Chronic Metabolic Acidosis

Give alkali

…. Is there anything else?

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Brief Bio

Orson Moe received his medical degree, residency, and nephrology fellowship from the University of Toronto. He trained in research in renal physiology at UTSW and subsequently joined the faculty in 1990. He has the administrative roles of the Director of the Charles and Jane Pak Center of Mineral Metabolism and Clinical Research and a member of the Nephrology Division. He is the holder of the Charles and Jane Pak Distinguished Chair in Mineral Metabolism Research and the Donald Seldin Professorship in Clinical Investigation. Moe conducts both basic science and patient-oriented research in epithelial biology, renal physiology, preclinical pathobiology, and mineral metabolism. He is editing *Current Opinion in Nephrology and Hypertension*, and the textbook *Seldin and Giebiesch's The Kidney: Physiology and Pathophysiology.* He is a member of the American Society of Clinical Research, Association of American Physicians, American Society of Nephrology, International Society of Nephrology, and American Physiologic Society.

Summary

Physicians are essentially human biologists and as such, should strive to understand organ function, and master the causes and effects of dysfunction, which are the roots of human disease. Knowledge of pathobiology is a critical and integral part of medicine. Unfortunately, a prevalent disconcerting trend is that we have replaced this philosophy with diagnostic and therapeutic algorithms that led, albeit unintentionally, to the continuous diminution of clinical pathophysiology. This lecture utilizes a common clinical condition, metabolic acidosis, as a vehicle to illustrate the inadequacy of conventional teaching that does not include understanding of mechanisms of disease.

Metabolic acidosis is a disorder resultant from increased acid production/addition, decreased excretion, or both. Each of the above have different underlying etiologies and pathophysiology, which should be identified by the clinician. The ill effects of acidosis and acid loading are often not generally appreciated by the practitioner. The treatment of chronic metabolic acidosis involves correction of the underlying pathophysiology and when such corrections are not possible, we prescribe alkali therapy.

At the conclusion of this presentation, one should:

1. Know some clinical physiology on acid-base homeostasis
2. Appreciate the power of clinical chemistry as a window to pathophysiology
3. Be aware of the limitations of the common classifications and algorithms in evaluating metabolic acidosis
4. Know the difference between acid load and acidosis
5. Be cognizant of the multi-organ ill effects of chronic metabolic acidosis
6. Know the available treatment options and pathobiologic basis for these therapies

INTRODUCTION

Patient 1

Plasma [HCO_3^-] = 15

20 year old white female
Diabetic ketoacidosis

Patient 2

Plasma [HCO_3^-] = 15

55 year old black male
CKD IV Hypertension

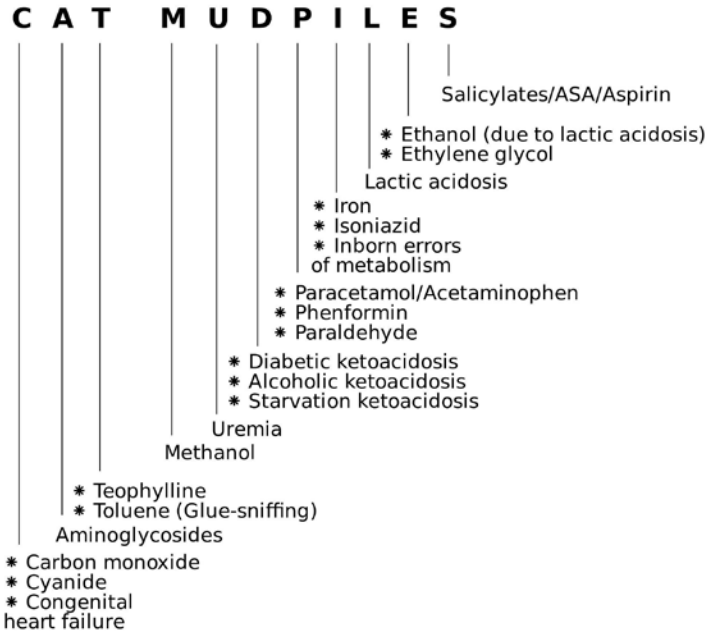
Acute life-threatening metabolic acidosis

Chronic stable metabolic acidosis

Two patients both have metabolic acidosis with plasma bicarbonate concentration of 15 mM. Patient 1 has an acute situation whereas Patient is stable. Both will require alkali therapy such as NaHCO3 but the route of administration and dosage differs. Overall, we give alkali to treat do for metabolic acidosis. A simple approach is to conclude that this is all one has to do for patients with metabolic acidosis.

In the presentation this morning, I will submit reasons why there is much more to understanding and managing chronic metabolic acidosis than the usual algorithm and alkali therapy. This will be used as an example that clinical physiology is still alive and should be embraced rather than forsaken.

Causes of high anion-gap acidosis



Causes of normal anion-gap acidosis

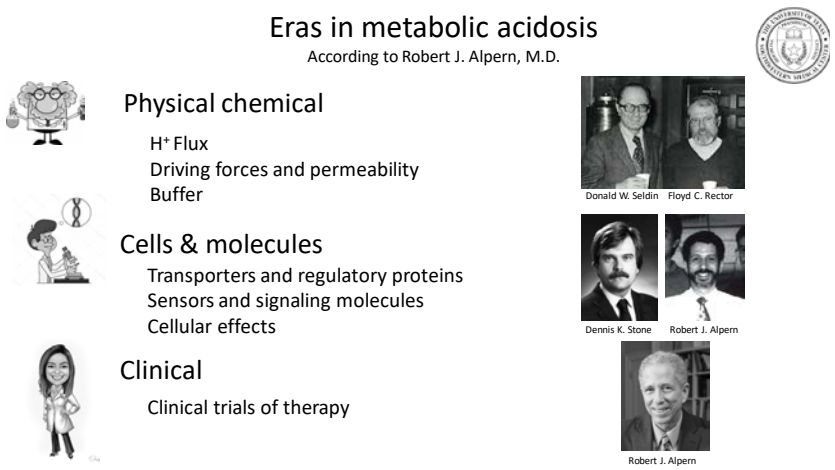
CAGE
- **C**hloride
- **A**cetazolamide/Addison's
- **G**I Loss
- **E**xtras – RTA, ingestion of acid, recovery from DKA

ABCD
- **A**ddison's
- **B**icarb loss (GI or renal)
- **C**hloride
- **D**rugs (e.g. acetazolamide, acids)

HARDUP
- **H**yperchloraemia
- **A**cetazolamide, Addison's disease
- **R**enal tubular acidosis
- **D**iarrhoea, ileostomies, fistulae
- **U**reteroenterostomies
- **P**ancreatoenterostomies

USED CRAP
- **U**reteroenterostomies
- **S**mall bowel fistula
- **E**xcess Chloride
- **D**iarrhea
- **C**arbonic anhydrase inhibitors
- **R**enal tubular acidosis
- **A**ddison's disease
- **P**ancreatoenterostomies

The typical teaching methods of evaluation of metabolic acidosis involves dividing it into two categories of normal vs. elevated anion gap. This promotes rote memory and not comprehension and is in fact quite inaccurate and inadequate. While the anion gap is useful in helping one discerns the etiology, it is not a dichotomous "normal vs. elevated" parameter.

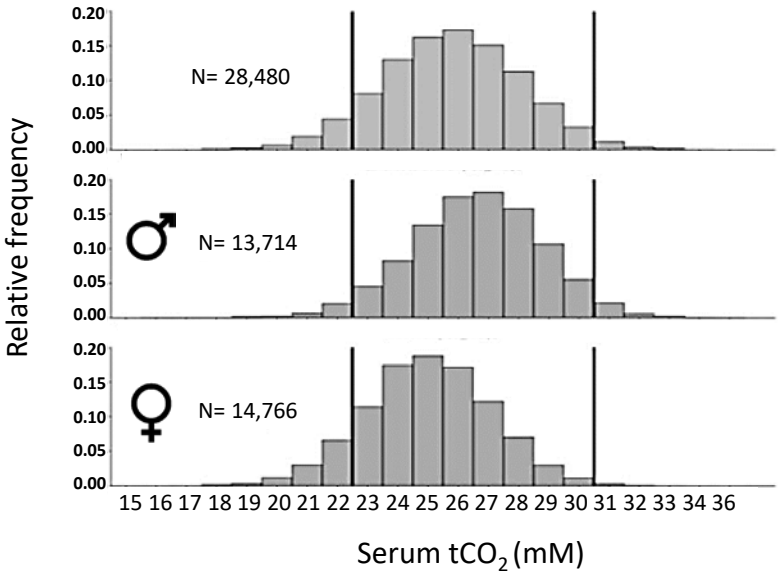


Robert J. Alpen, a prominent nephrologist/ renal physiologist, classified acid-base research into three eras. Physical chemical and phenomenological studies focused on variables such as H^+ and HCO_3^- fluxes, driving forces, permeability of ion, and buffers of H^+. When cloning was available, the attention zeroed down to cells and individual proteins. In the last decade, there was an emergence of clinical trials on therapy, which will be discussed below.

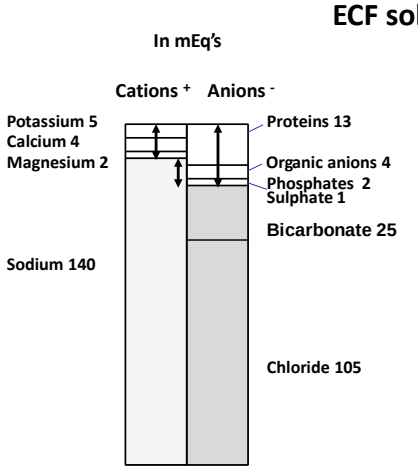
CLINICAL LABORATORY CHEMISTRY

The role of clinical bedside laboratory testing is diminishing in the practice of medicine. This is due to reduction in physician-conducted laboratory tests as well as inability to interpret the results scientifically. Often, the practitioner is reduced to only reacting to abnormal laboratory tests (labelled "high" or "low") and not critically analyzing each of the laboratory results.

The "normal" range of many acid-base parameters are difficult to interpret and seemingly "normal" values may in fact be abnormal. For example, the normal range of serum total CO_2 (HCO_3^- + CO_2) is rather broad in normal individuals (Kraut 2018).



Serum anion gap, which is used frequently in the clinical approach to metabolic acidosis, is defined as $Na^+ – (HCO_3^- + Cl^-)$. The term anion gap is more appropriately be called (all the anions that are not HCO_3^- or Cl^-) minus (all the cations that are not Na^+). This is of course not



Anion Gap = $Na^+ - [Cl^- + HCO_3^-]$

All the anions that are not Cl^- and HCO_3^-

Minus

All the cations that are not Na^+

Mean and range of anion gap

Population	N=	Mean	Range	Reference
Normal subjects	488	15 ± 2.5	10-20	Buckley-Sharp, *Lancet* 1973
Normal subjects	100	11 ± 2.5	6-16	Frohlich, *CMAJ* 1976
Patients (normal electrolytes)	1200	12 ± 2.0		Emmet, *Med* 1977
Normal subjects	124		5-12	Lolekha, *Clin Chim Acta* 2013
Patients (normal electrolytes)	18,987		10-18	Lipnick, *Crit Care Med* 2013

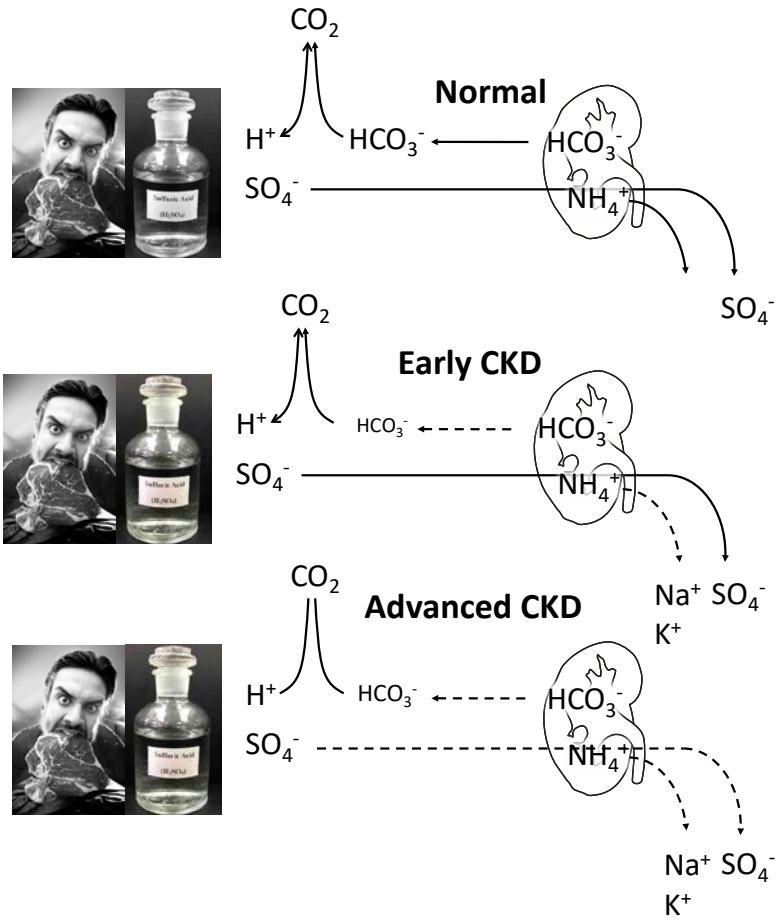
practical for common clinical parlance but it is accurate. Like serum tCO2, serum anion gap has a wide normal range. The most common use of the serum anion gap is to seek a clue for the presence of an anion from a strong acid. This is the “footprint”

BUSTING OF ALGORITHMS

Clinical algorithms are intended to streamline as well as create uniformity in our practice. The purpose is not to replace thinking with algorithms. Unfortunately, the effect, albeit unintended, has taken hold in a most dangerous fashion.

The dichotomous division of metabolic acidosis into high anion gap vs. normal anion gap is not valid. As indicated above, the normal range is very wide rendering it difficult to make the distinction. A more important reason is that the anion derived from the acid may not be retained but rather excreted in the urine, hence does not lead to a footprint in the blood.

Contrary to the textbook version of analysis of high anion gap metabolic acidosis, renal failure is a cause of high anion gap acidosis unless the renal failure is very advanced. In early mild CKD, the ability to replenish decomposed bicarbonate is impaired so hence the acidosis, However, the ability to excrete non-metabolizable anions (e.g. sulfate) is still intact so there is not accumulation of anion in the bleed. In advanced CKD, the ability to excrete sulfate is lost so sulfate starts accumulating in the urine, giving rise to metabolic acidosis with elevated anion gap.



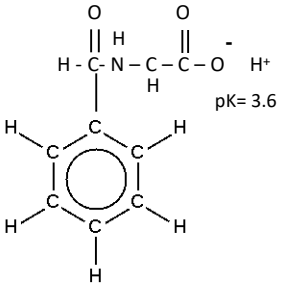
Take another example of two individuals with metabolic acidosis. Both have serum bicarbonate of 12 mM, but their anion gaps are very different.

Patient: Glue sniffer

$[HCO_3]$= 10 mM $[Na^+]$ = 137

pCO_2 = 20 mm Hg $[Cl^-]$ = 115

pH 7.32 AG = 12



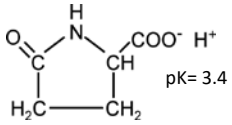
Hippuric acid

Patient: Analgesic abuser

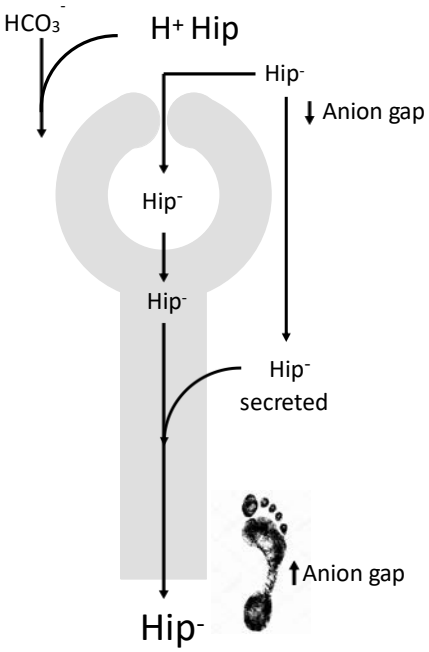
$[HCO_3]$= 10 mM $[Na^+]$ = 137

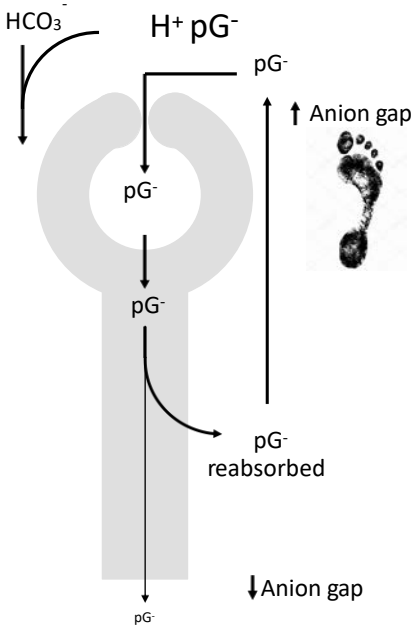
pCO_2 = 20 mm Hg $[Cl^-]$ = 100

pH 7.32 AG = 27



Pyroglutamic acid



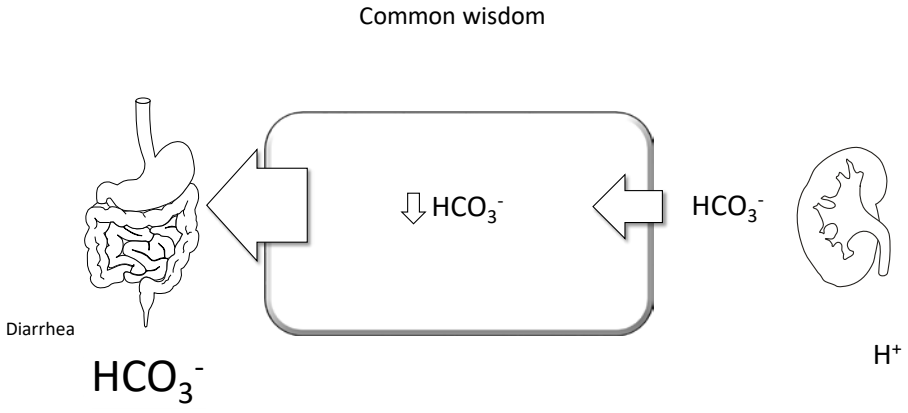


The glue sniffer has hippuric acidosis and hippurate is filtered and secreted in the urine so there is no accumulation in the blood. In contrast, the analgesic abuser has pyroglutamic acidosis and pyroglutamate is filtered but reabsorbed by the kidney. Therefore, there will be a serum anion gap for pyroglutamic acidosis but a urinary anion gap for hippuric acidosis.

Another incorrect notion is that the normal anion gap acidosis seen in diarrhea is due to massive base loss in the stool that overwhelms the kidneys' ability to regenerate bicarbonate. However, the capacity of the kidney to regenerate bicarbonate is very high (up to 250-300 mEq/day). It is very difficult to lose enough bicarbonate to sustain metabolic acidosis if the kidneys are truly completely normal. The normal gap acidosis seen in diarrhea is a combination of gut base loss and inability of the kidney to fully compensate.

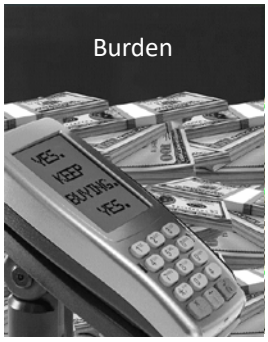
39 year old veteran with HIV-AIDS
Fever and watery diarrhea
Exam showed ECFV contraction

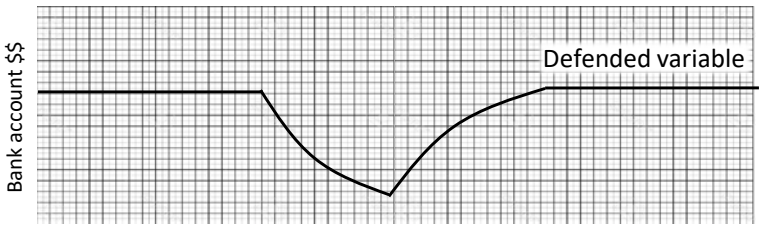
Na^+	138
K^+	3.0
HCO_3^-	10
Cl^-	119
Cr	1.3 (from 0.9)
Stool pH	7.8
Urine NH_4^+	12 mEq/L



ACIDEMIA, ACIDOSIS, OR ACID LOAD

Clinicians do not generally appreciate these 3 terms. *Acidemia* refers to acidic blood pH (<7.40). *Acidosis* means an excess of acid in the body. *Acid load* is an imposition on the body which may or may not lead to academia, acidosis or ill effects. A parallel monetary example is used to illustrate this concept.





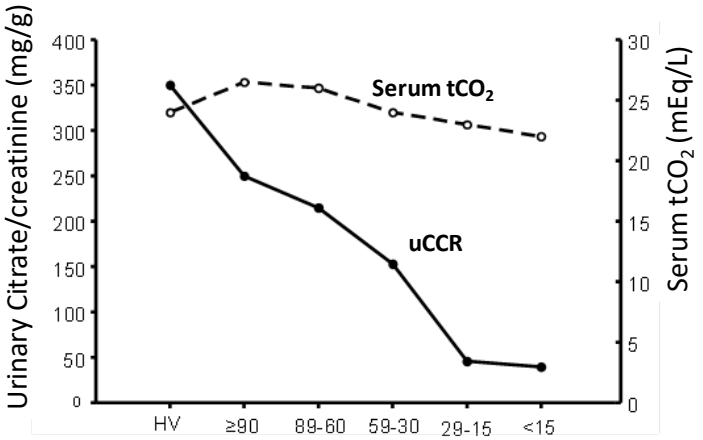
Take the financial books of a couple. When income equals expenditure, the bank account remains constant. When spending exceeds income, the bank account will start to shrink. If this couple now takes on moonlighting jobs to increase their income, they may replenish their saving and if the increased income is sustained to match the increased expenditure, the bank account will once again achieve the initial

balance and be constant again. If one only examines the balance, it will seem like nothing has happened and all is well. However, all is not well because the couple has to sustain four jobs to maintain their steady state. This may deprive them of any leisure time and may even impact on their health

When the *defense mechanism* succeeds in maintaining the *defended variable*, it creates an illusion that there is no strain on the system. In acid-base homeostasis, the increase in acid load although adequately excreted by the kidney, is a strain on the system and undesirable consequences may transpire.

This concept should be considered in clinical practice. In 1997, Sakhaee and Alpern described the phenomenon of *eubicarbonatemic acidosis* which is a state with normal common clinical lab vales but not a state of normalcy as there is a price to pay for the increased acid excretion (Sakhaee 1997).

A better parameter to assess clinically is the *defense mechanism* rather than the *defended parameter*. Once practical test to use is the spot urinary citrate to creatinine ratio. Hypocitraturia is the defense mechanisms whereas serum bicarbonate is the defended parameter.



As eGFR falls, serum bicarbonate remains stable until the eGFR is below 30. In contrast, urinary citrate to creatinine ratio (uCCR) is much more sensitive in reflecting the burden on the body.

END ORGAN EFFECTS

Animals evolved to have a very precisely regulated body fluid pH. While transient deviations may be tolerated, chronic dysregulation of pH have detrimental effects for just about every organ. The most studied effects are on metabolism and endocrine function (albumin, β2-microglobulin, growth hormone, IGF-1. Leptin, glucose tolerance, thyroid hormone), cardiovascular effect s (blood pressure), muscle, bone, and progression of CKD (Kraut 2017).

An important point to note is that many of these effects are not life threatening nor acute. Thus, the practitioner sometimes lowers the priority to treating acidosis even when the serum bicarbonate is low.

Adverse effects of chronic acidosis.

Metabolism and Endocrine
- Low albumin
- Glucose intolerance and insulin
- High b2-microglobulin
- Growth hormie-IGF-1
- Leptin and adiponectin

Cardiovascular
- Hypertension

Bone loss

Myopathy

Progression of CKD

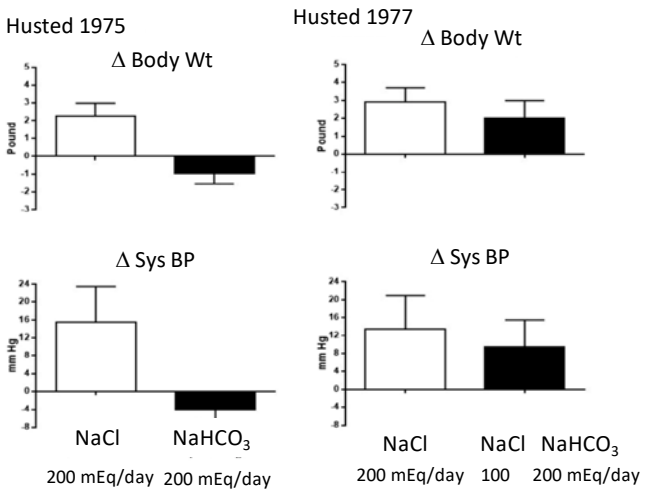
SHOULD WE AND HOW DO WE TREAT

The main therapy is provision of alkali as the kidney is not able to restore the blood chemistry back to normal. There have been many clinical trials examining the effect of therapy. The majority of these papers are quite nephrocentric using CKD progression as the endpoint. These studies are of variable quality with some involving small number of patients. Nonetheless, the overall results are largely positive. This is not the forum to exhaustively describe these data but the most important ones are summarized in a Table.
In terms of the choice of alkali, one can have inorganic (bicarbonate, carbonate) or organic anions (citrate, acetate). Citrate has certain advantages over bicarbonate. First, it does not produce the burping that occurs when bicarbonate is mixed with the HCl in the stomach. Second, because citrate has to be metabolized to confer a base load, it has a more gentle alkalinizing effect than the bolus action of bicarbonate.

The cation of choice to data is either sodium or potassium. Potassium has its clear dangers in CKD patients, as one cannot predict one can tolerate the additional potassium load. Even if hyperkalemia may not be common, the down side is very steep. Even a single life-threatening or fatal case of hyperkalemia is not acceptable. The ill effects of a sodium load on the other hand may be more prevalent but edema, weight gain, and worsening hypertension can be dealt with medically.

Direct comparison of $NaHCO_3$ vs. NaCl: Metabolic studies

Study	n	Test	Effect
Husted 1975	10	NaCl vs. $NaHCO_3$	NaCl ↑ BW and BP
Husted 1977	6	NaCl vs. $NaHCO_3$	NaCl = $NaHCO_3$ ↑ BW & BP
Kurtz 1987	5	NaCl vs. NaCit	NaCl = NaCit ↑BW Only NaCl ↑BP
Shore 1988	6	NaCl vs. $NaHCO_3$ + NaP	NaCl= $NaHCO_3$ ↑BW Only NaCl ↑ BP
Sharma 1992	7	NaCl vs. NaCit	NaCl=NaCIt ↑ pressor response Only NaCl ↑BP
Tomila 1990	8	NaCl vs. NaCit	NaCl > NaCit ↑ BW



Several studies have shown some increase in either blood pressure, body weight, or edema when a patient is placed on Na alkali therapy. While these complications may be inconvenient, they are relatively benign when compared to hyperkalemia.

There has been many trial of alkali therapy and the majority of them are on CKD patients because that is the most common cause of chronic metabolic acidosis. The majority of these trials examined progression of kidney disease as a read-out. A summary is provide below.

Published studies showing impact of metabolic acidosis on progression of CKD (Kraut 2018)

	Effect of sodium bicarbonate therapy on vascular endothelial function (2018) [14]	Effect of sodium bicarbonate therapy on muscle mass and renal function (2018) [15]	Phase 1/2 study of veverimer (2018) [16]	Phase 3 study of veverimer (2019) [17]
Study design	Pilot study, open-label, randomized crossover	Single-center, open-label, randomized, prospective parallel-groups	Randomized, double-blind, placebo-controlled, parallel-design, six-arm, fixed dose, multicenter, in-unit	Randomized, double-blind, placebo-controlled, parallel, multicenter
Study population	eGFR 15–44 ml/min per 1.73 m^2 and serum bicarbonate 16–21 mEq/l	CKD stage 3 and 4 and bicarbonate levels less than 22 mEq/l	eGFR 20 to <60 ml/min per 1.73 m^2 and serum bicarbonate 12–20 mEq/l	Adults with eGFR 20–40 ml/min per 1.73 m^2 and serum bicarbonate 12–20 mEq/l
Notable exclusion criteria	Uncontrolled hypertension; overt congestive heart failure (New York Heart Association Class unspecified)	Decompensated heart failure; prior bicarbonate therapy for a duration of more than 2 weeks	SBP at least 170 mmHg; heart failure with New York Heart Association Class III & IV	SBP at least 170 mmHg; heart failure with New York Heart Association Class IV
Sample size	20	188: 94 (treatment), 94 (control)	135: 104 (treatment), 31 (placebo)	217: 124 (treatment), 93 (placebo)
Intervention	Oral sodium bicarbonate for 6 weeks to goal serum bicarbonate of at least 23 mEq/l	Sodium bicarbonate supplementation to maintain bicarbonate levels at 24–26 mEq/l in addition to standard care per KDIGO 2012 guidelines	Veverimer 1.5 g twice daily, 3 g twice daily, 4.5 g twice daily or 6 g once daily	Veverimer 6 g once daily for 3 weeks, then titrated to a target bicarbonate of 22–29 mEq/l (0–9 g/day)
Control	No medication	Standard care per KDIGO 2012 guidelines	Placebo	Placebo
Diet	N/A	Participant received comprehensive nutritional counseling	Controlled, low protein diet (~0.7 g/kg/day)	Variable dietary protein intake; participants received dietary counseling
Duration	14 weeks (including a 2-week washout period)	6 months	2 weeks	12 weeks
Endpoints	Primary: change in brachial artery flow-mediated dilation Secondary: changes in markers of inflammation, bone turnover, mineral metabolism and calcification	Primary: change in mid-arm muscle circumference and lean body mass Secondary: change in eGFR from baseline	Primary: change of serum bicarbonate from baseline to the end of treatment	Primary: the difference between the treatment and placebo in the proportion of patients achieving either an increase of at least 4 mEq/l serum bicarbonate from the baseline or achieving a serum bicarbonate between 22 and 29 mEq/l Secondary: change from baseline to week 12 in total score of the KDQoL physical function domain and the duration of the repeated chair-stand test
Findings	Primary: flow-mediated dilation improved during the treatment period ($P=0.04$) while there was no change in the control period Secondary: no change in bone markers or transformation of serum calciprotein particles *in vitro*. Serum phosphorous and intact fibroblast growth factor 23 increased during the treatment period.	Primary: compared with the control group, participants in the treatment group had higher lean body mass and mid-arm muscle circumference Secondary: eGFR increased in the treatment group (from 29.2 to 32.7 ml/min per 1.73 m^2), but decreased in the control group (31.5–28.2 ml/min/1.73 m^2).	Primary: mean increase in bicarbonate of 3.2–3.9 mEq/l ($P<0.001$) in the treatment groups while there was no change in the placebo group.	Primary: 59% in the treatment group versus 22% in the placebo met the primary endpoint ($P<0.001$) Secondary: KDQoL physical function domain improved significantly in the treatment group versus placebo ($P=0.01$); no change in the repeated chair-stand time ($P=0.06$)
Major limitations	Small sample size, short study duration, open-label, no placebo control	Open-label study, high prevalence of CKD of unidentified cause	Short-study duration, only endpoint was the change in serum bicarbonate	Primary endpoint was the change in serum bicarbonate level

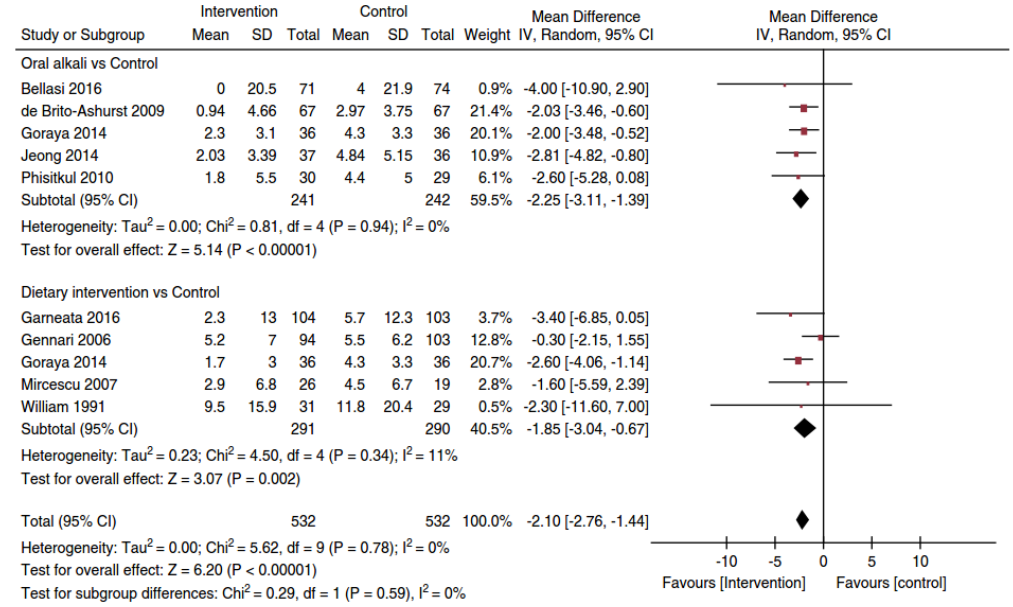
KDIGO, Kidney Disease: Improving Global Outcome; KDQoL, Kidney Disease and Quality of Life; N/A, not available.

Ongoing or unpublished trials of alkali therapy (Chen 2019)

Title	Design	Population	Site (s)	Sample size	Intervention	Control	Duration	Primary endpoint
Placebo-controlled randomized clinical trial of alkali therapy in patients with CKD (NCT01452412) [29]	Randomized, placebo-controlled	eGFR 15–45 ml/min per 1.73vm^2 and serum bicarbonate 20–25 mEq/l	Bronx, New York and Cleveland, Ohio	149	Sodium bicarbonate 0.4 mEq/kg/day ideal body weight to be taken once a day	Placebo	12 months	Sit to stand to sit speed and bone mineral density at the wrist
A prospective, controlled, randomized, multicentric study: correction of metabolic acidosis with use of bicarbonate in chronic renal insufficiency (NCT01640119) [30]	Multicentric, prospective, cohort, randomized, open-label and controlled	CKD stage 3b-4 with serum bicarbonate ≥18 mEq/l[a]	Italy	728	Sodium bicarbonate therapy to keep serum bicarbonate above 24 mEq/l	Usual care (no bicarbonate)	36 months	Doubling of creatinine
Does oral sodium bicarbonate therapy improve function and quality of life in older patients with CKD and low-grade acidosis? (EudraCT# 2011-005271-16) [31]	A multicenter randomized placebo-controlled trial	Age 60 and older, CKD stage 4–5, serum bicarbonate less than 22 mEq/l	United Kingdom (27 centers)	300	Sodium bicarbonate 500 mg three times a day, titrated up to 1 g three times a day after 3 months if bicarbonate is less than 22 mmol/l	Placebo	12 months	Change in Short Physical Performance Battery score
Investigations of the Optimum Serum Bicarbonate Level in Renal Disease (NCT01574157) [32]	Randomized, placebo-controlled	Diabetic, CKD stage 2–4 and serum bicarbonate 22–28 mEq/l	Salt Lake City, Utah	74	Sodium bicarbonate 0.5 mEq/kg/day ideal body weight to be taken twice a day	Placebo	6 months	Change in urinary transforming growth factor beta 1
Oral sodium bicarbonate supplementation in patients with chronic metabolic acidosis and CKD (EUDRACT# 2012-001824-36) [33]	Randomized, controlled, open-label	CKD stage 3–4 and serum bicarbonate less than 21 mEq/l	Austria	200	Sodium bicarbonate with a target serum bicarbonate of 24 ± 1 mEq/l	Rescue therapy with sodium bicarbonate with target serum bicarbonate of 20 ± 1 mEq/l	24 months	eGFR
The BASE Study: Bicarbonate Administration to Stabilize eGFR (NCT02521181) [36]	Randomized, placebo-controlled	eGFR 20–24 ml/min per 1.73 m^2, or 45–59 ml/min per 1.73 m^2 plus urine albumin:creatinine at least 100 mg/g	United states (6 centers)	194	Low-dose sodium bicarbonate: 0.5 mEq/kg/day lean body weight; or high-dose: 0.8 mEq/kg/day lean body weight	Placebo	28 weeks	Safety and tolerability

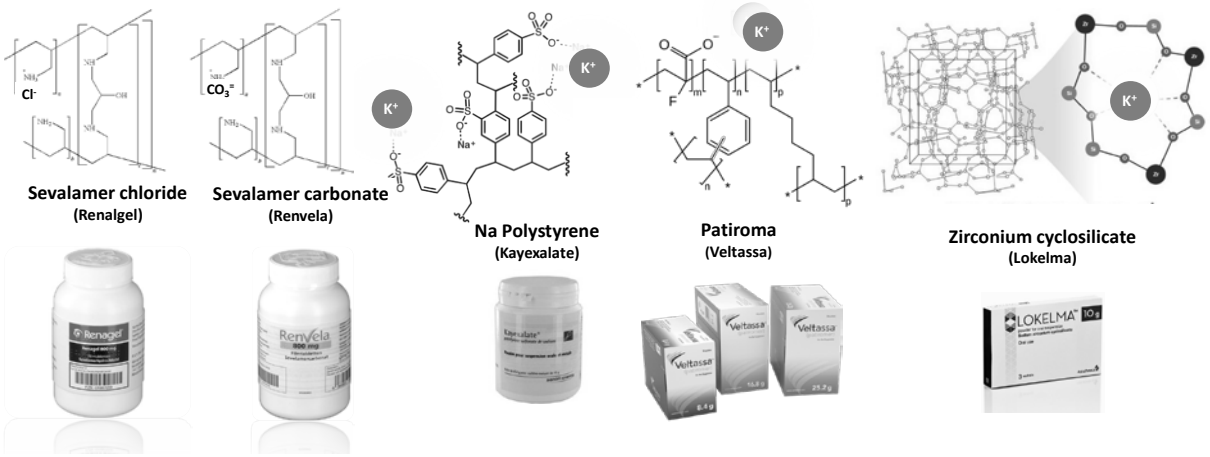
[a]Unclear whether there is an upper limit of serum bicarbonate level.

A recent meta-analysis of 14 clinical trials (n=1394 participants) concluded that treatment of metabolic acidosis with oral alkali or reduction of dietary acid increased serum bicarbonate, reduction in urinary albumin excretion, and risk of progression to ESRD (Navaneethan 2019).

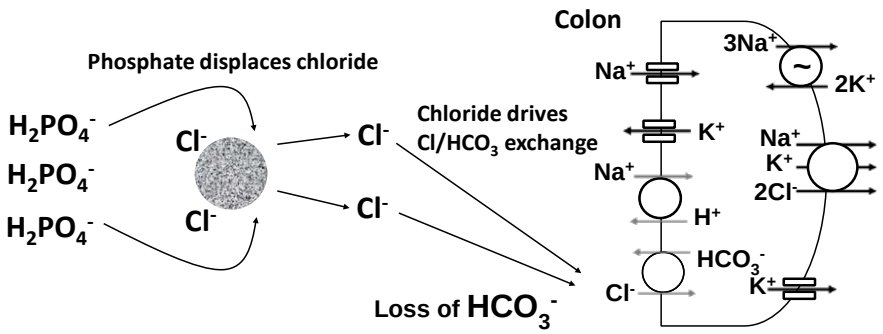


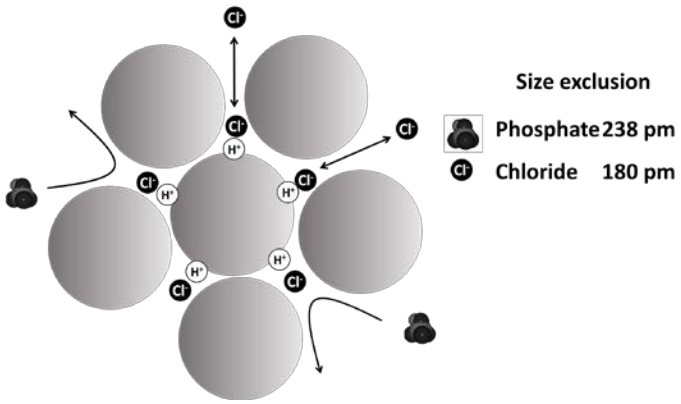
| **Forest plot shows slower decline in eGFR per year with oral akali supplementation or reduction of dietary acid intake.** I^2 for the combined effect estimate: (95% CI, 0% to 53%). df, degrees of freedom; IV, inverse variance.

There is another way of delivering alkali or “alkali equivalent” which is HCl binding. This is ion exchange resins. Cation exchange macromolecules are used as potassium binders (Kayexalate, Patiromer, and Zirconium silicate) and anion exchange macromolecules are used as phosphate binders (Sevelamer).



The same technology can be used for HCl binding. The removal of HCl from the body is tantamount to addition of bicarbonate to the blood. This is a well-known fact in vomiting or nasogastric suction. There is one inconvenient property about anion exchange. The potency by which anions interact with or affect a macromolecule is a universal property and follows a certain sequence known as the Hofmeister sequence.

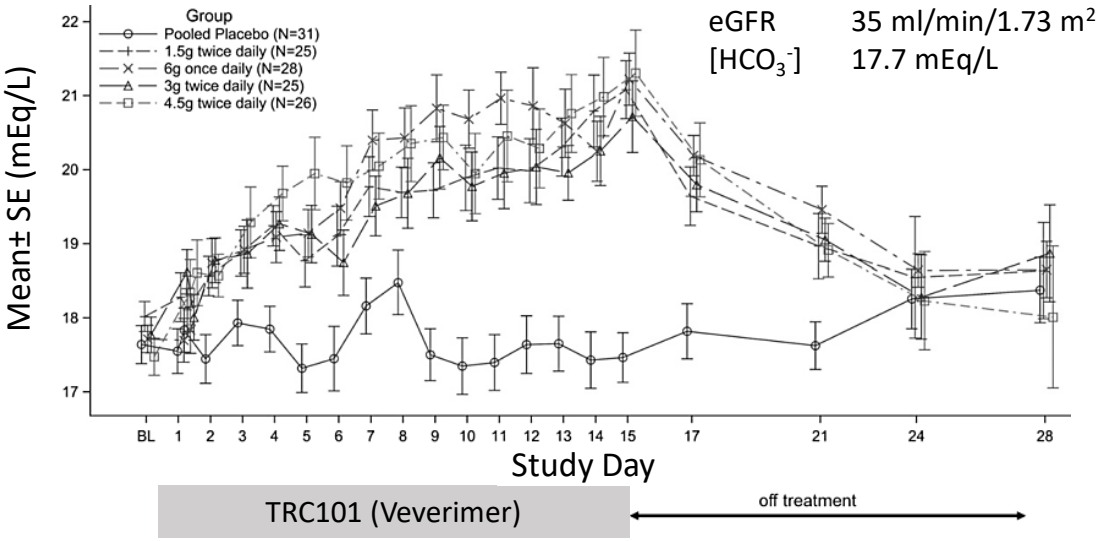




A chloride bound to a resin will soon have it “kicked off” and be replaced by a phosphate. The chloride (carried form the stomach) in the colonic lumen will activate chloride-bicarbonate exchange and fill the colonic lumen with bicarbonate. This nullifies the whole purpose of taking acid out of the body. The solution around this predicament exploits the differential ionic radii of chloride and phosphate. The arrangement of the

polymeric binder creates steric hindrance to phosphate movement so phosphate cannot reach the anion exchange site where chloride is bound.

Initial studies in humans with CKD showed that this HCl binder (TRC101 or Veverimer) can raise the serum bicarbonate effectively.



CONCLUSION

We offer the following take-home bullet points

Keep clinical physiology alive

- It is not that hard
- Work is more fun
- Good for our patients

Clinical laboratory chemistry

- More than just reacting to abnormal labs
- Window to pathophysiology

Busting of algorithms

- Use them but they do not replace your grey cells

Acidemia, acidosis, or acid load

- “defense” vs. “the defended”

End organ effects

- All organs are affected

Should we and how do we treat

- Know your drugs and how they act

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