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# Red Blood Cell Exchange for a Patient with Dapsone-Induced Methemoglobinemia, Severe Methylene Blue Allergy, and Refractoriness to Intravenous Vitamin C Therapy

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## Abstract

**The most common cause of acquired methemoglobinemia is dapsone toxicity. There are no definitive guidelines for the management of treatment-refractory methemoglobinemia or when methylene blue therapy is contraindicated. We present a case of recurrent acquired methemoglobinemia that was successfully treated with automated red blood cell exchange. Our patient was a female patient in her twenties with dapsone-induced methemoglobinemia complicated by hemolytic anemia secondary to high-dose intravenous vitamin C therapy. She first presented to the emergency department with a two-day history of progressive dyspnea, chest pain, cyanosis of lips and fingers, nausea, and headache. Given her prior history of severe methylene blue allergy, the patient was initially treated with intravenous vitamin C and simple transfusions. Her methemoglobin levels increased, and her symptoms remained. An automated red blood cell exchange resulted in a 42% relative decrease in methemoglobin level (from a level of 24.1% to 14%) and significant symptomatic improvement within hours of the exchange. While current therapeutic apheresis guidelines do not recommend red blood exchange for methemoglobinemia due to scarce evidence, this case report illustrates the potential role of red blood cell exchange in the management of acquired methemoglobinemia in a patient with severe methylene blue allergy for whom intravenous vitamin C therapy failed.**

**Keywords:** ***Methemoglobinemia, Red blood cell exchange; Dapsone***

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## 1. Introduction

Methemoglobinemia (MetHb) is an altered state of hemoglobin resulting from the oxygenation of iron from the ferrous state to the ferric state. This change yields a MetHb that is incapable of oxygen transport and shifts the oxygen dissociation curve left [1,2]. A small amount of methemoglobin (<1%) is generally present in the blood; however, increased levels beyond this threshold are often considered to be MetHb. The etiology can be either congenital or acquired. Congenital causes result from deficiencies in either nicotinamide adenine dinucleotide (NADH) cytochrome b5 reductase or the presence of abnormal hemoglobin that is incapable of being reduced [1]. The most common cause of acquired MetHb is dapsone [1,2].

Clinical manifestations of MetHb vary depending on the etiology. Congenital forms are typically asymptomatic during development, while acquired types present symptomatically due to exposure to direct or indirect oxidizing agents [1]. Patients with MetHb levels <30% usually present asymptomatically. When the level reaches 30%-50%, patients often begin to develop dyspnea, dizziness, confusion, chest pain, palpitations, headaches, and fatigue. Signs of tachypnea, metabolic acidosis, dysrhythmias, seizures, delirium, and coma appear when levels reach 50%-70%. MetHb levels >70% can lead to severe coma and death [2]. First-line therapy for MetHb is generally intravenous methylene blue (1-2 mg/kg) [2].

## 2. Case Report

Our patient was a female in her twenties with a history of recurrent MetHb associated with dapsone use and severe methylene blue allergy complicated by hemolytic anemia. The patient had multiple prior hospitalizations for acquired methemoglobinemia of unknown origin which had been treated with supplemental oxygen, vitamin C, and simple transfusions given her prior anaphylactic reaction to methylene blue. During prior hospitalizations, suspected culprits of MetHb included atovaquone, hydroxychloroquine, mycophenolate, ciprofloxacin, and dapsone.

Her most recent episodes were complicated by persistent DAT-negative hemolytic anemia, suspected to be due to high-dose vitamin C therapy. She had undergone extensive evaluation for causes of her methemoglobinemia, including negative quantitative G6PD, Heinz body stain, hereditary hemolytic anemia panel sequencing (CYB5R3, G6PD, and PKLR), cytochrome b5 reductase enzyme activity, hemoglobin M, benzocaine, and azo screenings. Her well water had tested negative for nitrites/nitrates.

She presented to the outside hospital's emergency department with several days of shortness of breath, chest pain, fatigue, and dizziness. Day 1 is defined as the patient's day of admission to the outside hospital. She had been taking 1000 mg of vitamin C every day following her last MetHb episode four weeks prior to the presentation. One week prior to the onset of symptoms, she began mycophenolate (500 mg BID) for urticarial vasculitis refractory to prednisone. Mycophenolate was discontinued following admission. The patient had been taking dapsone for the same indication, but she reported discontinuing it three months prior to the presentation given concern for dapsone-induced MetHb. However, dapsone serum levels continued to be elevated to 13 mcg/mL at the time of admission. Other laboratory studies included a venous blood gas with pH 7.36, pCO2 40 mmHg, pO2 53 mmHg, SpO2 88%, Hb 13.0 g/dL, reticulocyte count 1.9%, bilirubin 1.0 mg/dL, folate 11.7 ng/mL, LDH 150 U/L, and haptoglobin 84 mg/dL. A peripheral blood smear was unremarkable. MetHb level was elevated to 15.7% upon presentation and continued to rise to 29.9% on the fifth day of hospitalization despite initial management with 4 units of RBCs

via simple transfusion and non-invasive positive pressure ventilation (NPPV). The patient was initially started on 2 g of IV vitamin C q6h upon admission that was up-titrated to 6g IV q6h by the 5th day of hospitalization. Given worsening MetHb, she was transferred to the University of Wisconsin Hematology Service on day 5 of hospitalization. On arrival, she endorsed pleuritic chest pain, dyspnea, and headache. Physical examination was notable for increased respiratory effort and bluish discoloration on her lips and fingernails. Vitals were stable except SpO2 86% on 15 L non-rebreather. Arterial blood gas showed pH 7.53, pCO2 25 mmHg, pO2 305 mmHg, HCO3 21.3 mmol/L, and O2 saturation of 76.6%. MetHb was elevated to 22.9%. Her management overnight included transfusion with 1 unit of RBCs and IV vitamin C (8g q6h).

On day 6, an automated red blood cell exchange was performed via centrifugal apheresis with a target hematocrit of 39% and a target fraction of cells remaining of 30%. She tolerated the procedure well, and her SpO2 improved to 91% within hours. Her pre-procedure MetHb level was 24.10%. Her post-procedure MetHb level was 14% for a relative decrease of 42% (10.1/24.1).

The next morning, she reported significant improvement in chest pain, headache, abdominal pain, and shortness of breath. Her clinical course continued to improve with IV vitamin C therapy (8 g Q6H) and the patient was intermittently using 15 liters of oxygen for comfort. The patient was completely weaned off of oxygen and transitioned to room air on day 10 of hospitalization and her MetHb level normalized to 1.1% on day 11. She was subsequently discharged home on day 12 on oral Vitamin C therapy (2 g daily) with complete resolution of her chest pain, dyspnea, and cyanosis and normalization of her oxygen saturation off any supplemental oxygen. The serial MetHb levels during her hospitalization are listed in TABLE 1.

TABLE 1. **MetHb levels during hospitalization.**

| Day of Hospitalization | MetHb level |
|---|---|
| 1 | 15.70% |
| 2 | >29.9% |
| 3 | 27.20% |
| 4 | >29.9% |
| 5 | >29.9% |
| 6 ** | 22.90% |
| 6 | 25.20% |
| 6 | 24.10% |
| 6 † | 14% |
| 7 | 15.20% |
| 7 | 11.60% |
| 8 | 6.80% |
| 8 | 4.40% |
| 9 | 3.20% |
| 10 | 2.50% |
| 11 | 1.10% |
| 12 | 0.80% |

** patient transferred to UW Hospital and the MetHb levels reflect the value at our facility (reference MetHb range at UW 0-1.1%; reference at outside facility <1.9%).
† MetHb level immediately following RBC exchange.

## 3. Discussion

Acquired MetHb is most often secondary to exposure to medications and toxins specifically through direct and indirect oxidation by organic nitrates and amino- or nitro-derivatives of benzene (benzocaine, lidocaine, dapsone) [2]. Timely diagnosis and treatment of patients with acquired MetHb are paramount to recovery and mitigating complications.

The typical first-line therapy, methylene blue, was not an option for this patient given her prior anaphylactic reaction. In such cases, alternative therapies may be useful in the management of treatment-refractory MetHb or MetHb associated with G6PD deficiency when methylene blue is relatively contraindicated. RBC exchange usually replaces about 70% of the patient's RBCs with donor RBCs [3,4].

Some case reports indicate the potential for successful management of treatment-refractory acquired MetHb with RBC exchange [3,5-9]. One case reported that RBC exchange reduced a patient's MetHb level from 67% to 21% within six hours and appeared to resolve the patient's altered mental status and cyanosis [9]. Furthermore, a case series of five patients indicated the potential of RBC exchange to be an effective tool for the treatment of MetHb refractory to methylene blue with no apparent adverse effects [10]. The most common indication for RBC exchange was an inadequate response to methylene blue [10].

Interestingly, our patient had several previous episodes of recurrent MetHb that required hospitalization. There were multiple potential culprits discussed above, but it was ultimately felt that dapsone was the driver of her current presentation. Although the patient reported having discontinued dapsone 3 months prior, her dapsone level continued to be elevated following admission. During her diagnostic workup, it became clear that the patient had been surreptitiously taking dapsone for urticarial vasculitis and continued to fill her prescriptions from an out-of-network physician.

Following oral administration, dapsone generally reaches maximum plasma concentrations in 4 hrs with absorption and elimination half-lives of 1.1 and 30 hrs respectively. There are individual genetic differences in terms of the rate of drug acetylation, which may affect the half-life and clearance of the medication. However, the mono-acetylated dapsone to dapsone ratio was normal (>0.35), which refuted the possibility of a slow acetylator phenotype in this patient [11]. While a few cases have been reported of automated RBC exchange for recurrent MetHb when first-line therapy is contraindicated, to our knowledge, there have been no controlled studies evaluating the utility of this approach. We hasten to add that current guidelines do not recommend RBC exchange for MetHb [1,12].

## 4. Conclusion

We share our experience with using RBC exchange for a patient with recurrent dapsone-induced methemoglobinemia in the context of severe methylene blue allergy. Future controlled trials are needed to establish the definitive utility of RBC exchange in this patient population.

## 5. Conflicts of Interest

The authors report no conflicts of interest.

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