# A Multi-Center Retrospective Database Evaluation of Pediatric Subjects Diagnosed With Methemoglobinemia

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**ABSTRACT**

**BACKGROUND:** Methemoglobinemia requires early identification and treatment, but limited knowledge exists regarding the current therapeutic approach taken by clinicians as well as the outcomes that occur in children.

**OBJECTIVES:** To determine the current prevalence of this rare disease in the pediatric population, evaluate the impact of methemoglobin and functional hemoglobin levels, and assess how this disease is approached by clinicians. We hypothesize that methemoglobinemia prevalence is low and more methylene blue use would be observed in subjects with functional hemoglobin levels less than 7 g/dL.

**DESIGN:** This was a retrospective observational cohort study utilizing deidentified TriNetX® electronic health record (EHR) data.

**METHODS:** Using a multicenter EHR database, we evaluated subjective characteristics, diagnostic, laboratory results, medication, and procedural codes.

**RESULTS:** Ninety-eight children (mean age 5.3 ± 5.3 years) from 53 healthcare organizations were included. Methemoglobinemia prevalence was 0.0015% with an overall 30-day mortality of 6.1%. Subjects with methemoglobin percentages greater than 20% had a higher frequency of methylene blue administration (70.6% versus 24.7%, $P = .0005$). Critical care service requirements and methylene blue administration were similar in the subjects with functional hemoglobin less than 7 g/dL and more than 7 g/dL groups. Overall, 13 (13.2%) subjects underwent glucose-6-phosphate dehydrogenase deficiency (G6PD) testing.

**CONCLUSION:** In our study, we found methemoglobinemia prevalence in children is low, there is a low frequency of G6PD testing despite methylene blue hemolysis risk, and subjects appeared to be treated similarly despite a low functional hemoglobin. These findings highlight the continued critical nature of this disease and may highlight opportunities for education aimed at improving care in children diagnosed with methemoglobinemia, particularly related to G6PD testing.

**KEYWORDS:** Hypoxia, methemoglobinemia, pediatrics, critical care

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## Introduction

Methemoglobinemia is a rare disorder in which the iron within hemoglobin is oxidized from its divalent Fe2+ state to a trivalent Fe3+ state.[1] This results in an increased affinity for oxygen by the ferro-globin tetramer and shifts the oxygen dissociation curve to the left.[2] Consequently, this leads to impaired oxygen release by hemoglobin, tissue hypoxia, and metabolic acidosis.[1]

Methemoglobinemia can either be hereditary or acquired in nature. Inherited forms of methemoglobinemia are usually rare with a majority due to a deficiency of the cytochrome b5 reductase enzyme, the electron acceptor cytochrome b5, or missense gene mutations of globin chains resulting in an altered form of hemoglobin.[1,3] Acquired forms, however, are more common and are associated with substances including medications, contaminated water, food preservatives, and infections (particularly gastrointestinal illness in the pediatric population).[1,4] Exposure to these substances causes acceleration of Hb oxidization from the ferrous to the ferric form.[1] This can result in life-threatening symptoms including acute hypoxemia, dyspnea, and neurologic compromise.[1,5] Therefore, prompt recognition, evaluation, and treatment of this clinical situation are important to improve the blood's oxygen carrying capacity.[1,6]

While there are reports in the literature describing this entity, methemoglobinemia continues to be a rarely described disorder, limited to single centers, even when including subjects of all ages.[4,6-8] Thus, the impact of this disease on children and how clinicians universally approach this condition when it is identified is not clearly known.[9] In addition, while methemoglobin percentages are often measured to detect this disease and evaluate severity, severe anemia may not be accounted for.[4,10] Regardless of the methemoglobin percentage, anemia can cause a higher level of toxicity and severity of illness due to lower functional hemoglobin levels (total

hemoglobin – methemoglobin level).[4,10] It is unknown, however, if clinicians are aware of this or account for this important aspect when caring for these patients. Understanding the current diagnostic and treatment approach of children with this condition and the impact of functional anemia may highlight and allow the opportunity to reinforce best clinical practice.

The objective of this study is to determine the current prevalence of this rare disease in the pediatric population utilizing a multicenter electronic health record database, evaluate the impact of methemoglobin and functional hemoglobin levels, and assess how this disease is approached by clinicians. We hypothesize that methemoglobinemia prevalence is low and more methylene blue use would be observed in subjects with functional hemoglobin levels less than 7 g/dL.

## Materials and Methods

### *Study design*

This is a retrospective observational cohort study utilizing the TriNetX® electronic health record (EHR) database of pediatric subjects aged 0 to 18 years who underwent methemoglobin laboratory testing (Logical Observation Identifiers Names and Codes [LOINC] 2614-6, 2615-3, 2617-9, 71882-5, 71880-9, 71879-1, and 41607-3) for the first time in their EHR database history, had a result of greater than or equal to 5%, and had either undergone treatment for methemoglobinemia (ie, ascorbic acid, methylene blue, and hyperbaric oxygen) or were subsequently diagnosed with methemoglobinemia. TriNetX is a global federated research network. It is primarily based in the United States and it collects aggregated EHR data elements (including diagnoses, medications, procedures, and laboratory values) of approximately 68 million patients in 56 large health care organizations (HCOs). After de-identification, these data elements are made available within a user-friendly browser-based software in real-time. TriNetX, LLC is compliant with the Health Insurance Portability and Accountability Act (HIPAA). This is a United States federal law that protects the privacy and security of healthcare information, and any additional data privacy regulations applicable to the contributing HCO. TriNetX is certified to the ISO 27001:2013 standard. It maintains an Information Security Management System (ISMS) which ensures the protection of the healthcare data it is provided access to and meets HIPAA Security Rule requirements. The patient level data provided in a data set generated by the TriNetX Platform contains only de-identified data as per the de-identification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. The process of data de-identification process is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule.

### *Data collection*

The data used in this study was collected on July 31st, 2022 from the TriNetX Research Network. After the dataset was received, the following EHR data was analyzed: age, sex, race, ethnicity, International Classification of Diseases, 9th (ICD-9) and 10th edition diagnostic codes (ICD-10) associated with glucose-6-dehydrogenase (G6PD) deficiency and methemoglobinemia, medication codes of common agents that were available to evaluate and that trigger acquired methemoglobinemia two weeks prior to the initial methemoglobin laboratory test, inotropic and vasoactive agents utilized to support the cardiovascular system, procedure codes (Common Procedural Terminology [CPT], International Classification of Diseases Procedural Coding System [ICD-10-PCS], and Healthcare Common Procedure Coding System [HCPCS]) evaluating for critical care service, mechanical ventilation, transfusion, oxygen saturation vital sign results, hemoglobin and hematocrit laboratory level results, G6PD testing occurrence (not results), and the frequency of all-cause deaths within 30 days of methemoglobin laboratory evaluation. The data provided was de-identified, thus no date of birth was provided, and therefore, ages are approximate. For example, a subject born in 2000 reported to have undergone methemoglobin laboratory testing on January 1st, 2018 (ie, the first day of critical care services), the subject was determined to be 18 years of age. Exact time of oxygen saturation, hemoglobin, hematocrit, methemoglobin level was not available. Thus, we reported the maximum values with the exception of the methemoglobin level, where we reported the minimum value.

### *Inclusion and exclusion criteria*

We included subjects (1) aged 0 to 18 years, (2) underwent methemoglobin laboratory testing for the first time in their EHR database history, (3) had a methemoglobin laboratory result of greater than or equal to 5%, and (4) had either undergone treatment for methemoglobinemia (ie, ascorbic acid, methylene blue, and hyperbaric oxygen) or were subsequently diagnosed with methemoglobinemia. We excluded subjects that did not meet these criteria.

### *Cohort designation*

We first divided the cohort into two groups (methemoglobin concentration level greater than 20% and less than 20%) to evaluate how clinicians approach methemoglobinemia based on the methemoglobin level.[1] While therapies can be implemented at any moment, especially if the patient is symptomatic or if there is a preexisting condition, clinical documentation was not available to be reviewed. Thus, a cutoff value of 20% was selected as patients below this level are usually asymptomatic.[1] Functional hemoglobin levels are not utilized to guide therapy, but because we had access to EHR laboratory data from multiple centers, we were able to examine how clinicians

treat cases based on functional hemoglobin levels. Therefore, for subjects where a hemoglobin was available, we calculated the functional hemoglobin and divided the cohort into two groups (functional hemoglobin level greater than 7 g/dL and less than 7 g/dL). The cutoff value of 7 g/dL was selected as this is the lowest acceptable level in hemodynamically stable children.[11] Functional hemoglobin was calculated by subtracting the patient's methemoglobin concentration level from their hemoglobin to assess the amount of hemoglobin that can effectively carry oxygen.

### *Statistical analysis*

Summary statistics using mean and standard deviation or proportions were reported for clinical and demographic characteristics of the patients included in the study. Due to the small sample size, categorical variables were compared using the Fisher exact test. All p values are two-sided and a $P < .05$ was considered significant. Analyses were performed using R© software version 3.5.2 (R Core Team, Vienna, Austria) utilizing the built-in epitools package.[12] A power analysis was not conducted for the present study as the data were collected through convenience sampling.

## Results

### *Demographic characteristics of patients with methemoglobinemia*

Between January 1st, 2004 and May 28th, 2022, 6 324 523 pediatric subjects from over 53 healthcare organizations were reported to have an inpatient or emergency encounter in the TriNetX© EHR database. Ninety-eight subjects were found to have an elevated methemoglobin level prompting treatment. Prevalence of methemoglobinemia was 0.0015%. Mean age was 5.3 ± 5.3 years with 36 (36.7%) females and 62 (63.3%) males. Please see Table 1 for further demographic details.

### *Clinical characteristics of patients with methemoglobinemia*

Of the laboratory results available, the mean maximum hemoglobin level was 10.8 ± 2.2 g/dL. These subjects were found to have a methemoglobin concentration level of 1.4 ± 1.1 g/dL, mean methemoglobin percent of 13.4 ± 9.1%, and functional hemoglobin level of 9.4 ± 2.0 g/dL. On the day of methemoglobin laboratory evaluation, pulse oximetry value was available in 59/98 cases (60.2%) and partial pressure of oxygen in arterial blood (PaO2) was reported in 33/98 subjects (33.7%) with mean maximum oxygen saturation being 91.8 ± 11.8% and mean maximum PaO2 being 172.23 ± 140.3 mm Hg (Table 1).

A small proportion of subjects were reported to have a congenital methemoglobinemia diagnostic code (6 [6.1%]) before and/or after the first methemoglobin level obtained in the subject's database history. Twenty-seven (27.6%) patients had a surgical procedure code the day prior to methemoglobin level being obtained (Table 1).

**Table 1.** Overview of subject and clinical characteristics of subjects with methemoglobin levels above 5%.

| CHARACTERISTICS | SUBJECTS WITH METHEMOGLOBIN LEVEL ABOVE 5% |
|---|---|
| Age (mean years, standard deviation) | 5.3 ± 5.3 |
| Sex (n, %) | |
| Female | 36 (36.7%) |
| Male | 62 (63.3%) |
| Race (n, %) | |
| American Indian or Alaska Native | 4 (4.1%) |
| Asian | 2 (2.0%) |
| Black or African American | 23 (23.5%) |
| White | 62 (63.3%) |
| Ethnicity (n, %) | |
| Hispanic or Latino | 10 (10.2%) |
| Not Hispanic or Latino | 74 (75.5%) |
| Subjects reported to have a surgical procedure before methemoglobin level (n, %) | 27 (27.6%) |
| Glucose-6-phosphate dehydrogenase diagnostic code frequency before and/or after methemoglobin level (n, %) | 5 (5.1%) |
| Congenital methemoglobinemia diagnostic code frequency before and/or after methemoglobin level (n, %) | 6 (6.1%) |
| Maximum hemoglobin level on day 0 (mean g/dL, standard deviation) | 10.8 ± 2.2 |
| Maximum hematocrit level on day 0 (mean %, standard deviation) | 31.9 ± 6.4 |
| Minimum methemoglobin concentration level on day 0 (mean g/dL, standard deviation) | 1.4 ± 1.1 |
| Minimum methemoglobin level on day 0 (mean %, standard deviation) | 13.4 ± 9.1 |
| Functional hemoglobin on day 0 (mean g/dL, standard deviation) | 9.4 ± 2.0 |
| Maximum oxygen saturation on day 0 (mean %, standard deviation)[a] | 91.8 ± 11.8 |
| Maximum partial pressure of oxygen on day 0 (mean mm Hg, standard deviation)[b] | 172.23 ± 140.3 |
| Death within 30 days (n, %) | 6 (6.1%) |

[a]Reported in 59/98.
[b]reported in 33/98 cases.

### *Frequency of common agents known to induce methemoglobinemia*

Of the agents most likely to induce acquired methemoglobinemia, lidocaine was noted to be at the highest frequency (16.3%) followed by dapsone (12.2%). All other agents identified are summarized in Table 2.

### *Summary of methemoglobinemia treatment in subjects with a methemoglobin level above 20% and below 20%*

Subjects with methemoglobin levels greater than 20% received a higher frequency of methylene blue and a lower frequency of vitamin C as compared to children with methemoglobin levels less than 20 % (12 [70.6%] vs 20 [24.7%]; $P = .0005$, and 1 [5.9%] vs 26 [32.1%]; $P = .0350$ respectively). Transfusion was higher in the less than 20% group (3 [17.6%] vs 45 [55.6%], $P = .007$).

Other treatments identified in the less than 20% group included hyperbaric oxygen (1 [1.0%]) and *N*-acetylcysteine (3 [3.7%]). There was no difference in vasoactive/inotropic use, critical care services, mechanical ventilation, diagnostic code frequency of congenital methemoglobinemia, or all-cause mortality (Table 3).

### *Impact of functional hemoglobin calculation on methemoglobinemia treatment requirements*

Functional hemoglobin was calculated for 86 (87.8%) subjects with available hemoglobin results. Patients with a functional hemoglobin greater than 7 g/dL had a similar requirement of critical care services (18 [24.3%] vs 5 [41.7%], $P = .290$), mechanical ventilation (9 [12.2%] vs4 [33.3%], $P = .079$), and methylene blue (24 [32.4%] vs 4 [33.3%], $P > .999$) as compared to those with levels less than 7 g/dL functional hemoglobin. The mean hemoglobin level, mean methemoglobin concentration level, and methemoglobin percentage of subjects with less than 7 g/dL functional hemoglobin were $7.2 \pm 2.1$ g/dL, $1.4 \pm 1.5$ g/dL, and $16.8 \pm 12.6$% (Table 4).

### *Frequency of methemoglobinemia deaths*

Of the 98 subjects identified, 6 (6.1%) died within 30 days of diagnosis of methemoglobinemia. All had a methemoglobin level less than 20%. Five received ascorbic acid, 1 subject was reported to have congenital methemoglobinemia, and none had a diagnosis of G6PD deficiency, were tested for G6PD deficiency, or received methylene blue (Table 1).

### *Frequency of concomitant glucose-6-phosphate dehydrogenase deficiency*

A total of 2 (2.0%) subjects had a history of G6PD deficiency prior to the first methemoglobin laboratory test and 3 (3.1%) subjects had received a diagnosis thereafter. Testing occurred in 13 subjects (13.3%), who did not have a prior history of G6PD deficiency. No subjects with a diagnosis of G6PD were administered methylene blue.

**Table 2.** Frequency of common agents that were present and known to induce acquired methemoglobinemia.

| AGENT (N, %) | FREQUENCY (N, %) |
|---|---|
| Atovaquone | 1 (1.0%) |
| Benzocaine | 1 (1.0%) |
| Dapsone | 12 (12.2%) |
| Lidocaine | 16 (16.3%) |
| Nitric oxide | 2 (2.0%) |
| Nitroprusside | 1 (1.0%) |
| Phenazopyridine | 1 (1.0%) |
| Prilocaine | 6 (6.1%) |
| Sulfamethoxazole | 5 (5.1%) |

## Discussion

The current literature on methemoglobinemia is sparse, with most reports limited to individual case reports and single center studies.[4,6-8] Utilizing the TriNetX® EHR database, we aimed to address this gap by using data from multiple centers. To our knowledge, our study is the first to describe this rare entity in this fashion. We found that methemoglobinemia prevalence in children is low within this EHR database network, there is a low frequency of G6PD testing despite methylene blue hemolysis risk, and subjects had a similar frequency of critical care services despite functional hemoglobin levels. These findings reinforce the importance of early recognition, evaluation, and treatment of this condition and highlights opportunities to improve care in children diagnosed with methemoglobinemia.

Methemoglobinemia is a rare condition.[13,14] This, combined with the variability in clinical presentation and misleading pulse oximetry readings, can pose a diagnostic challenge during the early stages of the disease.[13,14] If this condition is not recognized, significant morbidity and possibly mortality can occur.[4,15] Thus, a high index of suspicion is needed to recognize, evaluate, and provide appropriate treatment of this condition.[1] This is especially true in patients with refractory hypoxemia on pulse oximetry, a "saturation gap" between pulse oximetry readings and partial pressure of oxygen level on arterial blood gas analysis, and dark brown blood samples.[16]

Children are more susceptible to developing acquired methemoglobinemia.[15] They have a lower baseline activity of the red blood cell (RBC) enzyme cytochrome b5 reductase, which results in increased methemoglobin formation when exposed to an agent associated with this disease.[15] Additionally, their exploratory nature puts them at higher risk of being

**Table 3.** Evaluation of the impact of a methemoglobin level above 20% compared to below 20%.

| VARIABLE | ABOVE 20% | LESS THAN 20% | *P* VALUE |
|---|---|---|---|
| Total number of subjects (n, %) | 17 (17.3%) | 81 (82.7%) | – |
| Age (years, mean, standard deviation) | 4.3 ± 5.6 | 5.5 ± 5.3 | – |
| Methemoglobinemia therapy (n, %) | | | |
| Acetylcysteine | 0 (0.0%) | 3 (3.7%) | – |
| Ascorbic acid | 1 (5.9%) | 26 (32.1%) | .035 |
| Methylene blue | 12 (70.6%) | 20 (24.7%) | .0005 |
| Hyperbaric oxygen | 0 (0.0%) | 1 (1.2%) | – |
| Transfusion | 3 (17.6%) | 45 (55.6%) | .007 |
| Inotropic/vasoactive presence (n, %) | 3 (17.6%) | 18 (22.2%) | >.999 |
| Dobutamine | 0 (0.0%) | 1 (1.2%) | – |
| Dopamine | 0 (0.0%) | 3 (3.7%) | – |
| Epinephrine | 3 (17.6%) | 13 (16.0%) | – |
| Norepinephrine | 0 (0.0%) | 4 (4.9%) | – |
| Phenylephrine | 0 (0.0%) | 3 (3.7%) | – |
| Vasopressin | 0 (0.0%) | 4 (4.9%) | – |
| Critical care services (n, %) | 5 (29.4%) | 18 (22.2%) | .538 |
| Mechanical ventilation (n, %) | 1 (5.9%) | 12 (14.8%) | .455 |
| Deaths within 30 days (n, %) | 0 (0.0%) | 6 (7.4%) | .586 |
| Congenital methemoglobinemia diagnostic code frequency before and/or after methemoglobin level (n, %) | 1 (5.9%) | 5 (6.2%) | >.999 |
| Any methemoglobinemia diagnostic code frequency before and/or after methemoglobin level (n, %) | 12 (70.6%) | 65 (80.2%) | .515 |
| Glucose-6-phosphate dehydrogenase diagnostic code frequency before and/or after methemoglobin level (n, %) | 0 (0.0%) | 5 (6.2%) | .584 |
| Maximum hemoglobin level on day 0 (mean g/dL, standard deviation) | 11.3 ± 1.8 | 10.7 ± 2.3 | – |
| Maximum hematocrit level on day 0 (mean %, standard deviation) | 32.4 ± 6.1 | 31.8 ± 6.5 | – |
| Minimum methemoglobin level on day 0 (mean %, standard deviation) | 29.6 ± 9.4 | 9.9 ± 4.0 | – |
| Minimum methemoglobin concentration level on day 0 (mean g/dL, standard deviation) | 3.2 ± 1.4 | 1.0 ± 0.5 | – |
| Functional hemoglobin on day 0 (mean g/dL, standard deviation) | 8.1 ± 1.4 | 9.6 ± 2.1 | – |
| Maximum oxygen saturation on day 0 (mean %, standard deviation) | 88.1 ± 17.0 | 92.8 ± 9.9 | – |
| Maximum partial pressure of oxygen on day 0 (mean mm Hg, standard deviation) | 287.4 ± 190.0 | 156.4 ± 128.4 | – |

exposed to household chemicals, some of which can trigger methohemoglobinemia.[15] Therefore, it is important to understand how children are managed when they develop this rare condition.

While a majority of patients with methemoglobinemia survive this condition, fatalities are possible.[1,4] To avoid this, the primary goal of treating a patient with methemoglobinemia is to remove the inciting agent, improve the oxygen carrying capacity of hemoglobin by providing a reducing agent, and ensure supportive care is provided.[15] Several factors need to be taken into consideration including the patient's age, total amount of methemoglobin, cause of methemoglobinemia, and symptoms.[4] Based on previous studies, it is recommended that symptomatic patients with methemoglobin levels greater than

**Table 4.** Evaluation of the impact of a functional hemoglobin level greater than 7 g/dL compared to below 7 g/dL.

| VARIABLE | FUNCTIONAL HEMOGLOBIN LEVEL GREATER THAN 7 g/dL | FUNCTIONAL HEMOGLOBIN LEVEL LESS THAN 7 g/dL | *P* VALUE |
|---|---|---|---|
| Total number of subjects (n, %) | 74 (86.0%) | 12 (14.0%) | – |
| Age (mean years, standard deviation) | 5.7 ± 5.6 | 3.7 ± 4.0 | |
| Methemoglobinemia therapy (n, %) | | | |
| Acetylcysteine | 3 (4.1%) | 0 (0.0%) | >.999 |
| Ascorbic acid | 22 (29.7%) | 3 (25.0%) | >.999 |
| Methylene blue | 24 (32.4%) | 4 (33.3%) | >.999 |
| Hyperbaric oxygen | 1 (1.4%) | 0 (0.0%) | >.999 |
| Transfusion | 38 (51.4%) | 7 (58.3%) | .760 |
| Inotrope/vasoactive presence (n, %) | 15 (20.3%) | 4 (33.3%) | .452 |
| Dobutamine | 1 (1.4%) | 0 (0.0%) | >.999 |
| Dopamine | 3 (4.1%) | 0 (0.0%) | >.999 |
| Epinephrine | 11 (14.9%) | 3 (25.0%) | .404 |
| Norepinephrine | 3 (4.1%) | 1 (8.3%) | .458 |
| Phenylephrine | 2 (2.7%) | 1 (8.3%) | .367 |
| Vasopressin | 3 (4.1%) | 1 (8.3%) | .458 |
| Critical care services (n, %) | 18 (24.3%) | 5 (41.7%) | .290 |
| Mechanical ventilation (n, %) | 9 (12.2%) | 4 (33.3%) | .079 |
| Deaths within 90 days (n, %) | 5 (6.8%) | 1 (8.3%) | >.999 |
| Congenital methemoglobinemia diagnostic code frequency before and/or after methemoglobin level (n, %) | 5 (6.8%) | 0 (0.0%) | >.999 |
| Any methemoglobinemia diagnostic code frequency before and/or after methemoglobin level (n, %) | 58 (78.4%) | 12 (100.0%) | .112 |
| Glucose-6-phosphate dehydrogenase diagnostic code frequency before and/or after methemoglobin level (n, %) | 3 (4.1%) | 2 (16.7%) | .141 |
| Maximum hemoglobin level on day 0 (mean g/dL, standard deviation) | 11.4 ± 1.6 | 7.2 ± 2.1 | – |
| Maximum hematocrit level on day 0 (mean %, standard deviation) | 33.4 ± 4.8 | 22.6 ± 7.7 | – |
| Minimum methemoglobin level on day 0 (mean %, standard deviation) | 12.3 ± 7.7 | 16.8 ± 12.6 | – |
| Minimum methemoglobin concentration level on day 0 (mean g/dL, standard deviation) | 1.4 ± 1.0 | 1.4 ± 1.5 | – |
| Functional hemoglobin on day 0 (mean g/dL, standard deviation) | 9.9 ± 1.5 | 5.8 ± 1.2 | – |
| Maximum oxygen saturation on day 0 (mean %, standard deviation) | 92.0 ± 12.4 | 89.1 ± 10.2 | – |
| Maximum partial pressure of oxygen on day 0 (mean mm Hg, standard deviation) | 191.3 ± 141.2 | 155.9 ± 148.4 | – |

20% and asymptomatic patients with levels above 30% receive treatment with methylene blue.[1] In the present study, subjects with a methemoglobin level above 20% received methylene blue, but did not have more critical care service needs or mortality when compared to subjects with levels less than 20%. One can surmise that since this population was probably symptomatic, they were likely treated urgently and appropriately with methylene blue. However, one needs to bear caution while

administering this drug. Individuals who have G6PD deficiency may present with significant hemolytic anemia since methylene blue is an oxidizing agent. Also, when used in higher doses, it may result in proportionately higher levels of oxidizing agent methylene blue, rather than the reducing agent, leukomethylene blue. Since G6PD is the first enzyme in the hexose monophosphate shunt, the only source of nicotinamide adenine dinucleotide phosphate (NADPH) in the erythrocyte, patients with G6PD deficiency may not produce sufficient NADPH to reduce methylene blue to leukomethylene blue. Thus, methylene blue therapy may be ineffective and potentially very dangerous in a G6PD patient with methemoglobinemia. Generally, symptom severity is related to methemoglobin level but pre-existing conditions can potentially intensify symptoms at lower levels. Thus, this may have resulted in the observed similarities in critical care service needs and mortality. Further study is needed to evaluate how frequently this occurs and its impact on mortality.

There are alternative treatments that may be utilized to treat methemoglobinemia. In our study, these treatments included ascorbic acid, hyperbaric oxygen therapy, and acetylcysteine. Ascorbic acid was the second most common medication administered. It has reducing potential and has the advantage of being administered to patients who are at risk or have G6PD deficiency.[1] In patients who are refractory to methylene blue or ascorbic acid, hyperbaric oxygen therapy may be utilized. Our study identified 1 patient who underwent this therapy. Hyperbaric oxygen therapy may be beneficial as it also acts a reducing agent, facilitates reoxygenation, and inhibits hemoglobin oxidation.[17] Acetylcysteine was also administered to 1 subject in our study. Its use has been described and it also can reduce methemoglobin levels, but its effectiveness is unclear.[1,18,19]

Ideally, all patients should have G6PD tested prior to methylene blue administration. In our study, a total of 5 subjects were diagnosed to have G6PD deficiency. This prevalence is consistent with previously reported United States based data.[20,21] No subjects with G6PD received methylene blue. Thirteen subjects who did not have a prior history or diagnosis of G6PD deficiency, however, were tested for it. Since G6PD testing is not universally screened during the neonatal period, many children may present without a prior diagnosis.[7,20] It is unknown why G6PD testing did not occur in a majority of subjects after a patient was evaluated and treated for methemoglobinemia. The test may not have been obtained because the patient did not have signs or symptoms of hemolysis. Alternatively, the patient may have had signs and symptoms of hemolysis which may result in a false negative if the test was obtained during this time period.[22] There may have been no family history to prompt testing. Finally, while it is reasonable to obtain testing for G6PD before starting an oxidant medication,[23] it is not recommended, to our knowledge, to obtain G6PD testing after methemoglobinemia diagnosis. When G6PD is clinically suspected (ie, unexplained acute hemolytic anemia in setting of an acute illness or after ingesting a medication or food), it is recommended that evaluation should occur especially since universal screening is not conducted.[20,22] Further research is necessary to determine the potential benefits of conducting such testing following a diagnosis of methemoglobinemia, similarly to protocols in other conditions like acute leukemia, where potentially hemolytic drugs such as rasburicase may be administered.[24]

When treating a patient with methemoglobinemia, it is recommended to calculate the methemoglobin level (hemoglobin [g/dL] × methemoglobin [%]), since clinical severity may differ significantly between two patients with the same methemoglobin % based on the degree of anemia. An acute drop in a person's functional hemoglobin may significantly impact the oxygen carrying capacity and these patients are often more symptomatic.[5,6] In our cohort, we found that patients with functional hemoglobin less than 7 g/dL had a similar critical care service requirement, transfusion needs, and methylene blue administration when compared to subjects with a functional hemoglobin above 7 g/dL. Despite being potentially more critically ill, it is unclear why. It is possible that the condition and severity of illness was unrecognized. Because the data is obtained from EHR medication codes, it is also possible more methylene blue was administered, but was not reported. Aggressive treatment in this subset of patients irrespective of methemoglobin percentage would ensure improvement in functional hemoglobin responsible for oxygen delivery.

This study has several limitations. First, our study was limited by sample size and retrospective design. Second, due to database limitations, no documentation of the clinical symptoms or clinical circumstances were available. Thus, the authors could not determine if and how the presence of severity of clinical symptoms played a role in determining therapeutic approach. Thirdly, there was no data available to suggest if other diagnostic modalities such as CO-oximetry was used to assist in the diagnosis of methemoglobinemia. Despite lidocaine being the most likely inciting agent causing methemoglobinemia, it is unclear what the indications were. Studies have linked the use of local anesthetics being used in procedures such as transesophageal echocardiography and bronchoscopy with methemoglobinemia.[14,15] It may also be used in routine procedures such as lumbar puncture or venipuncture.[25] While methemoglobinemia associated with lidocaine is possible (particularly in neonates), it has been rarely reported.[25] Though a significant number of patients received blood transfusion (especially in subjects with a methemoglobin level less than 20%), database limitations did not allow us to determine if this was utilized as a treatment of methemoglobinemia or if the patient had a pre-existing condition (ie, cardiac or pulmonary disease) that required this treatment.[1] We identified the cohort for this study by the presence of a methemoglobin level and result, assuming that the level was obtained in either an emergency or hospital

setting. Not all subjects had a reported encounter type (ie, emergency), thus the clinical indications for this test was not known. Furthermore, we selected 20% as the lower cutoff limit, as this is the lowest level therapies could be implemented for methemoglobinemia. It is recommended, however, that treatment at this level should only be initiated if the patient is symptomatic or has an underlying cardiac or pulmonary disease. Convenience sampling was utilized for this study thus a power analysis was not performed. Specific causes of death are not reported. Thus, while the death could be related to methemoglobinemia, it is also possible the death was due to a different etiology. Because we were unable to review clinical documentation due to database limitations, it is unknown if treatments were initiated because these conditions were present. The frequency of G6PD testing may have been lower as some subjects may have been lost to follow-up (and may have reestablished care with a healthcare organization outside the TriNetX© network). Finally, limitations of this database precluded us from analyzing with more granularity (ie, review of clinical notes to determine the reasoning of why therapies were instituted or why critical care was required). Further research may be necessary to further assess the prognostic factors and its impact on the outcomes measured in this study.

## Conclusion

Methemoglobinemia remains one of the rare, but potentially fatal, entities that the pediatric population is at higher risk for. Using a multi-center EHR database, we found that a low frequency of G6PD testing was performed after methemoglobinemia diagnosis. In our study, we found methemoglobinemia prevalence in children is low, there is a low frequency of G6PD testing despite methylene blue hemolysis risk, and subjects with functional hemoglobin less than 7 g/dL required similar critical care services and methylene blue administration when compared to subjects with a functional hemoglobin above 7 g/dL. These findings highlight the continued critical nature of this disease and may highlight opportunities to improve care in children diagnosed with methemoglobinemia in the area of G6PD testing.

## Declarations

### *Ethical Approval and Consent to Participate*

Because no protected health information is provided, the Penn State Health Institutional Review Board (IRB) pre-determined this study to be non-human research (IRB#: STUDY00020794). Informed consent was waived by the Penn State Health Institutional Review Board (IRB) as consent would be impossible or impracticable to obtain due to the deidentified nature of the TriNetX© database.

### *Consent for Publication*

Not applicable.

### *Author Contributions*

Neha Sinha: Conceptualization, Methodology, Writing original draft preparation, Data curation, and Data Analysis. Brooke Lichak: Data analysis, Writing—Reviewing, and Editing. Neal J Thomas: Methodology, Writing—Reviewing and Editing. Conrad Krawiec: Conceptualization, Methodology, Data Curation, Formal Analysis, Writing Reviewing, and Editing.

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### *Competing Interests*

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### *Availability of Data and Materials*

The data that support the findings of this study are available from TrinetX (c). Restrictions apply to the availability of these data, which were used under license for this study.

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