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

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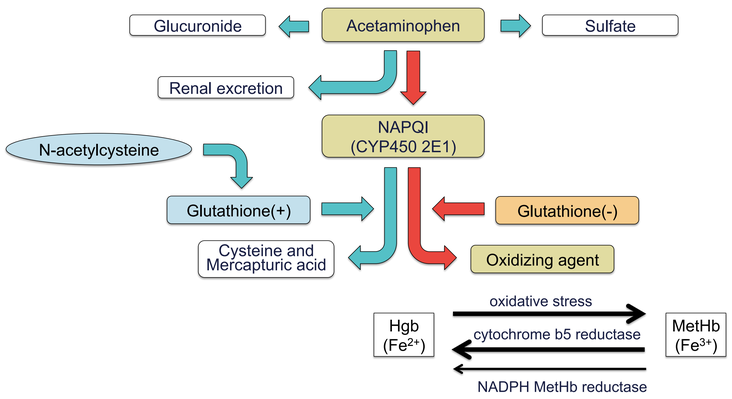
BACKGROUND

- Methemoglobin (MetHb) is formed when the iron moiety of hemoglobin (Hgb) is oxidized from ferrous (Fe^{2+}) to ferric (Fe^{3+}) state → impaired O_2 delivery to tissues
- Acetaminophen Metabolism:
  - ~90% is metabolized in liver via sulfation and glucuronidation
  - remainder is metabolized via CYP450 to a toxic oxidizing agent, N-acetyl-p-benzoquinone imine (NAPQI), which is detoxified via glutathione[1]
- Acute Acetaminophen Overdose:
  - saturates sulfation and glucuronidation pathways
  - depletes glutathione stores
  - leads to excess NAPQI → oxidative stress → methemoglobinemia[1]
- MetHb Reduction Pathway:
  - cytochrome b5 reductase removes 95% to 99% of endogenous MetHb
  - nicotinamide adenine dinucleotide phosphate (NADPH)-MetHb reductase eliminates approximately 5% of MetHb[2]

Acetaminophen-induced Methemoglobinemia Pathway[3,4]



Causes of Methemoglobinemia[2]

Hereditary	Acquired
cytochrome b5 reductase deficiency hemoglobin M	**acetaminophen**, acetanilide, chloroquine, copper sulfate, dapsone, flutamide, local anesthetic, metoclopramide, nitrate compounds, phenacetin, phenazopyridine, primaquine, sulfonamides, zopiclone

Symptoms Associated with Methemoglobin Blood Concentrations[5]

Methemoglobin concentration	Total hemoglobin (%)	Symptoms*
<1.5 g/dL	<10	None
1.5-3.0 g/dL	10-20	Cyanotic skin discoloration
3.0-4.5 g/dL	20-30	Anxiety, lightheadedness, headache, tachycardia
4.5-7.5 g/dL	30-50	Fatigue, confusion, dizziness, tachypnea, increased tachycardia
7.5-10.5 g/dL	50-70	Coma, seizures, dysrhythmias, acidosis
>10.5 g/dL	>70	Death

Note: Assumes hemoglobin is equal to 15 g/dL. Patients with lower hemoglobin concentrations may experience more severe symptoms for a given percentage of methemoglobin level.
*Patients with underlying cardiac, pulmonary, or hematologic disease may experience more severe symptoms for a given methemoglobin concentration.

CASE REPORT

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

140	89	21	44
4.4	25	**3.0**	

	11.6		
11.5		221	
	36.7		

29	40	
	2.58	

-	**39270**	
7.0	**9560**	
4.2	**254**	
	7.9	

- **Lactate: 4.5 mmol/L**
- **(+) Influenza A** → Oseltamivir 30 mg q24h
- **APAP: 25.2 mg/L** → N-acetylcysteine 21-hour regimen: total 300 mg/kg

Day 2

140	98	32	255
3.7	18	**5.1**	

	8.8		
12.1		196	
	29.1		

20.2	33	
	1.83	

-	25180	
5.2	4506	
3.2	204	
	11.6	

- Patient appeared clinically hypoxic.
- SpO_2: 80% and SaO_2: >99% on non-rebreather with 100% FiO_2
- **MetHb: 7.8%**

Day 3

140	96	43	89
-	12	**7.1**	

	7.7		
15.1		220	
	29.8		

24.7	31	
	2.21	

-	-	
5.4	-	
3.1	-	
	14.8	

- **Lactate: 7.6 mmol/L**
- **MetHb: 14.2%**
- Patient decompensated and emergently intubated. Continuous veno-venous hemodialysis (CVVHD) initiated.

Day 4

144	97	10	255
-	-	1.6	

	7.0		
16.6		89	
	24.7		

32.2	31	
	2.85	

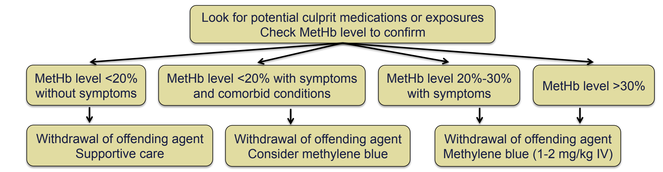
	-	
4.7	-	
2.5	-	
	12.4	

- **Lactate: 29.9 mmol/L**
- **MetHb: 8.6%**
- pH 6.93, pCO_2 40 mmHg, pO_2 51mmHg, HCO_3 8 mmol/L → $NaHCO_3$ drip
- Temp: 97°F, HR 125 bpm, RR 30 bpm, MAP 54 mmHg → vasopressors
- PEA arrest → Patient expired in the evening.

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

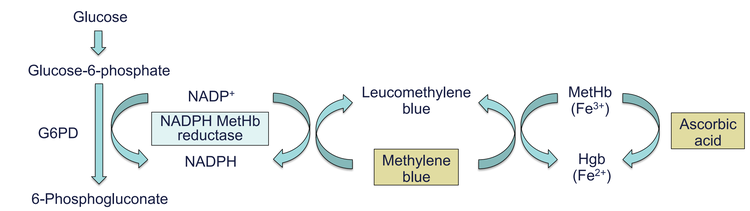
DISCUSSION

- N-acetylcysteine reduces risk of acetaminophen-induced hepatotoxicity → restores hepatic glutathione concentrations and enhances the sulfation pathway[3]
- Methemoglobinemia Treatment:
  - Methylene blue converted to leucomethylene blue → reduces MetHb to Hgb



    - patient did not receive methylene blue initially due to early clinical improvement and MetHb level <20%.
- G6PD Deficiency:
  - G6PD is a key enzyme in NADPH formation
  - NADPH is necessary to transform methylene blue to leucomethylene blue
  - accumulation of oxidant methylene blue can cause severe hemolysis and further exacerbate methemoglobinemia[2]
  - ascorbic acid can be considered as an alternative treatment due to its antioxidant properties[6]
    - use caution in preexisting renal dysfunction → oxalate nephropathy[7]

NADPH MetHb Reductase Pathway[8]



CONSIDERATIONS

- The resulting oxidative stress from an acute acetaminophen overdose can cause liver injury and methemoglobinemia.
- Suspect methemoglobinemia if there is >5% gap between the calculated saturation from the blood gas and measured saturation from pulse oximetry.
- Patients with a low hemoglobin concentration can exhibit more severe symptoms despite MetHb levels <20%.
- Consider G6PD deficiency if methylene blue is not effective or results in hemolysis when used as treatment. May use ascorbic acid as an alternative.

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