# Eating vegetables is not always a good advice. A case report and literature review of acquired methemoglobinemia

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## Abstract

Methemoglobinemia (MET) is a life-threatening condition resulting from the development of methemoglobin (MetHb), which binds oxygen irreversibly, causing refractory hypoxia and so-called "functional anemia". MET can be caused by hereditary or acquired processes. Acquired forms are the most common. Symptoms correlate with the MetHb level and range from cyanosis and dyspnea to dysrhythmias, metabolic acidosis, coma, and cardiac arrest. MetHb levels above 70% are fatal. Methylene blue (MB) is the specific antidote. In all cases, supportive treatment, including intravenous hydration, glucose correction, and oxygen supplementation, must be started immediately. Exchange transfusion has been used successfully to treat MET and may be appropriate in patients for whom MB is ineffective. We report the case of a 54-year-old woman who presented to our emergency department for the acute and sudden development of chest pain, shortness of breath, and severe cyanosis after drinking a significant amount of boiled courgette water. Arterial blood gas analysis revealed a MetHb level of 26%. She was treated immediately with MB, oxygen supplementation, and hydration with normalization of her MetHb in 12 hours. Our recommendation is to always investigate MET in patients with unexplained cyanosis and refractory hypoxia.

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### *Highlights*

- *Acquired methemoglobinemia (MET) is an acute life-threatening condition that can occur after exposure to hemoglobin-oxidizing agents.*
- *Drugs, nitrates-nitrites present in well water, vegetables, coloring compounds, cleaning solutions, and recreational drugs (poppers, cocaine adulterans) can cause MET.*
- *The diagnosis should be suspected in case of unexplained cyanosis and refractory hypoxia.*
- *Symptoms correlate with the methemoglobin level.*
- *Severe MET can lead to cardiovascular collapse and death.*
- *Methylene blue (MB) is the antidote to MET reserved for patients with significantly elevated methemoglobin levels. Caution should be taken in using MB, especially in case of hemolysis or when a history of G6PD deficiency is obscure.*
- *Exchange transfusion is appropriate and successful in patients for whom MB is ineffective.*

## Case Report

A 54-year-old woman presented to our emergency department complaining of sudden severe chest pain and shortness of breath. Her past medical history was unremarkable. She denied any allergies or drug assumptions. Physical examination revealed symmetrical air entry without wheezing or crackles, but severe cyanosis of the lips and extremities, most notably on her fingernails. Cardiovascular and abdominal evaluations were normal. Blood pressure was 110/80 mmHg, heart rate was 85 beats/min, body temperature was 36°C, respiratory rate was 18 breaths/min, and

oxygen saturation was 83% on room air. The electrocardiogram displayed a sinus rhythm with a normal P-R interval, QRS complex, and QTc. Lung ultrasound showed a normal A pattern. Echocardiography ruled out cardiac injury and pericardial effusion. The patient was immediately placed on 15 Lt/min of oxygen through a non-rebreather reservoir bag oxygen mask, but her oxygen saturation did not improve. Arterial blood gas (ABG) analysis with oxygen revealed a significantly elevated methemoglobin (MetHb) level of 26% (normal value 0-1.5) with a pH of 7.39, $pCO_2$ of 46.6 mmHg, $pO_2$ of 80 mmHg, $SpO_2$ 95%, and a $PaO_2/FiO_2$ ratio of 80 mmHg. A diagnosis of methemoglobinemia (MET) was made, and an intravenous injection of methylene blue (MB) 1% at 1 mg/kg over 5 minutes was initiated. Thirty minutes later, ABG analysis showed a MetHb level of 7.8%. The patient developed bradycardia with a heart rate of 38 beats per minute and was treated with atropine with a rapid increase in her heart rate. ABG analyses were done every 3 hours until a normal level of MetHb was reached (0.3% after 12 hours), with a complete resolution of cyanosis and chest pain. Supplemental oxygen was therefore discontinued. All the laboratory tests, including high-sensitivity cardiac troponin I, resulted in the normal range.

The patient claimed to have drunk a significant amount of water derived from cooked courgettes that she had prepared at home approximately two hours before the onset of her symptoms. A review of the online literature revealed that courgettes are a potential cause of MET having a high nitrate content.[1] After a 24-hour observation period in our emergency department observation unit, in the absence of clinical symptoms and with normal ECG monitoring, the patient was discharged home with a full recovery.

## Discussion

MET is an acute life-threatening condition that requires prompt diagnosis and treatment. This rare condition is characterized by the conversion of functional ferrous iron ($Fe^{2+}$) in hemoglobin (Hb) to ferric iron ($Fe^{3+}$), resulting in the formation of MetHb.[2,3] MetHb binds oxygen irreversibly and shifts the oxygen dissociation curve of Hb to the left, causing tissue hypoxia and a state of "functional anemia" without a decrease in Hb concentration.[4,5] Under physiological conditions, MetHb reduction is accomplished mainly by red cell NADH-cytochrome b5 reductase (NADH-MetHb reductase) so efficiently that there are insignificant amounts of MetHb in the circulating blood.[3]

### Hereditary and acquired methemoglobinemia

MET can result from either congenital or acquired mechanisms.[6] Inherited forms are due to autosomal recessive variants in the CYB5R3 gene or to autosomal dominant variants in the globin genes, collectively known as HbM disease.[3,7-9] Based on the severity of the enzyme deficiency, this condition can be classified into two different subtypes: type I, due to missense variants that cause production of an unstable enzyme purely in the red blood cells, associated with MetHb levels above 25%, cyanosis, headache, fatigue, and dyspnea; and type II, associated with high morbidity and mortality because of severe neurologic manifestations caused by variants that lead to low expression or low activity of the enzyme in all the tissues and the lipid metabolism.[7]

Acquired forms are the most common and can occur after the exposure to hemoglobin-oxidizing agents, such as drugs (*e.g.*, dapsone,[10-12] antimalarials, topical benzocaine,[13,14] lidocaine[15] nitrates, nitrites, rasburicase, and alanine dyes), and nitrates-nitrites present in well water[16,17] or vegetables (e.g., courgette, spinach, beets, and green beans),[1,18,19] or coloring compounds,[20] and cleaning solutions.[21] A well-studied exposure to a chemical that can cause MET in infants is nitrate (above 10 mg/L) in well water. Infants have a higher risk of developing MET, since they drink more water per body weight compared to children and adults, have lower NADH cyb5r reductase activity that converts MetHb to hemoglobin, and have a higher percentage of fetal hemoglobin, which is easier to convert to methemoglobin.[22] Acquired MET should be also suspected in infants presenting with acute severe diarrhea, sepsis, and cyanosis disproportionate to their clinical status.[23]

Some recreational drugs are also associated with acquired MET with very high levels of MetHb (>90%) and fatalities, including amyl nitrate (poppers),[24-26] nitrous oxide (laughing gas), and adulterants used in cocaine (local anesthetics, phenacetin).[27,28]

Sepsis-induced MET must be taken into consideration in patients with septic shock and unexplained acute hemolysis, since it may be the only early sign of Clostridium perfringens septicemia, and it should be promptly treated with antibiotics, control of the source of infection, oxygen supplementation, and massive blood transfusion.[29]

In addition but more rare, severe ascorbic deficiency can cause MET in patients with different hemoglobinopathies, including HbE β thalassemia,[30] and sickle-cell anemia, particularly when splenic function is defective.

### Diagnosis and clinical features of acquired methemoglobinemia

MET is a clinical diagnosis that should be suspected when an adult or child presents with unexplained cyanosis or hypoxia that does not resolve with supplemental oxygen and the likely presence of chocolate-colored blood. "Refractory hypoxia" is a diagnostic clue for MET. ABG is used to confirm the diagnosis by speciating hemoglobin and calculating the proportion and concentration of MetHb. Venous blood gas and pulse oximetry are not helpful,[31] and there is often a discrepancy between the oxygen saturation determined by ABG and the oxygen saturation measured by pulse oximetry.[5] After exposure to an oxidizing substance that induces MetHb formation, the onset of symptoms is typically abrupt. The symptoms correlate with the MetHb level[4,32] and range from cyanosis (MetHb < 10%), dyspnea, headache, fatigue, anxiety, and irritability (MetHb 20%), to dysrhythmias, metabolic acidosis, and coma (MetHb > 30%), which can be fatal if left untreated (33-36). Death occurs when MetHb levels rise above 70%.

### Treatment of acquired methemoglobinemia

When possible, the agent causing MetHb should be stopped or removed, and supportive treatment, including intravenous hydration, glucose correction, and oxygen supplementation, should be started immediately. High-flow oxygen delivered by non-rebreather masks increases oxygen delivery to tissues and enhances the natural degradation of MetHb.[5] If necessary, cardiopulmonary support with mechanical ventilation and pressure support are indicated. No studies have examined the treatment of MET in the context of cardiac arrest.[37]

### Methylene blue

The specific antidote of MET is methylene blue (MB), which is a serotonergic drug that is converted into leucomethylene blue and allows for the reduction of the heme group from MetHb to Hb via the NADPH-dependent HMP shunt.[32,38] There are no randomized trials evaluating methylene blue for the treatment of MET, but

observational data consistently demonstrate resolution or improvement after MB administration.[37] MB usually works rapidly and effectively. In cases of acquired MET, treatment with MB should occur when MetHb exceeds 20-30%, or at lower levels, if the patient is symptomatic. Treatment decisions should be made on clinical presentation and not withheld for confirmational laboratory values.[5] The usual starting dose is 1-2 mg/kg (0.2 mL/kg of a 1% solution) infused intravenously over 5 min.[32] The dose can be repeated at 1 mg/kg if MetHb does not significantly decrease within 30–60 min or the patient remains symptomatic. MB should reduce MetHb levels significantly in less than an hour. Benign side effects include green or blue discoloration of urine.

Patients with continued production of MetHb from long-acting oxidant stress such as after dapsone ingestion may require repeat dosing every 6-8 hr for up to 2-3 days, or MB may be given as a continuous IV infusion of 0.10-0.25 mg/kg/hr.[6]

Caution should be used in patients receiving selective serotonin reuptake inhibitors and other serotonergic antidepressants since MB, acting as a potent monoamine oxidase inhibitor (MAO-A), may precipitate serotonin syndrome.[39] MB should be used cautiously in pregnant women because of potential teratogenicity and intestinal atresia, and in patients with renal failure or in anesthetized patients since it may inhibit guanylate cyclase, decreasing nitric oxide-mediated vasodilatation, and leading to systemic and pulmonary hypertension.[6] In pregnant patients, the benefit-risk ratio must be always considered; despite potential (not evidenced) risks, MB should be evaluated with MetHb > 30% or high MetHb levels associated with lactic acidosis or hemodynamic disorders.

Since the reduction of the heme group from MetHb to Hb depends on NADPH, which in turn is generated by glucose-6-phosphate dehydrogenase (G6PD), MB is ineffective in individuals deficient in G6PD (favism) and can precipitate hemolysis.[40,41] In these cases, exchange transfusion and hyperbaric oxygen may be useful.[37]

## Ascorbic acid

If MB is not available or in patients with G6PD deficiency, high-dose ascorbic acid (vitamin C), up to 10 g/dose intravenously, has been used to treat MET.[42,43] However, most published case reports demonstrate its use in conjunction with other treatment modalities. The effect is slow and often requires multiple doses over several hours to have any significant effect.[43,45] Dosing is not standardized, ranging in adults from 0.5 g every 12 hr x 16 doses, 1 g every 12 hr x 14 doses, 1.5-2 g IV x 3-4 infusions, 5 g every 6 hr x 6 doses, or even 10 g x one dose, while doses in children have ranged from 0.5 g every 12 hr x 16 doses and 1 g every 4 hr x 8 doses.[6] High-dose ascorbic acid administration is associated with increased urinary excretion of oxalate. In the presence of renal insufficiency, high-dose ascorbic acid may be predisposed to renal failure due to hyperoxaluria.[46] Ascorbic acid is not likely to be effective in resuscitation situations.[37]

## N-acetylcysteine

N-acetylcysteine has been suggested for the treatment of MET in patients with G6PD deficiency and acetaminophen-induced MET, even if its mechanism of action is still unclear. N-acetylcysteine acts as a cofactor to enhance reduction and increase intracellular glutathione in vitro, however in a double-blind crossover human volunteer study, it was ineffective.[47]

## Other

If MB administration is ineffective after the second dose, G6PD and NADPH-MetHb reductase deficiency should be considered as reasons for refractoriness to treatment. Refractory MET can be treated with blood transfusions, red blood cell exchange, hemodialysis, and hyperbaric oxygen.[6,37] Recently, Williams *et al.* reported a rare case of secondary MET in a patient with hemoglobin Evans who was successfully treated with red blood cell exchange.48 Hyperbaric oxygen therapy can be used as monotherapy and in conjunction with other therapies. Since the reduction of MetHb concentrations can be delayed up to several hours,[49-51] its use is impractical in the setting of cardiopulmonary collapse or cardiac arrest.

## Conclusions

Our case highlights the importance for emergency clinicians to maintain a high degree of suspicion of MET in all patients, both adults and children, who present with unexplained cyanosis and hypoxia that does not resolve with supplemental oxygenation. Suspicion of MET must be confirmed by ABG analysis. If promptly recognized and treated, MET rapidly resolves with no significant acute sequelae, as in our patient. For this reason, a complete medical history that includes medications, drugs, and foods, especially homemade vegetable soups, is crucial in identifying and removing the trigger to restore normal tissue oxygenation and metabolism, avoid long-term consequences, and reduce the risk of subsequent episodes. Further research is needed to fully understand the underlying mechanisms of acquired MET and to develop guidelines for safe nitrate-rich food consumption.

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