

## CASE REPORT

# Cocaine and Volatile Nitrite–Induced Methemoglobinemia; a Case Report and Treatment Approach Review

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**Abstract:** Cyanosis is typically a sign of a potentially life-threatening condition in the emergency department and requires immediate workup and treatment. This case report highlights the diagnostic reasoning and clinical approach to cocaine- and volatile nitrite–induced methemoglobinemia (MHG). MHG is a rare, life-threatening cause of cyanosis. The diagnosis must be suspected in the emergency department in the presence of hypoxia and cyanosis disproportionate to cardiopulmonary repercussions and refractory to oxygen supplementation. Acquired causes are more prevalent than genetics, and recreational drugs should be highly suspected. Despite the rarity of this situation, cyanosis precipitants and the specificities of each hemoglobinopathy are reviewed in this article.

**Keywords:** Methemoglobinemia; Cocaine; Nitrites; Emergency Medicine; Case Reports

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## 1. Introduction

Acute cyanosis is a singular, potentially life-threatening sign and requires a fast emergency department (ED) approach. The most common disorders that accompany cyanosis are pulmonary and cardiovascular diseases due to systemic desaturation or increased oxygen extraction. Methemoglobinemia (MHG) is a rare, potentially fatal cause of cyanosis and should be considered in patients with cyanosis and hypoxia (1-3). This report presents an uncommon case of cocaine- and volatile nitrite–induced MHG in a patient admitted to the ED of Israelita Albert Einstein Hospital, São Paulo, Brazil. Further, this report aims to clarify the diagnostic approach to acute cyanosis.

## 2. Case Presentation

A previously healthy 31-year-old male patient presented to the emergency department with dizziness, sweating, anxiety,

muscle spasms, shortness of breath, and bluish hands and lips. The symptoms had started two hours before admission, about 90 minutes after using inhaled cocaine and "poppers" (volatile nitrites). The patient reported that it was the second time he had used cocaine in his lifetime, had used volatile nitrites, and had used cocaine and poppers simultaneously for the first time.

On admission, the vital signs were as follows: blood pressure of 138/75 mmHg, heart rate of 89 beats per minute, respiratory rate of 20 breaths per minute, and oxygen saturation of 88–90% while breathing in ambient air. He had cyanotic lips, hands, and feet but no remarkable findings on cardiopulmonary examination. The electrocardiogram (ECG) performed on admission showed an apiculate T wave in V3–V4 derivation, normalized in subsequent minutes (Figure 1, left). The chest radiograph showed normal lung tissue and cardiac area (Figure 1, right).

On arrival and after two hours, the troponin levels were < 40 pg/mL (within the normal range). Admission laboratory tests showed hemoglobin 17.1g/dL, leukocytes 13,760  $\mu$ L, neutrophils 12,246, platelets 298,000  $\mu$ L, and creatinine, sodium, potassium, calcium, d-dimer, and NT-proBNP within normal range. There was no improvement in oxygen saturation despite a progressive offer of supplementary oxygen.

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**Table 1:** Blood gas analysis during emergency department care

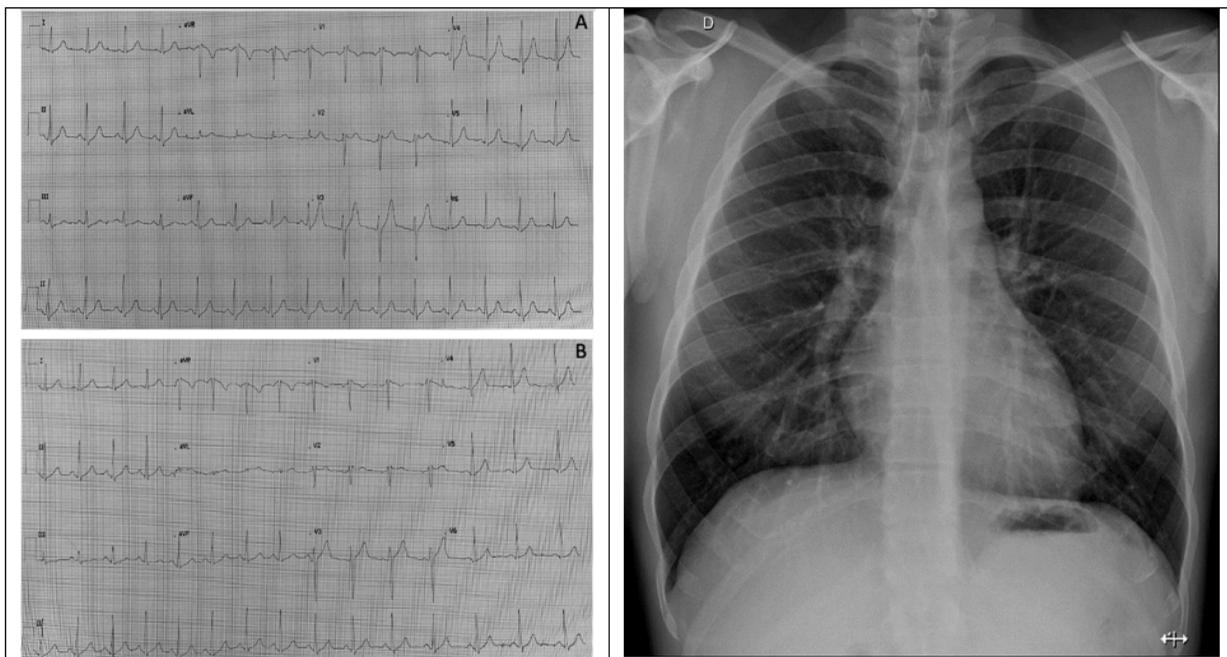
Variables	On admission		After treatment* <sup>A</sup>		Normal range
	Arterial	Venous	1mg/kg <sup>§</sup>	2mg/kg <sup>#</sup>	
pH	7.407	7.395	7.457	7.417	7.35–7.45
PCO <sub>2</sub> (mmHg)	35.0	36.6	31.7	36.8	35–45
PO <sub>2</sub> (mmHg)	62.4	25.5	297	74.1	80–90 <sup>A</sup> / 41–50 <sup>V</sup>
Base excess (mmol/L)	-1.8	-1.8	-0.2	-0.3	-2.0–2.0
Bicarbonate (mmol/L)	21.6	22.0	22.1	24.4	24–28
Oxygen saturation (%)	91.3	59.4	98.8	93.9	96–97 <sup>A</sup> / 40–70 <sup>V</sup>
Methemoglobin (%)	41.3	43.8	13.2	1.3	<1.5

\*: Treatment was done with methylene blue injection.

#Samples was collected while patient was breathing ambient air.

& Sample was collected while patient was receiving 15L/min of supplemental oxygen with non-rebreathing mask.

PCO<sub>2</sub> = partial pressure of carbon dioxide, PO<sub>2</sub> = partial pressure of oxygen, A: arterial blood sample, V: venous blood sample.



**Figure 1:** A) Admission electrocardiogram showing apiculate T wave in V3-V4 derivation, B) Spontaneously normalized electrocardiogram in subsequent minutes (left). Chest radiograph with normal lung tissue and cardiac area (right).

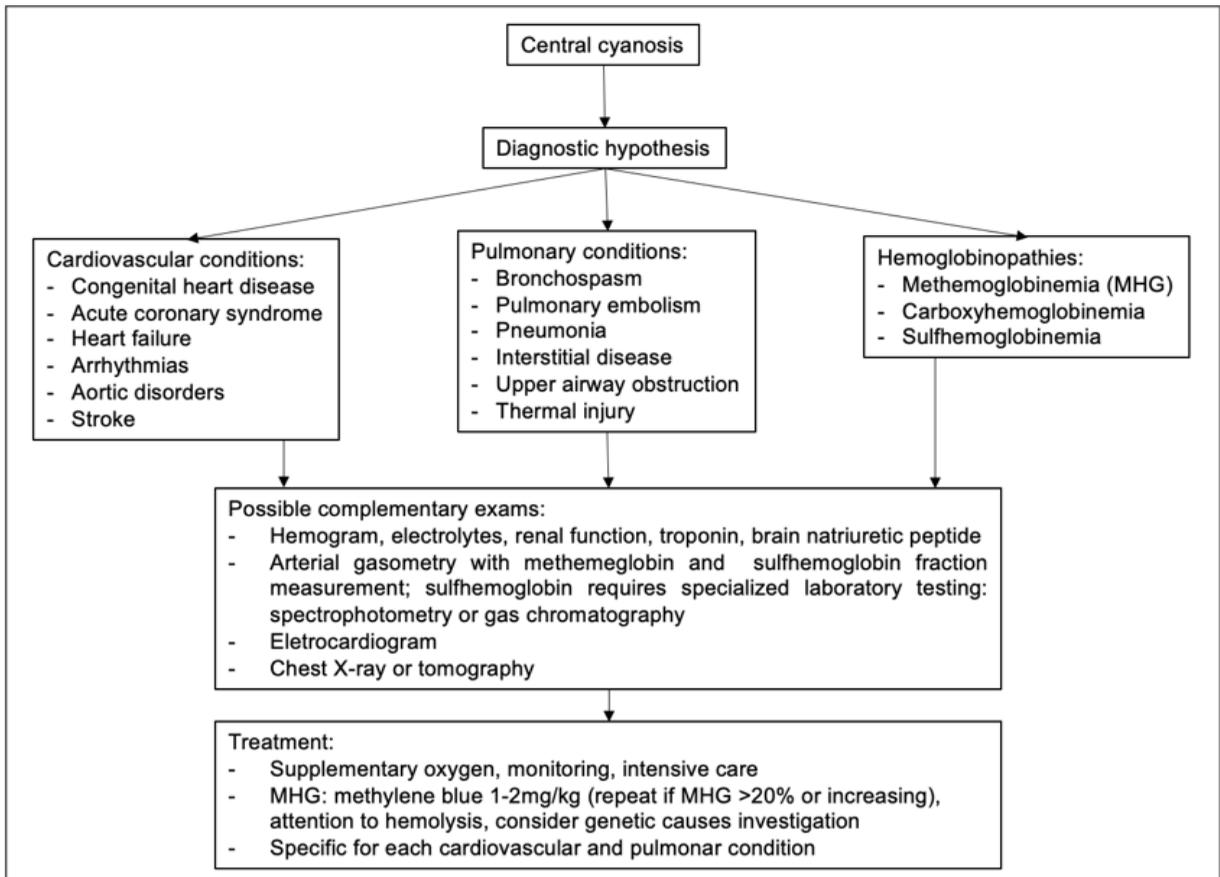
Cardiovascular causes of cyanosis were unlikely as the patient had no chest pain, heart sounds were normal, shock signs were absent, ECG abnormalities (V3-V4 apiculate T wave) did not progress to ST-elevation myocardial infarction, and troponin, NT-proBNP, and d-dimer levels were normal. Pulmonary diseases were also implausible since there were no history or pulmonary findings suggestive of bronchospasm, pulmonary embolism, pneumothorax, upper obstruction, aspiration, and infectious or chronic pulmonary diseases. MHG was suspected, especially after no improvement in saturation with progressive high oxygen offer. His venous and arterial blood samples were dark red. The arterial blood gas (table 1) was readily available and confirmed

methemoglobin levels > 40% (normal range < 1.5%).

He was treated with methylene blue at 1 mg/kg for 20 minutes with clinical improvement, and the methemoglobin level decreased to 13%. Another dose of 1 mg/kg was administered after one hour, with symptom resolution and methemoglobin level of 1.3%. The patient was discharged asymptomatic on the third day of hospitalization after performing echocardiogram and holter monitoring, the results of which were normal.

### 3. Discussion

MHG is potentially fatal because it impairs the oxygen-carrying capacity of blood by converting iron species from



**Figure 2:** Diagnosis and management of central cyanosis in the emergency department.

**Table 2:** Hemoglobinopathies’ characteristics

Character	Methemoglobin	Carboxyhemoglobin	Sulfhemoglobin
<b>Precipitants</b>	Hereditary, Medicine, Recreational, drugs Food poisoning	Inhalation of carbon monoxide during fires and the burning of gasoline, wood, coal, kerosene, and other fuels in poorly ventilated areas.	Induction by drugs (i.e., dapsons, sulphonamides, phenazopyridine)
<b>Blood color</b>	Dark red	Cherry red	Green
<b>Diagnosis</b>	Measurements through co-oximetry or blood gas	Measurements through co-oximetry or blood gas	Measurement through co-oximetry, spectrophotometry, or gas chromatography
<b>Treatment</b>	Methylene blue, Ascorbic acid, Oxygen, supplementation	High flow or hyperbaric oxygen	Support (no antidote) Resolution after erythrocyte turnover (definitively linked to hemoglobin), exchange transfusion in severe cases

the reduced ferrous (Fe 2+) to the oxidized ferric (Fe 3+) form in the circulation of hemoglobin. The latter is unable to adhere to and transport oxygen. Thus, the O<sub>2</sub> offered to the tissues is decreased, and the ferric heme shifts the oxyhemoglobin curve to the left (2).

In addition to cyanosis, other symptoms of MHG range from headaches, blurred vision, irritability, lack of short-term

memory, agitation, combativeness, confusion, lethargy, unconsciousness, and respiratory distress (4, 5).

Recreational drugs that cause MHG include e-cigarettes, volatile nitrites (known as "poppers" because of the sound the small glass containing the liquid makes on being crushed between the fingers), cocaine, heroin, and other substances used as diluting adulterants (6, 7). Less commonly, exoge-



nous intoxication with antifreeze, naphthalene balls, solvents, and pesticides were also reported as possible causes of MHG (8, 9).

Cocaine is widely consumed worldwide, with an estimated 20 million current users (10). In the emergency department, cocaine is responsible for 30% of all drug-related evaluations (11). Though cocaine itself is not a usual precipitant for MHG, its most frequent diluents are. These include phenacetin, lidocaine, benzocaine, and procaine (12-14).

The recreational use of volatile nitrites ("poppers") became popular since the 1970s, especially in the gay community, because of its property of relaxing smooth muscles, such as the throat and anal sphincter, in addition to inducing euphoria and warmth. Meanwhile, undesirable effects include headaches, dizziness, anxiety, ataxia, loss of vision (maculopathy), and MHG (15, 16). An estimated 3.3% of the adults in the United States have used poppers. In the gay man population, the prevalence is estimated at 35% (17).

MHG can also be acquired through medicine and food. Medicines that can precipitate MHG are local and inhaled anesthetics like lidocaine, benzocaine, prilocaine, and nitric oxide; antimalarial agents such as chloroquine and primaquine; dapson, used in Hansen's disease, as prophylaxis in *Pneumocystis pneumonia* in HIV, and present in some anti-acne agents; and acetaminophen (18-20). Food items include choy sum, fennel, root vegetables such as carrots and beetroots, meat and cheese contaminated with high nitrate content to preserve it longer, and possibly well water.

Hereditary MHG is a rare autosomal recessive disorder related to cytochrome B5 reductase deficiency. Because of the decrease in the enzyme that reduces ferric heme to ferrous heme, the conversion of methemoglobin to hemoglobin becomes difficult. In hemoglobin M disease, a dominant disorder leads iron to connect to phenolate, a complex that makes the reduction of ferric heme difficult. The final form of inherited MHG is cytochrome B5 deficiency, an unlikely disorder that disables the electron donation for methemoglobin conversion to hemoglobin (21, 22).

A structured reasoning flow from diagnosis to treatment for patients with central cyanosis in the ED is proposed in Figure 2. The starting point is the immediate work to differentiate cardiovascular and pulmonary diseases, and hemoglobinopathies. The symptoms are similar among the hemoglobinopathies (Table 2) (1-5, 23, 24). In these cases, typically, there is no improvement in oxygen saturation even with a progressive increase in oxygen supply; however, this is insufficient to exclude cardiovascular and pulmonary conditions.

Recently some colleagues have reported a case of MHG presumably induced by cocaine adulterants. They reinforced the importance of the laboratory routinely reporting methemoglobin and carboxyhemoglobin levels or at least report-

ing them when values are above the normal range even when not requested (25). Our hospital implemented the routine of alerting the team responsible for the patient about all the non-requested altered findings in the blood gas analysis (hemoglobin, glucose, creatinine, electrolytes, and lactate) to prevent adverse events due to lack of diagnosis.

## 4. Limitations

Because of the lack of tests to define the precipitant of MHG, we acknowledge that the precipitant could have been only volatile nitrite or cocaine diluents. However, knowing that the patient used these recreational drugs alone in the past without complications and that both can be related to MHG, we presumed the precipitant was their combination.

## 5. Conclusion

MHG is a rare, life-threatening cause of cyanosis. The diagnosis must be suspected in the emergency department in the presence of hypoxia and cyanosis disproportionate to cardiopulmonary repercussions and refractory to oxygen supplementation. Acquired causes are more prevalent than genetics, and recreational drugs should be highly suspected.

## 6. Declarations

### 6.1. Acknowledgments

INTEGRATE Investigators (EINsTein EmerGency ReseArch Team).

### 6.2. Authors' contributions

All authors met the criteria for authorship contribution based on recommendations of international committee of medical journal editors. Conception, planning, analysis, and interpretation of data: MRP, TADA. Data collection: LFLP, LZP, LSE, MRP. Writing of the article or its critical intellectual review: MRP, TADA, KAL, KFK. Responsibility for final review and approval for publication: all author.

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None.

### 6.4. Conflict of Interest

Authors have no conflict of interest.

### 6.5. Ethical consideration and consent

The study and consent waiver were approved by the Hospital Israelita Albert Einstein Review Board (CAAE Protocol Number: 52261321.0.0000.0071).



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