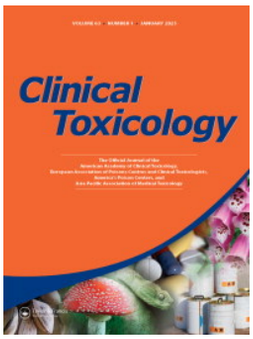

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CLINICAL RESEARCH

Regional readiness for sodium nitrite-induced methemoglobinemia: availability of methemoglobin testing and methylthioninium chloride (methylene blue) stocking in the Upper Midwestern United States

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ABSTRACT

Introduction: Sodium nitrite is a potent oxidizer, which may precipitate rapidly lethal methemoglobinemia. Prompt diagnosis and treatment may salvage otherwise fatal cases. It is unclear if emergency departments are prepared for increasing cases. We describe the availability and geographic distribution of real-time methemoglobin testing and methylthioninium chloride (methylene blue) availability in three contiguous United States.

Methods: This is a cross-sectional survey of hospitals served by a regional poison center in the Upper Midwestern United States. Hospitals were identified by cross-referencing poison center, health department, and state trauma databases. We queried methemoglobin testing capabilities of each site as well as immediate methylthioninium chloride availability. Resulting data are described with descriptive statistics, and predictors of testing and treatment availability are evaluated in multivariable logistic regression.

Results: We identified 320 hospitals with emergency care, analyzing 228 (71.3%) after exclusions. Real-time methemoglobin testing was available at 56 sites (30.6% of 183 respondents). Of hospitals describing methylthioninium chloride availability, 59.4% (130/219) reported having it on-site. A significant difference in real-time methemoglobin testing existed across largest and smallest population strata in adjusted analysis (OR: 64.6: 95% CI: 4.1–1,037). Similarly disparate availability of methylthioninium chloride was observed. Spatial distribution of methemoglobin testing and methylthioninium chloride availability demonstrated notable urban-rural disparities.

Discussion: These data demonstrate a wide disparity in the availability of real-time methemoglobin testing and methylthioninium chloride availability, suggesting that the region is ill-prepared to care for severe methemoglobinemia. Our analysis points to a disconnect between our current poison center recommendations and the capacities of our consulting institutions.

Conclusions: We demonstrate urban-rural disparities in diagnostic and therapeutic capacity for the management of acute methemoglobinemia in this region, as well as significant geographic variations in methylthioninium chloride stocking and poisoning preparedness. Poison centers must therefore maintain an awareness of antidote availability for this emerging toxicological emergency.

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Introduction

Acquired methemoglobinemia may be precipitated by environmental [1, 2] or therapeutic [3] exposures. Less commonly, hereditary enzyme deficiencies may also lead to the development of methemoglobinemia [4]. Both processes are characterized by the oxidation of hemoglobin from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state, rendering it unable to transport oxygen and resulting in a functional anemia, decreased oxygen transport capacity and, in more severe cases, to ischemic end organ damage. In addition, low levels of endogenous methemoglobin are normal, resulting from red blood cell turnover and endogenous autoxidation and reduction mechanisms [5,6]; methemoglobin levels may increase with exposure to oxidative stress. At levels greater than 15–20%, methemoglobinemia results in escalating symptoms and a characteristic phenotype of cyanosis, erroneous peripherally estimated hypoxemia, and a classically described "chocolate brown" hue to the blood [7–9]. Patients with methemoglobin levels of greater than 50% commonly present with coma, acidosis, and seizures, while levels greater than 70% are frequently fatal [10].

Recently published data from the National Poison Data System® revealed that more than half of all clinically significant cases of acquired methemoglobinemia reported to United States (US) poison centers over a 10-year period (2007–2017) were reportedly caused by dapsone, nitrates/nitrites, or other substances [11]. Many historically reported cases are subacute in nature and related to chronic exposures [12] or otherwise without fulminant course [13]; rarely

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are they fatal. However, there are signals in the literature to suggest that a new wave of acquired methemoglobinemia with substantially worse outcomes may be upon us, particularly as social media platforms increasingly provide evolving conduits of information and interactions associated with negative mental health outcomes, including suicidality [14–17]. In particular, reports of sodium nitrite ingestions have become increasingly common, with multiple deaths and critically ill patients recently described [18–24]. This particular form of self-harm is both highly lethal and highly treatable if addressed in a truly emergent fashion.

While methemoglobinemia is often a clinical diagnosis, co-oximetry remains the diagnostic standard of care. Methylthioninium chloride (methylene blue) is the preferred antidote to treat symptomatic patients and those with high methemoglobin levels [8,21]; immediate treatment with methylthioninium chloride is crucial to salvage rapidly progressive and critically ill cases.

Poison centers play a critical role in the management of poisoned patients [25], providing expert advice to callers remotely rather than at the bedside [26]. The implementation of these recommendations – including specific antidotal therapies – presumes the bedside availability of diagnostic and therapeutic modalities. Previously published consensus guidelines support the immediate availability of laboratory testing for methemoglobin in emergency department patients [27], as well as and for the stocking of methylthioninium chloride in hospitals providing emergency care [28], but neither the availability of real-time methemoglobin testing nor methylthioninium chloride is well-characterized. In light of the emergence of sodium nitrite ingestions as a cause of fulminant methemoglobinemia, the availability of testing and antidotes is increasingly important for bedside providers.

The aim of this study was to describe the availability and geographic distribution of real-time methemoglobin testing and methylthioninium chloride in a three-state area in the Upper Midwestern US served by a single regional poison center, and to identify predictors of availability of methemoglobin testing and methylthioninium chloride in the same region.

Methods

Study design and setting

This is a cross-sectional telephonic survey of all hospitals within Minnesota, North Dakota and South Dakota conducted during March and April 2022. The included states represent the catchment area for the Minnesota Regional Poison Center, one of 55 nationally accredited poison centers in the US [25].

Selection of participating sites

Hospitals were identified by review of state health department websites, trauma registries, and nondirected internet searches to seek out potential sites not otherwise listed. Where necessary, poison center records were reviewed for further inclusions. We included sites if they maintained a functioning emergency department at the time of the call, and if efforts to contact them were successful. Sites were excluded if no functioning emergency department was located on site, if the site or its emergency department were no longer operational, if attempts to contact the site were unsuccessful, or if respondents refused to answer questions.

Measurements

The outcomes of interest in this study were the availability of real-time methemoglobin testing and access to methylthioninium chloride onsite. In general, queries were initially directed to emergency departments, and within emergency departments to charge nurses. Callers introduced themselves and the purpose of their call, and asked to speak with the charge nurse, if available. Respondents were asked:

a. If methemoglobin testing is available as an order on site;
b. If methemoglobin results are available in real time ("stat");
c. If methylthioninium chloride is available on site; and
d. How many vials of methylthioninium chloride are available on site, if known.

Further query was directed at availability of non-real time testing and whether methylthioninium chloride was immediately available within the emergency department. In the US, methylthioninium chloride is available in 50 mg/10 mL, 1 mg/10 mL and 20 mg/2 mL preparations; due to time constraints, neither vial size nor concentration were queried. This study was deemed not human research by the institutional review board of Hennepin Healthcare.

When queries regarding methemoglobin testing availability and methylthioninium chloride availability were met with uncertainty, we requested transfer to providers better equipped to respond to these questions, including hospital laboratories for methemoglobin testing and pharmacies for methylthioninium chloride. We recorded the position of the respondent within the hospital (charge nurse, physician, pharmacist, laboratory professional) to account for potential reporting bias. If available response time was limited and/or appropriate personnel were unavailable, follow-up calls to the same site were undertaken as necessary to collect study data points.

To these data we added the population size of the city hosting the hospital, as well as the American College of Surgeons trauma designation for each hospital, the latter to provide a proxy assessment for resource availability. American College of Surgeons trauma designations are known to be a limited surrogate marker for resource availability based on published standards requiring the presence of higher levels of medical specialty coverage at higher American College of Surgeons trauma designations [29]. Categorization of city size was originally categorized according to US Census Bureau designations. The US Census Bureau defines areas as "rural" (<2,500 inhabitants), "urban clusters" (2,500–<50,000 inhabitants) or "urbanized areas" (≥50,000 inhabitants) [30]. However, because lost precision was identified as a potential risk of defining urban and rural areas via the US Census Bureau

definition, we defined our sites as populations of ≤2,500, 2,501–25,000, 25,001–250,000, and >250,000 inhabitants, in accordance with US Office of Management & Budget classifications [31].

Outcomes

We report the capability of all included hospitals to complete real-time methemoglobin testing, and the immediate availability of methylthioninium chloride. Availability and location of the methylthioninium chloride within the hospital were recorded, when known.

Analyses

Univariate analyses of data were conducted utilizing Pearson's χ^2 or Fisher's exact test as indicated. Multivariate logistic regression was applied to control for confounding by independent variables in predicting both methylthioninium chloride availability and methemoglobin testing availability. Data was entered into a REDCap [32] database in real time, and subsequently was analyzed utilizing Stata/BE 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). Regression output is reported as per Cole [33]. A sensitivity analysis was completed to compare our utilized US Office of Management & Budget population designations to an analysis using US Census Bureau population designations to compare urban to rural areas. Sites were geospatially distributed using ArcGIS Pro (Esri Inc. 2021. Redlands, CA: Esri™).

Results

Characteristics of healthcare facilities

Over the course of the study, we initially identified 320 healthcare facilities within the catchment area of the regional poison center. Further review and telephonic follow-up identified five duplicate records and one previously unidentified healthcare facility, and yielded successful contacts of four more previously unreachable institutions. In total, we added five sites and excluded 97 sites (30.3%): fifty-two (53.6%) duplicate records, 33 (34%) sites without emergency departments, six (6.2%) that had closed, four (4.1%) that we were unable to contact prior to analyses, and two (2.1%) that were not hospitals. Thus, after all exclusions and identification of eligible sites, 228 (71.3%) were included for analysis (Figure 1).

The majority of sites (132, 57.9%) were located in Minnesota; an additional 43 (18.9%) were located in North

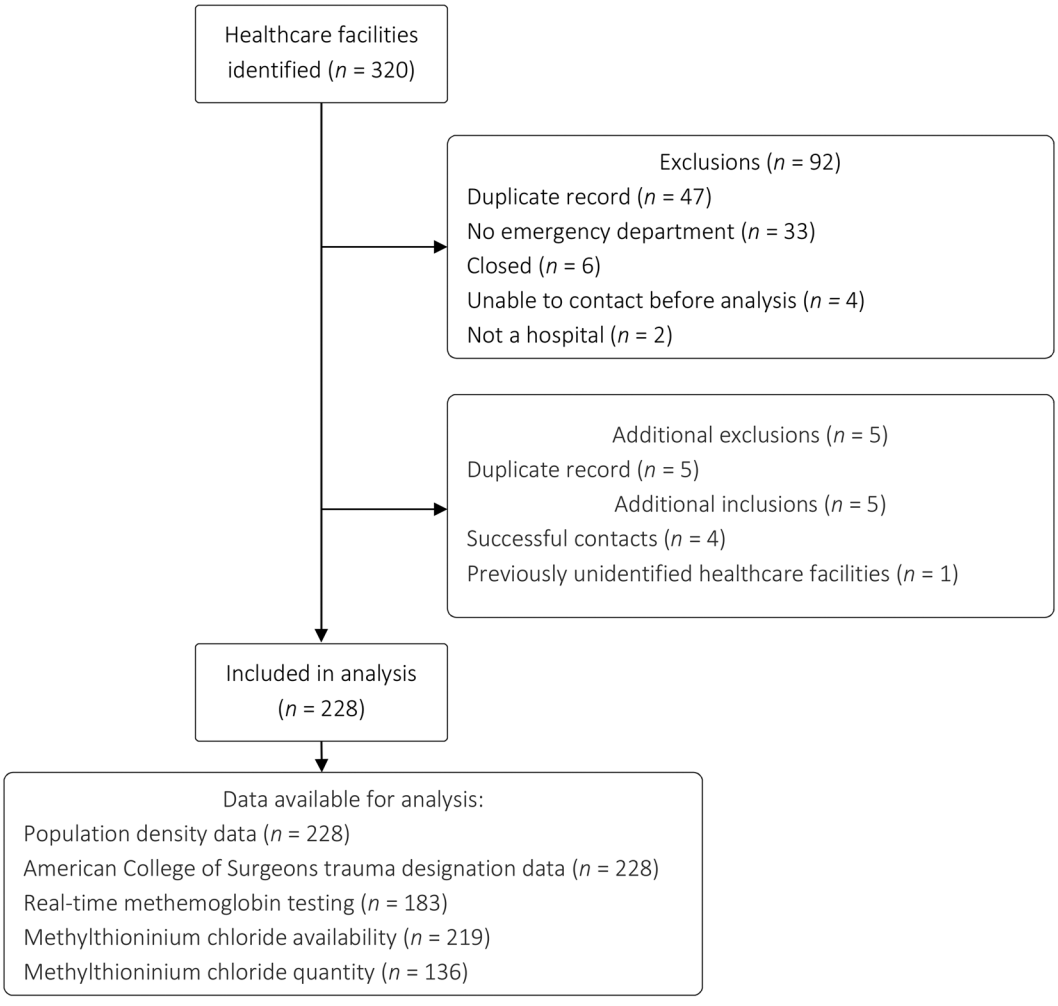


Figure 1. Study flowchart.

Dakota and 53 (23.3%) in South Dakota. Data describing population size was available for all 228 sites. The geographic distributions of real-time methemoglobin testing and methylthioninium chloride availability are illustrated in Figures 2 and 3, respectively.

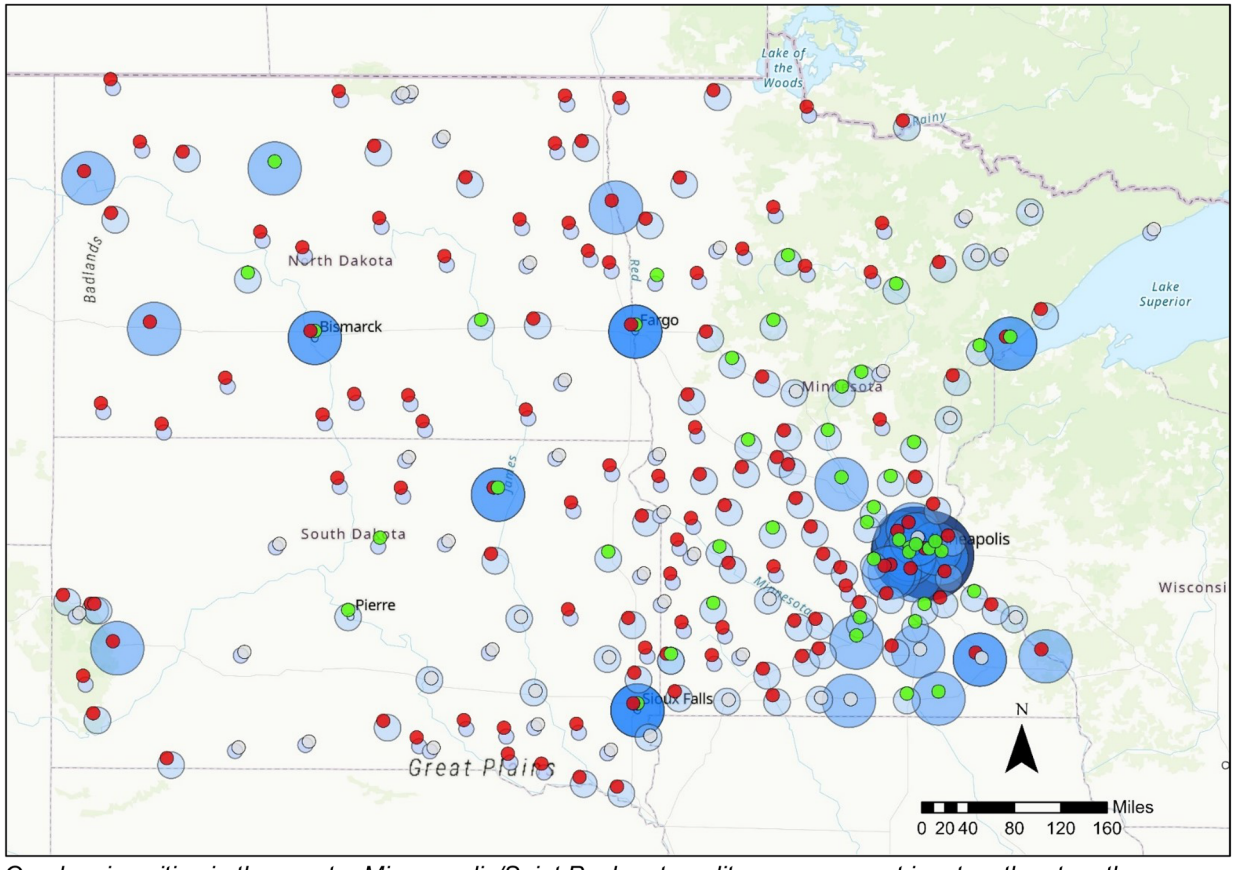
The American College of Surgeons trauma designation was available for all but 17 (7.5%) sites with other or unknown designations. Except for one level I trauma center in North Dakota, the remainder ($n = 5$) were located in Minnesota. Level IV and V designations accounted for the majority of hospitals in Minnesota (112, 84.9%), North Dakota (34, 79.1%), and South Dakota (43, 81.1%). Table 1 fully characterizes the American College of Surgeons trauma designations.

Main results

Of 228 responses to the availability of methemoglobin testing, 183 (80.3%) sites reported availability of methemoglobin testing, 42 (18.4%) reported no access to methemoglobin testing, and three (1.3%) were unknown. Information regarding methylthioninium chloride availability was provided by 219/228 (96.1%) sites: 130 (59.4%) sites reported methylthioninium chloride availability, 84 (38.4%) reported no methylthioninium chloride availability, and 5/219 (2.3%) sites were uncertain of methylthioninium chloride availability. Only 16 sites (7.34%) reported stocking of methylthioninium chloride within the emergency department, and correlation between methylthioninium chloride availability and real-time methemoglobin testing was poor (Pearson's correlation coefficient = 0.16).

Methemoglobin testing availability

Overall, 56/183 (30.6%) sites reported capacity for real-time methemoglobin testing, whereas 127 (69.4%) reported that such testing was unavailable or available only as a send out laboratory test. Availability of real-time testing varied



Overlapping cities in the greater Minneapolis/Saint Paul metropolitan area are not inset as they together represent a singular metropolitan area.

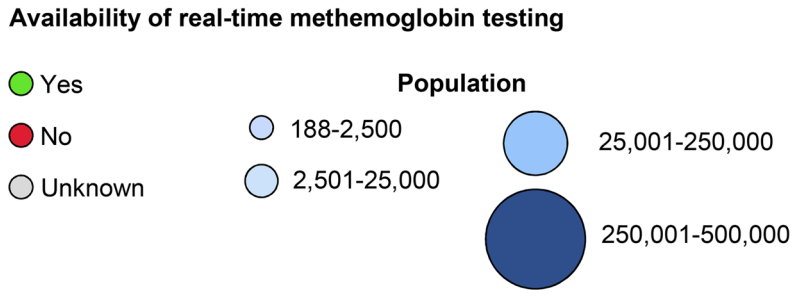


Figure 2. Geospatial distribution of real-time methemoglobin testing across three states in the Upper Midwestern United States.

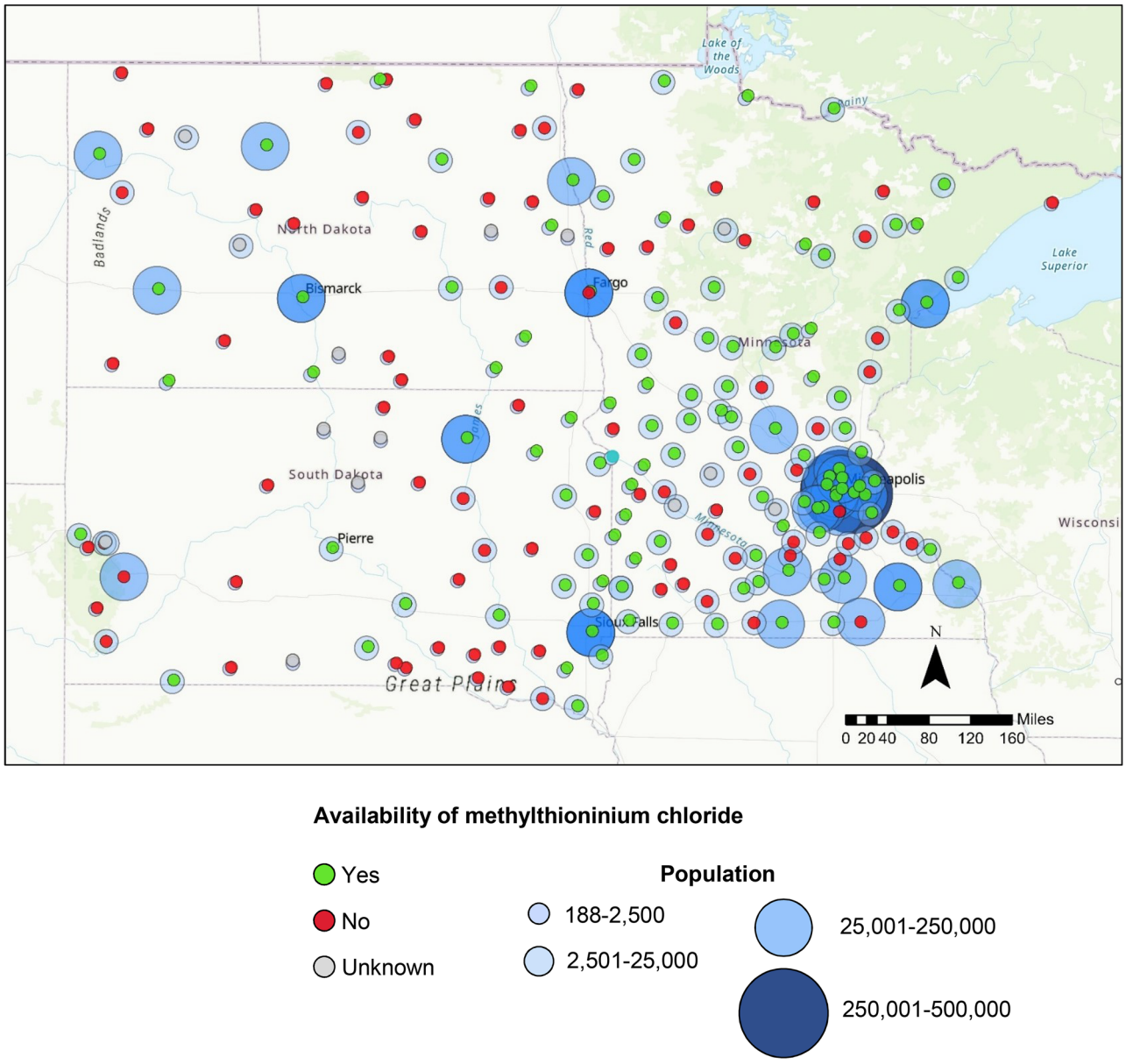


Figure 3. Geospatial distribution of methylthioninium chloride (methylene blue) across three states in the Upper Midwestern United States.

significantly by state (Pearson's χ^2 = 11.5, P=0.003) in univariate analyses. Pairwise comparisons revealed significant differences between Minnesota and North Dakota (Pearson's χ^2 = 7.4, P=0.007), and between Minnesota and South Dakota (Pearson's χ^2 = 6.14, P=0.013), but no difference was noted between North Dakota and South Dakota (Pearson's χ^2 = 0.024, P=0.88).

Availability of real-time methemoglobin testing by trauma designation ranged from 4.65% (Level V) to 83.3% (Level I) and was more likely among sites with higher American College of Surgeons trauma designations (Fisher's exact test P<0.001; Figure 4(A)). Stratification by urban or rural strata demonstrated a similar distribution of real-time methemoglobin testing that varied significantly across urban and rural populations in univariate analyses (Figure 4(C)), with healthcare facilities in urbanized areas significantly more likely to have real-time testing available (Fisher's exact test P<0.001).

Availability of real-time testing did not vary by respondent (Fisher's exact P=0.082). However, this univariate assessment was impacted by the distribution of respondents, with 175/183 (95.6%) of responses provided by laboratory staff, and only 8/183 (4.4%) of responses provided by nursing staff, pharmacists, or physicians.

When controlled for state, population size, the American College of Surgeons trauma designations, and data reporter via logistic regression, availability of real-time methemoglobin testing did not vary by state, American College of Surgeons designation, or respondent; the latter was ultimately excluded from the final model due to high collinearity. A significant difference in real-time methemoglobin testing availability remained across population strata in multivariate testing. Comparing largest and smallest strata, the odds ratio for real-time methemoglobin testing availability was 64.6 (P=0.003; 95% CI: 4.1–1037).

Methylthioninium chloride availability

Methylthioninium chloride was reported available at 130 (59.4%) of responding hospitals. Few sites (16/228, 7.34%) reported that methylthioninium chloride was physically stocked

Table 1. Real-time methemoblobin testing and on-site methylthioninium chloride availability.

		Respondents, *n* (%)	Reporting real-time methemoglobin testing, *n* (%)	Reporting methylthioninium chloride available, *n* (%)
State	Minnesota	132 (57.9)	44/132 (33.3)	90/132 (68.2)
	North Dakota	43 (18.9)	6/43 (14.0)	17/43 (39.5)
	South Dakota	53 (23.3)	6/53 (11.3)	23/53 (43.4)
American College of Surgeons trauma designation	I	6 (2.63)	5/6 (83.3)	6/6 (100.0)
	II	15 (6.58)	9/15 (60.0)	14/15 (93.3)
	III	22 (9.65)	11/22 (50.0)	19/22 (86.4)
	IV	108 (47.4)	27/108 (25.0)	67/108 (62.0)
	V	60 (26.3)	2/60 (3.33)	16/60 (26.7)
	No known designation	14 (6.14)	1/14 (7.14)	7/14 (50.0)
	Other/unknown	3 (1.32)	1/3 (33.3)	1/3 (33.3)
City size	≤2,500 inhabitants	83 (36.4)	2/55 (3.6)	25/77 (32.5)
	2,501–25,000	96 (42.1)	27/83 (32.5)	60/93 (64.5)
	25,001–250,000	38 (16.7)	17/34 (50)	34/38 (89.5)
	>250,000	11 (4.82)	10/11 (90.9)	11/11 (100)
Respondents				
Methemoglobin	Nurse	4/183 (2.2)	0/4	-
	Laboratory staff	175/183 (95.6)	53/175 (30.3)	-
	Pharmacist or pharmacy staff	1/183 (0.006)	1/1 (100)	-
	Physician	1/183 (0.006)	0/1	-
	Other	2/183 (0.007)	2/2 (100)	-
Methylthioninium chloride	Nurse	29/219 (13.2)	-	7/29 (24.1)
	Laboratory staff	17/219 (7.8)	-	3/17 (17.7)
	Pharmacist or pharmacy staff	172/219 (78.5)	-	119/172 (69.2)
	Physician	0/219	-	-
	Other	1/219 (0.005)	-	1/1 (100)
Total			56/183 (30.6)	130/219 (59.4)

- Indicates no respondents of this class.

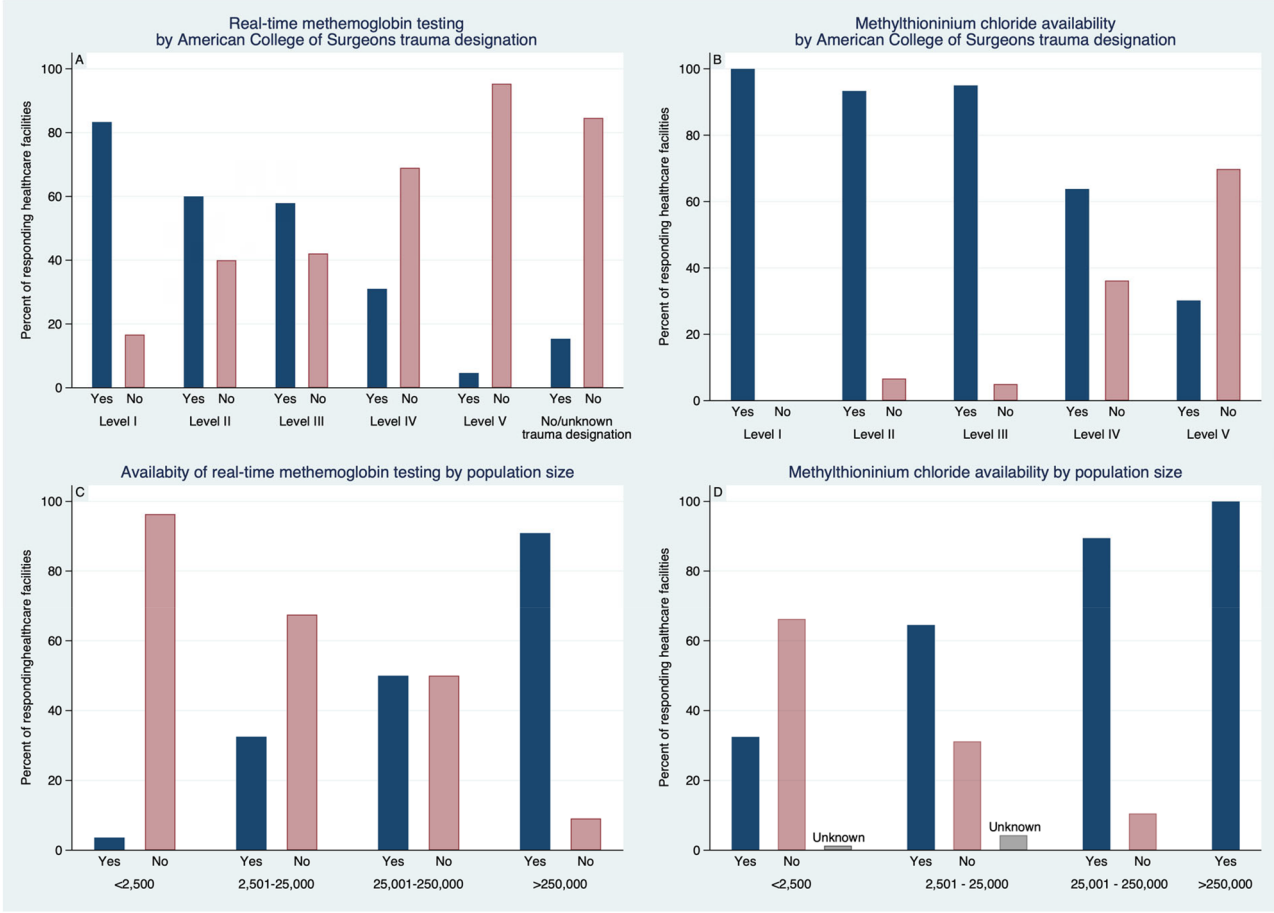


Figure 4. Methemoglobin testing and methylthioninium (methylene blue) availability by population size and American College of Surgeons trauma certification level.

in the emergency department. Availability of methylthioninium chloride varied across states (70.3% of hospitals in Minnesota, 44.7% in North Dakota, and 47.9% in South Dakota, Pearson's $\chi^2 = 12.31$; $P=0.002$). Among the 130 sites reporting methylthioninium chloride availability, 41 (31.5%) also reported access to real-time methemoglobin testing (Table 1).

Methylthioninium chloride availability varied significantly by respondent (Fisher's exact $P<0.001$); however, the variability of answers by respondent – 7/29 (24.1%) registered nurses, 3/17 (17.6%) laboratory staff, and 119/169 (70.4%) pharmacists reported methylthioninium chloride availability – suggested variability in knowledge regarding antidote stocking and a probable source of reporting bias (Table 1).

Level I and III trauma centers were significantly more likely to report availability of methylthioninium chloride than those with level V designations (level 3 versus level 5 OR: 21.7; 95% CI: 1.88–251) (Figure 4(B)). Availability varied by population strata in regression modeling, with sites from smaller strata significantly less likely to have available methylthioninium chloride than those from each larger strata (Figure 4(D)). Full results of logistic regression are reported in Tables 2 and 3. Because level I trauma designation and population >250,000 imperfectly predicted availability of methylthioninium chloride, odds ratios are not reported in regression modeling.

Table 2. Logistic regression results for availability of real-time methemoglobin testing.

	Odds ratio	Standard error	z	$P>z$	95% confidence interval
State					
Minnesota	Reference group				
North Dakota	0.99	0.69	−0.02	>0.9	0.253–3.85
South Dakota	1.32	0.91	0.4	0.7	0.341–5.1
City size					
≤2,500	Reference group				
2,501–25,000	7.4	5.9	2.55	0.01	1.6–34
25,001–250,000	10	9.1	2.53	0.01	1.68–60
>250,000	64.6	91.5	2.94	0.003	4–1037
American College of Surgeons trauma designation					
Level V	Reference group				
Level IV	5.3	5	1.78	0.07	0.85–33
Level III	9.9	10.8	2.1	0.04	1.17–84
Level II	8.5	9.5	1.92	0.06	0.96–75
Level I	13.3	21.3	1.62	0.1	0.58–306

z, z-value; $P>z$, 2-tailed P-value.

Table 3. Logistic regression results for real-time methylthioninium chloride availability.

	Odds ratio	Standard error	z	$P>z$	95% confidence interval
State					
Minnesota	Reference group				
North Dakota	1.04	0.65	0.06	>0.9	0.304–3.54
South Dakota	1.33	0.89	0.43	0.7	0.36–4.9
City size					
≤2,500	Reference group				
2,501–25,000	2.63	1.0	2.54	0.01	1.25–5.5
25,001–250,000	7.4	5.8	2.56	0.01	1.6–34
>250,000	Appears to predict outcome perfectly (11/11)				
American College of Surgeons trauma designation					
Level V	Reference group				
Level IV	2.95	1.9	1.66	0.1	0.82–10
Level III	21	27	2.46	0.01	1.88–251
Level II	6.5	8.6	1.43	0.2	0.5–85
Level I	Appears to predict outcome perfectly (6/6)				

z, z-value; $P>z$, 2-tailed P-value.

Sensitivity analysis

A sensitivity analysis utilizing US Census Bureau urban or rural population cutoffs in place of study population cutoffs revealed similar univariate relationships between population size and both methylthioninium chloride availability and real-time methemoglobin testing. Adjusted analysis of methylthioninium chloride availability was similar, noting that the significance of the relationship between the highest population tertile (>50,000) and methylthioninium chloride availability was lost in our adjusted analysis utilizing population quartiles. The relationship between population size and real-time testing availability did not change. See Supplementary material for full univariate and adjusted sensitivity analyses.

Geospatial mapping

Geospatial mapping revealed broad regions in all three states with neither the availability of real-time methemoglobin testing (Figure 2) nor methylthioninium chloride (Figure 3). While similar, the distribution of these two resources did not overlap perfectly; multiple regions lacked access to real-time methemoglobin testing despite availability of methylthioninium chloride, suggesting a confounder such as other uses of methylthioninium chloride (for tumor localization and as a vasopressor, for examples) unaccounted for in our modeling.

Discussion

We found meaningful differences in access to real-time methemoglobin testing, as well as in the availability of methylthioninium chloride for the treatment of acquired methemoglobinemia. Specifically, we found rural areas of our three-state region had substantially less access to both methylthioninium chloride and methemoglobin testing compared to urban regions, despite established guideline recommendations to maintain immediate access to both [27,28,34]. Our data call into question the ability of poison centers to provide actionable recommendations for life-threatening cases of methemoglobinemia in rural regions.

Drug-induced methemoglobinemia has been a staple of the toxicology literature for decades, having first been recognized in the late nineteenth century [35]. In recent history, drug-induced methemoglobinemia has largely been due to either local anesthetics (most commonly benzocaine), or dapsone [3,36]. While occasional fatalities were observed, severe cases were generally quite rare and the clinical course was often quite indolent, with patients often not requiring methylthioninium chloride [3,37]. Case series often describe symptoms as mild [3], with some authors warning of delayed symptoms. In contrast to the more traditional presentation, cases of ingestion of nitrite salts for the purpose of suicide present much differently, owing to several factors. First, sodium nitrite is an extremely potent oxidizer; small doses from 600 mg to 7 g may produce fatal methemoglobinemia [19]. Second, sodium nitrite is inexpensive and readily available; pounds of it can be ordered over the internet [38], and a recent analysis noted procurement of sodium nitrite via the internet was common in fatal cases [39]. Third, in contrast to the classic descriptions of drug-induced methemoglobinemia, reports of cases of sodium nitrite ingestions describe life-threatening symptoms and even death occurring rapidly,

often less than one hour after ingestion [21–23,40–48]. Cases reports in which methylthioninium chloride is administered within minutes of diagnosis describe survival, while even slight delays in antidote administration are associated with fatal outcomes [40,48]. Furthermore, such cases appear to be increasing. Data from Ontario, Canada demonstrate a parallel increase in nitrite-mediated methemoglobinemia deaths over a 20-year period, during which 80% were identified in the final two years reviewed [47]. Similarly, in the US, a query of the national violent death reporting system found 260 cases of nitrite or nitrate-related deaths from 2018 to 2020, with cases increasing each year [39]. Since timely methylthioninium chloride is critical to successfully treat such cases, our findings suggest there may be preventable poisoning deaths occurring disproportionately in rural US communities from methemoglobinemia.

Our findings are in direct contrast with best-practice antidote stocking guidelines, which recommend stocking at least 400 mg of methylthioninium chloride for treating a single patient for the first 8 h of illness [28]. It is possible hospitals may be attempting to curb expenses by centralizing resources for both testing and treatment of methemoglobinemia. While being mindful of cost is understandable, particularly for rural US hospitals that often face financial challenges, a lack of timely access to methylthioninium chloride may lead to preventable poisoning deaths. In such cases, we recommend prioritizing the stocking of methylthioninium chloride over making methemoglobinemia testing available, as the diagnosis of severe methemoglobinemia can often be established based on history and physical examination alone. Furthermore, the cost of methylthioninium chloride is not prohibitive. The current US average wholesale price is $312.50 per 500 mg vial [46]; thus the purchasing of a single vial would better align hospitals with best-practice antidote stocking guidelines. Last, we advise that methylthioninium chloride be stocked physically in the emergency department as well as in a central pharmacy, to accommodate critically ill patients likely to present to emergency departments and for those cases of methemoglobinemia (for examples, dapsone and benzocaine) which may occur in other areas of the hospital [49]. Similarly, some US ambulance services have created out-of-hospital protocols to ensure patients have timelier access to methylthioninium chloride [50].

Our findings may also have implications for the future of disaster preparedness. Sodium nitrite is used as a food preservative; for instance, it is often used in the curing of meats [51]. Given its proximity to food, sodium nitrite has caused chemical food poisoning outbreaks on multiple occasions around the world, resulting in multiple critically ill patients and even fatalities [52–58]. Many of these cases present similarly to cases of sodium nitrite ingested for the purpose of suicide. If such an outbreak were to occur in an unprepared region, multiple preventable deaths could occur. Furthermore, while we are unaware of any instance in which sodium nitrite has been used to poison the food supply for the purpose of chemical terrorism, previous episodes of chemical food poisoning demonstrate the feasibility of such a chemical weapons attack. Since acquired methemoglobinemia is a potentially fatal but treatable disease, our findings may represent a gap in chemical disaster preparedness.

Limitations

This study has several limitations. First, our survey is limited chiefly by its telephonic structure. While our interviewing structure provided for the opportunity to be transferred within the hospital (emergency department, pharmacy, laboratory) and to personnel (laboratory technician, charge nurse, pharmacist) best able to respond to specific questions, we were unable to verify the accuracy of responses. Because our focus was on the availability of methylthioninium chloride and methemoglobin testing in emergent settings, we initially directed our questions to emergency department charge nurses. However, we recognize this as a potential source of reporting bias and thus persisted in our queries beyond charge nurses as needed. We attempted to account for this in our multivariate models by excluding responses provided by charge nurses or other nursing staff. These analyses revealed no significant changes to our results (data not shown), suggesting that the effect of this potential limitation on our results was modest.

Second, while our use of American College of Surgeons trauma designation was intended as a surrogate marker for resource availability, it is an imperfect and broad marker. To our knowledge, few if any studies directly assess the availability of testing modalities in a manner similar to the present one. However, a previous study of the availability of carboxyhemoglobin testing in the same region yielded similar results, suggesting that American College of Surgeons trauma designation may function acceptably as a predictor of testing availability [59]. Nonetheless, the scope of our study precluded more detailed assessment of immediately available resources at individual sites.

Third, our study does not account for site-specific limitations to accessing methylthioninium chloride, such as location within facility (operating theater versus pharmacy versus emergency department) and staff-dependent access privileges (pharmacist versus nursing staff). It thus may incompletely represent the immediate availability of methylthioninium chloride for antidotal use in the setting of life-threatening methemoglobinemia. For example, in our experience, some smaller community hospitals, particularly in rural areas, do not have access to the hospital central pharmacy during evening and night hours, likely due to the use of methylthioninium chloride in other hospital areas for other uses, such as lymph node mapping [60,61], as a vasopressor [62], and for chromoendoscopy [63], among others. This may further limit access to methylthioninium chloride, potentially exacerbating the disparities we observed even further. Similarly, while data related to the number of available vials of methylthioninium chloride were collected, we were unable to collect data related to the volume and concentration of these vials, rendering analysis of this datapoint incomplete and potentially misleading. We thus deferred inclusion of this analysis.

Last, our results may not be generalizable to other regions within or outside the US. Further exploration may help to better characterize the extent of the disparities identified in this study in other regions.

Conclusions

We have identified significant differences in the availability of diagnostic and therapeutic modalities for acquired methemoglobinemia between urban and rural areas of the Upper Midwestern US. When controlled for American College of Surgeons trauma designation, reporter, population size, and state, the impact of rural geography on methylthioninium chloride availability and real-time methemoglobin testing remains. Simply stated, the short interval from intentional ingestion of sodium nitrite to the development of fatal methemoglobinemia makes this evolving clinical entity an emergency department problem rather than an intensive care unit problem. It thus is incumbent upon the Medical Toxicology and Emergency Medicine communities to ensure the rapid diagnosis and treatment of fulminant methemoglobinemia. Rural patients may be at disproportionate risk for preventable poisoning deaths from acquired methemoglobinemia.

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Data availability statement

Data may be made available by authors upon reasonable request.

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