

Demystifying Methemoglobinemia: A Clinically Pervasive Disorder with Ambiguous Symptoms Masking Prevalence, Morbidity, and Mortality.

Summary

Dysfunctional hemoglobins are among the most confounding compromises to patient health and safety. Dyshemoglobins impede the blood's ability to deliver oxygen to the tissues. Methemoglobin (MetHb) is a dyshemoglobin that normally exists in small concentrations in blood, accounting for less than 2% of the total available hemoglobin. Methemoglobinemia is defined as elevated levels of methemoglobin in the blood, is commonly induced (acquired) within virtually all acute care settings, presents with ambiguous symptomatology, and can be lethal at high levels. Because increases in MetHb often go undetected until dangerous levels are reached, the rapid diagnosis and treatment of methemoglobinemia have both quality and cost of care implications.

Patients presenting to the Emergency Department with equivocal flu-like symptoms should be evaluated for elevated MetHb levels as well as for carbon monoxide poisoning (carboxyhemoglobinemia, COHb). Nitrogen-based cardiac medications (e.g. nitroglycerin), Dapsone for immunosuppressed patients, and many common local anesthetic agents (e.g. benzocaine, prilocaine, lidocaine, EMLA creams for neonatal applications) are common MetHb inducing agents. Patients treated with inhaled nitric oxide (NO) are also candidates for continuous methemoglobin monitoring.

Published studies imply a relationship between elevated levels of MetHb and the onset of sepsis, suggesting that continuous measurement of MetHb may prove valuable in the ability to predict the onset of sepsis.

The conventional method for MetHb determination, blood CO-Oximetry, is invasive, non-continuous, and is subject to significant delays in reporting. It is estimated that CO-Oximeters are available in only 50% of the hospitals in the United States. The advent, market clearance, and validation of Pulse CO-Oximeter™ technology permits instantaneous, noninvasive and continuous MetHb and COHb monitoring. Pulse CO-Oximetry is an advancement and extension of Masimo SET® technology that measures arterial oxygen saturation through motion and low perfusion.

The focus of this paper is on acquired methemoglobinemia, and its clinical consequences.

The Physiology of Dyshemoglobins

Methemoglobin (MetHb) is a dysfunctional form of hemoglobin that is incapable of transporting oxygen, thus reducing blood oxygenation and potentially inducing tissue hypoxemia. In healthy subjects, blood methemoglobin levels are low, typically < 2% of the total hemoglobin in the blood. When MetHb concentrations are increased (a condition called methemoglobinemia), there is less available functional hemoglobin to carry oxygen for systemic delivery. The 'functional anemia' induced by increased levels of methemoglobin is exacerbated by the fact that MetHb induces a leftward shift of the oxyhemoglobin dissociation curve. This leftward shift impedes the unloading of oxygen from the normal hemoglobin. Thus, methemoglobinemia has a dual impact on blood and tissue oxygenation. MetHb reduces the amount of oxygen that can be bound for delivery to the tissues, and at the tissue level, MetHb influences the behavior of the normal hemoglobin, forcing it to bind more tightly to oxygen, thus releasing less oxygen to the tissues.

Acquired Methemoglobinemia

Exogenous agents can produce methemoglobinemia either by accelerating the production of methemoglobin or by inhibiting the protective enzymatic systems that normally maintain MetHb at low levels. The exogenous causes of methemoglobinemia, including commonly prescribed drugs, chemical fume inhalation, and clinical use of inhaled nitric oxide, are ubiquitous in the inpatient and outpatient settings. The Institute for Safe Medical Practice concluded in 2002 that “methemoglobinemia is unlikely to be a rare occurrence.” Unfortunately, elevations in methemoglobin levels are often unrecognized until symptoms become extreme. Because the symptoms are ambiguous and similar to those associated with general disorders like cold, flu, and viral infections, proper diagnosis is often delayed. While treatment efficacy is high, failure to treat or treatment delays may cause significant morbidity and mortality.

Drugs

From Table I, note that among the most common culprits contributing to generation of high levels of methemoglobin are local anesthetic agents such as benzocaine, lidocaine, prilocaine, etc., which are regularly used in “scoping” procedures such as endoscopy, laparoscopy, etc. In February 2006, the Veterans Health Administration issued an alert and a call to all VA facilities to discontinue the use of benzocaine on the peri-laryngotracheal regions and other airway structures due to several cases of severe and/or fatal methemoglobinemia. The FDA announced an ongoing review of the risk shortly thereafter.^{1,2} The popular EMLA cream, an epidermal anesthetic agent used primarily on children, contains 2.5% lidocaine and 2.5% prilocaine and has been linked to methemoglobinemia.³ The antibiotic dapsone, used to treat Hansen’s Disease (leprosy) has been found to produce methemoglobinemia.⁴

Table I

Select Drugs documented to contribute to Methemoglobinemia	
Benzocaine, Cetacaine, Prilocaine (the ‘caines’)	Anesthetic – endotracheal intubation, transesophageal echocardiography, bronchoscopy, topical for hemorrhoids and dental/teething preps.
Celecoxib	Arthritic Pain
Dapsone	Prophylaxis for pneumocystis carinii in patients with human immunodeficiency virus (HIV). Also dermatologic applications.
EMLA Creams	Eutectic Mixture of Local Anesthetics.
Flutamide	Prostate Cancer
Nitrates	Food additives, well water, by-product of fertilizer run-off and incorporation into foods. Preservative
Nitric Oxide	Pulmonary vasodilatation
Nitroglycerin	Cardiac vasodilatation
Sodium Nitroprusside	Intravenous Antihypertensive, Vasodilator
Sodium Nitrate	Preservative salt used in meat and fish
Sulfonamides	Broad spectrum antibiotics

Nitrates, Nitrites, and Nitric Oxide

Nitrates and nitrites are powerful oxidizing agents that can cause methemoglobinemia. Ingestion of barbecued foods containing nitrites has caused patients to present to the emergency department with methemoglobinemia.^{5,6} The fumes of carbon compound combustion (wood burning stoves, forest fires, etc.) contain variable levels of carbon monoxide, a hemoglobin poison. These fumes also produce nitric oxide (NO), which is a potent inducer of methemoglobin. When nitric oxide is inhaled, 85-90% goes to the direct formation of MetHb.⁷

Methemoglobinemia has been reported by several investigators as a result of ingesting nitrates in drinking water. A study of five residential regions in India with high nitrate levels in the water found that in the 178 people sampled, methemoglobin levels were significantly elevated, ranging from 7-27%.⁸ A University of Iowa review of nitrate toxicity and methemoglobinemia in rural America suggested that nitrate levels are increasing in the U.S. because of the use of nitrogenous fertilizers. Baby foods containing fennel, or prepared with rural well-water containing high nitrate levels associated with fertilizer run-off, have caused methemoglobinemia in infants.⁹ Newborns (to 6 months of age) are particularly susceptible to foods and water with high nitrate levels because fetal hemoglobin is more readily oxidized to methemoglobin when contaminated well water is unwittingly mixed with infant formula.¹⁰ A study of commercial baby food found that many have nitrate levels of greater than 45 ppm. The amount of nitrate in one four-ounce jar of beets contained the equivalent nitrate to 5.5 liters of water at 45 ppm raising concern for methemoglobinemia in infants.¹¹

Other Exogenous Sources of Acquired Methemoglobinemia

In the Emergency Department, methemoglobinemia has been linked to a wide array of substances, ranging from pesticides and insecticides, herbicides, automobile and boat engine exhaust fume inhalation, and inhalation of industrial chemicals such as nitrobenzene, nitroethane (commonly found in nail polish), common resins, and rubber adhesives. Dehydration is also associated with increased methemoglobin production. Infants suffering from diarrheal disease are particularly likely to become victims of methemoglobinemia associated with dehydration.¹²

Methemoglobin as a Potential Predictor of Sepsis

Small but measurable MetHb increases have been shown to occur prior to the onset of sepsis or septic shock. Because relatively large amounts of nitric oxide (NO) are released into the blood in patients who are septic or are transitioning into a septic state, the conversion of NO to methemoglobin contributes to elevated MetHb levels.¹³ During infection and other inflammatory processes, transient levels or “bursts” of NO occur within the patient. While the relationship is not completely understood, it is thought that the purpose of these rapid NO elevations is to destroy invading bacteria.¹⁴ The body converts most blood-based nitric oxide into MetHb. While further investigation is needed to fully understand the relationship between methemoglobinemia and sepsis, continuous methemoglobin monitoring as a sepsis predictor may offer a significant opportunity to impact healthcare quality, cost, and total efficacy.

The Johns Hopkins Study: Acquired Methemoglobinemia.¹⁵

In a major study by researchers at the Johns Hopkins University School of Medicine, a retrospective analysis was performed at two tertiary care hospitals and affiliated outpatient clinics over a period of 28 months. The Johns Hopkins study had several key findings. Patients characterized by elevated MetHb levels were found in every clinical department of the hospital system. Nearly 20% of all patients evaluated with traditional CO-Oximetry had elevated methemoglobin levels and 25% of the cases were accidentally found. Over 25 drugs that are frequently used in hospitals caused methemoglobinemia, including local anesthetics, nitroglycerin, EMLA cream for neonates, inhaled nitric oxide, and Dapsone. The study concluded that elevated MetHb in the sample population resulted in one death and three near deaths during the period of evaluation. When consideration is given to the fact that only 1.5% of all blood gas samples drawn in this study were subjected to CO-Oximetry analysis, the authors suggest that the actual number of patients afflicted with methemoglobinemia can be expected to be greater than captured by this retrospective analysis. If the ratio of CO-Oximetry evaluations to mortality outcomes due to methemoglobinemia in this study is applied to all US hospital admissions, up to 18,000 patients are potentially at risk annually for early mortality associated with untreated MetHb. Finally, the cost of traditional invasive testing for methemoglobin was \$25 for each evaluation. Despite the cost, the authors recommended measurement of MetHb each time blood was drawn for serial evaluations of MetHb during treatment.

The frequent occurrence of sources of acquired methemoglobinemia within the clinical setting is emphasized by the study. The use of the drug Dapsone (prescribed for immunocompromised patients and for dermatologic disorders) was the primary source of acquired methemoglobinemia in this study, followed by surgery (anesthetic-related). “Unknown” was listed as the third most common cause of methemoglobinemia as the condition often went unrecognized and untreated. Pediatric dehydration and others (fume inhalation, sepsis, and sickle cell crisis) completed the list. In the same study, methemoglobinemia did not discriminate by gender or age, with the exception of a higher rate in diarrheic infants.

A critical finding of the study: **“Methemoglobinemia does not discriminate significantly throughout areas of hospital care, with the operating room, outpatient clinics, and the intensive care units receiving similar distributions.”**¹⁵ (See Table II, created from various literature citations.)

Table II

Diagnosis of Methemoglobinemia in the Hospital	
Hospital Department	Why is CO-Oximetry Ordered?
Intensive Care Units, including NICU	Evaluation of Cyanosis/Dyspnea, iNO Therapy
Inpatient Surgery	Evaluation of Cyanosis/Dyspnea
General Med/Surg Floors	Evaluation of Cyanosis/Dyspnea
Pediatric Medicine	Dehydration with Gastroenteritis, sepsis
Outpatient Dermatology	Dyspnea secondary to Dapsone treatment
Rheumatology	Dyspnea secondary to Dapsone treatment
Human Immunodeficiency Virus Clinics	Dyspnea secondary to Dapsone treatment
Anesthesiology (intra and post operatively)	To obtain immediate hemoglobin status updates and/or to evaluate cyanosis
Cardiology/Cardiac Catheterization Labs	Serial CO-Oximetry tests to calculate Fick cardiac output
Respiratory Care: PFT Lab, Pulmonary Stress Lab: Bronchoscopy	Dyspnea on exertion related to methemoglobin. Bronchoscopy: local anesthetics may induce MetHb
Imaging, including gastrointestinal procedures	Transesophageal echocardiography - patent foramen ovale/intracardiac shunt. GI imaging - local anesthetic
Neurology	Changes in mental status/headache
Emergency Room	Cyanosis/Dyspnea that does not resolve with 100% oxygen treatment. Suspected acquired/toxin-induced methemoglobinemia

Methemoglobinemia Symptomatology

The signs and symptoms of methemoglobinemia are problematic because they are ambiguous and nonspecific. At levels of 20%-30%, symptoms include changes in mental status, headache, fatigue, exercise intolerance, dizziness, and syncope. Greater levels of methemoglobinemia are associated with dysrhythmias, seizures, and comas. (See Table III). Comorbidities such as sepsis, cardiac and lung disease, or the presence of other dyshemoglobins such as carboxyhemoglobin, will often cause significant symptoms to appear at lower levels of methemoglobinemia.¹⁵ Gross inspection of blood samples taken from afflicted patients reveal blood that is thick and “chocolate brown” in color.

Table III

Clinical Levels of Methemoglobin and Associated Symptoms ¹⁵		
Methemoglobin %	Symptoms	Notes
< 15%	Asymptomatic	Symptomatic with Anemia
20 - 30%	Cyanosis, headache, fatigue, mental status changes, syncope, dizziness, and exercise intolerance	Comorbidities: Anemia, cardiovascular disease, cardiopulmonary disease, sepsis, or the presence of other dyshemoglobins amplify the hypoxemic impact of methemoglobinemia.
30 - 50%	Shortness of breath and headache	
50 - 70%	Lethargy, stupor, dysrhythmias, seizure, coma	
Over 70%	Death	

Treatment

Mild methemoglobinemia symptoms can be adequately treated with supplemental oxygen therapy to maximize the oxygen carrying capacity of the remaining normal hemoglobin. Methylene blue is the most commonly prescribed treatment for moderate to severe methemoglobinemia.¹⁶ Interestingly, methylene blue therapy has also been shown to induce methemoglobinemia. In addition, repeated methylene blue treatments may be indicated in some cases, as rebound methemoglobinemia has also been reported up to 12 hours post-methylene blue.¹⁷ In extreme cases, a blood transfusion may be indicated to rapidly decrease MetHb levels that have escalated to near-fatal levels.

While serial methemoglobin measurements through CO-Oximetry can be used to monitor adequate response to treatment, continuous noninvasive monitoring may speed accurate diagnoses with faster therapeutic interventions when necessary.

Cost, Clinical Yield and Limitations of Current Diagnostics

The diagnostic dilemma is that the traditional detection of methemoglobinemia, CO-Oximetry, is costly and requires an invasive procedure - an arterial blood sample with subsequent laboratory analysis. In the Ash-Bernal study at Johns Hopkins, the authors state "if CO-Oximetry tests had been performed on every blood aliquot sent for arterial blood gas analysis during the 28-month study, the incurred cost at \$25.00 per test would have been approximately \$9 million."¹⁵

Obtaining an arterial blood gas evaluation requires a physician order. Therefore, the single methemoglobin spot-check value obtained from each ABG evaluation is rate-limited not only by the availability of CO-Oximetry devices, but also by the frequency of the physician order for serial blood gas evaluations. It has been estimated that less than 50% of U.S. Hospitals do not offer CO-Oximetry evaluations because they do not have immediate access to the device. When CO-Oximetry evaluations are indicated and ordered in hospitals with CO-Oximeters, delays average only about 10 minutes from the time the blood is sampled. Nonetheless, the test is ordered only a fraction of the time. In hospitals without CO-Oximeters samples are sent to laboratories outside the hospital for evaluation, with diagnostic delays averaging about 15 hours, providing a disincentive to order the test because of long delays.

Methemoglobinemia causes pulse oximetry technology devices to report different oxygen saturation than calculated by arterial blood gas measurement.^{18,19} Elevated methemoglobin 'pushes' the SpO₂ value to 85%, and the relationship between SpO₂ and actual arterial oxygen saturation during methemoglobinemia is impropportionate. When elevated methemoglobin is present, the SpO₂ values reported by conventional pulse oximetry are suspect, and may significantly misrepresent the actual clinical status of the patient.

Non-Invasive, Continuous Pulse CO-Oximetry

In 2005, Masimo Corporation (Irvine, CA) developed a new multi-wavelength Pulse CO-Oximetry™ technology called Rainbow® SET, that continuously and non-invasively measures the percentage of hemoglobin saturated with oxygen (SpO₂), as well as the percentage of methemoglobin (SpMet™), the percentage of carboxyhemoglobin (SpCO®), Pulse Rate and Perfusion Index (PI), all through a single sensor typically placed on the finger. This allows clinicians to perform simple and inexpensive spot-checks and/or continuous monitoring with clinician-set alarms for detection of elevated MetHb and COHb levels. Clinicians can, with confidence, perform sound clinical protocols by actively monitoring MetHb during treatment and reacting appropriately before methemoglobin escalates to dangerous levels. Continuous monitoring also allows clinicians to monitor for sufficient periods to ensure that the inciting etiologic agent has been fully removed and effects have completely abated.

Conclusion

Methemoglobinemia is a pervasive and significant clinical condition. Although treatable, its detection and proper diagnosis has been problematic due to:

- lack of awareness in the clinical community of its prevalence
- process limitations associated with the prescription of CO-Oximetry
- limited availability of current laboratory standard of measurement, invasive CO-Oximetry
- process limitations associated with spot testing, or MetHb 'snapshots' derived from blood CO-Oximetry

The cost of misdiagnosis of this condition can be significant, with ramifications for almost all hospital departments and specialty areas.

Masimo Rainbow SET Pulse CO-Oximetry provides the validated ability to noninvasively and continuously measure methemoglobin and carboxyhemoglobin levels that have been clinically proven to impact the reported morbidity, treatment costs, and mortality of many hospital patients. Because Pulse CO-Oximetry provides immediate measures of the dyshemoglobins MetHb and COHb, without a blood sample, it has value in settings with and without on-site CO-Oximetry. The ability to noninvasively and continuously evaluate methemoglobin becomes a powerful diagnostic tool in the armamentarium of methods used to evaluate the pervasive nature of methemoglobinemia in the acute care setting. The potential to trend changes in a patient's methemoglobin profile as an early marker for sepsis is an exciting possibility that warrants further investigation and clinical study.

References

1. Veteran's Administration Central Office. (2006 February 8). *Cessation of topical spray benzocaine usage to anesthetize the surfaces of the nasopharynx, oropharynx, laryngotracheal region and airway. affected products include, but are not limited to:* • *Hurricane® spray (benzocaine 20%)* • *Cetacaine® spray (benzocaine 14%, butyl aminobenzoate 2% and tetracaine 2%)* • *Topex® spray (benzocaine 20%)*. Retrieved August 21, 2007 from <http://www.va.gov/ncps/alerts/Benzocaine-WWWW.pdf>
2. Food and Drug Administration. (2006, February 10). *Benzocaine sprays marketed under different names, including Hurricane, Topex, and Cetacaine*. Retrieved August 21, 2007 from <http://www.fda.gov/cder/drug/advisory/benzocaine.htm>
3. Astra-Zeneca Pharmaceuticals. (2005, May). *EMLA Cream*. Retrieved August 21 from <http://astrazeneca-us.com/pi/emla.pdf>
4. Wagner A, Marosi C, Binder M, Roggla G, Staudinger T, Keil F, Locker GJ, Frass M. Fatal poisoning due to dapsone in a patient with grossly elevated methaemoglobin levels. *Br J Dermatol*. 1995 Nov;133(5):816-7.
5. Yang JJ, Lin N, Lv R, Sun J, Zhao F, Zhang J, Xu JG. Methemoglobinemia misdiagnosed as ruptured ectopic pregnancy. *Acta Anaesthesiol Scand*. 2005 Apr;49(4):586-8.
6. National Academy of Sciences - National Research Council Academy of Life Sciences. (1981). *The health effects of nitrate, nitrite and N-nitroso compounds*. Washington DC: National Academy Press.
7. Taylor MB, Christian KG, Patel N, Churchwell KB. Methemoglobinemia: Toxicity of inhaled nitric oxide therapy. *Pediatr Crit Care Med*. 2001 Jan;2(1):99-101.
8. Gupta SK, Gupta RC, Seth AK, Gupta AB, Bassin JK, Gupta A. Methaemoglobinaemia in areas with high nitrate concentration in drinking water. *Natl Med J India*. 2000 Mar-Apr;13(2):58-61.

9. Murone AJ, Stucki P, Roback MG, Gehri M. Severe methemoglobinemia due to food intoxication in infants. *Pediatr Emerg Care*. 2005 Aug;21(8):536-8.
10. Kross BC, Ayebo AD, Fuortes LJ. Methemoglobinemia: nitrate toxicity in rural America. *Am Fam Physician*. 1992 Jul;46(1):183-8.
11. Dusdieker LB, Getchell JP, Liarakos TM, Hausler WJ, Dungy CI. Nitrate in baby foods. adding to the nitrate mosaic. *Arch Pediatr Adolesc Med*. 1994 May;148(5):490-4.
12. Hanukoglu A, Dan on PN. Endogenous methemoglobinemia associated with diarrheal disease in infancy. *J Pediatr Gastroenterol Nutr*. 1996 Jul;23(1):1-7.
13. Ohashi K, Yukioka H, Hayashi M, Asada A. Elevated methemoglobin in patients with sepsis. *Acta Anaesthesiol Scand*. 1998 Jul;42(6):713-6.
14. Preiser JC, Reper P, Vlasselaer D, Vray B, Zhang H, Metz G, Vanderkelen A, Vincent JL. Nitric oxide production is increased in patients after burn injury. *J Trauma*. 1996 Mar;40(3):368-71.
15. Ash-Bernal R, Wise R, Wright SM. Acquired methemoglobinemia: a retrospective series of 138 cases at 2 teaching hospitals. *Medicine*. 2004 Sep;83(5):265-73.
16. Bilgin H, Ozcan B, Bilgin T. Methemoglobinemia induced by methylene blue perturbation during laparoscopy. *Acta Anaesthesiol Scand*. 1998 May;42(5):594-5.
17. Fitzsimons MG, Gaudette RR, Hurford WE. Critical rebound methemoglobinemia after methylene blue treatment: case report. *Pharmacotherapy*. 2004 Apr;24(4):538-40.
18. Barker S, Curry J, Morgan S, Bauder W. (2006). *New pulse oximeter measures methemoglobin levels in human volunteers*. Paper presented at the annual meeting of the Society for Technology in Anesthesia, San Diego, CA.
19. Barker SJ, Tremper KK, Hyatt J. Effects of methemoglobinemia on pulse oximetry and mixed venous oximetry. *Anesthesiology*. 1989 Jan;70(1):112-7.

Instruments containing Masimo Rainbow SET technology are identified with the Masimo Rainbow SET logo. Look for the Masimo designation on both the sensors and monitors to ensure accurate monitoring when needed most.



Masimo Corporation 40 Parker Irvine, California 92618 Tel 949-297-7000 Fax 949-297-7001 www.masimo.com

© 2007 Masimo Corporation. All rights reserved. Masimo, Rad, SET,  and Signal Extraction Technology are registered trademarks of Masimo Corporation. Pulse CO-Oximeter and Rad-57 are trademarks of Masimo Corporation. Rainbow, SpCO, CoHB, MetHB are trademarks of Masimo Laboratories.