Methemoglobinemia

**Key points:**
1. Pattern recognition is key to diagnosis of methemoglobinemia.
2. Methylene blue is the treatment of choice unless the patient is G6PD deficient.
3. Identification and removal of offending agents is critical to management.

**Definition:** Methemoglobinemia is an altered state of hemoglobin in which the ferrous (2+) form of heme is oxidized to the ferric form (3+) thus making the heme moiety unable to bind oxygen. In addition, the remaining monomers of ferrous heme within a hemoglobin tetramer bind their oxygen more tightly causing a left shift of the oxygen dissociation curve and reduced oxygen delivery at the tissue level.

**Diagram:**
- 1,3 DPG → Glyceraldehyde 3-P
- NADH → NAD+
- **Cytochrome b5 reductase (95%)**
- Ferric (3+) HgB (methemoglobin) → (non-enzymatic) → Ferrous (2+) HgB
- NADPH metHgb reductase (plus Methylene blue) (5%)
- NADPH → NADP+
- **6 phospho gluconate → glucose 6 phosphate**

**Causes:**
- **Hereditary/ Congenital:** Hemoglobin M, cytochrome b5 reductase deficiency (NADH deficiency)—responsible for 95% of MetHgb reduction, NADPH deficiency of the HMP shunt
- **Acquired:** multiple drugs and toxins including aniline dyes, benzene, chloroquine, dapsone, local anesthetic agents, reglan, naphthalene, nitrites (including NTG and NO), primaquine, phenazopyridine, and sulfonamides.

**Clinical presentation:**
- **Chronic methemoglobinemia:** chronically elevated levels of MetHgb often are asymptomatic or present with headache, fatiguability, or “slate blue skin” complaints.
- **Acquired (acute) methemoglobinemia:** typically symptomatic due to lack of compensatory mechanisms: cyanosis, dyspnea, fatigue, lethargy, AMS, shock, seizures and death. Severity depends on percent methemoglobinemia. (1% is normal)
  - 3-15% skin discoloration/ 20% cyanosis or asx / 25-50%, HA, lightheaded, weak, chest pain, confusion/ 50-70% delirium, seizure, lactic acidosis/ >70% arrhythmia and death.

**Diagnosis:**
- **Pattern recognition is key:** cyanosis, low hemoglobin oxygen saturation on pulse oximetry (typically 85-89% representing the absorbance spectrum of methemoglobin), normal PaO2 on ABG, “chocolate blood”. (Note, methemoglobinemia does not change color with the addition of oxygen whereas dark blood due to deoxyhemoglobin will turn red with oxygen.). Co-oximetry of ABG will quantify the percent of methemoglobinemia in a fresh arterial sample.
Treatment:
- **Identification/ avoidance/ discontinuation of offending agents is critical**
- Methylene blue, 1%; 1-2 mg/kg IV over 5 minutes. Serves as an electron acceptor for the HMP shunt (NADPH) pathway allowing ferric heme to be reduced to ferrous. Max dose 7 mg/kg.**

Pts with **G6PD deficiency** are unable to generate NADPH sufficiently, therefore methylene blue is not only ineffective for these patients, but paradoxically serves as an oxidant stress and can cause hemolysis.

- Vitamin C—safe in G-6PD deficiency as an electron acceptor.
- Exchange transfusion or Hyperbaric oxygen in severe, life-threatening cases.
- Tagamet can be used in dapsone induced MetHgbemia: activates p-450 and inhibits conversion of dapsone to its oxidizing metabolite. 300 mg po/IV q 6-8 hours. Prevents further MetHgbemia—does not treat pre-existing levels.

**Note: once Methylene Blue has been used, co-oximetry cannot be repeated as MB is read as methemoglobin by the machine.**

References:
UpTo Date on line: Methemoglobinemia
Koff, Jon. Handout: Methemoglobinemia.