Med & Health June 2026; 21(6)(Suppl): 56-61 https://doi.org/10.17576/MH.2026.s2106.09

CASE REPORT

Acquired Methaemoglobinaemia Secondary to Sepsis-Induced Oxidative Haemolysis: A Case Report

NUR IZZATI TUKIMAN[1,2], IZZATUL ALIAA BADARUDDIN[1]*, NUR AASYIRAH ZAKARIAH[2], MUNIRAH MD MANSOR[1]

[1]Chemical Pathology Unit, Department of Pathology, Faculty of Medicine, Universiti Kebangsaan Malaysia, 56000 Cheras, Kuala Lumpur, Malaysia

[2]Department of Pathology, Hospital Tuanku Ampuan Rahimah, Ministry of Health, 41200 Klang, Selangor, Malaysia

**Correspondence: izzatulaliaa@ukm.edu.my; Tel: +603 91455376*

Received: 26 May 2025 / Accepted: 17 July 2025

ABSTRAK

Methaemoglobin merupakan keadaan yang jarang berlaku yang mengganggu pengangkutan oksigen dengan menukarkan hemoglobin kepada bentuk yang tidak berfungsi. Pengenalpastian secara klinikal boleh tertangguh disebabkan spektrum gejala luas dan tidak ketara serta kekangan alat pemantauan konvensional. Seorang lelaki berusia 36 tahun mengalami sesak nafas akut selepas pengambilan antibiotik untuk merawat demam dan cirit-birit. Walaupun menerima terapi oksigen aliran tinggi, ketepuan oksigennya kekal rendah. Darah arteri kelihatan berwarna coklat gelap, mencetuskan syak terhadap ketepuan methemoglobin dalam darah, yang kemudiannya disahkan melalui bacaan ko-oksimetri dengan paras methaemoglobin sebanyak 19.6–24.0%. Pesakit juga menunjukkan tanda hemolisis oksidatif dan anemia teruk, walaupun ujian saringan glukosa-6-fosfat dehidrogenase adalah normal. Rawatan dengan metilena biru telah diberikan tetapi tidak menunjukkan kesan terapeutik lalu dihentikan. Rawatan sokongan serta antibiotik intravena diberikan bagi menangani stres oksidatif yang disyaki berpunca daripada jangkitan kuman. Pesakit beransur pulih dan didiscaj selepas 16 hari dengan gangguan fungsi buah pinggang yang masih berbaki akibat sepsis. Laporan kes ini menggambarkan cabaran diagnostik dalam mengendalikan kes methemoglobin, terutamanya tanpa ketiadaan tanda klasik seperti sianosis. Percanggahan antara bacaan oksimetri nadi dan ketepuan oksigen arteri ialah petunjuk penting dan seharusnya dititikberatkan. Kesedaran terhadap faktor penyumbang serta tafsiran keputusan makmal yang teliti adalah penting bagi memastikan rawatan yang selamat dan berkesan.

***Kata kunci**: Anemia; ko-oksimetri; glukosa-6-fosfat dehidrogenase; laporan kes; methaemoglobina; metilena biru; sepsis*

ABSTRACT

Methaemoglobinaemia is a rare condition that disrupts oxygen transport by converting haemoglobin into a non-functional form. Clinical recognition can be delayed due to subtle symptoms and limitations of standard monitoring tools. A 36-year-old man developed acute shortness of breath shortly after taking antibiotics for fever and diarrhoea. Despite high-flow oxygen therapy, his oxygen saturation remained unexpectedly low. Arterial blood appeared dark brown, prompting suspicion of methaemoglobinaemia, which was confirmed by co-oximetry showing methaemoglobin levels of 19.6–24.0%. He also showed evidence of oxidative haemolysis and severe anaemia, although his glucose-6-phosphate dehydrogenase screening test was normal. Methylene blue was administered but had no therapeutic effect and was

discontinued. Supportive care and intravenous antibiotics were given for presumed sepsis-related oxidative stress. The patient improved steadily and was discharged after 16 days with residual kidney impairment from the sepsis. This case illustrates the diagnostic challenge of methaemoglobinaemia, particularly in the absence of classic signs like cyanosis. A discrepancy between pulse oximetry and arterial saturation can offer an important clue. Awareness of contributing factors and thoughtful interpretation of laboratory results are essential to ensure safe and effective treatment.

Keywords: Anaemia; case report; co-oximetry; glucose-6-phosphate dehydrogenase; methaemoglobinaemia; methylene blue; sepsis

INTRODUCTION

Accurate diagnosis in patients presenting with unexplained hypoxia remains a challenge, particularly when classical signs are absent and initial investigations appear inconclusive. Among the differential diagnoses, methaemoglobinaemia is a potentially life-threatening condition that is often overlooked due to its non-specific presentation and low index of suspicion (Ivek et al. 2022; Soliman & Yassin 2018). As such, diagnostic acumen, particularly the ability to interpret subtle laboratory cues such as saturation gap, and atypical gross appearance of the sample based on colour changes, may provide important cues for further management.

This report presents a diagnostically challenging case of acquired methaemoglobinaemia secondary to oxidative haemolysis, where early recognition and the strategic use of laboratory markers were key to clinical decision-making. The aim is to highlight the importance of considering redox disturbances in acute care settings, especially when oxygen delivery appears impaired despite supportive therapy.

CASE REPORT

A 36-year-old man developed acute-onset dyspnoea 2 days after commencing unknown antibiotic therapy prescribed by a general practitioner for fever and diarrhoea. On presentation to the Emergency Department, he was hypoxic with oxygen saturation (SpO_2) measured by pulse oximetry of 63% on room air, febrile with a temperature of 38.8°C, tachycardic with 133 beats per minute, respiratory rate of 28 breaths per minute, and blood pressure was within normal limits. Despite high-flow oxygen via face mask, the patient remained persistently hypoxic, with a maximum SpO_2 of 86%, necessitating endotracheal intubation. Further history revealed no significant past medical conditions. The patient worked as a waiter for the past two years and reported active smoking and heavy alcohol consumption.

Initial venous blood gas analysis demonstrated metabolic acidosis (pH 7.34, HCO_3^- 17.3 mmol/L), and methaemoglobin (MetHb) levels were markedly elevated, ranging from 19.6% to 24.0% (reference range: 0-1.5%). Intravenous methylene blue (MB) was administered; however, the patient's SpO_2 paradoxically declined to 30%, with worsening methaemoglobinaemia (Table 1). Laboratory investigations were consistent with sepsis-induced oxidative haemolysis, evidenced by leukocytosis, bite and blister cells, and hyperbilirubinaemia. Heinz bodies were not observed on the peripheral blood smear, and the glucose-6-phosphate dehydrogenase (G6PD) spot test was normal. The patient was also anaemic, with a haemoglobin level of 7.1 g/dL (reference range: 12.0-15.0 g/dL) and had acute kidney injury suggested by elevated serum urea (20.5 mmol/L; reference range 3.2-8.2 mmol/L) and creatinine of 165 µmol/L (reference range 49.0-90.0 µmol/L).

There was no clinical cyanosis on reassessment, but dark, brown-coloured arterial blood was observed during sampling (Figure 1). Two additional doses of intravenous MB were administered, but MetHb levels did not improve.

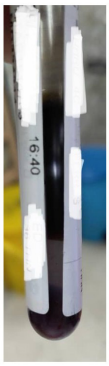

FIGURE 1: Dark brown discolouration of serum specimen at presentation

MB therapy was subsequently discontinued, and intravenous piperacillin/tazobactam 4.5 g three times daily (TDS) was initiated for presumed sepsis. The patient was transferred to the intensive care unit for further management.

During admission, serum creatinine increased in trend up to 395.6 µmol/L on day five of admission, which decreased later to 274.1 µmol/L (serum urea 14.9 mmol/L) after 1 week without any dialysis intervention. He was treated for occult sepsis and completed 10 days of intravenous antibiotics despite all negative cultures. Gradual improvement in MetHb and haemoglobin levels was observed, parallel with a downward trend in infective markers. A repeat peripheral smear showed resolution of haemolysis, with only reactive thrombocytosis noted in response to the infection. The patient was discharged on day sixteen after being clinically stable with an outpatient appointment for a repeat blood taking.

DISCUSSION

This case highlights the diagnostic complexity of acquired methaemoglobinaemia, particularly secondary to oxidative haemolysis. While symptoms such as dyspnoea and tachycardia may reflect impaired oxygen delivery due to red cell destruction, the absence of classical features, most notably cyanosis, a hallmark of methaemoglobinaemia (Iolascon et al. 2021), rendered the presentation atypical.

The G6PD spot test is generally expected to yield a positive result in G6PD-deficient individuals and may also remain insufficiently low during an acute haemolytic crisis (Eziokwu & Angelini 2018). Acute haemolysis triggers reticulocytosis, and since reticulocytes have higher G6PD activity than mature erythrocytes, this can cause a falsely normal spot test result during a haemolytic crisis (Cortesi et al. 2021). Confirmatory quantitative enzyme assay testing is best performed several weeks after resolving hemolysis. However, our patient's G6PD spot test was normal, and definitive confirmation could not be obtained as the patient defaulted on follow-up.

Interpreting both MetHb levels and G6PD activity during acute illness requires careful consideration. The haemolytic crisis here was likely multifactorial, potentially exacerbated by occult sepsis, metabolic acidosis and exposure to an unidentified antibiotic prescribed in the community. The patient's history of heavy alcohol consumption, smoking and recent antibiotic use may have increased his vulnerability to oxidative stress. Sepsis-related inflammation likely further disrupted redox balance, impairing the function of NADH–cytochrome b5 reductase, the primary enzyme responsible for MetHb reduction, thereby intensifying oxidative injury (Ludlow et al. 2023).

Ivek et al. (2022) reviewed the clinical severity of methaemoglobinaemia as correlated with MetHb concentration, baseline haemoglobin level, and cardiovascular reserve. While levels below 15% are often asymptomatic, concentrations exceeding 30-40% may result in severe manifestations, including dyspnoea, arrhythmias, seizures or death (Ivek et al. 2022). Our patient's initial MetHb level was 19.6%, equivalent to a concentration of 13.7 g/L at a concurrent haemoglobin of 7.1 g/dL. Cyanosis typically becomes evident when MetHb exceeds 15 g/L (Mobarak et al. 2024), possibly explaining the absence of cyanosis. Moreover, severe anaemia, as seen here, complicates interpretation since reduced total haemoglobin

may underestimate the severity of MetHb. The patient's haemoglobin dropped further to 4.6 g/dL by day three. In such scenarios, even a modest MetHb fraction can significantly compromise oxygen-carrying capacity, underscoring the importance of interpreting MetHb values in conjunction with haemoglobin levels.

A key diagnostic clue is the saturation gap, defined as a discrepancy between oxygen saturation measured by pulse oximetry and that determined by co-oximetry (Iolascon et al. 2021). Pulse oximetry, which utilises only two wavelengths (660 nm and 940 nm), tends to underestimate arterial oxygen saturation in the presence of MetHb. In contrast, co-oximetry employs multiple wavelengths, 600 nm (carboxyhaemoglobin), 631 nm (MetHb), 660 nm (deoxyhaemoglobin) and 940 nm (oxyhaemoglobin, COHb), allowing for accurate MetHb quantification (Iolascon et al. 2021). A saturation gap exceeding 5% was observed in our patient at initial presentation, which gradually decreased during admission and, when appropriately interpreted, provided valuable guidance for clinical management (Table 1).

Recognising that other dyshaemoglobins may interfere with MetHb measurement via co-oximetry is also pertinent. COHb and sulfhaemoglobin (SulfHb) overlap absorption spectra with MetHb (Chan et al. 2015). COHb strongly absorbs at 540 and 570 nm, potentially mimicking oxyhaemoglobin and resulting in falsely elevated SpO_2 readings. SulfHb, which absorbs across 620-635 nm, can similarly interfere with MetHb readings but may be distinguished using extended-wavelength co-oximetry (Barker et al. 2006; Chan et al. 2015). COHb was deemed unlikely in this case, given its typical presentation with cherry-pink blood, as opposed to the dark brown observed. However, SulfHb could not be definitively excluded. Potassium cyanide testing to induce a colour change was unavailable, and although the patient's history suggested possible exposure to sulphur-containing antibiotics, confirmatory testing with MALDI-TOF, as described by Docherty et al. (2020), was not accessible at our centre.

The possibility of congenital methaemoglobinaemia due to haemoglobin M (HbM) disease was also considered but deemed unlikely. HbM typically presents with lifelong cyanosis and persistently low SpO_2 from early childhood (Iolascon et al. 2021; Pjetraj et al. 2025; Shen et al. 2025). Our patient had no family history of cyanosis and demonstrated full clinical recovery without recurrence, making a congenital cause improbable. These findings are consistent with the final diagnosis of acquired methaemoglobinaemia, likely precipitated by sepsis-induced oxidative haemolysis in a patient with undetermined G6PD status.

While MB may still be considered, it must be used cautiously in individuals with G6PD deficiency. The efficacy of MB depends on

TABLE 1: Serial laboratory findings

Analyte	Method	Results					Reference intervals
		Day 1	Day 2	Day 3	Day 4	Day 5	
sPO_2 (%)	Pulse oximetry	75.0	78.0	73.0	90.0	100.0	95.0-100.0
sO_2 (%)	Co-oximetry	97.5	95.9	100.0	100.0	100.0	94.0-98.0
O_2 Hb (%)		75.6	76.3	86.2	92.1	96.0	90.0-95.0
HHb (%)		1.9	3.3	0	0	0	1.0-5.0
MetHb (%)		19.6-24.0	23.0	11.4	1.4	0.7	0.0-1.5
Haemoglobin (g/dL)	Sodium lauryl sulphate Photometry	7.1	5.0	4.6	9.5	10.2	12.0-15.0

NADPH, which is deficient in these patients, rendering the treatment less effective and potentially harmful by further depleting NADPH, reducing glutathione levels and triggering haemolysis. As alternatives, high-dose intravenous vitamins C and B2, which act as electron acceptors, may be incorporated into the treatment strategy (Iolascon et al. 2021). There was no documentation of this case of adjunctive therapy with vitamin C or B2.

CONCLUSION

This case underscores the diagnostic challenge of recognising acquired methaemoglobinaemia without classical signs such as cyanosis. A high index of suspicion is crucial when faced with unexplained hypoxia, particularly in the presence of a saturation gap and risk factors for oxidative stress. Prompt co-oximetry and careful interpretation of G6PD status are essential to guide appropriate management and avoid delays in life-saving interventions. Importantly, clinicians should be aware that MB may be ineffective if the underlying trigger, such as ongoing sepsis remains unaddressed which highlights the need for comprehensive management of the precipitating condition.

Funding: This research received no external funding.

Acknowledgment: The authors would like to thank the clinical and laboratory staff of the Ministry of Health Malaysia who were involved in the diagnostic work-up and management of this case. Special thanks are extended to Dr Hanisah Abdul Hamid, Consultant Chemical Pathologist, for her valuable guidance and contribution to the diagnostic evaluation and clinical management of this case.

Conflict of interest: The authors declare no conflicts of interest.

Ethics statement: Verbal informed consent for publication was obtained from the patient. Patient anonymity was maintained, and no identifiable information is included in this report.

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