Toxicology Reports 12 (2024) 331–337

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

# Causes of acquired methemoglobinemia – A retrospective study at a large academic hospital

Alex Belzer [a], Matthew D. Krasowski [b,*]

[a] Carver College of Medicine, University of Iowa, Iowa City, IA 52242, USA
[b] Department of Pathology, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242, USA

ARTICLE INFO

Handling Editor: Prof. L.H. Lash

*Keywords:*
Amyl nitrite
Cyanosis
Dapsone
Methemoglobinemia
Methylene blue
Nitrates
Nitric oxide
Sodium nitrite

ABSTRACT

Methemoglobinemia is a potentially life-threatening condition caused by the formation of methemoglobin, a form of hemoglobin that cannot bind oxygen. While there are some rare congenital causes of methemoglobinemia, most cases are acquired from the effects of specific drugs or environmental exposures. In this retrospective study, we analyzed a large data set of whole blood samples analyzed for methemoglobin at an academic medical center in Midwestern United States that provides both pediatric and adult services. For a 14 year timeframe (May 2009- June 2023), we performed detailed chart analysis of all patients with a methemoglobin concentration of 3.1 % or higher. For an earlier 13 year timeframe (January 1996-April 2009), we performed chart review for all patients with a methemoglobin concentration of 10.0 % or higher. For the 2009–2023 data, dapsone was the most frequent cause of methemoglobinemia (methemoglobin 3.1 % or higher) in both pediatric (73.3 %, 115 clinical encounters, 105 unique patients) and adult (65.3 %, 195 clinical encounters, 190 unique patients) populations. Inhaled nitric oxide as medical therapy was the next most frequent cause in both pediatric (18.1 %) and adult (13.2 %) populations. Causes associated with two or more unique episodes with methemoglobin concentrations of 10.0 % and higher included the following: dapsone (n = 40 episodes), benzocaine (n = 10), recreational use of amyl or isobutyl nitrite (n = 3), suicide attempt with sodium nitrite (n = 3 with 1 fatality; all 3 cases within last 3 years), food contaminated with nitrates (n = 2), and sepsis (n = 2). A total of 18 patients received treatment with methylene blue including 5 cases associated with benzocaine and all of the cases associated with amyl nitrite, isobutyl nitrite, sodium nitrite, and contaminated food. Only 3 patients with dapsone-associated methemoglobinemia received methylene blue, reflecting primary management by dose reduction or discontinuation of drug. Overall, our data reinforce previous studies showing dapsone, inhaled nitric oxide, and nitrites as common agents causing methemoglobinemia in a patient population seen at a medical center. Our data also are consistent with recent epidemiology trends showing increase in suicide attempts using sodium nitrite.

## 1. Introduction

Methemoglobinemia is a condition caused by the presence of high levels of an aberrant form of hemoglobin in the blood called methemoglobin [1–3]. Methemoglobin has the iron in the heme group in the $Fe^{3+}$ state (which cannot bind oxygen), not the $Fe^{2+}$ state of normal hemoglobin [4]. In addition, the oxidation of one or two of the iron atoms of the hemoglobin tetrameter causes the remaining iron atoms in the $Fe^{2+}$ state to bind oxygen more tightly. This leads to a leftward shift in the oxygen dissociation curve known as the Darling-Roughton effect, which further reduces tissue oxygen delivery [5]. High methemoglobin levels can cause hypoxic tissue damage, systemic inflammation, cyanosis, and chocolate-colored blood. The tissue damage associated with methemoglobinemia can be lethal if not identified and treated quickly. Methemoglobin exists at low levels (2 % or less) in healthy people, and biochemical processes exist to return methemoglobin back to Hb. The treatments for methemoglobinemia (e.g., methylene blue) are effective, usually well tolerated, and take advantage of and augment the body's inherent methemoglobin sequestration processes [1,2,6]. The half-life of methemoglobin is approximately 55 minutes [7]. There are some limitations to methylene blue therapy, including ineffectiveness in those with glucose-6-phosphate dehydrogenase deficiency [4,8].

* Correspondence to: University of Iowa Hospitals and Clinics, Department of Pathology, 200 Hawkins Drive, C-671 GH, Iowa City, IA 52242, USA.
*E-mail address:* matthew-krasowski@uiowa.edu (M.D. Krasowski).

https://doi.org/10.1016/j.toxrep.2024.03.004
Received 21 November 2023; Received in revised form 29 January 2024; Accepted 15 March 2024
Available online 16 March 2024

There are rare genetic disorders that can cause hereditary methemoglobinemia, particularly those involving genetic deficiencies of NADPH-diaphorase, a critical component of the system that recycles the vast majority of methemoglobin [2,9]. However, in clinical practice, methemoglobinemia is more commonly the result of exposure to one or more exogenous substances [1,10]. Many causal substances have been identified, including benzocaine and other topical anesthetics [11–19], dapsone (anti-infective used for treatment of leprosy, dermatitis herpetiformis, and *Pneumocystis jirovecii*) [10,20–29], antimalarial agents (e.g., chloroquine) [1,24], nitric oxide [30,31], and nitrites [32–39] (Table 1). Dietary nitrates and nitrites in food and drinking water is a major cause of methemoglobinemia in some parts of the world [10,33,40,41]. Methemoglobinemia in children has also been reported due to gastroenteritis, especially in infant less than 6 months old [42–44].

Methemoglobin percentages in whole blood are typically measured by CO-oximetry [4]. Standard pulse oximeters do not detect methemoglobin and thus give misleading values in the setting of methemoglobinemia. In otherwise healthy individuals, methemoglobin percentages of up to 20 % can cause cyanosis, slate-gray skin discoloration, and chocolate-brown blood [1,2,4,10] However, there are some individuals that may show effects (e.g., fatigue, headache, malaise, skin discoloration) at mildly elevated methemoglobin percentages (4–10 %). This can impact adherence to long-term therapy with a medication that can incite methemoglobin, as may occur with use of dapsone to treat leprosy or to prevent *Pneumocystis jirovecii* infection [4,10,20–29]. Skin discoloration may be more readily apparent in those with light complexions. High percentages of methemoglobin (20–50 %) can result in a range of symptoms that include angina, dizziness/loss of balance, fatigue, gastrointestinal pain, headache, and nausea/vomiting [4]. Percentages of 50–70 % can cause life-threatening effects including coma, dysrhythmias, metabolic acidosis, and seizures. At very high methemoglobin percentages (> 70 %), risk of death is high due to inadequate ability to deliver oxygen to tissues. There are some populations that are more vulnerable to severe consequences of methemoglobinemia including neonates as well as those with anemia and/or pre-existing cardiovascular disease such as congestive heart failure. Neonates are especially susceptible due to low levels of NAPHD-diaphorase and the vulnerability of hemoglobin F to oxidizing agents [4,30].

**Table 1**
Recognized causes of methemoglobinemia.

| Cause | Comments | References |
|---|---|---|
| Antimalarial drugs | Includes chloroquine and primaquine | [1,24] |
| Dapsone | Commonly identified cause of methemoglobinemia | [10,20–29] |
| Dietary nitrates in food or water | Risk varies based on location and concentrations of nitrates in food and drinking water | [10,33,40,41] |
| Gastroenteritis, infants | Infants 6 months and younger at highest risk | [42–44] |
| Nitric oxide | Infants receiving inhaled nitric oxide at highest risk | [30,31,52] |
| Nitrites (e.g., amyl, isobutyl) | Includes: amyl or isobutyl nitrites as recreational inhalants ('poppers'); sodium nitrite for suicide attempts; medical use of amyl nitrite for cyanide poisoning | [32,34–39] |
| Nitroglycerin | Intravenous route of administration highest risk | [56–58] |
| Nitroprusside | Known risk of therapy especially at the highest doses | [59] |
| Phenazopyridine | Uncommon cause of methemoglobinemia | [60–63] |
| Sepsis | Possibly caused by generation of nitric oxide | [52,64] |
| Smoke inhalation | Produced by generation of nitrites and oxides | [6,65,66] |
| Sulfonamides | Includes trimethoprim-sulfamethoxazole and sulfasalazine | [48,67] |
| Topical/local anesthetics | Benzocaine spray to mucus membranes poses highest risk of methemoglobinemia; bupivacaine, lidocaine, and prilocaine also implicated | [11–19] |

In the present study, we retrospectively analyzed methemoglobin testing from a large cohort of patients at an academic medical center in midwestern United States. Our objective was to identify using chart review the most likely causes of elevated methemoglobin levels in patient seen at our medical center.

## 2. Methods

### 2.1. Design and setting

This was a retrospective study of all patients (pediatric and adult) who had methemoglobin whole blood levels performed at the University of Iowa Hospitals and Clinics (UIHC) between January 1996 through June 2023. UIHC is the state of Iowa's only academic medical center and includes inpatient, outpatient, and emergency department services at the main medical center campus. The medical center is an 860-bed facility that includes the 190-bed University of Iowa Stead Family Children's Hospital. Clinical laboratories within the main medical center utilize blood gas analyzers that can differentiate and quantitate percentages of carboxyhemoglobin and methemoglobin in whole blood samples using blood gas analyzers (typically using arterial or venous specimens collected in blood gas syringes containing heparin as the anticoagulant). During the retrospective timeframe of analysis, the main blood gas analyzers used were Radiometer ABL800 FLEX or ABL90 FLEX models (Radiometer, Inc., Copenhagen, Denmark). Methemoglobin is a stand-alone order in our electronic medical record (EMR), although it is typically co-ordered with either arterial or venous blood gases.

### 2.2. Data retrieval

This study received approval from the University of Iowa Institutional Review Board (protocols #202101499 and 202306426) as a retrospective study with waiver of informed consent. UIHC switched to Epic Hyperspace (Epic, Inc.) as the EMR in May 2009. Historical data from the prior EMR were imported into Epic, although medical administration records and some clinical notes are incomplete for data prior to May 2009. As described in a previous study [45], Epic Reporting Workbench was used as a reporting tool to retrieve data based on specific query parameters. This search was for any methemoglobin analysis performed on a patient for clinical purposes. The present study did not influence test ordering, analysis, clinical management for any patient.

### 2.3. Chart review and data analysis

Demographic data collected included age at time of testing, legal sex, and clinical location at time of testing (e.g., emergency department, inpatient unit, outpatient clinic). Detailed chart review was performed for all patients who had a methemoglobin level of 3.1 % of higher between May 2009 and June 2023, and all patients who had methemoglobin level of 10.0 % or higher prior to May 2009. The more limited review of the data prior to May 2009 reflected the incompleteness of medication administration records in older dates. Exploratory analysis showed that a likely cause of the highest methemoglobin levels could be ascertained in nearly all cases in the older EMR data as the methemoglobinemia was likely important enough to be discussed in clinical notes. However, in the 3.1–9.9 % methemoglobin data, the incompleteness of the pre-May 2009 medical administration record precluded ascertainment of cause if methemoglobinemia was not mentioned in clinical notes.

Chart review focused on the most likely cause of methemoglobinemia during an episode of care (emergency department visit, inpatient encounter, outpatient clinic appointment, laboratory monitoring). Data regarding clinical signs and symptoms of methemoglobinemia were also collected from the medical record within temporal proximity to the abnormal laboratory value. For purposes of classification by

methemoglobin level, the highest methemoglobin level during an episode was used. Some patients had more than one clinically significant episode of methemoglobinemia. The chart review utilized data from clinical notes, medication administration records, and discharge summaries. Table 1 lists recognized causes of methemoglobinemia from the published literature that were considered as potential causes for methemoglobinemia in our chart review.

## 3. Results

### 3.1. Subject demographics – total cohort (May 2009 – June 2023)

Table 2 summarizes the demographics of the patients who had methemoglobin testing performed between May 2009 and June 2023, a time period in which complete chart review information was available. A total of 21,449 methemoglobin levels were performed on 2502 unique patients, with 546 levels (2.5 % of total; 303 unique patients) of 3.1 % or higher and only 33 levels (0.15 % of total; 27 unique patients) of 10.0 % or higher. Fig. 1 shows the distribution of methemoglobin concentrations by category for May 2009 to June 2023, demonstrating values of 3.1 % or higher are uncommon overall.

### 3.2. Suspected causes of methemoglobinemia from chart review (May 2009 -June 2023)

Table 3 summarizes the most likely cause for elevated methemoglobin (3.1 % or higher) for patients between May 2009 and June 2023. The data are broken down into pediatric (< 18 years old at time of methemoglobin level) and adult (18 years or older) based on age of patient at the time of laboratory testing. There were a total of 310 episodes of care (emergency department visit, inpatient admission, outpatient clinic appointment, or routine laboratory draw) with 195 of these in adult patients (190 unique patients) and 115 in pediatric patients (105 unique patients). Dapsone was the most frequent cause of methemoglobinemia in both pediatric (77 of 115 or 73.3 % of episodes of care

**Table 2**
Demographics and frequency of methemoglobin levels (January 1996 – June 2023).

| Sign/ Symptom | All test results for methemoglobin | Methemoglobin levels of 3.1 % or higher | Methemoglobin levels of 10.0 % or higher |
|---|---|---|---|
| *January 1996 - April 2009 (prior to current electronic medical record; incomplete chart review data available)* | | | |
| Total levels | 19,317 | 449 | 55 |
| Unique patients (F/M/U)[1] | 2401 (983/1417/1) | 167 (86/81/0) | 39 (21/18/0) |
| Average age (years) | 33.4 | 28.4 | 30.2 |
| Median age (years) | 36.5 | 20.9 | 31.8 |
| Standard deviation (years) | 28.9 | 23.9 | 22.5 |
| *May 2009 – June 2023 (complete chart review data available)* | | | |
| Total levels | 21,449 | 538 | 33 |
| Unique patients (F/M/U)[1] | 2502 (1070/1430/2) | 295 (149/146/0) | 27 (13/14/0) |
| Average age (years) | 26.6 | 37.4 | 32.0 |
| Median age (years) | 12.9 | 42.1 | 20.2 |
| Standard deviation (years) | 28.7 | 25.8 | 25.2 |

[1] Abbreviations: F, female; M, male; U, unknown. The two cases of unknown sex were from records where sex identifier was not documented.

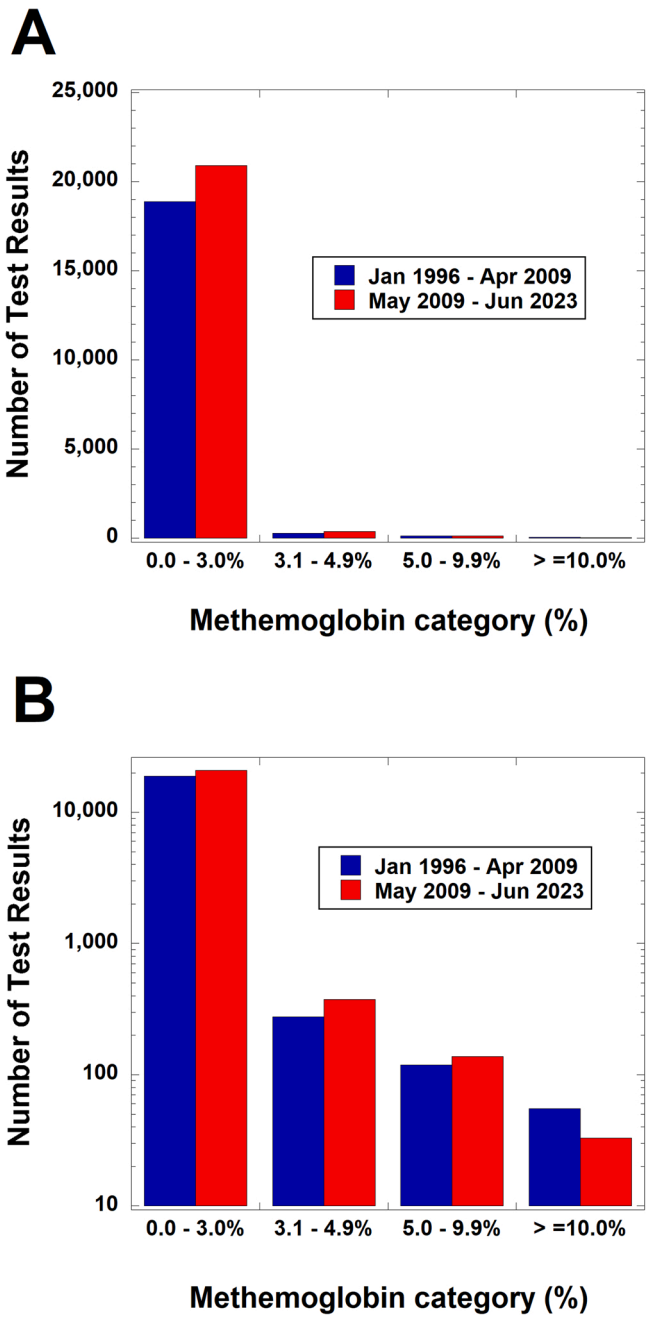


**Fig. 1.** Distribution of methemoglobin concentrations in two retrospective time periods (January 1996 – April 2009 and May 2009 – June 2023). A. Data shown in linear scale. B. Data shown in logarithmic scale to better illustrate the elevated methemoglobin categories.

with an elevated methemoglobin) and adult (124 of 195 or 65.3 % episodes of care) populations. Inhaled nitric oxide as medical therapy was the next most frequent cause in both pediatric (19 of 115, 18.1 %) and adult (25 of 195, 13.2 %) populations. Suspected causes only seen in adults include amyl or isoamyl nitrites (3 unique patients, all using as recreational inhalant), benzocaine (2 patients), nitroglycerine (3 patients, all administered intravenous formulation), primaquine (1 patient), smoke inhalation from housefire (4 patients), sodium nitrite (4 patients; 3 suicide attempts and 1 receiving as investigational drug for a clinical research study), sodium nitroprusside (1 patient), and sulfasalazine (1 patient). Gastroenteritis was the suspected cause of methemoglobinemia in 4 pediatric patients. An unusual case of severe methemoglobinemia in infant twins from ingestion of sorghum syrup

**Table 3**
Most Likely Underlying Cause of Elevated Methemoglobin (3.1 % or higher in an episode of care) in Pediatric and Adult Patients (May 2009 – June 2023).

| Cause | Pediatric Patients (115 episodes of care) | Adult Patients (195 episodes of care) |
|---|---|---|
| Amyl or isobutyl nitrite | 0 | 3 (1.5 %) |
| Benzocaine | 0 | 2 (1.0 %) |
| Bupivacaine | 1 (0.9 %) | 0 |
| Contaminated food (nitrate)[1] | 2 (1.7 %) | 0 |
| Dapsone | 77 (67.0 %) | 124 (63.6 %) |
| Gastroenteritis, infant | 2 (1.7 %) | 0 |
| Lidocaine | 1 (0.9 %) | 7 (3.6 %) |
| Miscellaneous or unknown cause[2] | 7 (6.1 %) | 11 (5.6 %) |
| Nitric oxide (iatrogenic) | 19 (16.5 %) | 25 (12.8 %) |
| Nitroglycerin | 0 | 3 (1.5 %) |
| Phenazopyridine | 2 (1.7 %) | 2 (1.0 %) |
| Primaquine | 0 | 1 (0.5 %) |
| Sepsis | 3 (2.6 %) | 4 (2.1 %) |
| Smoke inhalation | 0 | 4 (2.1 %) |
| Sodium nitrite | 0 | 4 (2.1 %) |
| Sodium nitroprusside | 0 | 1 (0.5 %) |
| Sulfasalazine | 0 | 1 (0.5 %) |
| Trimethoprim-sulfamethoxazole | 1 (0.9 %) | 3 (1.5 %) |

[1] This includes a set of twins with severe methemoglobinemia due to sorghum syrup contaminated with very high concentrations of nitrate from well water, based on investigation by state public health authorities.
[2] See Table 4 for more details.

contaminated with well water containing high concentrations of nitrates has been previously published [46]. There was a total of 18 patients (7 pediatric, 11 adult) whose underlying cause of methemoglobinemia was either not clear or due to a rare cause with only case reports in the literature (Table 4). This group included two intentional drug overdoses as suicide attempts (a multi-drug overdose that included 2,4-nitrophenol and memantine in one patient; massive acetaminophen overdose in another). There are prior reports of methemoglobinemia resulting from 2,4-dinitrophenol [47] and rarely from massive acetaminophen overdose [48–50].

**Table 4**
Patients without clear suspected cause for methemoglobinemia.

| Patient Number | Age (Years) at Time of Testing and Sex[1] | Medical History |
|---|---|---|
| 1 | Neonate, M | Bacterial meningitis |
| 2 | Neonate, M | Disseminated herpes simplex virus infection |
| 3 | Neonate, F | Prematurity |
| 4 | < 1 year old, F | Constellation of congenital anomalies include heart defects |
| 5 | 2, F | Hemolytic uremic syndrome |
| 6 | 7, F | Beta-thalassemia, also other complex medical issues |
| 7 | 16, F | Status epilepticus |
| 8 | 20, M | Systemic lupus erythematosus, gastrointestinal bleeding |
| 9 | 23, F | Acute pancreatitis |
| 10 | 43, M | Drug-induced hemolytic anemia |
| 11 | 44, F | H1N1 influenza |
| 12 | 45, F | 2,4-Dinitrophenol overdose (suicide attempt) |
| 13 | 49, F | Acetaminophen overdose (suicide attempt) |
| 14 | 54, M | Hemolytic anemia |
| 15 | 55, M | Diabetic ketoacidosis with metabolic acidosis |
| 16 | 55, M | Renal failure, deep venous thrombosis |
| 17 | 60, M | Myocardial infarction |
| 18 | 63, M | Pernicious anemia, alcohol use disorder |

[1] Abbreviations: F, female; M, male.

We divided the data in terms of highest methemoglobin level seen during an episode of care into 3 categories (3.1–4.9 %, 5.0–9.9 %, and 10.0+ %) (Table 5). Dapsone was the most common suspected cause of methemoglobinemia in all 3 categories, including accounting for 17 of 27 (63.0 %) of methemoglobin values of 10.0 % or higher. Only three patients with dapsone-induced methemoglobinemia were treated with methylene blue; in the remainder, dose was typically decreased or the medication discontinued if alternative therapy was feasible. Other than dapsone, there were limited cases where the methemoglobin level was 10.0 % or higher: intentional use of amyl or isobutyl nitrite as recreational drug/aphrodisiac (3 patients; all treated with methylene blue), benzocaine administration during surgical procedure (1 patient; treated with methylene blue), the infant twins mentioned above with regard to food contaminated with nitrate (both treated with methylene blue), overdose of phenazopyridine (1 patient, highest level was 10.1 % methemoglobin), and sodium nitrite for suicide attempt (3 patients, 1 fatality; all treated with methylene blue). All 3 cases of intentional sodium nitrite ingestion resulted in the highest methemoglobin level exceeding 30.0 % (the upper reporting limit for our assay), as did the 2 cases of recreational amyl nitrite use (the 1 case of isobutyl nitrite use resulted in maximum methemoglobin level of 27.0 %), and the infant twins with nitrate poisoning. For iatrogenic nitric oxide, only 2 of 44 episodes with elevated methemoglobin exceeded maximum methemoglobin level of 5.0 % (6.4 % and 7.3 %, respectively).

### *3.3. Signs and Symptoms Related to Methemoglobinemia (May 2009 – June 2023)*

Table 6 summarizes the signs and symptoms associated with patients with methemoglobin levels of 3.1 % or higher. The signs and symptoms listed are those in the described in literature on the clinical features of methemoglobinemia [1,2,10]. The most frequent presentation for both pediatric and adult patients was asymptomatic (79 of 115, 68.7 % of episodes involving pediatric patients; 73 of 195, 37.4 % for adult patients). The asymptomatic category was mostly comprised of patients who were routinely monitored for methemoglobinemia due to ongoing

**Table 5**
Most likely causes of elevated methemoglobin, by methemoglobin level.

| Cause[1] | 3.1–4.9 % (195 total levels) *May 2009 – June 2023* | 5.0–9.9 % (88 total levels) | 10.0+ % (27 total levels) | 10.0+ % (39 total levels) *January 1996 – April 2009* |
|---|---|---|---|---|
| Amyl or isobutyl nitrite | 0 | 0 | 3 (11.1 %) | 0 |
| Benzocaine | 1 (0.5 %) | 0 | 1 (3.7 %) | 9 (23.1 %) |
| Bupivacaine | 1 (0.5 %) | 0 | 0 | 0 |
| Contaminated food | 0 | 0 | 2 (7.4 %) | 0 |
| Dapsone | 111 (56.9 %) | 73 (83.0 %) | 17 (63.0 %) | 23 (59.0 %) |
| Gastroenteritis, infant | 2 (1.0 %) | 0 | 0 | 1 (2.6 %) |
| Lidocaine | 7 (3.6 %) | 1 (1.1 %) | 0 | 0 |
| Miscellaneous or unknown cause | 12 (6.2 %)[1] | 6 (6.8 %)[1] | 0 | 1 (2.6 %)[2] |
| Nitric oxide (iatrogenic) | 42 (21.5 %) | 2 (2.3 %) | 0 | 1 (2.6 %) |
| Nitroglycerin | 3 (1.5 %) | 0 | 0 | 0 |
| Phenazopyridine | 2 (1.0 %) | 1 (1.1 %) | 1 (3.7 %) | 0 |
| Primaquine | 1 (0.5 %) | 0 | 0 | 2 (5.2 %) |
| Sepsis | 5 (2.6 %) | 2 (2.3 %) | 0 | 0 |
| Smoke inhalation | 2 (1.0 %) | 2 (2.3 %) | 0 | 1 (2.6 %) |
| Sodium nitrite | 1 (0.5 %) | 0 | 3 (11.1 %) | 0 |
| Sodium nitroprusside | 0 | 1 (1.1 %) | 0 | 0 |
| Sulfasalazine | 1 (0.5 %) | 0 | 0 | 0 |
| Trimethoprim-sulfamethoxazole | 4 (2.1 %) | 0 | 0 | 1 (2.6 %) |

[1] See comments from Table 3.
2 This was a 31 year old woman with amniotic fluid embolism.

**Table 6**
Signs and symptoms present in pediatric and adult patients with elevated methemoglobin.

| Sign/Symptom[1] | Pediatric Patients (115 episodes of care) | Adult Patients (195 episodes of care) |
|---|---|---|
| Asymptomatic | 79 (68.7 %) | 73 (37.4 %) |
| Cardiovascular symptoms (including chest pain) | 0 (0 %) | 9 (4.6 %) |
| Cough | 5 (4.3 %) | 20 (10.3 %) |
| Cyanosis | 7 (6.1 %) | 8 (4.1 %) |
| Death during episode of care[2] | 7 (6.1 %) | 19 (9.7 %) |
| Dizziness and/or loss of balance | 2 (1.7 %) | 18 (9.2 %) |
| Edema | 8 (7.0 %) | 8 (4.1 %) |
| Fatigue | 8 (7.0 %) | 62 (31.8 %) |
| Gastrointestinal pain | 3 (2.6 %) | 4 (2.1 %) |
| Nausea/vomiting | 2 (1.7 %) | 17 (8.7 %) |
| Respiratory difficulties | 10 (8.7 %) | 54 (27.7 %) |

[1] Some patients had more than one sign or symptom.
[2] A total of 26 patients died during an inpatient or emergency department episode of care that included the elevated methemoglobin level. Only 1 fatality appeared directly related to methemoglobinemia (intentional overdose of sodium nitrite in a suicide). Two additional cases involved death from acute complications of burns and smoke inhalation, for which methemoglobinemia may have played a contributing role.

therapy with dapsone or inhaled nitric oxide. The higher proportion of pediatric patients who are asymptomatic despite methemoglobin level of 3.1 % or higher may be influenced by more routine monitoring of methemoglobin, particularly in settings such as the neonatal or pediatric intensive care units. In addition, dizziness/loss of balance and fatigue can be hard to assess in infants and young children. In the adult population, fatigue (62 of 195 episodes, 31.8 %) and respiratory difficulties (54 of 195, 27.7 %) were the most common symptoms associated with methemoglobinemia.

Table 7 breaks down signs and symptoms into the three categories of high methemoglobin levels seen during an episode of care. Only 7 of 27 patients (25.9 %) who had methemoglobin levels of 10.0 % or higher were asymptomatic. Cyanosis and respiratory difficulties were more common in those with the highest methemoglobin levels. A total of 26 patients expired during the episode of care in which there was methemoglobinemia. From chart review of medical information including inpatient unit discharge summaries, only one of the fatalities was clearly linked to methemoglobinemia as the primary cause. This was a case involving intentional ingestion of sodium nitrite for suicide attempt by a 20-year-old woman. Three additional fatalities involved sequelae of severe burns and smoke inhalation, for which methemoglobinemia may have played a contributing role in the death. Other fatalities during an episode of care with methemoglobinemia did not appear to directly involve methemoglobinemia as a major contributor to death: bacterial pneumonia (1 patient), cardiac failure (3 patients), congenital anomalies from complex genetic disorder (1 patient), gastrointestinal hemorrhage (2 patients), disseminated herpes simplex virus infection (1 patient), end stage interstitial lung disease (1 patient), *Pneumocystis jirovecii* pneumonia (2 patients), pulmonary embolus (1 patient), renal failure (1 patient), respiratory failure (3 patients), and sepsis (6 patients).

**Table 7**
Signs and symptoms present with elevated methemoglobin, by methemoglobin level.

| Sign/Symptom[1] | 3.1–4.9 % (n = 195) | 5.0–9.9 % (n = 88) | 10.0+ % (n = 27) |
|---|---|---|---|
| Asymptomatic | 91 (46.7 %) | 54 (61.4 %) | 7 (25.9 %) |
| Cardiovascular symptoms (including chest pain) | 4 (2.1 %) | 2 (2.3 %) | 3 (11.1 %) |
| Cough | 17 (8.7 %) | 8 (9,1 %) | 0 (0.0 %) |
| Cyanosis | 2 (1.0 %) | 5 (5.7 %) | 8 (29.6 %) |
| Death during episode of care | 21 (10.8 %) | 3 (3.4 %) | 2 (7.4 %) |
| Dizziness and/or loss of balance | 12 (6.2 %) | 5 (5.7 %) | 3 (11.1 %) |
| Edema | 14 (7.2 %) | 1 (1.1 %) | 1 (3.7 %) |
| Fatigue | 52 (26.7 %) | 12 (13.6 %) | 6 (22.2 %) |
| Gastrointestinal pain | 6 (3.1 %) | 1 (1.1 %) | 0 (0.0 %) |
| Nausea/vomiting | 13 (6.7 %) | 5 (5.7 %) | 1 (3.7 %) |
| Respiratory difficulties | 35 (17.9 %) | 19 (21.6 %) | 10 (37.0 %) |

[1] See footnotes to Table 6.

### 3.4. Distribution of methemoglobin concentrations January 1996 - April 2009 and Causes of Severe Methemoglobinemia during that Time Period

We also analyzed methemoglobin concentrations for January 1996 to April 2009. Because this timeframe was before implementation of our current EMR, some data from the previous EMR were not available. This particularly impacted availability of inpatient unit notes and medication administration records. We therefore restricted chart review to only the patients with methemoglobin concentrations of 10.0 % or higher. Overall, the distribution of methemoglobin values between January 1996 to April 2009 was very similar to that for May 2009 to June 2023 (Fig. 1, Table 2). As with the May 2009 to June 2023 data, dapsone was the most frequent suspected underlying cause of methemoglobin concentrations of 10.0 % or higher for January 1996 to April 2009 (Table 5, right-most column), accounting for 23 of 39 (59.0 %) episodes of care (10 of 16 or 62.5 % for pediatric patients; 13 of 23 or 56.5 % for adult patients). Interestingly, benzocaine accounted for 9 of 39 (23.1 %) episodes of care with methemoglobin concentration of 10.0 % or higher for January 1996 to April 2009, with 4 patients requiring therapy with methylene blue. This compares with only 1 of 27 (3.7 %) episodes of care involving methemoglobin concentrations or 10.0 % or higher for May 2009 to June 2023. The remaining suspected causes for methemoglobin concentration of 10.0 % or higher for January 1996 to April 2009 were as follows: infant gastroenteritis (1 patient), iatrogenic nitric oxide (1 patient), sepsis (2 patients; one treated with methylene blue), smoke inhalation (1 patient), and trimethoprim-sulfamethoxazole (1 patient) (Table 5). There was a single additional case with severe methemoglobinemia in a mother with amniotic fluid embolism following delivery; she was treated with methylene blue and recovered. Table 8 summarizes the signs and symptoms present in pediatric and adult patients with methemoglobin concentrations of 10.0 % or higher for August 1996 to April 2009, with cyanosis and respiratory difficulties being the most common symptoms (14 of 39 or 35.9 % of the episodes of care for both).

## 4. Discussion

In the present study, we analyzed causes of methemoglobinemia across approximately 27 years at an academic medical center, with complete chart review data for 14 years (May 2009 to June 2023). We did not encounter any congenital causes of methemoglobinemia. Dapsone was the most common cause of methemoglobinemia for both pediatric and adult patients, including the subset of patients with methemoglobin concentrations of 10.0 % or higher. Our data are consistent with other studies demonstrating that dapsone has remained

**Table 8**
Signs and Symptoms Present in Pediatric and Adult Patients with Elevated Methemoglobin of 10.0 % or higher (August 1996 – April 2009).

| Sign/Symptom[1] | Pediatric Patients (16 episodes of care) | Adult Patients (23 episodes of care) | Total |
|---|---|---|---|
| Asymptomatic | 5 | 5 | 10 |
| Cardiovascular symptoms (including chest pain) | 0 | 1 | 1 |
| Cyanosis | 6 | 8 | 14 |
| Fatigue | 0 | 1 | 1 |
| Respiratory difficulties | 5 | 9 | 14 |

a common cause of methemoglobinemia across the last several decades [10,20–29]. Interestingly, our chart review did not reveal any fatalities related to dapsone, although this may be related to all cases being associated with therapeutic dosing and not overdoses. Life-threatening methemoglobinemia has been known to occur with intentional overdoses of dapsone [51]. Routine protocols for monitoring methemoglobin levels as part of ongoing therapy with dapsone at our institution may have contributed to the high percentage of methemoglobinemia accounted for by dapsone, as many patients showing methemoglobinemia related to dapsone were asymptomatic at the time of testing. This may contrast with other possible causes of methemoglobinemia that would only be discovered if there was clinical suspicion of an inciting factor. There were also only 3 patients who received methylene blue for dapsone-induced methemoglobinemia; the remainder were managed with dose adjustments or continued careful monitoring. The second most common cause of methemoglobinemia in our study was iatrogenic nitric oxide (seen mostly with mild methemoglobinemia between 3.1 % and 4.9 %); this is also a well-recognized cause of methemoglobinemia in the published literature [30,31,52]. In the 2009–2023 data, benzocaine and other local anesthetics were infrequent causes of methemoglobinemia (only 3 patients total); however, benzocaine accounted for 9 of 39 cases of severe methemoglobinemia in the 1996–2009 timeframe, with 4 patients receiving methylene blue therapy. This may be accounted for by changes at our institution in clinical use of local anesthetic administration (especially topical benzocaine applied to mucus membranes) related to the risk of methemoglobinemia with these agents that has been well-described in the published literature since the 1990s [1,11,12,20]. In general, we were able to assign a suspected cause of methemoglobinemia to the vast majority of cases using factors well-described in the published literature (summarized in Table 1). Some cases, especially those involving sepsis or other conditions such as severe burns and smoke inhalation in critically ill patients, may have multiple factors contributing to methemoglobinemia.

Aside from the 17 cases involving prescribed dapsone, the remaining 10 severe methemoglobinemia (10.0 % or higher) cases in our 2009–2023 data included 6 intentional ingestions that included either suicide attempt with sodium nitrite (3 patients, 1 fatality) or recreational use of amyl or isobutyl nitrite (3 patients). The 6 patients with intentional nitrite use all received methylene blue therapy. Increases in suicide attempts with sodium nitrite have been reported to be increasing, in part due to online information on its toxic effects coupled with availability of this compound through internet sources [37,53–55]. A set of twin infants had life-threatening methemoglobinemia from food contaminated with nitrates in a case investigated by public health authorities; both infants were treated with methylene blue [46]. We additionally documented suicide attempts with 2,4-dinitrophenol (1 patient) and acetaminophen (1 patient) that resulted in modest elevations of methemoglobin. Both of these drugs are recognized as uncommon potential causes of methemoglobinemia [47–50].

Limitations of the study include analysis at a single academic medical center that serves as a regional center for specialized medical care. The high frequency of dapsone and inhaled nitric oxide as causes of methemoglobinemia in our study are influenced by our medical center providing complex hematology/oncology, cardiovascular, and critical care in both pediatric and adult patients. Our medical center is also a referral site for poisonings and other toxicity. The geographic region of our medical center is not commonly associated with contamination of the food or water supply with environmental nitrates.

## 5. Conclusion

In our study at an academic medical center in the midwestern United States, therapy with dapsone and inhaled nitric oxide were the dominant causes of methemoglobinemia, but with many cases found by routine methemoglobin measurements in asymptomatic patients. Most of the remaining cases of methemoglobinemia identified in our study could be explained by causes documented in the published literature. Cases of severe methemoglobinemia resulting in either death or life-threatening complications were associated with either intentional ingestion of nitrites (suicide attempts with sodium nitrite or recreational use of amyl or isobutyl nitrite) or a single case involving twin infants ingesting food and water contaminated with nitrates.

## Ethics approval

This study was conducted with ethical approval from the University of Iowa Institutional Review Board as a retrospective study with waiver of informed consent with the approval numbers 202101499 and 202306426.

## Funding statement

There was no external funding for this study.

## Author contribution statement

Alex Belzer: Conceived and designed the experiments; Performed investigation and formal analysis; Drafted and edited the paper. Matthew Krasowski: Supervised, conceived, and designed the experiments; Provided project administration; Analyzed and interpreted the data; Drafted and edited the manuscript.

## CRediT authorship contribution statement

**Matthew D. Krasowski:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization. **Alex Belzer:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data shared in Mendeley. Link provided in manuscript.

## Acknowledgements

None

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