# Chapter 2

## Fluid, Electrolytes, and Acid-Base Balance

# A. Guidelines for Fluid and Electrolyte Therapy

## 2.1 Maintenance Fluids

These fluids are given during first 24 hour postoperative period.

To calculate the daily fluid requirements use the following methods:

*Body Weight Method:*

< 10 kg 100 mL/kg/day or approximately 4 mL/kg/hour.

11-20 kg 1000 mL + 50 mL/kg (for each Kg > 10 kg) / day or approximately (2 mL/kg/hour).

> 20 kg 1500 mL + 20 mL/Kg (for each Kg > 20 kg)/day or approximately (1 mL/kg/hour).

E.g. 25 kg child's daily fluid requirement:

*First 10 kg body weight:*

100 mL × 10 = 1000 mL/day or

(4 mL ×10 kg/hour) = 40 mL/hour

Plus (+)

*Second 10 kg body weight:*

50 mL × 10 = 500 mL/day or

(2 mL × 10 kg/hour) = 20 mL/hour

Plus (+)

*Next 5 kg:*

20 mL × 5 = 100 mL/day or

(1 mL × 5 kg/hour)= 5 mL/hour

*Total daily fluids:*

1600 mL or a fluid rate of 65 mL/hour.

*Alternate Calculation for hourly fluid intake for > 20 kg child:*

40 mL + body weight in Kg

Eg: 25 kg child's hourly fluid intake: = 40+25 mL

*Body Surface Area Method:*

Commonly used in children > 10 kg

1500-2000 mL/m ²day.

*Maintenance electrolytes in fluids:*

Sodium: 3 mEq/100 mL of water

Potassium: 2 mEq/100 mL of water

Chloride: 2 mEq/100 mL of water

### 2.1.1 Maintenance Fluid Orders for Post Cardiac Surgery Pediatric Patients

These orders are used in first 24 to 48 hours.

*For Cardiopulmonary Bypass (CPB) cases:*

- < 3 months: Give D10W 2/3 of daily maintenance
- 3 months: Give D5W 2/3 of daily maintenance

If blood glucose > 200 mg% in > 3 months infant:

Give D2.5W ½ NS (0.45% NaCl)

*For Non- Cardiopulmonary Bypass (CPB) cases:*

- < 3 months: Give D10W ¼ NS (0.2% NaCl) daily maintenance fluid.
- > 3 months: Give D5W ¼ NS (0.2% NaCl) daily maintenance fluid.

If Blood Glucose > 200 mg% in > 3 months infant:

Give D2.5W ½ NS (0.45% NaCl)

### 2.1.2 Additional Fluid Orders for Post Cardiac Surgery Pediatric Patients

These fluid orders are used duing the immediate postoperative period in addition to maintenance fluids and are gauzed in an individual patient by assessing the following:

1) Hemodynamic status.
2) Adequacy of circulating volume / perfusion.
3) Ongoing fluid losses (e.g., bloody chest tube drainage).

*Infusion rate in severe hypovolemia and / or 15 to 20% fluid volume loss:*

- Give 20 mL/kg crystalloid solution as rapid infusion (e.g., 15-30 minutes).

  (Use either of ringers lactate, 0.9% NS or 0.45% saline).

- Give two aliquots of above solution to achieve adequate perfusion and homodynamic stability.
- If adequate perfusion is not achieved infuse:

  Plasma, or 5% albumin, or whole blood at a rate of 10 mL/kg in15 minutes to 20 minutes. Blood is preferred for continued blood loss or if blood volume is low. Ideal hematocrit during post operative period is 30% to 35%. Infuse the red cells at the rate of 15 to 20 mL/kg over 3 to 4 hours.

### 2.1.3 Adjustments to Maintenance Fluids

The following maintenance fluid orders may be required after 24 to 48 hours postoperatively. Need of these orders is individualized by the following:

*Renal Failure:* Maintenance fluids equals to insensible loss (300 mL/m$^2$) + Urine volume replacement (mL per mL).

*Excessive sweating:* Increase maintenance by 10-25 mL/100 kcal of basal energy expenditure (BEE).

*Hyperventilation:* Increase maintenance fluid by 10-60 mL/100 Kcal of BEE.

*Fever:* Increase maintenance fluid by 5 mL/kg/day for each degree of temperature raise above 38 ℃.

## 2.2 Specific Fluid and Electrolyte Orders

Beyond 24 to 48 hours postoperatively, if the patient is not on oral intake, in addition to maintenance fluids and electrolytes, the patient requires additional fluid and electrolytes to replace any existing water deficit and ongoing losses.

One should replace ongoing losses mL / per / mL. The composition of the electrolytes depends on the type of losses incurred. In a prolonged convalescence or post illness, the patient might develop certain degree of water deficit or water deficits may also be coexistent before a planned operative procedure (see Figure 1).

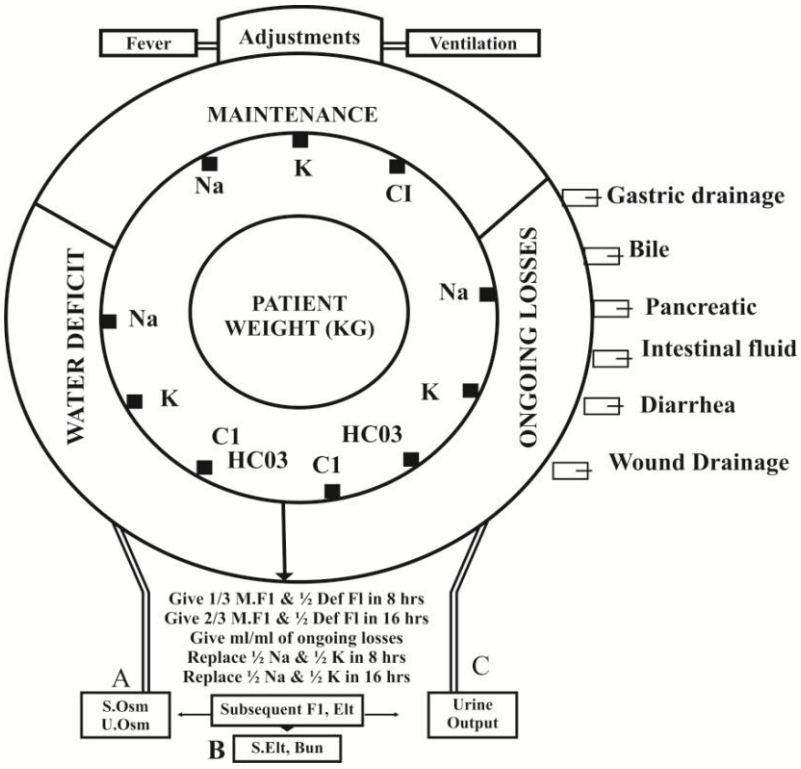



***Figure 1*** *Fluid and electrolyte therapy wheel in a preoperatively depleted patient and in a postoperative patient with a complicated postoperative course or a prolonged intensive care unit stay: After initial 24 hour replacement of depleted fluid and electrolytes, subsequent fluid and electrolyte therapy is guided by three gauzes (A, B and C). M.FL= Maintenance fluid, Def Fl= Deficit fluid, S. Osm= Serum osmalarity, U. Osm= Urine osmalarity, S. Elt= Serum electrolytes, Fl= fluid, Elt=Electrolytes, Bun =Blood urea nitrogen.*

## 2.2.1 Ongoing Losses

The composition of the fluid losses (see *Table 2.1A*) may be analyzed in individual cases or generalization may be applied for the most patients.

***Table 2.1A*** *Electrolyte composition of gastrointestinal losses.*

| **(mEq / litre)** | | | | |
|---|---|---|---|---|
| | **Sodium** | **Potassium** | **Chloride** | **Bicarbonate** |
| Gastric: | 20-120 | 5-25 | 90-160 | 0-5 |
| Duodenal: | 20-140 | 3-30 | 30-120 | 10-50 |
| Biliary tract: | 120-160 | 3-12 | 70-130 | 30-50 |
| Pancreas: | 110-160 | 4-15 | 30-80 | 70-100 |
| Small intestine: | 100-140 | 4-40 | 60-100 | 30-100 |
| Diarrhea: | 10-25 | 10-30 | 30-120 | 10-50 |

### 2.2.2 Water Deficit Therapy

Deficits in free water are estimated by recognizing the degree of dehydration first. Then the deficit in free water is calculated depending on the extent of dehydration. The severity of dehydration is calculated by either patient body weight method or by clinical assessment of the patient as follows:

*Body weight method:*

$$\text{Dehydration (\%)} = \frac{\text{Preillness weight} - \text{Postillness weight}}{\text{Preillness weight}} \times 100$$

*Clinical Assessment Method:*

Differentiate types of dehydration due to water deficit by clinical examination into mild, moderate, and severe. This quantifies the degree of dehydration as shown (see Table 2.1B). The next step is to qualify dehydration by determining the tonicity of the body fluids, which is usually done checking the serum sodium concentration as shown below:

- Isotonic dehydration: Serum $Na^+$: 130-150 mEq/L
- Hypotonic dehydration: Serum $Na^+$: < 130 mEq/L
- Hypertonic dehydration: Serum $Na^+$: > 150 mEq/L

***Table 2.1B*** *Quantification of dehydration by clinical examination.*

| Mild Dehydration | Moderate Dehydration | Severe Dehydration |
|---|---|---|
| Normal BP | Normal BP | ↓ BP |
| ------ | -------- | Obtundation |
| Urine output ↓ Concentrated urine | Oliguria | Azotemia |
| Pale skin | Grey skin | Mottled skin |
| --------- | Decreased skin turgor | Poor capillary refill |
| Mucous membranes: | | |
| Dry | Very dry | Parched |
| Normal heart rate / or 10% above baseline | ↑ heart rate | ↑ heart rate |
| Flat fontanelle (< 7 months age) | Soft fontanelle | Sunken fontanelle |

*Estimation of Free Water Loss in Types of Dehydration:*

Quantity of water deficit is related to i) serum osmalarity or sodium concentration and ii) classification of dehydration based on clinical assessment as shown in table 2.2.

***Table 2.2*** *Percentage of free water deficit in types of dehydration.*

| Serum Na | Mild Dehydration | Moderate Dehydration | Severe Dehydration |
|---|---|---|---|
| Isotonic | 5% loss | 10% loss | 15% loss |
| Hypotonic | 4% loss | 6% loss | 8% loss |
| Hypertonic | 7% loss | 12% loss | 17% loss |

*Calculation of Free Water Deficit:*

Use table 2.2 to calculate the water deficit.

$$\text{Water deficit} = \frac{\%\ \text{water loss} \times \text{patient weight in Kg} \times 1000\ \text{g/Kg}}{100}$$

Illustration: Water deficit in10 kg infant with moderate isotonic dehydration =

$$10 \times 10 \times 1000/100 = 1000\ \text{mL}$$

Illustration: Water deficit in 14 kg infant with severe hypertonic dehydration =

$$17 \times 14 \times 1000/100 = 2380\ \text{mL}$$

In dehydration, in addition to free water deficit the electrolyte deficis coexist, especially, during prolonged illness or prolonged convalescence, and in practice both water and electrolyte deficits should be corrected simultaneously. The empirical estimate of water and electrolyte deficits in moderate to severe dehydration is shown in table 2.3A.

***Table 2.3A*** *Water and electrolyte deficits in moderate/severe dehydration.*

| Tonicity | Water (mL/kg) | $Na^+$ (mEq/kg) | $K^+$ (mEq/kg) | $Cl^-$ and $HCO_3^-$ (mEq/kg) |
|---|---|---|---|---|
| Isotonic | 100-150 | 8-10 | 8-10 | 16-20 |
| Hypertonic | 120-180 | 2-5 | 2-5 | 4-10 |
| Hypotonic | 50-100 | 10-14 | 10-14 | 20-28 |

## 2.2.3 Daily Maintenance Electrolytes

These daily electrolytes are replaced if the patient is not on oral intake beyond 24 to 48 hours potoperatively or during prolonged illness.

*Sodium:* 3-4 mEq/kg/day or 30-50 mEq/$m^2$/day.

*Potassium:* 2-3 mEq/kg/day or 20-40 mEq/$m^2$/day.

*Magnesium: (elemental magnesium)*

| | |
|---|---|
| 6 months: 30 mg/day | 6-12 months: 75 mg/day |
| 1-3 years: 65 mg/day | 4-8 years: 110 mg/day. |
| 9-13 years: 200 mg/day | 14-18 years (male): 340 mg/day |
| | (female): 300 mg/day |
| Adult (male): 330 mg/day | Adult (female): 255 mg/day |

*Elemental content of magnesium Salts:*

Magnesium carbonate: 1 gm of salt= 280 mg or 23.4 mEq.

Magnesium chloride: 1 gm of salt= 118 mg or 9.8 mEq.

Magnesium sulphate: 1 gm of salt = 98.6 mg or 8.2 mEq.

Magnesium oxide: 1 gm of salt= 604 mg or 100 mEq.

50 mg of elemental magnesium= 4 mEq of $Mg^{2+}$

*Calcium: (elemental calcium)*

| | |
|---|---|
| < 6 months: 210 mg/day | 6-12 months: 270 mg/day |
| 1-3 years: 500 mg/day | 4-8 years: 800 mg/day |
| 9-18 years: | 1300 mg/day. |
| Adult: 1000 mg/dayAdult (> 50 yrs): | 1200 mg/day |

*Elemental calcium content of calcium salts:*

Calcium carbonate: 1 gm of salt = 400 mg or 20 mEq

Calcium chloride: 1 gm of salt = 270 mg or 13.5 mEq

Calcium gluconate: 1 gm of salt = 90 mg or 4.5 mEq

Calcium phosphate: 1 gm of salt = 390 mg or 19.3 mEq

Calcium lactate: 1 gm of sal t= 130 mg or 6.5 mEq

20 mg of elemental calcium= 1 mEq of $Ca^{2+}$.

### 2.2.4 Fluid and Electrolyte Orders in Practice

In patients with prolonged ICU satay or during prolonged convalescence without oral intake, the clinical and laboratory evaluation suggests the existing water and electrolyte deficits. For fluid orders

in such patients, one may use table 2.3A to calculate empirical water and electrolytes requirements to correct the deficits in addition to administering daily maintenance fluid and electrolytes. In addition, any ongoing losses should be replacd (see Table 2.1A). The general rule is to try to do an under correction rather than over correcting the deficits. The adequacy of correction is monitored by urine output, clinical, and laboratory evaluation of the patient.

*Illustration:*

Calculation of total fluid requirement for 12 kg infant with moderate isotonic dehydration (see Table 2.3B):

***Table 2.3B*** *Calculation of 24 hour total fluid and electrolytes requirement for 12 kg infant with moderate isotonic dehydration.*

| | **Water** | **Sodium** | **Potassium** |
|---|---|---|---|
| Maintenance: | 1000 mL + 100 mL | 48 mEq | 24 mEq |
| | (First 10 kg + next 2 kg) | (4 mEq/kg/day) | (2 mEq/kg/day) |
| Deficit: | 1200 mL | 96 mEq | 96 mEq |
| Total / 24 hours | 2300 mL | 144 mEq | 120 mEq |

Replace 1/3 maintenance water and 1/2 deficit water in first 8 hours = (365 mL) + (600 mL) = 965 mL/8 hours or 120 mL/hr.

Replace 1/2 of $Na^+$ and 1/2 $K^+$ in first 8 hours: $Na^+$= 72 mEq, $K^+$= 60 mEq.

The maximum potassium used in IV fluids should not exceed 40 mEq/litre.

Potassium is not started until urine output is established.

The fluid order: D5W/0.45 NS to run 120 mL/hr for 8 hours. Add Kcl 40 mEq/litre after urine out put is established.

Replace 2/3 maintenance water and 1/2 defict water in next 16 hours i.e., (735 mL) + (600 mL) = 1335 mL/16 hours or 83 mL/hour.

Replace the remainder of $Na^+$ and $K^+$.

The fluid order: D5W 1/3 NS to run 83 mL/hr. Add Kcl 40 mEq/litre.

Any on going losses are also added to the fluids.

## B. Diagnosis of Common Electrolyte Disorders and Management

Though the common electrolyte abnormality found in the postoperative pediatric cardiac surgical patient includes hypokalemia, hypocalcaemia, and less frequently hyponatremia, abnormalities in other electrolyte disorders may been countered either due to prolonged intensive unit stay or as a result of complicated postoperative course and/or underlying organ dysfunction. Recognition of these disorders and optimal management improves patient outcome and shortens intensive care unit stay.

# 2.3 Sodium Abnormalities

## 2.3.1 Hyponatremia

### (I) Definition

Serum sodium of < 135 mEq/litre.

To further classify hyponatremia and to do adequate correction, estimate:

1) Serum osmolarity.
2) Assess patient by clinical examination.

### (II) Classification of Hyponatremia

It is based on serum osmolarity and is differentiated into three tonicities:

*Isotonic hyponatremia:*

1) Serum osmolarity is 280-285 mOsm/kg $H_2O$.
2) Causes:
   - Hyperlipidemia and hyperprotinemia.
   - Infusions of *isotonic solutions* of mannitol or glucose.

*Hypertonic hyponatremia:*

Serum osmalarity is > 280-285 mOsm/kg $H_2$ O.

Causes: Hyperglycemia or infusions of hypertonic solutions of mannitol or glucose.

Serum $Na^+$ falls 1.6 mEq/L for every 100 mg/dL increase in glucose or mannitol.

*Hypotonic hyponatremia:*

Serum osmalarity is < 280 mOsm/kg $H_2O$.

1) Evaluate the volume status (extracellular fluid volume) of the patient both by clinical and / or hemodynamic assessment and differentate into the following:
   - Euvolemic hypotonic hyponatremia
   - Hypervolemic hypotonic hyponatremia
   - Hypovolemic hypotonic hyponatremia
2) Do the following laboratory evaluation for differentiation and diagnosis of the above hypotonicity:
   - Serum electrolytes, blood urea nitrogen, and serum creatinine, serum uric acid.
   - Urine sodium, urine osmolarity and classify hyponatremia as below:

*Euvolemic hypotonic hyponatremia:*

*Clinical examination:*

Normal BP, normal perfusion, and normal pulse, no signs of edema.

***Table 2.4*** *Laboratory evaluation of euvolemic hypotonic hyponatremia.*

| BUN | Serum Cr | * Uric acid | Urine osmalarity | Urine $Na^+$ | Probable cause |
|---|---|---|---|---|---|
| ↑↑ | ↑↑ | ↓ | iso-osmolar, | ↑ | Renal failure |
| ↓ | ↓ | ↓ | ↓↑ | ↓ | $H_2O$ intoxication |
| ↑ | ↑ | ↓↓ | ↑ | ↑ | SIADH |

BUN = blood urea nitrogen, Cr = creatinine, SIADH = serum inappropriate antidiuretic hormone secretion. $H_2O$ = water, * serum.

*Hypervolemic hypotonic hyponatremia:*

*Clinical examination:*

Nomal or altered BP, normal or altered perfusion, altered pulse, and signs of tissue edema.

***Table 2.5*** *Laboratory evaluation of hypervolemic hypotonic hyponatremia.*

| BUN | Serum Cr | *Uric acid | Urine osmolarity | Urine $Na^+$ | Probable cause |
|---|---|---|---|---|---|
| ↑↑ | ↑ | ↑ | ↑ | ↓ | CHF |
| ↑↑ | ↑ | ↑ | ↑ | ↓ | Liver disease |
| ↑↑ | ↑ | ↑ | ↑ / iso | ↑ | Nephrotic syndrome |

BUN = blood urea nitrogen, Cr = creatinine, CHF = congestive heart failure,* serum.

*Hypovolemic hypotonic hyponatremia:*

*Clinical examination:*

Low BP, decreased skin perfusion, tachycardia, and no signs of tissue edema:

***Table 2.6*** *Laboratory evaluation of hypovolemic hypotonic hyponatremia.*

| BUN | *Cr | * uric acid | U.osmolarity | Urine $Na^+$ | Probable cause |
|---|---|---|---|---|---|
| ↑↑ | ↑ | ↑ | ↑↑ | ↓↓ | 3rd spacing, GI, insensibleloss |
| ↑↑ | ↑ | ↓ | ↓ | ↑ | Adrenal insuffiency |
| ↑↑ | ↑↑ | ↓ | ↑ / iso | ↑ | Renal losses (diuretics/renal damage) |

BUN = blood urea nitrogen, *Cr = serum creatinine, * serum, U = urine.

## (III) Clinical Symptoms of Hyponatremia

Lethargy, nausea, vomiting, seizures, and coma.

The above symptoms occur usually if serum $Na^+$ < 120-125 mEq/L.

The severity of symptoms correlate with rate of fall in serum $Na^+$.

## (IV) Treatment of Hyponatremia

*A. Correction of underlying cause:*

*1) Isotonic/hypertonic hyponatremia:*

Correct underlying mteabolic disorder, and may require insulin for hyperglycemia.

*2) Hypotonic hyponatremia:*

Differentiate into i) euvolemic, ii) hypervolemic, iii) hypovolemic, and treat.

*3) Euvolemic hypotonic hyponatremia:*

Water restriction (give fluids to replace insensible losses and urine output).

Give additional Rx if cause of hyponatremia is SIADH (see Chapter 9).

*4) Hypervolemic hypotonic hyponatremia:*

Water restriction and diuretics.

*5) Hypovolemic hypotonic hyponatremia:*

Isotonic saline infusion to restore extracellular fluid volume.

*B. Alleviation of symptoms of hyponatremia:*

Requires aggressive correction initially, with hypertonic saline to rise serum $Na^+$ to 120-125 mEq/L. Correct $Na^+$ deficit no faster than 2 mEq/L/hour or 20 mEq/L/24 hours (More rapid correction of $Na^+$ causes pontine myelinosis and premanent brain injury). After resolution of symptoms and / or serum $Na^+$ rises to 125 mEq/L, stop the infusion of hypertonic saline and correct underlying cause of disorder as mentioned above.

*Estimate of serum sodium correction:*

*1) Severe and symptomatic hyponatremia:*

$$Required\ mEq\ of\ \ Na^+ = Desired \text{ serum } Na^+(mEq) - Actual \text{ serum } Na^+\ (mEq) \times 0.6 \times Weight\ in\ Kg$$

Give only 1 mEq/kg/hour (Maximum rate of infusion).

Do not correct serum $Na^+$ > 20 mEq/L/day.

Acute correction of serum sodium is done in 5 mEq/L / dose increments until serum $NA^+$ of 125 mEq/L is reached. Hypertonic saline solution (> 0.9%) is used only at initial stages.

Rate of 3% NS (hypertonic saline) administration:

$$\text{To raise serum } Na^+ \text{ at 2 mEq/L/hour} = \frac{(2\text{mEq /L}) \times 0.6 \times \text{BW (in Kg)} \times 1000}{513 \text{ mEq /L}}$$

In 10 kg infant rate of 3% saline infusion to raise serum $Na^+$ 2 mEq/hr = 23 mL/hr

*2) Asymptomatic and moderate to mild hyponatremia:*

Gradual correction in increments of 10 mEq/L/day.

## 2.3.2 Hypernatremia

### (I) Definition

The serum $Na^+$ > 144 mEq/L is hypernatremia. It is always associated with hypertonicity or increased serum osmolarity. The empirical estimate of serum osmolarity is calculated as below:

$$(2 \times \text{serum } Na^+ \text{ serum BUN mg/dL / 2.8 + serum glucose mg/dL/18}) = \text{mOsm/litre (milli osmoles / litre)}$$

### (II) Clinical Assessment

The extracellular fluid volume of the patient should be assessed clinically, aided by laboratory evaluation, and hypernatremia is differentiated into the following classification:

- Euvolemic hypernatremia.

- Hypovolemic hypernatremia.
- Hpervolemic hypernatremia.

### (III) Laboratory Confirmation

The following laboratory tests are usually performed to confirm the type of above hypertonicity.

Tests: serum electrolytes, BUN, serum creatinine, urine $Na^+$, and urine osmolarity.

*Euvolemic hypernatremia:*

The loss of free water without Na loss leads to this disorder.

***Table 2.7*** *Laboratory evaluation of euvolemic hypernatremia.*

| BUN | * Creatinine | Urine $Na^+$ | Urine Osmolarity | Probabale cause |
|---|---|---|---|---|
| ↑ | normal | normal | ↓ | Diabetes inspidus |
| Normal | normal | normal / varies | ↑ | Iatrogenic |

BUN= blood urea nitrogen, * levels in serum.

*Hypovolemic hypernatremia:*

Loss of water > $Na^+$ loss results in this disorder.

***Table 2.8*** *Laboratory evaluation of hypovolemic hypernatremia.*

| BUN | * Creatinine | Urine $Na^+$ | Urine Osmolarity | Probabale cause |
|---|---|---|---|---|
| ↑↑ | ↑↑ | ↑ | ↓ | Renal causes and diuretics |
| ↑↑ | ↑ | ↓ | ↑ | GI and insensible losses |
| ↑↑ | ↑↑ | ↑ | ↑ | Adrenal disease (deficiency) |

BUN = blood urea nitrogen, * levels in serum, GI = gastrointestinal.

*Hypervolemic hypernatremia:*

Net $Na^+$ intake > water intake in this disorder.

***Table 2.9*** *Laboratory evaluation of hypervolemic hypernatremia.*

| BUN | * Creatinine | Urine $Na^+$ | +Osmolarity | Probabale cause |
|---|---|---|---|---|
| Normal | normal | normal | varies. | Gluco / minrealocorticoid excess |
| normal / ↑ | normal / ↑ | ↓ | varies. | Iatrogenic intake |

BUN = blood urea nitrogen, * levels in serum, + urine sample.

### (IV) Clinical Symptoms

The symptoms of hypernatremia depend on the rate and severity of hypernatremia and volume status of the patient. The neurological symptoms usually predominate such as restlessness, lethargy, tremulousness, seizures, and delirium. The cerebral blood vessels may tear due to shrinkage of brain cells, resulting in subarachnoid and subcortical hemorrhages that lead to strokes.

### (V) Treatment

Depends on the volume status and severity of disorder and rate of correction depends upon the presence or absence of neurological signs/symptoms.

*Euvolemic hypernatremia:*

Water replacement‘is given either orally or by (D5W) intravenous infusion.

*Hypervolemic hypernatremia:*

Give diuretics such as furosemide. Diuretic therapy is usually given in conjunction with infusion of D5W or D5W 0.25NS.

Consider dialysis in renal failure.

*Hypovolemic hypernatremia:*

Infuse isotonic saline solution until hypovolemia is corrected, then infuse D5W or hypotonic saline solution to correct water deficit.

$$\text{Calculation of water deficit: } 0.6 \times \text{ BW in kg } \frac{\text{Current serum } Na^+ \text{ (mEq /L)}}{\text{Expected normal serum } Na^+ \text{ ( 140 mEq /L)}} - 1$$

Illustration: In a 20 kg child with a serum $Na^+$ of 165 mEq/L, the water deficit by above calculation is shown below:

$$0.6 \times 20 \frac{165}{140} - 1 = 12 \times 0.17 = 2.04 \text{ liters}$$

If the diabetes inspidus is the cause of the defect in tonicity, consider Rx with aqueous vasopressin either SQ or IV infusion (see Chapter 9). IV dose of vasopressin: The initial dose of 0.5 mU (0.0005 unit)/kg/hour is given as a continuous infusion to tailor the urine out put to 1.5 mL to 2 mL/kg/hour.

The dose may be doubled every 30 minutes to achieve the desired urine flow.

*Rates of correction of hypernatremia:*

1. Rapid correction:

If hypernatremia (as in acutely developing) is associated with neurological signs, correct it in a period of a few hours to prevent neurological sequelae.

2. Slow correction:

If hypernatremia is chronic or slowly developed correct it slowly over a period of 48 hours. Do not correct faster than 2 mOsm/hr. Since compensatory mechanisms maintain osmolarity of brain cells in chronic hypernatremia, rapid correction would lead to cerebral edema.

## 2.4 Potassium Homeostasis and Serum Potassium Abnormalities

Potassium is the most abundant intracellular cation, only less than 1.5% of total body potassium is in the serum. Serum $K^+$ level is therefore, a poor indicator of total body $K^+$ stores.

Normal total body content of $K^+$ is about 50 mEq/kg (40 mEq/kg in females).

Body potassium is easily redistributed with transcellular movement, exogenous intake, and depletion and affect the serum potassium levels.

Serum $K^+$ levels, therefore, reflect total-body potassium homeostasis Both external and internal potassium balances are regulated to maintain the extracellular fluid (ECF) concentration of 3.5 to 5.5 mEq/L.

Excess or deficits in total body potassium may correlate with serum potassium, at varying pH. This principle may help in estimating potassium deficit in treating hypokalemia.

$K^+$ defict is 9 mEq/kg (adult 600 mEq), 6 mEq/kg (adult 400 mEq), and 3 mEq/kg (adult 200 mEq) at serum $K^+$ levels of 1.5 mEq/L, 1.8 mEq/L and 2 mEq/L respectively.

The body potassium is normal between $K^+$ of 3.5 mEq and 4.5 mEq/L.

Normal intestinal absorption results in daily excess intake of about 1 mEq/kg/day. Excess K is excreted 90% through the kidneys (90%) and 10% by the gut.

Potassium homeostasis is maintained predominantly by regulation of renal excretion. The most important site for renal regulation is in distal convoluted tubule, ascending limb of the loop of Henle, and collecting tubule through aldosterone receptors present at these sites. Aldosterone controls $Na^+$ resorbtion through sodium channels located on the apical membrane of tubular cells. It creates in tubular lumen negative electrical potential that drives the secretion of potassium through specific potassium channels.

*WNK (with no K [lysine] kinases:*

These kinases are important in the regulation of sodium and potassium transport in the distal nephron.

*$K^+$ excretion is increased in the following settings:*

1) Increased aldosterone secretion, high sodium delivery to the distal tubule as in patients on use of diuretics.
2) High urine flow (e.g. osmotic diuresis), high serum potassium level.
3) Increased delivery of negatively charged ions (e.g. bicarbonate) to the distal tubule ($Na^+$ absorption increases in exchange for $K^+$ excretion).

*$K^+$ excretion is decreased in the following settings:*

1) Renal failure, low urine flow.
2) Hypo-aldosteronism, low serum potassium level.

When exogenous potassium intake is high, renal excretion also is increased.

In the absence of potassium intake, obligatory renal losses are 10-15 mEq/day.

Renal adaptive mechanisms maintain potassium homeostasis until the glomerular filtration (GFR) drops to less than 15-20 mL/min.

Colon is the major site of gut regulation of potassium excretion. In the presence of renal failure, some proportion of potassium is excreted through the gut and serum levels can remain relatively normal.

An excess of 100-200 mEq of body potassium may increase the serum $K^+$ by only about 1 mEq/L

*Factors regulating transcellular movement of Potassium:*

*1) Gluco-regulatory hormones:*

Insulin enhances potassium entry into cells.

Glucagon impairs potassium entry into cells.

*2) Adrenergic stimuli:*

Beta-adrenergic stimulators: Enhance potassium entry into cells and cause hyokalemia.

Beta-adrenergic blocking drugs inhibit potassium entry into cells and cause hyperkalemia.

Alpha-adrenergic stimulators inhibit potassium entry into cells and result in hyperkalemia.

*3) pH of Blood:*

Alkalosis enhances potassium entry into cells. Acidosis causes shift of potassium from intracellular space into extracellular space.

*4) Shifts from intracellular pool:*

Acute change in osmolality (hyperglycemia) causes potassium to exit from cells.

Acute cell-tissue breakdown releases potassium into extacellular space.

### 2.4.1 Hypokalemia

**(I) Definition**

Serum potassium of < 3.5 mEq/L

**(II) Causes**

*1) Poor intake of exogenous potassium.*

*2) Potassium depletion:*

The causes of potassium depletions are as follows.

*A. Gastrointestinal losses:*

Diarrhea, intestinal fistulae, villous tumors: The urinary potassium may be conserved in these situations.

NG sucction, vomiting: Potassium loss is compounded by increased urinary loss of $K^+$ (> 0.3 mEq/kg/day) due to associated metabolic alkalosis.

*B. Urinary (renal) losses:*

- Osmotic diuresis due to priming solution of CPB, thiazide diuretics (hydrochlorthiazide), loop diuretics (furosemide) as well as various laxatives.
- Diuretic phase of ATN, renal tubular acidosis.
- Increased levels of serum bicarbonate: Obligates increased renal excretion of bicarbonate and potassium will be excreted as an obligate cation partner to the bicarbonate.
- Diabetic ketoacidosis: In addition to loss of $K^+$ from polyuria and volume contraction, obligate loss of $K^+$ occurs from kidney tubules as a cation partner to the anion, B- hydroxybutyrate.

- Adrenal disease resulting in excessive secretion of gluco- and mineralo-corticoids and hyperaldosteronism.
- Heriditary defects of renal salt transporters (as in Bartter syndrome or Gitelman syndrome) $K^+$ loss is similar to diuretics, and blood pressure is normal or low unlike hyperaldosteronism in which BP is elevated.
- Hypomagnesemia: Causes hypokalemia as magnesium is required for maintenance of potassium balance. It is evident when hypokalemia persists despite potassium supplementation.
- Amphotercin-B has also been associated with hypokalemia.

*C. Transcellular potassium movement (Cellular influx):*

- Metabolic and respiratory alkalosis:

  For every 0.1 unit change (↑) in pH, there is 0.6 mEq change (↓) in serum $K^+$. Alkalosis causes $K^+$ shift from the plasma and interstitial fluids into cells.

  It is mediated by stimulation of $Na^+/H^+$ ion exchange pump (through $Na^+/K^+$-ATPase enzyme activity).
- Glucose and insulin infusion causes cellular influx of $K^+$.
- Bicarbonate administration causes cellular influx of K.

  Cellular uptake of $K^+$ by serum $HCO_3^-$ concentration is independent of blood pH.
- $Na^+/K^+$-ATPase activation:

  Agents that activate $Na^+/K^+$-ATPase cause cellular $K^+$ influx and decrease serum $K^+$.

  E.g. insulin, beta-1 + beta-2 agonists (epinephrine and isoproterenol).

  Beta-2 agonists (salbutemol, terbutaline) and xanthines.
- Defects of muscular ion channels and transporters:

  As in familial periodic paralysis, attacks of severe hypokalemia and muscle weakness are due to ↑ sensitivity to cellular influx of $K^+$ caused by the above agents.

**(III) Clinical Signs and Symptoms of Hypokalemia**

Skeletal muscle weakness, paralysis, respiratory arrest, rhabdomyolysis, metabolic alkalosis, fall in glomerular filtration, and increased renin release from the kidney.

Cardiac effects: The cardiac arrhythmogenic potential ↑ with PVCs, PACs, ventricular tachycardia, and digoxin toxicity. The following EKG changes occur in hypokalemia (see Figure 2). The amplitude of the P wave ↑, prolongation of the P-R interval, widening of the QRS, decreased amplitude of the T wave or inversion of the T wave. The amplitude of the U wave ↑, and prolongation of the Q-T interval occur.

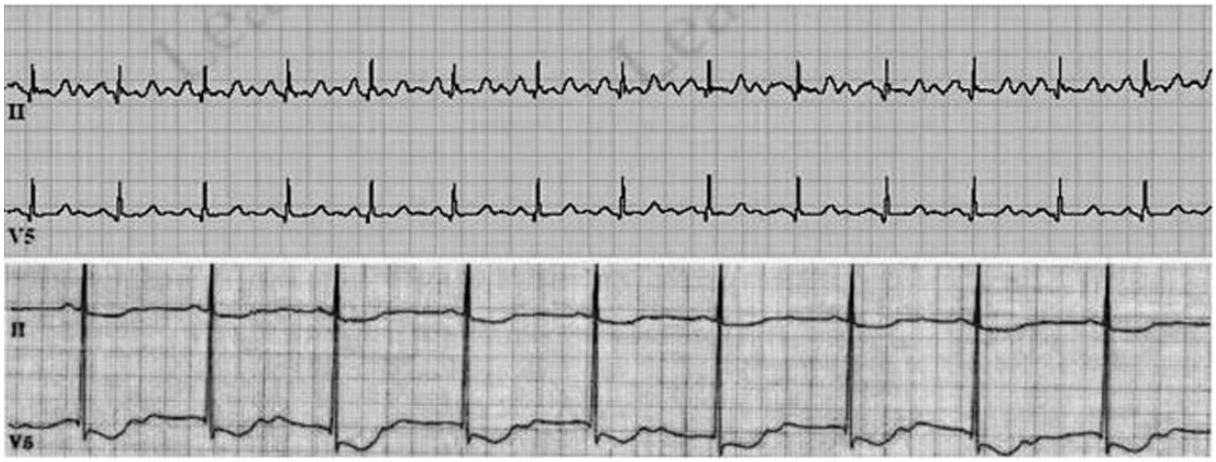



***Figure 2*** *Top strip: EKG strip of leads II and V5 showing changes in hypokalemia. Tall P waves and flattening of the T waves. U waves occur just after the T wave and is usually of smaller amplitude than the T wave. Bottom strip: EKG strip of leads II and V5 showing changes characteristic of hypokalemia. It shows a long QT interval, ST depression, low T waves, and TU wave fusion. Prolonged QT or QTc (corrected QT) increases the risk of torsades de pointes.*

**(IV) Treatment of Hypokalemia**

The most important treatment in hypokalemia is addressing the cause such as:

1. Improviing the diet (in non-emergency situations and if the patient is on diet).

(Potassium-containing foods may be recommended: leafy green vegetables, bananas, oranges, citrus fruits or tomatoes).

2. Stop an offending medication: Dietary and potassium supplements are also used for those on diuretic medications. Resistant cases of hypokalemia may be treated with a potassium-sparing diuretic such as amiloride, triamterene, and spironolactone.

The treatment varies depending on the severity of hypokalemia:

*Mild hypokalemia (> 3.0 mEq/L):*

May be treated with oral potassium chloride supplements such as Klor-Con, Sando-K, Slow-K.

PO supplementation: 2-4 mEq/kg/daily PO in divided doses (divided doses may avoid gastric distress).

*Severe hypokalemia (< 3.0 mEq/L):*

May require intravenous supplementation.

*Usual dose:* 0.5-1 mEq/kg IV; not to exceed 30-40 mEq/dose.

Typically diluted in saline and infused 0.3 to 0.6 mEq/kg over 3-4 hours.

(Adults: 20-40 mEq KCl per liter over 3-4 hours).

*Safe rate ofinfusion:* 0.15 mEq/Kg/hour diluted in 100 mL saline.

(Adults: 10 mEq/hr) diluted in 100-150 mL saline.

*Maximum Infusion rate:* It should not to exceed 0.3-0.5 mEq/kg/hr for non-critical hypokalemia.

(Adults 40 mEq/hr).

*If above rate is inadequate as in life-threatening hypokalemia such as fatal arrhythmia, or ventricular dysrhythmia:*

Give infiusion rate of > 0.5 mEq/kg/hr, but requires careful EKG monitoring.

*Note:*

*When replacing potassium intravenously, infusion via central line is encouraged to avoid the frequent occurrence of a burning sensation or damage to the vein at the site of a peripheral IV site.*

Peripheral veins may tolerate infusion at a rate of 0.07 to 0.15 mEq/kg/hr (or 5-10 mEq/hr in adults).

Consider also $K^+$ deficit in replacing $K^+$. May be give 1-2 mEq/kg/day (or 80-120 mEq/day in adults).

## 2.4.2 Hyperkalemia

### (I) Definition

It is an electrolyte disorder in which serum $K^+$ is > 5.4 mEq/liter.

### (II) Mechanisms and Causes of Hyperkalemia

1. Pseudohyperkalemia:

Occurs secondary to hemolyzed blood sample or

Leukocytosis > $5\times 10^5$ (1, 00,000) per cubic mm.

Thrombocytosis with > $7.5\times 10^7$ per cubic mm.

$K^+$ is released from above cells during clotting.

$K^+$ level is normal on heparanized blood sample and patient has no EKG changes.

2. Increased $K^+$ load:

Exogenous: Increased K intake from foods and $K^+$ supplements, blood transfusion (stored blood), K containg drugs. Endogenous: Rhabdomyolysis, crush injury, major surgical procedures, massive hemolysis, and GI bleeding.

3. Decreased Excretion:

Renal failure, adrenal insufficiency, and hypoaldosteronism.

Drugs that interfere renal excretion of $K^+$.

4. Cellular efflux and redistribution:

Serum acidosis causes shift of $K^+$ from cells to extracellular space.

0.1 unit decrease in pH increases serum $K^+$ by 0.6 mEq/L

*Exogenous (excessive) $K^+$ intake:*

It alone is an uncommon cause of hyperkalemia.

(It is usually caused by a relatively high potassium intake with impaired renal excretion. or impaired mechanisms for the intracellular shift of potassium).

(Parenteral administration of as much as 0.9 mEq/Kg/hour for several hours creates only a minimal increase in serum potassium concentration in healthy.

Exogenous sources of $K^+$:

Potassium-rich foods (meats, beans, fruits, and potatoes).

High-potassium-low-sodium diets and potassium supplements.

High concentrations of potassium in intravenous fluids or total parenteral nutrition (TPN), penicillin potassium therapy or salt substitutes, blood transfusion (stored blood), and $K^+$ containing drugs.

*Decreased $K^+$ excretion:*

Decreased renal excretion coupled with excessive intake is the most common cause. Mild renal failure does not cause resting hyperkalemia due to compensatory mechanisms in the kidneys and gastrointestinal tract. Fall in GFR < 15-20 mL/min, results in hyperkalemia even in the absence of

potassium load. But hyperkalemia can occur in normal or only mildly decreased renal function, as a result of drugs or renal tubular acidosis.

Other causes of decreased excretion of $K^+$ include reduced sodium delivery to distal tubule and reduced tubular fluid flow rate.

*Causes of decreased renal potassium excretion:*

1. Renal failure.

2. Ingestion of drugs that interfere with potassium excretion: Potassium-sparing diuretics, spironolactone, triamterene, amiloride, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, cyclosporine, tacrolimus, trimethoprim/sulfamethoxazole, ketoconazole, and heparin.

3. Impaired responsiveness of the distal tubule to aldosterone:

Type IV renal tubular acidosis as in diabetes mellitus, sickle cell disease, chronic partial urinary tract obstruction, and adrenal insufficiency.

4. Disorders of steroid metabolism (enzyme deficiencies):

21-hydroxylase deficiency, aldosterone synthase deficiency, and mutation of the mineralocorticoid receptor.

5. Impaired sodium reabsorption and impaired potassium secretion in the distal tubule, e.g., type I pseudohypoaldosteronism.

6. Mutations of protein kinases (WNK1 or WNK4) in the distal tubule impairs normal $Na^+$ and $K^+$ transport, e.g., Gordon syndrome or Type II pseudohypoaldosteronism.

*Cellular transport of potassium:*

Shift of $K^+$ from intracellular to extracellular space occurs or transport of $K^+$ to cells from extracellular compartment is impaired resulting in hyperkalemia.

This alone is a relatively uncommon cause of hyperkalemia but coupled with high intake or impaired renal excretion leads to hyperkalemia. The following conditions cause hyperkalemia due to impaired cellular transport.

1. Hyperkalemic periodic paralysis.

2. Tissue breakdown:

Rhabdomyolysis, tumor lysis syndrome, and massive hemolysis.

3. Insulin deficiency or insulin resistance (impairment of intracellular shifting of potassium): Type I or type II diabetes.

4. Drugs:

Inhibits $Na^+/K^+$-ATPase pump (impair $K^+$ entry into the cells and facilitate $K^+$ exit from the cells), e.g., nonselective beta blockers and digitalis toxicity.

Depolarization of the cell membrane and membrane leak that exits $K^+$ from cells, e.g., succinylcholine.

5. Hypertonicity (hyperosmolality):

Loss of intracellular water with increased intracellular potassium concentration establishes a gradient for potassium to move out of the cells.

"Solvent drag" which sweeps potassium along with water exit from the cells, e.g., hyperglycemia, in uncontrolled diabetes mellitus, hypernatremia and hypertonic mannitol.

6. Aldosterone deficiency:

Long-term aldosterone deficiency may impair cell potassium uptake.

7. Acute acidosis:

IV administration of amicar (epsilon amino caproic acid, EACA).

(Similarity in structure of EACA to arginine and lysine enters muscle cells in exchange for potassium leading to an increase in extracellular potassium).

**(III) Incidence, Mortality, Predisposing Factors of Hyperkalemia**

*Incidence:*

In hospitalized patients the incidence is approximately 1.4% to 10%.

Premature (due to renal immaturity) infants and elderly are at high risk.

Elderly (age > 60 years is an independent risk factor): The glomerular filtration rate (GFR) ↓ by 1 mL/min/year of age > 30 years.

Renal blood flow ↓, Oral intake ↓ resulting in decreased urine flow rates.

Plasma renin activity ↓and aldosterone levels ↓.

Increase in $K^+$ is likely on medications that interfere with potassium secretion, e.g., NSAIDS, ACE inhibitors, and $K^+$ sparing diuretics.

Increase in $K^+$ is likely on subcutaneous heparin which decreases aldosterone secretion. In hospitalized patients and drugs are implicated in 75% of cases.

*Mortality:*

In hospitalized patient, it is an independent risk factor for death.

Overall mortality rate in patients with hyperkalemia was 14.3%.

The risk of mortality ↑ as the $K^+$ level increases.

Mortality is 28% with a serum potassium > 7 mEq/L.

Mortality is 9% with a potassium < 6.5 mEq/L.

*Predisposing factors:*

Decreased renal function, genitourinary disease, congestive failure, cancer, severe diabetes, and polypharmacy.

*a). Diabetes constitutes a unique high-risk group with presence of the following factors:*

1) Defects in all aspects of potassium metabolism.
2) Diabetic diet often is high in potassium and low in sodium.
3) Hypo-reninemic hypoaldosteronism in diabetics is due to renal disease (i.e., decreased aldosterone secondary to suppressed renin levels and impaired renal $K^+$ excretion).
4) Angiotensin-converting enzyme inhibitors or angiotensin receptor blocker use for Rx of diabetic nephropathy exacerbates impaired $K^+$ excretion.
5) Insulin deficiency and/or resistance to insulin limit cellular flux of $K^+$.
6) The following risk factors predict hyperkalemia in diabetics:

   Renal insufficiency, duration of diabetes mellitus, age, glycosylated hemoglobin levels, and retinopathy.

*b). Usage of angiotensin-converting enzyme (ACE) inhibitors:*

Hyperkalemia occurs in < 6% with normal renal function. The risk factors for hyperkalemia in patients on ACE inhibitors are:

Elevated blood urea nitrogen (BUN) and serum creatinine, severe diabetes mellitus, congestive heart failure, peripheral vascular disease, and use of a long-acting drug.

*c). Congestive heart failure (CHF) constitutes a high-risk group:*

Promoting factors for hyperkalemia in CHF:

Renal insufficiency due to poor cardiac output and ↓ renal blood flow.

Prevalence of diabetes mellitus ↑ in patients with heart failure, ↑ use of ACE inhibitors, angiotensin receptor blockers, and aldosterone inhibitors.

### (IV) Clinical Symptoms and Signs

The most common are weakness and fatigue.

Occasionally, frank muscle paralysis or respiratory muscle weakness manifests with shortness of breath. Muscle tenderness accompanies muscle weakness, suggesting rhabdomyolysis.

Cardiac conduction disturbances with EKG changes (i.e., heart block or bradycardia, peaked T waves, and widening of QRS) and cardiac arrest occurs. The EKG changes may not correlate with serum $K^+$ levels and is rare to see EKG changes with $K^+ < 6.5$ mEq/L (see Figure 3).

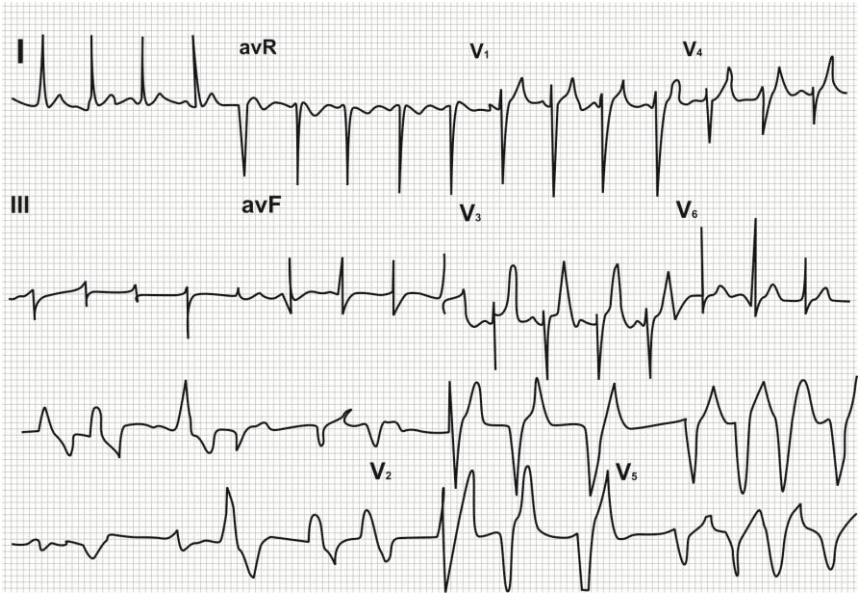



***Figure 3*** *Top strip: Early EKG changes of hyperkalemia include peaked T waves, shortened QT interval, and ST-segment depression (serum $K^+$ level of around 6 mEq/L). Bottom strip: Above EKG changes are followed by bundle-branch blocks causing a widening of the QRS complex, increases in the PR interval, and decreased amplitude of the P wave ($K^+$ level of around or above 7 mEq/L.) Absent P wave with widen QRS complex means that atrial activity is lost and stage is set for ventricular tachycardia/fibrillation. ($K^+$ of level around 8-9 mEq/L).*

### (V) Treatment

Depends on the level of potassium and EKG changes. In all cases, identify the cause and correct the underlying problem.

*1) $K^+$ < 6.5 mEq/L and with no EKG changes:*

Stop giving all supplemental $K^+$ orally or in infusions.

Repeat serum $K^+$ with heparanized blood sample to rule out pseudohyperkalemia.

*2) $K^+$ < 6.5 mEq/L and with EKG changes: (only peaked T waves):*

Stop giving all supplemental $K^+$ orally or in infusions.

Give $K^+$ exchange resin orally or rectally.

Give loop diuretics.

*3) $K^+$ > 6.5 mEq/L (severe hyperkalemia) or any level of $K^+$ with severe EKG changes (e.g. peaked T waves and widening QRS):*

Rapid development of hyperkalemia and evidence of cardiotoxicity.

May institute following aggressive (A to G) measures simultaneously:

*A) Perform an EKG to look for cardiotoxicity.*

Administer intravenous calcium to ameliorate cardiac toxicity. Calcium antagonizes cardiotoxicity of hyperkalemia by stabilizing cardiac cell membrane against undesirable depolarization.

Calcium has no effect on serum level of potassium.

Onset of action is rapid within 15 minutes. Duration of effect is short.

*Calcium Gluconate:*

Infants and children:

2 mg/kg of elemental calcium IV (about 20 mg/kg of calcium gluconate 10%).

*Adult:*

100-300 mg elemental calcium IV diluted in 150 mL D5W over 10 min. The initial rate of infusion should be 0.3-2 mg of elemental calcium per kg/hr.

*Calcium Chloride:*

Alternate choice to calcium gluconate.

Has irritating effects when administered parenterally.

Infants and children:

0.2 mL (20 mg)/kg of IV (10% solution).

*Adult:*

Known or suspected hyperkalemia ($K^+$ > 6 mEq/L):

2-4 mg/kg IV (10% solution).

*B) Remove exogenous sources of potassium intake:*

Change the diet to a low-potassium tube feed or 20 mg/kg $K^+$ ad-lib diet.

Remove oral and parenteral potassium supplements.

Remove potassium-containing salt substitutes.

*C) Enhance $K^+$ uptake by cells to decrease serum $K^+$:*

*1. Glucose and Insulin infusion:*

It increases cellular uptake of potassium.

Administer glucose along with insulin to prevent hypoglycemia.

Glucose stimulates insulin secretion, but glucose infusion alone is not effective.

Onset of action 20-30 minutes. Duration of action from 2-6 hours.

May use continuous infusions of glucose and insulin containing intravenous fluids for a prolonged effect.

Measure glucose and serum $K^+$ every 2 hours.

Infants and Children:

0.5-1 Gm/kg of dextrose IV followed or simultaneously with 1 U of regular insulin given for each 3 Gm of administered glucose.

Adult:

10 U of IV insulin with 50 mL of D50 bolus or 500 mL D10W over 1 hour.

*2. Infusion of sodium bicarbonate:*

Onset of action: 15-30 minutes; Duration of effect: 1 to 2 hours. Routine use is not recommended as it is less effective and less predictable in producing a hypokalemic response. May use to correct associated metabolic acidosis, but its effect is variable on different forms of metabolic acidosis and serum $K^+$ level, e.g., as in chronic renal failure.

A trial of parenteral sodium bicarbonate is warranted in severe acidosis, bicarbonate-responsive acidosis and hyperkalemia, and overdose of tricyclic antidepressants or phenobarbital.

Estimate (initial) the dose of $HCO_3^-$ in mEq administered by using following formula:

$$[HCO_3^-] \text{ in mEq} = (0.5 \times \text{body weight in kg}) \times (24 - \text{serum } [HCO_3^-] \text{ in mEq/L})$$

Subsequent doses should be titrated against the pH and anion gap.

Adolescents and Adult dose:

1-2 amps (50-100 mEq) of IV sodium bicarbonate is adequate / or 650-1300 mg PO b.i.d. or t.i.d.

If serum $HCO_3^-$ level is normal, but ECG shows severe changes of hyperkalemia:

Infuse 50 mEq $NaHCO_3$ q. 15 min, monitoring serum bicarbonate and sodium/or 1 L of 10% DW with 100 mEq $NaHCO_3$, infuse at 250-500 mL/hr if tolerated.

Actual pediatric dosage is not established.

*3. Beta-adrenergic agonists:*

Activate cyclic adenosine monophosphate (cAMP) which in-turn stimulates the adenosine triphosphatase ($Na^+/K^+$-ATPase) pump, thereby causing cellular influx of potassium.

Isoproterenol: Beta-1 and beta-2 adrenergic receptor stimulant.

Infants and Children:

0.1 mcg/kg/min IV, titrate to response; not to exceed 2 mcg/min.

Adult:

5 mcg/kg/min IV, titrate to response; not to exceed 20 mcg/min.

Albuterol:

Beta-2 receptor agonist and also increases plasma insulin concentrations.

Increase in insulin may shift potassium into intracellular space.

Infants and Children:

2.5 mg IV and repeat in 2 hours prn.

Adult:

10-20 mg of nebulized aerosol or 0.5 mg IV over 15 min.

Nebulized dose (10 mg) for treating hyperkalemia is substantially higher than the usual dose for the treatment of bronchospasm and requires the assistance of a respiratory therapist. This therapy is highly effective and preferred over alkali therapy in patients with renal failure.

*D) Increase potassium excretion from the body:*

1) Increase renal excretion of $K^+$:

*Diuretics:*

Loop diuretics enhance renal potassium excretion (give in patients with normal kidney function). Intravenous drug has a rapid onset of action and is preferable in emergent situations. Simultaneous administration of saline prevents volume depletion. Monitor volume status and aim to maintain normovolemia.

*Furosemide:*

Interferes with chloride-binding co-transport system and inhibits $Na^+$, $K^+$, and $Cl^+$ reabsorption in distal renal tubule and ascending loop of Henle.

*Dose:*

Infants and Children:

1 mg/kg IV/IM slowly under close supervision; not to exceed 6 mg/kg.

Titrate with increments of 1 mg/kg per dose until a satisfactory effect is achieved.

Administer increments no sooner than 6-8 hrs after the previous dose.

Continuous infusion as high as 40 mg/hr may be used for severe edema but rarely is required for Rx of hyperkalemia.

Adult:

20-80 mg / dose PO/IV/IM; titrate as high as 600 mg/dose.

Administer increments of 20-40 mg no sooner than 6-8 hrs after the previous dose.

Infusion of furosemide as high as 40 mg/hr may be used for severe edema but rarely is required for Rx of hyperkalemia.

*Bumetanide (Bumex):*

Interferes with chloride-binding co-transport system and inhibits $Na^+$, $K^+$, and $Cl^+$ reabsorption in distal renal tubule and ascending loop of Henle and increases excretion of water and $K^+$.

Adult:

Oral: 0.5-2 mg/dose q. daily/b.i.d.; not to exceed 10 mg/day.

IV/IM: 0.5-1 mg/dose; not to exceed 10 mg/day.

Rarely, doses as high as 24 mg/day are used for edema but is not needed for Rx of hyperkalemia.

Pediatric dose is not established.

*Aldosterone analogues:*

Renal excretion of $K^+$ ↑ by aldosterone analogue, 9-alpha fluorohydrocortisone acetate (Florinef). Florinef is used in hyporeninemia and / or hypoaldosteronism.

*Discontinue drugs that inhibit renal potassium excretion:*

E.g., potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers.

2) Increase gastrointestinal excretion of $K^+$:

Sodium ploystyrene sulfonate (kayexalate):

A cation exchange resin and is administered orally or rectally.

Exchanges $Na^+$ for $K^+$; binds it in the gut, primarily in the large intestine; and decreases total body potassium.

Rectal administration is preferred. Give as retention enema that can be retained for an hour. Repeated enemas can be used.

The onset of action: 2 hours. Duration: Long lasting (many hours).

The serum $K^+$ level decreases 2 mEq/L with a single enema.

Infants and Children: 1 g/kg PO in sorbitol q. 6 h.

2 g/kg PR in sorbitol as retention enema q. 6 h.

Adult: 25-50 g PO (per oral) in 25-50 mL of sorbitol q. 6 h.

25-50 g PR (per rectum) in 25-50 mL of sorbitol as retention enema q. 6 h.

*E) Emergency dialysis:*

If hyperkalemia is unresponsive (lethal hyperkalemia) to above conservative measures dialysis is indicated as in patients with complete renal failure. As initiation of dialysis can take few hours, initiate conservative therapy first.

*F) Manage causes of hyperkalemia:*

1) Potassium intake:

(2 g of potassium/day (in adult) is recommended to minimize potassium intake). In children limit to 30 to 40 mg/kg/day.

2) Decreased renal $K^+$ excretion: Try to improve renal excretion.

3) Impaired cellular uptake of $K^+$: Try to improve cellular uptake of K.

*G) Surgical interventions:*

Emergency pacemaker placement is required for refractory heart block.

Hyperkalemia due to ischemic gut requires abdominal exploration.

Rhabdomyolysis may need surgical decompression of ischemic muscle compartments.

Insert a hemodialysis catheter for emergency dialysis in end stage renal disease (ESRD).

May institute CPB for progressive acidosis and hyperkalemia post cardiac surgery.

## 2.5 Calcium Homeostasis and Calcium Abnormalities

Of the body's total calcium, serum calcium constitute only < 1% and 99% is in the bone. Total serum calcium level includes both the ionized fraction and the bound fraction.

Ionized calcium is the active and physiologically important component.

At a physiologic pH of 7.4, of the total serum calcium:

- 40% is bound to albumin.
- 10% is combined with bicarbonate, phosphate, or citrate.
- 50% is free ionized calcium.

The normal range for ionized calcium is 1-1.25 mmol/L (4-5 mg/dL).

*Factors affecting ionized calcium level:*

1) Serum levels of albumin, phosphate, magnesium, bicarbonate, and blood pH.

2) Exogenous causes: Bind calcium and reduce the ionized levels such as citrate from transfused blood and free fatty acids from TPN.

*Regulators of Calcium Homeostasis:*

1) Parathormone (PTH).

2) Vitamin D.

3) Hepatic and renal function (important for conversion of vitamin D to active metabolites).

4) Serum phosphate and serum magnesium levels.

Above regulate the calcium homeostasis and maintain serum calcium within a narrow range of normal.

### 2.5.1 Hypocalcaemia

#### (I) Definition

A total serum calcium level of

< 2.1 mmol/L (8.5 mg/dL) in children,

< 2 mmol/L (8 mg/dL) in term neonates,

< 1.75 mmol/L (7 mg/dL) in preterm neonates.

Hypocalcaemia in ICU children has mortality rate higher than children with normal calcium levels.

#### (II) Common Causes of Hypocalcaemia in Infants and Children

*Decreased Parathormone:*

1) Aplasia or hypoplasia of parathyroids:

   DiGeorge syndrome, gestational diabetes mellitus, velocardiofacial syndrome, VATER complex (vertebral defects, anal atresia, tracheo-esophageal fistula with esophageal atresia, radial (radius), and renal abnormalities), CHARGE syndrome (coloboma, heart defects, choanal atresia, renal abnormalities, growth retardation, male genital anomalies, and ear abnormalities).

2) Parathormone (PTH) receptor defects:

   Pseudohypoparathyroidism.

3) Mutations of the calcium-sensing receptor gene:

   It leads to inappropriately ↓ PTH secretion.

4) Autoimmune disease.

5) Infiltrative lesions such as hemosiderosis, thalassemia, and Wilson disease.

6) Idiopathic.

*Vitamin D related causes:*

Acquired or inherited disorders of vitamin D metabolism and vitamin D deficiency, dietary deficiency, and maternal use of anticonvulsants resistance to vitamin D.

Liver disease: Affect 25-hydroxylation of vitamin D.

Drugs (phenytoin, isoniazid, and rifampin) that increase the activity of P-450 enzymes and the catabolism of vitamin D.

*Hyperphosphatemia related:*

Exogenous loading of phosphate: Total parenteral nutrition (TPN), increased intake because of improper formula, and inappropriate use of phosphate-containing enemas.

*Increased endogenous loading of phosphate:*

Occurs in anoxia, chemotherapy, rhabdomyolysis, and renal failure.

*Miscellaneous causes:*

Alkalosis: Respiratory and metabolic and diuretic use.

Chelating agents: High doses of citrates taken in during massive blood transfusions.

Pseudohypocalcaemia (i.e., hypoalbuminemia).

Hungry bones syndrome: Rapid skeletal mineral deposition in rickets or hypoparathyroidism after starting vitamin D therapy.

**(III) Neonatal Hypocalcaemia**

Early neonatal hypocalcemia occurs within 48-72 hrs of birth and may be due to the following:

*1) Prematurity:*

- Decreased responsiveness to vitamin D.
- Increased calcitonin.
- Hypoalbuminemia: Decreased total but normal ionized calcium.

*2) Birth asphyxia:*

- Delayed introduction of feeds. ↑ calcitonin production.

*3) Diabetes mellitus in the mother:*

Magnesium depletion in diabetic mothers causes hypomagnesemic state in the foetus. Hypomagnesemia induces functional hypoparathyroidism and hypocalcaemia in the infant.

Late neonatal hypocalcaemia occurs 1 week after birth and may be due to the following:

a) Exogenous phosphate load: Feeding with phosphate-rich formula or cow's milk. Cow's milk has 7 times the phosphate load of breast milk (956 vs. 140 mg/L in breast milk).

b) Magnesium deficiency and / or transient hypoparathyroidism of newborn.

c) Gentamicin use: Especially with the newer brands and every-24-hour dosing.

**(IV) Clinical Manifestations of Hypocalcaemia**

CNS irritability and poor muscular contractility occur. Hypocalcaemia impedes acetylcholine release at neuromuscular junctions, therefore, inhibits muscle contraction. Impaired cardiac function occurs because of poor muscle contractility and changes in cardiac conduction can be noted on EKG (see Figure 4).

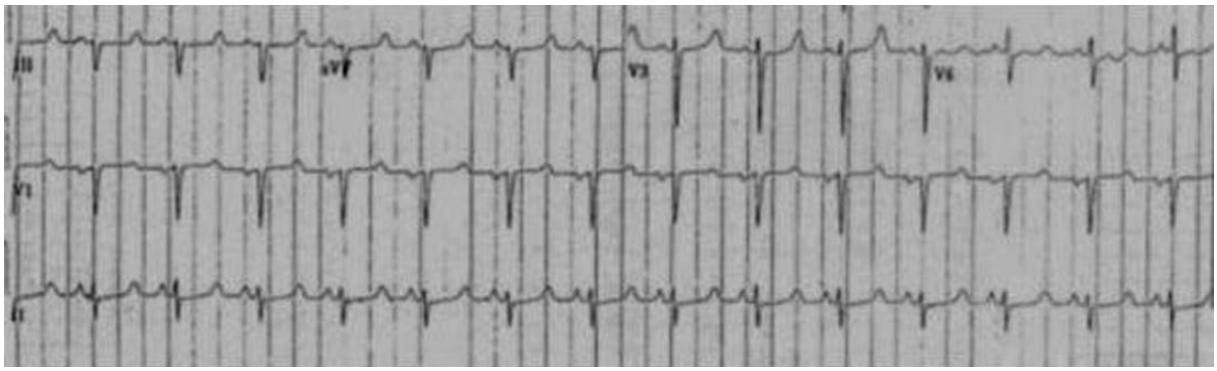


***Figure 4*** *EKG strip showing changes suggestive of hypocalcaemia with short PR interval and prolonged QT. The strips shows PR interval: 132 ms, QRS: 80 ms, QT/QC: 424/513 ms. Hypocalcaemia may result in intermittently prolonged QT or QTc (corrected QT) and increases the risk of torsades de pointes.*

Low calcium levels ↓ threshold of excitation of both sensory and motor neurons and produces a wide range of peripheral and CNS effects, including paresthesia, tetany (i.e., contraction of hands, arms, feet, larynx, and bronchioles), and seizures.

Most pediatric patients with hypocalcaemia are newborns, infants of mothers with diabetes mellitus, and infants with birth asphyxia.

Hypocalcaemia in older children is usually associated with any of the following:

Critical illness, acquired hypoparathyroidism, mutations of the calcium-sensing receptor gene or defects in vitamin D supply or metabolism.

Symptoms of hypocalcaemia vary depending on age:

*Newborns:*

Lethargy, poor feeding, vomiting, and abdominal distension.

*Manifestation in children:*

Seizures, twitching, cramping, and tetany may occur. Signs of nerve irritability such as the Chvostek sign, carpopedal spasm, the Trousseau sign, or stridor may be a rare initial manifestation.

One of the most common causes of hypocalcaemia is renal failure due to inadequate 1-hydroxylation of 25-hydroxyvitamin D and hyperphosphatemia due to diminished glomerular filtration. Though hypocalcaemia is most commonly observed in neonates, it commonly occurs in older children and adolescents, especially in ICU.

The causes of hypocalcaemia may be classified by the child's age at presentation.

**(V) Treatment of Hypocalcemia**

Treatment of asymptomatic hypocalcaemia in neonates is controversial.

Hypocalcaemia should be treated promptly in any symptomatic neonate or older infant.

Calcium therapy:

IV calcium is the most effective and rapid means of elevating serum calcium concentration.

*Indications:*

Pre and postoperative patients.

Patients with seizures and critically ill.

*Important considerations:*

Stabilize the patient's airway and breathing if seizures occur.

Anticonvulsants may be administered before hypocalcaemia is confirmed (seizures usually do not respond to the usual anti-convulsant medications until calcium is intravenously administered).

Avoid full correction of hypocalcaemia in rhabdomyolysis as the patient may develop hypercalcaemia due to the release of complexed calcium.

With concurrent acidemia, correct hypocalcaemia first. If acidemia is corrected first, it further decreases ionized calcium levels (acidemia increases the ionized calcium levels by displacing calcium from albumin).

Oral calcium therapy:

After hypocalcaemia is controlled, it is used as follow-up to IV calcium therapy.

It is also used in asymptomatic patients and therapy with oral calcium alone may be adequate in these patients.

The vitamin D or its metabolites are also indicated, depending on abnormality present, but in newborns it has not been effective to prevent or treat hypocalcaemia.

The management of hypocalcaemia of newborns requires resolution of primary cause such as hyperphosphatemia and hypomagnesemia.

Recommended dose of Vitamin D:

400 IU of vitamin D (minimum daily intake).

Begin first few days following birth and continue through adolescence.

Recombinant parathormone (PTH):

May be used in infants for hypocalcaemia refractory to calcitriol and calcium supplementation but not used routinely, due to risk of osteosarcoma.

Calcium compounds:

Calcium Gluconate:

10% (100 mg/mL) IV solution contains 9.8 mg/mL (0.45 mEq/mL) of elemental calcium.

Calcium Chloride ($CaCl_2$):

10% (100 mg/mL) contains 27 mg/mL (1.4 mEq/mL) of elemental calcium.

Calcium chloride is avoided in infants as it may affect pH, due to its irritating effect on the veins.

Calcium Glubionate (Neo-Calglucon):

It is a calcium supplement for PO use (contains 115 mg elemental calcium / 5 mL).

*Infants and Children:*

10-20 mg/kg of elemental calcium IV slowly over 5-10 min to control seizures (1-2 mL of 10% calcium gluconate/kg body weight), followed by a continuous IV infusion at 50-75 mg/kg/day over 24 hrs.

*Larger adolescents and Adults:*

200-1500 mg (as elemental calcium) IV infusion over 24 hrs. (20 to150 mL of 10% calcium gluconate or 7.4 to 55.5 mL of 10% $CaCl_2$).

Dose of Calcium Glubionate (Neo-Calglucon)

*Infants and Children:*

50-75 mg/kg/day of elemental calcium divided q.6-8h (2.1 mL-3.2 mL/kg/day).

*Larger adolescents and Adults:*

1-2 g of elemental calcium/day divided t.i.d./q.i.d. (43 mL-85 mL)/day.

Calcium carbonate (Oyster Cal, Caltrate, and Os-Cal):

Ideal calcium supplement for PO use.

1 g of calcium carbonate = 400 mg of elemental calcium.

*Larger adolescents and Adults:*

1-2 g of elemental calcium/day divided t.i.d./q.i.d. (2.5-5 g/day of calcium carbonate).

*Infants and Children:*

Neonates: 30-150 mg/kg of elemental calcium/day divided q.i.d. (75-375 mg/kg/day of calcium carbonate salt).

Children: 20-65 mg/kg / of elemental calcium / day divided b.i.d./q.i.d. (50-160 mg/kg/day of calcium carbonate salt)

Vitamin D metabolites:

$\uparrow Ca^{2+}$ levels, by ↑ absorption of calcium in intestines, and retention in the kidneys.

*Calcitriol (1, 25-dihydroxy-chole-calciferol):*

Active metabolite of vitamin D and is useful in liver or renal impairment.

It is rapid-acting and is used to treat acute hypocalcaemia.

It acts slowly in neonates and preterm infants, who may be resistant to its actions.

*Infants and Children:*

0.01-0.05 mcg/kg/day IV initially.

Adjust dosage until normocalcaemia attained.

*Adult:*

0.25 mcg PO q daily initially.

May increase by 0.25 mcg every 3-4 wks (range 0.5-2 mcg/day).

*Dihydrotachysterol (DHT):*

It is synthetic analog of vitamin D.

Does not require activation by renal 1-hydroxylase for activity.

*Infants and Children:*

Neonates: 0.05-0.1 mg PO/daily.

Children: 0.5-2 mg PO/daily.

Liquid for use in infants and young children (1 mg is equivalent to 120,000 U or 3 mg of vitamin D-2).

*Adult:*

0.75-2.5 mg PO/daily for 2-3 days initially.

Maintain with 0.1-2 mg/day.

## 2.5.2 Hypercalcaemia

### (I) Definition

Total serum $Ca^{2+}$ > 10.4 mg/dL (> 5.2 mEq/L) (males).

Total serum $Ca^{2+}$ > 10.1 mg/dL (> 5.0 mEq/L) (females) or Ionized calcium > 1.23 mEq/L.

Increase in total serum proteins (TP) elevates total serum $Ca^{2+}$.

For every gram increase in TP/dL of blood, serum $Ca^{2+}$ increases by 0.8 mEq/dL.

### (II) Causes of Hypercalcemia

Commn causes:

Primary hyperparathyroidism and it manifests as hypercalcemia, hypophosphatemia, ↑ 25-hydroxy vitamin D, and hypercalcuria.

Hormonal hypercalcaemias of malignancy (HHM).

Granulomatous disease such as sarcoidosis.

Other uncommon causes:

Thiazide diuretics, hypophosphatemia, vitamin D or vitamin A intoxication, milk-alkali syndrome, and TPN use.

Thyrotoxicosis or chronic adrenal insuffiency.

HMM: Ectopic secretion of PTHrP as in squamous cell carcinomas of lung, esophagus, head and neck, and skin etc.

Ectopic Calcitrol: Lymphomas, cytokiones, and myeloma.

### (III) Clinical Symptoms and Signs

Malaise, fatigue, weakness, letargy, confusion, changes in memory, polydypsia, polyuria, renal failure, nasuea, vomiting, constipation, bradycardia, heart block, and EKG changes suggestive of hypercalcaemia (see Figure 5).

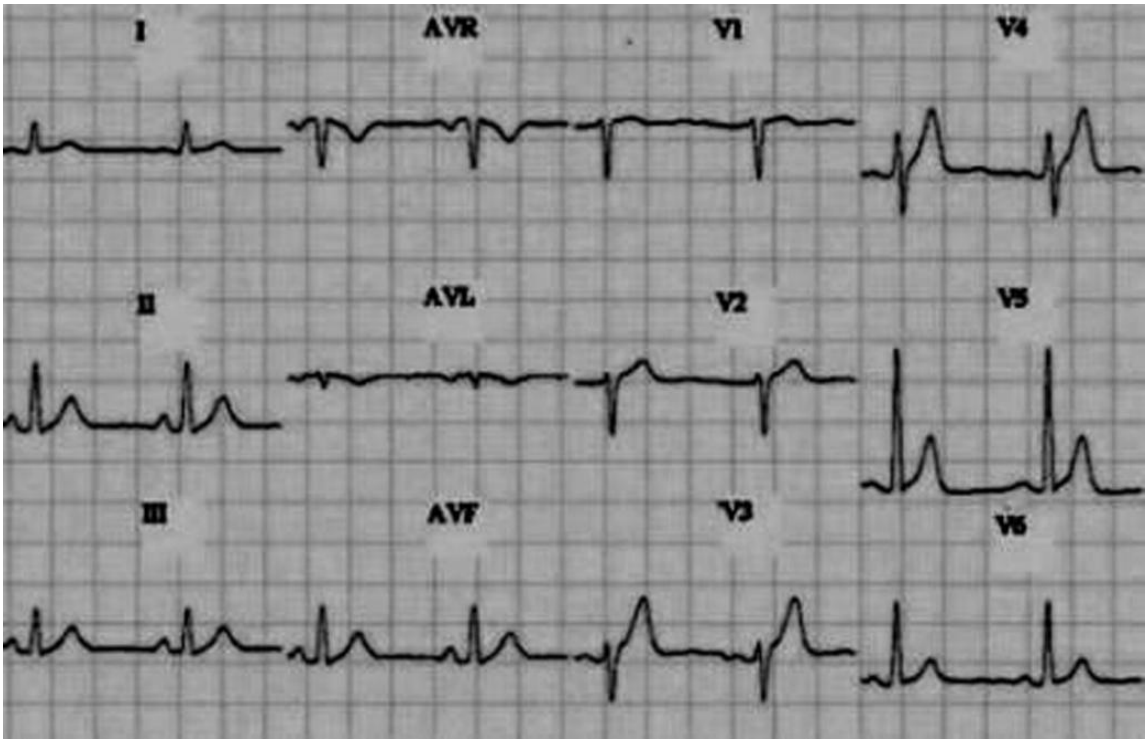



***Figure 5*** *EKG showing findings of a short QT interval and a widened T wave suggesting hypercalcaemia. Decrease in QT is at the expense of the ST segment which becomes shortened or absent. Significant hypercalcaemia can cause EKG changes mimicking an acute myocardial infarction. If serum Ca > 16 mEq/L there may be a QT prolongation.*

### (IV) Treatment

The essentials are correction of the underlying problem and the institution of supportive measures.

Supportive treatment:

*A) Furosemide and Normal saline infusion:*

Initial treatment is hydration to improve urinary calcium output.

Isotonic NaCl solution is used. ↑ sodium excretion increases calcium excretion.

Addition of a loop diuretic inhibits tubular reabsorption of calcium (diuretic is used q. 2 hours).

Pay attention to electrolytes magnesium and potassium during saline diuresis.

Normal saline (NS) infusion Dose:

15 to 30 mL/kg over 1 to 2 hours, followed by 2.5 to 5 mL/kg/hour.

Give also furosemide 0.5 mg/kg to 1 mg/kg IV q 8 hours or ↑ frequency.

Carefully monitor for fluid overload, ↓ the rate of infusion for over hydration.

Total serum $Ca^{2+}$ may drop by 1-3 mg/dL in 24 hours.

*Furosemide (Lasix):*

First line of Rx for hypercalcaemia with concomitant intense hydration.

It induces calciuresis.

IV administration: Diuretic effect begins within 5 min and peaks at 2 hrs.

Administer only by IV for emergency treatment of hypercalcaemia.

*Infants and Children:*

1 mg/kg/dose PO/IV every 8 hours or more frequently in severe hypercalcaemia.

*Adult:*

20 mg/dose PO/IV initially if patient has not been on furosemide.

Increase the dose to a desired effect.

*Precautions:*

Persistent PDA (patent ductus arteriosus) if used in first weeks of life.

Antagonizes muscle-relaxing effect of tubocurarine.

Auditory toxicity is increased with co-administration with aminoglycosides.

Antihypertensive use with diuretic may lead to excessive hypotension.

Severe electrolyte depletion (↓ serum $K^+$, $Na^+$, $Mg^{2+}$, and ↑ blood glucose) occurs.

*B) Phosphate salts:*

Removes $Ca^{2+}$ from blood and deposits in extravascluar tissues.

It may be given if serum phosphate is < 3 mg/dL until serum $P^{2-}$ increases to 5 mg/dL.

Oral Phosphate: It is a preferred method of administration.

Phophosoda 5 mL (600 mg) PO 3 or 4 times a day

Children: 8 mg/kg (PO) 3 or 4 times a day.

IV Phosphate: Used in severe hypercalcaemia (serum $Ca^{2+}$ > 15 mg/dL)

0.16 mmol/kg (5 mg/kg) infused over 6 hours until serum $P^{2-}$ is 5-6 mg/dL.

*C) Steroids:*

Decrease intestinal calcium absorption and inhibit bone resorption.

Onset of action is 2-3 days.

Prednisone 5-15 mg PO q 6 hours / or (0.3-0.9 mg/kg/day).

*D) Bisphosphonates, Bone-resorption inhibitors:*

Inhibit bone resorption and decrease serum calcium levels.

Absorbs into the hydroxyapatite and ↓ life span of osteoclasts, thus blocking bone resorption over the next 24-48 hours.

May lead to osteonecrosis of the jaw and renal compromise.

*Indications:* Commonly used for:

1) Rx of conditions with ↑ bone resorption (e.g., osteoporosis and Paget disease).

2) Management of hypercalcaemia (especially associated with malignancy).

IV administration ↓ serum calcium in 2-4 days. Maximum effect occurs in 4-7 days.

Safety and efficacy for use of etidronate and pamidronate in children is proven.

*Etidronate (Didronel):*

A first-generation bisphosphonate which inhibits formation, growth, and dissolution of hydroxyapatite crystals by chemisorption to calcium phosphate surfaces. Results in hyperphosphatemia and transient ↑ in creatinine.

Inhibits bone mineralization leading to bone pain and fractures and rarely causes nephrotic syndrome.

IV dose can be used for a short term or PO for a long term.

*Usual dose of Infants and Children:*

Rachitic syndromes may occur if continued > 1 year.

Though actual therapeutic dose is not established following doses are tried.

Oral Dose: 5-20 mg/kg/day for 3-12 months.

IV Dose: 7.5 mg/kg/day given over 2 hours for 3-7 days.

*Adolescents and Adults:*

IV Dose: 7.5 mg/kg/day in 250 mL 0.9% NaCl, infused over 2 hours for 3 days.

*Oral dose:*

10-20 mg/kg/day for 3 months or 5-10 mg/kg/day for 6 months.

*Adverse effects:* (with PO/IV administration):

Hypophosphatemia, hypocalcaemia, GI complaints, leg cramps, arthralgia, agranulocytosis, ↑ prothrombin time in patients on warfarin, EKG changes, and bleeding in animal studies if the patient is on > 27 mg/kg/day.

*Pamidronate (Aredia):*

A bisphosphonate works with similar mechanism as etidronate.

Inhibits formation, growth, and dissolution of hydroxyapatite crystals by chemisorption to calcium phosphate surfaces.

Lowers serum calcium levels over a period of days to months. Redosing is based on a rise in serum calcium levels and it should not be repeated more than once a month.

Only IV use is approved although a few studies have attempted PO administration.

*Usual dosing:*

IV Dose: 1-1.5 mg/kg (adult dose of 90 mg).

Oral Dose: 4-8 mg/kg/day.

*Infants and Children:*

1 mg/kg IV infusion over 2 hours though dose is not well established.

*Adolescents and Adults:*

*Moderate hypercalcaemia* (12-13.5 mg/dL):

60 mg IV infusion over 4 hours.

*Severe hypercalcaemia* (> 13.5 mg/dL):

90 mg IV as a continuous infusion over 24 hours.

Do not repeat the dose for at least 1 month.

*Adverse effects:*

Hypophosphatemia, hypocalcaemia, hypomagnesemia, hypokalemia, uveitis and episcleritis, bone pain, hypertension, GI adverse effects, anemia, arthralgias, musculoskeletal pains, and seizures.

*Alendronate (Fosamax):*

It is a more potent bisphosphonate.

Causes less tensile strength of bones and mineralization defects.

It has potential hepatotoxicity and lowers serum phosphorus.

*E) Calcitonin:*

Serum $Ca^{2+}$ decreases by acting primarily on the bone; acts on the kidney and GI tract.

↑ calcium mineral stores in bone and ↑ renal calcium excretion.

Lowers serum calcium within hours by ↓ skeletal reabsorption of calcium and ↓ or inhibiting renal $Ca^{2+}$ reabsorption. Also lowers serum alkaline phosphatase levels by inhibiting bone turnover.

Calcium-lowering effect begins 2 hrs after the first injection and lasts 6-8 hrs. Serum $Ca^{2+}$ ↓ by 0.5 mmol/L. The effect is maintained for 5-8 days.

Serum calcium ↓ only for 2-3 days because of tachyphylaxis.

*Usual Dose:*

Subcutaneous or Intramuscular: 3-6 mcg/kg every 6 hours.

*Adverse effects:*

Nausea, cramping, abdominal pain, and flushing.

Alternate dosing in international units (IU):

*Adult:*

4 IU/kg q.12 h SC or IM, increase to 8 IU/kg q. 12 h if it is ineffective.

Pediatric:

5-10 IU/kg.

*F) Gallium nitrate:*

It is a naturally occurring heavy metal that reduces increased bone turnover and inhibits bone resorption by reducing the solubility of hydroxyapatite.

Usually given as 200 mg/$m^2$/day IV as a continuous infusion for 5-7 days.

Nephrotoxicity ↑ if it is administered with amphotericin and aminoglycoside.

Must be discontinued if serum creatinine exceeds 2.5 mg/dL.

Hydrate patient before and several days following infusion to prevent nephrotoxicity, i.e., maintain urine output > 30 mL/kg/day.

*Adverse effects:*

Fever, rash, vomiting, diarrhea, nephrotoxicity, hypocalcaemia, hypophosphatemia, acidemia, hypotension, anemia, and optic neuritis.

*G) Calcimimetic drugs:*

*(Cinacalcet hydrochloride) (Sensipar):*

Increases sensitivity of calcium sensing receptors on chief cells of parathyroid and ↓ PTH.

Decreases renal calcium reabsorption and results in decrease of serum calcium levels.

Often used in chronic renal disease with secondary hyperparathyroidism.

Pediatric use has not been well studied.

*Precautions:*

Serum calcium reduction may cause lower seizure threshold.

Monitor serum $Ca^{2+}$ and $P^{2-}$ levels within 1 wk following an initial dose.

Adynamic bone disease may occur if PTH levels are suppressed < 100 pg/mL.

Serum levels of flecainide ↑.

Ketoconazole, erythromycin, and itraconazole may decrease cinacalcet clearance.

*Infants* and *Children:*

Secondary hyperparathyroidism (chronic renal disease):

Dose of 0.25 mg/kg/day.

*Adult:*

Initial Dose: 30 mg PO q. daily, then titrate dose upward slowly (no more frequent than q. 2-4 week intervals) by 30-mg increments. Achieve target PTH levels of 150-300 pg/mL.

*H) Mithramycin:*

Lowers calcium by inhibiting RNA synthesis, and it kills of osteoclasts.

A dose of 25 mcg/kg/day is given IV over 3-4 days; the onset of action is within 24-48 hours.

Its use was discontinued in US.

*Adverse effects:*

Thrombocytopenia, hepatocellular necrosis, coagulopathy, azotemia, proteinuria, and electrolyte imbalance. These are more common with repeated dosing.

*I) Calcitriol and Vitamin D analogues: Procalcitrol*

These drugs do not acutely lower serum calcium levels, but raise them.

Bind to vitamin D receptors and chronically inhibit secretion of parathyroid hormone (PTH). Use in symptomatic hypercalcaemia is limited.

*J) Peritoneal dialysis or hemodialysis:*

Used in extreme situations such as in severe renal failure, Address carefully the serum phosphorus level following dialysis.

*K) Surgical intervention:*

*Indication:*

Hyperparathyroidism (i.e., if serum $Ca^{2+}$ > 12.5 mg/dL persistently) that is associated with recurrent renal stones, a subtotal parathyroidectomy is performed.

## 2.6 Phosphate Homeostasis and Phosphate Abnormalities

Phosphate is the most abundant intracellular anion.

Of the total body's phosphorus, 85% is in the bone as hydroxyapatite and (15%) is in soft tissues. Only 0.1% of phosphorus is present in the extracellular fluid (blood).

Serum phosphate levels may not reflect total body stores of phosphorous, but in severe hypophosphatemia it reflects a deeper state of total body phosphate depletion.

Normal levels of serum phosphate (phosphorus):

2.5-4.5 mg/dL (0.81-1.45 mmol/L) in children ≥ 16 years and in adults.

3.2-6.3 mg/dL (1.03-1.78 mmol/L) in children and adolescents up to 15 years.

4.2-9.0 mg/dL (1.56-2.29 mmol/L) in infants < 1 year.

Phosphorus homeostasis is complex and regulated by the actions of several hormones:

1) Parathyroid hormone (PTH) releases phosphate from bone, but PTH also inhibits renal reabsorption of phosphorus causing phosphaturia and hypophosphatemia.
2) Thyroid hormone and growth hormones increase renal reabsorption of phosphate.

3) Vitamin D enhances the absorption of both phosphate and calcium.

4) Estrogen down regulates renal sodium phosphate cotransporter and causes phosphaturia.

5) Phosphatonins, the phosphate-regulating factors are important in phosphate-wasting diseases such as:

X-linked and autosomal dominant hypophosphatemic rickets, autosomal recessive hypophosphatemia, tumoral calcinosis, and oncogenic osteomalacia.

Physiology of Phosphorus:

- Phosphorus is essential for production of ATP which provides energy for nearly all cell functions.
- Phosphorus is essential component of DNA and RNA.
- Phosphorus is essential for production of red cell 2, 3-diphosphoglycerate (2, 3-DPG) which facilitates release of oxygen from hemoglobin.
- Phosphorus is essential for cell membrane structure, energy storage, and cellular transport functions in all cells.

## 2.6.1 Hypophosphatemia

### (I) Definition

Mild hypophosphatemia: 2 to 2.5 mg/dL or 0.65-0.81 mmol/L.

Moderate hypophosphatemia: 1 to 2 mg/dL or 0.32-0.65 mmol/L.

Severe hypophosphatemia: < 1 mg/dL or 0.32 mmol/L.

The above abnormalities occur in 2-3% of hospitalized and 30% of ICU patients.

The above values represent only in the adults and one should take into account the low normal values depending on the age of infants and children for defining hypophosphatemia.

### (II) Causes of Hypophosphatemia

Decreased dietary intake.

Decreased intestinal absorption of phosphate.

Increased urinary excretion of phosphate.

Intracellular shift of phosphate from serum.

*Intracellular shift of Phosphorous:*

The intracellular shift of phosphorous occurs in the underlying five conditions:

*1. Respiratory alkalosis (hyperventilation):*

It is one of the most common causes of hypophosphatemia. One should search for the serious causes of hyperventilation such as:

Sepsis, diabetic ketoacidosis (DKA), hepatic encephalopathy, salicylate poisoning, anxiety, pain, and heat stroke. In alkalosis phosphate enters into cells by activating phospho-fructokinase.

Phosphofructokinase stimulates intracellular glycolysis which leads to phosphate consumption and production of phosphorylated glucose precursors.

*2. Carbohydrate intake:*

It stimulates insulin release which moves phosphate and glucose into cells and ↓ serum phosphate. If starving or chronically malnourished patients are refed or given IV glucose, hypophosphatemia occurs day 3 or 4.

*3. Diabetic keto-acidosis (DKA):*

Metabolic acidosis and insulin deficiency shifts intracellular phosphate stores to extracellular fluid, leading to increased urinary loss of phosphorus.

Treatment of DKA with insulin shifts phosphate into cells resulting in ↓ serum phosphate.

*4. Catecholamines and beta-receptor agonists:*

These drugs stimulate phosphate entry into cells.

*5. Malignancies:*

Rapidly growing malignancies such as acute leukemia or lymphomas may consume phosphate preferentially, leading to hypophosphatemia.

In most cases of cellular shift of $P^{2-}$, serum phosphate normalizes once the cause is removed.

*Increased urinary excretion of phosphorous:*

The urinary excretion of phosphorous is increased in the following conditions:

1) Primary and secondary hyperparathyroidism:

PTH increases renal excretion of phosphate and causes hypophosphatemia.

2) Acute volume expansion:

Increases urinary loss of phosphate. Acute volume expansion also causes dilution of serum calcium which stimulates release of parathyroid hormone.

3) Osmotic diuresis:

The urinary excretion of $P^{2-}$ ↑ as in hyperosmolar hyperglycemic syndrome.

4) Diuretic Use:

Diuretics that interfere with proximal tubular reabsorbtion of phosphorus such as loop diuretics, thiazides, and carbonic anhydrase inhibitors, all produce hyperphosphaturia, and lead to hypophosphatemia.

5) Estrogens:

It is a downregulator of a renal sodium phosphate co transporter, causing significant phosphaturia and hypophosphatemia.

6) Other causes:

Transplantation: Renal excretion of phosphorous ↑ in kidney transplants.

Congenital defects: Hypophosphatemic rickets (x-linked and autosomal dominant) and Fanconi syndrome (proximal tubule dysfunction).

*Decreased intestinal absorption of phosphorous:*

The intestinal absorption of phosphorous ↓ in the following:

1) Use of phosphate binders:

Binds phosphorous in the gut thus preventing absorption.

Eg., chronic use of sucralfate, phosphate-binding antacids such as aluminum hydroxide, aluminum carbonate, and calcium carbonate.

2) Phosphate may be lost via the gut:

Eg., chronic diarrhea, malabsorption syndromes, severe vomiting, or NG suctioning.

3) Intestinal (novel) factors:

Intestine “senses” luminal concentrations of phosphate and regulates renal excretion of phosphorous by elaborating novel factors.

*Decreased dietary intake of phosphorous:*

It is a rare cause of hypophosphatemia as normal food intake contains phosphate rich foods like fruits, vegetables, meats, and dairy products.

*Anorexia nervosa or chronic alcoholism* may cause hypophosphatemia due to decreased intake and increased renal excretion.

*Intravenous feeding (total parenteral nutrition):*

Patients on total parenteral nutrition (TPN) with inadequate phosphate supplementation has low blood phosphate levels.

*Thyrotoxic periodic paralysis (TPP):*

Serum phosphorus is low with elevated levels of serum thyroxin, and it is associated with myopathy. In spontaneous periodic paralysis, phosphorus levels are normal.

**(III) Clinical Symptoms and Signs of Phosphate Deficiency**

Mild to moderately severe hypophosphatemia is usually asymptomatic.

Major clinical symptoms usually occur in severe hypophosphatemia.

1) Muscular weakness is the most common manifestation and involves both smooth muscle and skeletal muscle groups occurring either in a single group or in combination with other muscle groups (i.e. ophthalmoplegia (diplopia), dysarthria, dysphagia, ileus, and trunk or proximal arm myopathy). Weakness of the large muscle groups is common.
2) Rhabdomyolysis:

   Occurs due to depletion of ATP and loss of muscle cell membrane integrity.

   It is common after acute alcohol withdrawal that causes rapid uptake of phosphate into muscle. It is rare after Rx for DKA or in re-feeding after starvation.
3) Respiratory insufficiency:

   Occurs in some patients if underlying cause is malnourishment.

   ↓ Red cell DPG with leftward shift in hemoglobin-$O_2$ dissociation curve, and

   ↓ oxygen delivery to the tissues and brain (tissue hypoxia).

   (signs: ↓ respiratory rate and ↓ tidal volume or tachypnea).
4) Myocardial depression and impaired cardiac contractility:

Reduced threshold for ventricular arrhythmias. Cardiac output (CO) ↓ and BP ↓, and both improve if serum phosphorus is normalized.

5) Neurological dysfunction:

It is common and manifest as confusion, profound alterations in mental status, seizures, and coma. Other manifestations are extrapontine myelinolysis, peripheral neuropathy, and ascending motor paralysis (as in Guillain-Barré Syndrome).

6) Hematologic function:

Hemolytic anemia due to loss of red cell membrane integrity and destruction in the spleen. Impaired chemotaxis and phagocytosis.

**(IV) Laboratory Studies**

Serum phosphate levels that are shown below suggests the degree of hypophosphatemia.

Mild Hypophosphatemia: (2-2.5 mg/dL).

Moderate Hypophosphatemia: (1-2 mg/dL).

Severe Hypophosphatemia (< 1 mg/dL).

Abnormalities in serum magnesium, calcium, and potassium levels may occur.

Hypomagnesemia often is associated with the shift of phosphate into cells.

Hypercalcemia is common in primary hyperparathyroidism.

Derangements in serum $K^+$ may occur if hypophosphatemia is due to diabetic ketoacidosis and alcoholism.

**(V) Treatment of Hypophosphatemia**

Correct causes of hypophosphatemia and replace total body phosphates.

*Since the serum phosphate level may not accurately reflect the level of intracellular phosphate, correlate serum phosphate levels with clinical findings, before initiating aggressive therapy.*

Replacements options:

Dietary phosphate, oral phosphate salts, and intravenous phosphate.

In DKA replace with a potassium salt (as hypophosphatemia and hypokalemia coexist). If phosphate depletion is symptomatic or severe, the choice of Rx is very important.

A) Mild to moderate or asymptomatic hypophosphatemia:

*Address the factors:*

Managing factors that led to hypophosphatemia is often adequate.

Serum phosphate level spontaneously normalizes over several days.

*Oral phosphate replacement:*

Advised for patients with minimal symptoms or moderate hypophosphatemia (i.e., serum phosphorus 1-2 mg/dL).

Daily average intake of phosphorus is 15 mg/kg / body weight (adult 1 gram) or as below:

***Table 2.10*** *Daily Phosphorous intake by age.*

| | |
|---|---|
| Infants: 0-6 months: 100 mg /daily. | 7-12 months: 275 mg /daily. |
| Children: 1-3 years: 460 mg (RDA*). | 4-8 years: 500 mg (RDA*). |
| 9-18 years: 1250 mg (RDA*). | |

* Recommended daily allowance

*Intake of dairy products:*

These are suitable for oral phosphorous replacement (cow's milk has 1 mg phosphorus/mL). Provides absorbable calcium and prevents hypocalcaemia associated with phosphorous replacement.

*Sodium and Potassium phosphate:*

Provides oral phosphorus, but causes diarrhea, volume overload, or hyperkalemia.

Usual starting dose: 28-42 mg/kg/day of elemental phosphorus in divided doses.

B) Symptomatic or Severe hypophosphatemia:

Serum phosphate < 1 mg/dL requires IV phosphate.

Predicting the amount required to replenish cellular stores, nearly is impossible.

Avoid hyperphosphatemia when replacing phosphorus intravenously.

Hyperphosphatemia may lead to hypocalcaemia (leading to tetany), calcium-phosphate deposition in tissues (i.e., eye, heart, kidney, and lung), and produce hypokalemia.

*Intravenous phosphate salts:*

Sodium phosphate or potassium phosphate are commonly used salts.

Initial dosage and infusion rate is based on symptoms and severity of hypophosphatemia.

Serum $K^+$ level may limit amount of potassium phosphate that can be given safely.

*Infants and Children:*

0.25-0.5 mmol/kg IV over 4-6 h; repeat if symptoms persists.

*Adult dosing:*

1) 8 mmol of potassium phosphate IV q. 6 h initially (or 32 mmol/24 hrs).

Aggressive IV replacement: 15 mmol of potassium phosphate over 6 hrs.

(Above dose is based on recent studies in adults).

2) Severe hypophosphatemia:

30 mmol of potassium phosphate via central line over 3 hours.

3) Moderate hypophosphatemia:

15 mmol of potassium phosphate via central line over 3 hours.

*Precautions:*

1) Use of phosphate binders decrease serum phosphate levels:

E.g., Magnesium- and aluminum-containing antacids or sucralfate.

2) Drugs that increase serum phosphate levels:

Potassium-sparing diuretics, ACE inhibitors, and salt substitutes.

## 2.6.2 Hyperphosphatemia

### (I) Definition

Serum phosphate of > 5 mg/dL in patients with normal renal function.

The above value represents only in the adults and one should take into account the high normal values depending on the age of infants and children for defining hyperphosphatemia.

### (II) Causes of Hyperphosphatemia

The most common cause of hyperphosphatemia is renal failure.

Less common causes are:

1) Increased intake:

Excessive oral or rectal use of a laxative (phospho-soda).

Excessive parenteral administration of phosphate.

Milk-alkali syndrome and vitamin D intoxication.

2) Decreased excretion:

Renal failure, i.e., acute or chronic.

Hypoparathyroidism and pseudohypoparathyroidism.

Severe hypomagnesemia and bisphosphonate therapy.

3) Shift of phosphate from intracellular to extracellular space:

Acute metabolic or respiratory acidosis, rhabdomyolysis, acute hemolysis, and tumor lysis.

4) Spurious:

Blood sample containing heparin or alteplase, hyperlipidemia, hyperbilirubinemia, and in vitro hemolysis.

**(III) Clinical Signs and Symptoms of Hyperphosphatemia**

1) Most of the patients are asymptomatic.
2) Occasional patient experiences hypocalcemic symptoms, i.e., muscle cramps, tetany, and perioral numbness or tingling.
3) Symptoms related to underlying cause of hyperphosphatemia may be common,

i.e., uremic symptoms like fatigue, shortness of breath, anorexia, nausea, and vomiting.

4) No specific findings on physical exminatiion.
5) Sgns of hypocalcemia are present in acute hyperphosphatemia (as in IV phosphate administration),

e.g., Trousseau or Chvostek sign, hyperreflexia, carpopedal spasm, or seizure.

**(IV) Principles of Treatment**

1. Address the cause of hyperphosphatemia.
2. Limit or curtail intake of phosphate.
3. Increase renal excretion of phosphate.

Address the Cause:

1) Excess ingestion/administration of phosphate:

Decrease or discontine phosphate supplements: i.e., phosphate-containing laxatives and intravenous phosphate, and in presence of normal renal function, it would be adequte to correct the problem. The renal excretion of $P^{2-}$ maintains it's homeostasis despite high phosphate content of a typical diet and intestinal absorption of ingested phosphate.

2) Renal failure / renal dysfunction:

Limit or cutail phosphate intake and institute dialysis if needed. Dietary phosphate intake is a significant contributor to hyperphosphatemia in renal failure, and dietary phosphate restriction is appropriate.

(Foods high in phosphate are dairy products, meats, nuts, and other high-protein foods). Limiting intake is suffice for control in mild renal insufficiency.

Limiting intake alone is inadequate for control in advanced or complete renal failure, and phosphate binders are used to inhibit gastrointestinal absorption of phosphate. The daily nocturnal dialysis may decrease or even abolish the necessity for phosphate binders for dialysis-dependent patients.

Phosphate binders:

1) Aluminum-containing:

Lately are abandoned because of the toxic effects of absorbed aluminum such as dementia, severe osteomalacia, prevention of normal bone mineralization, and anemia.

*Aluminum hydroxide (Amphojel):*

Available in tablet form or liquid form. Commonly used as an antacid.

Not a first-line therapy because of potential for aluminum intoxication with prolonged use.

Infants and Children:

Not recommended because of potential for aluminum absorption and intoxication if used in high quantities over extended periods.

*Adult:*

1-6 tab PO with meals (not between meals) or/

Alternatively, 1-6 tbsp liquid PO with meals; titrate dose according to serum phosphate concentrations.

*Precautions:*

Corticosteroids may decrease the effects of aluminum in hyperphosphatemia.

Caution in patients with recent massive upper GI hemorrhage.

Renal failure may cause aluminum toxicity.

2) Calcium-containing:

Calcium carbonate, calcium citrate, and calcium acetate.

These salts combines with dietary phosphate to form insoluble calcium phosphate which is excreted in feces.

*Advantages:*

Provides calcium food source along with inhibition of phosphate absorption.

*Disadvantages:*

High incidence hypercalcemia and soft tissue calcification as well calcification in cardiovascular tissues. The binders could perpetuate or worsen existing vascular calcification. Vascular calcification correlates with cardiovascular mortality in chronic kidney disease.

*Precautions:*

Hypercalcemia or hypercalcuria may occur even at therapeutic doses, therefore, serum calcium should be monitored.

*Calcium carbonate (Oystercal, Caltrate):*

Normalizes phosphate concentrations in patients on dialysis.

*Infants and Children:*

45-65 mg/kg/d PO divided q.i.d.

*Adult:*

250-1500 mg PO with meals and snacks; titrate dose with serum $P^{2-}$ levels.

*Calcium acetate (Calphron):*

*Adult:*

2 tab PO with each meal and increase to bring serum phosphate value to 4 mg/dL as long as hypercalcemia does not develop; may require up to 4 tablets/day.

3) Magnesium Containing: (Phillips Milk of Magnesia)

Reduces absorption of dietary phosphate.

*Adult:*

650-mg to 1.3-g tab PO q.i.d. with meals; titrate the dose depending on serum phosphate levels.

4) Non-magnesium / aluminum or Non-calcium phosphate binders:

No definitive studies suggest that chronic use of these binders ↓ mortality or confers a disadvantage.

*Sevelamer hydrochloride (Renagel):*

Alternative to calcium-containing binder in extraskeletal calcification or recurrent hypercalcemia. It controls serum phosphorus levels well in dialysis patients.

May be used together with calcium-containing binders to minimize adverse effects of binders.

*Lanthanum carbonate (Fosrenol):*

Safe and efficacious agent for short-term use.

Should concern of long-term administration as toxicity exists.

Furthermore, these agents are significantly more expensive than calcium salts.

Secondary hyperparathyroidism:

Good control of secondary hyperparathyroidism achieves better control of blood phosphate levels in renal failure and control of hyperphosphatemia, which in turn prevents development of secondary hyperparathyroidism.

Other Agents:

Vitamin D metabolites and calcium-sensing receptor agonists tend to decrease serum phosphate levels.

Hypoparathyroidism:

Give calcium and vitamin D for treatment of hypocalcemia.

Oral calcium can ameliorate the hyperphosphatemia of hypoparathyroidism.

Hyperphosphatemia with Normal Renal function:

As it occurs in tumor lysis syndrome, measures to enhance renal excretion of phosphate are instituted.

Volume repletion with NS and forced diuresis with a loop diuretic such as furosemide or bumetanide ↑ intravascular volume, ↓ proximal tubule absorption of phosphate and solutes promoting

phosphaturia. ↑ distal tubule delivery of phosphate exceeds the ability of the nephron to reabsorb phosphate.

Diuretics:

Furosemide:

*Adult:*

20-80 mg/dose PO/IV/IM; titrate to effect; not to exceed 600 mg/day.

*Pediatric:*

1-2 mg/kg/dose PO; not to exceed 6 mg/kg/dose; do not administer > q.6 h;

or 1 mg/kg IV/IM slowly under close supervision; not to exceed 6 mg/kg/dose.

Surgical treatment:

Tertiary hyperparathyroidism with hypercalcemia, hyperphosphatemia, and severe bone disease requires parathyroidectomy.

## 2.7 Magnesium Abnormalities and Magnesium Homeostasis

Magnesium ($Mg^{2+}$) is the second-most abundant intracellular cation.

The total body content of magnesium in adults is about 2,000 mEq or 28 mEq/kg or 340 mg/Kg (24 g). No exact data are available for children.

Of the total body magnesium, 60% is in the bone, 38% in the soft tissues, and < 2% is in the extracellular fluid (ECF). The serum levels, therefore, may not reflect total body stores.

Normal serum level is from 1.8-2.5 mEq/L.

Two-thirds of serum magnesiuim is a free fraction of magnesium which is the active component (analogous to plasma calcium). One-third of serum $Mg^{2+}$ is protein-bound.

No accurate method exists to estimate the ionized serum magnesium.

*Daily requirements of Magnesium:*

0.3 mEq/kg is required to prevent deficiency.

Infants and children require higher amounts.

Magnesium absorption is primarily in jejunum and ileum by passive and active transport processes, but some magnesium is absorbed in the sigmoid colon.

*Magnesium homeostasis is regulated primarily by renal excretion:*

Ninety-six % of glumerular filtered magnesium is reabsorbed in the renal tubules through active and passive transport system:

- Active: 10% occurs in the distal convoluted tubule.
- Passive: 70% occurs in the ascending loop of Henle through lumen-positive trans-epithelial voltage and negatively charged tight junction protein, claudin-16.

*Physiology:*

Magnesium is important for DNA and protein synthesis, glycolysis, and oxidative phosphorylation. Several enzymatic reactions using adenosine triphosphate (ATP) requires magnesium for activation. Magnesium is bound to ATP in the cell. Changes in intracellular magnesium regulate mitochondrial respiration and cell energetics. The extracellular magnesium interferes with the release of acetyl choline and blocks neurosynaptic transmission. Magnesium interferes with the release of catecholamines from the adrenal medulla, and is an endogenous modulator of catecholamine response to physiologic stress.

### 2.7.1 Hypomagnesemia

It is common in hospitalized patients and may occur in 60% of ICU patients.

Neonates are predisposed to develop hypomagnesemia due to unknown mechanism or due to increased requirement for intracellular magnesium in growing tissues.

Major causes of magnesium deficiency include the following:

1) Long-term parenteral fluid therapy without supplementation.

2) Gastrointestinal causes:

Prolonged nasogastric suction/vomiting, acute pancreatitis, malabsorption syndrome, malnutrition, extensive bowel resection, intestinal or biliary fistulas, and diarrhea.

3) Renal Causes:

Diabetics: Ineffective cellular uptake of $Mg^{2+}$ (insulin-mediated) as well as osmotic diuresis.

Diuretic phase of acute tubular necrosis and hypercalcemia.

Medications (e.g., diuretics, aminoglycosides, calcineurin inhibitors) and alcohol.

Inherited tubular defects: Disorders of tubular $Na^{+}$ or $Mg^{2+}$ reabsorption (e.g., Gitelman syndrome and familial hypomagnesemia with hypercalciuria/nephrocalcinosis).

Primary infantile hypomagnesemia (autosomal recessive disease).

**(I) Clinical Symptoms and Signs**

Rate of development of hypomagnesemia may be more important than an absolute value in symptom development.

Patients are usually asymptomatic.

Early manifestations: muscle cramps, nausea, vomiting, and lethargy.

Symptoms of severe hypomagnesemia or serum magnesium < 1 mEq/L:

Tremor, seizures, hyperactive deep-tendon reflexes, hyper reactivity to sensory stimuli, muscular fibrillations, positive Chvostek and Trousseau signs, and carpopedal spasms progressing to tetany.

Other symptoms are mental changes (irritability, disorientation, depression, psychosis), cardiac arrhythmias, and reversible respiratory muscle failure.

**(II) Treatment**

Identify underlying cause of hypomagnesemia and correct the problem if possible.

Asymptomatic or mild hypomagnesemia (serum $Mg^{2+}$ > 1.2 mEq/L):

Oral replacement is preferred.

The exact dose needed to correct deficiency is unknown as it varies depending on the specific cause of hypomagnesemia and renal function.

Dose: Children: 10-20 mg of elemental magnesium / kg 3-4 times daily.

Usual duration of administration is for 4-5 days.

*Recommended diet in Chronic / Asymptomatic hypomagnesemia:*

Good sources of Magnesium:

Green vegetables such as spinach (chlorophyll contains magnesium), whole unrefined grains, beans, peas, nuts, and seeds.

*Magnesium salts for oral administartion:*

Magnesium oxide or magnesium gluconate.

*Precautions:*

Magnesium toxicity occurs in renal impairment if > 50 mEq (600 mg of elemental magnesium) is given q. daily.

May decrease effects of corticosteroids, digoxin, dilantin, and $H_2$ antagonists.

May increase the effects of dicoumarol, quinidine, and sulfonylureas.

*Magnesium oxide:*

(600 mg of salt contains 28 mEq of $Mg^{2+}$ or 336 mg of elemental $Mg^{2+}$).

*Infants* and *Children:*

65-130 mg of salt /kg/day divided t.i.d.-q.i.d. PO.

*Adult:*

2000 mg of salt /day divided t.i.d.-q.i.d. PO.

*Magnesium gluconate:*

(500 mg contains 2 mEq of $Mg^{2+}$ or 27 mg of elemental $Mg^{2+}$).

*Infants* and *Children:*

10-20 mg/kg elemental $Mg^{2+}$ PO t.i.d./q.i.d; not to exceed 400 mg/day.

(185-370 mg/kg salt PO t.i.d./q.i.d, not to exceed 7.5 gm of salt/day.

*Adult:*

500-1000 mg of salt PO t.i.d.

*Severe Hypomagnesemia:*

(Serum $Mg^{2+}$ < 1 mEq/dL).

If manifests with seizures and tetany, intravenous magnesium should be used.

Intermittent Intravenous infusion:

25-50 mg of magnesium sulfate/kg body weight (maximum 2 g) is given slowly.

This dose can be repeated every 4-6 hours as needed.

Continuous infusion:

100-200 mg of magnesium sulfate/kg/body weight/day.

*Magnesium sulfate:*

1 g of salt contains 8.12 mEq of $Mg^{2+}$ or 98 mg of elemental $Mg^{2+}$.

*Infants* and *Children:*

1 mEq/kg IV is infused over 2-6 h. on day 1 and then half of that amount is given over next 3 days.

*Adult:*

Give 2 g IV solution over 20 min, then 1 g q. 6 h. until levels are corrected (usually takes 4-5 days).

Intravenous use cautions:

Rapid IV use leads to dysrhythmias, hypotension, flushing, sweating, and/or warmth. Dilute to 5-20% before IV administration; maximum allowed concentration for infusion is 20%.

The maximum rate of administration:

It should be < 1.5 mL of 10% solution or equivalent per minute (150 mg/min with ECG monitoring).

In overdose (i.e., clinically significant hypermagnesemia and/or hypotension), give calcium gluconate 10-20 mL IV of 10% solution.

*Precautions:*

Diarrhea is the most common adverse effect.

Exercise caution in renal failure; Heart block may occur in digitalized patients.

Monitor respiratory rate and deep tendon reflexes in parenteral use.

Produces significant hypertension, hypocalcaemia, and asystole.

Concurrent use with nifedipine may cause hypotension and neuromuscular blockade. May potentiate neuromuscular blockade produced by tubocurarine, vecuronium, and succinylcholine or concomitant use with aminoglycosides.

May increase CNS effects and toxicity of CNS depressants.

## 2.7.2 Hypermagnesemia

Hypermagnesemia is defined as a serum concentration > 2.5 mEq/L of $Mg^{2+}$.

(The normal range is 1.8-2.5 mEq/L).

**(I) Causes of hypermagnesemia**

A) Impaired excretion:

Renal failure:

Most of the cases are due to administration of magnesium containing medications in severe renal failure (i.e., enemas containing magnesium, antacids etc).

Hypermagnesemia rarely occurs with a normal glomerular filtration rate (GFR).

In acute renal failure and hypermagnesemia, serum levels are usually < 4 mEq/L.

B) Transcellular shift:

Rapid mobilization of magnesium from soft tissues into ECF.

E.g., trauma, burns, shock, cardiac arrest, and diabetic ketoacidosis.

Diabetic ketoacidosis (DKA):

Hypermagnesemia initially occurs followed by hypomagnesemia during insulin administration.

C) Iatrogenic and Neonatal hypermagnesemia:

Occurs in infants whose mothers have been treated with magnesium sulfate for eclampsia and infants who are born with respiratory impairment, generalized hypotonic, and gastro-intestinal hypomotility (serum $Mg^{2+}$ concentration ranges 3-11 mEq/L).

**(II) Clinical Symptoms and Signs**

Rate of rise of serum $Mg^{2+}$ is even more important than absolute value in determining the nature of symptoms and signs. A fast rise can produce cardiovascular symptoms more readily than can a slower rise in serum $Mg^{2+}$.

*Nonspecific:*

Occur at levels 2-4 mEq/L and may include the following:

Nausea, vomiting, flushing lethargy, weakness, and dizziness.

*Central Nervous System:*

Loss of deep-tendon reflexes (at 4-6 mEq/L).

Drowsiness, depressed sensorium to coma (at > 5 mEq/L).

*Cardiovascular:*

(At 4.5 mEq/L): Negative inotropic and chronotropic activity, ↓ sinoatrial node activity, and atrial fibrillation.

(At 5-8 mEq/L): Vaso depression of vascular smooth muscle leading to systemic hypotension.

(At level > 15 mEq/L): ↑ P-R interval, wideninig of QRS, and complete heart block and asystole.

*Respiratory:*

Weakness of respiratory muscles, respiratory depression, and apnea (> 10 mEq/L). In newborn infants these occur at much lower levels.

**(III) Treatment of Hypermagnesemia**

Treatment depends on the degree of hypermagnesemia and symptoms.

1. Mildly increased levels / non specific and minimal symptoms:

Remove the source of magnesium.

I.e. oral laxatives, antacids, or other preparations that contain magnesium.

2. Moderate to higher levels of magnesium / or severe symptoms:

*1) Remove the source of magnesium.*

*2) Promote excretion of magnesium:*

- Cathartics or enemas (non-magnesium containing).

  These enhance gastrointestinal clearance of excess ingested magnesium.

- Renal excretion:
  - Patients with normal urine output and renal function:

    Intravenous saline infusions and furosemide diuresis.
  - Patients with poor renal function: (renal insufficiency):
- Dialysis:
  - Dialysis may also be used for patients with the following:

    Severe asymptomatic hypermagnesemia (> 8 mEq/L).

    Serious cardiovascular or neuromuscular symptoms at any serum $Mg^{2+}$ level.

*3) Life-threatening symptoms of hypermagnesemia:*

- E.g., arrhythmias or severe respiratory depression.
- Calcium administration and treatments as mentioned above.
- Calcium chloride (5 mL of a 10% sol) is administered IV over 30 seconds.
- Monitor patients in an ICU with close attention to ECG parameters.

Intravenous fluids:

Dilution of the extracellular $Mg^{2+}$ concentration is the rationale behind intravenous use and given with diuretics to promote diuresis of magnesium by the kidneys.

0.9% sodium chloride infusion:

*Infants and Children:*

< 10 kg: 100 mL/kg/day, 10-20 kg: 50 mL/kg/day, > 20 kg: 20 mL/kg/day.

*Furosemide (lasix):*

Inhibits $Na^+$ and $Cl^-$ reabsorption by interfering with chloride-binding co-transport system in the ascending loop of Henle and distal renal tubule, and increases water excretion, and promotes excretion of magnesium.

*Infants and Children:*

1 mg/kg/dose q. 6-12 h prn; titrate to effect.

*Adolescents and Adults:*

20-80 mg/dose IV; not to exceed 6 mg/kg/dose; titrate to effect.

*Calcium:*

Calcium directly antagonizes cardiac and neuromuscular effects of extracellular magnesium, and improves nerve and muscle performance by regulating action potential excitation threshold.

Calcium chloride (10% solution has calcium chloride 100 mg/mL).

*Infants and Children:*

20 mg/kg IV of calcium chloride (not elemental calcium) may repeat in 10 minutes if necessary.

*Adolescents and Adults:*

2-4 mg/kg IV of calcium chloride (not elemental calcium) over 10 min; followed by 2-4 mg/kg/hour of calcium chloride as a continuous infusion.

## C. Acid Base Disorders and Management

Though the common acid base abnormality found in the postoperative pediatric cardiac surgical patient includes mild metabolic alkalosis and acidosis, severe abnormalities of acid-base balance may be encountered due to prolonged intensive unit stay as a result of complicated postoperative course or due to underlying organ dysfunction. Recognition of these disorders and optimal management may improve patient outcomes.

## 2.8 Physiology of Normal Acid-Base Balance

The human body maintains in the body fluids a physiologic pH (a negative logarithm of $[H^+]$ ion concentration) in the range of 7.34 to 7.42 for ideal performance of several enzymatic reactions, contractile proteins, and blood coagulation.

Oxidative metabolism liberates an average 4 mL /kg / minute of $CO_2$, which dissolves in $H_2O$ to form $H_2CO_3$. $H_2CO_3$ exists in equilibrium with CO2 and dissociates into $[HCO_3^-]$ and $[H^+]$. $H_2CO_3$ (volatile acid) is readily eliminated by lungs in the form of $CO_2$:

$$CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^-$$

Protien catabolism and incomplete oxidation of fats and carbohydrates produce 50-100 mEq/day of non-volatile acids ($H_2SO_4$ and $H_2PO_4$), which do not exist in equilibrium with $CO_2$, and are mainly excreted by the kidney.

$CO_2$ represents major acid load than non-volatile acids and a major determinant of the blood pH. $CO_2$ exists in the blood and ECF in equlibrium between $CO_2$, $[HCO_3^-]$, and $[H^+]$ ions. It is represented by Henderson-Hasselbach equation:

$$pH = pK + \frac{\log [HCO_3^-]}{0.03 \times PaCO_2}$$

pK= 6.1 (pH of the bicarbonate buffer, where the ions of the buffer are in equilibrium), 0.03 = solubility constant of $CO_2$ in the blood.

If the serum $HCO_3^-$ is 24 mEq/L and $PaCO_2$ is 40 mm Hg, calculate the pH as shown:

$$pH = 6.1 + \log 24/ 0.03 \times 40 = 6.1 + \log 24/1.2 = 6.1 + \log 20 = 6.1 + 1.24 = 7.34$$

Metabolic alterations in acid base balance is reflected by changes in the serum $HCO_3^-$ and respiratory alterations, by changes in $PaCO_2$, and both affect the blood pH.

Based on Henderson-Hasselbach equation a change in pH of 0.01 corresponds inversely with 10 mEq/L change in $H^+$ ion concentration.

Blood pH is maintained in a normal physiologic range by excreting daily acid load by compensatory mechanisms of kidneys, lungs, and action of body buffers.

### 2.8.1 Buffers

These are a mixture of a weak acid and its conjugate salt of a base or a mixture of a weak base and its conjugate salt of an acid. Buffers have their own pK (dissociation constant) or pH, at which point

the weak base (or acid) and it's salt dissociates in equilibrium within a physiologic range of acid base status.

If an $H^+$ ion or $OH^-$ ion is added to a fluid, buffer shows only minimal change in the pH of the fluid within one unit on either side of its pK.

Buffers of the body are both intracellular and extracellular.

*Extracellular buffers:*

Bicarbonate buffer (BB) is the most important extracellular buffer.

Non-volatle acids: 45% of non-volatile acid is buffered by bicarbonate system to release $CO_2$, which is excreted by lungs as shown below:

$$H_2SO_4 + BB = CO_2 + H_2O + Na_2SO_4,\ H_2PO_4 + BB = CO_2 + H_2O + Na_2PO_4$$

Volatile acids: volatile acid like $H_2CO_3$ can not be buffered by bicarbonate system as it regenerates $H_2CO_3$. $CO_2$ is dissolved in the blood with $H_2O$, and is readily eliminated by lungs. Only 0.3 mL (7%) of $CO_2$/dL of blood is carried in the dissolved form.

*Intracellular buffers:*

Hemoglobin, proteins, organic phosphates, and bone are important buffers.

Non-volatle acids: 50% of non-volatile acid is not buffered by extracellular buffer. Over the course of several minutes or a few hours $H^+$ ion moves intracellular and is buffered by organic phosphates, proteins, and bone.

Volatile acid: Majority of the volatile acid in the body is $H_2CO_3$ and is not buffered by extracellular buffer (i.e., bicarbonate buffer), but 97% of it is buffered intracellularly by deoxygenated Hb molecule in red blood cells (70% as red cell bicarbonate, 27% carbamino-hemoglobin and in combination with plasma proteins).

## 2.8.2 Respiratory Compensation

Chemreceptors located in the brain stem and carotid body respond to changes in $PaO_2$ and $PaCO_2$ and regulate $CO_2$ exchange through lung ventilation and maintain the blood pH. Hypoxia and hypercarbia ↑ ventilation, hypocarbia ↓ ventilation. The efficiency of bicarbonate buffer system improves many fold by rapidity at which the lungs respond to changes in $PaCO_2$.

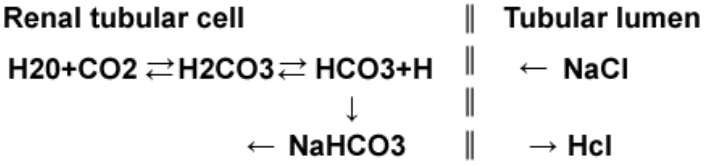
Since bicarbonate system is important to buffer non-volatle acid, lungs play an indirect role for elimination of non-volatile acid and replenishing bicarbonate buffer system.

### 2.8.3 Renal Compensation

Kidneys excrete $H^+$ ion (50-100 mEq/day) generated by non-volatile acid by the following mechanisms:

$HCO_3^-$ *Reabsorption:*

Under normal conditions most of the glomerular filtered $HCO_3^-$ is reabsorbed by the kidney. The ratio of reabsorbed $HCO_3^-$/ filtered $HCO_3^-$ increases if serum $HCO_3^-$ falls below 26 mEq/L. The $HCO_3^-$ reabsorbtion equals to $H^+$ ion excretion and is mediated by carbonicanhydrase enzyme. If serum $HCO_3^-$ levels ↑ above normal levels, the ratio of $HCO_3^-$ reabsorption to filtered $HCO_3^-$ ↓ with increased renal losses of $HCO_3^-$.




*$H^+$ ion Secretion:*

The $H^+$ ion excretion through $HCO_3^-$ reabsorption by kidneys is limited and it represents only 0.04 mEq/liter of $H^+$ ion concentration in the blood.

The rest of the acid load is excreted in two forms:

*Phosphate buffers:* 10-40 mEq. day of $H^+$ ion is buffered by intracellular pohospahte buffers of kidney as a titratable acid:

$$HCl + Na_2HPO_4 \rightarrow NaCl + NaH_2PO_4$$

*Ammonium buffer:* Normally 30-50 mEq/day of $H^+$ ion is excreted by the kidney as $NH_4^+$. Glutamine metabolism of renal cell generates NH3. The pK of the NH3 buffer is 9.3 and readily accepts the proton to form $NH_4^+$. In metabolic acidosis, increased glutamine metabolism of renal cell generates excess of NH3 and can excrete > 300-400 mEq/day of H ion, but may take several days to reach its peak.

## 2.9 Metabolic Alkalosis (MAk)

### 2.9.1 Definition

A primary elevation in serum $HCO_3^-$ concentration > 27 mEq/L leading to a pH > 7.44.

MAk refers to a loss of acid or gain of base in the extracellular fluid (ECF).

Most common acid-base disorder in hospitalized patients and has a high incidence after pediatric cardiacsurgery. The cause of MAk after pediatric cardiac surgery is multifactorial and pathogenesis is not well understood.

### 2.9.2 Post Pediatric Cardiac Surgery MAk

Predisposing factors:

Younger age, cardiopulmonary bypass (CPB), perioperative hemodilution, and preoperative ductal dependency.

More common in CPB patients than non-CPB.

Acid-base management on CPB and deep hypothermic cardiac arrest.

MAk may develop gradually with alpha-stat than pH stat management.

But the incidence of pH > 7.6 postoperatively with pH-stat and alpha-stat is not significantly different.

Untreated MAk is associated with ↑ morbidity and mortality in pediatric ICU patients. Severe MAk affects multiple organ systems and causes tissue anoxia, due to shift of the oxygen-dissociation curve to the left and hypoventilation, and it culminates in ↑ morbidity and mortality.

### 2.9.3 Pathophysiology

MAk is caused mostly by a) loss $H^+$ ions by the kidney (renal $H^+$ losses exceed H production from cellular metabolism). b) loss H ions through GI tract (as in vomiting).

*Other causes:*

1. Disproportionate chloride loss compared with $HCO_3^-$ loss (i.e., plasma $HCO_3^-$ increases upon restriction to a smaller space of distribution).

2. Actual gain of $HCO_3^-$ from exogenous administration (usually additional $HCO_3^-$ is very quickly eliminated by the kidneys).

3. Post-hypercapnia syndrome.

*Gastric losses:*

For each meq of $H^+$ ion secreted in gatric juice, one meq of $HCO_3^-$ is generated in plasma. But ↑ in plasma $HCO_3^-$ is countered by gastric acid stimulation of the pancreas to secrete $HCO_3^-$.

Gastric losses (e.g., vomiting, NG drainage) of acid removes the stimulus for the pancreas, thus allowing plasma $HCO_3^-$ levels to increase.

The loss of $K^+$ and volume contraction due to vomiting also potentiate MAk.

*Kidney losses and diuretic use:*

Diuretics increase renal losses of sodium, which is followed by ↑ excretion of chloride. The obligate $Na^+$ reabsorption follows ↑$HCO_3^-$ reabsorption due to loss of $Cl^-$ in the proximal tubules.

Additionally, ↑ delivery of $Na^+$ in the distal tubules increases sodium-potassium exchange with increased excretion of $K^+$.

The loss of $K^+$, leads to increased $H^+$ ions secretion for $Na^+$ exchange in the distal tubules.

Diuretics promote loss of $Mg^{2+}$ in the urine, which further ↓$K^+$ through an unknown mechanism.

*Decrease in ECF volume (i.e., volume contraction):*

Volume contraction concentrates (smaller space distribution) the existing levels of $HCO_3^-$. Volume contraction stimulates renin-angiotensin-aldosterone secretion. Aldosterone increases $K^+$ and $H^+$ ion losses in the kidney for exchange of $Na^+$.

*Post-hypercapnia syndrome:*

Chronic $CO_2$ retention causes compensatory ↑ in $HCO_3^-$ levels with ↑ renal excretion of $Cl^-$. MAk ensues if a patient abruptly drops the $CO_2$ level after treatment for hypercapnia.

### 2.9.4 Types of Metabolic Alkalosis

MAk is broadly divided into chloride-responsive and chloride-resistant depending on the response with chloride administration.

*Chloride-responsive MAk:*

Features:

1) Urine chloride < 10 mEq/L.
2) Decreased ECF volume and low serum chloride levels (as occurs in vomiting).
3) Responds to administration of chloride salts.

*Causes:*

Gastric fluid loss (e.g., vomiting, prologed NG drainage), posthypercapnia syndrome (especially in mechanically ventilated patients with chronic lung disease), volume contraction, (e.g., secondary to loop or thiazide diuretics), congenital chloride diarrhea, and cystic fibrosis.

*Chloride-resistant MAk:*

Features:

Urine chloride > 20 mEq/L.

Increased ECF volume.

Does not respond to administration of chloride salt.

Causes:

Chronic potassium depletion, primary aldosteronism, primary reninism, hyperglucocorticoidism, deoxycorticosterone (DOC) excess syndrome (congenital adrenal hyperplasia variant), milk-alkali syndrome (excess calcium plus bicarbonate intake and vomiting), Liddle syndrome (autosomal dominant unregulated $Na^+$ resorption in renal collecting duct), Bartter syndrome (renal $Na^+$, $K^+$, and $Cl^-$ wasting; often presents as a failure to thrive).

## 2.9.5 Compensatory Mechanisms in Metabolic Alkalosis

1. Hypoventilation:

Within several hours after MAk, elevated $HCO_3^-$ inhibits respiratory center resulting in hypoventilation with increased $PCO_2$ levels.

↑ in $PaCO_2$ of 0.7 mm Hg occurs for each 1-mEq/L ↑ in serum $HCO_3^-$.

Hypoventilation may also result in hypoxemia.

2. Intracellular buffering:

Buffering of excess $HCO_3^-$ occurs through $Na^+$ / $H^+$ and $K^+$ / $H^+$ ion exchange,

Above results in formation of $CO_2$ and $H_2O$ from $HCO_3^-$.

## 2.9.6 Sequelae of Severe Metabolic Alkalosis

Determined by the severity of alkalemia and the degree of respiratory compensation; in uncompensated MAk, the pH elevation is severe and its effects on organ function.

Respiratory:

Shift of the oxyhemoglobin dissociation curve to the left (i.e., ↑ binding of hemoglobin to oxygen).

↓ Delivery of oxygen to the tissues with cellular hypoxia.

Hypoxemia is worsened by compensatory hypoventilation that already exists (to elevate $PCO_2$ and increase in $H^+$ ion) in Mak.

Hypoventilation may be severe enough to cause apnea and respiratory arrest.

Cardiovascular:

Ventricular and supraventricular arrhythmias occur unresponsive to anti-arrhythmic drugs. Direct arteriolar constriction which increases ventricular afterload may occur.

Arteriolar constriction is further worsened by associated electrolyte disturbances.

Neuromuscular:

Headaches, seizures, obtundation, and marked muscle weakness.

Above resolve only with correction of the pH.

Electrolytes:

Serum ionized $Ca^{2+}$ ↓ due to ↑ binding of $Ca^{2+}$ to proteins and causes tetany and seizures.

Intracellular shift of $K^+$ occurs in alkalemia with hypokalemia.

Total-body potassium loss also contributes to alkalemia.

Severe hypokalemia results in muscle weakness and cardiac arrhythmias.

Other effects:

Stimulates phosphofructokinase which converts fructose-6-phosphate to fructose-1, 6-diphosphate and increases lactic acid production.

Increases renal tubular reabsorption of $Ca^{2+}$ and ↓ renal excretion.

### 2.9.7 Clinical Symptoms and Signs

Loss of gastric fluid and HCl due to vomiting is the most common cause of metabolic alkalosis. Most of the patients have prior history of vomiting or gastric fluid loss and long-term nasogastric tube drainage or diuretic use.

Prior diuretic use may lead to increased chloride losses or hypokalemia.

Patients with vomiting manifest the following:

Symptoms of severe volume contraction with signs of dehydration, e.g., tachycardia, dry mucous membranes, ↓ skin turgor, postural hypotension, poor peripheral perfusion, and weight loss.

Children present with watery diarrhea, metabolic alkalosis, and hypovolemia as in congenital chloride diarrhea (stools containing significant amounts of $Cl^-$ though diarrhea usually results in hyperchloremic metabolic acidosis).

Signs and symptoms may relate to the specific disease process causing MAk such as primary hyperaldosteronism, reninism, hyperglucocorticoidism, Bartter syndrome, deoxycorticosterone excess syndromes, milkalkali syndrome, or Liddle syndrome.

Tetany or seizures, or generalized weakness (if hypokalemic) occurs.

Hypertension and weight gain with Mak results from a hypermineralocorticoid state.

### 2.9.8 Laboratory Evaluation

ABG: Elevated pH with a high $HCO_3^-$ level.

With compensation, the $PCO_2$ level may be near a normal range or is elevated. Serum electrolytes reveal hypokalemia, hypocalcaemia, hypochloremia, or hyponatremia.

Spot urine chloride:

Urine chloride < 10 mEq/L: chloride-responsive metabolic alkalosis.

Urine chloride > 20 mEq/L: chloride-resistant metabolic alkalosis.

Other specific tests:

Indicators of underlying diseases (conditions) causing MAk:

Primary aldosteronism: Metabolic alkalosis, hypokalemia, and urine chloride > 20 mEq/L. The levels of aldosterone are increased despite controlled sodium intake of 3-4 mEq/kg/daily for 5 days (170 mg/kg or 12-15 g of Nacl daily in adults).

Cushing syndrome: Increased serum cortisol.

Primary reninism: Tests are done to prove renovascular disease with hypertension.

Bartter syndrome: Secondary hyperaldosteronism, hypokalemia, and ↑ renal losses of $K^+$ and $Cl^-$.

Milk-alkali syndrome (excessive oral intake of calcium, vitamin D metabolites, and absorbable alkali): Hypercalcaemia is associated with MAk.

Prolonged NG drainage:

Marked hypochloremia, hyponatremia, and volume contraction is associated with MAk.

### 2.9.9 Management of MAk

Principles of therapy:

Mild or moderate MAk rarely requires correction.

Volume replacement (along with chloride salts) corrects MAk due to chloride depletion and volume contraction. Persistent severe MAk requires more specific therapy directed at moderating the alkalemia.

Goal is to prevent life-threatening complications with the least amount of correction.

Address the underlying disease state, correct MAk to moderate levels.

The initial target pH is approximately 7.55 mmol/L and $HCO_3^-$ level is 40 mmol/L.

Correct associated hypovolemia or hypokalemia if Mak is due to chloride loss (from vomiting or other GI losses).

(Note infants and children with protacted vomiting may develop hypovolemic shock).

Intravascular volume expansion with isotonic crystalloid solution is necessary.

Monitor CVP to determine adequacy of volume resuscitation.

Administer potassium as a chloride salt in hypokalemia to replenish chloride losses. Potassium chloride rate should not exceed prescribed safe levels to correct hypochloremia.

Therefore administration of HCl or ($NH_4$ Cl) may be considered for persistent severe MAk.

Diuretic Use:

Acetazolamide is a drug of choice in chloride-resistant MAk and diuretic induced

MAk in pediatric cardiac surgery patients.

MAk secondary to long-term diuretic use:

Discontinue chloruretic diuretics (e.g., furosemide, bumetanide, and ethacrynic acid).

For patients requiring continued diuretic therapy in MAk, use potassium-sparing diuretics and carbonic anhydrase inhibitors. Use of potassium salt supplements helps avoid metabolic alkalosis.

Renal failure with severe MAk:

Hemodialysis or continuous renal replacement therapy corrects MAk.

(Use dialysate containing high levels of chloride and low levels of $HCO_3^-$).

Amiloride (potassium sparing diuretic):

It is potassium conserving (anti-kaliuretic) drug and possesses a weak natriuretic, antihypertensive, and hypocalciuric effects (as compared to thiazides).

Reduces the magnesium loss caused by thiazides.

It is not an aldosterone antagonist, so its effects are observed even in the absence of aldosterone. It inhibits $Na^+$ reabsorption at distal convoluted tubule, collecting tubule, and collecting duct.

Thus, tubular lumen has a less negative potential, reducing $K^+$ and $H^+$ secretion and excretion.

Amiloride is not to be used alone, due to an increased risk of hyperkalemia if it is administered by itself. May use alone only in persistent hypokalemia, and monitor serum electrolytes closely for dose titration. The drug effect begins within 2 hours after an oral dose and reaches peak 6-10 hrs, and lasts about 24 hours.

*Infants and Children:*

< 6 kg: Not well established.

6-20 kg: 0.625 mg/kg/day PO (maximum dose 10 mg/day).

> 20 kg: *Administer as in adults*

Adolescents and Adults:

5-20 mg PO q. daily.

Precaution:

Use of nonsteroidal anti-inflammatory agents (NSAIDs):

Concomitant administration of NSAIDs reduces diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics.

Indomethacin and potassium-sparing diuretics are associated with increased serum potassium levels.

Chloride solutions:

These solutions are the recommended for rapid correction of severe MAk.

(Used especially due to losses of chloride from gastric source).

Hydrochloric acid (HCl):

IV HCl may be indicated in severe MAk (pH > 7.55) if the following conditions do apply.

Rapid correction is warranted (cardiac arrhythmia, hepatic encephalopathy or digoxin toxicity).

NaCl or KCl cannot be administered due to volume overload or advanced renal failure.

Determine the amount of HCl required by calculating the pH deficit, the volume, and the infusion rate of HCl.

$H^+$ ion deficit (mEq) = 0.3 × weight (kg) ×(measured $HCO_3^-$ − desired $HCO_3^-$) [mEq/L].

Typical HCl preparation contains 0.1 N solution.

(i.e., 100 mg $H^+$/litre or 100 mmol $H^+$/L or 100 mEq/L in D5W or 0.9% NaCl).

*Infants and Children:*

Safe dose is not established, limited data have been reported.

*Adolescents and Adults:*

IV via central venous catheter:

Rate of $H^+$ replacement: 0.1-0.2 mEq/kg/hour.

0.1 N solution IV at 100 mL/hr provides about 10 mEq/hr, 10 mL/hr provides about 1 mEq/hr. Solutions of > 0.1 N produce corrosive effects, even administered through a central line.

Solutions of > 0.2 N produce increased venous irritation and potential hemolysis.

Injection of HCl into a peripheral vein cause extravasation and produce severe tissue necrosis.

Monitor ABGs and serum electrolyte levels.

Ammonium chloride ($NH_4Cl$):

$NH_4Cl$ is converted to ammonia and HCl by the liver. Released HCl corrects metabolic alkalosis.

Oral form: 500-mg tabs, IV use: 26.75% solution.

The solution has 5 mEq/mL or 267.5 mg/mL $NH_4Cl$.

*Infants and Children:*

Oral dose: 75 mg/kg/day divided q. 6 hours, not to exceed 6 g/day.

IV dose: 75 mg/kg/day divided q. 6 hours, not to exceed 6 g/day.

Dilute solution prior to administration to a concentration < 0.4 mEq/mL.

Do not exceed the infusion rate of 1 mEq/kg/hour.

Cautions: Renal failure, hepatic encephalopathy.

Monitor chloride levels, serum ammonia levels, and acid-base status.

*Adult:*

Oral Dose: 8-12 g/day divided q. 6 h.

IV Dose:1.5 g q. 6 h.

Dilute $NH_4Cl$ solution prior to administration to a concentration < 0.4 mEq/mL.

(Add 10 mL of 26.75% solution in D5W to make 150 mL).

Do not to exceed infusion rate of 1 mEq/kg/hour.

Potassium chloride:

*Infants and Children:*

IV dose: 0.5-1 mEq/kg/dose.

Dilute in adequate IV fluid for administering by either a peripheral or a central IV.

Do not exceed administration rate of 10 mEq/hr unless cardiac monitoring is in place and do not exceed 10 mEq in any single dose, even if per/kg calculation indicates higher dose.

Recheck $K^+$ level and administer additional doses as needed.

*Adult:*

Oral dose: 20-120 mEq daily.

IV dose: Up to 20 mEq/dose.

Peripheral IV infusion: Dilute in > 500 mL IV fluid.

Central IV infusion: Dilute in > 100 mL IV fluid.

Do not to exceed administration rate of 10 mEq/h unless cardiac monitoring is in place. When a concentration > 40 mEq/L is infused, local pain and phlebitis may also develop.

Carbonic Anhydrase Inhibitors:

Used to treat chloride-resistant metabolic alkalosis.

Acetazolamide (Diamox):

It is a diuretic and ↓ ECF volume that accompanies chloride-resistant metabolic alkalosis. It blocks $HCO_3^-$ reabsorption in the proximal renal tubules and increases renal excretion of sodium vs. chloride, causing a net increase in plasma chloride.

*Infants and Children:*

Oral dose: 5 mg/kg daily or every other day (q.o.d).

Parenteral dose: 8-30 mg/kg/day IV/IM divided q. 6-8 h.

Do not to exceed 1 g/day.

*Adult:*

5-10 mg/kg/day PO/IV divided q.6. h.

## 2.10 Respiratory Acidosis (RA)

### 2.10.1 Definition

It is characterized by ↑ arterial carbon dioxide ($PaCO_2$) tension of > 44 mm Hg, leading to the blood pH of < 7.35. RA may result from an acute or chronic process, and acute RA is life threatening if it is associated with severe hypoxemia and acidemia. Chronic RA (> 24 h) is characterized by a gradual and sustained increase in $PaCO_2$.

### 2.10.2 Pathophysiology

RA results from an imbalance between $CO_2$ production by the body and $CO_2$ excretion by the lungs through adequate minute ventilation (MV). $PaCO_2$ is directly proportional to $CO_2$ production and inversely proportional to alveolar ventilation.

$$\text{Alveolar ventilation} = \text{Respiratory Rate} \times (\text{Tidal volume} - \text{Physiologic dead space}).$$

Defects in MV can occur either centrally or at any level in respiratory tree to the level of capillary alveolar interface.

Respiratory center (located in the Pons and the medulla.) controls ventilation.

$CO_2$ Production:

Body metabolism generates volatile acid (carbon dioxide) and nonvolatile acid.

Carbohydrate and fat metabolism leads to the formation of a large amount of $CO_2$. $CO_2$ combines with $H_2O$ to form carbonic acid ($HCO_3^-$). $HCO_3^-$ dissociates into $H^+$ ion and $HCO_3^-$ ion. $CO_2$ is carried in the blood in 3 forms:

Dissolved gas, bicarbonate, and protein bound.

Excess $CO_2$ production (hypercapnia) $\uparrow HCO_3^-$ formation and accumulation of $H^+$ ions. $CO_2$ diffuses freely across cell membranes, and in hypercapnia excess $CO_2$ shifts intracellularly and decreases intracellular pH.

### 2.10.3 Compensatory Mechanisms of RA

These following compensatory mechanisms tend to minimize decrease in pH:

1) Ventilation regulators and regulation of ventilation:

Ventilation Regulators:

Chemo receptors in the brainstem and carotid body sensitive to changes in $PaCO_2$, $PaO_2$, and pH regulate ventilation.

Neural impulses from lung-stretch receptors and impulses from the cerebral cortex also regulate ventilation.

Regulation of ventilation (MV) by CNS:

Improves minute ventilation and elimination of $CO_2$ by the lungs.

In acute hypercapnia, $CO_2$ rapidly diffuses across the blood-brain barrier resulting in accumulation of hydrogen ions in the cerebrospinal fluid (CSF).

This change in pH is detected by chemo receptors of the brainstem, and brainstem tries to rapidly compensate by improving MV and elimination of $CO_2$ by the lungs.

If the CSF acidosis persists for several hours, cerebrospinal fluid $HCO_3^-$ levels gradually increase (see below) to normalize the pH.

2) Intracellular buffering:

Buffers: Intracellular proteins, inorganic phosphates, and hemoglobin.

Hemoglobin (Hb) is an important blood buffer (deoxygenated Hb molecule accepts $H^+$ ions to prevent substantial changes in pH).

10% of $CO_2$ is bound to Hb to form carbamino-hemoglobin.

Buffering occurs over minutes to hours by intracellular proteins and inorganic phosphates. By buffering effect, plasma $HCO_3^-$ ↑ by 1 mEq/L for every 10-mm Hg increase in $PaCO_2$.

Estimation of an expected change in pH in acute respiratory acidosis:

$$\text{Change in pH} = 0.008 \times (40 - PaCO_2)$$

Renal compensation:

Begins in 6-12 hours, but maximal compensation occurs in 3-5 days (as in chronic respiratory acidosis).

↑ Renal excretion of carbonic acid and ↑reabsorption of bicarbonate occur.

Kidneys increase $H^+$ ion excretion (predominantly in the form of $NH_4^+$ and $Cl^-$) while retaining $HCO_3^-$ and sodium. This increases the plasma $HCO_3^-$ concentration by approximately 3.5-4 mEq/L for every 10-mm Hg increase in $PaCO_2$.

Estimate of an expected change in pH in chronic respiratory acidosis:

$$\text{Change in pH} = 0.003 \times (40 - PaCO_2)$$

Blood and interstitial fluid account for a large proportion of body water in infants, and neonates and ↑ in plasma $HCO_3^-$ and ↓ in plasma $H^+$ ion concentrations are greater than those of older children.

Serum electrolytes:

RA does not have a great effect on serum electrolytes. Acidosis ↓ binding of calcium to albumin and tends to ↑ serum ionized calcium levels.

Acidemia causes an extracellular shift of potassium, but respiratory acidosis rarely causes clinically significant hyperkalemia.

Alveolar Gas Equation, Alveolar Oxygen and Carbon dioxide tensions:

$$(PAO_2) = FiO_2(PB - PH_2O) - PACO_2$$

($PACO_2$ = $PaCO_2$ (systemic arterial carbon dioxide tension).

$$\text{Alveolar carbon dioxide tension } (PACO_2) = FiO_2\ (PB - PH_2O) - PAO_2$$

$FiO_2$= inspired oxygen concentration, PB= atmospheric pressure (760 mm Hg),

$PH_2O$) = water vapor pressure (47 mm Hg), $PACO_2$ usually equals to $PaCO_2$.

Based on alveolar gas equation, if a person is breathing room air ($FiO_2$ = 0.21), the expected normal $PACO_2$ + $PAO_2$ is = 150 mm Hg.

If $PaCO_2$ raised acutely > 80-90 mm Hg, and the patient is breathing room air hypoxemia ensues.

E.g., if $PaCO_2$ is 90 mm Hg, and the patient is breathing room air ($FiO_2$ = 0.21), the calculated $PAO_2$ = [0.21 (760 mm Hg − 47 mm Hg)] − 90 mm Hg = 60 mm Hg.

If the patient is breathing supplemental oxygen, hypoventilation can only lead to significant hypercarbia without hypoxemia. E.g., if $PaCO_2$ is 80 mm Hg, and the patient is breathing supplemental oxygen ($FiO_2$ = 0.60), the calculated $PAO_2$ = [0.6 (760 mm Hg − 47 mm Hg)] − 80 mm Hg = 347 mm Hg.

### 2.10.4 Causes of Respiratory Acidosis

Nervous system related:

Central nervous system related (by suppression of respiratory drive):

Trauma, infection (encephalitis, meningitis, respiratory syncytial virus),

neoplasm, stroke, hypoxia, toxins, overdose (narcotics, alcohol), and

seizures - postictal state.

Spinal causes:

Trauma (C-spine C3-C5, and loss of phrenic nerve function).

Peripheral nerve related:

Phrenic nerve trauma, spinal muscular atrophy,

Guillain-Barr'e syndrome, and poliomyelitis.

Neuromuscular junction related:

Neuromuscular blockade (by drugs), myasthenia gravis, and botulism.

**Airway causes:**

Trauma, angioedema, tonsillar adenoid hypertrophy, burns, bronchiolitis, asthma, laryngotracheobronchitis (croup), foreign body, pharyngeal abscess, epiglottitis, paralyzed vocal cords, neoplasm, mediastinal mass, subglottic stenosis, laryngomalacia, craniofacial abnormalities, tracheal rings, and vascular slings.

**Parenchymal lung Disease:**

Acute:

Pneumonia, pulmonary edema, lung contusion, and bronchiolitis.

Chronic:

Bronchopulmonary dysplasia, cystic fibrosis, chronic bronchitis, and chronic obstructive pulmonary disease.

**Chest wall restriction and reduced respiratory compliance:**

Flail chest, pneumothorax, pleural effusions, and abdominal distension.

**Increased $CO_2$ production:**

Malignant hyperthermia, extensive burns, and overfeeding.

Rate of Development of RA:

1) Acute and rapid increase in $PaCO_2$ occurs in the following:

Depressed central respiratory drive, acute paralysis of the respiratory muscles, acute parenchymal lung and airway diseases, and increased dead space or wasted ventilation.

When $PaCO_2$ accumulates acutely, other organ systems also are affected.

2) Hypercarbia develops slowly in the following:

Progressive neuromuscular disease, restrictive lung disease, and chronic pulmonary disease. The persistently elevated $PaCO_2$ leads to an effective compensatory mechanism.

The increased $CO_2$ production may exceed the patient's ability to compensate in hypermetabolic states, such as extensive burn injury, malignant hyperthermia, or fever.

### 2.10.5 Clinical Symptoms and Signs of RA

General:

Patient is diaphoretic, irritable, and anxious.

The skin is warm, flushed, or mottled.

Respiratory:

Tachypnea, dyspnea or deep labored breaths, use of accessory muscles, and nasal flaring occurs due to increased work of breathing in acute hypercapnia.

Respiratory distress may be absent in CNS or peripheral nervous system disease.

Decreased air entry, rales, wheezes, or other signs of airway disease.

Clubbing (chronic respiratory disease).

Cardiovascular:

Acute and moderate respiratory acidosis:

Tachycardia, bounding arterial pulses, ↑ cardiac output, ↓ systemic vascular resistance,↑ epinephrine and norepinephrine release, ↓ Myocardial contractility is not seen in humans (in contrast to experimental animals).

Severe respiratory acidosis or acidemia (and hypoxemia):

(At serum pH < 7.20):

Bradycardia is often a first sign of the problem.

Blunted catecholamine response with ↓ cardiac output and hypotension.

Supraventricular arrhythmias (caused by hypoxemia, electrolyte shifts and ↑ catecholamines).

↑ pulmonary vascular resistance occurs in hypercapnia. The pulmonary vasoconstriction is severe and life threatening in hypercapnia with acidemia and hypoxemia. The decrease in serum pH rather than an absolute $PaCO_2$ has great effect on pulmonary vascular tone.

Note:

$CO_2$ administered to neonates with hypoplastic left heart syndrome with increased systemic arterial $CO_2$ saturations (> 85%) and ↓ systemic cardiac output may improve systemic perfusion by balancing the systemic/pulmonary circulation. The $PaCO_2$ may be maintained > 40 mm Hg, while the patient is on mechanical ventilation. Inspired 3% $CO_2$ may improve cerebral oxygenation and mean arterial pressure in preoperative neonates with single ventricle physiology (see Section II, Chapter 14).

Central nervous system:

The clinical manifestations of acute hypercapnia are primarily neurologic.

(if $PaCO_2$ is > 60 mm Hg): Headache, anxiety, confusion, leading to drowsiness, ↓ consciousness, or coma.

(if $PaCO_2$ is > 70 mm Hg): Somnolence or coma.

The clinical signs also vary with severity of RA.

Mild-to-moderate respiratory acidosis: Tremor, myoclonus, and brisk deep tendon reflexes.

Severe respiratory acidosis: Depressed deep tendon reflexes, papilledema, or blurring of the optic disc.

Neurologic changes associated with hypercarbia are reversible if these are not associated with hypoxemia.

Acute ↑ in $PaCO_2$ increases intracranial pressure by ↑ cerebral blood flow (CBF) and cerebral blood volume (secondary to vasodilatation).

With $PaCO_2$ of 40-80 mm Hg, CBF increases 1-2 mL per 100 g of brain / minute / for each 1-mm Hg increase in $PaCO_2$.

During sustained hypercapnia, CBF returns to baseline after 36 hours as brain extracellular pH is corrected.

## 2.10.6 Laboratory and Radiological Studies

Arterial blood gases:

pH, $PaCO_2$, and $PaO_2$.

↓ pH (< 7.35) and ↑ $PaCO_2$ (> 45 mm Hg) indicate a primary respiratory acidosis.

If pH is > 7.45, ↑ $PaCO_2$ is indicative of compensation for metabolic alkalosis (not a primary respiratory acidosis).

Hypoxemia with respiratory acidosis is suggestive of pulmonary disease.

Serum $HCO_3^-$ level and arterial pH distinguishes acute from chronic hypercapnia.

(Reference normals: pH 7.44, serum $HCO_3^-$ 24 mEq/L)

**Acute Hypercapnia:**

pH decreases by 0.08 for every 10-mm Hg increase in $PaCO_2$.

$HCO_3^-$ increases by 1 mEq/L for every 10-mm Hg increase in $PaCO_2$.

If $PaCO_2$ increases acutely to 80 mm Hg, the pH is 7.12 and the $HCO_3^-$ value is 28 mEq/L.

**Chronic Hypercapnia:**

pH decreases by 0.03 for every 10-mm Hg increase in $PaCO_2$.

$HCO_3^-$ increases by 4 mEq/L for every 10-mm Hg increase in $PaCO_2$ greater than 40 mm Hg.

If $PaCO_2$ is 80 mm Hg, the pH is 7.28, and the $HCO_3^-$ value is 40 mEq/L.

Complete blood cell count:

Secondary polycythemia is a result of chronic hypercapnia with hypoxemia.

Seum electrolytes:

Determine serum calcium, potassium, phosphorous, and magnesium.

Acidosis may result in hyperkalemia and hypercalcaemia.

Respiratory muscle weakness may be related to electrolyte deficits such as hypophosphatemia, hypokalemia, hypomagnesemia, and hypocalcaemia.

TSH and T4:

Hypothyroidism and obesity:

It is a cause of hypoventilation and leads to chronic RA as seen in obstructive sleep apnea.

Drug screening: For unexplained hypercapnia (benzodiazepines, opiates, and barbiturates).

Chest radiography: The findings suggest underlying disorder as well as the consequences of hypercapnia.

Pulmonary infiltrates → pulmonary disease, pneumonias, and pulmonary emboli.

Hyperinflation and diaphragm flattening → obstructive airway disease or pneumothorax. The elevated diaphragm → diaphragmatic weakness or paralysis, pneumothorax and atelectasis. The prominent hilar vasculature and enlarged cardiac silhouette occurs due to RV enlargement and pulmonary hypertension.

Chest fluoroscopy:

Sniff test:

Paradoxical elevation of the diaphragm during inspiration is suggestive of paralysis of diaphragm. It is positive even in the presence of a normal chest radiograph. The test is not a useful test in bilateral diaphragmatic paralysis.

CT scan of the chest:

Indicated if suspicion of a pulmonary disorder is high with inconclusive chest x-ray.

CT scan of the brain:

Perform if a central cause of RA is suspected.

MRI of the brain:

Perform if a central cause is suspected, and brain CT is negative or inconclusive.

Discloses also abnormalities of the brain stem, not observed on CT scans.

Pulmonary function tests:

Performed for diagnosis and assessment of the severity of obstructive lung disease.

FEV1 (Forced expiratory volume in 1 second) is the most commonly used index of airflow obstruction.

TLC (total lung capacity), FRC (functional residual capacity), and RV (residual volume) are increased in airflow obstruction. If FEV1/FVC (forced vital capacity) is reduced, it is the diagnostic of airflow obstruction.

IP and EP (inspiratory and expiratory pressures): The decreases in maximal IP and EP suggests respiratory muscle weakness.

Electromyography (EMG) and nerve conduction velocity (NCV):

Perform if neuromuscular disorder is suspected as in myasthenia gravis, Guillain-Barr ésyndrome, and amyotrophic lateral sclerosis.

Transdiaphragmatic pressure:

A specialized balloon catheter is placed in the esophagus and upper stomach.

Pressure differential is measured at esophageal balloon and gastric balloon.

↓ Maximal transdiaphragmatic pressure → Diaphragmatic dysfunction and paralysis.

Polysomnography or sleep study:

It is done to evaluate obstructive or central sleep apnea

### 2.10.7 Management of RA

A. Remove the underlying cause:

Narcotic induced hypoventilation: Use Naloxone.

Overdose of benzodiazepines: Administer flumazenil (romazicon).

Pneumonia and hypoventilation: Administer antibiotics.

Asthma and chroic obstructive lung disease: Use bronchodilators (e.g., albuterol and steroids).

B. Supplemental oxygen therapy:

Oxygen is given if hypoxemia accompanies hypercapnia.

Note: In chronic hypercapnia (as in COPD), $O_2$ therapy may worsen hypercapnia by the following mechanisms:

i) $O_2$ decreases hypoxiic respiratory drive / or

ii) $O_2$ increases dead-space ventilation due to a loss of hypoxic pulmonary vasoconstriction.

iii) Hypercapnia worsens in COPD patient after $O_2$ therapy, due to ventilation-perfusion mismatching.

Oxygen Rx in hypoxemic COPD patient ↓ mortality and ↓ pulmonary hypertension.

Titrate $O_2$ delivery to avoid worsening of hypercapnia, and maintain arterial blood $SaO_2$ low 90% and $PaO_2$ of 60-65 mm Hg.

C. Mechanical ventilation (MV):

Increases minute ventilation, decreases dead space, and useful in the following:

i. Acute hypercapnia:

MV is mainstay of treatment, and $PaCO_2$ can be quickly corrected to a normal level.

ii. Chronic hypercapnia:

Consider MV support, carefully due to ↓ baseline pulmonary reserve with associated disease. Weaning from MV support and extubation is usually difficult. Goal of MV should be near-normal pH with the patient's baseline $PaCO_2$.

$PaCO_2$ may be normalized over 2-3 days to prevent ↑ cerebrospinal fluid (CSF) pH and seizures.

iii. Permissive hypercapnia:

Indications:

Acute lung injury (ARDS) and strategy of low tidal volume (4-6 mL/kg).

1) Prevents stretch induced lung injury, and allows $PaCO_2$ to rise to 60-70 mm Hg.

2) MV with a low tidal volumes may ↓ mortality and ↓ ventilator dependency.

3) RA (pH > 7.25) is acceptable if cardiovascular stability and oxygenation are maintained.

Contraindications:

Pulmonary hypertension, renal disease, and brain injury (elevated $PaCO_2$ levels worsen in these).

D. Noninvasive positive-pressure ventilation (NPPV):

It is nasal continuous positive-pressure ventilation and nasal bilevel ventilation.

It is delivered either continuously or intermittently.

It decreases work of breathing and improves alveolar ventilation.

It is indicated in restrictive lung disease with chronic respiratory failure, neuromuscular disease or kyphoscoliosis.

Beneficial Rx of COPD with hypercapnia (type II respiratory failure), and decreases the need for MV.

Nasal bilevel ventilation improves Pa $O_2$ and ↓ PaC $O_2$, and is preferred treatment in obesity-hypoventilation syndrome and neuromuscular disorders.

↑ patient comfort, with decrease in nosocomial infection rate, length of hospital stay, and hospital costs.

Facial skin necrosis, conjunctivitis, and aspiration are known complications.

E. Noninvasive negative-pressure ventilation:

Devices are available for the treatment of selected patients with chronic respiratory failure.

F. Intratracheal pulmonary ventilation:

Indication:

If mechanical ventilation is inadequate in reducing hypercapnia (intractable hypercapnia) due to ↑ dead space, a catheter is placed down the endotracheal tube to produce a reverse air flow up the tube. The dead space gas is flushed out, and rebreathing of $CO_2$ decreases.

G. Extra corporeal membrane oxygenation (ECMO):

ECMO is used by some to reduce high $PaCO_2$ in treating patients with severe asthma.

H. Medications:

1. Alkalinizing agents:

(Tromethamine (THAM) and sodium bicarbonate).

Mechanical ventilation is the mainstay of therapy for respiratory failure and hypercapnia until the precipitating disease state is reversed.

Alkalinizing agents usually are used for the following in RA:

i). Correction of concurrent metabolic acidosis or acidemia of RA.

ii). Cardiopulmonary arrest.

Infusion of sodium bicarbonate may be used in arrest with an extremely low pH (< 7.0-7.1). THAM is administered short-term during therapeutic window to correct acute RA. $NaHCO_3$ infusion should be used carefully (increases the amount of $CO_2$ to be excreted).

2. Bronchodilators:

Used in obstructive lung disease and in severe bronchospasm.

Theophylline may improve diaphragm muscle contractility and stimulates the respiratory center.

i) Beta-agonists (eg., albuterol, salmeterol). ii) Methylxanthines (e.g., theophylline). iii) Anticholinergic agents (e.g., ipratropium bromide, tiotropium).

3. Medroxyprogesterone:

↑ central respiratory drive, and is effective in treating obesity-hypoventilation syndrome.

I. Dietary management:

Respiratory quotient (RQ) = $CO_2$ produced / $O_2$ consumed. The RQs for carbohydrate is 1.0, for protein 0.8, and for fat it is 0.7. High carbohydrate intake requires ↑ minute ventilation in order to excrete increased $CO_2$ load. Diet with a low carbohydrate and at least 40% fat is encouraged.

The weight-reduction and exercise program should be part of the management plan in obstructive sleep apnea.

Specialized enteral formula (Oxepa, Abbott lab):

Adjunctive in the management of ARDS as it ↓ lung inflammation and improves oxygenation. It is a low-carbohydrate and calorically dense formula containing eicosapentaenoic acid (EPA) from fish oil, gamma-linolenic acid (GLA) from borage oil, and high levels of antioxidants (vitamin E, C, carotenoids) and micronutrients.

J. Surgical treatment:

a) Diaphragmatic pacing:

Indicated in primary alveolar hypoventilation and congenital central alveolar hypoventilation syndrome.

b) Weight reduction surgery:

Indicated in patients with obesity-hypoventilation syndrome with a body mass index > 40 kg/$m^2$ and obesity-related co-morbidities with patient body mass index > 35 kg/$m^2$.

c) Other procedures: Vertical banded gastroplasty, adjustable gastric banding, and Roux-en-Y gastric bypass.

Spine fusion: Indicated in severe kyphoscoliosis with angles > 40 °.

Detailed note of medications for treatment of RA:

Alkalinizing agents (THAM and $NaHCO_3$):

Mechanical ventilation is the mainstay of therapy for respiratory failure associated with hypercapnia until the precipitating disease state can be reversed.

Alkalinizing agents are used to correct concomitant metabolic acidosis and respiratory acidosis. Use them short-term during therapeutic window to correct acute respiratory acidosis.

Tromethamine or tris-hydroxymethyl-aminomethane (THAM):

It is an inert weak base that buffers excess $CO_2$

It combines with hydrogen ions to form $HCO_3^-$ buffer as below:

$$\text{R-N}H_2 + CO_2 + H_2O = \text{R-N}H_3^+ + HCO_3^-$$

In physiologic blood pH range, its pKa is 7.8; therefore, more effective buffer than $NaHCO_3$. The drug is distributed primarily in the extracellular space, and it is not protein bound. When bound to protein, it is excreted by the kidneys and acts as an osmotic diuretic.

Adults:

Intravenous Dose:

Estimate the loading dose by the following equation:

$$\text{Volume (mL) of 0.3-molar solution} = \text{Lean body weight (kg)} \times \text{Base deficit (mEq/L)} \times 1.1$$

Typical adult dose:500 mL (150 mEq) of 0.3-molar solution.

May use up to 1000 mL in severe situations.

Titrate to serum pH / or give half of the calculated replacement dose.

Consider further replacement based on pH results.

1 mMol = 3.3 mL of 0.3 molar solution.

Bronchodilators:

↓ muscle tone in both small and large airways of the lungs, and increases ventilation. E.g., beta-adrenergics, methylxanthines, and anticholinergics.

Albuterol (Proventil, Ventolin)

Beta-2 adrenergic agonist. Relaxes bronchial smooth muscle.

It has little effect on cardiac muscle contractility.

Relieves bronchospasm that is refractory to epinephrine.

Infants and Children:

Oral Dose:

< 2 years: Not well documented.

2-5 years: 0.1-0.2 mg/kg/dose PO three times a day.

Do not exceed 12 mg/day.

5-12 years: 2 mg/dose PO t.i.d. / q.i.d.; Do not exceed 24 mg/day.

> 12 years: Administer as in adults.

MDI (Metered Dose Inhaler):

< 12 years: 1-2 inhalations q.i.d. with a tube spacer.

> 12 years: Administer as in adults.

Nebulizer:

< 5 years: Dilute 0.25-0.5 mL (1.25-2.5 mg) of 0.5% inhalation solution in 1 mL to 2.5 mL of NS and administer q. 4-6 h.

> 5 years: Administer as in adults.

Adults:

Oral Dose:

2-4 mg per dose PO t.i.d./q.i.d.; Do not exceed 32 mg/day.

MDI:

1-2 puffs q. 4-6 h.; Do not exceed 12 inhalations per day.

Nebulizer:

Dilute 0.5 mL (2.5 mg) of 0.5% inhalation solution in 1 to 2.5 mL of NS. Administer 2.5-5 mg q. 4-6 h.

Precautions:

Use cautiously in hyperthyroidism, diabetes mellitus, and cardiovascular disorders.

Metaproterenol (Alupent)

It is a beta-2 adrenergic receptor agonist. Relaxes bronchial smooth muscle with little effect on heart rate. Exercise caution in hypertension, cardiovascular disease, and congestive heart failure.

Adverse reactions:

Tachycardia, headache, hypertension, paradoxical bronchospasm, and cough.

Infants and Children:

Nebulizer:

0.1-0.2 mL of 5% solution diluted in 3 mL of 0.45% or 0.9% NS.

Give over 5-15 min q. 4 h.

Adult:

0.3 mL of 5% solution diluted in 2.5 mL of 0.45% or 0.9% NS.

Give over 5-15 min q. 4 h.

Ipratropium (Atrovent)

Anticholinergic bronchodilator chemically related to atropine.

Infants and Children:

Nebulizer:

250 mcg diluted with NS t.i.d.

MDI:

1-2 puffs t.i.d.; Do not to exceed 6 puffs per day.

Adults:

Nebulizer:

250 mcg diluted with 2.5 mL NS q. 4-6 h.

MDI:

2-4 puffs q. 4-6 h.

Theophylline (aminophyllin, theolair)

Stimulates endogenous catecholamine release, and promotes diaphragmatic muscular relaxation. These effects in turn, stimulate bronchodilation. Potentiates exogenous catecholamines.

Xanthines have narrow therapeutic range, and are associated with frequent toxicity.

Therapeutic range is 10-20 mg/dL.

Bronchodilation requires near-toxic levels (> 20 mg/dL).

Clinical efficacy is controversial in the acute setting.

Infants and Children:

< 6 weeks: Dosage is not established.

6 weeks to 6 months:

Loading dose: 0.5 mg/kg/hour IV in first 12 hours (based on aminophylline) followed by a maintenance infusion: 12 mg/kg/day.

Administer calculated daily dose in 24 hours as an hourly slow infusion.

6 months to 1 year:

Loading dose: 0.6-0.7 mg/kg/hour IV in first 12 hours, followed by a maintenance infusion of 15 mg/kg/day.

Administer as an hourly infusion by dividing total daily dose by 24.

> 1 year: Administer as in adults.

Do not infuse IV solution > 25 mg/min.

Patients with pulmonary edema or liver dysfunction are at greater risk of toxicity.

Exercise caution in hypertension, tachyarrhythmias, hyperthyroidism, and compromised cardiac function.

Adults:

Oral dose:

Initial: 10 mg/kg/day PO divided q. 8-12 h.

Maintenance: 10 mg/kg/day PO q. daily or divided b.i.d.

Do not exceed 800 mg/day.

Intravenous:

Loading dose: 5.6 mg/kg IV over 20 min (based on aminophylline), followed by a maintenance infusion of 0.1-1.1 mg/kg/hour.

Adjust dose in increments of 25% (do not exceed 800 mg/day).

Maintain serum theophylline level of 5-15 mcg/mL.

Tiotropium (spiriva):

A quaternary ammonium compound having anticholinergic/antimuscarinic effect.

Inhibits $M_3$ receptors on airway smooth muscles, leading to bronchodilation.

In COPD it dilates narrowed airways keeping them open for 24 hours.

Use for maintenance treatment of bronchospasm only.

It is not effective for acute (rescue) therapy of bronchospasm.

Available as dry powder for oral inhalation via Handi-Haler inhalation device.

Adverse reactions:

Dry mouth, increased heart rate, blurred vision, glaucoma, urinary difficulty or retention.

Adults:

Inhale contents of 1 cap (18 mcg) of dry powder via Handi-Haler device q. daily.

Infants and Children:

The dosage is not established

Benzodiazepine Antagonist:

Flumazenil (Romazicon)

Romazicon selectively antagonizes the GABA/benzodiazepine receptor complex.

It reverses CNS-depressant effects of benzodiazepine overdose, but the reversal of the benzodiazepine-induced respiratory depression is unpredictable.

If there is no response after 5 min of administering a cumulative dose of 5 mg, sedation is unlikely due to benzodiazepines.

Precaution:

Reversal of benzodiazepine may produce toxic effects due to other drugs taken in overdose. Multiple doses (as it is a short acting drug) should be given for not to relapse into sedative state. Monitor for resedation, respiratory depression, seizures, or residual effects (for at least 2 h).

Infants and Children:

Initial dose: 0.01 mg/kg intravenous over 15 seconds.

Repeat 1-min intervals with 0.005-0.01 mg/kg; not to exceed 0.2 mg per dose.

Adult:

Initial dose: 0.2 mg intravenous over 30 seconds.

Repeat doses: Give 1-min intervals with 0.5 mg over 30 seconds until satisfactory response is noted, or a dose of 3 mg is administered; may require additional titration to a total dose of 5 mg.

Opioid antagonists:

These are used in opioid overdose as it's potential etiology of hypoventilation and RA.

Naloxone (narcan):

Reverses opioid effects by displacing opiates from their receptors.

Opioid effects are hypotension, respiratory depression, and sedation.

Infants and children:

0.1 mg/kg IV/IM/SC, repeat q. 2-3 min. prn.

Adult:

0.4-2 mg IV/IM/SC q. 2-3 min. prn; use increments of 0.1-0.2 mg in opioid dependents; may need to repeat dose q. 20-60 min; if no response is observed after administering 10 mg, question the diagnosis of opioid overdose.

## 2.11 Metabolic Acidosis (MA)

### 2.11.1 Definition

Acid-base disorder is characterized by a decrease in serum pH (< 7.35) due to a primary decrease in plasma [$HCO_3^-$] concentration (< 22 mmol/L), or an increase in [$H^+$] ion concentration in the absence of an elevated $PaCO_2$.

### 2.11.2 Pathophysiology

Basic mechanisms causing metabolic acidosis are:

(1) Increased production of acids, (2) decreased excretion of acids, or

(3) loss of alkali.

The chemoreceptors of medulla compensate for MA through ↑ in alveolar ventilation. This results in tachypnea and hyperpnea, ↓$PaCO_2$ in an attempt to ↑ pH toward normal. The degree of acute respiratory compensation can be predicted by the following equation:

a) Expected $PaCO_2$ = (1.5 ×[$HCO_3^-$]) + 8 ± 2

I.e: $PaCO_2$ (33) = (1.5 ×18 ($HCO_3^-$) + 8 ± 2 or/

b) $PaCO_2$ changes (↓) by 0.7 mm Hg for every 1 mEq/L change (↓) in serum $HCO_3^-$.

Respiratory acidosis is coexistant if $PaCO_2$ is greater than expected $PaCO_2$.

Normocapnia (normal $PaCO_2$) or hypercapnia (↑$PaCO_2$) in severe metabolic acidosis indicates respiratory muscle fatigue, impending respiratory failure and signals possible need for mechanical ventilation.

The kidneys normally eliminate the daily acid load (generated from protein metabolism) by reabsorbtion of filtered bicarbonate ($HCO_3^-$) and formation of titratable acids and ammonium. The kidneys attempt to compensate for the acidosis by increased reabsorption of ($HCO_3^-$). Hyperventilation begins first and $H^+$ ion excretion then continues for 1-3 days.

The severity of the acidosis depends on the rapidity of bicarbonate loss and the ability of the kidney to replenish bicarbonate and excrete $H^+$ ion.

Anion gap:

To maintain electrochemical balance, ions in the ECF must equal a net charge of zero. The number of (anions) should equal the number of positively charged ions (cations).

Measured serum anions (negatively charged ions): Chloride and bicarbonate.

Unmeasured serum anions: Phosphates, sulfates, and proteins (e.g., albumin).

Measured primary serum cation is sodium.

Other cations: Calcium, potassium, and magnesium.

Under normal conditions as the unmeasured anions are greater than unmeasured cations, therefore, the measured anions are lower than measured cations to maintain a net charge of zero and noted as anion gap.

i) Normal anion gap = (Chloride + Bicarbonate) + Unmeasured anions =Sodium + Unmeasured cations.

ii) Unmeasured anions – Unmeasured cations = Sodium – (Chloride + Bicarbonate).

Anion Gap = (Sodium) – (Chloride + Bicarbonate) = (8-12 meq/L)

Low anion gap: Hypoalbuminemia is the most common cause of a low anion gap. Albumin constitutes half of the total unmeasured anion pool; for every 1 gm/dL decrease of serum albumin level, the serum anion gap decreases by 2.5 meq/L.

Metabolic acidosis and Anion gap:

Clinically metabolic acidosis is divided into:

1) Normal anion gap (8-12 mEq/L) metabolic acidosis.

2) Elevated anion gap (> 12 meq/L) metaboic acidosis.

### 2.11.3 Normal Anion Gap Metabolic Acidosis

It occurs due to gain of unmeasured anions over cations. To maintain a net zero charge, serum $Cl^-$ replaces depleted bicarbonate and hyperchloremia ensues.

Causes of normal anion gap metabolic acidosis:

Loss of excessive bicarbonate from the kidneys or GI tract, or inadequate hydrogen ions secretion from kidneys due to renal failure. Mnemonic USEDCARP:

Ureterosigmoidostomy, small bowel fistula, pancreatic fistula, extra chloride administration, diarrhea, carbonic anhydrase inhibitors, adrenal insufficiency, and renal tubular acidosis (RTA).

In infants loss of ($HCO_3^-$) in diarrhea is one of the most common causes.

(bicarbonate content of stool may be as much as 70-80 mEq/L).

Ureterosigmoidostomy: Loses $HCO_3^-$ in exchange for reabsorption of $Cl^-$ and $NH_4^+$ as urine accumulates in sigmoid colon.

Congenital or acquired RTA: Loses large amounts of $HCO_3^-$, with or without potassium loss.

### 2.11.4 Elevated Anion Gap Metabolic Acidosis

It is caused when extra unmeasured anions are added to the blood.

Causes of elevated anion gap metabolic acidosis:

It occurs as accumulated acids in blood are incompletely neutralized by bicarbonate.

Mnemonic for elevated anion gap metabolic acidosis: MUDPILES

i) Methanol, uremia, DKA (diabetic ketoacidosis), paraledhyde, and isoniazid.

ii) Lactic acid, ethylene glycol, ethanol, and salicylates.

In infants and children, metabolic acidosis is frequently caused by lactate.

Lactate is the end product of anaerobic glycolysis.

Hydrogen ions generated by the hydrolysis of ATP converts lactate to lactic acid.

Liver converts small amounts of lactic acid to pyruvic acid which metabolizes to $CO_2$ and $H_2O$. Tissue $O_2$ deprivation and ↓ oxygen delivery produces excessive amounts of lactic acid. Processes causing ↓ oxygen delivery frequently lead to diminished hepatic function, which further compounds lactic acid accumulation.

Processes that frequently lead to lactic acidosis:

Shock, diabetic keto-acidosis, sepsis, cellular poisoning (e.g., cyanide toxicity), and thiamine deficiency.

## 2.11.5 Clinical Evaluation, Clinical Signs, and Symptoms of MA

Clinical findings generally depend on the etiology and severity of the metabolic acidosis. One should evaluate the patient for probable causes of metabolic acidosis.

i) Metabolic acidosis during postoperative period / secondary to trauma / fever:

---- suggests lactic acidosis due to hypovolemia, sepsis, low cardiac output, or spinal shock.

ii) Dry mucous membranes, tachycardia, and delayed capillary refill:

----- suggestive of associated severe dehydration.

iii) Failure to thrive:

---- suggestive of chronic metabolic acidosis due to renal tubular acidosis (RTA).

iv) Healthy infant rapidly develops a metabolic acidosis:

----suggestive of poisoning with salicylates, ethylene glycol, and methanol.

v) Polyuria, polydipsia, and weight loss:

----- suggestive of undiagnosed diabetes mellitus and diabetic ketoacidosis.

## 2.11.6 Sequelae of Metabolic Acidosis (Acidemia)

↑ protein degradation, ↓ ATP synthesis and insulin resistance, and shift of $HbO_2$ dissociation curve to the right with ↓ affinity of oxygen for hemoglobin.

i) Respiratory:

Patients initially develop a compensatory tachypnea and hyperpnea.

Hyperventilation (Kussmaul breathing) may be the first sign of a metabolic acidosis in a child. Breath sounds are often clear to auscultation. Significant work of breathing and distress develops if the acidemia is severe.

ii) Cardiovascular:

Tachycardia (most common), weak pulses or cardiac gallop (sign of a low cardiac output) are observed. Elevated serum hydrogen ion concentration causes pulmonary vasoconstriction, leading to ↑ pulmonary vascular resistance and ↑ pulmonary artery pressure. Increased right ventricular afterload may result in right ventricular dysfunction.

As pH falls < 7.2, myocardial depression and peripheral vasodilation occurs.

$H^+$ ion is a negative inotrope. Acidemia decreases cardiovascular response to endogenous and exogenous catecholamines, which can exacerbate hypotension due to volume depletion or shock.

During metabolic acidosis, $H^+$ ions move intracellular and $K^+$ moves out of the cell into extracellular fluid (ECF) causing hyperkalemia. For every ↓ in serum pH by 0.1, serum $K^+$ ↑ by 0.5 mEq. Hyperkalemic arrhythmias (peaked T waves and QRS widening) and ventricular fibrillation may occur.

iii) Central Nervous System:

Seizures, headache, lethargy, confusion, and changes in mental status occur (due to ↓ intracerebral pH). Cerebral vasodilation occurs and contributes to rise in intracranial pressure. One has to evaluate for sepsis or inborn errors of metabloism in neonates in the presence of above symptoms.

iv) Gastrointestinal:

Nausea, vomiting, or diarrhea occur. Diarrhea is the most common cause of a metabolic acidosis in infants and children. Poor feeding or failure to thrive is common in associated left-sided obstructive cardiac lesions.

## 2.11.7 Laboratory Evaluation

i) ABG (arterial blood gas):

It reveals degree of acidemia and degree of respiratory compensation.

Winter formula: Expected $PaCO_2 = (1.5 \times [HCO_3^-]) + 8 \pm 2$

The above formula determines if respiratory compensation is adequate or a mixed metabolic and respiratory acidosis is present. With serum $HCO_3^-$ of 18, if respiratory compensation is adequate, expected $PaCO_2$ is 35 mm Hg.

If $PaCO_2$ is significantly higher than the above level, it signifies a mixed metabolic and respiratory acidosis. Exclude airway obstruction, respiratory muscle fatigue, or depressed mental

state if compensation is inadequate. Patient with diabetic ketoacidosis (DKA) has ↑ risk for cerebral edema if compensation is inadequate.

ii) Serum chemistry and urinalysis:

Serum chemistry (serum electrolytes, BUN, creatinine, glucose, ketones) is routinely done.

Determine the anion gap from the serum electrolyte levels.

a) Abnormal serum potassium: Hyperkalemia: It occurs in renal insufficiency, tissue breakdown, or shift of potassium from the intracellular space to the extracellular space due to acidemia. Hypokalemia: It occurs due to excessive body losses of potassium.

b) BUN / Creatinine ratio:

Greater than 20:1 supports the diagnosis of prerenal azotemia and hypovolemia.

c) Hyperglycemia, glycosuria, ketonuria:

Present in DKA (or rarely due to inborn error of metabolism).

d) Hypoglycemia:

Present in metabolic acidosis related to adrenal insufficiency or liver failure.

e) Normoglycemia, glycosuria:

Presents in Fanconi syndrome (type II renal tubular acidosis).

f) Elevated serum ketones and ketonuria:

Associated with absent or mild metabolic acidosis (bicarbonate level > 18) and may suggest nutritional deprivation.

iii) Serum lactate /pyruvate:

Metabolic acidosis of post cardiac surgery results in the appearance of following lactate levels:

Serum lactate > 2 mmol/L and ii) serum lactate / pyruvate ratio > 20.

The increase in duration of inotropic support, ventilatory support, and PICU stay by 0.29 days, 0.27 days, and 0.42 days respectively will increase in serum lactate by 1 mmol/L.

Hyperlactatemia per se is associated with ↑ PICU stay, but not increased lactate/pyruvate ratio or metabolic acidosis. ↑ lactate/pyruvate ratio may be seen with mild MA, and is associated with low PICU mortality.

iv) Serum osmolality and osmole gap:

Monitors as an adjunct to evaluate the response to therapy of metabolic acidosis.

Useful also in diagnosing a suspected ingestion of a toxic substance.

$$\text{Estimated serum osmolality} = 2\,[Na^+] + [\text{blood glucose} / 18] + [\text{BUN} / 2.8]$$

Normal serum osmolality: 280-295 mOsm/L.

$$\text{Osmole gap} = \text{measured serum osmolality} - \text{estimated serum osmolality.}$$

Increased osmole gap (> 20 mOsm/L) suggests osmotically active agents such as:

Methanol, ethylene glycol, or ethanol as cause of metabolic acidosis.

v) Echocardiography:

It is performed for the following.

Diagnosis of left-sided obstructive lesions in a neonate with metabolic acidosis.

Diagnosis of new onset cardiac failure (cardiomyopathy) presenting with a lactic acidosis.

CT scans of abdomen and chest:

It is useful for diagnosis of an infectious source or ischemic viscera.

### 2.11.8 Management of Metabolic Acidosis

A. Manage the underlying disorder causing MA:

i) Improve cardiac output and tissue perfusion.

Measures to improve circulation and tissue perfusion are discussed in chapter 1,4 and 11.

ii) Dehydration / hyovolemia: Administer crystalloids to restore adequate perfusion. Normal saline infusion is as effective as albumin for hydration of infants and children with metabolic acidosis due to acute diarrhea.

iii) Administer insulin in cases of diabetic ketoacidosis.

iv) Surgical management of ischemic bowel, bowel obstruction or necrotizing enterocolitis may be required.

v) Evaluate ABG ($PaO_2$ and $PaCO_2$):

Normocapnia or hypercapnia (elevated $PaCO_2$) in presence of MA suggests inadequate respiratory compensation due to respiratory muscle fatigue and / or impending respiratory failure and probable need for mechanical ventilation.

vi) Evaluate serum $HCO_3^-$

a) Serum $HCO_3^-$ is only mild to moderately decreased (i.e., > 15 mEq/L).

Replacement of $HCO_3^-$ is not necessary if the underlying disease is treated (normal kidneys replenish bicarbonate stores within 3-4 days).

Replacement of $HCO_3^-$ is necessary in chronic renal failure or renal tubular acidosis (RTA) (due to ongoing $HCO_3^-$ losses), and salicylate intoxication (alkalemic environment enhances toxin elimination).

b) Serum bicarbonate level is severly decreased (i.e., < 10 mEq/L):

Emergent $HCO_3^-$ therapy is needed as significant myocardial and CNS dysfunction can occur. Sodium bicarbonate administration:

It is a gastric, systemic, and urinary alkalinizer. It is an agent for treating metabolic acidosis when significant bicarbonate losses have occurred.

It is used for treating respiratory acidosis and metabolic acidosis of diarrhea, kidney disease, and shock. Therapy with bicarbonate in diabetic ketoacidosis (DKA) and lactic acidosis is controversial. DKA patients treated with sodium bicarbonate are at increased risk for cerebral edema. Calculation of the amount of bicarbonate replacement is as discussed below.

(desired serum bicarbonate – measured serum bicarbonate) ×weight (kg) × 0.6*

(* total volume of distribution is used for calculation).

Replace half of the total bicarbonate deficit during the first few hours of therapy then reassess the need for further therapy.

Dosage: Infants and children

0.5-1 mEq/kg/dose, intravenous

Adults:

1-2 mEq/kg/dose IV.

c) Precautions:

i) Do not overestimate or overcorrect the bicarbonate deficit.

Doses of bicarbonate exceeding 1 mEq/kg per dose may lead to an alkaline overshoot.

For each 0.1 ↑ in pH, oxygen availability ↓ by 10% (left shift of $O_2$-Hb dissociation curve).

ii) Problems due to rapid infusion of $HCO_3^-$ or overcorrection of metabolic acidosis:

Hypernatremia, alkalosis, hypokalemia, hypocalcaemia, pulmonary edema, tetany, and seizures.

To prevent sodium load, it is given as a continuous infusion as part of the maintenance solution, i.e., 34 mEq/L of $NaHCO_3$ is added to a 0.22% NaCl solution to make up a 0.45% salt solution for maintenance intravenous therapy.

iii) Paradoxical CNS acidosis:

$HCO_3$ dissociates into $CO_2$ and $H_2O$. $CO_2$ diffuses through the blood-brain barrier.

iv) Induced urinary alkalinization:

It may decrease concentrations of chlorpropamide, methotrexate, and salicylates.

It increases levels of flecainide, quinidine, and quinine.

B. Hemodialysis:

Useful in severe MA complicating renal failure or intoxication of methanol, and ethylene glycol.

C. Thiamine deficiency and thiamine administration:

Thiamine is an essential vitamin for brain development in infants.

Lack of thiamine intake can lead to depleted stores within 10 days, and deficiency is likely in a patient on TPN without vitamin supplementation for 2 or more weeks.

Thiamine deficiency leads to MA, lactic acidosis, and shock resistance to inotropic support.

Thiamine is a cocarboxylase. It is a coenzyme for pyruvate dehydrogenase and oxidative decarboxylation of alpha-ketoglutarate to succinyl-CoA. Thiamine catalyzes decarboxylation of pyruvic acid and acetyl-coenzyme A. Thiamine deficiency causes excess pyruvate levels and impaired fatty acid metabolism through the Krebs cycle and impaired generation of nicotinamide adenine dinucleotide (NADH). This stimulates anaerobic glycolysis, leading to increased lactate production.

i) Clinical presentation of thiamine deficiency:

Polyneuropathy, weakness, paralysis, and cardiac failure.

In postoperative or ICU patients, it manifests as severe metabolic acidosis, lactic acidosis, and shock resistance to inotropic support. Thiamine administration rapidly corrects clinical symptoms.

ii) Thiamine hydrochloride administration:

Infants and children:

Parenteral: 10-25 mg/dose IV/IM daily (if critically ill) or/

Oral: 10-50 mg PO daily for 2 weeks, then 5-10 mg/dose PO daily for 1 month.

Adult:

5-30 mg IV/IM t.i.d. for 2 weeks, followed by 5-30 mg PO daily for 1 month.

Wernicke syndrome: 100 mg IV for 1 dose, then 50-100 mg/daily IV/IM until patient resumes normal diet.

D. Tromethamine (tris- hydroxymethyl-aminomethane) (THAM):

THAM is a buffering agent that increases pH without increasing levels of $PaCO_2$.

It may be used to correct metabolic acidosis if sodium bicarbonate is contraindicated. It combines with hydrogen ions to form the bicarbonate buffer as shown below.

$$THAM + H_2CO_3 = THAM\text{-}H^+ + HCO_3^-$$

One mole of THAM has 120 gm/L of solution (1000 mEq).

Available as 0.3-mol/L IV solution. It contains 18 g (150 mEq) per 500 mL (0.3 mEq/mL).

Infants and children:

Dose: 0.5-1 mEq/kg/dose IV (i.e., 1.66-3.33 mL/kg/dose).

Alternate dosing: May also calculate the dose with the following formula:

ML (cc) of 0.3 mol/L THAM needed = Body weight (kg) × base deficit (mEq/L) ×1.1 (factor of 1.1 accounts for about a 10% reduction in buffering capacity by the presence of acetic acid in solution).

Usual initial dose: 3-16 mL/kg/hour IV; titrate according to serum pH.

Precautions:

Causes respiratory depression and may require ventilatory assistance.

Causes hypoglycemia and may need administration of glucose.

Reduce dose in renal impairment; monitor serum and urine pH.

## 2.12 Respiratory Alkalosis (RAK)

It is characterized by ↓ arterial carbon dioxide ($PaCO_2$) tension < 40 mm Hg, leading to a blood pH > 7.44. Alkalemia is defined as a blood pH > 7.44. It is one of the common acid-base disorders found in critically ill patients. Patient can have an alkalosis with a normal pH if compensation has occurred. RAK refers to a primary respiratory mechanism responsible for the change. It is detected by ABG and serum electrolytes.

### 2.12.1 Pathophysiology

Hypocapnia (low $PaCO_2$) develops if $CO_2$ elimination by the lungs > tissue $CO_2$ production.

Three basic mechanisms lead to respiratory alkalosis:

Hypoxia, metabolic acidosis, and direct CNS stimulation of the respiratory center (see Figure 6).

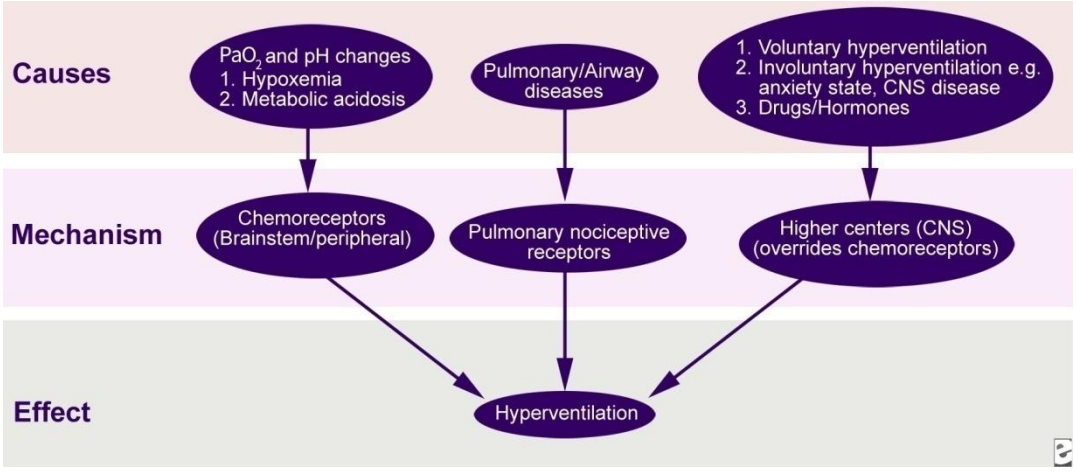



***Figure 6*** *Schematic presentation of pathophysiology of hyperventilation.*

Compensatory changes in Respiratory Alkalosis (RAK):

Alteration in ventilation ($PCO_2$) is the primary problem in RAK.

Compensation occurs by alterations in plasma bicarbonate.

In acute RAK, small ↓ in plasma $HCO_3^-$ occurs due to chemical mass action at initial stages.

Hypocapnia leads to ↑ formation of $H_2CO_3$ in response to ↓ plasma $H^+$ ion.

Above ↓ plasma bicarbonate is less profound than renal compensation.

In chronic RAK, ↑ urinary bicarbonate excretion resists the pH change caused by hypocapnia. Renal compensation begins in several hours and takes several days for a peak response.

Formulas for estimating pH in respiratory alkalosis:

(limit of compensation of [$HCO_3^-$] is of approximately 15 mEq/L)

Acute alkalosis: Change in pH = (change in $PaCO_2$) $\times 0.008$

E.g., If PaCo2 is 35 mm Hg, the pH increases by 0.28 from normal.

Chronic alkalosis: Change in pH = (change in $PaCO_2$) $\times 0.003$

E.g., If $PaCO_2$ is 35 mm Hg, the pH increases by 0.10 from normal.

## 2.12.2 Causes of Respiratory Alkalosis

a) Mechanical ventilation:

High ventilatory rate, high tidal volume, or the patient triggers excessive additional breaths.

b) Hypoxia and hypoxemia:

Any condition associated with ↓ $PaO_2$ of < 55 mm Hg or ↓ delivery of $O_2$ to tissues increases minute ventilation and causes RAK, e.g., anemia, hypotension, lung disease, high altitude/low fraction of inspired oxygen ($FiO_2$).

c) Pulmonary disorders:

These disorders decrease $PaO_2$ more significantly than elevating $PaCO_2$, with consequent hyperventilation.

Stimulation of baroreceptors in the airways and parenchyma also causes hyperventilation in the following diseases:

Interstitial lung disease, pulmonary edema, pulmonary embolism, pneumonia (Pneumocystitis pneumonia), and airway obstruction/inflammation.

d) Extrapulmonary disorders:

Though the patient's lung function is normal, but overriding ventilatory drive causes RAK as in anxiety and stress, neurologic disorders (e.g., stroke, infection, trauma, tumor), sepsis, liver failure, usage of hormones/drugs (catecholamines, methylxanthines, salicylates), and hyperthermia.

## 2.12.3 Clinical Symptoms and Signs

Symptoms of chronic RAk (due to renal compensation) are less intense than acute RAK.

Rapid ↓ $PaCO_2$ causes dizziness, mental confusion, and (rarely) seizures, even $PaO_2$ is normal.

Hypocarbia causes cerebral vasoconstriction and decreased cerebral blood flow (CBF).

CBF decreases by 1-2 mL/100 g/min for each 1 mm Hg fall in $PaCO_2$.

(Maximum fall in CBF of 40-50% may occur with a $PaCO_2$ of 20-25 mm Hg).

Alkalosis ↓ ionized calcium (↑ binding of $Ca^{2+}$ to albumin) in blood, and results in tetany.

Symptomatic hypocalcaemia is more common with respiratory alkalosis than with metabolic alkalosis. Patients may also have symptoms and signs of underlying disorders.

Signs of RAK: Fever (infectious process), tachycardia (acute RAK),↑ respiratory rate (RR), and normal BP.

If hyperventilation is due to ↑ tidal volume, RR is not increased as in diabetic ketoacidosis. BP is decreased if RAK is caused by sepsis or massive pulmonary embolism Dysrhythmias may occur in patients with underlying heart disease (due to electrolyte imbalance resulting from RAK).

### 2.12.4 Laboratory Evaluation

i) Arterial blood gas:

A pH > 7.4 suggests alkalosis and $PaCO_2$ < 35 mm Hg indicates alveolar hyperventilation and RAK.

A pH < 7.4 is observed with compensatory alveolar hyperventilation in metabolic acidosis (overcompensation for metabolic acidosis does not occur)

Duration of RAK: A pH > 7.45, with a normal range of serum $HCO_3^-$ suggests acute hyperventilation.

A pH of 7.4-7.45 with low $HCO_3^-$ suggests a chronic and partially compensated process.

ii) Alveolar- arterial oxygen gradient (A-a02):

Normal alveolar- arterial oxygen gradient and a pH > 7.4 is suggestive of normal lung function (RAK is due to direct CNS stimulation).

Decreased alveolar – arterial oxygen gradient and a pH > 7.4 is suggestive of abnormal lung function.

iii) Transcutaneous or end-tidal $PCO_2$:

It is a substitute measure for $PaCO_2$ if skin perfusion is adequate and lung function is normal.

iv) Standard Acid-Base nomograms:

These are not helpful in patients with changing clinical status, since they lose precision at extremes of values. Overlap also occurs with other mixed disorders, and require clinical judgment for a correct diagnosis.

v) Drug screening:

vi) Imaging studies:

Radiography and CT imaging of chest, ventilation/perfusion scan, and MRI of the brain.

### 2.12.5 Treatment of Respiratory Alkalosis

Address primarily the underlying etiology.

Direct measures to correct respiratory alkalosis (RAK) may not work and unnecessary unless cause is treated. If RAk is caused by patient-triggered ventilator breaths, act immediately and ↓ rate or ↓ TV (tidal volume) or use sedation and paralysis.

Hyperventilation syndrome: Re-breathing into a small-volume paper bag, and address patient's psychological stress.