

## Objectives

1. Recognize the electrolyte and blood gas findings that characterize simple and mixed metabolic alkaloses.
2. Understand the contributory roles of bicarbonate load,  $H^+$  loss, and increased tubular bicarbonate reabsorption.
3. Understand the generation and maintenance phases of metabolic alkalosis.
4. Understand the categorization and pathophysiology of chloride responsive and chloride resistant alkalosis.
5. Understand the roles of aldosterone and hypokalemia.
6. Review the therapy of metabolic alkalosis.

## Readings

Rose and Rennke, pages 140-151.  
Rennke and Denker, pages 145-156.

## I. Recognition

### A. Simple Disorder

1. Elevated pH (reduced  $H^+$  concentration)
2. Elevated  $HCO_3^-$
3. Adaptive (compensatory) rise in  $PaCO_2$   
0.6 - 0.7 mm Hg per 1 mEq/L rise in  $HCO_3^-$

### Example:

pH 7.48  
 $PaCO_2$  46 mm Hg  
 $HCO_3^-$  34 mEq/L

**B. Mixed Disorder**

Bicarbonate increased beyond levels anticipated in response to another disorder

**Example:**

pH 7.38  
PaCO<sub>2</sub> 65 mm Hg  
HCO<sub>3</sub><sup>-</sup> 37 mEq/L

Pathophysiologic Diagnosis: Mixed respiratory acidosis and metabolic alkalosis

- a. Low pH indicates acidemia (though mild)
- b. High PaCO<sub>2</sub> of 65 identifies a respiratory acidosis
- c. In simple respiratory acidosis, HCO<sub>3</sub><sup>-</sup> rises ~ 0.3mEq/L for each 1 mm Hg rise in PaCO<sub>2</sub> (to about 32 mEq/L for PaCO<sub>2</sub> 65)
- d. Further increase in HCO<sub>3</sub><sup>-</sup> to 37 indicates metabolic alkalosis

Clinical Diagnosis: COPD and diuretic therapy

**C. Clinical Importance**

1. Clue to an underlying disorder like volume depletion or primary aldosteronism
2. Interferes with ventilation in COPD
3. Combined metabolic and respiratory alkaloses can be severe

**II. Physiology and Pathogenesis****A. Generation - HCO<sub>3</sub><sup>-</sup> load or loss of H<sup>+</sup> initially raises plasma HCO<sub>3</sub><sup>-</sup>**

1. Bicarbonate load: If not sustained, the bicarbonate is filtered by the glomerulus and excreted as alkaline urine. Exceptions include:
  - a. Excessive NaHCO<sub>3</sub> supplementation in which a new steady state is achieved, especially with reduced kidney function.
  - b. Massive blood transfusions (citrate preservative is converted into alkali)
  - c. Milk-alkali syndrome (calcium + alkali + kidney disease)
2. H<sup>+</sup> loss (e.g. vomiting) only transiently elevates plasma HCO<sub>3</sub><sup>-</sup>, which is then rapidly excreted in urine. The exception is perpetual vomiting or constant NG suction.

B. Maintenance - for increased  $\text{HCO}_3^-$  to persist (metabolic alkalosis), a defect in kidney  $\text{HCO}_3^-$  excretion must be present

1. Elevated bicarbonate must be maintained via increased tubular reabsorption of  $\text{HCO}_3^-$  (in turn caused by increased  $\text{H}^+$  secretion)
2. Synonyms for defective  $\text{HCO}_3^-$  excretion:
  - a. Persistent stimulus to  $\text{HCO}_3^-$  reabsorption
  - b. Accelerated tubular  $\text{H}^+$  secretion
  - c. "Paradoxical aciduria"

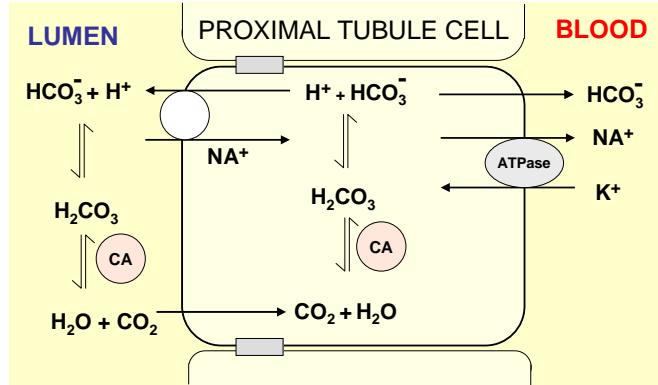


Figure 1

All synonyms refer to failure to produce appropriate alkaline diuresis.

3. To understand the maintenance phase, we need to consider two groups of disorders and their pathophysiology:

A. Chloride responsive	B. Chloride resistant
Extracellular volume and chloride depletion 1. Vomiting 2. NG suction 3. Diuretics 4. Villous adenoma (5. Post-hypercapnia)	Direct Stimulus to $\text{H}^+$ secretion 1. Primary aldosteronism 2. Cushing's syndrome 3. Steroid administration 4. Ectopic ACTH production 5. Adrenogenital syndrome 6. Licorice 7. Bartter's syndrome 8. Severe hypokalemia

Table 1

### III. Pathophysiology of Chloride Responsive Alkalosis

- A. Generation of chloride responsive alkalosis is a result of a loss of ECF disproportionately rich in  $\text{Cl}^-$  and usually in  $\text{H}^+$ 
  1.  $\text{H}^+$  loss directly increases plasma  $\text{HCO}_3^-$
  2. Disproportionate  $\text{Na}^+$  and  $\text{Cl}^-$  loss will raise plasma  $\text{HCO}_3^-$ , even in absence of  $\text{H}^+$  loss (same  $\text{HCO}_3^-$  content in smaller distribution space will raise the  $\text{HCO}_3^-$  concentration). This is referred to as a contraction alkalosis. The term is often used incorrectly.

- a. Pure contraction alkaloses are rare, since  $\text{Cl}^-$  loss is usually accompanied by some  $\text{H}^+$  loss (even with diuretics)
- b. Loss of fluid identical to plasma anionic composition (e.g. bleeding) leads to contraction but no alkalosis

B. Maintenance of increased plasma  $\text{HCO}_3^-$

- 1. Volume contraction leads to a reduction in GFR. Total bicarbonate filtration per nephron is reduced allowing greater reabsorption per nephron.
- 2. Proximal tubule  $\text{Na}^+$  reabsorption is up regulated.  $\text{Na}^+$  reabsorption is coupled to  $\text{HCO}_3^-$  reabsorption, because of  $\text{Na}^+/\text{H}^+$ -exchanger (see Figure 1).

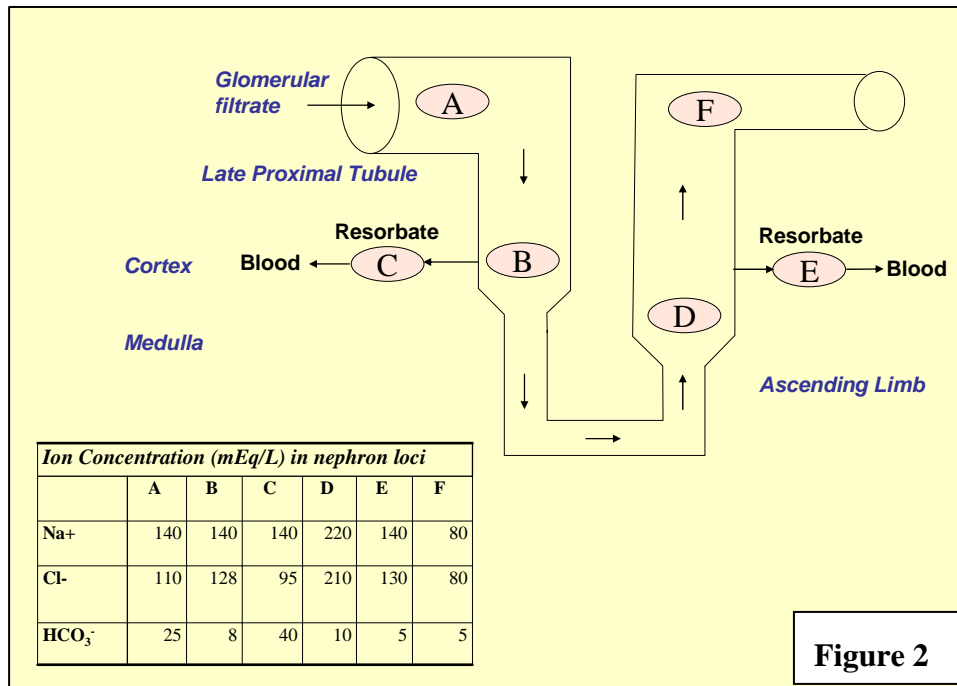


Figure 2

- 3. Reduction in filtered  $\text{Cl}^-$  reduces luminal  $\text{Cl}^-$  concentration in the collecting tubule and collecting duct. Low luminal  $\text{Cl}^-$  concentration:
  - a. Impairs  $\text{HCO}_3^-$  secretion in exchange for  $\text{Cl}^-$  reabsorption in collecting tubule.
  - b. Amplifies  $\text{H}^+/\text{Cl}^-$  co-secretion in collecting duct as  $\text{Cl}^-$  moves down concentration gradient.

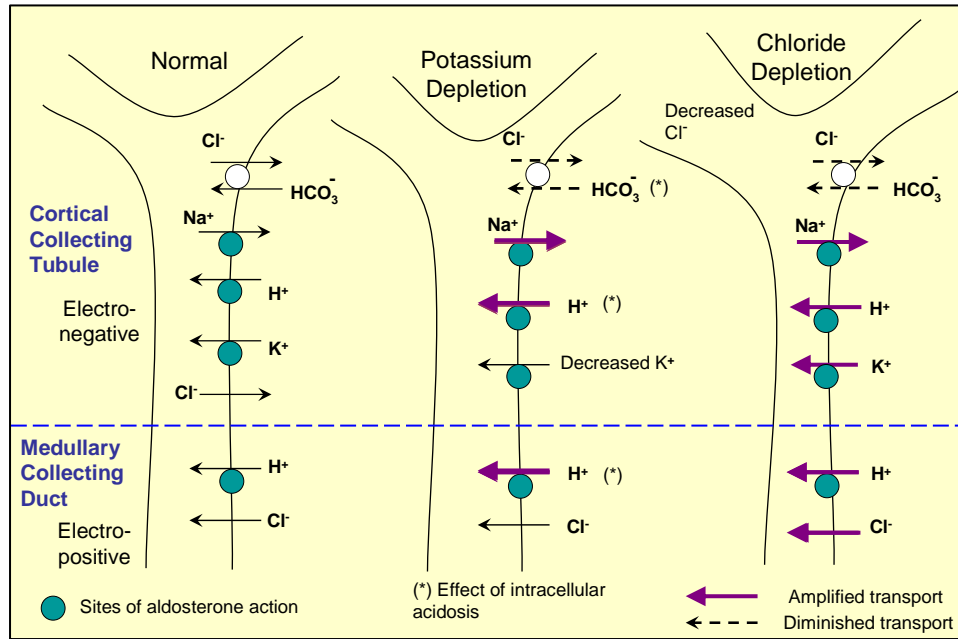


Figure 3

4. ECF volume loss → renin secretion → aldosterone secretion. Aldosterone stimulates collecting tubule Na<sup>+</sup> reabsorption, which creates a more lumen negative charge and enhances H<sup>+</sup> and K<sup>+</sup> secretion.
5. Oversimplified but helpful view: Avid Na<sup>+</sup> reabsorption is necessitated by volume depletion. However, disproportionate Cl<sup>-</sup> losses and upregulated proximal Cl<sup>-</sup> reabsorption result in inadequate Cl<sup>-</sup> available for collecting tubule reabsorption. To maintain electroneutral Na<sup>+</sup> exchange, Na<sup>+</sup> reabsorption must be accompanied by H<sup>+</sup> and K<sup>+</sup> secretion.
6. Summary: Via several mechanisms, after initial increase in HCO<sub>3</sub><sup>-</sup>, volume and Cl<sup>-</sup> deficits result in accelerated H<sup>+</sup> secretion, an inability to mount an alkaline diuresis, and a persistent alkalosis.

C. Importance of urine  $\text{Cl}^-$  concentration

1. Urine  $\text{Cl}^-$  is below 25 mEq/l in “chloride responsive alkalosis,” assisting in diagnosis. It indicates preserved  $\text{Na}^+$  and  $\text{Cl}^-$  retention by the kidney due to volume depletion and chloride depletion.
2. Low urine  $\text{Cl}^-$  is important in the pathogenesis of metabolic alkalosis.
3. The term “chloride responsive alkalosis” is drawn from the fact that correction of alkalosis is achieved by  $\text{Cl}^-$  administration (NaCl, KCl, or HCl).
  - a.  $\text{Cl}^-$  administration improves  $\text{HCO}_3^-$  for  $\text{Cl}^-$  exchange (B3a) and reduces  $\text{H}^+/\text{Cl}^-$  co-secretion (B3b) in the collecting duct
  - b.  $\text{Na}^+$  administration along with  $\text{Cl}^-$  also restores GFR and bicarbonate filtration (B1), reduces proximal tubule  $\text{Na}^+$  avidity that reclaims  $\text{HCO}_3^-$  (B2), and suppresses aldosterone (B4).
4. Low urine  $\text{Na}^+$  also helpful in categorization, but may not be low in refractory vomiting while urine  $\text{Cl}^-$  remains low.

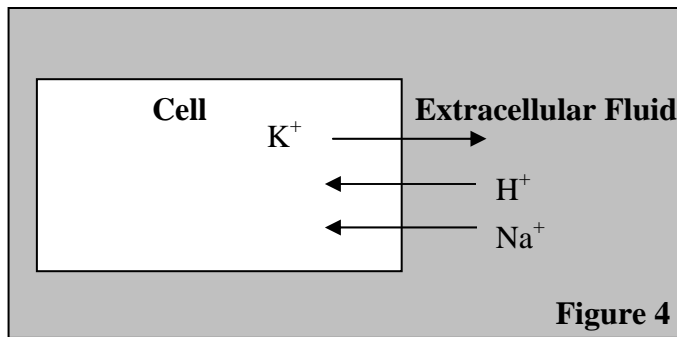
**IV. Pathophysiology of Chloride Resistant Alkalosis**

In chloride resistant alkaloses,  $\text{Cl}^-$  deficiency plays no role in accelerated tubular  $\text{H}^+$  secretion (bicarbonate reabsorption). There is no loss of  $\text{Cl}^-$  rich fluid, and usually no volume depletion. What then causes the increased tubular  $\text{H}^+$  secretion to maintain the alkalosis?

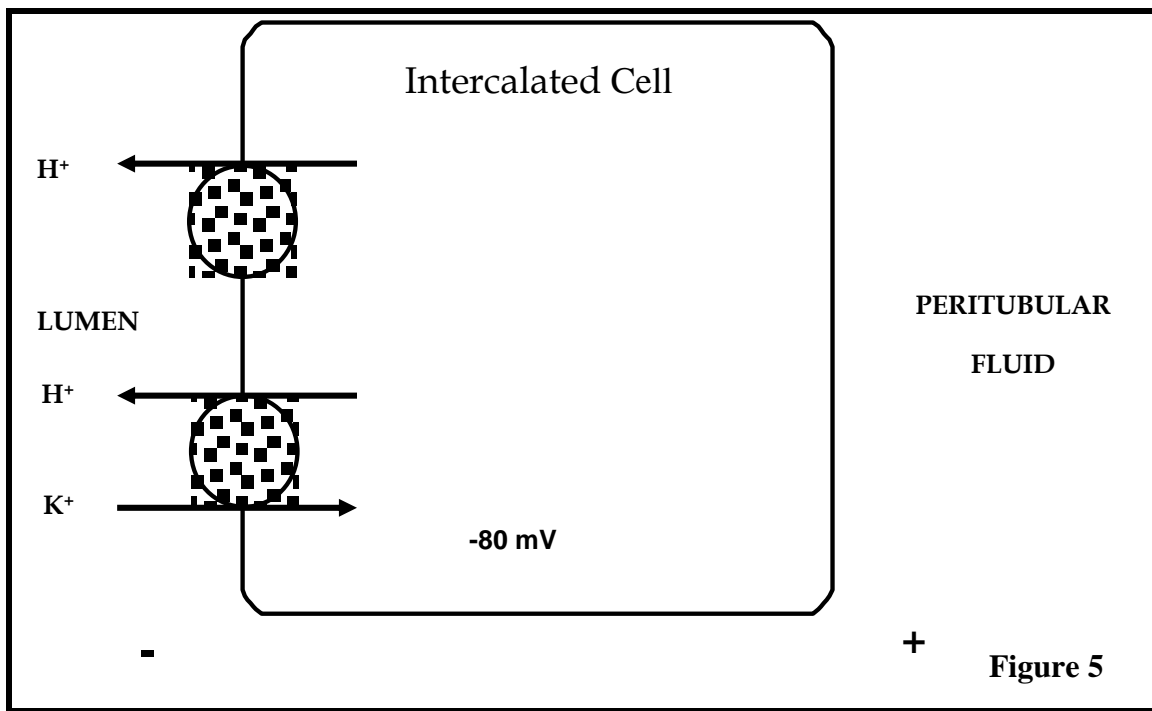
- A. There is mineralocorticoid excess, but volume depletion or ineffective ECF volume does not induce it. Increased mineralocorticoid is due to unregulated steroid production (tumors, metabolic defects) or exogenous administration (steroid therapy, licorice).
  1. No distinction of the level of aldosterone from that in  $\text{Cl}^-$  responsive alkalosis.
  2. Distinction is that the increased level is not predicated on volume deficit.
  3. Since volume and  $\text{Cl}^-$  not deficient,  $\text{Cl}^-$  not avidly reabsorbed and present in urine (usually > 40 mEq/l).
  4.  $\text{Cl}^-$  replacement does not correct alkalosis.

B. Potassium depletion

1. Important contributor to alkalosis of steroid excess states.
2.  $K^+$  deficiency may be a consequence of mineralocorticoid excess stimulating  $K^+$  secretion in collecting tubule.
3. Severe hypokalemia results in  $K^+$  exit from cells and reciprocal entry of  $Na^+$  and  $H^+$ . The  $H^+$  entry raises plasma  $HCO_3^-$ .



4. Increased intracellular  $H^+$  facilitates tubular  $H^+$  secretion (see right-hand panel of figure 3).
5.  $H^+/K^+$  exchanger is stimulated by  $K^+$  depletion.



- 6. With very severe hypokalemia ( $K^+$  close to 2mEq/l), this may be the sole cause of alkalosis (without steroid excess).
  - 7. Hypokalemia is a common byproduct of metabolic alkalosis, apart from its pathogenetic role – it is nearly always present in metabolic alkalosis.
- C. Generation and maintenance phases are less distinct in  $Cl^-$  resistant than in  $Cl^-$  responsive alkalosis. In  $Cl^-$  resistant, aldosterone excess and  $K^+$  depletion involved throughout.

**V. Treatment**

A. Chloride responsive	B. Chloride resistant
Volume, $Cl^-$ , $K^+$ repletion	Increase $K^+$ , block aldosterone
1. NaCl	1. $K^+$ sparing diuretics
2. KCl	2. Resect tumor
3. Stop diuretics	3. Reduce steroid dose
4. H2 Blockers (NG suction)	4. Replace $K^+$
5. $K^+$ sparing diuretics	5. Low salt diet
6. Acetazolamide	6. HCl infusion

Table 2

**VI. Summary**

- A. Metabolic alkalosis is recognized as primary disorder by an increased pH, increased  $HCO_3^-$ , and compensatory increased  $PaCO_2$ . In mixed disorder, it is suspected by an inappropriately high  $HCO_3^-$ .
- B. The unifying feature in the maintenance phase of metabolic alkalosis is accelerated  $H^+$  secretion that allows increased bicarbonate reabsorption. This results in a paradoxical aciduria. Sometimes a distinct generation phase raises the  $HCO_3^-$  initially.
- C. Increased  $HCO_3^-$  reabsorption by the kidney can be caused by one of two distinct categories of disorders:  $Cl^-$  responsive and  $Cl^-$  resistant.
- D. Chloride responsive disorders are caused by volume (or “effective volume”) depletion and  $Cl^-$  depletion, with increased  $HCO_3^-$  reabsorption (i.e. accelerated  $H^+$  secretion).
- E. Chloride resistant disorders are caused by direct mineralocorticoid excess and by  $K^+$  depletion, which result in accelerated  $H^+$  secretion.
- F. Treatment is based upon proper categorization.

**VIII. Self-Assessment Problems****Problem 1.**

A 57-year-old man with long-standing hypertension and mild heart failure developed progressive muscle weakness and generalized fatigue. He had been following a salt-restricted diet and taking a diuretic daily (furosemide) for 3 weeks. He had lost 5 kg in weight. Physical examination revealed decreased skin turgor, clear lungs and blood pressure of 135/85 mmHg while lying and 105/60 mmHg upon standing. He was admitted to the hospital where the following data was obtained:

Sodium	132	mEq/L	pH	7.55
Potassium	2.5	mEq/L	PaCO <sub>2</sub>	51 mmHg
Chloride	75	mEq/L		
Bicarbonate	43	mEq/L		
BUN	84	mg/dL		
Creatinine	3.0	mg/dL		
GFR	25	ml/min/1.73m <sup>2</sup>		

1. What is the acid-base disturbance? What generates the alkalosis? What sustains it?
2. What is the urine pH likely to be?
3. What additional urine test would be helpful in making a diagnosis?
4. What is the most likely etiology of the acid-base disturbance, and what other clinical situations may result in a similar picture?
5. What abnormality might account for the patient's weakness, and what is its relationship to the acid-base disorder?
6. What is the appropriate initial therapy?

**Problem 2**

A 35-year-old woman is seen by her physician for headaches. She has no past medical history and takes no medication. Her blood pressure is 150/100, and lab data shows:

<u>Blood</u>			<u>Urine</u>		
Sodium	143	mEq/L	Sodium	60	mEq/L
Potassium	3.0	mEq/L	Potassium	60	mEq/L
Chloride	100	mEq/L	Chloride	130	mEq/L
Bicarbonate	32	mEq/L			
BUN	14	mg/dL			
Creatinine	0.8	mg/dL			
GFR	>90	ml/min/1.73m <sup>2</sup>			
pH	7.46				
PaCO <sub>2</sub>	45	mmHg			

1. What is the acid-base disorder?
2. Is this a chloride responsive or chloride resistant alkalosis?
3. What factors maintain the alkalosis?
4. A plasma aldosterone level is checked, and returns elevated. What might cause this?

**Problem 3**

A 50-year-old house-painter with known alcoholic cirrhosis is admitted to the hospital following 4 days of abdominal pain and vomiting. Physical examination reveals confusion, asterixis, and ascites. Initial laboratory data includes:

Sodium	128	mEq/L	pH	7.60	
Potassium	2.8	mEq/L	PaCO <sub>2</sub>	35	mmHg
Chloride	81	mEq/L			
Bicarbonate	35	mEq/L			
BUN	30	mg/dL			
Creatinine	1.3	mg/dL			
GFR	75	ml/min/1.73m <sup>2</sup>			

1. What is the acid-base disturbance and what is its pathogenesis?
2. Is there an additional disorder besides metabolic alkalosis that is contributing to the high pH?
3. How would you treat the mixed acid-base disturbance?