**Symptoms Associated with Methemoglobin Blood Concentrations**

**Causes of Methemoglobinemia**

**Hereditary**
- cytochrome b5 reductase deficiency
- hemoglobin M

**Acquired**
- acetaminophen, aspirin, chloral hydrate, copper salts, dapsone, phenacetin, phenylbutazone, primidone, sulfonamides, zopiclone

**Symptoms**

- Cyanotic skin discoloration
- Anxiety, lightheadedness, headache, tachycardia
- Cyanotic skin discoloration
- Hypertension, vasodilation, dizziness, dizziness, increased lactic acid
- Coxa, seizures, dysphagia, acidosis
- Death

**Note:** Assumes hemoglobin is equal to 10 g/dL. Patients with lower hemoglobin concentrations may experience more severe symptoms for a given percentage of methemoglobin level.

**Methemoglobinemia in Acetaminophen Overdose and Glucose-6-phosphate Dehydrogenase Deficiency**

**A 66-year-old woman with a past medical history significant for hypertension, asthma and congestive heart failure presented to the emergency department with four days of fever, chills, and cough followed by nausea, vomiting and dyspnea. For pain relief, the patient consumed approximately 14 grams of acetaminophen (APAP) per day for four days prior to admission.**

**Clinical Timeline**

**Day 1**
- Lactate: 4.5 mmol/L
- (+) Influenza A
- APAP: 25.2 mg/L
- MetHb: 8.6%

**Day 2**
- Patient appeared clinically hypoxic.
- SpO2: 80% and SaO2: >90% on non-rebreather with 100% FiO2
- MethHb: 1.7%

**Day 3**
- Lactate: 7.6 mmol/L
- MethHb: 1.42%
- Patient decompensated and emergently intubated. Continuous veno-venous hemodialysis (CVVHD) initiated.

**Day 4**
- Lactate: 29.9 mmol/L
- MethHb: 8.6%
- pH 6.93, pCO2 40 mmHg, pO2 11mmHg, HCO3 8 mmol/L, NaHCO3 drip
- Temp: 97°F, HR 125 bpm, RR 30 bpm, MAP 54 mmHg
- MetHb: 7.8%

Two days after the patient expired, she was found to have a glucose-6-phosphate dehydrogenase (G6PD) deficiency.

**CASE REPORT**

**BACKGROUND**

- Methemoglobin (MetHb) is formed when the iron moiety of hemoglobin (Hgb) is oxidized from ferrous (Fe2+) to ferric (Fe3+) state.
- Acetaminophen Metabolism:
  - ~90% is metabolized in liver via glucuronidation and sulfation pathways.
  - remainder is metabolized via CYP450 to a toxic oxidizing agent, N-acetyl-p-benzoquinone imine (NAPQI), which is detoxified via glutathione1
- Acute Acetaminophen Overdose:
  - cytochrome b5 reductase removes 95% to 99% of endogenous MetHb
  - nicotinamide adenine dinucleotide phosphate (NADPH)-MetHb reductase eliminates approximately 5% of MetHb2

**Acetaminophen-induced Methemoglobinemia Pathway3,4**

- Acetaminophen (APAP) oxidizes Hgb to MetHb.
- MetHb is toxic and can cause tissue oxygenation.
- MetHb can be reduced back to Hgb by NADPH MetHb reductase.
- NADPH MetHb reductase is inhibited by oxidizing agents, such as NAPQI and metyrapone.

**CONSIDERATIONS**

- N-acetylcysteine reduces risk of acetaminophen-induced hepatotoxicity → restores hepatic glutathione concentrations and enhances the sulfation pathway5
- Methemoglobinemia Treatment:
  - Methylen blue converted to leucymethenylene blue → reduces MetHb to Hgb

**REFERENCES**