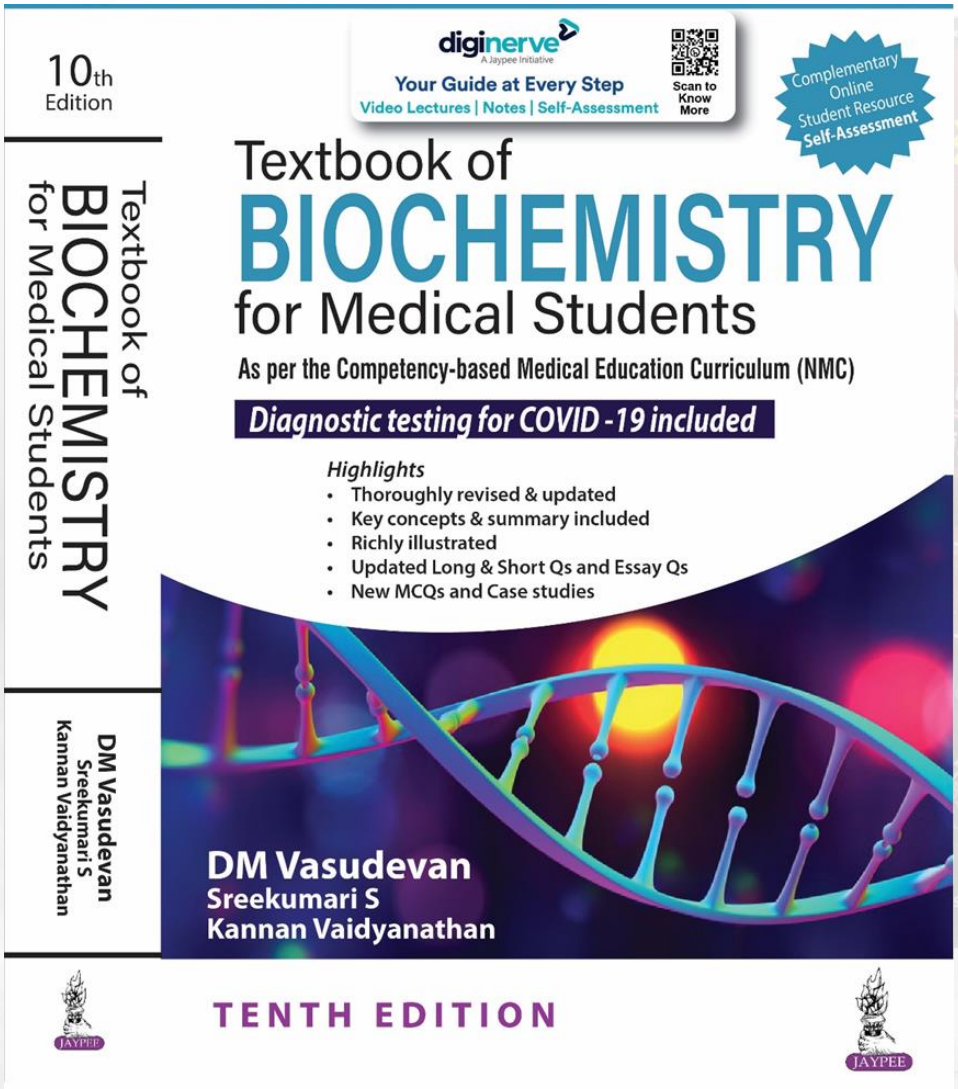
# Chapter 24B:

# Acid Base Balance and pH Clinical Review




Textbook of
BIOCHEMISTRY
for Medical Students

By DM Vasudevan, *et al.*

TENTH EDITION

# Classification of Acid-Base Disturbances

1. Acidosis (fall in pH)
    a. Respiratory acidosis:
        Primary excess of carbonic acid.
    b. Metabolic acidosis:
        Primary deficit of bicarbonate.
2. Alkalosis (Rise in pH)
    a. Respiratory alkalosis:
        Primary deficit of carbonic acid.
    b. Metabolic alkalosis:
        Primary excess of bicarbonate
3. Compensatory responses
    a. Uncompensated
    b. Partially compensated
    c. Fully compensated.

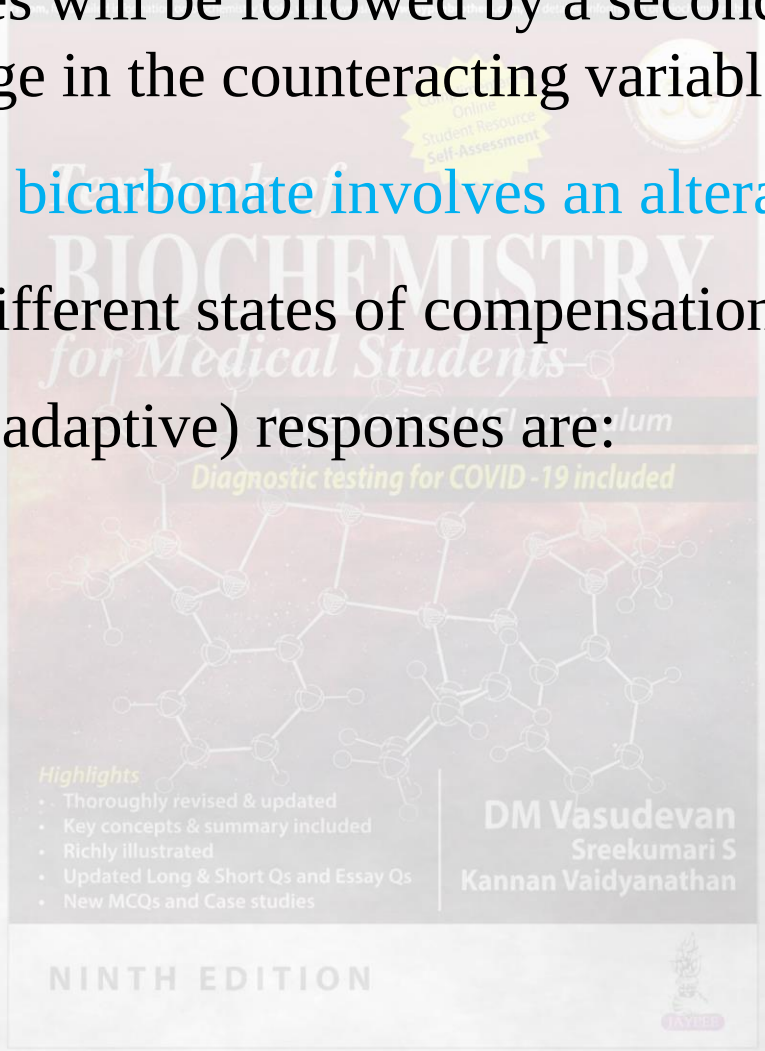
# Compensatory Responses

Primary disturbances will be followed by a secondary compensatory change in the counteracting variable, e.g.

a primary change in bicarbonate involves an alteration in pCO2.

Patients will have different states of compensation

The compensatory (adaptive) responses are:

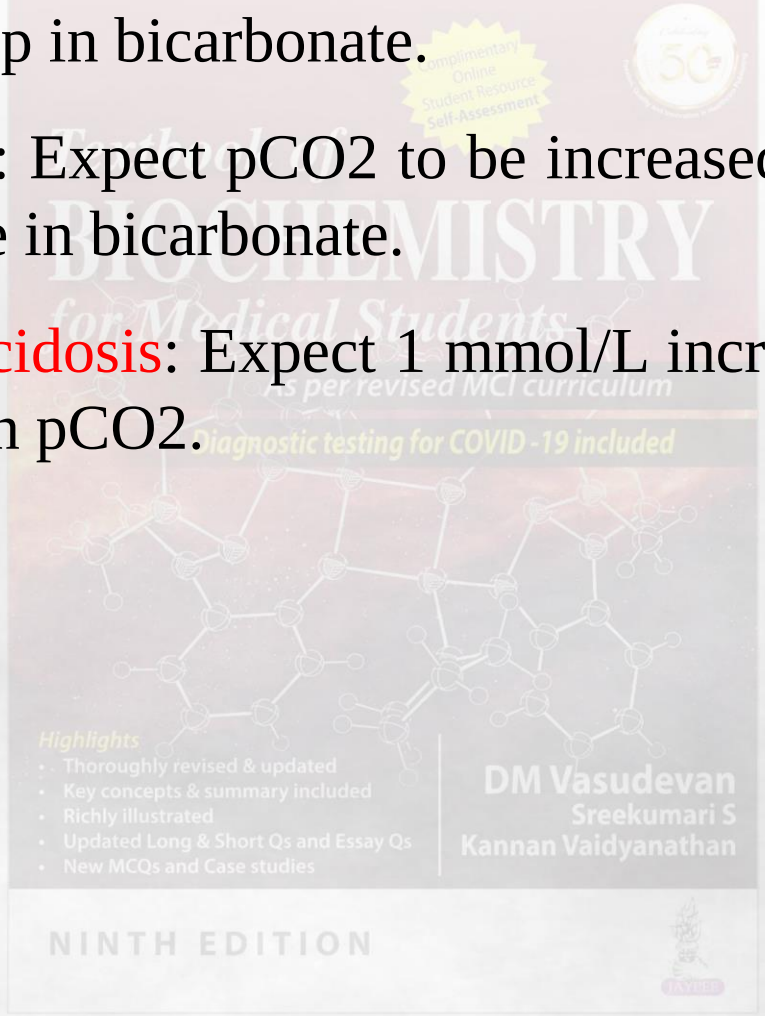


# Renal and Respiratory Compensations

Metabolic acidosis: Expect pCO2 to be reduced by 1 mmHg for every 1 mmol/L drop in bicarbonate.

Metabolic alkalosis: Expect pCO2 to be increased by 0.6 mmHg for every 1 mmol/L rise in bicarbonate.

Acute respiratory acidosis: Expect 1 mmol/L increase in bicarbonate per 10 mmHg rise in pCO2.

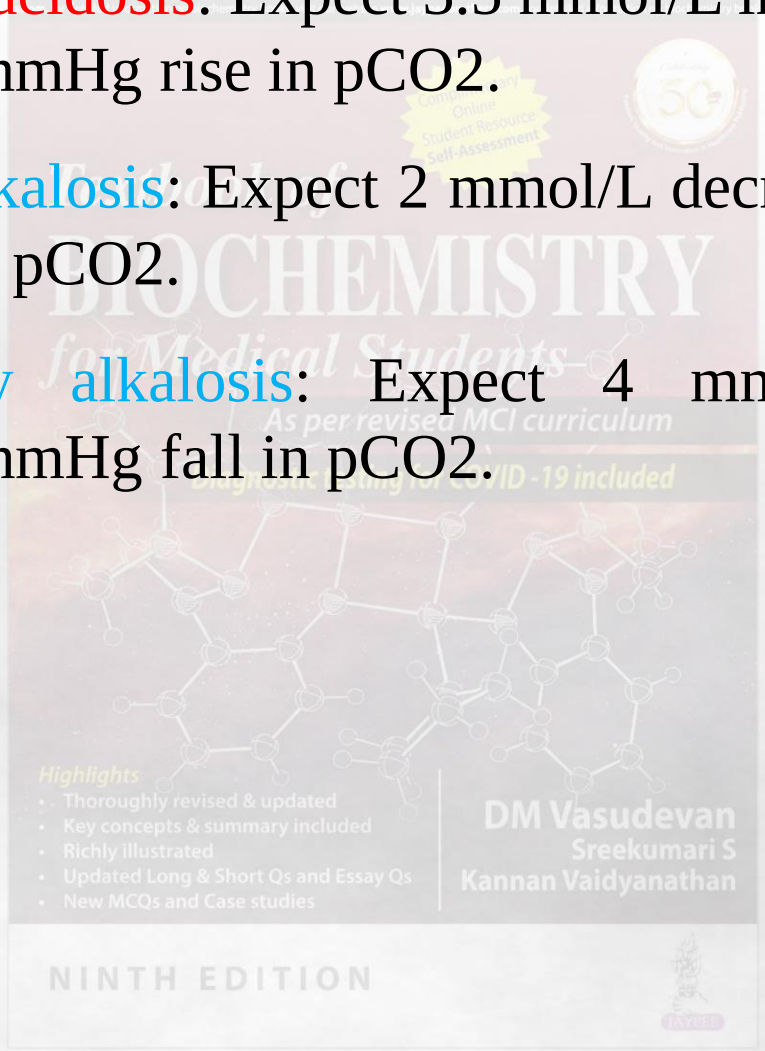


# Renal and Respiratory Compensations

Chronic respiratory acidosis: Expect 3.5 mmol/L increase in bicarbonate per 10 mmHg rise in pCO2.

Acute respiratory alkalosis: Expect 2 mmol/L decrease in bicarbonate per 10 mmHg fall in pCO2.

Chronic respiratory alkalosis: Expect 4 mmol/L decrease in bicarbonate per 10 mmHg fall in pCO2.



# Types of Acid-base Disturbances

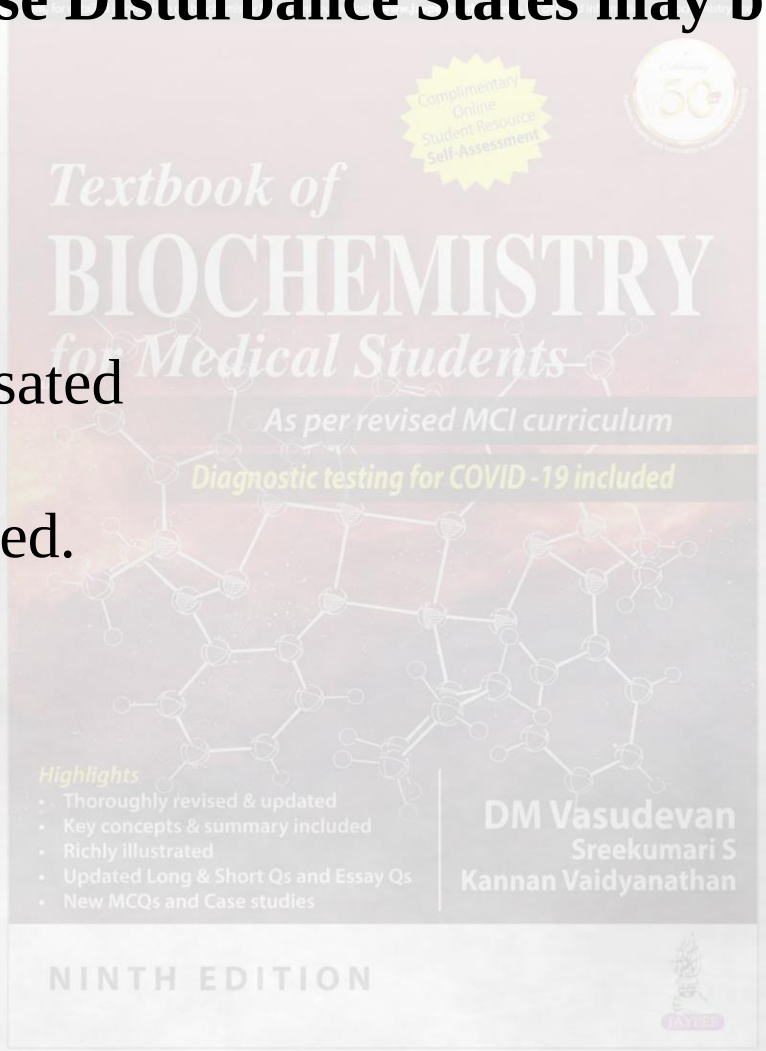
| Distur-bance | pH | Primary change | Ratio | Secondary change |
|---|---|---|---|---|
| Metabolic Acidosis | Decrease | Deficit of bicarb | <20 | Decrease in PaCO2 |
| Metabolic alkalosis | Increased | Excess of bicarb | >20 | Increase in PaCO2 |
| Respiratory acidosis | Decrease | Excess of carbonic acid | <20 | Increase in bicarb |
| Respiratory alkalosis | Increased | Deficit of carbonic acid | >20 | Decrease in bicarb |

**Clinically, Acid-base Disturbance States may be Divided into:**

i. Uncompensated

ii. Partially compensated

iii. Fully compensated.

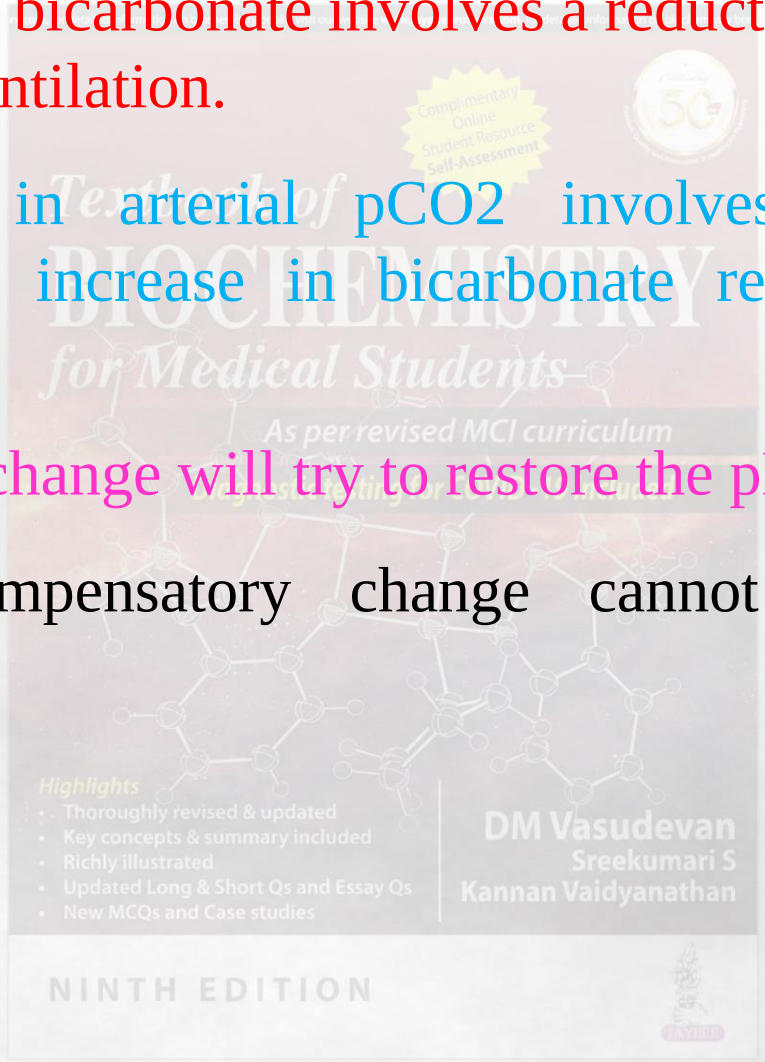


Primary decrease in bicarbonate involves a reduction in blood pCO2 by alveolar hyperventilation.

Primary increase in arterial pCO2 involves an increase in bicarbonate by an increase in bicarbonate reabsorption by the kidney.

The compensatory change will try to restore the pH to normal.

However, the compensatory change cannot fully correct a disturbance.

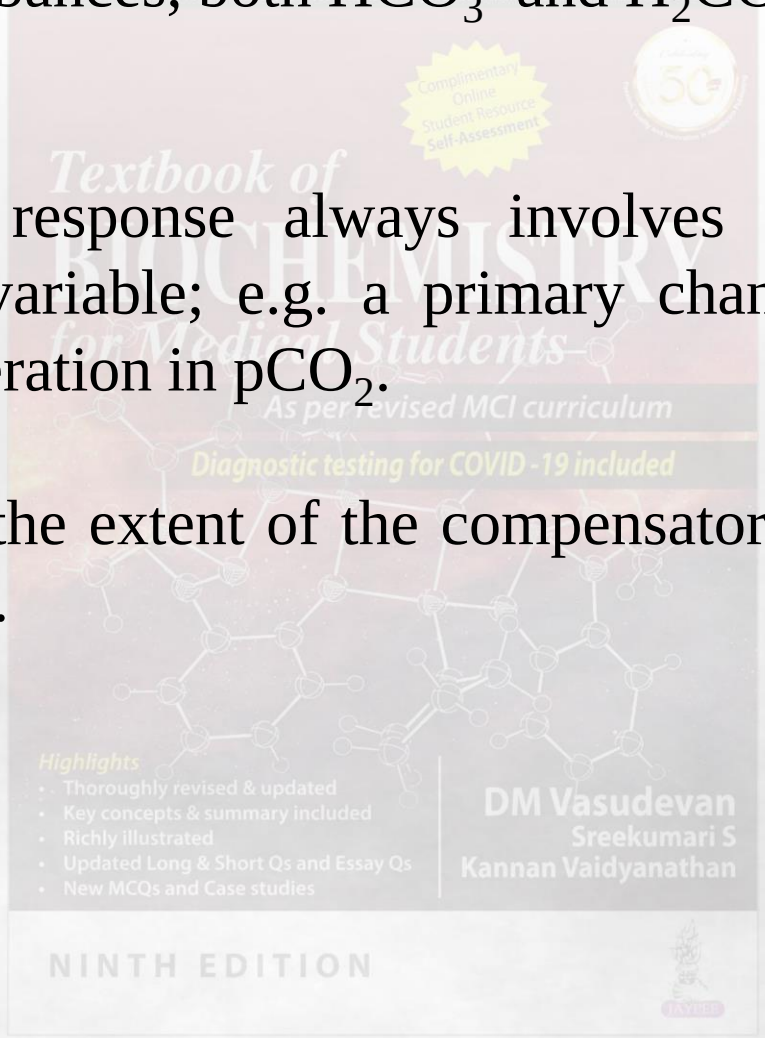


# Mixed Responses

i. In mixed disturbances, both $HCO_3^-$ and $H_2CO_3$ levels are altered

ii. The adaptive response always involves a change in the counteracting variable; e.g. a primary change in bicarbonate involves an alteration in $pCO_2$.

iii. Depending on the extent of the compensatory change there are different stages.



# Acid-base Disturbances: Expected Renal and Respiratory Compensations

- **Metabolic Acidosis**: Expect pCO2 to be reduced by 1 mm Hg for every 1 mmol/L drop in bicarbonate.
- **Metabolic Alkalosis**: Expect pCO2 to be increased by 0.6 mm Hg for every 1 mmol/L rise in bicarbonate.
- **Acute Respiratory Acidosis**: Expect 1 mmol/L increase in bicarbonate per 10 mm Hg rise in pCO2.
- **Chronic Respiratory Acidosis**: Expect 3.5 mmol/L increase in bicarbonate per 10 mm Hg rise in pCO2.
- **Acute Respiratory Alkalosis**: Expect 2 mmol/L decrease in bicarbonate per 10 mm Hg fall in pCO2.
- **Chronic Respiratory Alkalosis**: Expect 4 mmol/L decrease in bicarbonate per 10 mm Hg fall in pCO2.

# Stages of Compensation

| Stage | pH | HCO3 | PaCO2 | Ratio |
|---|---|---|---|---|
| Metabolic acidosis | Low | Low | N | < 20 |
| Partially compensated | Low | Low | Low | < 20 |
| Fully compensated | N | Low | Low | 20 |
| Metabolic alkalosis | High | High | N | > 20 |
| Partially compensated | High | High | High | > 20 |
| Fully compensated | N | High | High | 20 |

| Stage | pH | HCO3 | PaCO2 | Ratio |
|---|---|---|---|---|
| Respiratory acidosis | Low | N | High | <20 |
| Partially compensated | Low | High | High | <20 |
| Fully compensated | N | High | High | 20 |
| Respiratory alkalosis | High | N | Low | >20 |
| Partially compensated | High | Low | Low | >20 |
| Fully compensated | N | Low | Low | 20 |

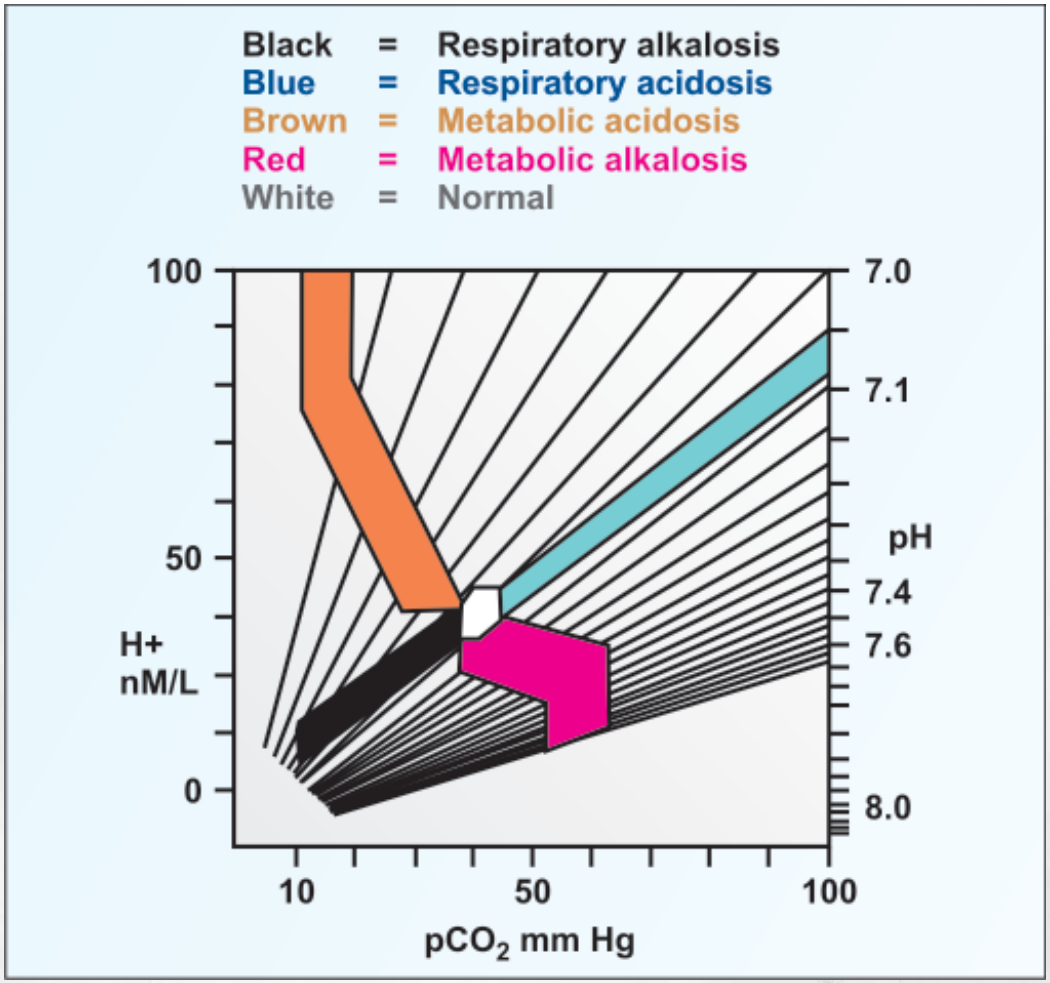


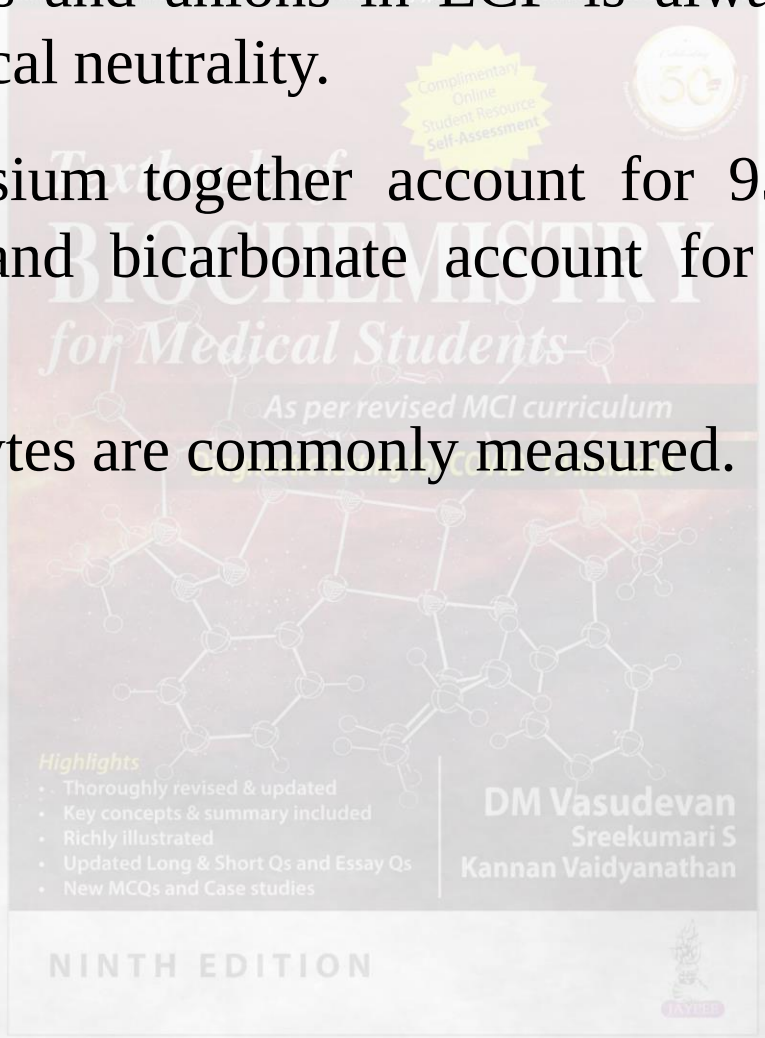

Fig. 29.6. Bicarbonate Diagram

# Anion Gap

The sum of cations and anions in ECF is always equal, so as to maintain the electrical neutrality.

Sodium and potassium together account for 95% of the cations whereas chloride and bicarbonate account for only 86% of the anions.

Only these electrolytes are commonly measured.

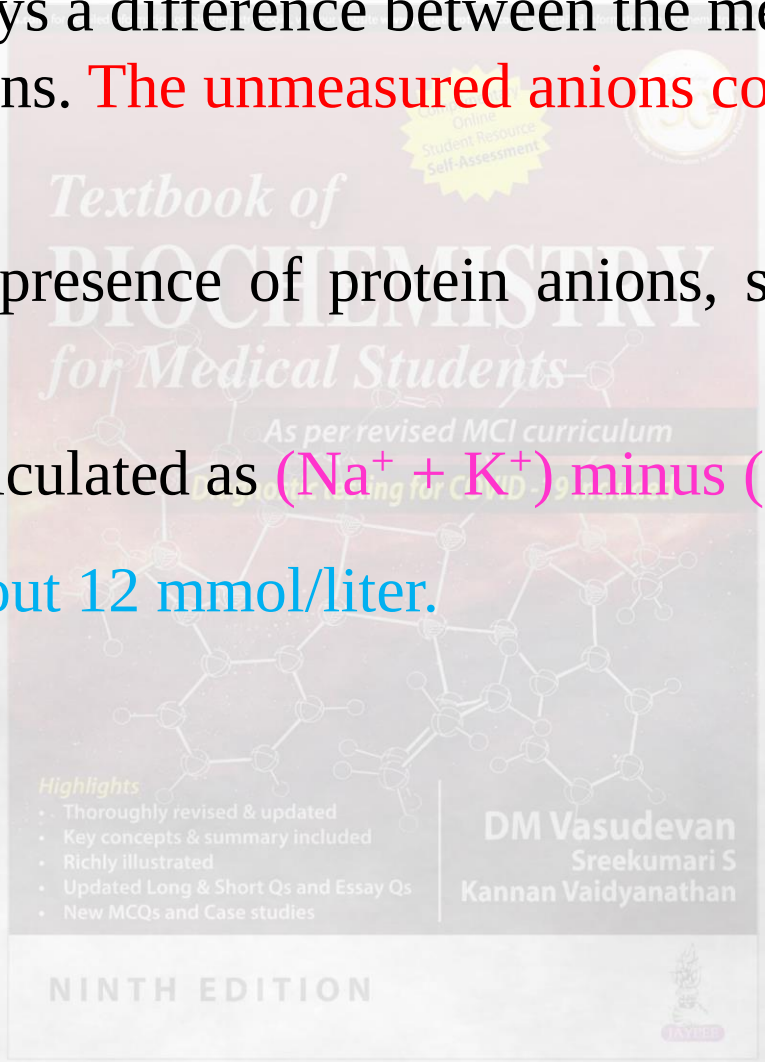


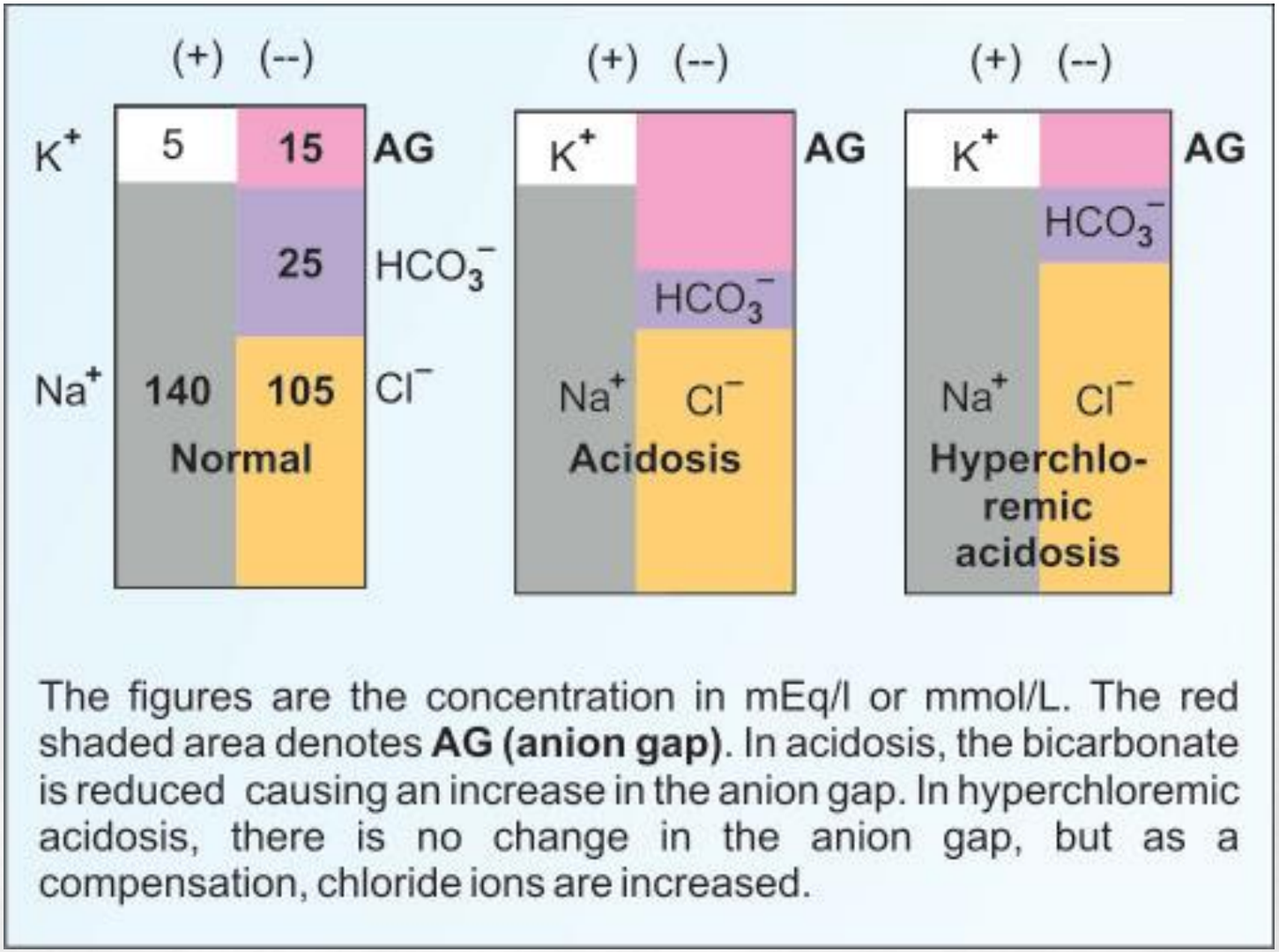
Hence there is always a difference between the measured cations and the anions. The unmeasured anions constitute the anion gap.

This is due to the presence of protein anions, sulphate, phosphate and organic acids.

The anion gap is calculated as $(Na^+ + K^+)$ minus $(HCO_3^- + Cl^-)$.

Normally this is about 12 mmol/liter.



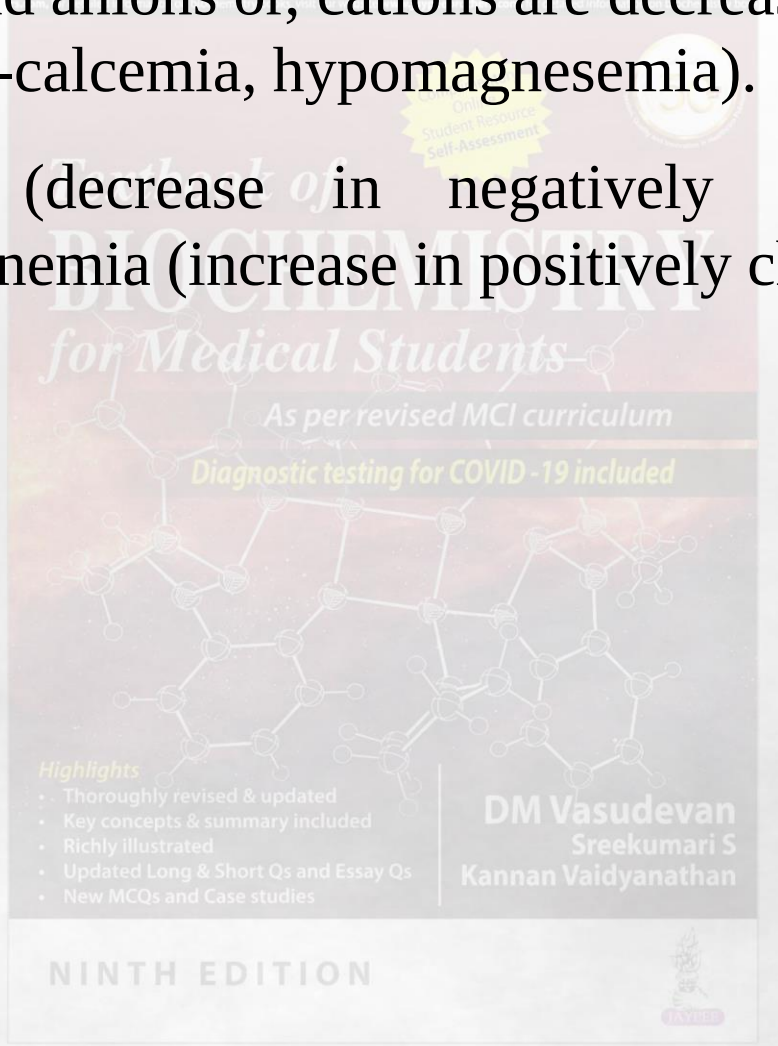



The figures are the concentration in mEq/l or mmol/L. The red shaded area denotes **AG (anion gap)**. In acidosis, the bicarbonate is reduced causing an increase in the anion gap. In hyperchloremic acidosis, there is no change in the anion gap, but as a compensation, chloride ions are increased.

# High Anion Gap Metabolic Acidosis (HAGMA)

Accumulation of acid anions or, cations are decreased (hypokalemia, hypo-calcemia, hypomagnesemia).

Hypoalbuminemia (decrease in negatively charged protein), hypergammaglobulinemia (increase in positively charged protein).



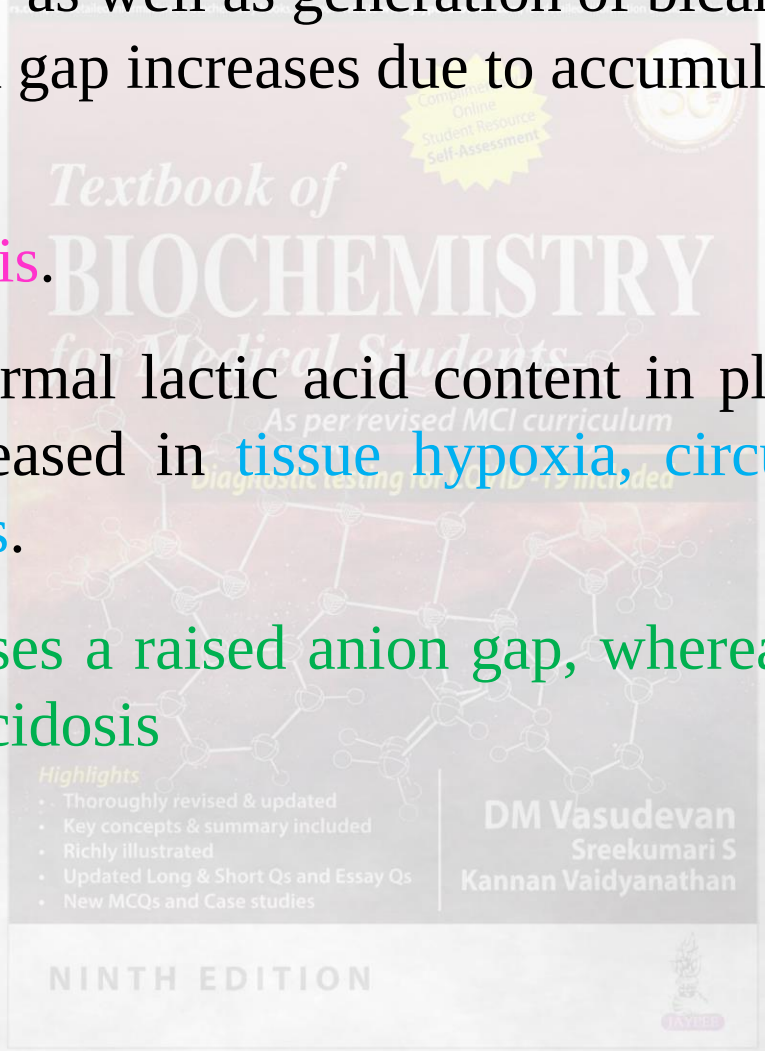
# Renal Failure

The excretion of H+ as well as generation of bicarbonate are both deficient. The anion gap increases due to accumulation of other buffer anions.

Diabetic ketoacidosis.

Lactic acidosis: Normal lactic acid content in plasma is less than 2 mmol/L. It is increased in tissue hypoxia, circulatory failure, and intake of biguanides.

Lactic acidosis causes a raised anion gap, whereas diarrhea causes a normal anion gap acidosis

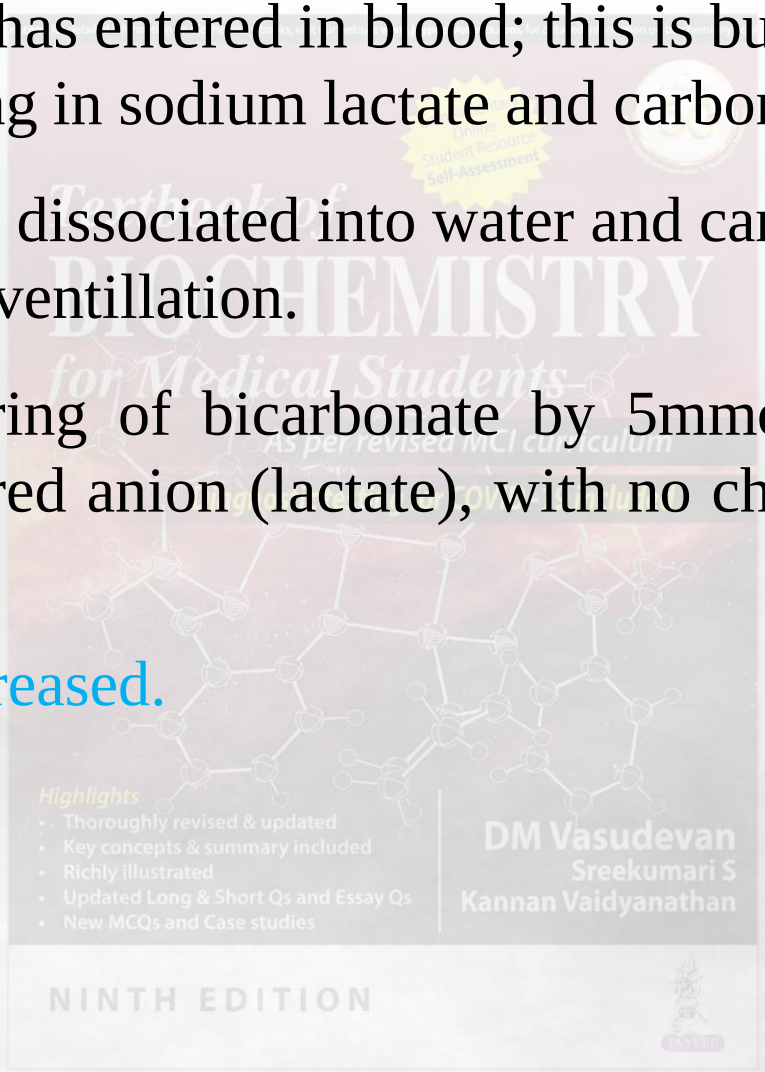


Suppose lactic acid has entered in blood; this is buffered by bicarbonate, resulting in sodium lactate and carbonic acid.

The carbonic acid is dissociated into water and carbon dioxide, which is removed by lung ventillation.

The result is lowering of bicarbonate by 5mmol and presence of 5mmol of unmeasured anion (lactate), with no changes in sodium or chloride.

So, anion gap is increased.

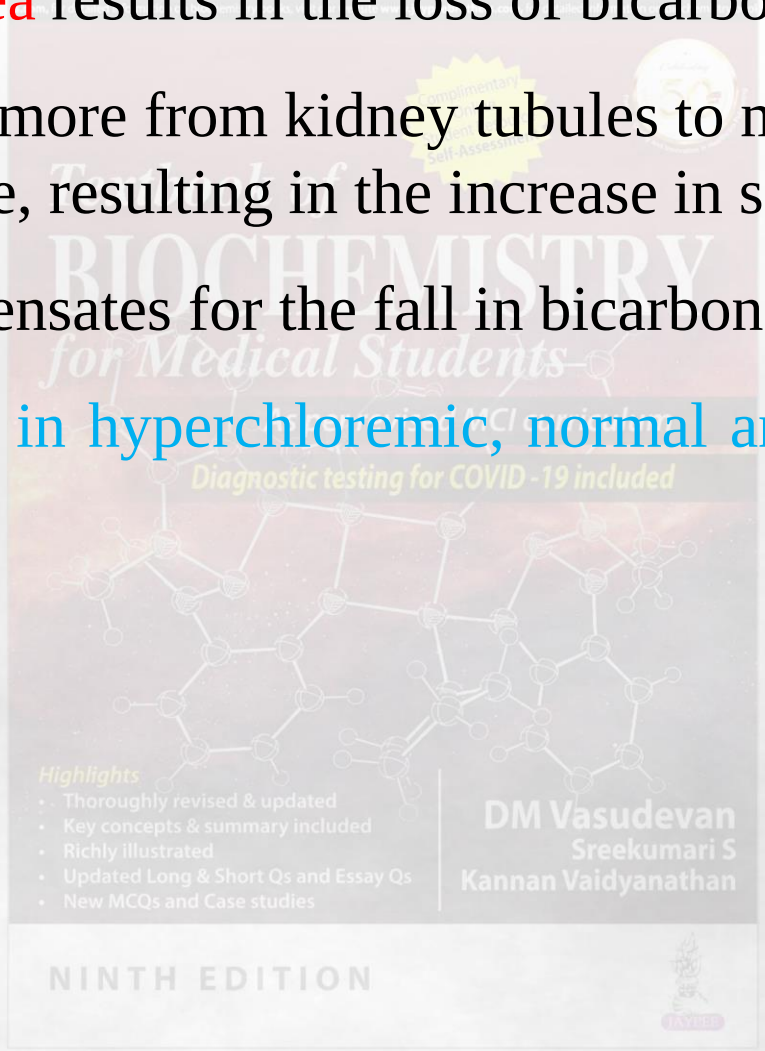


In contrast, diarrhoea results in the loss of bicarbonate.

NaCl is reabsorbed more from kidney tubules to maintain the extracellular volume, resulting in the increase in serum chloride.

This chloride compensates for the fall in bicarbonate.

So, diarrhea results in hyperchloremic, normal anion gap, metabolic acidosis.



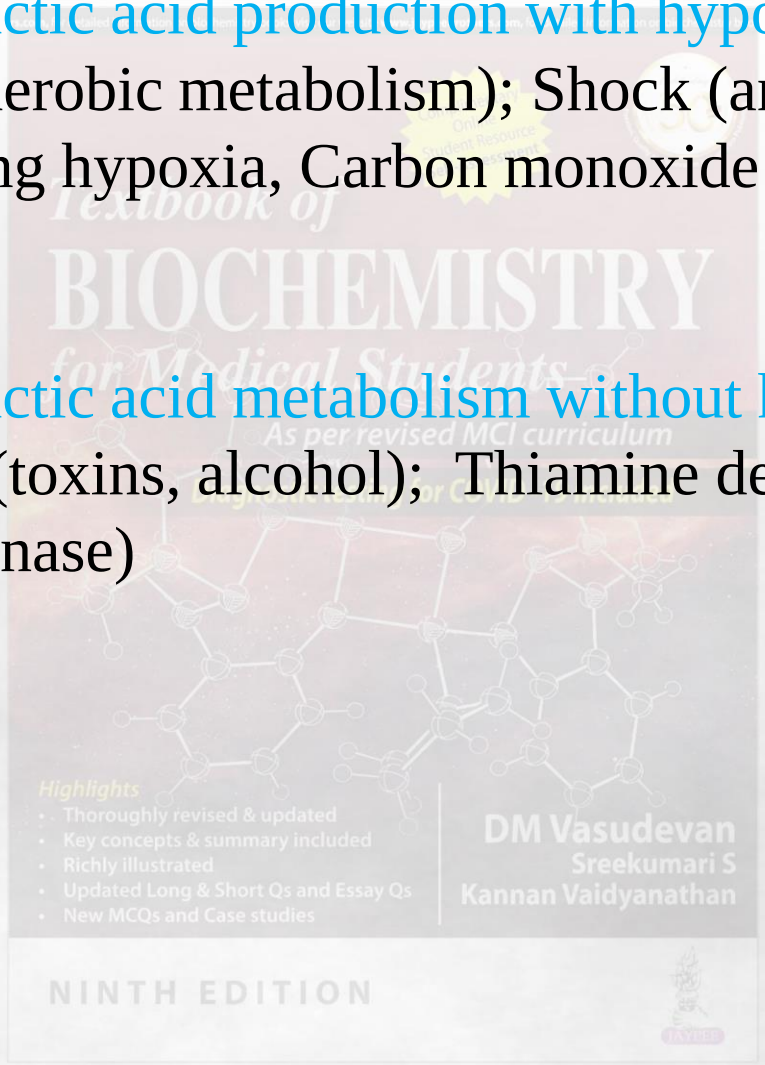
# Types of Lactic Acidosis

Type A: Impaired lactic acid production with hypoxia.

Tissue hypoxia (anaerobic metabolism); Shock (anaphylactic, septic, cardiac); Lung hypoxia, Carbon monoxide poisoning, seizures

Type B: Impaired lactic acid metabolism without hypoxia.

Liver dysfunctions (toxins, alcohol); Thiamine deficiency (defective pyruvate dehydrogenase)

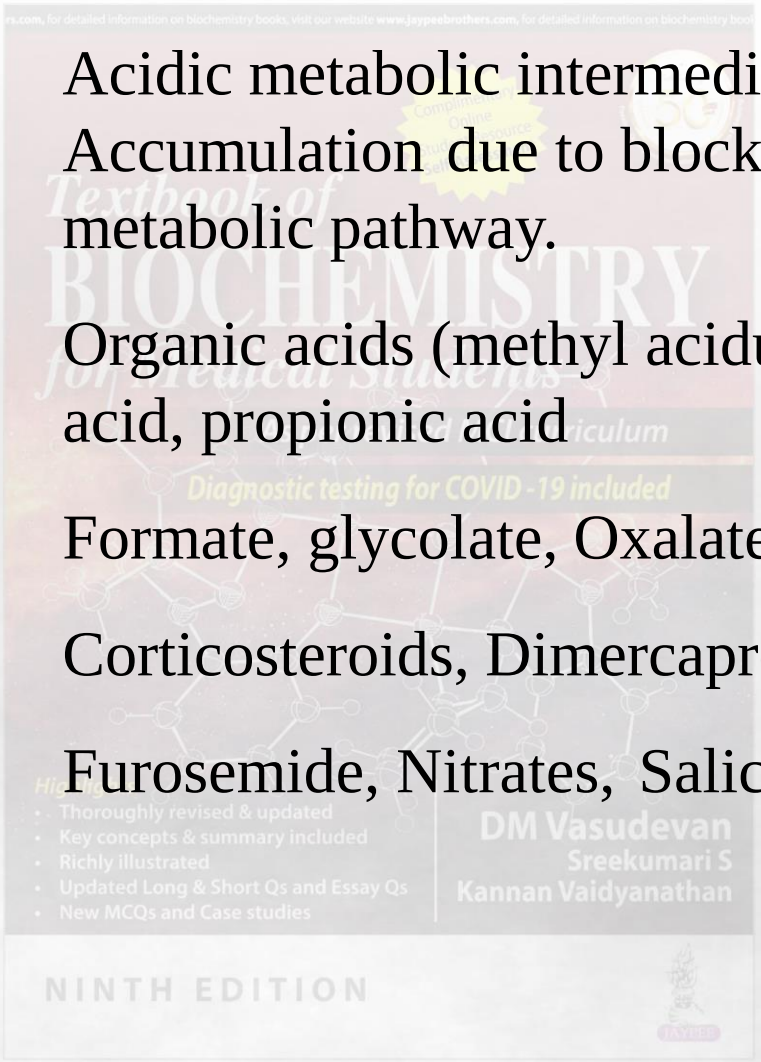


# High Anion Gap Metabolic Acidosis (HAGMA) (Organic Acidosis)

| Cause | Remarks |
|---|---|
| Renal failure | Sulfuric, phosphoric, organic anions. Decreased ammonium ion formation. Na+/H+ exchange results in decreased acid excretion. |
| Ketosis | Acetoacetate; beta hydroxy butyrate anions. Seen in diabetes mellitus starvation. |
| Lactic | Lactate anion accumulates acidosis when the rate of production exceeds rate of consumption. |
| Salicylate | Aspirin poisoning |

# High Anion Gap Metabolic Acidosis (HAGMA) (Organic Acidosis)

| | |
|---|---|
| Amino Acidurias | Acidic metabolic intermediates. Accumulation due to block in normal metabolic pathway. |
| Organic | Organic acids (methyl acidurias malonic acid, propionic acid |
| Methanol | Formate, glycolate, Oxalate ions. |
| Drugs | Corticosteroids, Dimercaprol, Furosemide, Nitrates, Salicylates, Thiazides |

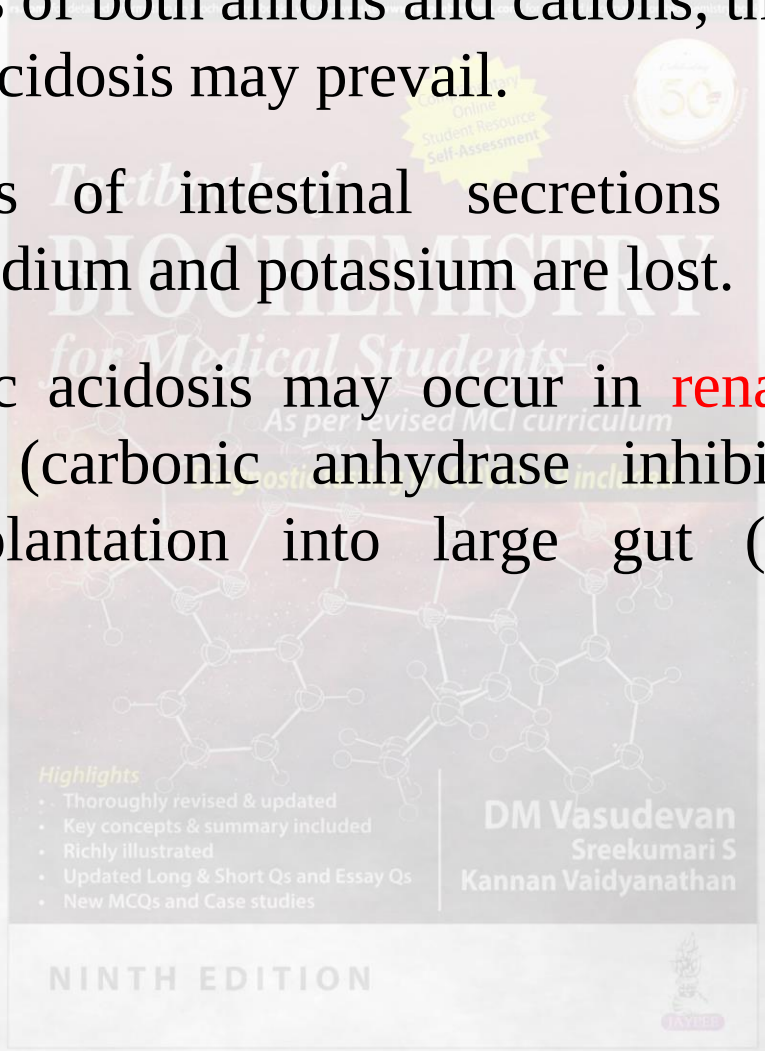


# Normal Anion Gap Metabolic Acidosis (NAGMA)

When there is a loss of both anions and cations, the anion gap is normal, but acidosis may prevail.

i. Diarrhea: Loss of intestinal secretions lead to acidosis. Bicarbonate, sodium and potassium are lost.

ii. Hyperchloremic acidosis may occur in renal tubular acidosis, acetazolamide (carbonic anhydrase inhibitor) therapy, and ureteric transplantation into large gut (done for bladder carcinoma).



a. Renal tubular acidosis: failure to excrete acid or reabsorb bicarbonate.

b. Chloride is elevated since electrical neutrality has to be maintained.

c. In ureteric transplantation, the chloride ions are reabsorbed in exchange for bicarbonate ions lost, leading to hyperchloremic acidosis.

d. Acetazolamide therapy results in metabolic acidosis because HCO3– generation and H+ secretion are affected.

# Urine Anion Gap (UAG)

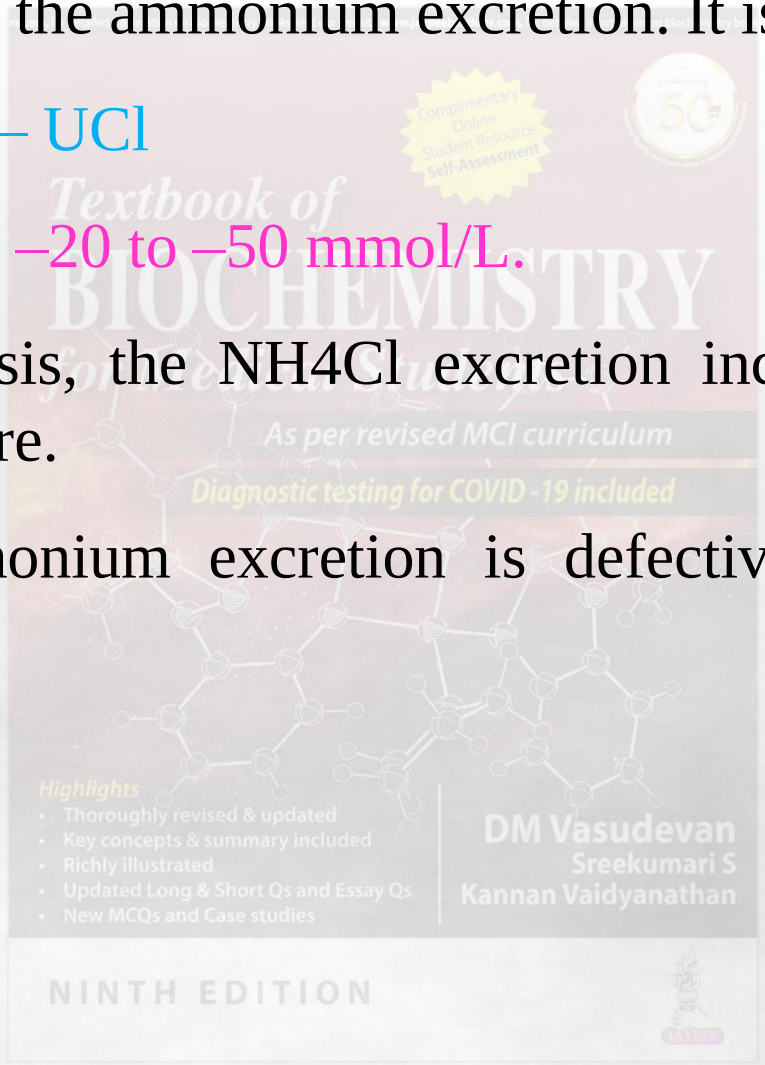
is useful to estimate the ammonium excretion. It is calculated as

UAG = UNa + UK – UCl

The normal value is –20 to –50 mmol/L.

In metabolic acidosis, the NH4Cl excretion increases, and UAG becomes –75 or more.

But in RTA, ammonium excretion is defective, and UAG has positive value.

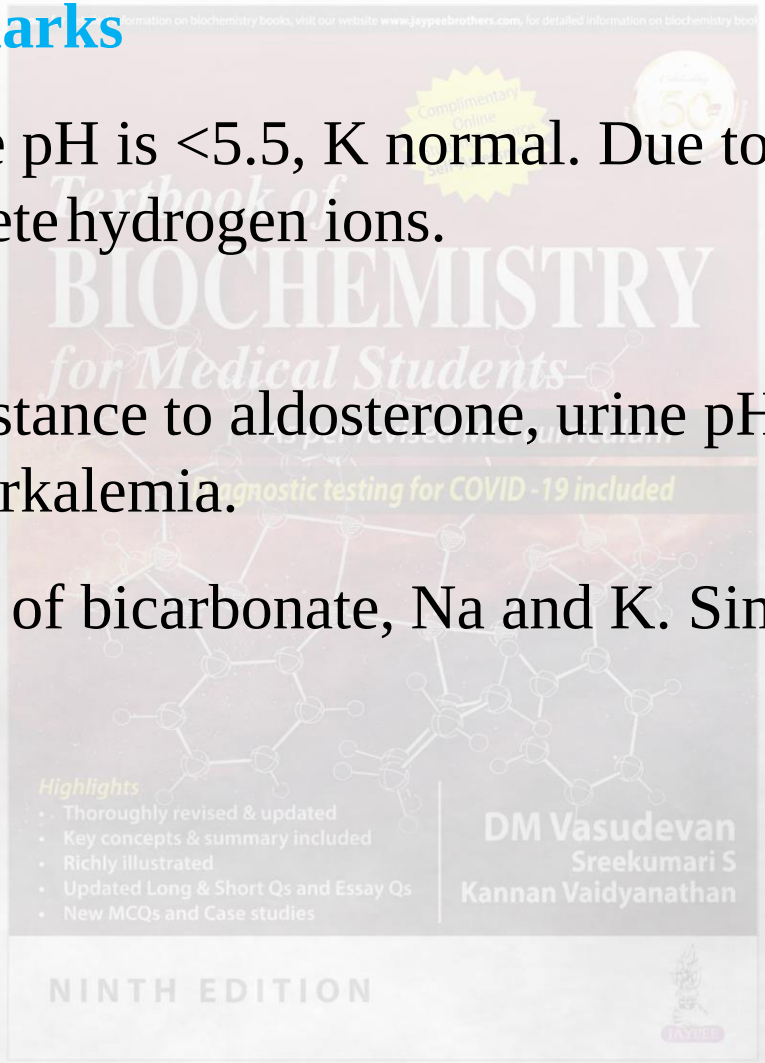


# Normal Anion Gap Metabolic Acidosis (NAGMA) (Inorganic Acidosis)

| Cause | Remarks |
|---|---|
| Diarrhea, intestinal fistula | Loss of bicarbonate and cations. Sodium or Potassium or both. |
| RTA | Defective acidification of Type I urine. urine pH is >5.5 or distal with hypokalemia. |
| RTA | Due to inability to reabsorb bicarbonate. Compensatory increase in chloride (hyperchloremic acidosis). |

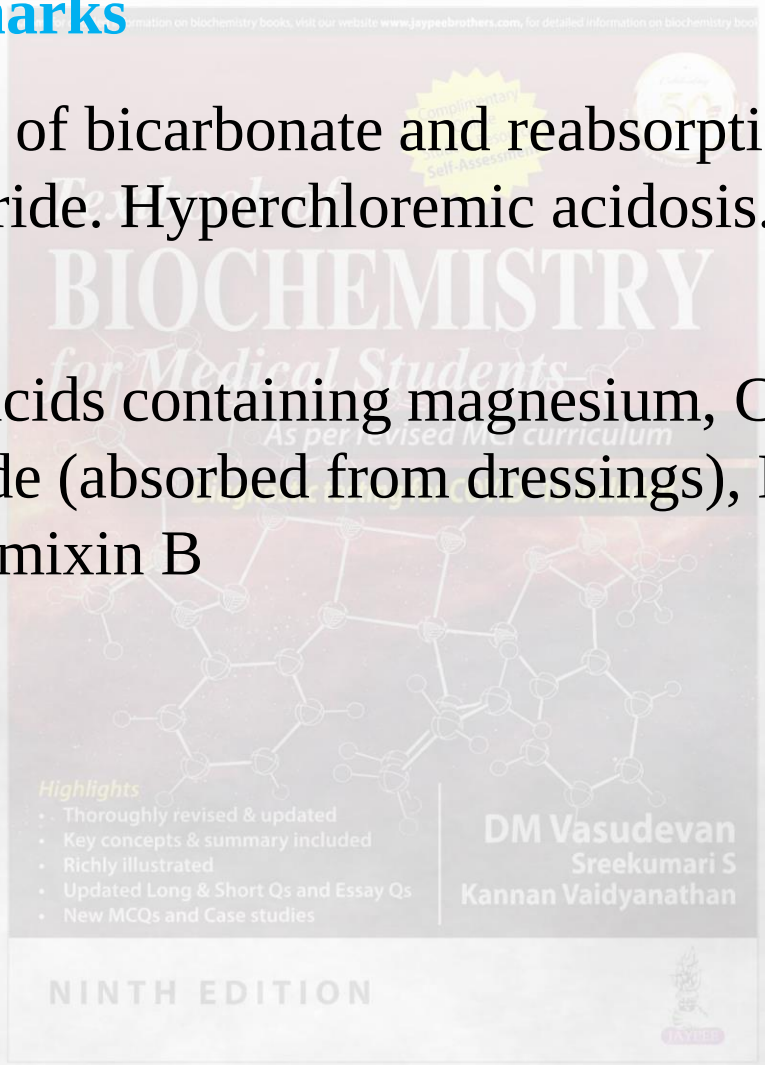
# Normal Anion Gap Metabolic Acidosis (NAGMA) (Inorganic Acidosis)

| Cause | Remarks |
|---|---|
| Type II or proximal RTA | urine pH is <5.5, K normal. Due to inability to excrete hydrogen ions. |
| Type IV | Resistance to aldosterone, urine pH <5.5, hyperkalemia. |
| Carbonic anhydrase inhibitors | Loss of bicarbonate, Na and K. Similar to proximal RTA |



# Normal Anion Gap Metabolic Acidosis

| Cause | Remarks |
|---|---|
| Uretero-sigmioido-stomy | Loss of bicarbonate and reabsorption of chloride. Hyperchloremic acidosis. |
| Drugs | Antacids containing magnesium, Chlorpropamide, Iodide (absorbed from dressings), Lithium, Polymixin B |



# Causes of Renal Tubular Acidosis

## Type I (Proximal RTA)

Multiple myeloma, Amyloidosis, Heavy metals; lead, mercury, Wilson's disease Galactosemia, Hyperparathyroidism Paroxysmal nocturnal hemoglobinuria Acetazolamide

## Type II (Distal RTA)

Autoimmune disorders; SLE, rheumatoid Hypercalciuria, Amphotericin B, Lithium Obstructive uropathy, Marfan's syndrome

## Type IV

Impaired aldosterone secretion

# Decreased Anion Gap is seen in

Hypo albuminemia

Multiple myeloma (paraproteinemia)

Bromide intoxication

Hypercalcemia

## Osmolal Gap

Difference between the measured plasma osmolality and the calculated osmolality,

2 x [Na] + [glucose] + [urea]

The normal osmolal gap is<10 mOsm.

A high osmolal gap (> 25) implies the presence of unmeasured osmoles such as alcohol, methanol, ethylene glycol, etc.

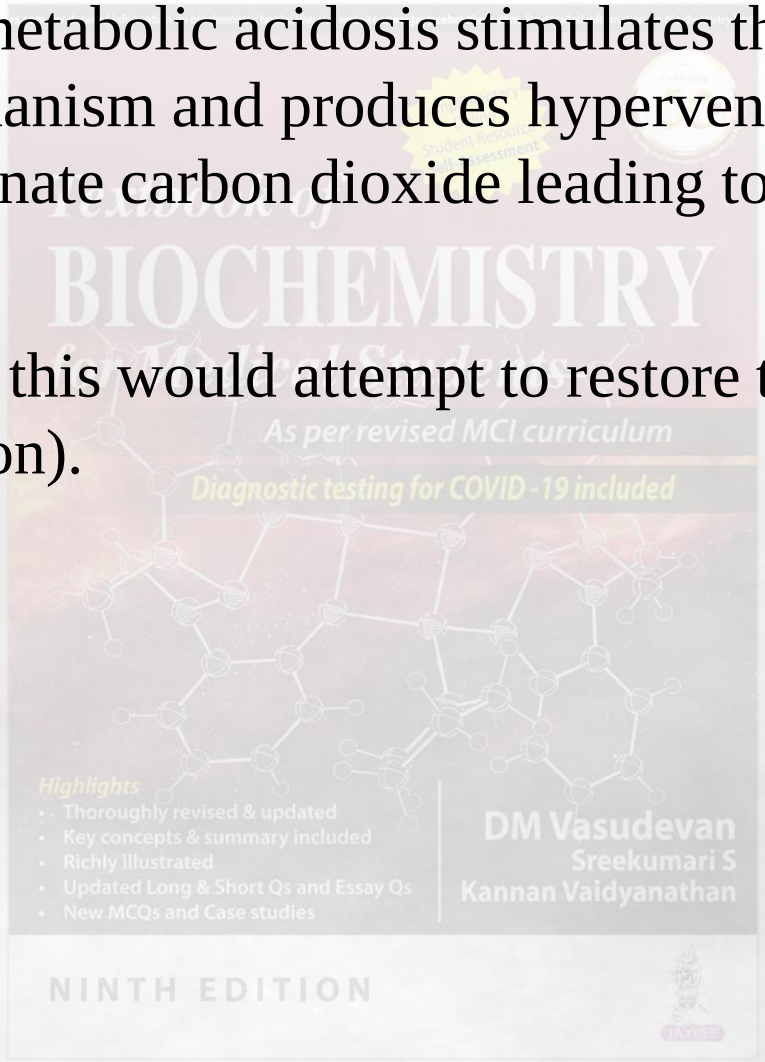
Acute poisoning = a raised anion gap metabolic acidosis and an increased plasma osmolal gap. Poisoning with methanol and ethylene glycol should be considered. They are metabolized to formic acid and oxalic acids correspondingly.

Methanol will produce blindness. Ethylene glycol will lead to oxalate crystalluria and renal failure.

# Compensated Metabolic Acidosis

Decrease in pH in metabolic acidosis stimulates the respiratory compensatory mechanism and produces hyperventilation (Kussmaul respiration) to eliminate carbon dioxide leading to hypocapnia (Hypocarbia).

The pCO2 falls and this would attempt to restore the ratio towards 20 (partial compensation).



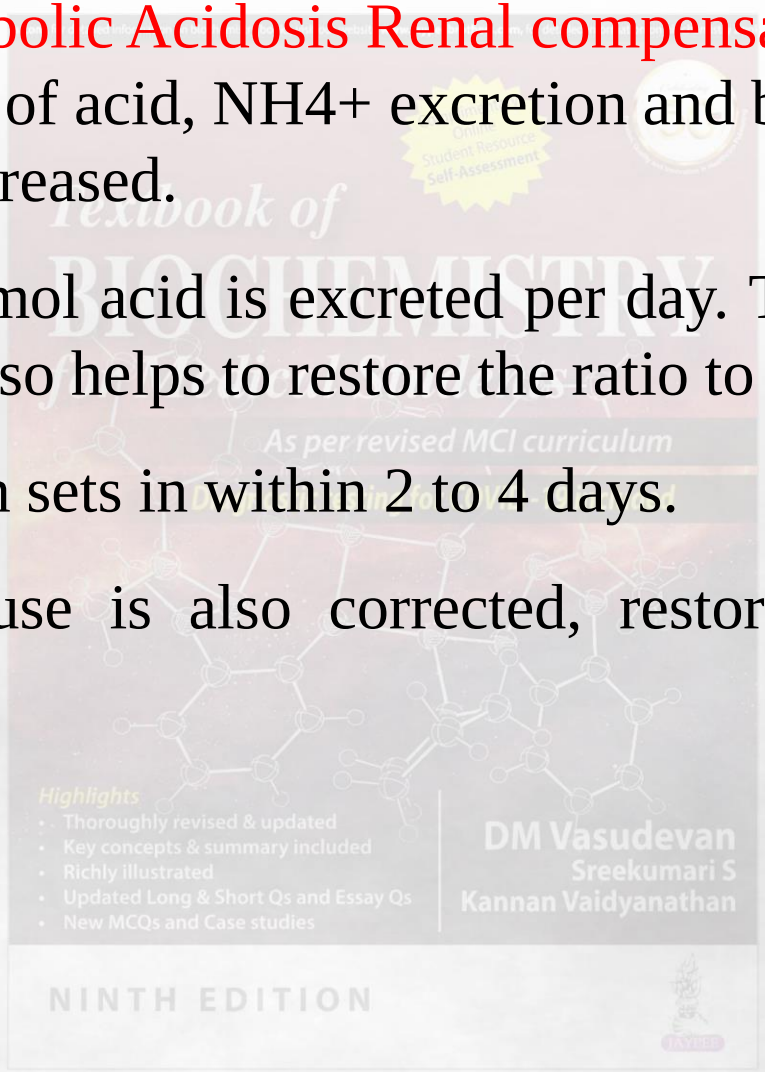
## Compensated Metabolic Acidosis Renal compensation:

Increased excretion of acid, NH4+ excretion and bicarbonate reabsorption are increased.

As much as 500 mmol acid is excreted per day. The reabsorption of more bicarbonate also helps to restore the ratio to 20.

Renal compensation sets in within 2 to 4 days.

But unless the cause is also corrected, restoration of normalcy cannot occur.

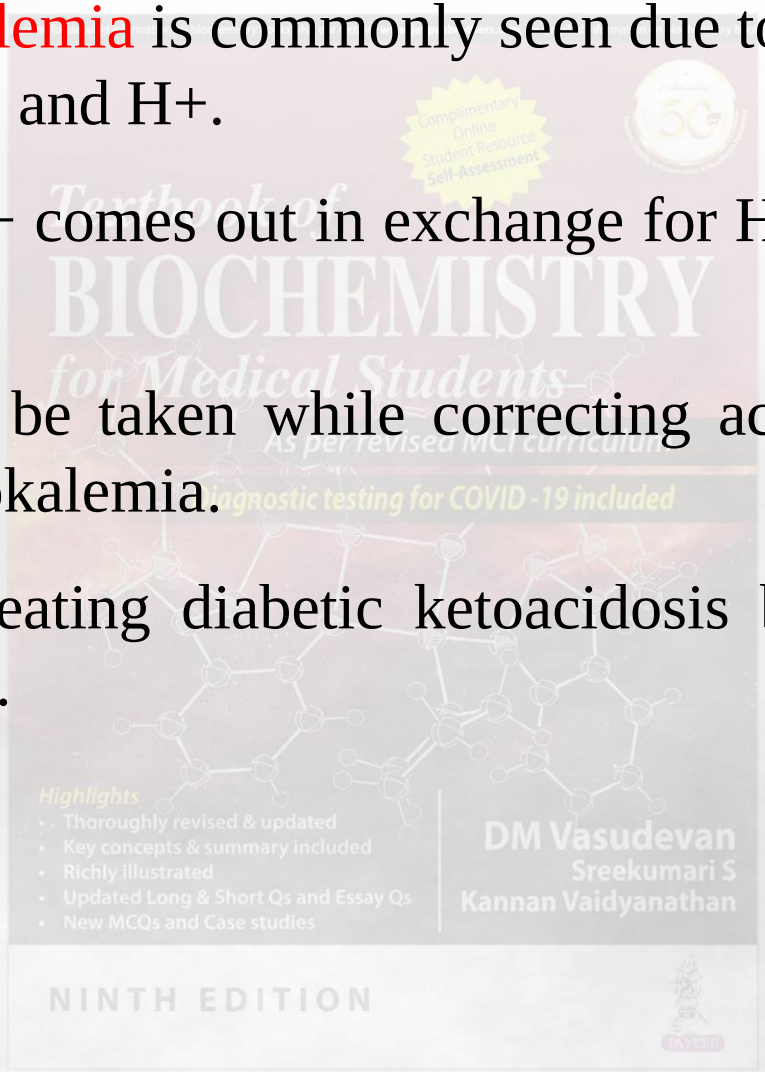


Associated hyperkalemia is commonly seen due to a redistribution of K+ and H+.

The intracellular K+ comes out in exchange for H+ moving into the cells.

Hence care should be taken while correcting acidosis which may lead to sudden hypokalemia.

Especially when treating diabetic ketoacidosis by giving glucose and insulin together.

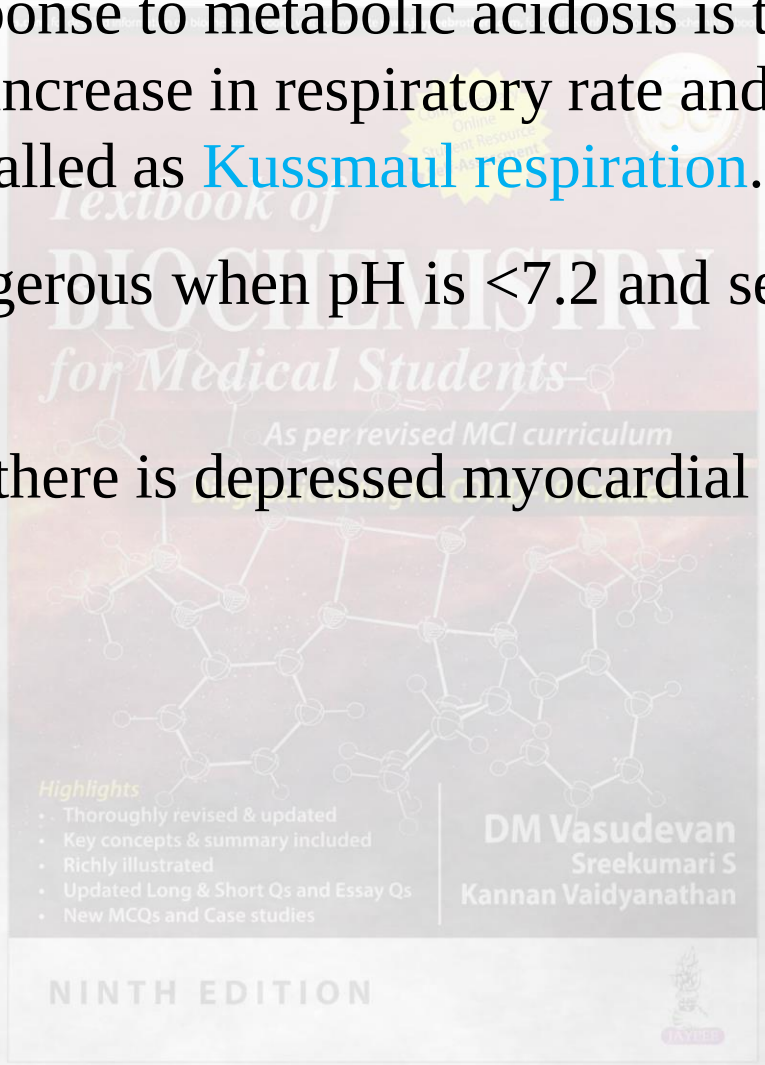


# Clinical Features of Metabolic Acidosis

The respiratory response to metabolic acidosis is to hyperventillate. So there is marked increase in respiratory rate and depth of respiration; this is called as Kussmaul respiration.

The acidosis is dangerous when pH is <7.2 and serum bicarbonate is <10 mmol/L.

In such conditions, there is depressed myocardial contractility.



# Treatment of Metabolic Acidosis

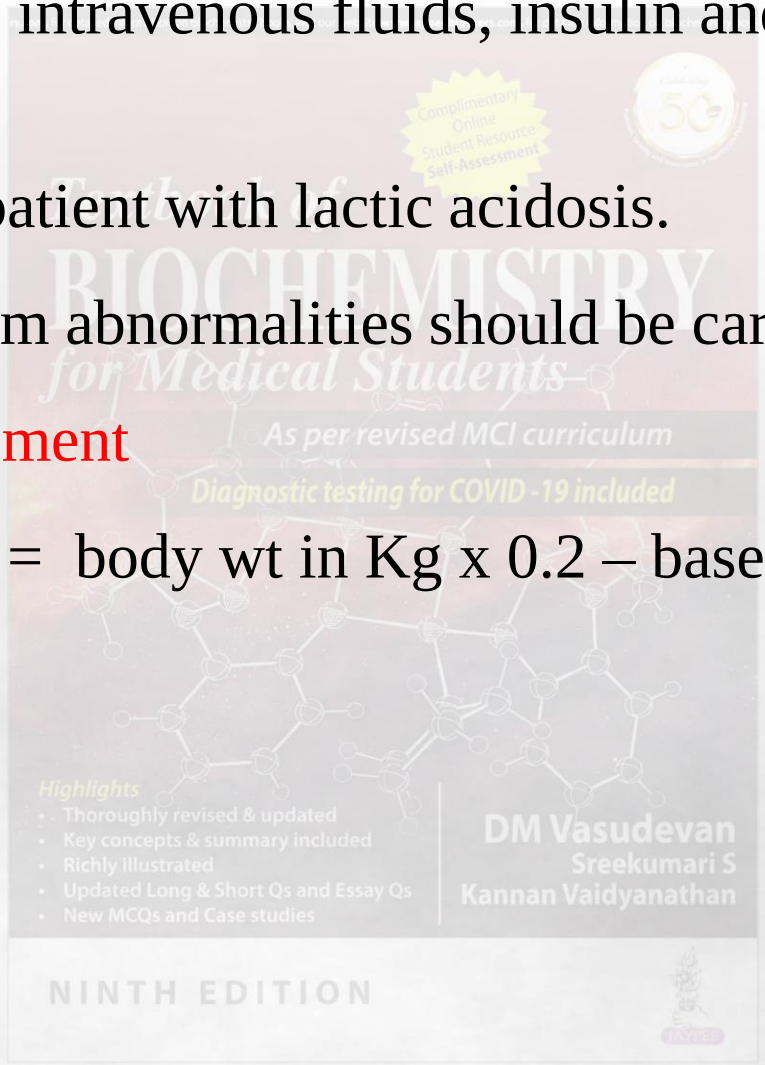
In ketoacidosis, give intravenous fluids, insulin and potassium replacement.

Oxygen is given in patient with lactic acidosis.

In all cases, potassium abnormalities should be carefully treated.

## Bicarbonate Requirement

mEq of base needed = body wt in Kg x 0.2 – base excess in mEq/L.



# Metabolic Alkalosis

Primary excess of bicarbonate.

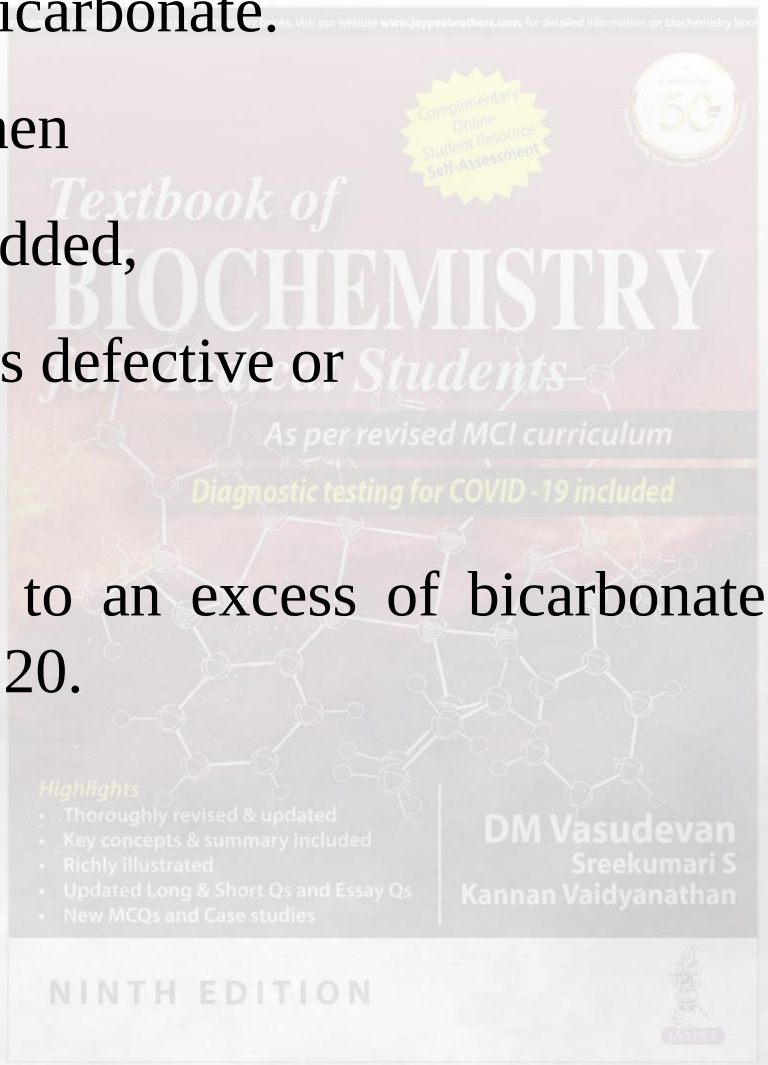
Alkalosis occurs when

a) excess base is added,

b) base excretion is defective or

c) acid is lost.

All these will lead to an excess of bicarbonate, so that the ratio becomes more than 20.



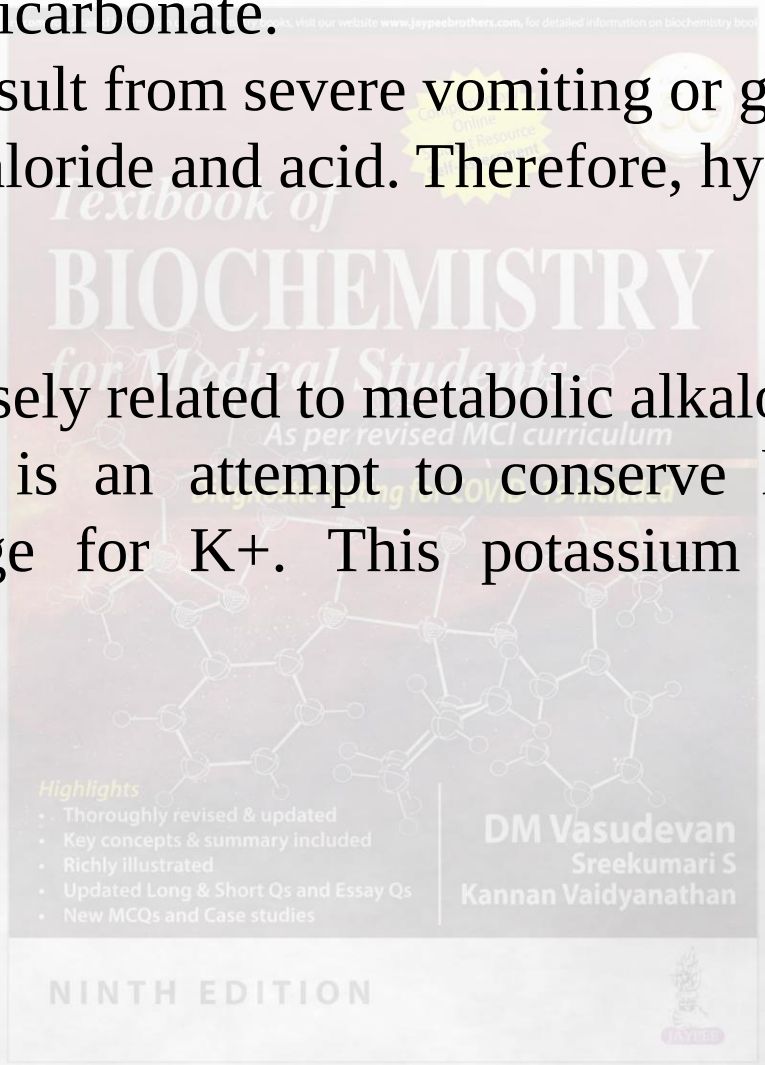
# Metabolic Alkalosis

Primary excess of bicarbonate.

Loss of acid may result from severe vomiting or gastric aspiration leading to loss of chloride and acid. Therefore, hypochloremic alkalosis results.

Hypokalemia is closely related to metabolic alkalosis.

In alkalosis, there is an attempt to conserve hydrogen ions by kidney in exchange for K+. This potassium loss can lead to hypokalemia.

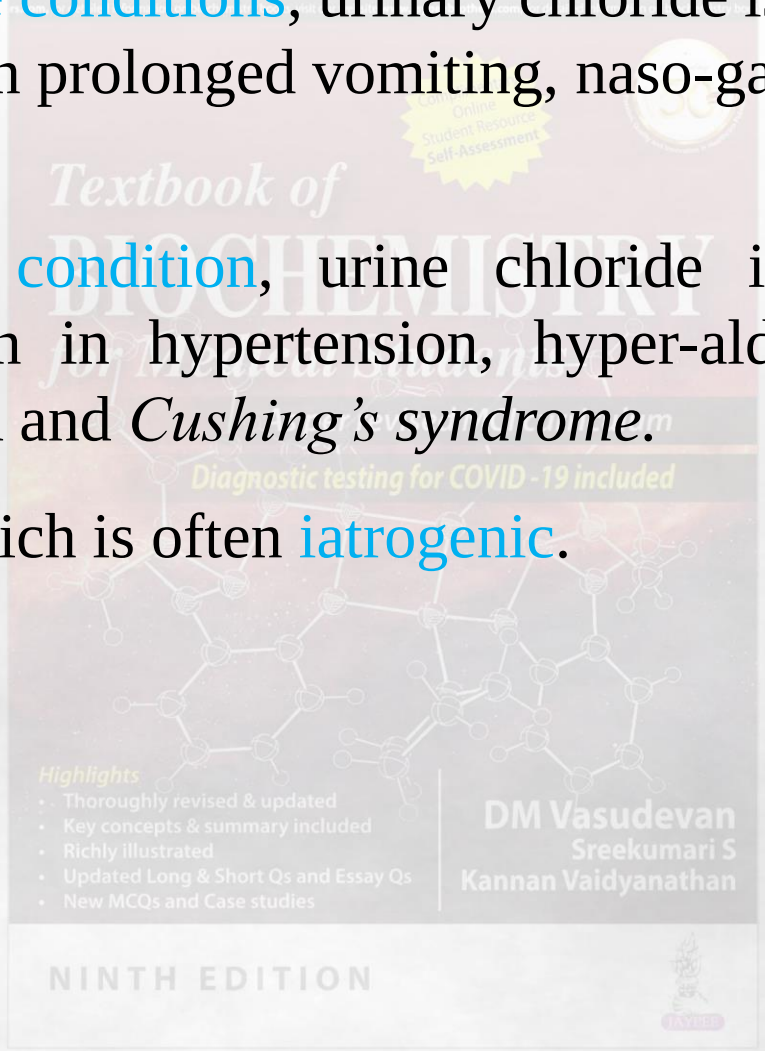


# Subclassification of Metabolic Alkalosis

Chloride responsive conditions, urinary chloride is less than 10 mmol/L. It is seen in prolonged vomiting, naso-gastric aspiration or diuretics.

Chloride resistant condition, urine chloride is greater than 10 mmol/L; it is seen in hypertension, hyper-aldosteronism, severe potassium depletion and *Cushing's syndrome*.

Exogenous base which is often iatrogenic.



# Metabolic Alkalosis

| Type | Causes | Changes |
|---|---|---|
| Chloride Responsive Alkalosis; Contraction alkalosis | Prolonged vomiting, Nasogastric suction, Upper GI obstruction | Urine Chloride <10 mmol/L; Hypovolemia, increased loss of Cl, K, H ions. Increased reabsorption of Na with bicarbonate; Loss of H+ and K+. Hypokalemia leads to alkalosis due to H+-K+ exchange. Cl is reabsorbed along with Na. Hence urine chloride is low. Alkalosis responds to administration of NaCl |
| Loop diuretics | Blocks reabsorption of Na, K and Cl | Aldosterone secretion occurs causing Na retention and wastage of K+ and H+ |

# Metabolic Alkalosis

| Type | Causes | Changes |
|---|---|---|
| Chloride resistant metabolic alkalosis | Mineralocorti-coid excess, Primary and secondary hyper aldo-steronism, Glucocorticoid excess, Cushing's, Adrenal tumor | Urine chloride > 20 mmol/L Defective renal Cl- reabsorption Associated with an underlying cause where excess mineralocorticoid activity results in Bartter's syndrome, increased sodium retention with wastage of H and K ions at the renal tubules |
| Exogenous base | Intravenous bicarbonate, Massive blood transfusion, Antacids, Milk alkali syndrome, Sodium Citrate overload | Excess base enters the body or potential generation of bicarbonate from metabolism of organic acids like lactate, ketoacids, citrate and salicylate |

# Clinical Features of Metabolic Alkalosis

The respiratory center is depressed leading to hypoventilation. Accumulation of $CO_2$ in an attempt to lower the $HCO_3^-$ / $H_2CO_3$ ratio.

The renal mechanism conserves $H^+$ and excretes more $HCO_3^-$. However, complete correction of alkalosis will be effective only if potassium is administered and the cause is removed

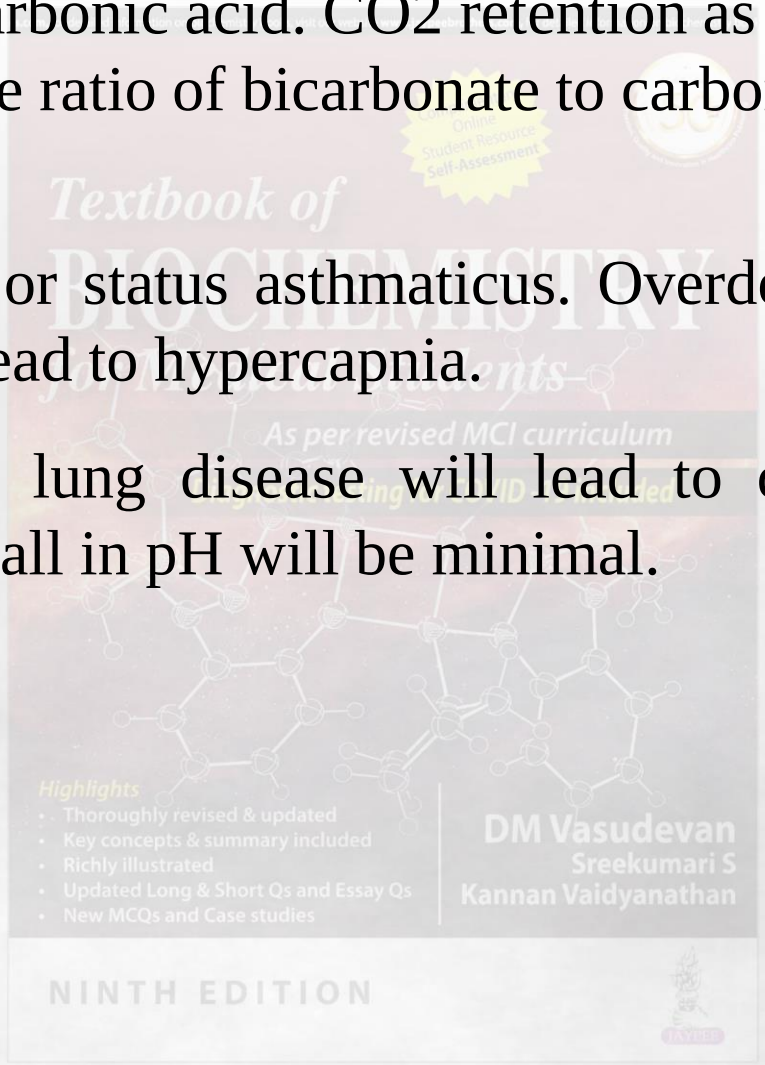
Increased neuromuscular activity when pH is above 7.55. Tetany results even in the presence of normal serum calcium.

# Respiratory Acidosis

Primary excess of carbonic acid. CO2 retention as a result of hypoventillation. The ratio of bicarbonate to carbonic acid will be less than 20.

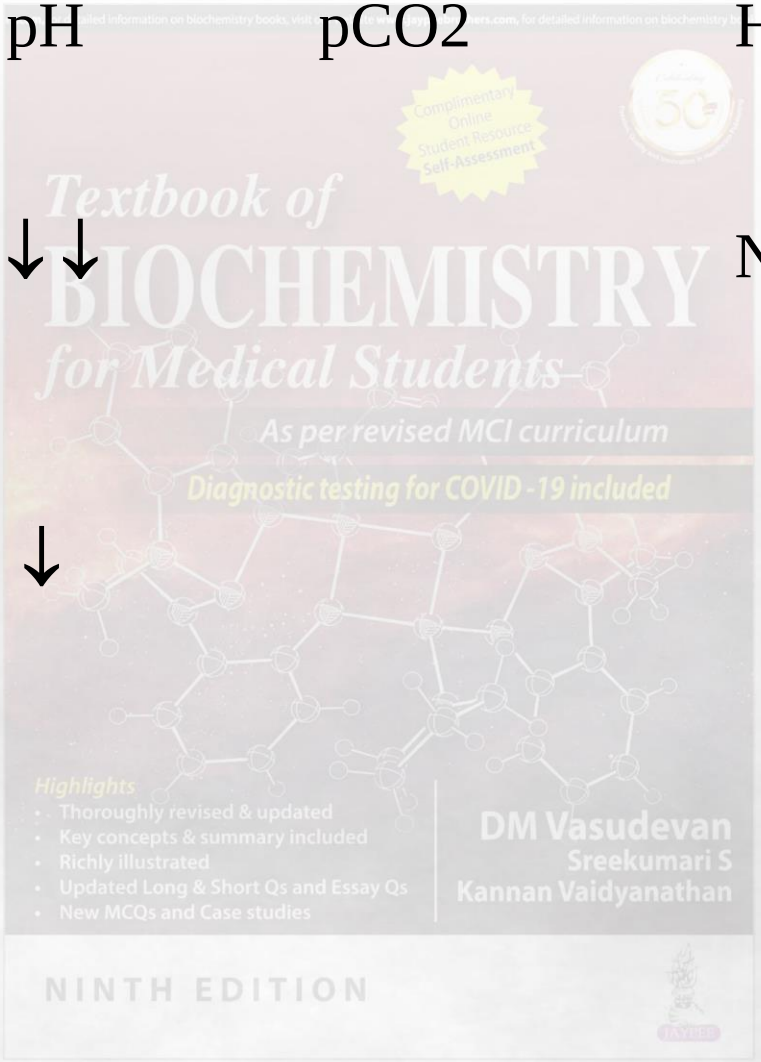
Bronchopneumonia or status asthmaticus. Overdose of sedatives or narcotics may also lead to hypercapnia.

Chronic obstructive lung disease will lead to chronic respiratory acidosis, where the fall in pH will be minimal.



# Lab Findings in Respiratory Acidosis

| | pH | pCO2 | $HCO_3^-$ |
|---|---|---|---|
| Acute respiratory Acidosis | ↓ | ↓ | N or |
| Chronic respiratory acidosis (partially compensated) | | ↓ | |



# Respiratory Alkalosis

Primary deficit of carbonic acid. Hyperventilation will result in washing out of $CO_2$.

Bicarbonate : carbonic acid ratio is > 20.

Hysterica, raised intracranial pressure and brain stem injury.

Early stage of salicylate poisoning causes respiratory alkalosis due to stimulation of respiratory center. But later, it ends up in metabolic acidosis due to accumulation of organic acids, lactic and keto acids. Lung diseases (pneumonia).

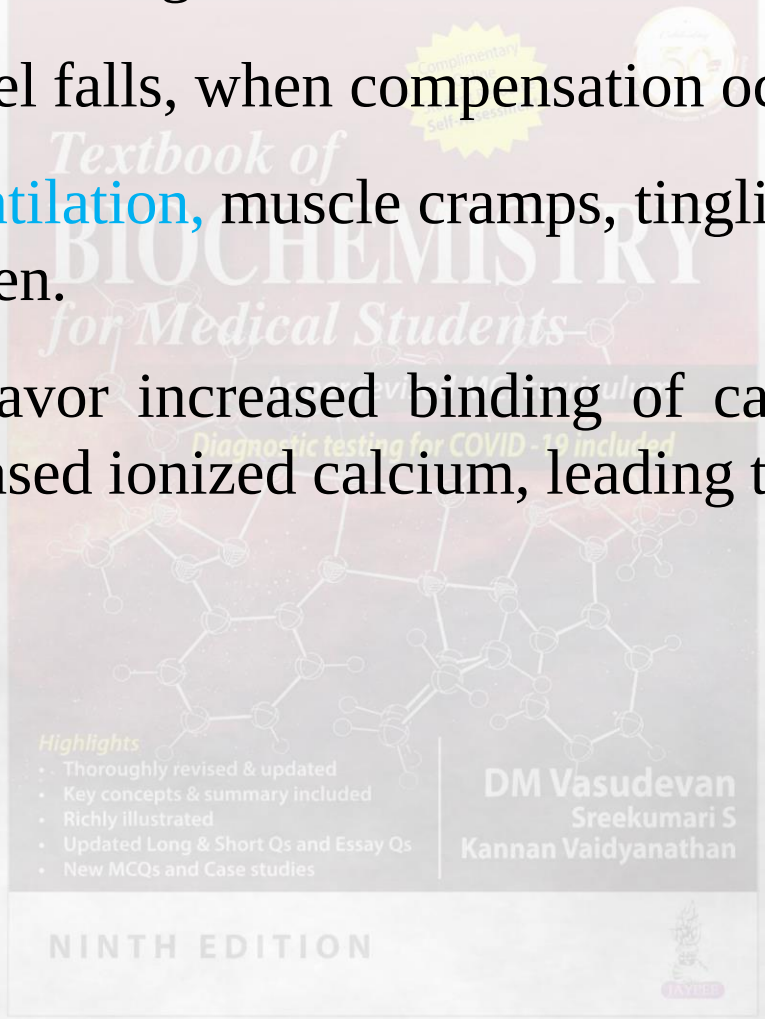
# Respiratory Alkalosis

The pCO2 is low, pH is high and bicarbonate level increases.

But bicarbonate level falls, when compensation occurs.

Clinically, hyperventilation, muscle cramps, tingling and paraesthesias are seen.

Alkaline pH will favor increased binding of calcium to proteins, resulting in a decreased ionized calcium, leading to paraesthesia.

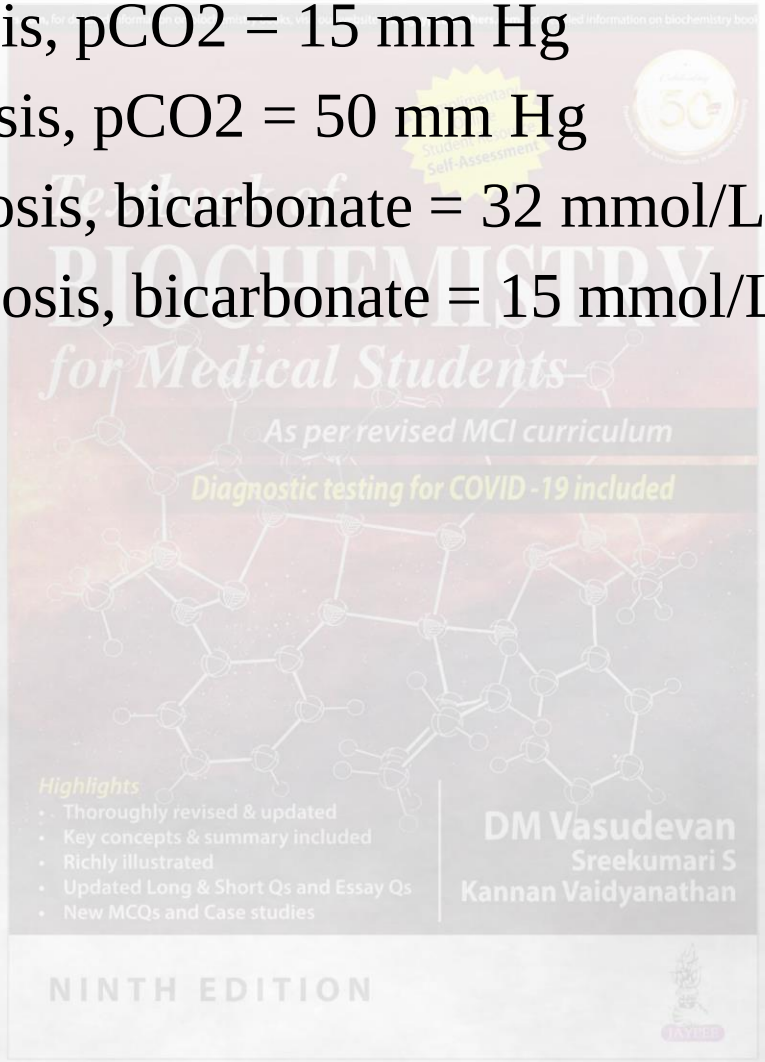


# Stepwise Approach to a Patient with Acid-base Disturbance

1. Acidemic or alkalemic
2. Primary metabolic or respiratory
3. If respiratory, whether acute or chronic
4. For metabolic acidosis, calculate anion gap
5. HAGMA or NAGMA
6. Assess whether compensatory change is within the predicted limits
7. Decide whether a simple disorder or mixed disorder
8. Check whether the values agrees with your clinical judgement

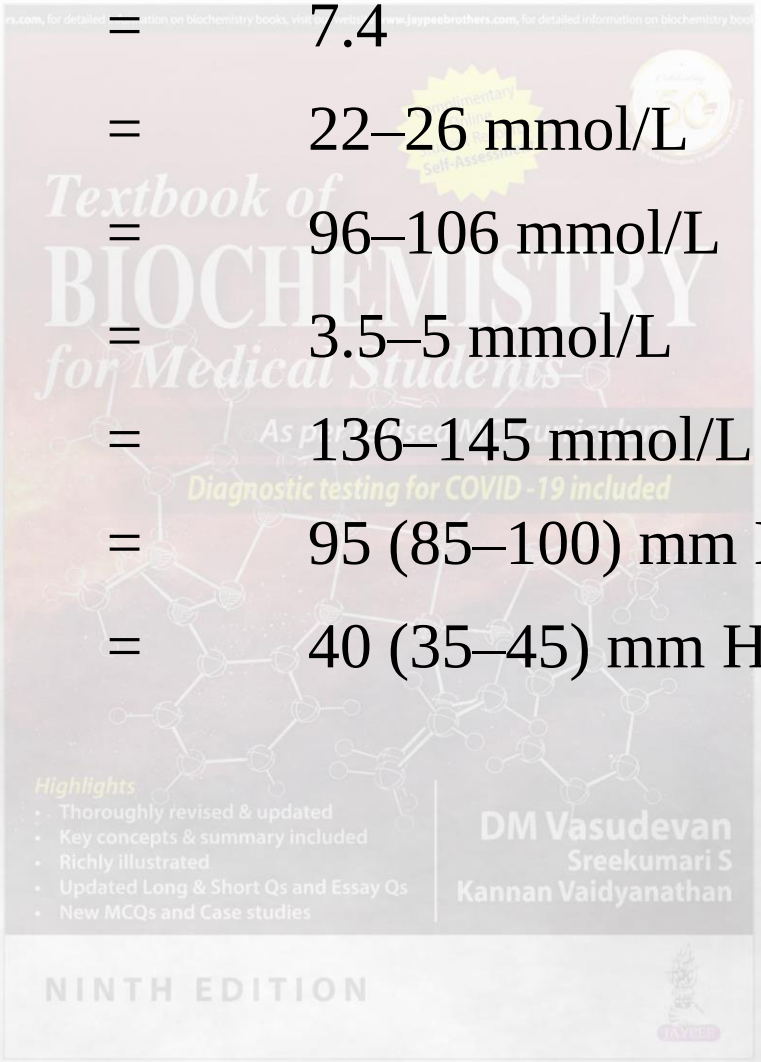
# Maximum Limits of Compensation

- Metabolic acidosis, pCO2 = 15 mm Hg
- Metabolic alkalosis, pCO2 = 50 mm Hg
- Respiratory acidosis, bicarbonate = 32 mmol/L
- Respiratory alkalosis, bicarbonate = 15 mmol/L.



# Normal Serum Electrolyte and Arterial Blood Gas Values

| | | | |
|---|---|---|---|
| ✓ | pH | = | 7.4 |
| ✓ | Bicarbonate | = | 22–26 mmol/L |
| ✓ | Chloride | = | 96–106 mmol/L |
| ✓ | Potassium | = | 3.5–5 mmol/L |
| ✓ | Sodium | = | 136–145 mmol/L |
| ✓ | pO2 | = | 95 (85–100) mm Hg |
| ✓ | pCO2 | = | 40 (35–45) mm Hg |



**Respiratory Acidosis**

A. Pneumonia
B. Bronchitis, Asthma , COPD
C. Pneumothorax
D. Narcotics, Sedatives
E. Paralysis of respiratory muscles
F. CNS trauma
G. Ascites, Peritonitis

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**Metabolic Acidosis**

i. High anion gap
   - A. Diabetic ketosis
   - B. Lactic acidosis
   - C. Renal failure

ii. Normal anion gap
   - A. Renal tubular acidosis
   - B. CA Inhibitors
   - C. Diarrhea

| Respiratory Acidosis | Respiratory Alkalosis |
|---|---|
| A. Pneumonia<br>B. Bronchitis, Asthma , COPD<br>C. Pneumothorax<br>D. Narcotics, Sedatives<br>E. Paralysis of respiratory muscles<br>F. CNS trauma<br>G. Ascites, Peritonitis | A. High altitude<br>B. Hyperventilation<br>C. Hysteria<br>D. Febrile conditions<br>E. Septicemia<br>F. Meningitis<br>G. Congestive Cardiac Failure |
| **Metabolic Acidosis**<br>i. High anion gap<br>A. Diabetic ketosis<br>B. Lactic acidosis<br>C. Renal failure<br>ii. Normal anion gap<br>A. Renal tubular acidosis<br>B. CA Inhibitors<br>C. Diarrhea | |

| Respiratory Acidosis | Respiratory Alkalosis |
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| **Metabolic Acidosis**<br>i. High anion gap<br>A. Diabetic ketosis<br>B. Lactic acidosis<br>C. Renal failure<br>ii. Normal anion gap<br>A. Renal tubular acidosis<br>B. CA Inhibitors<br>C. Diarrhea | **Metabolic Alkalosis**<br>A. Severe vomiting<br>B. Cushing Syndrome<br>C. Milk alkali syndrome<br>D. Diuretic therapy (K loss) |