Metabolic Acidosis and Chronic Kidney Disease

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Before You Start: Facts You Need to Know

- A reduction in bicarbonate and blood pH (metabolic acidosis) is a common but not inevitable occurrence with CKD.
- Metabolic acidosis usually occurs when the estimated glomerular filtration rate (eGFR) falls below 25–30 mL/min but can occur earlier with certain disorders which affect renal function such as hyporeninemic hypoaldosteronism.
- Major adverse effects of untreated metabolic acidosis include muscle wasting, bone disease, progression of CKD, and increased mortality.
- Acid-base parameters including pH, PCO_2, and serum [HCO_3^-] should be checked upon first evaluation, and then serum bicarbonate should be checked at least annually in stage 3 CKD and approximately every 3 months in stages 4 and 5 CKD.
- Treatment of metabolic acidosis with base leads to slowing of progression of CKD, decreased muscle wasting, and improvement in bone disease.
- Recommendations are to initiate base treatment with serum bicarbonate ≤22 mEq/L, although the precise bicarbonate range to be targeted remains under study.

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7.1 Introduction

A decrease in serum bicarbonate in association with a reduction in blood pH (metabolic acidosis) is a frequent although not inevitable occurrence in progressive chronic kidney disease (CKD) [1]. The hypobicarbonatemia usually develops when glomerular filtration rate (GFR) falls below 25–30 mL/min. It is usually mild in degree with serum bicarbonate ranging from 15 to 23 mmol/L [1]. However, despite being mild, it can be associated with several adverse effects including muscle wasting, bone disease, progression of CKD, and increased mortality [2]. Although traditionally it has been considered to be a high anion gap metabolic acidosis, it can present as a

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nongap, mixed nongap and high anion gap, or high anion gap alone [3, 4]. CKD is the most common cause of chronic metabolic acidosis; therefore, the clinician must know how to recognize this disorder and distinguish it from other causes of metabolic acidosis. This chapter reviews the genesis of the acidosis of CKD, the impact of this acid-base disorder on cellular function, and the present recommendations for its evaluation and treatment.

7.2 Pathophysiology

The serum bicarbonate is normally maintained between 23 and 29 mEq/L (mean, 24 mmol/L) and blood pH between 7.38 and 7.42 (mean, 7.40). As shown in Fig. 7.1, in adults approximately 1 mEq/kg body weight of fixed acid is generated from the combined effects of the metabolism of ingested food stuffs and the absorption of organic anions from the gastrointestinal tract. The kidney must generate equivalent quantities of base to neutralize this endogenous acid load and also reabsorb the large quantity of bicarbonate filtered by the glomerulus (~4,500 mEq/day) to maintain acid-base balance. Excretion of the acid load by the kidneys occurs via urinary excretion of hydrogen ions, both in the form of titratable acid ($H_2PO_4^-$) (approximately 1/3 of the acid load) and as ammonium (approximately 2/3 of the acid load). However, an increase in urinary ammonium excretion (NH_4) accounts for the vast majority of the increased renal acid excretion observed in response to an acid load.

A defect in bicarbonate reabsorption observed in some patients with CKD can contribute to the development of metabolic acidosis [1]. However, the major mechanism producing metabolic acidosis with CKD is decreased ammonium excretion. This decrease in ammonium excretion is primarily a consequence of a reduction in the number of functioning nephrons, as ammonium excretion per residual nephron is actually substantially increased above normal. As a result, net acid excretion falls below acid production leading to positive hydrogen ion balance. Studies in patients with a stable, albeit reduced GFR, have demonstrated that they are actually in continual positive hydrogen balance despite having a stable serum bicarbonate concentration. The stability of serum bicarbonate at any given level of GFR has been attributed to buffering of retained hydrogen by body buffers, primarily those residing in bone [5]. This process might contribute to some of the adverse effects of metabolic acidosis.

In some patients, a superimposed defect in tubular hydrogen secretion and/or ammonia production can lead to a more severe metabolic acidosis or its appearance earlier in the course of CKD. The most common explanation for this exacerbation of metabolic acidosis is a reduction in aldosterone synthesis found with hyporeninemic hypoaldosteronism. However, it can also be due to impaired proton excretion resulting from renal damage to the medullary interstitium in

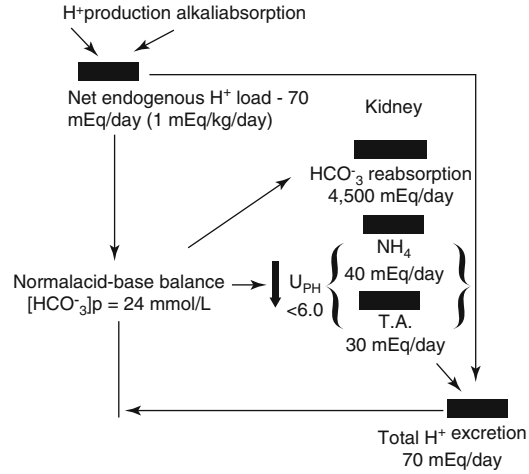

Fig. 7.1 Normal acid-base balance in health. Ingestion of foodstuffs and absorption of base lead to the net production of approximately 1 mEq/kg/day of hydrogen ions in adults. The kidney generates an equivalent quantity of base and also reabsorbs approximately 4,500 mEq of filtered bicarbonate each day to maintain serum bicarbonate concentration at 24 mEq/L. With the development of chronic kidney disease, there is usually a decrease in ammonium excretion leading to positive hydrogen balance and metabolic acidosis. In a small number of patients, there might also be a defect in bicarbonate reabsorption leading to bicarbonaturia

patients with diseases such as sickle cell disease. Hyperkalemia out of proportion to the decrease in GFR accompanying these disorders contributes to the suppression of ammonia production and thereby the development of metabolic acidosis [1].

7.3 Clinical Characteristics

Approximately 80 % of patients with CKD will develop hypobicarbonatemia once GFR falls below 25–30 mL/min [1]. However, a small percentage of patients will maintain a normal serum bicarbonate concentration even in the presence of severe kidney failure (GFR <20 mL/min), findings theoretically consistent with normal acid-base balance. The explanation for this discrepancy is presently unclear. However, it has been recently shown in experimental studies of animals with CKD that acid retention with an increase in interstitial acidity of various tissues can precede an overt fall in serum bicarbonate concentration [6]. These findings might suggest that patients with CKD and normal serum bicarbonate might actually have so-called subclinical metabolic acidosis. Thus, overt metabolic acidosis or so-called subclinical metabolic acidosis might be present in the vast majority of patients with CKD at all stages of renal failure.

When present, the metabolic acidosis is usually mild: serum bicarbonate ranging from 15 to 23 mmol/L and rarely falling below 15 mEq/L in the absence of an increased acid load. There is usually a direct correlation with the severity of kidney failure: the lower the GFR, the more severe the hypobicarbonatemia [1]. However, there can be great variability in the severity of the metabolic acidosis among individuals with similar levels of GFR. This has been attributed, in part, to differences in dietary intake of protein and fruits and vegetables, differences in buffering capacity arising from differences in bone disease, and differences in tubular function [1]. However, the precise explanation for this variability remains to be determined.

Early in the course of CKD, the metabolic acidosis might be of the normal anion gap variety [7]. Subsequently it can evolve into a mixed pattern with both a normal anion gap and a high anion gap metabolic acidosis and then finally a high anion gap metabolic acidosis alone. However, all three patterns can be observed both early and late in the course of CKD [1]. Patients with hyporeninemic hypoaldosteronism or medullary damage and CKD will usually manifest primarily a nongap metabolic acidosis. In addition, serum potassium concentration in these patients will be elevated out of proportion to the decrease in GFR.

Assuming there is no abnormality in renal bicarbonate reabsorption causing urinary bicarbonate wasting, most patients with uncomplicated CKD and hypobicarbonatemia will be able to acidify their urine to a pH <5.5. However, despite the ability to develop a large proton gradient between tubular fluid and blood, urinary ammonium excretion will be low (as reflected by a positive urine anion gap or abnormal urine osmolal gap). This is illustrated in Table 7.1.

Patients with CKD and hyporeninemic hypoaldosteronism will also be able to appropriately acidify their urine making the distinction between these patients and those with CKD alone difficult. On the other hand, those with medullary damage have a defect in urinary acidification with urine pH > 5.5 despite the presence of hypobicarbonatemia [1]. The clinical characteristics of different types of metabolic acidosis observed with CKD are summarized in Table 7.1.

7.4 Assessment of Acid-Base Balance in CKD

Since hypobicarbonatemia is often mild in patients with CKD, it sometimes can be difficult to distinguish the metabolic acidosis of CKD from chronic hypocapnia. Therefore, we recommend blood gases be obtained upon first evaluation of these patients, even if the serum bicarbonate concentration is minimally perturbed.

Table 7.1 Clinical characteristics of disorders associated with metabolic acidosis in patients with chronic kidney disease

Disorder	Electrolyte pattern	Urine NH_4	[a]Urine anion gap and [b]urine osmolal gap	Urine pH	Comments
Chronic kidney disease	Nongap early; mixed pattern, and high anion gap with severe disease	Low	Positive anion gap Low urine osmolal gap	<5.5	Most common cause of metabolic acidosis with kidney disease
Hyporeninemic hypoaldosteronism	Nongap pattern throughout course	Low	Positive anion gap Low urine osmolal gap	<5.5	More frequent in patients with diabetes mellitus, acidosis earlier than predicted on basis of glomerular filtration rate, hyperkalemia common
Renal disorders affecting medullary interstitium	Nongap pattern throughout course	Low	Positive anion gap Low urine osmolal gap	>5.0	Acidosis earlier than predicted based on glomerular filtration rate, hyperkalemia common

[a]Urine anion gap is defined as $Na^+ + K^+ - Cl^-$. In patients with ability to excrete acid appropriately, it is approximately −30 mEq/L, whereas it is positive in patients with impaired ability to excrete acid such as those with CKD

[b]The urine osmolal gap is defined as measured urine osmolality $- 2 \times Na^+ + K^+ +$ urea nitrogen/2.8 + glucose/18. The difference if divided by 2 gives an approximation of NH^4 excretion. In normal patients it increases from 30 mmol/day to more than 150 mmol/day. It is considerably less in patients with impaired acid excretion

Although arterial blood gases are traditionally utilized for this purpose, recent studies have demonstrated that venous blood gases can suffice [8, 9].

Measurement of urine pH in patients with a reduced serum bicarbonate concentration (obtained immediately upon voiding or collected under oil to prevent dissipation of CO_2) can be helpful in distinguishing patients with CKD alone or in combination with hypoaldosteronism from those with medullary damage. Therefore, it can be worthwhile obtaining a measurement of urine pH in patients with hypobicarbonatemia.

Urinary ammonium excretion will be low in all patients with metabolic acidosis arising from kidney dysfunction, and therefore, estimates of urinary ammonium excretion are helpful in distinguishing the acidosis related to the presence of kidney disease to that caused by nonrenal mechanisms. Either indirect estimates of urinary ammonium excretion, such as urine anion gap or osmolal gap, or direct determination of urinary ammonium excretion can be utilized. However, given the complexity of indirect estimates of urinary ammonium excretion, we have found direct measurement of urinary ammonium excretion to be the most cost-effective [4]. In patients in whom kidney dysfunction is the only mechanism underlying the metabolic acidosis, urine ammonium excretion will be considerably less than the normal value of 40 mmol/day. On the other hand, if there is an increased acid load, urinary ammonium excretion can be greater than this value but substantially less than the 200 mmol/day observed in patients with metabolic acidosis and intact kidney function [4].

Once acid-base parameters have been assessed and the presence of metabolic acidosis has been confirmed, blood gases need not be obtained again, but rather serum bicarbonate alone can be monitored. The recommended appropriate time of assessment for this parameter is shown in Table 7.2. If patients are being treated with base or there is a subsequent reduction in GFR, more frequent determinations of serum bicarbonate might be necessary.

7.5 Adverse Effects of Chronic Metabolic Acidosis and Rationale for Treatment

Although chronic metabolic acidosis in CKD has a number of potential adverse effects as summarized in Box 7.1, arguably the most important are acceleration of the progression of CKD, generation or exacerbation of bone disease, increased protein degradation with muscle wasting, impaired protein synthesis with hypoalbuminemia, and increased mortality (Box 7.1).

Both animal and human studies have documented that metabolic acidosis is associated with the progression of CKD [6, 10]. The potential mechanism(s) underlying this effect has been an area of intense investigation and are summarized in Fig. 7.2. Based on elegant studies performed in

Table 7.2 Recommended frequency of measurement of acid-base parameters in patients with chronic kidney disease

CKD stage (G)	GFR range (mL/min/1.73 m^2)	Frequency of measurements
2	60–90	At least every 12 months
3	30–59	At least every 12 months
4	15–29	At least every 3 months
5	<15	At least every 3 months

Measurement of pH, PCO_2, and [HCO_3^-] should be obtained upon first detection of reduction in serum bicarbonate; subsequently only serum bicarbonate needs be measured

Box 7.1. Major Adverse Effects of Chronic Metabolic Acidosis

Progression of chronic kidney disease
Stunted growth in children
Generation or exacerbation of bone disease
Muscle wasting with increased protein degradation
Decreased albumin synthesis with tendency to hypoalbuminemia
Increased mortality

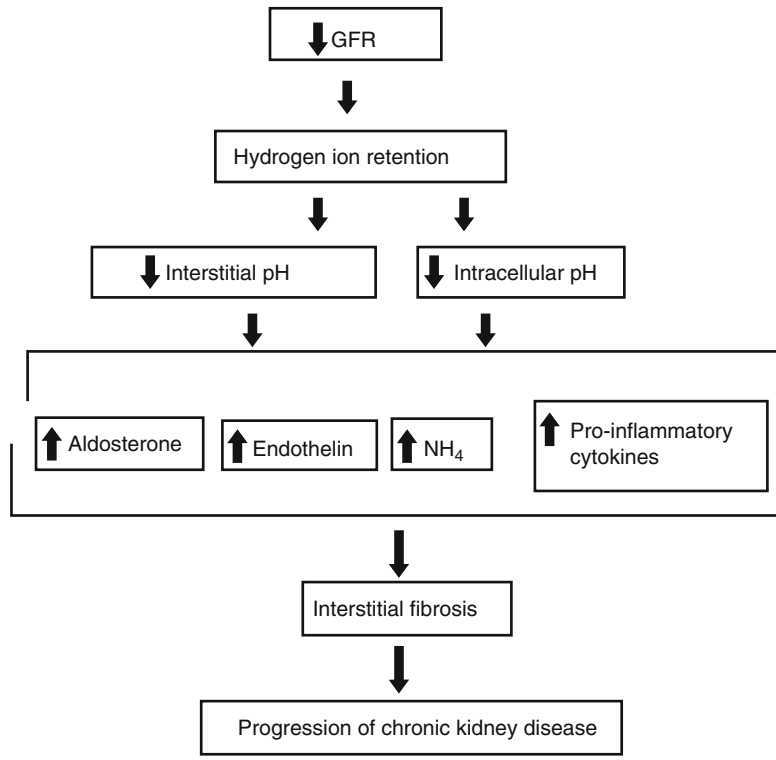

Fig. 7.2 Factors contributing to the progression of chronic kidney disease in patients with metabolic acidosis. Kidney impairment leads to a retention of protons and an increase in interstitial acidity of the kidney, with or without a concomitant fall in serum bicarbonate concentration. The increase in interstitial acidity is associated with a rise in endothelin, aldosterone, and proinflammatory cytokines. There is also stimulation of ammonia production and activation of the complement cascade. All four factors cause tubulointerstitial inflammation and eventual renal fibrosis and decline in GFR

animals and man, it appears that the hydrogen ion retention occurring with CKD leads to an increase in the acidity of the renal interstitium (and presumably intracellular pH of renal tubules) with resultant stimulation of endothelin production [11]. There is also increased production of aldosterone [6, 10] and possibly direct renal synthesis of proinflammatory cytokines [12]. Finally, the increased ammonia production per nephron found with CKD can be associated with activation of the complement cascade. These alterations in hormones, cytokines, and the complement cascade can individually induce tubulointerstitial inflammation and eventually renal fibrosis [10, 13]. Therefore, the composite effects on renal function of the individual changes of these factors are likely to be magnified. Of note, as mentioned previously the alterations in concentrations of endothelin and aldosterone have been reported even when there is little or no change in serum bicarbonate concentration [14]. Whether the changes in proinflammatory cytokines and the activation of the complement cascade noted with enhanced ammonia production are also found without overt hypobicarbonatemia remains unknown. Be that as it may, the data on endothelin and aldosterone suggest that neutralization of the endogenous acid load in patients with CKD might be of value even if serum bicarbonate concentration is normal. As discussed below, the criteria for initiating base therapy remains an area of intense interest.

Recent clinical trials involving small numbers of patients have demonstrated that treatment of the metabolic acidosis complicating advanced CKD with bicarbonate supplementation, sodium citrate, or increased intake of fruits and vegetables appears to slow the progression of CKD [6, 15, 16]. Although these studies support the benefits of base therapy in slowing the progression of CKD, a recent meta-analysis and editorial have called for larger randomized controlled studies to confirm the value of this therapeutic maneuver [17, 18]. At least two such studies are in progress and should provide valuable information about the impact of base therapy on renal progression [18].

Metabolic acidosis of CKD has also been implicated in the stunting of growth in children, as well as the generation of bone disease and/or the exacerbation of preexisting bone disease. The mechanisms underlying this effect are multiple and can include direct buffering of acid by bone, stimulation of parathyroid hormone secretion, or enhancement of the effects of parathyroid hormone on bone [19]. Various types of bone disease can be observed including osteomalacia and osteitis fibrosa cystica. Clinical assessment using x-rays might show changes typical of a specific bone disease, but bone biopsy is the most effective method of confirming the type of bone disease present [5]. Base therapy in individuals with CKD with minimally impaired kidney function and severe CKD receiving chronic dialysis improves growth in children and promotes healing of bone in children and adults [2].

The metabolic acidosis complicating CKD has been shown to result in increased protein degradation and muscle wasting, a process thought to be mediated in part by increased release of cortisol and decreased release of insulin-like growth factor. The muscle wasting associated with metabolic acidosis is improved by alkali therapy, resulting in clinical improvement in muscle strength. However, it is unclear whether reversing muscle wasting and improving muscle strength ultimately translate into improvements in functional status, and this will undoubtedly be a topic of further study. In addition to its effects on lean body mass, administration of base has been demonstrated in some but not all studies to cause an improvement in albumin synthesis and rise in serum albumin concentration.

Many factors affect mortality in patients with CKD. Several studies in patients with CKD, both before and after initiation of chronic maintenance dialysis, have shown a correlation between metabolic acidosis and increased mortality. The mechanism(s) underlying this effect is unclear, but it provides additional reasons for the correction of the metabolic acidosis.

In summary, the development of metabolic acidosis is associated with myriad adverse effects which can have a dramatic effect on the quality of life and mortality of patients with CKD. The clinical studies performed so far indicate base therapy is beneficial in ameliorating many of these

adverse effects but further randomized controlled studies are necessary to provide sufficient information for generation of guidelines.

7.6 Treatment of Metabolic Acidosis of CKD

Based on evidence that metabolic acidosis is associated with progression of chronic kidney disease, production or worsening of bone disease, and increased mortality, several experts have suggested administering base to patients with serum bicarbonate concentrations ≤22 mEq/L [2, 20, 21]. No randomized controlled studies have determined whether this criterion is appropriate and this remains an important issue to assess. In addition, the goal of therapy remains elusive with some [2] recommending normalization of acid-base parameters and others being more noncommittal [21].

Both the precise serum bicarbonate at which to initiate therapy and the goal of therapy are extremely important to determine. Given that some studies have suggested that acid retention can be observed early in the course of CKD which can contribute to progression of CKD (and possibly other adverse effects) despite the absence of overt hypobicarbonatemia [14], there could be an inclination to initiate base therapy even with minimal or no reductions in serum bicarbonate. On the other hand, there remains potential risk of base therapy should it rise even slightly above normal. A recent randomized study indicated that although base therapy slowed progression of CKD, a serum bicarbonate above 24 mEq/L even when produced by measures other than base therapy was associated with a higher prevalence of congestive heart failure [22]. Moreover, others have suggested that an increased serum bicarbonate might provide an alkaline milieu that would predispose to deposition of calcium and phosphorus in tissues with resultant organ dysfunction.

Be that as it may, we conclude that until randomized controlled studies which evaluate the risks and benefits of base therapy with CKD allow for the development of evidence-based guidelines for therapy, we recommend that base be given to all patients with any reduction in serum bicarbonate with the goal of approximating mean normal values of 24 mmol/L. The clinician should be very vigilant to assess patients for possible complications such as volume overload with exacerbation of hypertension and congestive heart failure. Also, strong emphasis should be given on control of serum calcium and phosphorus to lessen the risk of calcifications. An increase in serum bicarbonate above normal should be prevented at all costs because of concern for exacerbation of heart failure or promotion of tissue calcifications.

Studies of different forms of base have indicated that sodium bicarbonate, sodium citrate (Shohl's solution), or dietary fruits and vegetables are all effective in raising serum bicarbonate concentration [15, 23]. Sodium bicarbonate is inexpensive, but has the complication of producing excess carbon dioxide which can be uncomfortable for the patient. The use of enteric-coated tablets might lessen this complication. The administration of sodium citrate (Shohl's solution) is effective and relatively inexpensive, but caution should be advised in patients that are taking aluminum binders. Citrate enhances the gastrointestinal absorption of aluminum. Changes in dietary habits rather than administration of supplements might be the most cost-effective means of raising serum bicarbonate concentration. A reduction in protein intake with increased intake of fruits and vegetables has been shown to be very successful in raising serum bicarbonate with little complications [23]. Given the high potassium content of fruits and vegetables, however, one has to be cautious about a possible increase in serum potassium with this regimen.

No matter what regimen is utilized, an estimate of base deficit should be obtained before embarking on therapy. This can easily be accomplished by subtracting the prevailing serum bicarbonate from the desired serum bicarbonate and multiplying this value by the approximate space of distribution of administered bicarbonate, usually 50 % body weight. This calculation will allow the clinician to estimate not only how much

base should be given but also how long it will take before the target bicarbonate is reached.

The serum bicarbonate can be raised slowly over a matter of days while observing the patient for evidence of various complications particularly exacerbation of hypertension or congestive heart failure. Once the target serum bicarbonate has been reached, base administration can be reduced to values that approximate the rate of endogenous acid production. This precaution will aid in ensuring the clinician does not overshoot the target serum bicarbonate concentration. Recommendations for therapy of patients with CKD are summarized in Box 7.2.

Box 7.2. Recommendations for Treatment of Acidosis in Chronic Kidney Disease [2, 8, 11, 21, 23]

Reduce protein intake to decrease acid generation while maintaining sufficient protein to preserve muscle mass.

Increase slightly intake of fruits and vegetables while avoiding hyperkalemia.

In patients with CKD, but not on maintenance dialysis, base can be given in the form of sodium bicarbonate or sodium citrate (Shohl's solution) once serum bicarbonate falls below the normal mean value of 24 mmol/L.

Calculate the bicarbonate deficit prior to administering base to get an estimate of base requirements. Use 50 % body weight as space of distribution for administered bicarbonate.

Correct the base deficit over 3–4 days. Once serum bicarbonate has reached the target value, reduce base administration to the quantity required to neutralize net endogenous acid load.

Be careful not to raise serum bicarbonate above 24 mmol/L.

Monitor patient for adverse effects of bicarbonate administration such as exacerbation of hypertension and congestive heart failure. If these are present, reduce dosage accordingly.

Conclusions

Acid retention is a common complication of chronic progressive kidney disease. This often leads to the development of metabolic acidosis. Although the acidosis can be mild, it can adversely affect several organ systems and thereby be an important contributory factor to the signs and symptoms of CKD. Several important questions remain unanswered that are relevant to the diagnosis and treatment of this disorder. Is base treatment beneficial in patients with early CKD in the absence of a fall in serum bicarbonate concentration? What serum bicarbonate should be targeted? What are the complications of base therapy? The answers to these questions should facilitate the development of evidence-based guidelines for the treatment of metabolic acidosis of CKD and aid in the prevention of progression of CKD and amelioration of some of its complications.

Before You Finish: Practice Pearls for the Clinician

- Alkali therapy should be used to maintain a serum bicarbonate of approximately 24 mEq/L.
- Commonly used alkalis include sodium bicarbonate and sodium citrate.
- Sodium bicarbonate can be given at a daily dose of 0.5–1 mEq/kg/day, although it can cause gastrointestinal discomfort from generated CO_2.
- Sodium citrate (Shohl's solution) can also be used, although it should be avoided in patients taking aluminum-containing antacids.

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References

1. Kraut JA, Kurtz I. Metabolic acidosis of CKD: diagnosis, clinical characteristics, and treatment. Am J Kidney Dis. 2005;45(6):978–93.

2. Kraut JA, Madias NE. Consequences and therapy of the metabolic acidosis of chronic kidney disease. Pediatr Nephrol. 2011;26(1):19–28.
3. Kraut JA, Madias NE. Serum anion gap: its uses and limitations in clinical medicine. Clin J Am Soc Nephrol. 2007;2(1):162–74.
4. Kraut JA, Madias NE. Differential diagnosis of non-gap metabolic acidosis: value of a systematic approach. Clin J Am Soc Nephrol. 2012;7(4): 671–9.
5. Kraut JA. Disturbances of acid–base balance and bone disease in end-stage renal disease. Semin Dial. 2000;13:261–5.
6. Wesson DE, Simoni J. Acid retention during kidney failure induces endothelin and aldosterone production which lead to progressive GFR decline, a situation ameliorated by alkali diet. Kidney Int. 2010;78(11): 1128–35.
7. Widmer B, Gerhardt RE, Harrington JT, Cohen JJ. Serum electrolytes and acid base composition the influence of graded degrees of chronic renal failure. Arch Intern Med. 1979;139:1099–102.
8. Kraut JA, Madias NE. Metabolic acidosis: pathophysiology, diagnosis and management. Nat Rev Nephrol. 2010;6(5):274–85.
9. Kraut JA, Madias NE. Treatment of acute metabolic acidosis: a pathophysiologic approach. Nat Rev Nephrol. 2012;8(10):589–601.
10. Kraut JA. Effect of metabolic acidosis on progression of chronic kidney disease. Am J Physiol. 2011;300(4): F828–9.
11. Goraya N, Wesson DE. Does correction of metabolic acidosis slow chronic kidney disease progression? Curr Opin Nephrol Hypertens. 2013;22(2):193–7.
12. Raj S, Scott DR, Nguyen T, Sachs G, Kraut JA. Acid stress increases gene expression of proinflammatory cytokines in Madin-Darby canine kidney cells. Am J Physiol Renal Physiol. 2013;304(1):F41–8.
13. Scialla JJ, Anderson CA. Dietary Acid load: a novel nutritional target in chronic kidney disease? Adv Chronic Kidney Dis. 2013;20(2):141–9.
14. Wesson DE, Simoni J, Broglio K, Sheather SJ. Acid retention accompanies reduced GFR in humans and increases plasma levels of aldosterone and endothelin. Am J Physiol. 2011;300:F830–7.
15. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol. 2009;20:2075–84.
16. Goraya N, Simoni J, Jo C, Wesson DE. Dietary acid reduction with fruits and vegetables or bicarbonate attenuates kidney injury in patients with a moderately reduced glomerular filtration rate due to hypertensive nephropathy. Kidney Int. 2012;81(1):86–93.
17. Susantitaphong P, Sewaralthahab K, Balk EM, Jaber BL, Madias NE. Short- and long-term effects of alkali therapy in chronic kidney disease: a systematic review. Am J Nephrol. 2012;35(6):540–7.
18. Kraut JA, Madias NE. Association of serum bicarbonate with clinical outcome in CKD: could an increase in serum bicarbonate be a double edge sword. Am J Kidney Dis. 2013;62(4):647–9.
19. Alpern R, Shakhaee K. The Clinical Spectrum of Chronic metabolic acidosis: homeostatic mechanisms produce significant morbidity. Am J Kidney Dis. 1997;29:291–302.
20. Kovesdy CP. Metabolic acidosis and kidney disease: does bicarbonate therapy slow the progression of CKD? Nephrol Dial Transplant. 2012;27(8):3056–62.
21. Foundation NK. KDOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease 2003. Am J Kidney Dis. 2003;42:s3–201.
22. Dobre M, Yang W, Chen J, et al. Association of serum bicarbonate with risk of renal and cardiovascular outcomes in chronic kidney disease. A report from the Chronic Renal Insufficiency Cohort (CRIC) study. Am J Kidney Dis. 2013;62(4):670–8.
23. Goraya N, Simoni J, Jo C, Wesson DE. A comparison of treating metabolic acidosis in CKD stage 4 hypertensive kidney disease with fruits and vegetables or sodium bicarbonate. Clin J Am Soc Nephrol. 2013;8(3):371–81.