbonate-supplemented bath [112]. The predialysis plasma bicarbonate concentrations were 15.6 and 24 mEq/L, respectively. At 18 months, osteoid and osteoblastic surfaces and the plasma parathyroid hormone (PTH) level increased in the control group but were unchanged in patients in whom the acidosis was corrected. A similar benefit in terms of improved PTH control with bicarbonate therapy was observed in a randomized trial of patients with mild to moderate CKD [113].

Correction of acidosis may act in part by diminishing the stimulus to hyperparathyroidism [44]. This mechanism was suggested in a report of eight patients on maintenance hemodialysis [44]. Enhanced therapy of acidosis with bicarbonate-supplemented dialysate (40 mEq/L) resulted in increased sensitivity of the parathyroid glands to ionized calcium.

By contrast, a placebo-controlled trial of 149 patients with stage 3 or 4 CKD (eGFR 15 to 59 mL/min/1.73 m^2) and a baseline mean serum bicarbonate of 22 mmol/L found no benefit of bicarbonate supplementation (0.4 mEq per kg of ideal body weight daily) on bone mineral density and muscle function at one year [115], despite a significant increase in serum bicarbonate levels. The lack of benefit on bone density and muscle function may have been because many of the patients had a normal serum bicarbonate at baseline.

Improved nutritional status and lean body mass — Uremic acidosis can increase skeletal muscle breakdown and diminish albumin synthesis, leading to muscle wasting and muscle weakness [116-120]. The hypercatabolic state appears to be mediated by acidosis, acting in part by increased release of cortisol and diminished release of insulin-like growth factor (IGF) 1 [116-118,121] and by inhibition of insulin signaling through phosphoinositide 3-kinase [35], leading to loss of lean body mass and muscle weakness [116]. The degree of muscle breakdown may be exacerbated by institution of a low-protein diet, which is occasionally used in an attempt to minimize progressive kidney injury [116]. (See "Dietary recommendations for patients with nondialysis chronic kidney disease".)

These abnormalities in muscle function and/or albumin metabolism can be reversed by alkali therapy to correct the acidosis [118,122,123], including optimal correction of acidosis in patients undergoing chronic dialysis [124,125]. In the previously cited randomized trial, bicarbonate significantly improved dietary protein intake and decreased protein catabolism in parallel with increased serum albumin and lean body mass in patients with CKD [102]. In a small pilot study, the administration of sodium bicarbonate to 20 patients with an eGFR of 15 to 45 ml/min/1.73 m^2 resulted in a dose-dependent improvement in muscle strength [122]. Another small trial of patients with CKD and metabolic acidosis found that bicarbonate supplementation increased muscle mass but not muscle strength [123].

Alkali therapy may also be beneficial in children in whom acidemia can contribute to the impairment in growth [91,119]. Experimental studies have identified a number of abnormalities in the growth hormone axis that are induced by metabolic acidosis and may contribute to the inhibition of growth. These include impaired pulsatile growth hormone secretion, decreased production and plasma levels of IGF-1 due at least in part to an impaired hepatic response to circulating growth hormone, and reduced hepatic mRNA for the growth hormone receptor [121,126-128]. Improvement in growth hormone sensitivity has also been described in adults [129]. (See "Growth failure in children with chronic kidney disease: Treatment with growth hormone".)

Choice of therapy — Alkali therapy usually consists of sodium bicarbonate or sodium citrate (citrate is rapidly metabolized to bicarbonate), typically in a dose of 0.5 to 1 mEq/kg per day (table 2) [130]. We generally prefer citrate, which does not produce the bloating associated with bicarbonate therapy. However, sodium citrate should be avoided in patients also taking aluminum-containing antacids, as citrate markedly enhances intestinal aluminum absorption both by keeping aluminum soluble (via the formation of aluminum citrate) and by complexing with calcium in the intestinal lumen; the ensuing fall in the free calcium concentration can increase the permeability of the tight junctions of bowel epithelia, a change that can markedly enhance the passive absorption of aluminum (figure 2) [131,132]. As a result, patients taking aluminum-containing antacids to control hyperphosphatemia are at increased risk of developing aluminum intoxication if they are treated with sodium citrate [132,133]. However, aluminum-based phosphate binders are seldom used. The specific regimen for treating metabolic acidosis in patients with CKD should be individualized based upon patient tolerance, affordability, and individual comorbidities and biochemical characteristics.

Metabolic acidosis can also be treated using calcium citrate, calcium acetate, calcium carbonate, or a diet that is high in alkaline foods and low in dietary acid (ie, an alkaline-ash diet). A small study of normokalemic patients with stage 4 CKD showed that dietary modification to increase

consumption of fruits and vegetables (an alkaline-ash diet) increased the serum bicarbonate above baseline levels but to a lesser degree than sodium bicarbonate supplementation [134]. In a larger trial, 108 patients with CKD and metabolic acidosis were randomly assigned to a diet of fruits and vegetables, bicarbonate supplementation, or usual care [135]. The fruit and vegetable diet and bicarbonate supplementation had similar effects on the serum bicarbonate concentration and decline in eGFR; both were superior to usual care. A post-hoc analysis of this trial found that the fruit and vegetable diet was no more costly than bicarbonate supplementation and might have other health benefits, such as fewer cardiovascular events [136]. Other eating plans that lower the dietary acid load may similarly mitigate metabolic acidosis [137-139]. Alkaline-ash diets are generally high in potassium, which may be associated with greater risk of hyperkalemia in patients with reduced kidney function [140]. However, the concomitant alkalinizing effect and the decrease in intestinal transit time that is typical of such diets may mitigate their impact on the serum potassium concentration [141].

Administration of the potassium binder sodium zirconium cyclosilicate for the treatment of hyperkalemia may result in improved serum bicarbonate by virtue of also capturing intestinal ammonium [142].

An additional, investigational method to increase serum bicarbonate is the oral administration of a nonabsorbable hydrochloric acid binder. In a trial of 217 patients with a mean baseline eGFR of 29 mL/min/1.73 m^2 and mean baseline serum bicarbonate concentration of 17 mEq/L, administration of veverimer (a sodium-free oral hydrochloric acid binder) for 12 weeks increased serum bicarbonate (4.5 versus 1.7 mEq/L) and the proportion of patients attaining a serum bicarbonate of at least 22 mEq/L (50 versus 17 percent), compared with placebo [143]. Normal bicarbonate concentrations were maintained at one year in patients who continued veverimer [144]. A meta-analysis that pooled data from three trials reported a mean increase in serum bicarbonate of 3.1 mEq/L (95% CI, 2.4-3.8 mEq/L) and improvement in physical function in patients treated with veverimer [145].

In patients on maintenance dialysis, an alternative method to correct the metabolic acidosis is to increase the bicarbonate concentration of the dialysate [112,133]. Levels as high as 42 mEq/L may be required with hemodialysis to prevent predialysis acidosis. When implemented correctly, this regimen is generally well tolerated and does not induce significant postdialysis alkalosis [146]. However, it is possible that dialysate preparations containing higher amounts of bicarbonate equivalents (such as acetate or citrate) could induce significant metabolic alkalosis [147].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Fluid and electrolyte disorders in adults".)

SUMMARY AND RECOMMENDATIONS

- Acid-base balance is normally maintained by the renal excretion of the daily acid load; elimination of this acid load is achieved by the urinary excretion of hydrogen ions, both as titratable acidity and as ammonium. Near-normal balance can be maintained even if the acid load is modestly increased since acid excretion rises appropriately, primarily via increased ammonium production and excretion (figure 1). (See 'Acid-base balance in CKD' above.)

- As the number of functioning nephrons declines in chronic kidney disease (CKD), acid excretion is initially maintained by an increase in the ammonium excreted per nephron. However, total ammonium excretion begins to fall when the glomerular filtration rate (GFR) is below 40 to 50 mL/min. As a result, CKD leads to retention of hydrogen ions. The retained acid is buffered by bicarbonate in the extracellular fluid, tissue buffers, and bone. With worsening kidney function, however, progressive metabolic acidosis can develop. (See 'Development of metabolic acidosis' above.)

- Chronic metabolic acidosis in patients with CKD may produce a variety of pathophysiologic changes (see 'Consequences of metabolic acidosis in CKD' above):
  - Bone resorption and osteopenia
  - Increased muscle protein catabolism
  - Aggravation of secondary hyperparathyroidism
  - Reduced respiratory reserve and exhaustion of body buffer systems, resulting in increased severity of acute intercurrent illnesses
  - Reduced Na^+-K^+-ATPase activity in red blood cells and myocardial cells, which could impair myocardial contractility and produce congestive heart failure
  - Endocrine disorders such as resistance to growth hormone, insulin resistance, and hypertriglyceridemia
  - Systemic inflammation

- Hypotension and malaise
- Cognitive dysfunction

- Observational studies in patients with nondialysis-dependent CKD and end-stage kidney disease (ESKD) have described a significant association of metabolic acidosis with higher mortality. (See 'Association with mortality' above.)

- Observational studies in patients with nondialysis-dependent CKD have found that lower serum bicarbonate concentrations are associated with a higher risk of progressive kidney function loss. The reason for this association is not clear, but several mechanisms have been proposed. (See 'Association with progression of CKD' above and 'Potential mechanisms for progression of CKD' above.)

- Our approach to therapy of metabolic acidosis in patients with CKD (described in the next bullet) is based upon randomized trials showing benefits of alkali therapy on (see 'Evidence supporting bicarbonate therapy' above):
  - Progression of CKD (see 'Slowing of CKD progression' above)
  - Bone health (see 'Prevention of bone buffering' above)
  - Nutritional status

- In patients with CKD who have metabolic acidosis, we suggest alkali therapy (**Grade 2B**). We aim to maintain the serum bicarbonate concentration in the normal range. Alkali therapy in such patients usually consists of sodium bicarbonate or sodium citrate (citrate is rapidly metabolized to bicarbonate), typically in a daily dose of 0.5 to 1 mEq/kg per day. Sodium citrate should be avoided in patients also taking aluminum-containing antacids. In patients on maintenance dialysis, an alternative method to correct the metabolic acidosis is to increase the bicarbonate concentration in the dialysate. (See 'Therapeutic approach' above and 'Choice of therapy' above.)

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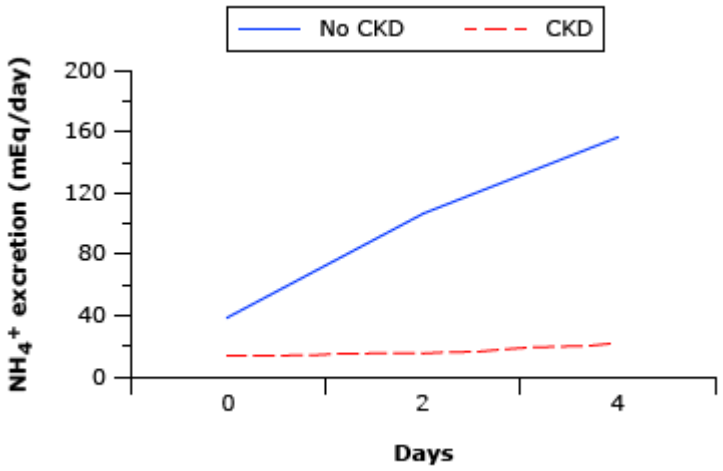
Topic 2293 Version 29.0

GRAPHICS

Impaired ammonium excretion in chronic kidney disease



Urinary excretion of NH_4^+ in patients without CKD (solid line) and patients with CKD (dashed line) at baseline and after an acid load. The plasma bicarbonate concentration fell from 27 to 22 mEq/L in patients without CKD and from 22 to 14 mEq/L in CKD following the acid load. NH_4^+ excretion rose markedly in patients without CKD but was low at baseline and did not increase in the patients with CKD despite a greater degree of metabolic acidosis.

CKD: chronic kidney disease; NH_4^+: ammonium.

Graphic 60880 Version 6.0

Chronic kidney disease classification based upon glomerular filtration rate and albuminuria

GFR stages	GFR (mL/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60 to 89	Mildly decreased
G3a	45 to 59	Mildly to moderately decreased
G3b	30 to 44	Moderately to severely decreased
G4	15 to 29	Severely decreased
G5	<15	Kidney failure (add D if treated by dialysis)
Albuminuria stages	**AER (mg/day)**	**Terms**
A1	<30	Normal to mildly increased (may be subdivided for risk prediction)
A2	30 to 300	Moderately increased
A3	>300	Severely increased (may be subdivided into nephrotic and nonnephrotic for differential diagnosis, management, and risk prediction)

The cause of CKD is also included in the KDIGO revised classification but is not included in this table.

GFR: glomerular filtration rate; AER: albumin excretion rate; CKD: chronic kidney disease; KDIGO: Kidney Disease Improving Global Outcomes.

Data from:

1. *KDIGO. Summary of recommendation statements. Kidney Int 2013; 3 (Suppl):5.*
2. *National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39 (Suppl 1):S1.*

Graphic 70597 Version 17.0

Oral bicarbonate and bicarbonate equivalent salts used for systemic and/or urinary alkalinization

Generic name	Common brand names (US) and form	Electrolyte and bicarbonate content*
Potassium citrate	Urocit-K (tablet, controlled release)	Tablet: Each pill contains 5, 10, or 15 mE potassium and delivers the equivalent o 5, 10, or 15 mEq bicarbonate.
Potassium citrate-citric acid	Polycitra K, Cytra-K (powder or solution)	Powder: Each packet contains 30 mEq potassium and delivers the equivalent o 30 mEq of bicarbonate. Solution: Each 5 mL contains 10 mEq potassium and delivers the equivalent o 10 mEq bicarbonate.
Sodium citrate-citric acid	Bicitra, Cytra-2, Oracit, Shohl's solution modified (solution)	Solution: Each 5 mL contains 5 mEq sodium and delivers the equivalent of 5 mEq bicarbonate.
Sodium citrate-potassium citrate-citric acid	Polycitra, Cytra-3 (solution, syrup)	Solution (syrup): Each 5 mL contains 5 mEq potassium and 5 mEq sodium and delivers equivalent of 10 mEq bicarbonate.
Potassium bicarbonate-potassium citrate	Klor-Con/EF, Effer-K, K-Effervescent (effervescent tablet)	Effervescent tablet (diluted in water): Each tablet contains 10, 20, or 25 mEq potassium and delivers approximately 10, 20 or 25 mEq bicarbonate or equivalent.
Sodium bicarbonate	Tablet	Tablet: Each 650 mg tablet contains 7.7 mEq of sodium and 7.7 mEq of bicarbonate (325 mg tablet contains 3.8 mEq of bicarbonate).
	Baking soda (powder)	Powder: One-half teaspoonful (2.4 grams) contains approximately 29 mEq of sodium and 29 mEq bicarbonate (roughly equivalent to three 650 mg sodium bicarbonate tablets).[1]

For approach to product selection, dosing recommendations, and target urine pH for alkalinization therapy, refer to separate UpToDate clinical reviews of uric acid nephrolithiasis and cystine stones.

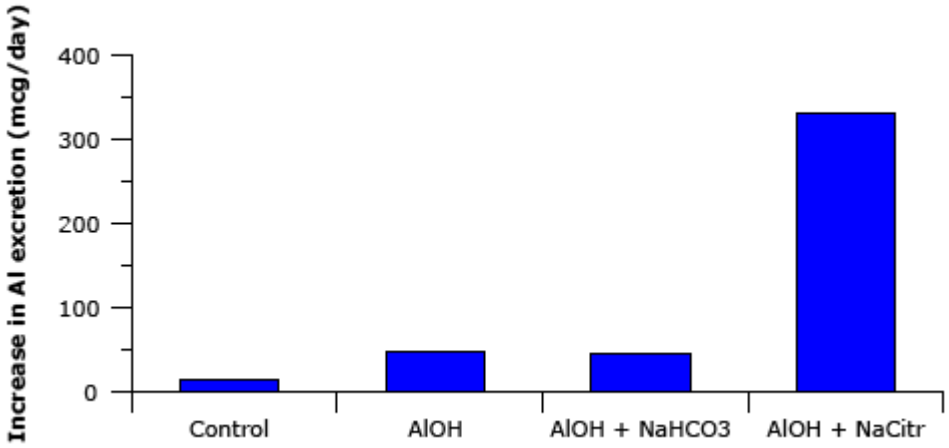
* Orally administered citrate is a bicarbonate equivalent.

Reference:

1. *Al-Abri SA, Kearney T. Baking soda misuse as a home remedy: case experience of the California Poison Control System. J Clin Pharm Ther 2014; 39:73.*

Graphic 118006 Version 7.0

Increase in urinary aluminum excretion with administration of aluminum hydroxide, sodium bicarbonate, and citrate



Increase in urinary aluminum excretion in subjects on a control diet and those given AlOH alone or with sodium bicarbonate or sodium citrate. Aluminum excretion rose markedly in the last group due to increased intestinal absorption.

Al: aluminum; AlOH: aluminum hydroxide; NaHCO3: sodium bicarbonate; NaCitr: sodium citrate.

Data from: Walker JA, Sherman RA, Cody RF. The effect of oral bases on enteral aluminum absorption. Arch Intern Med 1990; 150:2037.

Graphic 55777 Version 5.0