Oxygen TRANSPORT, CYANOSIS – An Overview

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- Transport of O_2 and CO_2 are vital components of all body functions including maintenance of Acid-Base balance;

- Let us briefly review Oxygen transport in relation to Acid-Base balance

What is the significance of PO_2?

- Partial pressure of O_2 (pO_2) is an indirect measure of O_2 content of arterial blood;
- pO_2 is measure of tension (pressure) of O_2 dissolved in blood plasma;
- It determines force of O_2 to diffuse across Pulmonary Alveoli membrane;
- It is use to determine the effectiveness of O_2 therapy;

What conditions can result in decrease levels of pO_2?

Some conditions likely to cause decreased pO_2 :

- Patients that are unable to oxygenate arterial blood because of O_2 diffusion difficulties, Examples:
  - Pneumonia,
  - Shock Lung,
  - Congestive failure
- Patients in whom venous blood mixes prematurely with arterial blood, e.g.: Congestive heart disease;
- Patients with under-ventilated and over-perfuse Pulmonary Alveoli, Examples:
  - Pickwickian syndrome: i.e., Obese patients who cannot breath properly when in the supine position or
  - Patients with significant Atelectasis

What is the significance of O_2 saturation?

- Percentage of Hb saturated with O_2 is indicated by O_2 saturation;
- Tissues are adequately provided with O_2, when 92 – 100% of Hb exist as OxyHb;
- Decrease in the level of pO_2 causes decrease in percent saturation of Hb (OxyHb-dissociation curve);
- When O_2 saturation of Hb falls below 70% some tissues are unable to extract enough O_2 to function normally;

What is O_2 content?

- O_2 content is the calculated amount of oxygen in blood;
- The O_2 content is calculated thus:

  O_2 content = (O_2 saturation x Hb x 1.34) + (pO_2 x 0.03)

- Total O_2 content in blood is the sum of dissolved O_2 and OxyHb;
- Total O_2 capacity of blood = 20ml of O_2 per 100ml blood;
- Normally, 97 – 98% of O_2 is transported as OxyHb from Lungs to tissues;
- About 0.33ml of O_2 is dissolved in 100ml of blood;

Question: The Hb level in a male subject is 12.5g/dl;
(a) Calculate the amount of O_2 present as OxyHb in blood;
(b) Calculate the % O_2 carried in the blood of this individual;

- **Answer**:

(a) **1.0g Hb, when fully saturated, carries 1.34ml O_2**

- **Given that Hb level = 12.5g/dl of blood,**
- **Amount of O_2 that can be transported as OxyHb equal to:**

12.5 x 1.34 = 16.75ml of O_2 per 100ml of blood;

(b) **Total O_2 capacity of blood = 20ml of O_2 per 100ml blood;**

- **In this individual total O_2 capacity of blood = 16.75ml /100ml**
- **Thus, % O_2 carried = (16.75 / 20.0) x 100 = 84.0%**
- **Thus 84.0% of oxygen can be transported as OxyHb;**

How can O_2 composition of blood be characterized?

- Ability of blood to carry O_2 to tissues can be assessed by estimating % of total Hb present as OxyHb (blood O_2 Saturation);
- Blood O_2 saturation depends on: relative amounts of O_2 and Hb, and their ability to bind together;
- Characterization of O_2 composition of blood requires Measurement of **pO_2, Hb level** and **% O_2** saturation;
- Measurement of pO_2 in Arterial blood are important and valuable in assessing efficiency of O_2 therapy;

- Result of only pO_2 may be misleading in conditions where O_2-carrying capacity of blood is grossly impaired, as in patients with either:
  - **Severe Anemia**,
  - **Carbon Monoxide poisoning**,
  - **High amount of Methemoglobin,**
  - **Smokers;**
- PO_2 may be within normal limits but O_2 saturation may be severely reduced because:
  - Carbon Monoxide binds Hb (CarboxyHb) with greater affinity than Oxygen
  - CarboxyHb concentration in blood of some smokers may be greater than 10%, which reduces supply of O_2 to tissues;

- In this group of patient measurement of Hb and % O_2 saturation are required in addition to pO_2
  - Significant of these assessment is that when metabolic needs exceeds supply of O_2, cells obtain energy via Anaerobic Glycolysis, leading to production and accumulation of Lactic acid (Lactic acidosis);
- Assessment of Lactate level in plasma can provide additional evidence of adequacy of O_2 supply to tissues;
- Delivery of O_2 to tissues also depends on blood flow, which is influenced by several other factors, such as Cardiac Output and Peripheral Perfusion;

What is the significance of PCO_2?

- pCO_2 (partial pressure of CO_2) in a measure of the pressure of CO_2 dissolved in blood;
- The faster and more deeply a patient breathes, the more CO_2 is passed out and the pCO_2 level in blood drops;
- pCO_2 is the respiratory component in Acid-base balance, because it is controlled by Lungs;
- Increase in the level of pCO_2 in blood leads to decrease in pH of blood (Respiratory Acidosis);
- pCO_2 in blood and CSF is a major stimulant to breathing center in the Brain;

- As level of pCO_2 in blood increases (Acidosis), breathing is stimulated, ventilation is increased to pass out more CO_2
- If pCO_2 level in blood increase too high, breathing cannot keep up with the corresponding demand to further increase ventilation;
- Further increase in level of pCO_2 in blood may depress brain function, resulting in significant decrease in rate of ventilation, causing coma;

- pCO_2 in blood are increased in Primary Respiratory Acidosis:
- Some conditions resulting in increased PCO_2 include:
  - Airways obstruction;
  - Sedatives,
  - Anesthetics,
  - Respiratory Distress Syndrome,
  - Chronic Obstructive Pulmonary Disease
- pCO_2 in blood are decreased in Primary Respiratory Alkalosis:
- Some conditions resulting in decreased PCO_2 include:
  - Hypoxia (resulting in hyperventilation) due to Chronic Heart Failure,
  - Edema,
  - Neurological disorders,
  - Mechanical Hyperventilation

Is the pCO_2 the same as CO_2 content in blood?

- pCO_2 in blood is not the same as CO_2 content in blood
- pCO_2 is a direct measurement of the pressure (tension) of CO_2 in blood;
- pCO_2 is regulated by the Lungs;
- pCO_2 is the respiratory component in Acid-base balance;

- CO_2 content in blood is an indirect measurement of Bicarbonate ion (HCO_3^-) in blood,
- HCO_3^- is the metabolic component in Acid-base balance;
- HCO_3^- is regulated by the Kidneys;
- Carbonic Anhydrase catalyzes the reversible reaction linking CO_2 and HCO_3^-

BICARBONATE BUFFER SYSTEM

Carbonic Anhydrase

$$CO_2 + H_2O \xleftrightarrow{\text{Carbonic Anhydrase}} H_2CO_3 \xleftrightarrow{} H^+ + HCO_3^-$$

$$pH = pKa + \log_{10} \frac{[HCO_3^-]}{PCO_2}$$

$$pH = pKa + \log_{10} \frac{\text{Kidneys}}{\text{Lungs}}$$

What is the significance of HCO_3^-?

- Most of the CO_2 content in blood is present as HCO_3^-
- HCO_3^- is an indicator of buffering capacity of blood;
- HCO_3^- is a measure of the metabolic (Renal) component in Acid-base balance;
- HCO_3^- can be measured directly or calculated thus:

$$\mathbf{[HCO_3^-] = pCO_2 \times 0.03}$$

- $[HCO_3^-]$ in blood is directly proportional to pH level in blood;

- [HCO_3^-] in blood is decreased in Primary Metabolic Acidosis;
- Some causes of primary metabolic acidosis:
  - Ketoacidosis,
  - Lactate acidosis (Hypoxia),
  - Diarrhea,
  - Renal failure
- [HCO_3^-] in blood is elevated in Primary Metabolic Alkalosis;
- Some causes of primary metabolic alkalosis:
  - Prolonged vomiting,
  - Antacid treatment,
  - Nasogastric drainage

What is Base Excess (deficit)?

- Base Excess is the amount of H^+ ions required to return the pH of blood to 7.35 if pCO_2 were adjusted to normal;
- Base Excess is usually calculated by blood gas machine using pH, PCO_2 and Hematocrit;
- Base Excess represents the amount of buffering Anions (HCO_3^-, Hb, Proteins, Phosphates, etc) in the blood;
- Base Excess provides an estimate of the metabolic component of Acid-Base Balance;

- Negative-Base Excess (deficit) indicates Metabolic Acidosis
  - Base Excess < – 3

- Positive-Base Excess indicates Metabolic Alkalosis or Compensation to prolonged Respiratory Acidosis
  - Base Excess > + 3

Arterial Blood Gas (ABG) data obtained in a patient with uncompensated primary acid-base disturbances

Acidosis pH < 7.35 (note that pH less than 6.8 is incompatible with life)

Alkalosis pH > 7.45 (note that pH more than 8.0 is incompatible with life)

Table 1: Normal values and changes during uncompensated Primary Acid-Base disturbances

Acid-base disturbance	**pH**	**PCO_2 (mm Hg)**	**HCO_3^- (m Eq/L)**
None (Normal Values)	7.35 – 7.45	35 – 45	22 – 26
Metabolic Acidosis	Low ↓	Normal	Low ↓
Metabolic Alkalosis	Elevated ↑	Normal	Elevated ↑
Respiratory Acidosis	Low ↓	Elevated ↑	Normal
Respiratory Alkalosis	Elevated ↑	Low ↓	Normal

How can the ABG data from a patient with compensatory acid-base disturbance be interpreted?

Table 2: Normal values and compensatory mechanisms during primary Acid-base disturbance				
Acid-base disturbance	**pH**	**PCO_2 (mm Hg)**	**HCO_3^- (m Eq/L)**	**Mode of compensation**
None (Normal Values)	7.35 – 7.45	35 – 45	22 – 26	None
Metabolic Acidosis	Low ↓	Low ↓	Low ↓*	**Increase ventilation to reduce CO_2 in blood to raise pH**
Metabolic Alkalosis	Elevated ↑	Elevated ↑	Elevated ↑*	**Decrease ventilation to increase CO_2 in blood to lower pH**
Respiratory Acidosis	Low ↓	Elevated ↑*	Elevated ↑	**Kidneys will retain HCO_3^- to increase pH**
Respiratory Alkalosis	Elevated ↑	Low ↓*	Low ↓	**Increase excretion of HCO_3^- by Kidneys to lower pH**
*Primary Event				

Interpretation of ABG data can be separated into steps (Table 2)

- **Step 1: Check the pH values**:
  - Acidosis is present if pH < 7.35
  - Alkalosis is present if pH > 7.45
- **Step 2: Check the PCO_2 values**:
- If in step 1 the patient has Acidosis (pH < 7.35) then:
  - If pCO_2 is elevated: patient has Respiratory Acidosis;
  - If pCO_2 is low: patient has Metabolic Acidosis and is compensating for that situation by blowing off CO_2
- If in step 1 the patient has Alkalosis (pH > 7.45) then:
  - If pCO_2 is low: patient has Respiratory Alkalosis;
  - If pCO_2 is elevated: patient has Metabolic Alkalosis and is compensating for that situation by retaining CO_2

Step 3: Check the HCO_3^- values

- Expected [HCO_3^-] outcomes in each of the four situations are as follows:
  - Patient with Respiratory Acidosis, as compensatory mechanism, [HCO_3^-] is expected to be elevated;
  - Patient with Metabolic Acidosis, [HCO_3^-] is expected to be low;
  - Patient with Respiratory Alkalosis, as a compensatory mechanism, [HCO_3^-] is expected to be low;
  - Patient with Metabolic Alkalosis, [HCO_3^-] is expected to be raised;

What is Anion gap and how is it calculated?

- Anion gap is the difference between commonly measured Cations and Anions;
- Physiologically the Plasma is electrochemically neutral **[Cations] = [Anions]**
- Anion gap is used as a diagnostic parameter to detect organic acidosis due to increase in Anions that are difficult to measure;
- An increase Anion gap indicates increase in unmeasured Anions in plasma;
- By calculation: **Anion gap = $[Na^+] - \{[Cl^-] + [HCO_3^-]\}$**
- Normal Anion gap = 12 – 18 m Eq/L

How is metabolic acidosis classified using Anion gap?

- Anion can be used to classify Metabolic Acidosis:
- Increased Anion gap metabolic acidosis
- Normal [Cl-]; Normal or Low [HCO_3^-] (Increased Anions)
- May be due to:
  - Diabetic Ketoacidosis,
  - Uremic acidosis (Sulfates, Phosphates, Fixed acids)
  - Starvation (Ketoacids)
  - Alcoholic ketosis (Ethanol metabolites, Lactate)
  - Lactic acidosis (Lactate Hypoxia/ Hypoperfusion)
  - Exogenous poisons (Ketones, Lactate, Salicylates, Alcohols)

- Normal Anion gap metabolic acidosis,
  - Hyperchloremic Acidosis
- May be due to:
  - Diarrhea,
  - Renal Tubular Acidosis,
  - Early Renal Failure

CYANOSIS: CAUSES AND CONSEQUENCES

What is Cyanosis?

- Condition that causes Skin, Lips, Mucous Membrane and/or Fingernails to appear bluish in color or (in severe cases) purple-magenta;
- Higher than normal Deoxygenated Hb (HHb) in small superficial blood vessels;
- Higher than normal MetHb in blood;

What are some of the causes of Cyanosis?

Several causes of Cyanosis:

- Some basic mechanisms that can cause Cyanosis are:
  - O_2 saturation of Arterial blood is lower than normal;
  - Circulation may be slowed causing more extraction of O_2 per gram of Hb, thus increasing the concentration of HHb in capillaries;

- A variety of diseases and factors may cause Cyanosis:
  - Lack of O_2 (such as in suffocation or Cyanotic Heart disease),
  - Congenital Heart disease,
  - Pulmonary disease,
  - Terminal event as in Cardiopulmonary Arrest
  - Abnormal Hb (such as, Met-Hemoglobinemia)
  - Toxins (such as Cyanide, Carbon Monoxide)
  - Exposure to Cold Air or Cold Water,
  - High Altitude,
  - Shock,
  - Breath holding,
  - Asthma,
  - Seizures,
  - Drug Overdoses (Narcotics, Sedatives), etc.

When can cyanosis be observed?

- Cyanosis may be observed when:
  - O_2 saturation of blood is below 80%;
  - Mean capillary concentration of HHb in blood is greater than 50g/L;

- **Bluish color characteristic of Cyanosis is due to the presence of more than 50g/L of HHb in Capillary Blood**;

- **In "Healthy" Individuals (Hb $\geq$ 150g/L) Cyanosis occurs when more than One-third of their Hemoglobin is Deoxygenated;**

Can signs of Cyanosis be seen in severely Anemic Patients?

- In anemic individuals with lower Hb levels:
  - Greater proportion of their Hb would have to be deoxygenated before there would be 50g/L of HHb in their blood,
- Thus, anemic individuals are not easily cyanosed;
- For example:
  - If an anemic patient had only 75g/L of Hb, cyanosis would occur when greater than Two thirds (50g/L) of their Hb was deoxygenated;

- Furthermore, if an anemic patient is exposed to Hypoxic Hypoxia, such patient will become cyanosed only at a much more severe degree of hypoxia than would a normal individual;
- **<u>IMPOROTANT TO NOTE</u>:**
- **Presence of Cyanosis indicates that Hypoxia is present,**
- **Absence of Cyanosis does not mean that there is no Hypoxia,**
- **Absence of Cyanosis in a patient is not a guarantee of the absence of Hypoxia,**

METHEMOGLOBINEMIA AND CYANOSIS

How is Met-Hemoglobinemia (Met-Hb) related to Cyanosis?

- Met-Hb is formed when **Fe^{2+} ion** in Heme is converted to **Fe^{3+} ion;**
- Met-Hb is incapable of binding and releasing Oxygen;
- Cyanosis can be due to increased Met-Hb in blood;
- Cyanosis may occur when over 10% of total Hb in blood is Met-Hb;

What are the major classes of Met-Hemoglobinemia?

- There are Two major classes:
  - **Inherited Met-Hemoglobinemia**
  - **Acquired Met-Hemoglobinemia**

What are the different types of Met-Hemoglobinemia?

Types of Inherited Met-Hemoglobinemia:

- **First type:**
  - Is due to deficient activity or absence of **Methemoglobin Reductase** that converts **Met-Hb to Hb**;
- **Second type** called **Hemoglobin M** (Hb M) disease:
  - Autosomal dominant trait characterized by production of an abnormal Met-Hemoglobin;

  - **Hemoglobin M (Hb M)**:
    - Mutation changes the Amino Acid residue to which Heme is attached thus altering its affinity for Oxygen and favoring its oxidation;

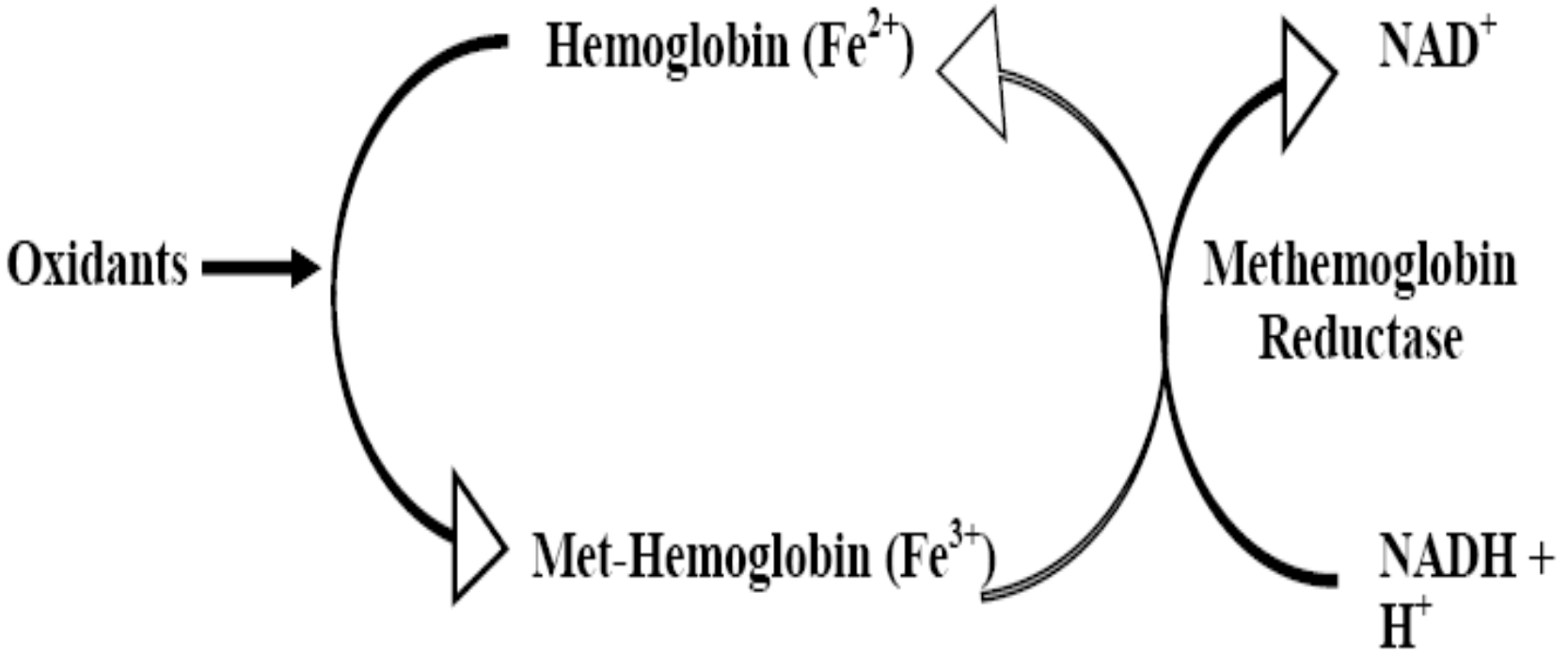
What are some causes of Acquired Met-Hemoglobinemia?

Acquired Met-Hemoglobinemia can be due to:

- Ingestion of certain drugs and chemical:
  - Sulfonamides,
  - Aniline dyes (in brightly colored cloths),
  - Nitrobenzene,
  - Nitrites (used commonly to prevent spoilage of meat),
  - Nitrates (present in food and water), etc.

- Met-Hb is produced when Nitric Oxide or other Oxidants converts Fe^{2+} ion in Heme to Fe^{3+} ion (**Fig. 1)**

Fig. 1: Diagram showing formation of Met-Hemoglobin by Oxidants and action of Methemoglobin Reductase that converts MetHb back to Hb



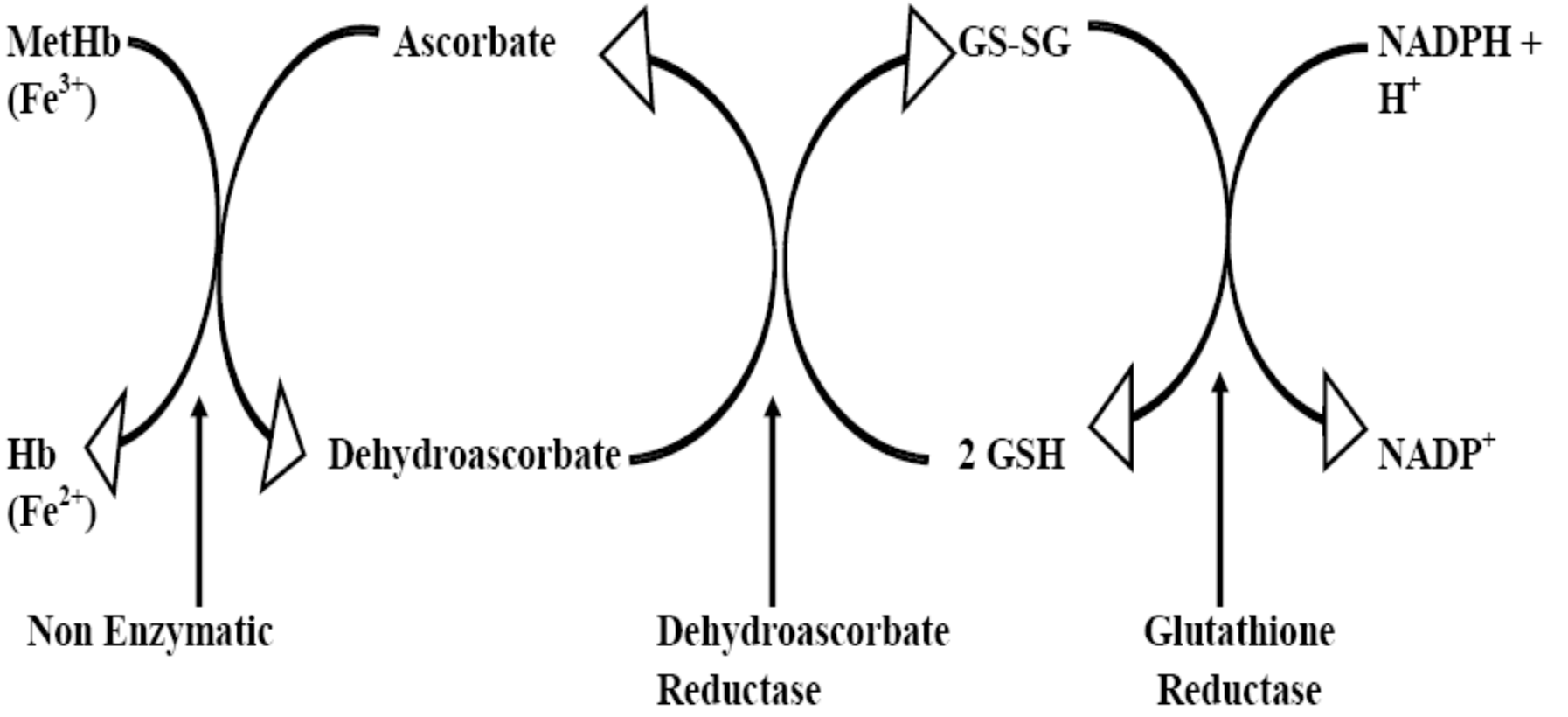
How can acquired Met-Hemoglobinemia be controlled?

- Methylene Blue (Red-Ox Dye) and Ascorbic Acid (both are Reducing Agents) can be used to control Acquired Met-Hemoglobinemia;

- Ascorbic Acid can be used to control Mild forms of Met-Hemoglobinemia due to enzyme deficiency (**Figs. 2**)

Fig. 2: Diagram showing non-enzymatic action of Ascorbate (Vitamin C) in the conversion of MetHb to Hb. Dehydroascorbate is soluble and can be passed out in the urine.

Role of Reduced Glutathione (GSH) in the conversion of Dehydroascorbate to Ascorbate, and actions of enzymes involved are shown. Note that NADPH is obtained from G-6-Phosphate Dehydrogenase reaction in HMP-shunt.



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