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Severity Markers in Acute Nitrite Poisoning in Neonates and Infants: A Six-Year Retrospective Study

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Abstract

Acute nitrite poisoning in neonates and infants may cause severe methemoglobinemia; however, methemoglobin (MetHb) levels alone may not fully reflect metabolic impairment. This study aimed to identify potential biomarkers of severity that may support intensive care unit (ICU) admission decisions and to assess changes in MetHb and lactate, including lactate clearance, 60 min after methylene blue administration and initiation of fluid, electrolyte, and acid–base correction. We retrospectively analyzed 38 cases of acute nitrite poisoning involving 36 neonates and infants between 2020 and 2025. At presentation, median MetHb and lactate levels were 30.0% and 2.9 mmol/L, respectively; nine cases (23.7%) required ICU admission. ICU cases had higher lactate levels and more severe metabolic acidosis, with no significant differences in MetHb levels. At 60 min, MetHb decreased to 5.05% and lactate to 1.80 mmol/L; the relative MetHb reduction was 81.8%, and lactate clearance was 43.65%. These findings underscore the potential value of identifying severity biomarkers associated with the need for ICU admission and of assessing the biological response to treatment through monitoring MetHb dynamics and lactate clearance.

Keywords: acute nitrite poisoning; methemoglobinemia; neonates and infants; lactate; lactate clearance; acid–base balance; severity biomarkers; pediatric intensive care

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1. Introduction

Acute nitrite poisoning is an important cause of acquired methemoglobinemia in neonates and infants. A major source of exposure in these age groups is nitrate-contaminated water used for infant formula preparation [1]. Water from private wells represents a potential source of exposure, particularly in rural communities where water quality monitoring may be insufficient [2]. The World Health Organization emphasizes the importance of monitoring nitrate and nitrite concentrations in drinking water, particularly to protect infants [3]. Following ingestion, nitrates (NO_3^-) may be converted

into nitrites (NO_2^-) through bacterial reduction in the oral cavity and gastrointestinal tract. The resulting nitrites are directly responsible for hemoglobin oxidation and methemoglobin formation [1,3].

The increased susceptibility of neonates and infants, particularly during the first months of life, is associated with a higher proportion of fetal hemoglobin (HbF), reduced methemoglobin reductase activity, lower gastric acidity, and greater water intake per kilogram of body weight [4]. Epidemiological studies conducted in Romania have documented an association between well-water consumption and infant methemoglobinemia [5–7].

At the molecular level, methemoglobin formation involves the oxidation of iron in hemoglobin from the ferrous state (Fe^{2+}), present in functional hemoglobin (Hb) capable of binding oxygen, to the ferric state (Fe^{3+}), which cannot reversibly bind oxygen. This process impairs oxygen transport and delivery to tissues.

Clinical manifestations may range from cyanosis and nonspecific symptoms to neurological disturbances, hemodynamic instability, and severe systemic involvement. Measurement of methemoglobin (MetHb) levels by co-oximetry is essential for confirming methemoglobinemia, while methylene blue is the specific antidote when treatment is indicated [4]. However, clinical severity is not determined solely by MetHb levels and may also be influenced by patient age, duration of exposure, and associated medical conditions [8].

Reduced oxygen availability at the tissue level may contribute to metabolic disturbances, including increased lactate concentrations and alterations in acid–base parameters. Lactate is a biomarker used in the assessment of patients with severe acute illnesses; however, elevated lactate levels are not specific to tissue hypoxia and may reflect multiple pathophysiological mechanisms [9]. Pediatric reports have described methemoglobinemia associated with gastrointestinal manifestations and metabolic disturbances [10]. Consequently, the combined assessment of MetHb, lactate, pH, bicarbonate, and the anion gap (AG) may provide complementary information regarding poisoning severity.

Acquired methemoglobinemia is a rare condition in pediatric practice but may have severe clinical consequences. The literature includes numerous case reports and small case series, whereas systematic clinical studies are less common [11]. This may limit clinical experience and complicate early recognition, severity assessment, and monitoring of treatment response [8]. Furthermore, the relationships between MetHb, lactate, acid–base parameters, and the severity of acute nitrite poisoning in infants, as well as early changes in these parameters following antidote administration, remain insufficiently characterized.

In the context of a rare but potentially severe condition, rapid access to treatment and collaboration between healthcare facilities are important aspects of pediatric patient care.

The present study aimed to evaluate the relationships between MetHb, lactate, pH, bicarbonate, and AG in neonates and infants diagnosed with acute nitrite poisoning, as well as the associations between these parameters and the need for intensive care unit (ICU) admission. A secondary objective was to assess early changes in MetHb and lactate following methylene blue administration. The findings may contribute to a better understanding of poisoning severity and provide a foundation for future multicenter studies.

2. Materials and Methods

2.1. Study Design and Study Population

This single-center retrospective study was based on a review of the medical records of neonates and infants hospitalized with a diagnosis of acute nitrite poisoning between

2020 and 2025 at Saint Mary Emergency Children's Hospital in Iași, Romania. The study was approved by the hospital's Ethics Committee.

The study population comprised 38 cases of acute nitrite poisoning involving 36 neonates and infants. Two patients experienced two episodes of poisoning each, requiring separate hospital admissions. The unit of analysis was the poisoning case, with each hospitalization assessed individually.

The inclusion criteria were: (1) neonatal age (≤28 days) or infancy (>28 days and ≤12 months); (2) methemoglobinemia confirmed by co-oximetry at presentation (MetHb > 1.5% of total hemoglobin); (3) use of well water for infant feeding preparation, according to information provided by caregivers and documented in the medical records; and (4) administration of the first dose of methylene blue in the Emergency Department (ED), following collection of the initial venous blood sample for laboratory assessment.

The MetHb threshold of >1.5% was established based on the upper limit of the general reference interval (0–1.5%) specified in the manual of the GEM Premier 4000 point-of-care analyzer [12]. This threshold was used to identify elevated MetHb levels and was not intended as a criterion for assessing the clinical severity of poisoning.

The exclusion criteria were congenital methemoglobinemia; methemoglobinemia attributed to other causes, including drug-induced and sepsis-associated methemoglobinemia; cases in which commercially bottled water or municipal tap water was used for infant feeding preparation; and patients who had received methylene blue and/or vitamin C before presentation to the ED.

Information regarding the use of well water for infant feeding preparation was obtained retrospectively from medical records, based on the medical history documented at admission. Results of chemical analyses of the water used by the patients included in the study were not available.

2.2. Data Collection, Assessment of Laboratory Parameters, and Statistical Analysis

Data were retrospectively extracted from the medical records corresponding to each poisoning case and organized in a Microsoft Excel database. The variables analyzed included demographic and epidemiological characteristics (age, sex, area of residence, county of residence, and temporal distribution of cases—annual, monthly, and seasonal), associated diagnoses, the need for intensive care unit (ICU) admission, and length of hospital stay.

Laboratory assessment included methemoglobin (MetHb, expressed as a percentage of total hemoglobin), lactate (mmol/L), blood pH, bicarbonate (mmol/L), and the anion gap (AG, mmol/L).

Venous whole-blood samples were collected into pre-heparinized syringes containing dry heparin and analyzed using point-of-care testing (POCT) with the GEM Premier 4000 analyzer (Instrumentation Laboratory, USA). The use of dry heparin avoids the dilution effect associated with the addition of liquid heparin, thereby reducing the risk of preanalytical errors [12].

Methemoglobin was measured by spectrophotometric co-oximetry, pH by potentiometry, and lactate by amperometry. Bicarbonate and the anion gap were automatically calculated by the analyzer. The AG was calculated according to the formula $AG = (Na^+ + K^+) - (Cl^- + HCO_3^-)$, based on measured electrolytes and calculated bicarbonate, in accordance with the manufacturer's technical documentation [12].

The general reference intervals specified in the analyzer documentation for the investigated parameters were as follows: MetHb, 0–1.5%; lactate, 0.9–1.7 mmol/L; venous pH, 7.32–7.43; bicarbonate, 22–29 mmol/L; and AG, 10–20 mmol/L. These intervals were used as reference values to guide the interpretation of results [12].

Two venous blood samples were collected for each poisoning case. The first sample was obtained in the ED before administration of methylene blue.

The antidote used was methylthioninium chloride (Metiltioninio Cloruro Bioindustria L.I.M., 100 mg/10 mL), administered by slow intravenous injection over 5 min without prior dilution. Neonates and infants aged up to and including 3 months received a dose of 0.5 mg/kg body weight, whereas infants older than 3 months received 1 mg/kg body weight [13].

The second venous blood sample was collected in the ED 60 min after methylene blue administration, before hospital admission, through an intravenous line different from that used for antidote administration, to reduce the risk of sample contamination and analytical interference.

The 60-min interval for laboratory reassessment was used as part of our institutional protocol for patient assessment and monitoring. The selection of this interval is supported by recommendations in the literature regarding the early MetHb response following intravenous methylene blue administration [4]. Concurrent lactate measurement enabled an exploratory assessment of early metabolic changes, without assuming lactate normalization within this interval.

Both samples were analyzed using the same POCT analyzer, equipped with an automated quality management system. According to the manufacturer's specifications, the analytical turnaround time for the panel including co-oximetry is approximately 95 s from sample insertion into the analyzer [12].

Early changes in MetHb and lactate following antidote administration were assessed using paired measurements obtained before and 60 min after methylene blue administration, available for all 38 cases of acute nitrite poisoning.

Absolute reductions were calculated as the difference between baseline values and those obtained at 60 min. Relative reductions were calculated by dividing this difference by the baseline value and multiplying by 100. For lactate, the relative reduction was expressed as relative lactate clearance.

Categorical variables were expressed as frequencies and percentages, while continuous variables were summarized using medians and interquartile ranges (IQRs), or means and standard deviations, as appropriate.

Correlations were assessed using Spearman's rank correlation coefficient (ϱ). Comparisons between independent groups were performed using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables.

Changes between baseline measurements and those obtained 60 min after antidote administration were evaluated using the Wilcoxon signed-rank test for paired samples.

The threshold for statistical significance was set at $p < 0.05$. All analyses were exploratory, and no adjustment for multiple comparisons was applied.

Each hospitalization was treated as a separate observation in the statistical analysis, including those of the two patients with recurrent poisoning.

3. Results

3.1. Demographic and Epidemiological Characteristics

During the period 2020–2025, 38 cases of acute nitrite poisoning, corresponding to 36 neonates and infants, were recorded. The mean age at admission was 2.32 ± 2.99 months, while the median age was 1 month (IQR: 0.25–3 months). Neonates accounted for 26.3% of cases (n = 10), while infants aged 1–3 months accounted for 50.0% (n = 19). The remaining cases were distributed as follows: 4–6 months, 13.2% (n = 5); 7–9 months, 5.3% (n = 2); and 10–12 months, 5.3% (n = 2). Overall, 76.3% (n = 29) of acute nitrite poisoning cases occurred in neonates and infants aged up to three months.

The demographic and epidemiological characteristics of the study population are presented in Table 1.

Table 1. Demographic and epidemiological characteristics of the study population (*N* = 38).

Characteristic	Value	Characteristic	Value
Age		**County of residence**	
Mean ± SD (months)	2.32 ± 2.99	Iași	21 (55.3%)
Median (IQR), months	1 (0.25–3)	Vaslui	6 (15.8%)
Range, months	0–12	Botoșani	4 (10.5%)
Age groups		Suceava	3 (7.9%)
Neonates (0–28 days)	10 (26.3%)	Neamț	3 (7.9%)
1–3 months	19 (50.0%)	Bacău	1 (2.6%)
4–6 months	5 (13.2%)	**Year of admission**	
7–9 months	2 (5.3%)	2020	6 (15.8%)
10–12 months	2 (5.3%)	2021	6 (15.8%)
Sex		2022	5 (13.2%)
Male	20 (52.6%)	2023	7 (18.4%)
Female	18 (47.4%)	2024	9 (23.7%)
Area of residence		2025	5 (13.2%)
Rural	33 (86.8%)	**Season of admission**	
Urban	5 (13.2%)	Winter	14 (36.8%)
		Spring	9 (23.7%)
		Summer	9 (23.7%)
		Autumn	6 (15.8%)

Note: Data are presented as *n* (%) unless otherwise specified. *N* = total number of cases analyzed; *n* = number of cases in each category or subgroup; SD = standard deviation; IQR = interquartile range. Neonates: 0–28 days; infants: >28 days up to and including 12 months. Age was recorded in completed months; neonates ("NN") were considered to be 0 months for descriptive statistics.

The annual distribution of cases showed moderate variation, ranging from five to nine cases per year, with the highest number recorded in 2024 (*n* = 9). Cases were diagnosed throughout the entire calendar year, with the highest proportion observed during winter (36.8%, *n* = 14). December had the highest number of cases (*n* = 6). The monthly distribution of acute nitrite poisoning cases during the study period is illustrated in Figure 1.

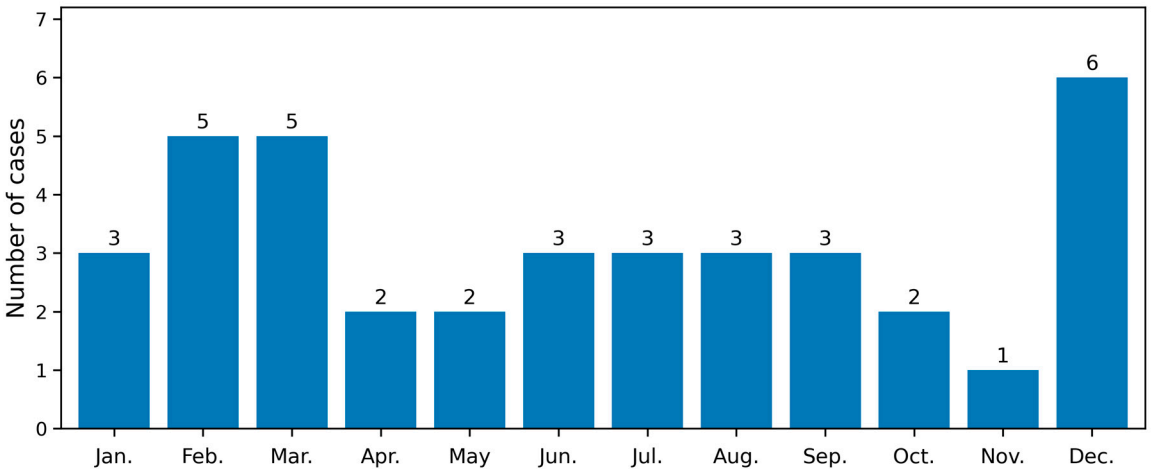


Figure 1. Monthly distribution of acute nitrite poisoning cases among neonates and infants hospitalized during 2020–2025 (*N* = 38).

3.2. Laboratory Parameters and Hospitalization Outcomes

At the initial measurement, performed upon presentation to the Emergency Department (ED), the median methemoglobin (MetHb) level was 30.0% (IQR: 18.7–48.2%), and the median lactate concentration was 2.9 mmol/L (IQR: 2.0–5.0 mmol/L). Blood gas analysis revealed acid–base disturbances of varying severity, with a median blood pH of 7.35 (IQR: 7.25–7.40) and a median bicarbonate concentration of 18.25 mmol/L (IQR: 11.3–21.9 mmol/L). The median anion gap (AG) was 12.0 mmol/L (IQR: 9.0–14.0 mmol/L). Based on the analyzer's reference interval (10–20 mmol/L), 12 cases (31.6%) had AG values below the lower reference limit, 24 cases (63.2%) had values within the reference interval, and two cases (5.3%) had values above the upper reference limit.

Intensive care unit (ICU) admission was required in 9 of the 38 cases (23.7%). The median total length of hospital stay was 4.5 days (IQR: 3.25–10.0 days). Additional laboratory parameters and hospitalization outcomes are presented in Table 2.

Table 2. Laboratory parameters and hospitalization outcomes in neonates and infants with acute nitrite poisoning (*N* = 38).

Characteristic	Available *N*	Mean ± SD	Median (IQR)
Laboratory parameters at initial assessment (ED)			
Methemoglobin (%)	38	35.1 ± 19.8	30.0 (18.7–48.2)
Lactate (mmol/L)	38	4.9 ± 4.9	2.9 (2.0–5.0)
Anion gap (mmol/L)	38	12.1 ± 3.9	12.0 (9.0–14.0)
Blood pH	38	7.30 ± 0.15	7.35 (7.25–7.40)
Bicarbonate (mmol/L)	38	16.4 ± 6.3	18.25 (11.3–21.9)
Hospitalization outcomes			
Total length of hospital stay (days)	38	7.5 ± 7.0	4.5 (3.25–10.00)
ICU length of stay (days; ICU cases only)	9	3.1 ± 3.1	2.0 (2.0–3.0)
ICU admission, *n* (%)	38	9 (23.7%)	—

Note: Values are expressed as mean ± SD, median (IQR), or *n* (%). The total length of hospital stay includes days spent in the ICU and other hospital departments. ICU length of stay includes only cases admitted to the ICU.

For descriptive purposes, MetHb concentrations at the initial measurement were divided into five categories based on concentration ranges associated with clinical manifestations described in the literature: below 10% (usually asymptomatic), 10% to less than 30% (cyanosis, chocolate-brown blood), 30% to less than 50% (dyspnea, dizziness, syncope), 50–70% (metabolic acidosis, seizures, arrhythmias, coma), and above 70% (severe hypoxemia, risk of death) [4]. This classification was used exclusively to describe the distribution of MetHb concentrations and did not represent a validated classification of clinical severity or an independent criterion for ICU admission.

MetHb concentrations were below 10% in 2 cases (5.3%), between 10% and less than 30% in 15 cases (39.5%), between 30% and less than 50% in 12 cases (31.6%), between 50% and 70% in 8 cases (21.1%), and above 70% in one case (2.6%). Overall, 21 cases (55.3%) had MetHb concentrations of at least 30% at the initial measurement.

Among the 9 cases requiring ICU admission, one case (11.1%) had an initial MetHb concentration between 10% and less than 30%, 6 cases (66.7%) had concentrations between 30% and less than 50%, and 2 cases (22.2%) had concentrations between 50% and 70%.

Regarding associated diagnoses, at least one additional diagnosis was clinically and/or laboratory documented in 29 of the 38 cases (76.3%), whereas 9 cases (23.7%) had no associated diagnoses. Gastrointestinal disorders, predominantly acute diarrheal disease, gastroenteritis, and enterocolitis, were identified in 20 cases (52.6%). Respiratory disorders were documented in 6 cases (15.8%), and acute dehydration syndrome in 6 cases (15.8%). Beckwith–Wiedemann syndrome was documented in one case (2.6%). Some cases had multiple associated diagnoses; therefore, these categories were not mutually exclusive.

Two infants experienced recurrent poisoning requiring separate hospital admissions. In one infant, the second admission was characterized by lower MetHb and lactate concentrations but more pronounced metabolic acidosis, without requiring ICU admission during either hospitalization. In the other infant, MetHb concentrations were comparable between the two admissions; however, the first poisoning episode was associated with severe hyperlactatemia and metabolic acidosis, requiring ICU admission.

3.3. Baseline Laboratory Parameters and Lactate Changes in the ICU and Non-ICU Subgroups

At the initial laboratory assessment, median MetHb concentrations were higher in the subgroup of cases subsequently requiring ICU admission than in the non-ICU subgroup (41.0% versus 25.9%), although the difference did not reach statistical significance ($p = 0.066$).

Median lactate concentrations were significantly higher in the ICU subgroup (8.0 versus 2.7 mmol/L; $p = 0.028$). Furthermore, cases requiring ICU admission had significantly lower median blood pH values (7.20 versus 7.36; $p = 0.0025$) and bicarbonate concentrations (9.16 versus 19.9 mmol/L; $p = 0.012$).

Regarding AG, the median was 11.0 mmol/L in the ICU subgroup and 12.0 mmol/L in the non-ICU subgroup, with no statistically significant difference ($p = 0.641$).

Correlation analysis of baseline laboratory parameters revealed a positive association between MetHb and lactate concentrations (Spearman $\varrho = 0.655$; $p < 0.001$). Lactate concentrations were negatively correlated with blood pH ($\varrho = -0.420$; $p = 0.009$) and bicarbonate concentrations ($\varrho = -0.566$; $p < 0.001$). Furthermore, a negative correlation was observed between MetHb and bicarbonate ($\varrho = -0.419$; $p = 0.009$).

At the second measurement, performed 60 min after methylene blue administration in the context of supportive therapy, the median lactate concentration in the entire cohort decreased from 2.90 to 1.80 mmol/L (Wilcoxon signed-rank test, $p < 0.001$). The median individual relative lactate clearance was 43.65% (IQR: 24.58–56.81%). Lactate

concentrations decreased in 32 cases, increased in 5 cases, and remained unchanged in one case.

In the comparative analysis of lactate changes between the two measurements, the median absolute reduction was greater in the ICU subgroup than in the non-ICU subgroup (5.8 versus 1.0 mmol/L; $p = 0.011$). Similarly, median relative lactate clearance was 50.0% in the ICU subgroup and 33.33% in the non-ICU subgroup ($p = 0.043$).

The results of the baseline laboratory assessment and lactate changes in the two subgroups are summarized in Table 3.

Table 3. Baseline laboratory parameters and lactate changes in the ICU and non-ICU subgroups.

Parameter	ICU ($n = 9$)	Non-ICU ($n = 29$)	p-Value
Measurement I—baseline laboratory assessment			
Methemoglobin (%)	41.0	25.9	0.066
Lactate (mmol/L)	8.0	2.7	0.028
Blood pH	7.20	7.36	0.0025
Bicarbonate (mmol/L)	9.16	19.9	0.012
Anion gap (mmol/L)	11.0	12.0	0.641
Measurement II—60 min after treatment initiation			
Absolute lactate reduction (mmol/L)	5.8	1.0	0.011
Relative lactate clearance (%)	50.0	33.33	0.043

Note: Values are presented as medians. Both measurements were performed in the ED, before admission to the ICU or other hospital departments. The first measurement preceded methylene blue administration, whereas the second was performed 60 min after its administration in the context of supportive therapy.

Absolute lactate reduction and relative lactate clearance represent the medians of individually calculated changes. Relative lactate clearance (%) = [(lactate I − lactate II)/lactate I] × 100.

The p-values were obtained using the two-sided Mann–Whitney U test. The analyses were exploratory, without adjustment for multiple comparisons.

An exploratory analysis according to the presence of gastrointestinal disorders revealed no statistically significant differences in the laboratory parameters measured at ED presentation. Median MetHb concentrations were comparable between cases with and without gastrointestinal disorders (30.01% versus 30.28%; $p = 0.953$). Cases with gastrointestinal disorders had a median lactate concentration of 3.15 mmol/L, compared with 2.70 mmol/L in cases without these disorders ($p = 0.640$). Median blood pH values were 7.325 versus 7.350 ($p = 0.770$), while median bicarbonate concentrations were 17.0 versus 19.65 mmol/L ($p = 0.792$).

ICU admission was required in 6 of the 20 cases with gastrointestinal disorders (30.0%), compared with 3 of the 18 cases without gastrointestinal disorders (16.7%). This difference was not statistically significant ($p = 0.454$).

3.4. Changes in Methemoglobin Concentrations Between the Two Measurements

Changes in methemoglobin (MetHb) concentrations between the two measurements were assessed in all 38 cases of acute nitrite poisoning. The median MetHb concentration decreased from 30.0% before antidote administration (IQR: 18.7–48.2%) to 5.05% at 60 min after administration (IQR: 3.1–8.0%), with a statistically significant difference (Wilcoxon signed-rank test, $p < 0.001$). The median absolute reduction was 26.43 percentage points,

while the median individual relative reduction was 81.8% (IQR: 77.6–87.0%). A decrease in MetHb concentrations was observed in all 38 cases.

In the exploratory analysis of the relative reduction in MetHb according to the need for ICU admission, the median was 78.1% in the ICU subgroup and 82.3% in the non-ICU subgroup, without a statistically significant difference ($p = 0.181$).

As a complementary analysis of MetHb changes, correlations between changes in MetHb and lactate, the latter having been presented in Section 3.3, were evaluated. A statistically significant positive correlation between the absolute reductions in the two parameters was identified (Spearman $\varrho = 0.627$; $p < 0.001$). In contrast, the correlation between the relative reductions in MetHb and lactate was not statistically significant ($\varrho = -0.023$; $p = 0.891$).

4. Discussion

4.1. Demographic and Epidemiological Characteristics

This retrospective study, conducted over a six-year period (2020–2025) at a tertiary pediatric hospital in northeastern Romania, highlights the persistence of acute nitrite poisoning cases associated with the reported use of well water for infant feeding. A total of 38 cases of acute nitrite poisoning involving 36 neonates and infants were analyzed, originating from both Iași County and other counties in the region. This reflects the hospital's role as a regional referral center, receiving patients transferred from other counties, including cases in which the specific antidote was unavailable at the referring healthcare facilities. The limited availability of methylene blue in some hospitals may be related to the low frequency of cases, acquisition costs, and the single-use nature of the ampoules. This issue has also been reported internationally. Bianchi et al. [14] reported that methylene blue was available in 14 of the 16 hospitals surveyed in a region of Italy, whereas Eljaoudi et al. [15] documented its absence from the stocks of all 17 hospitals participating in a study conducted in Morocco. These observations underscore the importance of prompt access to the antidote and collaboration among healthcare facilities in the management of rare poisonings.

The median age at admission was one month, and 76.3% ($n = 29$) of poisoning cases occurred in neonates and infants aged up to three months. This distribution is consistent with the increased physiological susceptibility of young infants to methemoglobinemia, attributed to a higher proportion of fetal hemoglobin, relatively reduced activity of enzymatic methemoglobin reduction systems, and increased water intake relative to body weight. Furthermore, higher gastric pH may promote the proliferation of bacteria capable of reducing nitrates to nitrites, thereby increasing the risk of methemoglobinemia [2,4].

Takahashi et al. [16] described an outbreak of acquired methemoglobinemia affecting ten neonates in a hospital setting, reported in the New England Journal of Medicine, associated with contamination of the water used for infant formula preparation. Although the circumstances of exposure differed from those in our study, this report highlights neonatal vulnerability and the importance of identifying the source of contamination.

An important epidemiological finding was the predominance of poisoning cases among infants from rural areas (86.8%). This observation is relevant in the context of using individual water sources for infant formula preparation. In a case–control study conducted in Transylvania, Romania, Zeman et al. [6] investigated risk factors for methemoglobinemia in children, identifying an association with dietary exposure to nitrates/nitrites and a possible contribution of diarrheal illnesses. These findings provide a relevant point of comparison for the epidemiological characteristics of our study population. However, in our study, the use of well water was documented based on the medical history recorded in patient records, without chemical measurements to confirm nitrate or nitrite concentrations in the respective water sources.

Regarding sex distribution, a slight male predominance was observed (52.6%). However, the small difference between sexes does not support conclusions regarding sex-related differences in susceptibility.

The analysis of temporal distribution revealed that cases occurred throughout the study period, with the highest annual number recorded in 2024 ($n = 9$) and a descriptively higher frequency during winter (36.8%; $n = 14$). This distribution may be influenced by seasonal variations in hydrological conditions, as precipitation and snowmelt may promote the mobilization and infiltration of nitrates from agricultural fertilizers, animal manure, or leaking septic systems into the groundwater supplying wells. Hydrogeological studies have documented seasonal variations in nitrate concentrations, including elevated levels during cold and wet periods, depending on local soil and aquifer characteristics and contamination sources [17–19]. However, this possible explanation should be interpreted with caution, as the relatively small number of cases, the absence of nitrate and nitrite measurements in the water sources, and the lack of an analysis of hydrometeorological conditions do not allow a causal relationship to be established between season and the occurrence of poisoning.

From a preventive perspective, the American Academy of Pediatrics recommends annual testing of private well water for nitrates and coliform bacteria [2]. Our findings support the importance of monitoring the quality of individual water sources, avoiding the use of water with nitrate concentrations exceeding recommended limits for infant formula preparation, and educating families, particularly in rural communities. The occurrence of recurrent poisoning in two infants, each requiring two separate hospital admissions, further emphasizes the importance of family health education, prevention of re-exposure, and adherence to the recommendations documented in discharge records regarding avoidance of water from untested sources.

The persistence of these poisoning cases represents a warning signal for local public health, highlighting the need to strengthen preventive measures and expand access to safe drinking water sources, particularly in rural communities.

4.2. Biological Profile and Clinical Characteristics of Acute Nitrite Poisoning

Laboratory assessment of the neonates and infants included in the study comprised the measurement of methemoglobin (MetHb), lactate, pH, bicarbonate, and anion gap (AG), allowing the simultaneous characterization of methemoglobinemia and associated metabolic alterations. At presentation to the Emergency Department (ED), MetHb concentrations showed considerable variability and were accompanied by varying degrees of hyperlactatemia and acid–base disturbances. These findings highlight the importance of an integrated interpretation of laboratory parameters in the assessment of acute nitrite poisoning.

From a pathophysiological perspective, the oxidation of iron in hemoglobin from the ferrous to the ferric state reduces its oxygen-carrying capacity, while the increased oxygen affinity of the remaining functional hemoglobin further limits oxygen release to tissues. In severe cases, tissue hypoxia may contribute to lactate accumulation and the development of metabolic acidosis. Iolascon et al. [4] emphasized the importance of correlating MetHb concentrations with clinical manifestations and individual patient characteristics when assessing the severity of methemoglobinemia.

In our study, 55.3% of cases had initial MetHb concentrations of at least 30%, whereas 23.7% required intensive care unit (ICU) admission. The distribution of initial MetHb concentrations revealed a broad biological spectrum, including values below 10% and a value exceeding 70%. However, the concentration ranges associated with clinical manifestations described in the literature cannot automatically be equated with degrees of clinical severity and must be interpreted in relation to the clinical presentation and

associated metabolic alterations. Sinha et al. [8] investigated the clinical characteristics and management of methemoglobinemia in a multicenter retrospective study involving 98 children with different etiologies. In contrast, our study focused exclusively on acute nitrite poisoning in neonates and infants in the context of well-water use for infant feeding.

Kraut and Nagami [20] highlighted the limitations of using AG alone in the assessment of acid–base disturbances. In our study, the median AG, calculated for all 38 cases, was 12.0 mmol/L (IQR: 9.0–14.0 mmol/L), falling within the analyzer's reference interval (10–20 mmol/L). Nevertheless, individual values below the lower limit of the reference interval were also recorded. These findings highlight the need to interpret AG in conjunction with pH, bicarbonate, lactate, and the clinical context, as a normal or low AG does not exclude the presence of significant metabolic disturbances.

Gastrointestinal disorders were the most frequently documented associated diagnoses (20 cases; 52.6%). Acute diarrhea, gastroenteritis, and enterocolitis may contribute to dehydration and the development of metabolic disturbances, while intestinal bacterial activity may influence the reduction of nitrates to nitrites [6]. Jajoo et al. [21] reported acquired methemoglobinemia associated with acute diarrhea in infants, whereas Kurian et al. [22] described an association between methemoglobinemia and cow's milk protein allergy.

In the study population, comparisons between cases with and without associated gastrointestinal diagnoses revealed no statistically significant differences in MetHb and lactate concentrations, blood pH and bicarbonate values, or the frequency of ICU admission. This finding does not contradict the results reported by Zeman et al. [6], as their study investigated risk factors for the development of methemoglobinemia, whereas our study examined laboratory characteristics and the need for intensive care in children with established poisoning. Therefore, the absence of a statistically significant association with the laboratory parameters analyzed or with the need for ICU admission in our population does not exclude a contribution of gastrointestinal disorders to individual susceptibility.

Overall, the observed laboratory profile indicates that acute nitrite poisoning in neonates and infants may be accompanied by metabolic alterations of varying severity. The simultaneous assessment of MetHb, lactate, and acid–base parameters allows a comprehensive characterization of these alterations and provides a basis for examining their relationship with the need for ICU admission.

4.3. Relationship Between Laboratory Parameters at Emergency Department Presentation and the Need for ICU Admission

One of the main findings of our study was the positive correlation between baseline methemoglobin (MetHb) and lactate concentrations ($\varrho = 0.655$; $p < 0.001$). This association is consistent with the pathophysiological mechanism of acute nitrite poisoning, in which impaired oxygen transport and release may contribute to tissue hypoxia and disturbances in energy metabolism. However, lactate concentrations are also influenced by other factors, including tissue perfusion, hemodynamic status, and concomitant conditions. Therefore, the observed relationship should be interpreted as a biological association rather than evidence of a direct causal relationship [9].

The negative correlations between lactate and pH ($\varrho = -0.420$; $p = 0.009$), and between lactate and bicarbonate ($\varrho = -0.566$; $p < 0.001$), as well as between MetHb and bicarbonate ($\varrho = -0.419$; $p = 0.009$), highlight the association between methemoglobinemia, hyperlactatemia, and acid–base disturbances, supporting the value of an integrated laboratory assessment.

Comparison of cases that subsequently required ICU admission with those in the non-ICU subgroup revealed significantly higher baseline lactate concentrations and lower

pH and bicarbonate values. Although MetHb concentrations were higher in the ICU subgroup, the difference did not reach statistical significance ($p = 0.066$). Eight of the nine ICU cases had MetHb concentrations ≥30%, whereas one case required intensive care despite having a concentration below this threshold. In contrast, AG did not differ significantly between the subgroups ($p = 0.641$). These observations suggest that metabolic alterations may provide complementary information to MetHb concentrations in assessing poisoning severity, without demonstrating the superiority of any individual biomarker.

The interpretation of AG also requires consideration of albumin, the main plasma protein contributing to the fraction of unmeasured anions. In our cohort, 12 cases (31.6%) had AG values below the lower reference limit. Hypoalbuminemia may reduce AG and mask certain acid–base disturbances, as highlighted by Kraut and Nagami and Durward et al. [20,23]. Because albumin was not systematically measured, its influence on AG could not be retrospectively assessed. Albumin measurement and calculation of albumin-corrected AG may represent useful directions for future research in the multiparametric assessment of acute nitrite poisoning.

Our findings can be considered in relation to the multicenter study by Sinha et al. [8], which included 98 children with methemoglobinemia of various etiologies. In contrast, our study investigated the association between laboratory parameters and the need for ICU admission exclusively in neonates and infants with acute nitrite poisoning. The recommendations by Iolascon et al. [4] emphasize the need to individualize assessment according to MetHb concentrations, clinical manifestations, and patient characteristics, a principle also supported by our observations.

An additional finding was the greater absolute reduction in lactate in the ICU subgroup (5.8 versus 1.0 mmol/L; $p = 0.011$), associated with higher relative lactate clearance (50.0% versus 33.33%; $p = 0.043$). These differences should be interpreted in the context of higher baseline lactate concentrations in the ICU subgroup and the treatment initiated in the ED before admission to the hospital wards. These findings support the potential value of dynamic lactate monitoring, without demonstrating superior treatment efficacy or the independent predictive value of lactate clearance.

ICU admission is a clinical outcome influenced by multiple factors rather than an exclusive measure of biological severity. The small number of ICU cases and the exploratory nature of the analyses performed without adjustment for multiple comparisons preclude the establishment of decision thresholds or demonstration of the independent predictive value of the investigated parameters. Nevertheless, these findings warrant prospective evaluation of severity stratification models integrating MetHb, lactate, and acid–base parameters.

4.4. Changes in Methemoglobin and Lactate Following Antidote Administration

An important finding of our study was the significant reduction in methemoglobin (MetHb) and lactate concentrations 60 min after antidote administration. A decrease in MetHb was observed in all 38 cases analyzed, with a median relative reduction of 81.8%. This response is consistent with the mechanism of action of methylene blue, which promotes the reduction of MetHb to functional hemoglobin. Iolascon et al. [4] highlighted that a substantial reduction in MetHb concentrations is expected within the first 30–60 min following treatment administration, emphasizing the importance of laboratory reassessment.

In parallel, lactate concentrations decreased significantly, with a median relative lactate clearance of 43.65%, calculated from paired measurements in all 38 cases. In the exploratory analysis, lactate clearance was higher in the ICU subgroup than in the non-ICU subgroup (50.0% versus 33.33%; $p = 0.043$). This difference should be interpreted with

caution, considering the higher baseline lactate concentrations in the ICU subgroup, the small number of cases, and the exploratory nature of the analysis. Micherová [24] described a case of nitrate poisoning in an infant associated with severe methemoglobinemia and lactic acidosis, highlighting the relevance of simultaneously assessing hemoglobin dysfunction and metabolic disturbances.

The interpretation of lactate clearance requires consideration of the multiple mechanisms influencing lactate metabolism. Bakker et al. [9] emphasized that hyperlactatemia may result from both reduced tissue oxygen delivery and metabolic mechanisms independent of hypoxia. In our study, associated gastrointestinal disorders, present in 52.6% of cases, included manifestations such as vomiting and diarrhea, which may contribute to dehydration, impaired tissue perfusion, and fluid, electrolyte, and acid–base disturbances. The reduction in lactate concentrations may reflect improved tissue oxygenation following correction of methemoglobinemia but may also be influenced by concomitant therapeutic interventions, such as oxygen therapy and fluid and electrolyte replacement. Correction of acid–base disturbances may further modify metabolic status without representing a direct mechanism of lactate elimination. Therefore, lactate clearance should be interpreted as an indicator of metabolic changes observed following treatment, without attributing these changes exclusively to the action of the antidote.

A relevant finding was the positive correlation between the absolute reductions in MetHb and lactate ($\varrho = 0.627$; $p < 0.001$). In contrast, the relative reductions in these two parameters were not significantly correlated ($\varrho = -0.023$; $p = 0.891$). This observation does not demonstrate that the changes in these two parameters are independent but is consistent with the possibility of different underlying mechanisms and biological kinetics. While the reduction in MetHb reflects the conversion of oxidized hemoglobin into functional hemoglobin, changes in lactate concentrations depend on the balance between its production, utilization, and elimination, processes influenced by clinical status and therapeutic interventions. The literature emphasizes that a reduction in blood lactate concentration does not represent a direct measurement of its metabolic clearance [25,26]. Furthermore, the two measurements performed in our study do not allow a complete characterization of the biological kinetics or estimation of the half-lives of either parameter.

One contribution of our study is the assessment of changes in lactate concentrations in parallel with the reduction in MetHb following antidote administration. Although the pediatric literature describes hyperlactatemia and lactic acidosis in nitrate and nitrite poisoning, the analysis of changes in lactate concentrations as a potential complementary indicator of treatment response remains insufficiently explored. Our findings support the potential usefulness of an integrated interpretation of these two parameters in monitoring the biological response to treatment, without demonstrating the independent predictive value of lactate clearance. Validation of these observations requires prospective studies with repeated laboratory measurements and assessment of the influence of concomitant therapeutic interventions.

4.5. Study Limitations

The retrospective, single-center design and relatively small sample size, comprising 38 cases of acute nitrite poisoning involving 36 neonates and infants, analyzed over a six-year period (2020–2025), limit the generalizability of the findings and the statistical power of the analyses. The small number of ICU admissions ($n = 9$), as well as the inclusion of two poisoning cases for each of two patients, warrant caution when interpreting the statistical results. Furthermore, the tertiary care setting, which also receives patients transferred from other healthcare facilities, may affect the representativeness of the study population.

The comparability of our findings with international data is limited by the relatively small number of recent clinical series focusing exclusively on acute nitrite poisoning in neonates and infants, as the available literature predominantly comprises individual case reports and studies of methemoglobinemia with diverse etiologies.

Exposure to well water was documented based on caregiver-reported histories recorded in the medical records, without measurements of nitrate and nitrite concentrations to analytically confirm the source of poisoning. Furthermore, serum albumin was not included in the retrospective analysis; therefore, AG values were interpreted without correction for albumin levels.

Our study focused on assessing the biological response during the initial phase of emergency management. The two measurements provide relevant information on the initial response, whereas a comprehensive characterization of biological kinetics requires serial assessments over longer periods. Confirmation of the identified associations and evaluation of the clinical utility of the investigated parameters, including lactate clearance, require larger, prospective multicenter studies with dynamic laboratory monitoring.

5. Conclusions

Our study highlights the vulnerability of neonates and infants to acute nitrite poisoning associated with the use of well water for infant feeding, particularly during the first months of life and in rural areas. The findings support the relevance of a multiparametric clinical and laboratory assessment of poisoning severity through the integration of methemoglobin (MetHb), lactate, and acid–base parameters. The differences observed between cases requiring intensive care unit (ICU) admission and those managed outside the ICU, particularly regarding lactate, pH, and bicarbonate, highlight the importance of metabolic disturbances as complementary indicators to MetHb concentrations in characterizing poisoning severity.

A distinctive contribution of this study is the simultaneous assessment of changes in MetHb and lactate during the initial phase of emergency management, following antidote administration and individualized supportive therapy. The significant reductions in both parameters, in the absence of a statistically significant correlation between their relative reductions, support further investigation of lactate clearance as a potential complementary indicator of the biological response to treatment. However, its clinical utility requires confirmation in prospective studies.

By addressing a potentially severe form of poisoning that is relatively rarely documented in pediatric clinical series, our study contributes to expanding the clinical evidence regarding the identification and integrated interpretation of severity markers, providing a foundation for the development of evidence-based assessment and monitoring strategies. Furthermore, the findings emphasize the importance of preventing initial and repeated exposure by ensuring access to safe water sources for neonatal and infant feeding and educating families about the risks associated with the use of untested well water.

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Informed Consent Statement: Written informed consent was obtained from the parents or legal guardians of all patients included in the study at the time of hospital presentation, using the standardized institutional consent form, which includes provisions for the use of biological samples for scientific research and the statistical processing of personal data. No separate study-specific consent was obtained.

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