



Clinical Pharmacology & Toxicology Pearl of the Week

~ Acquired Methemoglobinemia ~

Definition

Methemoglobinemia occurs when there are increased quantities of hemoglobin containing heme with iron in the oxidized ferric (Fe^{3+}) form, which is unable to bind oxygen leading to cyanosis and hypoxia. Methemoglobinemia can be congenital (e.g. genetic defect in red cell metabolism or hemoglobin structure) or acquired due to various drugs and toxins.

Clinical Presentation

Patients will present with varying symptoms related to inadequate tissue oxygen delivery, depending on the level of methemoglobinemia:

- **0-2%:** Physiologic
- **10-20%:** May be asymptomatic
- **20-30%:** Moderate symptoms (fatigue, dyspnea, tachycardia, confusion, nausea/vomiting)
- **>40%:** Severe symptoms (arrhythmias, seizures, coma, circulatory failure)
- Note that certain patients may have more severe presentations at lower thresholds of methemoglobinemia. Severity of symptoms depend on factors such as the patient's total hemoglobin concentration and cardiovascular reserve, as well as the rapidity of methemoglobin formation.

In acquired methemoglobinemia, the patient will often have an **identifiable trigger**. Those triggers with an asterisk * are the most common culprits:

Medications	Environmental/Occupational exposures
Local anesthetics: <ul style="list-style-type: none">- Benzocaine*, prilocaine, tetracaine, lidocaine Nitrates: <ul style="list-style-type: none">- Nitroglycerine*, inhaled NO*, nitroprusside, oral nitrates Antibiotics: <ul style="list-style-type: none">- Dapsone*, rifampin, sulfonamides, antimalarials (e.g. chloroquine) Other: <ul style="list-style-type: none">- Rasburicase (associated with G6PD deficiency)- Cyclophosphamide- Metoclopramide- Zopiclone	<ul style="list-style-type: none">- Fertilizers, weed killers- Plastics- Dyes, paints, rubber

Additional clues to methemoglobinemia:

1. **Cyanosis that does not improve with oxygen therapy.**
2. **Refractory hypoxemia:** e.g. saturation in the 80s despite 100% FiO₂
3. **Cyanosis-saturation gap:** Cyanosis despite an oxygen saturation in the 80s
4. **Saturation-PaO₂ gap:** e.g. saturation in the 80s with normal or elevated PaO₂ on gas
5. **Chocolate brown blood:** blood on a piece of white gauze will remain brown as it dries, in comparison to normal deoxygenated blood which will absorb oxygen and turn red

Treatment

1. **Discontinue the offending agent**
2. **Methylene Blue:** functions as an electron shuttle to promote reduction of methemoglobin back to hemoglobin, thereby restoring oxygen carrying capacity

Mechanism of action of methylene blue



INDICATIONS: methemoglobin > 20% or symptomatic

- a. NOTE: may consider treatment at lower thresholds for patients with reduced reserve (i.e. 15%)

DOSE: 1-2mg/kg IV over 5 minutes

- a. May see transient worsening in oxygen saturation due to blue pigment interfering with sat probe
- b. Should expect clinical improvement within minutes; resolution of cyanosis may take up to an hour.

CAUTIONS:

- i) G6PD deficiency
 - a. G6PD deficiency causes a deficiency in NADPH, which in turn causes deficiency in glutathione resulting in hemolysis.
 - b. Methylene blue may be ineffective in G6PD patients (due to NADPH deficiency) or may work but reduce NADPH further causing hemolysis.
 - c. IV vitamin C is an alternative reducing agent that works independently from NADPH and may be considered in these cases.
- ii) Risk of serotonin syndrome
 - a. Methylene blue is a MAO and may increase risk of serotonin syndrome when combined with other serotonergic medications

3. **Additional treatment options:** IV vitamin C, exchange transfusion in refractory cases

References:

1. Rehman HU. Methemoglobinemia. West J Med. 2001 Sep;175(3):193-6. doi: 10.1136/ewjm.175.3.193. PMID: 11527852; PMCID: PMC1071541.
2. EM Crit Methemoglobinemia. <https://emcrit.org/ibcc/methemoglobinemia/>

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the [Alberta Referral Directory](#) (ARD) by searching “Pharmacology” from the ARD home page. Click [HERE](#) for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in [Alberta Referral Directory](#) (ARD) by searching “Toxicology” from the ARD home page.

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