

# Eight Blue Babies

Lynda Knobeloch, PhD; Mary Proctor, PhD

## ABSTRACT

Methemoglobinemia is a serious medical condition that affects hundreds of infants in the United States each year. The condition involves the oxidation of red cell hemoglobin to a state that is unable to transport oxygen. Affected infants appear cyanotic and may have altered mental status. The condition is readily reversible if recognized and treated appropriately. The Wisconsin Division of Public Health investigates all cases of infant methemoglobinemia in an attempt to determine their cause. Between January 1990 and September 1999, 8 infants were diagnosed with this condition. Review of their hospitalization records found that 3 of these cases involved infants whose formula was prepared with water from nitrate-contaminated wells. Risk factors identified in the remaining cases included use of folk remedies, misuse of over-the-counter analgesics, and an inherited enzyme deficiency. Causes were not identified for 2 of the cases. All of the affected infants recovered.

## INTRODUCTION

Methemoglobinemia is an uncommon medical condition that requires rapid diagnosis and treatment. It occurs when the iron molecule in red blood cell hemoglobin is oxidized from the ferrous ( $\text{Fe}^{2+}$ ) to the ferric ( $\text{Fe}^{3+}$ ) state. Because  $\text{Fe}^{3+}$  cannot transport oxygen, elevated methemoglobin levels reduce the oxygen carrying capacity of the blood and can lead to tissue hypoxia. In healthy infants and adults, methemoglobin levels typically range between 1% and 3%. When levels exceed 10%, patients develop a characteristic blue-gray or lavender skin color. Other presenting symptoms may include a rapid heart and respiratory rate, headaches, dizziness, and syncope.

Authors are with the Wisconsin Department of Health and Family Services, Division of Public Health. Doctor Knobeloch is a Senior Toxicologist; Dr. Proctor is the Chief of Communicable Disease, Epidemiology Section. Address reprint requests to: Lynda Knobeloch, PhD, Division of Public Health, DHFS, 1 W Wilson St, Madison, WI 53703-3044.

Affected infants are often described as irritable or lethargic. Infants who are suffering from gastrointestinal infections are particularly vulnerable to the condition.

Public health experts typically associate infant methemoglobinemia with nitrate-contaminated water. The condition is sometimes referred to as "blue-baby syndrome" since the skin of affected infants becomes blue-gray or lavender in color. This association was first described by an Iowa City physician in 1945.<sup>1</sup> However, the condition has also been linked to enzyme deficiencies, metabolic disorders, persistence of fetal hemoglobin after birth, and exposure to a wide variety of environmental and therapeutic agents.<sup>2-8</sup> Regulation of nitrate levels in public water supplies and public education efforts have reduced the incidence of infant methemoglobinemia to a level where most pediatricians and public health nurses have never seen a case. However, the condition continues to occur and can quickly lead to death if it is not recognized and treated appropriately. This article summarizes clinical, demographic, and environmental findings from 8 cases of infant methemoglobinemia that occurred in Wisconsin between January 1990 and September 1999.

## METHODS

Six of these cases were identified by searching electronic hospital discharge records for the period between January 1, 1990 and June 1, 1999. Two cases were reported to state health officials by local or state agencies. Patient records were reviewed if the following conditions were met: 1) the patient was less than 1 year of age on his/her admission date, 2) any of the diagnoses listed were ICD code 289.7 (Congenital NADH-methemoglobin-reductase deficiency; hemoglobin M disease; and methemoglobinemia: not otherwise specified, acquired, hereditary, toxic, Stokvis' disease, and sulfhemoglobinemia).

### Case 1

April 1991, Milwaukee County — A 2-month-old,

10 lb 2oz female Hmong infant was transported by ambulance to a regional medical center. On arrival, she was described as limp and gray. She was breathing rapidly, had a heart rate of 215 beats per minute, and was moderately to severely dehydrated. Her parents reported a 1-day history of vomiting and diarrhea. Blood tests revealed metabolic acidosis and a methemoglobin level of 15.2% (normal < 3%). This infant was treated with 100% oxygen by mask, oral fluids, 2 doses of bicarbonate and an intravenous infusion of cefotaxime. Over a 6-hour period, her methemoglobin level dropped to 7.2%. She was discharged 72 hours after admission, at which time her methemoglobin level was 1.5%.

Several hours before being brought to the hospital, this infant had been given a traditional Thai remedy that her family used to treat gastric upsets. Although the ingredients in this medication were not known, it was considered a possible cause of her methemoglobinemia. The family lived in Milwaukee and presumably used municipal water to prepare this infant's soy-based formula.

#### Case 2

June 1991, Rock County — A 7-week-old, 8lb 10oz male infant was taken by his mother to a local emergency room. On admission, he appeared "dusky and wasted" and had a 2-week history of vomiting after feedings. He had recently been started on a soy-based formula due to a suspected milk intolerance. On physical examination, he was severely dehydrated and tachypneic. Pulse oximetry indicated an oxygen saturation of 66%-67%. He was air lifted to a regional medical center where he was found to have a methemoglobin concentration of 33%. His treatment consisted of intravenous infusions of methylene blue, fluids, and antibiotics. The infant was discharged 72 hours after admission.

The cause of methemoglobinemia in this case was never determined. Tests for methemoglobin reductase deficiencies, hemoglobin M alterations, and infections were negative. His formula had been diluted with water from a municipal supply. Although this water supply was not tested at the time of his illness, previous sampling indicated that nitrate-nitrogen levels averaged around 7 mg/L, which is below the federal drinking water standard of 10 mg/L. Possible exposure to another water supply, nitrate/nitrite-containing food, or another methemoglobin-inducing substance could not be ruled out.

#### Case 3

February 1992, Wood County — A 10-day-old, 7lb 15oz male infant was referred to a regional neonatal

intensive care nursery with a diagnosis of persistent methemoglobinemia. Four days earlier his mother had taken him to a local emergency room after she noticed that his skin was "blue" in color. A blood test indicated that he had a methemoglobin level of 29.4% and the infant was treated with a single dose of methylene blue. He was discharged the next morning, at which time the level was 1.3%. One day later, his methemoglobin level had risen to 11.0%. By evening, the level had increased to 29% and the infant was treated with a second dose of methylene blue and sent home. When his methemoglobin continued to be elevated (8.7%) the following morning, he was referred to a regional medical center for further evaluation. On admission that afternoon, the methemoglobin level was 3.5%. The morning after admission, the level was within normal range at 0.8%.

This baby had been doing well at home and was breastfed, but had been given one supplement of formula mixed with water from the family's rural well on the day that he was first noted to be dusky. Analysis of the well water indicated an acceptable nitrate-nitrogen concentration of 3.1 mg/L. On further discussion with the family, this infant's mother mentioned that she had used an over-the-counter ointment to treat her son's diaper rash. The ointment was formulated for adult use and contained benzocaine and resorcinol. Further evaluation confirmed that this infant's bouts of methemoglobinemia were caused by his exposure to these drugs.

#### Case 4

June 1992, Eau Claire County<sup>9</sup> — A 6-week-old, 6lb 10oz female infant was admitted to a hospital for treatment of dehydration. She had been doing well until her fifth week of life when she developed loose stools and began to vomit after feedings. Admission diagnoses included vomiting, failure to thrive, and dehydration secondary to vomiting. She was rehydrated and discharged the following day, but was readmitted 6 days later, at which time she was described as "wasted and dusky." Due to her cyanotic appearance, a methemoglobin level was ordered and found to be elevated at 21.4%. This infant was treated with oxygen via nasal cannula and oral fluids. During her hospitalization, she tolerated her formula without vomiting, and her methemoglobin level returned to normal. Laboratory tests failed to reveal any underlying genetic or metabolic disorders.

This family's water was obtained from a 28-foot deep private well. Because the well water had a history of nitrate contamination, the home was equipped

with a reverse osmosis (R/O) unit that supplied water to a separate faucet at the kitchen sink. Water samples collected from the well and the R/O unit during the infant's initial hospitalization contained nitrate-nitrogen concentrations of 58 and 9.9 mg/L, respectively. Additional testing indicated that the water was naturally corrosive (pH of 6.3, alkalinity of 16 mg/L) and free of coliform bacteria. A first draw water sample from the kitchen faucet contained a copper level of 7.8 mg/L, which is 6 times higher than the federal action level of 1.3 mg/L. Water samples collected from the R/O unit several weeks after the infant's illness contained nitrate-nitrogen concentrations of 12.5 mg/L and 23.5 mg/L, indicating that levels varied depending on the frequency of use. Investigators concluded that this infant's vomiting, diarrhea and secondary dehydration and weight loss were induced by her exposure to copper-contaminated water that was used to dilute her formula. Her methemoglobinemia was apparently due to her exposure to nitrate.

#### Case 5

July 1992, Racine County — A 4-week-old, 8lb 9oz black male infant was admitted to a hospital with a 3-day history of gastroenteritis and dehydration. The following day, he developed a fever of 100.8°F. An arterial blood gas revealed a pH of 7.22, pO<sub>2</sub> of 102, an oxygen saturation of 72% and a methemoglobin level of 28%. After being stabilized with bicarbonate and ascorbic acid, this infant was transferred to a regional medical center. On arrival there he was described as lethargic with dry lips and cool, cyanotic extremities. His heart rate was elevated at 170 beats per minute. He was immediately started on 100% oxygen, and treated with ampicillin and cefotaxime. Blood tests revealed a methemoglobin level of 25.6% and glucose-6-phosphate dehydrogenase deficiency (G-6-PD deficiency).

Because of his G-6-PD deficiency, this infant was not a candidate for methylene blue therapy and was instead given an exchange transfusion with 240 cc of blood and started on ascorbic acid. After the transfusion, his extremities were better perfused and his tachycardia had resolved with a heart rate of 120. He was discharged 8 days after admission, at which time his mother was instructed to give him 200 mg ascorbic acid 3 times a day.

This infant's methemoglobinemia was attributed to the stress of diarrheal disease, in conjunction with an immature methemoglobin reductase system and a hereditary G-6-PD deficiency. A test for hemoglobin M was negative. Urine, blood, and spinal fluid cul-

tures were negative, however he was treated for *Candida albicans* diaper rash and oral thrush. In addition, a stool sample yielded a pure culture of yeast. Toxicology screens revealed traces of caffeine and Benadryl, apparently due to the use of over-the-counter medications prior to hospitalization. At follow-up visits 1 and 4 months after hospitalization his methemoglobin levels were normal (0.6% - 0.8%). Methemoglobin reductase levels were not evaluated during his hospitalization because of the exchange transfusion, but were normal at age 5 months.

#### Case 6

February 1993, Brown County — A 7-week-old, 8lb 4oz Native American male infant was taken to the hospital by his mother. On admission, he was described as mottled and gray and had a temperature of 102.6°F. Capillary blood gas revealed a pO<sub>2</sub> of 36, and oxygen saturation of 48%, and a pH of 7.06. A cardiovascular or respiratory disorder was suspected and the infant was placed in an oxygen hood. When his oxygen saturations and skin color remained unchanged, additional laboratory tests were ordered and the infant was found to have a methemoglobin level of greater than 10%. This infant was treated with oxygen, ceftriaxone, methylene blue, pedalyte, and bicarbonate and discharged the following day.

This patient had a 3-week history of upper respiratory infection and a 1-week history of vomiting and diarrhea. Over the course of these illnesses, his formula was switched several times. Water used to prepare this infant's formula came from a city supply and was low in nitrate (< 1 mg/L as N). Tests for rotavirus and Respiratory Syncytial Virus (RSV) were negative. An Influenza B titer was positive. Blood and spinal fluid cultures were negative.

#### Case 7

June 1998, Columbia County — Public health nurses in Columbia County noted that a 7-month-old, 19 lb male infant who was brought in for immunizations had a blue-gray skin color around his mouth and nose. According to his parents, the infant had been "gray" and "crabbier than normal" for a couple of weeks. They also reported that he had developed loose stools and began to "spit up" his formula. A public health nurse visited the family's home the following day and collected water samples for nitrate and bacteriological analysis. The laboratory tests indicated that the well was bacteriologically safe but had a nitrate-nitrogen level of 22.9 mg/L. The family was notified of these results and advised to use bottled water for formula preparation. One week later, his parents reported a marked improvement in this

infants' skin color and temperament. He was examined by a private health care provider 12 days after being placed on bottled water. At that time he appeared healthy and had a methemoglobin level of 0.5% (normal range 0.1 to 1.9%).

#### Case 8

April 1999, Grant County — A 3-week-old, 4 lb 10oz female infant was transported by her parents to an emergency room. They stated that she had been healthy until the previous evening when she became irritable and fussy. On the day of admission, they reported that she had turned "completely blue" and was having difficulty breathing. Local emergency room staff noted that the infant was dehydrated, dusky, and cold to the touch. Her temperature was 90°F and her oxygen saturation was 85%. She was placed in an incubator with supplemental oxygen. When her oxygen saturations remained in the low 80s, air transport to a regional medical center was requested.

Emergency air transport staff arrived to find a "hypothermic, pale, extremely blue infant with a blood pressure in the 60s/30s." Their differential diagnosis included sepsis, congenital heart disease, and a metabolic disorder. After stabilizing the infant with warming blankets, intravenous fluids, glucose, oxygen via face mask, and ceftriaxone, they transported her to a regional pediatric intensive care unit.

On arrival, the infant's vital signs included a temperature of 92.3°F, pulse 107, respiratory rate 57, blood pressure 105/76 and O<sub>2</sub> saturation of 85%. She was intubated and placed on a ventilator. A blood gas analysis revealed a PCO<sub>2</sub> of 20, PO<sub>2</sub> of over 200, pH 6.72 and a methemoglobin level of 91.2%. An echocardiogram ruled out congenital heart disease. The infant was treated with methylene blue, oral bicarbonate, and intravenous fluids. She responded favorably and was removed from the ventilator the day after her admission.

Case 8 lived with her parents and paternal grandparents on a dairy farm. She was born 1 month before her due date and had been doing well on liquid concentrate formula that was diluted with bottled water or water that her family obtained from a municipal supply. Her illness began 1 or 2 days after the family ran out of bottled water and began to use boiled water from their household well to prepare her formula. Water samples collected from the well 2 days after she was hospitalized tested positive for *E. coli* bacteria and had a nitrate-nitrogen level of 28 mg/L. Copper and lead levels were normal.

This infant's illness was apparently caused by ingestion of nitrate-contaminated well water.

Metabolic disorders were ruled out after serum amino acids, urine organic acids and metabolic screening were all within normal limits. Infectious illnesses apparently did not contribute to her illness since she remained afebrile throughout her hospitalization and did not require antibiotic therapy. The infant was discharged 17 days after admission, at which time her parents were instructed not to use well water to prepare her formula.

#### DISCUSSION

Between 1990 and 1999, 7 Wisconsin infants were hospitalized with illnesses that were characterized, either solely or in part, by an elevated methemoglobin level. The average age of these infants was 5 weeks (range 1-8 weeks). In addition to these cases, a 5-month-old infant developed symptoms consistent with methemoglobinemia after his family moved to a home that had a nitrate-contaminated well. His presumptive diagnosis was made by county health nurses and managed on an outpatient basis. Perhaps because he was older and had a higher body weight than the other cases, this child's symptoms were less severe and did not require medical intervention.

All but one of the cases described in this review involved infants who were fed formula concentrates that had been diluted with tap water. The exception was a breast-fed infant who developed cyanosis after being treated with an over-the-counter ointment that contained benzocaine and resorcinol. All of these infants displayed characteristic symptoms of methemoglobinemia including blue-gray skin color, tachycardia and tachypnea. Several of them also presented with a history of gastrointestinal or respiratory illnesses.

Methemoglobin levels were quantified in 6 of these cases. Five of these ranged between 15% and 30%. These levels are consistent with mild to moderate symptoms, but are not considered life-threatening. The most recent case involved a 3-week-old infant whose methemoglobin level was 91.2%. Her illness began a day or two after her parents began using boiled water from their farm well to prepare her formula. Her methemoglobin level is the highest that has ever been reported in Wisconsin and is considered incompatible with life. Her life was saved by aggressive medical intervention.

Less than 5% of Wisconsin families are believed to consume water that is high in nitrate. The observation that 3 of these cases (37%) involved nitrate-contaminated water suggests that infants living in these households have a much higher risk of developing methemoglobinemia than others. Nitrate-

## Differential Diagnosis and Treatment of Methemoglobinemia

Methemoglobinemia can be acquired or congenital. The acquired form may result from drug overdoses, but can also occur at standard doses in individuals with hereditary deficiencies in cytochrome b5 reductase (b5R). Infants are particularly susceptible because their erythrocyte b5R activity is only 50% to 60% of adult activity. Nitrate-contaminated well water is a common cause of acquired methemoglobinemia in rural, formula-fed infants. Congenital or hereditary methemoglobinemia is seen in infants born with autosomal recessive deficiencies of cytochrome b5 reductase or cytochrome b5; and infants born with autosomal dominant hemoglobin M disease.

The hallmark sign of methemoglobinemia is the slate-blue skin color, termed cyanosis, in the presence of a normal partial pressure of arterial oxygen. Other clinical symptoms, including headache, fatigue, dyspnea and lethargy are generally seen only in cases of acquired methemoglobinemia. Cyanosis becomes apparent when the methemoglobin level exceeds 1.5 g/dL (usually 1%-15% total hemoglobin).<sup>1</sup> Blood from an affected patient has a characteristic chocolate-brown appearance that does not change when the sample is exposed to oxygen. Laboratory confirmation of the condition is based on methemoglobin's peak absorption at 631 nm. However, sulfhemoglobin and methylene blue can produce false-positive readings.

If the patient is symptomatic, specific therapy should be administered. Methylene blue reduces methemoglobin via the NADPH-reductase dependent pathway. The normal treatment involves intravenous administration of 1 to 2 mg/kg methylene blue 1% solution infused over a period of several minutes.<sup>1</sup> Recovery is usually rapid and complete. Patients with G6PD deficiencies should not be given methylene blue because of the potential development of hemolysis, but can be treated with ascorbic acid. Ethnic groups with a high incidence of G6PD deficiencies (blacks, Mediterraneans, and Southeast Asians) should be screened prior to the administration of methylene blue. In severe cases, these patients may require an exchange transfusion.

### Reference

1. Goldman L, Bennett J. Cecil Textbook of Medicine, 21st Edition, Vol.1. W.B. Saunders Co. Philadelphia, 2000.

nitrogen levels associated with these cases ranged from 28 mg/L to 52 mg/L, roughly 3 to 5 times the level of the federal drinking water standard of 10 mg/L for this parameter. Risk factors that were identified in the remaining cases include gastrointestinal and respiratory illnesses, dehydration, an Asian folk remedy, an over-the-counter medication, and an inherited enzyme deficiency.

Several recent groundwater quality surveys have identified nitrate contamination as one of the most common water supply problems in the midwestern United States. In Wisconsin, the problem is most severe in the southern half of the state, which is heavily agricultural. Popular crops grown in this region include corn, hay, peas, potatoes, and soybeans. A 1993 study of private water supplies in 9 midwestern states determined that 6% to 7% of Wisconsin's private wells had nitrate-nitrogen levels that exceeded the federal drinking water standard of 10 mg/L.<sup>10</sup> Groundwater nitrate levels often follow seasonal patterns with the highest levels occurring in late spring and early summer, shortly after the planting season when fertilizers are applied. It is interesting to note that the cases in this report which were associated with nitrate-contaminated well water occurred in April, May, and June, which are months when nitrate levels would tend to be highest in shallow, rural wells.

### REFERENCES

1. Comly H. Cyanosis in infants caused by nitrates in well water. *JAMA* 1945;129:112-116.
2. Hanukoglu A, Danon PH. Endogenous methemoglobinemia associated with diarrheal disease in infancy. *J Ped Gastroenterol and Nutri* 1996;23:1-7.
3. Krafte-Jacobs B, Brilli R, Szabo C, Denenberg A, Moore L, Salzman AL. Circulating methemoglobin and nitrite/nitrate concentrations as indicators of nitric oxide overproduction in critically ill children with septic shock. *Crit Care Med* 1997;25(9):1588-93.
4. Hjelt K, Lund JT, Scherling B, et al. Methaemoglobinaemia among neonates in a neonatal intensive care unit. *Acta Paediatr* 1995;84(4):365-70.
5. Laney RF, Hoffman RS. Methemoglobinemia secondary to automobile exhaust fumes. *Amer J Emerg Med* 1992;10(5):426-429.
6. Dean BS, Lopez G, Krenzelok EP. Environmentally-induced methemoglobinemia in an infant. *J Toxicol Clin Toxicol* 1992;30(1):127-133.
7. Slaughter MS, Gordon PJ, Roberts JC, Pappas PS. An unusual case of hypoxia from benzocaine-induced methemoglobinemia. *Ann Thorac Surg* 1999;67(6):1776-8.
8. Johnson CJ, Bonrud P. Methemoglobinemia: Is it coming back to haunt us? *Health and Environment Digest* 1988;1(12):3-4.
9. MMWR. Methemoglobinemia in an infant - Wisconsin 1992. *MMWR* 42(12):217-219.
10. Center for Disease Control and Prevention. A survey of the quality of water drawn from domestic wells in nine Midwestern states. September 1998.



The mission of the *Wisconsin Medical Journal* is to provide a vehicle for professional communication and continuing education of Wisconsin physicians.

The *WMJ* (ISSN 1098-1861) is the official publication of the State Medical Society of Wisconsin and is devoted to the interests of the medical profession and health care in Wisconsin. The managing editor is responsible for overseeing the production, business operation and contents of *WMJ*. The editorial board, chaired by the medical editor, solicits and peer reviews all scientific articles; it does not screen public health, socioeconomic or organizational articles. Although letters to the editor are reviewed by the medical editor, all signed expressions of opinion belong to the author(s) for which neither the *WMJ* nor the SMS take responsibility. The *WMJ* is indexed in Index Medicus, Hospital Literature Index and Cambridge Scientific Abstracts.

For reprints of this article contact the *WMJ* Managing Editor at 800.362.9080 or e-mail [wmj@wismed.org](mailto:wmj@wismed.org).

© 2001 State Medical Society of Wisconsin