# Lidocaine-Induced Methemoglobinemia: A Clinical Reminder

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**Methemoglobinemia is a rare condition in which the iron in hemoglobin is stabilized in the ferric ($Fe^{3+}$) form, making it unable to bind oxygen and leading to tissue hypoxia and possibly death. The condition may be hereditary or acquired, the latter resulting from ingestion or application of common oxidizing agents such as lidocaine. As management of methemoglobinemia depends on prompt recognition, clinicians who administer or prescribe oxidizing agents must be aware of the clinical symptoms of methemoglobinemia, including cyanosis, pulse oximetry values that do not respond to increased oxygen delivery, and altered mental status. Currently, methylene blue is the drug of choice for the management of methemoglobinemia.**

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Lidocaine is a common anesthetic used by clinicians for procedures including laryngoscopy, bronchoscopy, and upper gastrointestinal endoscopy. It may be applied topically or injected subcutaneously for local analgesia. *Methemoglobinemia*, or excessive levels of methemoglobin (MetHb) in the blood,[1] is a rare and unusual complication associated with lidocaine use, and many clinicians—particularly those who infrequently use lidocaine or similar compounds—may be unaware of this potentially fatal condition.

In patients with methemoglobinemia, iron is oxidized from a ferrous ($Fe^{2+}$) to a ferric ($Fe^{3+}$) form.[2] Methemoglobinemia leads to a "left shift" of the oxygen-hemoglobin dissociation curve, making hemoglobin a poor candidate for effective oxygen transport to the tissues. In contrast, a "right shift" is often attributed to factors like acidosis, hyperthermia, and elevated 2,3-diphosphoglycerate levels, which lead to more efficient oxygen transport and unloading.[2] In the present article, we review the current medical literature on methemoglobinemia with a focus on lidocaine, as its particular incidence appears to be both uncommon and underreported.

## Symptoms and Risk

Methemoglobinemia symptoms range from anxiety to cyanosis to cardiac arrhythmias.[3] Generally, higher levels of MetHb lead to more severe symptoms and higher risk of morbidity and mortality (*Table*).[2,3] However, MetHb levels as high as 81.5% have been reported with full resolution of symptoms after treatment.[4] In addition, MetHb levels are not always associated with symptom severity. In a prospective study of patients receiving fiberoptic bronchoscopy with topical lidocaine anesthesia, De[5] reported no correlation between symptom severity scores, MetHb levels, or amount of lidocaine used. Palpitation was the most common symptom.

Certain patient populations are at higher risk for methemoglobinemia and warrant careful monitoring by clinicians. For example, comorbidities that impair oxygen transport, including anemia, heart disease, and pulmonary disease (chronic obstructive pulmonary disease, pneumonia), predispose patients to methemoglobinemia. Symptom development is thought to be related to a preexisting inability to buffer oxidant stress.[6] Patients with liver cirrhosis must also be closely monitored. The red blood cells in patients with cirrhosis are already under extreme oxidative stress; therefore, any further increase in oxidative stress may lead to methemoglobinemia.[7] Similarly, neonates often have underdeveloped hepatic and renal function and are at increased risk for methemoglobinemia.[8] In addition, clinicians should closely monitor patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. As methylene blue uses the nicotinamide adenine dinucleotide phosphate (NADPH)-MetHb reductase system (in which G6PD is a major cofactor), patients with G6PD deficiency are unable to respond to methylene blue.[2,7]

Methylene blue can also paradoxically exacerbate methemoglobinemia in all patients at doses between 4 mg/kg and 15 mg/kg. Normally, methylene blue is metabolized to leukomethylene blue, which is capable of reducing oxygen to hydrogen peroxide. If enough methylene blue is administered, the hexose monophosphate shunt's ability to detoxify hydrogen peroxide and reduce glutathione is depleted, and the remaining hydrogen peroxide converts hemoglobin to MetHb.[9]

## Pathophysiology

Methemoglobin is produced as a result of normal oxidant stress and comprises approximately 3% of a person's total hemoglobin.[2] Two primary adaptive mechanisms can restrict this value to less than 1%: the cytochrome b5-MetHb reductase pathway and the NADPH-MetHb reductase pathway.[2] The cytochrome b5-MetHb reductase pathway is responsible for 95% to 99% of the reductive activity that converts $Fe^{3+}$ to $Fe^{2+}$ and essentially restores normal hemoglobin functioning. It uses nicotinamide adenine dinucleotide (NADH) as a major cofactor. This pathway is capable of operating at a conversion rate of up to 15% per hour. The NADPH-MetHb reductase pathway accounts for up to 5% of the reductive activity that converts $Fe^{3+}$ to $Fe^{2+}$. The production of NADPH relies on the availability of G6PD and is provided by the hexose monophosphate shunt.[2] This pathway can be induced with the administration of methylene blue.[10] Ascorbic acid and glutathione account for small amounts of reducing activity.[3] *N*-acetylcysteine and riboflavin have been studied as well, with conflicting results.[11]

Two forms of methemoglobinemia exist: hereditary and acquired. The hereditary form is associated with a deficiency of intrinsic cytochrome b5-MetHb reductase or with the presence of congenital hemoglobin M, a form of hemoglobin unable to bind oxygen.[7] Acquired forms of methemoglobinemia are much more common[6] and are a result of exposure to a long list of common oxidants (*Figure*), most notably nitrates, chlorates, aniline compounds, benzocaine, and dapsone.

**Table.**
**Symptoms Associated With Methemoglobin Blood Concentrations[3]**

| Methemoglobin Concentration, g/dL | Total Hemoglobin, % | Symptoms |
|---|---|---|
| <1.5 | <10 | None |
| 1.5-3.0 | 10-20 | Cyanotic skin discoloration |
| 3.0-4.5 | 20-30 | Anxiety, lightheadedness, headache, tachycardia |
| 4.5-7.5 | 30-50 | Fatigue, confusion, dizziness, tachypnea, increased tachycardia |
| 7.4-10.5 | 50-70 | Coma, seizure, arrhythmia, acidosis |
| >10.5 | >70 | Death |

Benzocaine, prilocaine, and dapsone are among the most commonly studied oxidants. Prilocaine, a common anesthetic in dental procedures, appears to be the most potent topical anesthetic to cause methemoglobinemia.[12] Sambrook et al[13] looked at 221 adverse reactions to dental local anesthetics and found that prilocaine was used in 59% of all cases and in all 6 cases of methemoglobinemia. In a separate study[14] of 242 cases of methemoglobinemia, 60.7% of cases were associated with dental procedures. Currently, few systemic reports of methemoglobinemia in a hospital setting exist. One such report[15] details dapsone being the cause of 42% of methemoglobinemia cases, whereas another report[16] implicated benzocaine in 82% of cases. In the perioperative period, most methemoglobinemia cases manifest as a result of local anesthetic use, most commonly topical benzocaine used for laryngoscopy, bronchoscopy, or upper gastrointestinal endoscopic procedures.[9,17] A class of recreational drugs, often referred to as poppers, have also been implicated in methemoglobinemia, as they contain the ingredient methyl nitrite (used to manage cyanide toxicity) and carry a high abuse poten-

tial.[18] Although the exact prevalence of methemoglobinemia is unknown, these compounds are well-documented causes of the disorder.

## Lidocaine-Induced Methemoglobinemia

Lidocaine is an amino-amide drug typically injected subcutaneously or applied topically for procedures such as esophagogastroduodenoscopy and fiberoptic bronchoscopy. The majority of reported cases of lidocaine-induced methemoglobinemia have been associated with upper airway or upper gastrointestinal procedures.[5,6,16,19] Absorption in these cases has occurred via the mucous membranes. Methemoglobinemia secondary to lidocaine exposure is a relatively rare complication. It has been described in adult,[6,19] pediatric,[20,21] and gynecologic patients.[22] Lidocaine is metabolized by the cytochrome P-450 3A4 enzyme in the liver.[23] It has a half-life of approximately 96 minutes, which is among the lowest of all local anesthetics.[24] When used alone, the recommended maximum dose is 4 to 5 mg/kg, or 300 mg total. If used in combination with epinephrine, a dose of up to 7 mg/kg, or 500 mg total, is tolerable.[24] Currently, few estimates of the incidence of lidocaine-induced methemoglobinemia exist. In a 2009 study of locally injected anesthetics at clinically significant doses and without concomitant use of other oxidants, lidocaine was responsible for 3 of 242 reviewed cases of methemoglobinemia, or a 1% incidence.[14]

Certain conditions may predispose a patient to developing methemoglobinemia specifically caused by lidocaine, including drug displacement and impaired clearance. Compared with other basic drugs, bupivacaine hydrochloride has been shown to have the greatest effect at displacing lidocaine from its protein-bound state and increasing its concentration in the blood.[12] This finding is important, as some physicians tend to use a mixture of bupivacaine hydrochloride and lidocaine for various procedures. To this extent, an overall decrease in plasma protein concentrations, such as in severely malnourished individuals or in individuals with decompensated cirrhotics, may increase toxicity.[24] β-Blockers impair lidocaine clearance by means of either direct inhibition or inhibition of metabolism via inhibition of hepatic blood flow.[12] Patients with preexisting comorbidities, hepatic insufficiency, or G6PD deficiency as described previously remain at increased risk. Studies have not reported a minimum dosage at which lidocaine is a risk for methemoglobinemia.

## Diagnosis

Diagnosis of methemoglobinemia is based on clinical and laboratory diagnostic criteria. Patients may exhibit central and peripheral cyanosis out of proportion to measured oxygen saturation, chocolate-brown blood that does not change color when exposed to 100% oxygen, and clinical signs of hypoxia.[2]

Standard pulse oximetry is unable to differentiate between oxyhemoglobin/deoxyhemoglobin and MetHb because MetHb absorbs light at both wavelengths normally used to differentiate oxyhemoglobin from deoxyhemoglobin. As MetHb levels rise, pulse oximetry readings drop initially. However, as MetHb levels approach 30% or higher, pulse oximetry readings generally plateau near 85%, irrespective of actual MetHb content in the blood, thus resulting in a falsely elevated pulse oximetry reading.[2,3] Pulse oximetry levels nearing 65% have been documented when MetHb was present,[25] however, so methemoglobinemia should not be excluded if a plateau near 85% is not observed.

Co-oximetry is more definitive than standard pulse oximetry in identifying methemoglobinemia. In practice, co-oximetry requires drawing blood and yields a definitive diagnosis. Co-oximetry uses multiple wavelengths of light to differentiate between MetHb, oxyhemoglobin, deoxyhemoglobin, and carboxyhemoglobin.[2] A pulse oximetry reading that is resilient to change when increased supplemental oxygen is administered should raise a clinician's suspicion of methemoglobinemia.

An oxygen saturation gap calculation is an easy way for a clinician to better assess the risk for methemoglobinemia. The saturation gap is the difference between an oxyhemoglobin measurement from an arterial blood gas sample and an oxyhemoglobin measurement from pulse oximetry ($SaO_2 - SpO_2$). A gap greater than 5% is considered an important clinical clue to the presence of methemoglobinemia.[26]

## Treatment

Initial management of methemoglobinemia begins with withdrawal of the offending substance and symptomatic support. Supplemental oxygen should be started immediately and titrated up as needed. As a guideline, methylene blue may be given to a symptomatic patient with a MetHb level less than 20% or an asymptomatic patient with a MetHb level greater than 30%.[2] For severe cases, hyperbaric oxygenation may also be used if available.[27] Likewise, clinicians may have a lower threshold for administration of methylene blue in patients with comorbidities described previously.[2]

Methylene blue should be administrated in 1- to 2-mg/kg doses given as 0.1 mL/kg of a 1% solution (10 mg/mL) intravenously over 5 to 10 minutes. Methylene blue has a shorter half-life than many oxidant substances,[10] and clinicians should be vigilant in monitoring for signs of recurring methemoglobinemia. Repeated doses may be necessary within 30 to 60 minutes of the initial dose.[10]

Multispecialty coordination of patient care, particularly for those with comorbidities, may be warranted; cardiologists, pulmonologists, and hematologists should be consulted as needed. In addition, availability of methylene blue—in endoscopy or bronchoscopy suites, for example—may facilitate more timely treatment and reduce the number of adverse reactions to methemoglobinemia. Timely diagnosis and treatment is necessary for a positive clinical outcome without lasting sequelae.

| **Chemicals** |
|---|
| Aniline dyes |
| Fava beans |
| Fumes (wood, plastic, automobile exhaust) |
| *Ginkgo biloba* |
| Herbicides |
| Mothballs |
| Nitrates |
| Octane boosters |
| Petrol |
| Well water |
| **Medications** |
| Acetaminophen |
| Acetanilide |
| Benzocaine |
| Bismuth subnitrate |
| Chloramine |
| Chloroquine |
| Copper sulfate |
| Dapsone |
| Flutamide |
| Lidocaine |
| Metoclopramide |
| Nitric oxide |
| Nitromethane |
| Nitrofurans |
| Nitroglycerin |
| Nitroprusside |
| Paraquat |
| Phenacetin |
| Phenazopyridine |
| Prilocaine |
| Primaquine |
| Silver nitrate |
| Sodium nitrate |
| Sodium valproate |
| Sulfasalazine |
| Sulfonamides |
| Zopiclone |

**Figure.**
Causes of acquired methemoglobinemia.[2,3]

## Conclusion

Methemoglobinemia is a potentially fatal condition that, although generally rare, must be part of the differential diagnosis for any patient exhibiting clinical signs of hypoxia, cyanosis, or depressed pulse oximetry readings or who has been exposed to a substance with strong oxidative potential. As methemoglobinemia may occur even at manufacturer-specified doses of oxidative compounds, no specific method of preventing this condition currently exists, and clinical prowess is the best tool clinicians have for preventing complications. Physicians who commonly use oxidant compounds such as lidocaine should identify factors in their patients that put them at increased risk of developing methemoglobinemia. Additional research is needed to identify the minimum dosage at which lidocaine is a risk for methemoglobinemia.

### Author Contributions

All authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; Drs Barash and Reich drafted the article or revised it critically for important intellectual content; and all authors gave final approval of the version of the article to be published.

### References


1. *Dorland's Illustrated Medical Dictionary.* 32nd ed. Philadelphia, PA: Elsevier Saunders; 2012:1146.
2. Skold A, Cosco DL, Klein R. Methemoglobinemia: pathogenesis, diagnosis, and management. *South Med J.* 2011;104(11):757-761. doi:10.1097/SMJ.0b013e318232139f.
3. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. *Ann Emerg Med.* 1999;34(5):646-656.
4. Caudill L, Walbridge J, Kuhn G. Methemoglobinemia as a cause of coma. *Ann Emerg Med.* 1990;19(6):677-679.
5. De S. Assessment of severity of methaemoglobinemia following fibreoptic bronchoscopy with lidocaine. *Indian J Chest Dis Allied Sci.* 2011;53(4):211-214.
6. Kwok S, Fischer JL, Rogers JD. Benzocaine and lidocaine induced methemoglobinemia after bronchoscopy: a case report. *J Med Case Rep.* 2008;2(1):16. doi:10.1186/1752-1947-2-16.
7. Ashurst J, Wasson M. Methemoglobinemia: a systematic review of the pathophysiology, detection, and treatment. *Del Med J.* 2011;83(7):203-208.
8. Ng JS, Edwards EM, Egelund TA. Methemoglobinemia induced by rasburicase in a pediatric patient: a case report and literature review [published online December 21, 2011]. *J Oncol Pharm Pract.* 2012;18(4):425-431. doi:10.1177/1078155211429385.
9. Barclay JA, Ziemba SE, Ibrahim RB. Dapsone-induced methemoglobinemia: a primer for clinicians [published online August 18, 2011]. *Ann Pharmacother.* 2011;45(9):1103-1115. doi:10.1345/aph.1Q139.
10. Clifton J 2nd, Leikin JB. Methylene blue. *Am J Ther.* 2003;10(4):289-291.
11. Byrne MF, Mitchell RM, Gerke H, et al. The need for caution with topical anesthesia during endoscopic procedures, as liberal use may result in methemoglobinemia. *J Clin Gastroenterol.* 2004;38(3):225-229.
12. Schroeder TH, Dieterich HJ, Mühlbauer B. Methemoglobinemia after axillary block with bupivacaine and additional injection of lidocaine in the operative field. *Acta Anaesthesiol Scand.* 1999;43(4):480-482.
13. Sambrook PJ, Smith W, Elijah J, Goss AN. Severe adverse reactions to dental local anaesthetics: systemic reactions. *Aust Dent J.* 2001;56(2):148-153. doi:10.1111/j.1834-7819.2011.01316.x.
14. Guay J. Methemoglobinemia related to local anesthetics: a summary of 242 episodes. *Anesth Analg.* 2009;108(3):837-845. doi:10.1213/ane.0b013e318187c4b1.
15. Ash-Bernal R. Acquired methemoglobinemia: a retrospective series of 138 cases at 2 teaching hospitals. *Medicine (Baltimore).* 2004;83(5):265-273.
16. Vallurupalli, S. Methemoglobinemia due to topical pharyngeal anesthesia during endoscopic procedures [published online December 1, 2010]. *Local Reg Anesth.* 2010;3:137-142. doi:10.2147/LRA.S12227.
17. Talarico JF, Metro DG. Presentation of dapsone-induced methemoglobinemia in a patient status post small bowel transplant. *J Clin Anesth.* 2005;17(7):568-570.
18. Faley B, Chase H. A case of severe amyl nitrite induced methemoglobinemia managed with methylene blue. *J Clin Toxicol.* 2012;2(4):126-127. doi:10.4172/2161-0495.1000127.
19. Karim A, Ahmed S, Siddiqui R, Mattana J. Methemoglobinemia complicating topical lidocaine used during endoscopic procedures. *Am J Med.* 2001;111(2):150-153.
20. Neuhaeuser C, Weigand N, Schaaf H, et al. Postoperative methemoglobinemia following infiltrative lidocaine administration for combined anesthesia in pediatric craniofacial surgery. *Pediatr Anaesth.* 2008;18(2):125-131. doi:10.1111/j.1460-9592.2007.02358.x.
21. Bayat A, Kosinski RW. Methemoglobinemia in a newborn: a case report. *Pediatr Dent.* 2011;33(3):252-254.
22. Conroy JM, Baker JD III, Martin WJ, Bailey MK, Dorman BH. Acquired methemoglobinemia from multiple oxidants. *South Med J.* 1993;86(10):1156-1159.
23. Dillane D, Finucane BT. Local anesthetic systemic toxicity [published online February 12, 2010]. *Can J Anaesth.* 2010;57(4):368-380. doi:10.1007/s12630-010-9275-7.
24. Cox B, Durieux ME, Marcus MA. Toxicity of local anaesthetics. *Best Pract Res Clin Anaesthesiol.* 2003;17(1):111-136.
25. Lorelli DR, Morris DE, Lewis JW Jr. Drug-induced methemoglobinemia during thoracoscopic lung biopsy. *Ann Thorac Surg.* 2001;71(2):703-705.
26. El-Husseini A, Azarov N. Is threshold for treatment of methemoglobinemia the same for all? a case report and literature review [published online March 26, 2010]. *Am J Emerg Med.* 2010;28(6):748.e5-748.e10. doi:10.1016/j.ajem.2009.10.014.
27. Lindenmann J, Matzi V, Kaufmann P, et al. Hyperbaric oxygenation in the treatment of life-threatening isobutyl nitrite-induced methemoglobinemia—a case report. *Inhal Toxicol.* 2006;18(13):1047-1049.