Methemoglobinemia: Etiology, Pharmacology, and Clinical Management

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Methemoglobin (MHb) may arise from a variety of etiologies including genetic, dietary, idiopathic, and toxicologic sources. Symptoms vary from mild headache to coma/death and may not correlate with measured MHb concentrations. Toxin-induced MHb may be complicated by the drug's effect on other organ systems such as the liver or lungs. The existence of underlying heart, lung, or blood disease may exacerbate the toxicity of MHb. The diagnosis may be complicated by the effect of MHb on arterial blood gas and pulse oximeter oxygen saturation results. In addition, other dyshemoglobins may be confused with MHb. Treatment with methylene blue can be complicated by the presence of underlying enzyme deficiencies, including glucose-6-phosphate dehydrogenase deficiency. Experimental antidotes for MHb may provide alternative treatments in the future, but require further study.

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INTRODUCTION

Methemoglobinemia refers to the oxidation of ferrous iron (Fe^{++}) to ferric iron (Fe^{+++}) within the hemoglobin molecule.[1] This reaction impairs the ability of hemoglobin to transport oxygen and carbon dioxide, leading to tissue hypoxemia and in severe cases, death. Methemoglobinemia most commonly results from exposure to an oxidizing chemical, but may also arise from genetic, dietary, or even idiopathic etiologies.[2,3] This review focuses on acquired forms of methemoglobinemia. Because of these disparate causes, confusion may arise in the recognition and management of methemoglobinemia. Physicians may be aware of one etiology, such as dietary nitrites in well water, but may be unfamiliar with others, such as the ingestion of teething gels. Furthermore, laboratory data, which clinicians may

believe to be diagnostic, may instead be falsely normal in methemoglobinemia, leading to misdiagnosis and underrecognition of the condition. Therefore, the purposes of this review are fourfold: (1) to summarize the biochemical properties by which methemoglobin (MHb) is formed, (2) to bring together its disparate etiologies into their common endpoints, (3) to illustrate diagnostic tests that yield falsely normal results in methemoglobinemia and those that provide reliable results, and (4) to highlight issues surrounding treatment and its potential complications.

METHEMOGLOBINEMIA AND INTRACELLULAR OXIDATION

To understand oxidative toxicity and its potential complications, certain biochemical properties must first be reviewed. Oxidation involves the extraction of electrons from a substrate. Reduction involves the transfer of electrons to a substrate. A substance has been oxidized if it loses an electron, and if it gains an electron, it has been reduced.

Oxidation/reduction reactions are termed "redox" reactions because they always occur together, that is, for one substance to be reduced, another must be oxidized.[1] Highly reactive, unstable molecules with redox potential are often termed "free radicals." These free radicals can oxidize cellular enzymes inhibiting their function. These reactions may in turn lead to the formation of more free radicals. Some reactions cause the formation of covalent bonds between the arylating oxidant agent and cellular/membrane proteins.[4] This covalent bond may cause disruption of cellular membrane integrity and enzymatic function. Unchecked, the process ultimately leads to cell lysis and death.[5,6] When oxidation occurs within the heme moiety of hemoglobin, MHb is formed. Inevitably, oxidation is also occurring elsewhere in the cell and may cause damage to other cellular enzymes and organelles. Whereas some agents may be specific in reacting with hemoglobin, most are not and methemoglobinemia is usually accompanied by some degree of hemolysis. In addition, if these oxidative reactions occur outside the vascular space, cell damage may also occur in other organs, such as the lungs or liver.

RBCs are uniquely susceptible to oxidant stress. RBCs carry oxygen in high concentration and are therefore continuously exposed to oxygen free radicals.[7,8] Blood serves as the transport medium for oxidant xenobiotic agents after absorption from the gut, exposing RBCs to further potential oxidation. To combat these processes, a wide variety of enzymatic systems exist that protect the RBC from oxidation reactions. However, unlike other cells, RBCs lack a nucleus and cannot synthesize new protein.[9] Enzymes that normally detoxify oxidant agents degrade with time. Therefore, older cells are more susceptible to oxidation, as they cannot detoxify drugs as well as younger cells.[9] Furthermore, RBCs also lack mitochondria and are less efficient than other cells in generating energy and cofactors necessary for chemical detoxification. These properties explain why blood toxicity, manifesting as hemolysis and methemoglobinemia, occurs more frequently than oxidative toxicity in other tissues.

PHYSICAL PROPERTIES OF METHEMOGLOBIN

Hemoglobin molecules contain iron within a porphyrin heme structure. The iron in hemoglobin is normally found in the Fe^{++} state. The iron moiety of hemoglobin can be oxidized to the Fe^{+++} state to form MHb.[10] Once MHb is formed, the molecule loses its ability to carry molecular oxygen. Because RBCs are bathed in oxygen, a certain amount of physiologic MHb formation occurs continuously.[10] Several endogenous reduction systems exist to maintain MHb in the reduced state, and in normal individuals only about 1% of total hemoglobin is MHb at any given time.[10] Because oxidized hemoglobin is incapable of carrying oxygen (or carbon dioxide), excess MHb leads to cyanosis, impaired aerobic respiration, metabolic acidosis, and in severe cases, death.

Hemoglobin is a tetrameric molecule, and the complete oxidation to MHb would represent a 4-electron loss. However, under conditions of oxidative stress, partial oxidation of the individual subunits predominates, and as such 8 different dimers may exist (there are 4 subunits to hemoglobin ($\alpha_2\beta_2$) and 2 iron valences (Fe^{++} and Fe^{+++}); thus, 8 different states can exist.[1,10] The nonoxidized portions of these hybrid valence forms have a high affinity for oxygen and shift the oxygen dissociation curve to the left.[10] In other words, any oxygen that is carried by the nonoxidized hemoglobin subunits is held on to more tightly and poorly released to tissues. This property is important clinically. For example, a patient with 35% MHb has a theoretical oxygen-carrying capacity of 65% of his or her hemoglobin. Functionally, however, this is not the case, because allosteric changes to the hemoglobin molecule cause oxygen to bind more tightly in the partially oxidized hemoglobin molecules. This increased affinity causes a left shift in the hemoglobin-oxygen saturation curve.

Oxidation also results in a net positive charge to the MHb molecule compared with normal hemoglobin. MHb has high affinity for negative anions such as cyanide, fluoride, or chloride (CN^-, F^-, and Cl^-) as opposed to the uncharged binding ligands (CO_2, CO, and O_2) of normal hemoglobin.[1,10]

DIRECT ENDOGENOUS REDUCTION

Even in the absence of exogenous oxidative stress, endogenous oxidation from molecular oxygen would eventually convert enough hemoglobin to MHb to impair cellular respiration.[10] To combat this process, there are several enzyme systems in the RBC that inhibit oxidation or reduce MHb back to hemoglobin. The cytochrome-b_5–MHb reductase system is the predominant system and accounts for approximately 99% of daily MHb reduction.[10] Ascorbic acid and glutathione account for small amounts of reduction. Other endogenous reducing agents include reduced flavin, tetrahydropterin, cysteamine, and reduced cysteine on protein molecules.[2,3,10] The reconversion rate of MHb to hemoglobin in normal individuals is about 15% per hour.[11] This assumes no ongoing MHb production. This is a first-order kinetic reaction. For example, a subject with 40% MHb would be expected to have a level of 34% 1 hour later. Under normal circumstances, these enzymes/molecules play a minor role in reduction. However, patients with methemoglobinemia as a result of complete congenital cytochrome-b_5 reductase deficiency are able to maintain MHb levels below 50%, and sometimes as low as 10%, suggesting that these minor pathways can reduce significant amounts of MHb when the cytochrome-b_5 reductase pathway is overwhelmed.[2]

Cytochrome-b_5 (reduced nicotinamide adenine dinucleotide–dependent)–MHb reductase mechanism of action

The predominant pathway by which MHb is reduced in the cell is a 2-enzyme system. Cytochrome b_5 is a cytosolic cytochrome. A second enzyme with a flavin moiety called cytochrome-b_5 reductase is also necessary to reduce MHb.[2,10] Glycolytic intermediates that produce reduced nicotinamide adenine dinucleotide (NADH) serve as the original electron donors. NADH is a cofactor to cytochrome b_5 reductase. Electrons travel from glycolytic intermediates to NADH to cytochrome-b_5 reductase to cytochrome b_5 and finally to MHb (Figure 1). Older nomenclature may be confusing because the 2-enzyme system is referred to as a single enzyme, NADH-MHb reductase.

Reduced nicotinamide adenine dinucleotide phosphate–MHb reductase

Another enzyme that reduces MHb is reduced nicotinamide adenine dinucleotide phosphate (NADPH)–MHb reductase. Also known as NADPH-flavin reductase and NADPH-MHb–diaphorase, under normal conditions this enzyme plays a negligible role in reducing MHb. It is actually a generalized reductase with an affinity for dyes, such as methylene blue, Nile blue, and divicine.[12-14] In the presence of the cofactor NADPH, this enzyme will reduce these dyes, which in turn reduce MHb (Figure 1). The primary function of this reductase is probably to metabolize oxidant xenobiotics and not MHb. It is somewhat fortuitous that the reduced form of methylene blue has a high affinity for MHb.

INDIRECT ENDOGENOUS PROTECTIVE MECHANISMS

Protective mechanisms against oxidative stress include sulfation enzymes, ascorbic acid, and glutathione. These enzymes and peptides serve to detoxify oxidative exogenous chemicals and thereby indirectly prevent methemoglobinemia. Reduced glutathione is quantitatively the most important cellular antioxidant, and is of key importance in all cells for the preservation of protein sulfhydryl groups and to prevent oxidative damage in general.[15,16] Glutathione is a minor pathway in the reduction of MHb. Glutathione may also metabolize potentially toxic xenobiotics to nontoxic intermediates by forming mercapturic acid conjugates.[6] Oxidized glutathione is cytotoxic and will diffuse out of cells if it is not reduced back to reduced glutathione.[15] Hence, oxidative stress in the presence of glucose-6-phosphate dehydrogenase (G6PD) deficiency leads to intracellular depletion of total glutathione.[16] Other enzymes involved in free radical metabolism include superoxide dismutase, catalase, and glutathione peroxidase. Despite the role these enzymes play in detoxifying agents that cause methemoglobinemia, congenital deficiencies of virtually all these proteins have been described, and none are associated with methemoglobinemia.[10] This is likely due to the extraordinary efficiency of the cytochrome b_5/cytochrome-b_5 reductase system in reducing MHb.

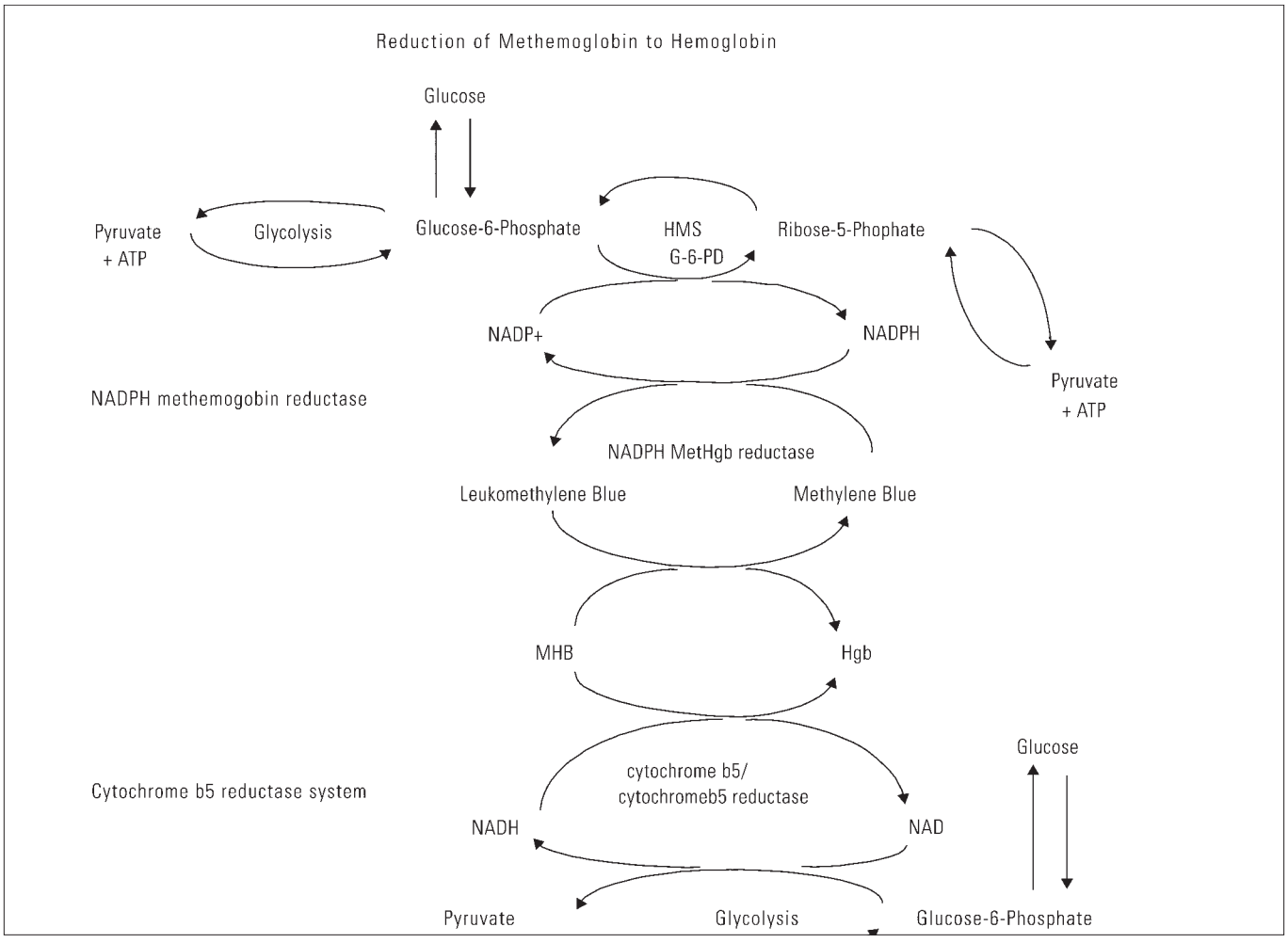
CLINICAL ETIOLOGY OF METHEMOGLOBIN

Toxin-induced

The most common cause of MHb is ingestion or skin exposure to an oxidizing agent. MHb is most common in children older than 6 months. Common agents are aniline, benzocaine, dapsone, phenazopyridine (pyridium), nitrites, nitrates, and naphthalene (Table 1). Oxidizing agents can be divided into those that directly oxidize hemoglobin and those that indirectly oxidize hemoglobin. Direct oxidizers react directly with hemoglobin to form MHb. Indirect oxidizers are actually powerful reducing agents that reduce oxygen to the free radical O_2^-, or water to H_2O_2, which in turn oxidizes hemoglobin to MHb.

Many drugs that produce MHb are not themselves the causative agents. Instead these drugs are metabolized to an oxidative free radical. For example, aniline is metabolized by the cytochrome P-450 system to a free radical phenylhydroxylamine, which, like nitrite, reacts with O_2 to form oxygen free radicals and then MHb. Because of the variability in metabolism among individuals, not every patient may experience methemoglobinemia when exposed to such agents. This may explain why not every child who ingests benzocaine develops MHb. Only those who metabolize a significant amount of parent drug to the

Figure 1.
*Reduction of methemoglobin to hemoglobin. **ATP,** Adenosine triphosphate; **HMS,** hexose monophosphate shunt; **MHb,** methemoglobin; **Hgb,** hemoglobin. Cytochrome b_5 and cytochrome-b_5 reductase are actually 2 separate enzymes that transfer electrons from NADH to MHb to form reduced hemoglobin.*



toxic metabolite develop methemoglobinemia. Other factors, such as rate of absorption or enterohepatic recirculation, may influence the duration of toxin-induced methemoglobinemia. Chlorates (ie, sodium, potassium, barium) are very potent oxidizing agents used in the manufacture of explosives, matches, dyes, weed killers, as a mouthwash, and weak antiseptic. Poisoning is characterized by a latent period of several hours followed by nausea, vomiting, diarrhea, and then cyanosis (ie, methemoglobinemia), hemolysis, and renal failure.[17] Nitrites can be absorbed through the skin and gastrointestinal tract, and others, like dapsone, may undergo enterohepatic circulation and produce prolonged MHb.[18]

Acidosis

The second most common cause of MHb is idiopathic, but related to systemic acidosis. MHb can be formed in young infants (<6 months) who develop severe metabolic acidosis, most commonly as a result of diarrhea and dehydration.[19,20] Several risk factors may predispose young infants to develop methemoglobinemia. Small infants have quantitatively lower RBC levels of cytochrome-b_5 reductase.[21] Levels at birth are only 50% to 60% of adult levels. Fetal hemoglobin is also more easily oxidized than adult-type hemoglobin, and the higher intestinal pH of infants may promote the growth of gram-negative organisms that convert dietary nitrates to nitrites, potent MHb inducers. Whether the oxidation is caused by nitrites formed by intestinal gram-negative bacterial flora, the presence of fetal hemoglobin, lower MHb-reducing enzyme levels during the first month of life, or formation of oxidative metabolites is unclear. No association with oxidant drugs has been established and the MHb resolves with time, suggesting that it is not inherited. An association with certain gram-negative, nitrite-forming bacteria, such as *Escherichia coli* or *Campylobacter jejuni*, has been suggested from clusters of cases; however, a definite etiologic pathogen has not been identified in all cases.[22,23] In addition, some cases have been associated with noninfectious diarrhea, such as cow's milk protein intolerance. There are also reports of infants with MHb and acidosis in the absence of diarrhea, specifically in an infant with renal tubular acidosis and vomiting but no diarrhea.[24] It may be that the common endpoint of acidosis is the greatest predisposing factor. There is evidence that endogenous MHb reduction is inhibited by an acidic pH and promoted by an alkaline pH.[25,26] The exact cause, while still unknown, is likely multifactorial.

Table 1.
Common agents that produce methemoglobinemia.

Acetanilid	Hydroxylamine	Nitroprusside
Alloxan	Lidocaine	Paraquat/Diquat
Aniline(dyes, ink)	Menadione	Phenacetin
Antipyrine	Metoclopramide	Phenazopyridine
Arsine	Methylene blue	Phenol
Benzene derivatives	Naphthalene	Phenylhydrazine
Benzocaine	Nitrates*	Phenytoin
Chlorates	Nitric oxide	Prilocaine
Chlorobenzene	Nitrites	Primaquine
Chloroquine	Nitroalkanes	Smoke inhalation
Dapsone	Nitrochlorobenzene	Sulfonamide antibiotics
Dinitrophenol	Nitrofuran	Trinitrotoluene
Dinitrotoluene	Nitroglycerin	

Many chemicals may have oxidizing properties and this list is not complete.
*Chemical and food sources.

Dietary

A third cause of MHb is dietary and is related to well water nitrates. This exposure deserves special consideration because it occurs in very young infants in whom toxic ingestions are extremely uncommon and often leads to delayed diagnosis and recurrent symptoms. A classic description of this syndrome was first noted in Iowa.[27] Typically, affected patients are very young infants who live in rural areas where the water source is a well containing high levels of nitrates, possibly from fertilizer runoff. Intestinal bacterial flora convert the nitrates to nitrites, which are potent Mhb-forming agents.[28]

Genetic

The fourth cause of MHb is genetic. These patients present at, or very shortly after, birth with cyanosis. Two different deficiencies may be present: cytochrome-b_5 reductase deficiency or cytochrome-b_5 deficiency.[2,10] Both are transmitted in an autosomal recessive pattern. These subjects have moderately elevated MHb levels that are usually well tolerated. Hemoglobin M describes a group of abnormal hemoglobin molecules.[10] This disorder is inherited in an autosomal dominant pattern. Presumably, the homozygous form is not compatible with life.

NADPH-MHb reductase deficiency

NADPH-MHb reductase deficiency has also been described, but does not lead to methemoglobinemia.[10] This enzyme is not responsible for endogenous MHb reduction, and only reduces MHb in the presence of an exogenous catalyzing agent such as methylene blue. When patients with this disorder develop chemically induced methemoglobin, they do not respond to con-

ventional methylene blue therapy, because methylene blue is dependent on this enzyme to reduce MHb.

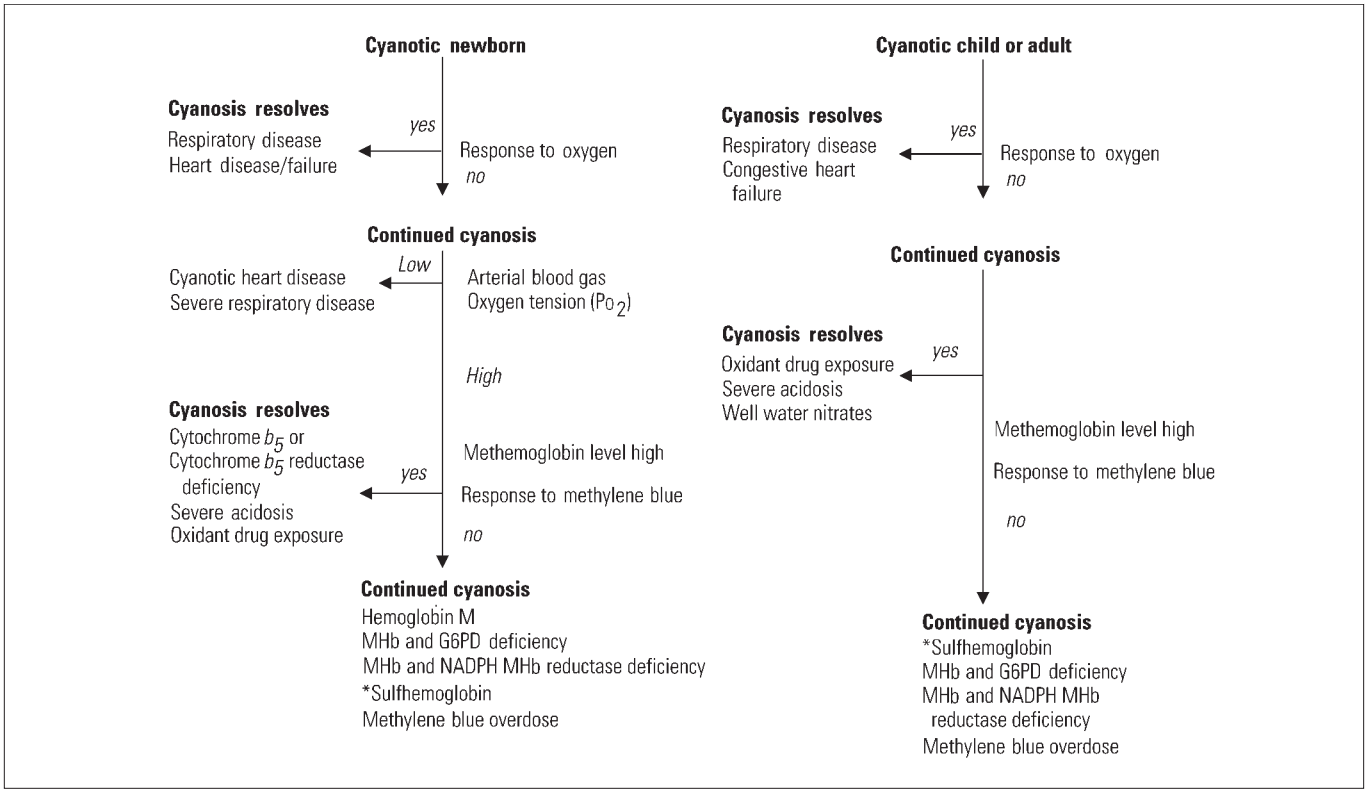
DIFFERENTIAL DIAGNOSIS AND CLINICAL EFFECTS

The differential diagnosis for a small infant with cyanosis is much broader than that of a toddler, adolescent, or adult. Congenital causes of MHb are more likely to present in the first few hours or days of life. Idiopathic MHb associated with acidosis occurs in this age group, as well as MHb caused by well water nitrites. At 4 months and older, infants may be exposed to benzocaine in teething gels as a cause of MHb. Benzocaine is an analogue of aniline and can be metabolized to the same oxidative metabolite as aniline. Figure 2 summarizes the clinical decisionmaking in determining the etiology of cyanosis in children.

Small infants with methemoglobinemia present similarly to patients with cyanotic congenital heart disease, with cyanosis that fails to respond to supplemental oxygen, a lack of significant pulmonary findings, and clear chest radiographs. Depending on the degree of cyanosis, metabolic acidosis may also develop. A distinguishing feature of MHb on an arterial blood gas analysis is the paradoxical elevation of Po_2 despite clinical cyanosis, and a normal calculated oxygen saturation. In contrast, children with cyanotic heart disease receiving supplemental oxygen have a low Po_2 and low calculated oxygen saturation. Interpretation of arterial blood gas analysis in patients with MHb is discussed later in this review.

Infants with sepsis may present with symptoms similar to methemoglobinemia, but usually respond to supplemental oxygen; although the patient with diarrhea, acidosis, and methemoglobinemia may also be septic. Congenital methemoglobinemia usually becomes apparent shortly after birth and produces few symptoms. Slightly older infants (from birth up to 4 to 6 months) may develop methemoglobinemia in the context of severe dehydration, diarrhea, and metabolic acidosis.

Figure 2.
*Clinical decisionmaking in methemoglobinemia. *Some co-oximeters may misread sulfhemoglobin as MHb.*



In older children, the most likely cause of MHb is the ingestion of an oxidizing drug such as dapsone, phenazopyridine (Pyridium), or the nitroalkanes found in some nail polish removers. Patients exposed to an oxidizing agent usually develop cyanosis shortly after ingestion. In adolescents and adults, inhalant abuse may lead to methemoglobinemia resulting from volatile nitrites. A more complete list of agents associated with MHb is found in Table 1.

Toxin-induced sulfhemoglobin is a consideration in older children but is much less common than MHb. Sulfhemoglobinemia refers to the incorporation of a sulfur molecule into the heme moiety. The reaction requires that the heme moiety first be oxidized to MHb, then a second reaction occurs in which sulfur is bound covalently to the heme. Endogenous glutathione may serve as the sulfur donor. Most drugs that produce MHb can also produce sulfhemoglobin, and sulfhemoglobinemia may be confused with methemoglobinemia.[29] Sulfhemoglobin cannot be reduced to hemoglobin and does not respond to methylene blue or other antidotal therapy.[30,31] Symptoms, which tend to be milder than in patients with MHb, typically last for 1 to 6 months depending on the level of sulfhemoglobin. The diagnosis is confirmed by the finding of elevated levels of sulfhemoglobin by either spectrophotometry or gas chromatography/mass spectrometry.[31] Treatment is supportive; in severe cases, exchange transfusion may be useful.

Regardless of etiology, the severity of symptoms depends on the MHb level (Table 2). Levels are reported as a percentage of total hemoglobin. Cyanosis caused by MHb becomes clinically apparent at an MHb level of 1.5 g/dL. In a normal person, this is usually about 15% of total hemoglobin. Levels above 70% may cause death. Unfortunately, because MHb is generally expressed as a percent of total hemoglobin, levels may not correspond with symptoms in some patients. An anemic patient may have greater symptoms at a level of 20% than a nonanemic patient, because the oxygen-carrying capacity is lower and more easily compromised. For example, a patient with an MHb level of 20% and total hemoglobin of 15 g/dL still has 12 g/dL of functioning hemoglobin, whereas a patient with an MHb level of 20% and total hemoglobin of 8 g/dL has only 6.4 g/dL of functioning hemoglobin. Anemia, acidosis, respiratory compromise, and cardiac disease may make patients more symptomatic than expected for a given MHb level. Table 2 serves only as a guideline.

Drugs and chemicals that induce MHb may have toxicity separate from the MHb-inducing property. For example, paraquat causes pulmonary fibrosis and patients with overdoses of this herbicide may present with a potentially misleading picture of hypoxia, shortness of breath, and cyanosis. Nitrites and nitrates are potent vasodilators and may lead to significant hypotension, exacerbating the toxicity of the methemoglobinemia. Quinones such as primaquine or chloroquine may be cardiotoxic. Oxidant-induced hemolysis frequently follows methemoglobinemia, although the onset of hemolysis is usually delayed by 12 to 24 hours after drug exposure. Some drugs, such as dapsone and aniline, produce a rebound methemoglobinemia, in which MHb levels increase 4 to 12 hours after successful methylene blue therapy.[16,32,33] Discussion of all the potential toxicities of MHb-inducing agents is beyond the scope of this article; when treating a patient with known exposure to a specific agent, consultation with the regional poison control center and a clinical toxicologist is recommended.

Laboratory diagnosis

When a patient presents with obvious cyanosis, an arterial blood gas analysis and pulse oximetry reading are usually performed. Unfortunately, results of these tests may be normal or near normal in a patient with significant methemoglobinemia. Unless the clinician is familiar with the effect of MHb on these tests, the results may delay diagnosis.

Arterial blood gas analysis. Arterial blood gas analyzers are based on electrochemistry. Voltage changes are determined with high-impedance electrodes to measure pH and P_{CO_2} and electrical current changes deter-

Table 2.
Symptoms associated with MHb blood concentrations.

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, arrhythmias, acidosis
>10.5 g/dL	>70	Death

*Assumes hemoglobin = 15 g/dL. Patients with lower hemoglobin concentrations may experience more severe symptoms for a given percentage of MHb level.
†Patients with underlying cardiac, pulmonary, or hematologic disease may experience more severe symptoms for a given MHb concentration.

mined to measure Po_2.[34,35] Po_2 refers to dissolved gas and not to oxygen molecules bound to hemoglobin. Subjects with MHb may have normal Po_2 levels despite life-threatening MHb. Serum bicarbonate and hemoglobin oxygen saturation are then calculated from the pH and Pco_2 values using the Henderson-Hasselbach equation[34,35] for serum bicarbonate and the standard oxygen-hemoglobin saturation curve for oxygen saturation. Unfortunately, this conversion relies on the assumption that normal hemoglobin is present. The presence of dyshemoglobins that cannot carry oxygen, but do not interfere with pulmonary oxygen diffusion, results in falsely elevated oxygen saturation values. MHb, sulfhemoglobin, and carboxyhemoglobin falsely elevate the calculated oxygen saturation.

Pulse oximetry. The pulse oximeter measures light absorbance at only 2 wavelengths: 660 nm and 940 nm.[36,37] The device measures the pulsatile and background light absorbance to create a pulse-added absorbance at each wavelength. This pulsatile absorbance corresponds to arteriolar contributions to absorbance above the tissue and venous background and primarily reflects arteriolar hemoglobin absorbance. Both oxy- and deoxyhemoglobin absorb light at 660 and 940 nm; it is the ratio of the absorbance at the 2 wavelengths from which a pulse oximeter determines oxygen saturation. The machines are calibrated from empiric data on healthy individuals who had simultaneous co-oximetry measurement of arterial oxygen saturation. A ratio of absorbance (660 nm/940 nm) of 0.43 corresponds to 100% oxygen saturation, and a ratio of 3.4 corresponds to 0% oxygen saturation. In the absence of a dyshemoglobin, an absorbance ratio of 1.0 corresponds to an oxygen saturation of approximately 85%.[36,37] MHb absorbs light almost equally at both 660 and 940 nm. In the presence of 100% methemoglobin, therefore, the absorbance ratio of light at 660 nm over 940 nm is about 1.0 and the pulse oximeter reading is approximately 85% oxygen saturation.[36,37] At lower levels of MHb, oxygen saturation measured by pulse oximetry is slightly lower. However, when MHb levels reach 30% to 35%, the light absorbance ratio reaches a plateau, and the pulse oximeter reading becomes stable in the 82% to 86% range independent of actual MHb levels. Only the presence of deoxyhemoglobin can lower the pulse oximeter reading below this range. The pulse oximeter detects significant levels of MHb as mild to moderate oxygen desaturation; unfortunately, it cannot be used to determine the actual percentage of MHb in the blood.

Co-oximetry

Co-oximetry is an accurate method of measuring MHb. A co-oximeter is also a simplified spectrophotometer, but unlike a pulse oximeter, it measures light absorbance at 4 different wavelengths. These wavelengths correspond to specific absorbance characteristics of deoxyhemoglobin, oxyhemoglobin, carboxyhemoglobin, and hemoglobin.[38] A peak absorbance of light at 630 nm is used to characterize MHb. This machine also measures carboxyhemoglobin, oxyhemoglobin, and deoxyhemoglobin directly. In some newer models, blood pH, Po_2 and Pco_2, sulfhemoglobin, or cyanomethemoglobin may be measured. Sulfhemoglobin has a high absorbance peak at 614 nm, which overlaps to 630 nm and may be reported as methemoglobin on older machines. In the case of combined co-oximeters and blood gas analysis machines, oxygen saturations values reflect the contributions of all 4 types of hemoglobin and will be reliable. However, these machines are not universally available in clinical laboratories. Therefore, clinicians must be familiar with the type of machine used in their clinical laboratory to correctly interpret the result. Interpreting the results from a blood gas analyzer without co-oximetry may lead to misdiagnosis since the oxygen saturation will have been calculated and not measured.

Bedside tests. The primary diagnostic consideration in a patient with cyanosis is to differentiate deoxyhemoglobin from MHb. Blood containing high concentrations of MHb appears chocolate brown as opposed to the dark red/violet of deoxygenated blood. A simple bedside test is to place 1 or 2 drops of the patient's blood on white filter paper. The chocolate brown appearance of MHb does not change with time; deoxyhemoglobin appears dark red/violet initially but brightens after exposure to atmospheric oxygen. Gently blowing supplemental oxygen onto the filter paper hastens the reaction with deoxyhemoglobin but does not affect MHb.

Potassium cyanide test. The potassium cyanide test can distinguish between sulfhemoglobin and MHb. MHb reacts with cyanide to form cyanomethemoglobin. Cyanomethemoglobin is bright red, as opposed to the chocolate brown color of MHb. Sulfhemoglobin is similar in appearance to MHb. However, this dyshemoglobin is inert and does not bind cyanide.[39] After the addition of a few drops of potassium cyanide, MHb turns bright red, but sulfhemoglobin remains dark brown.[39] The potassium cyanide reagent added is known as Drabkin's reagent and may be found in most analytical chemistry laboratories.

CURRENT TREATMENT

Once recognized and confirmed, life-threatening methemoglobinemia must be treated rapidly. However, not all patients require antidotal therapy, and many do well with only supportive care. Furthermore, patients with chronic congenital methemoglobinemia, like the patient with cyanotic heart disease, may have adapted to the chronic cyanosis, such that very high levels of MHb are tolerated without any overt symptoms. Treatment of these patients and patients with acute MHb is summarized in the following text.

Toxin/dietary/idiopathic MHb

After an acute exposure to an oxidizing agent, the treatment action level is considered to be approximately 20% MHb in symptomatic patients and 30% in asymptomatic patients.[40] Patients who are symptomatic or have significant concurrent problems that compromise oxygen delivery (heart disease, lung disease, carbon monoxide poisoning, or anemia) should be treated at levels between 10% and 30%. Treatment of patients with ischemic heart disease or a history of cerebral vascular disease must be individualized. Because MHb levels are typically reported as a percentage, the symptomatology may vary depending on the total hemoglobin level. The treatment of choice for severe acute MHb is methylene blue. Methylene blue is provided as a 1% solution (10 mg/mL). The dose is 1 to 2 mg/kg (0.2 mL/kg of a 1% solution) infused intravenously over 3 to 5 minutes. The dose may be repeated at 1 mg/kg if MHb does not resolve within 30 minutes. Methylene blue should reduce MHb levels significantly in less than an hour.[41] Infants with methemoglobinemia resulting from diarrhea and acidosis may improve with aggressive hydration and bicarbonate to correct the acidosis. However, MHB levels greater than 20% should be treated with methylene blue.

A sometimes forgotten treatment measure is dextrose. The major source of NADH in the RBC is the catabolism of sugar through glycolysis. For endogenous reducing enzymes to be effective, glucose must be in adequate supply. Dextrose is also necessary to form NADPH via the hexose monophosphate shunt, which is necessary for methylene blue to be effective. Although there are no specific data with respect to MHb, we believe maintenance amounts of dextrose should be provided for normoglycemic patients and standard dextrose therapy should be administered to hypoglycemic patients.

Methylene blue: Complications of therapy

Complications of methylene blue treatment have been reported in 2 groups: patients with G6PD deficiency and small infants. Patients with G6PD deficiency may develop a Heinz body hemolytic anemia from methylene blue.[32,42] Paradoxically, methylene blue is actually an oxidant; the metabolic product leukomethylene blue is the reducing agent. Large doses of the drug (4 mg/kg) may result in proportionately higher levels of the oxidizing agent, methylene blue, rather than the reducing agent, leukomethylene blue.[32] Thus, methylene blue (1 to 2 mg/kg) may induce both hemolysis, and paradoxically, methemoglobinemia in patients with G6PD deficiency. The perinatal administration of higher doses of methylene blue (4 mg/kg) given amniotically has been reported to induce hemolysis and methemoglobinemia in non–G6PD-deficient infants.[43]

A second caution regarding methylene blue in G6PD deficiency is related to the efficacy of the drug in reducing MHb in these patients. G6PD is the first enzyme in the hexose monophosphate shunt, which is the sole source of NADPH in the RBC. Patients with G6PD deficiency may not produce sufficient NADPH to reduce methylene blue to leukomethylene blue; thus, methylene blue therapy may be ineffective.[32,42]

Given the increased risk with methylene blue and the potential ineffectiveness of the drug, the most effective treatment in severely G6PD-deficient patients with life-threatening methemoglobinemia may be exchange transfusion.[44] However, many patients have only a partial enzyme deficiency. Methylene blue may still lower MHb levels, and the resultant hemolysis may be mild. Therefore, methylene blue is still the first-line treatment in G6PD-deficient patients with life-threatening MHb, and exchange transfusion is reserved only for patients in whom methylene blue treatment is ineffective. We recommend starting with a lower dose of methylene blue (0.3 to 0.5 mg/kg) and titrating upward to further reduce MHb, if necessary. If the patient's condition worsens, methylene blue treatment is abandoned and exchange transfusion considered.

An additional caveat involves the patient with relapsing MHb, in which MHb levels decrease after methylene blue, but subsequently rise again to toxic levels. These patients may have had inadequate decontamination, or may have ingested an agent that produces MHb cyclically such as aniline, benzocaine, or dapsone. These agents are metabolized to reactive metabolites that oxidize hemoglobin. The redox reaction to form MHb

regenerates the parent compound, which can then be remetabolized to the oxidative metabolite.[32] Attention should be paid to adequate decontamination with charcoal. The use of continuous infusions of methylene blue, cytochrome P-450 inhibitors, and exchange transfusions have all been used in the management of such patients, but cannot be considered standard therapy.[17,44-46]

ALTERNATIVE TREATMENTS

Several investigators have recently suggested alternatives to methylene blue therapy. Given that MHb can be caused and reversed by various agents, multiple potential antidotes exist and can be tailored to specific drugs. Two potential mechanisms of action exist: altering the metabolism of the toxin or directly reducing MHb.

Antidotes that alter metabolism

Coleman et al[47] have studied the use of cytochrome P-450 inhibitors to prevent the formation of reactive metabolites from agents such as dapsone. Dapsone is converted by the cytochrome P-450 system to a highly reactive hydroxylamine intermediate, This metabolite oxidizes hemoglobin to MHb and in the process regenerates dapsone, which cycles to the hydroxylamine intermediate again, subsequently inducing further MHb. The cyclic nature of dapsone-induced methemoglobinemia may account for the frequently cited "rebound" MHb caused by this agent.[17,45,46] There are multiple reports of patients with dapsone poisoning successfully treated with methylene blue who subsequently redevelop methemoglobinemia. Several treatment modalities have been suggested. Berlin et al[46] described a patient with dapsone overdose and recurrent MHb treated with a continuous infusion of methylene blue.[46] Others have recommended repetitive charcoal to interrupt the suspected enterohepatic circulation of dapsone.[45] Tingle et al[48] have demonstrated that P-450 inhibitors such as cimetidine and ketoconazole block the formation of the hydroxylamine intermediate from dapsone and sulfasalazine in vitro. Both agents produce MHb via reactive metabolites. A controlled study in patients receiving long-term dapsone treatment for dermatitis herpetiformis demonstrated significantly lower levels of MHb in patients receiving cimetidine than in control patients.[47] However, the efficacy of cimetidine in dapsone overdose has not been reported.

Direct reducing agents

Another potential alternative to methylene blue is *N*-acetylcysteine (NAC). NAC is currently used as the antidote for acetaminophen poisoning. Cysteine is a component of glutathione, and contains a reduced sulfhydryl group. NAC, unlike glutathione, is permeable to cell membranes. In the context of acetaminophen poisoning, NAC is believed to act both as a precursor to glutathione synthesis and as an electron donor, directly reducing the reactive metabolite or modifying the inflammation induced by oxidation.[49] In an in vitro study, we demonstrated that NAC significantly increases the rate of MHb reduction compared with controls.[49] We have also shown that NAC is effective during G6PD inhibition in vitro.[50] One previous in vivo study also demonstrated that NAC increased the rate of reduction of MHb induced by acetaminophen poisoning in cats.[51] Because glutathione synthesis is not dependent on NADPH, it is possible that NAC may be a more effective and safe antidote for MHb in patients with G6PD deficiency than methylene blue. However, these studies are preliminary, and further study is necessary before NAC can be recommended as an alternative MHb antidote.

In summary, the most common etiology of MHb is exposure to an oxidizing agent. These drugs may have additional toxicity that is independent of their MHB-forming property. Most standard tests of oxygenation, such as arterial blood gas analysis and pulse oximetry, either do not detect MHb or underestimate its severity. Co-oximetry measurement is the most accurate test for MHb, but some rare diseases, such as sulfhemoglobin, may interfere with this test. Prompt recognition of the disease is paramount in providing adequate therapy. Treatment of this disorder may be lifesaving but is complicated in patients with G6PD deficiency and young infants.

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