

Singing the Blues: Is It Really Cyanosis?

Amy Baernstein MD, Kelly M Smith MD, and Joann G Elmore MD MPH

Introduction

A patient with a bluish tinge to the skin is alarming to a medical provider. Such a patient may be severely hypoxemic, which is a medical emergency. However, there are other causes of bluish coloring, both acute and chronic. We present a case of a patient who was referred for care because he appeared blue. We discuss common and uncommon causes of bluish appearance and suggest a diagnostic approach to such patients.

Case Summary

Staff at a homeless shelter noticed that a 46-year-old man appeared blue. Paramedics were called. On arrival to the emergency department he appeared in no acute distress and had obvious blue-gray discoloration (Fig. 1). History-taking was challenging because the patient's report of symptoms was inconsistent. He initially denied shortness of breath, but later stated that he had come to the hospital because of shortness of breath. On further history-taking, the patient reported that his skin became discolored "over the last few days" and that the discoloration waxed and waned. However, a clinic note from one year prior to this emergency department visit described the same skin changes.

The patient had neurogenic bladder, multiple episodes of urinary tract infection, and longstanding use of an indwelling urinary catheter. He stated that he had treated these infections by ingesting colloidal silver for several years; the last treatment was approximately one year prior to this visit. He obtained the silver from a jeweler and prepared it in his kitchen. He ceased using silver when he



Fig. 1. Patient referred to the emergency department for evaluation of blue-gray discoloration. (Courtesy of Kyle Garton MD, Division of Dermatology, Department of Medicine, University of Washington, Seattle, Washington.)

could no longer afford it. He denied exposure to other metals and denied ingestion of gold, amiodarone, minocycline, chlorpromazine, or antimalarial drugs.

His vital signs on room air were oxygen saturation 98%, blood pressure 148/81 mm Hg, respiratory rate 16 breaths/min, heart rate 88 beats/min, and temperature 38.4°C. Physical examination revealed generalized blue-gray coloring of the skin. Cardiopulmonary examination was normal. A suprapubic catheter was present. While on supplemental oxygen at 15 L/min his arterial blood values included pH 7.64, P_{aCO_2} 18 mm Hg, P_{aO_2} 133 mm Hg, HCO_3^- 20 mEq/L, lactate 2.1 mmol/L, carboxyhemoglobin 1%, and hemoglobin 12.9 g/dL. The laboratory did not remark on the color of the blood sample.

Amy Baernstein MD, Kelly M Smith MD, and Joann G Elmore MD MPH are affiliated with the Division of General Internal Medicine, Department of Medicine, University of Washington, Seattle, Washington.

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Correspondence: Amy Baernstein MD, Emergency Services, Box 359702, Harborview Medical Center, 325 Ninth Avenue, Seattle WA 98104. E-mail: abaer@u.washington.edu.

This patient's blue-gray discoloration was attributed to argyria, based on his normal oxygen level, history of silver ingestion, and denial of exposure to other metals or medications that can discolor skin. Confirmation would require a skin biopsy or serum silver assay, which were not obtained because they were not thought clinically necessary.

Discussion

Hypoxia is the most common cause of bluish color. It is essential to diagnose hypoxia immediately. In hypoxia the blue color is from deoxygenated hemoglobin in the blood, not because of the hypoxia itself. Deoxygenated hemoglobin reflects blue wavelengths of light. A bluish tinge is first visible on the lips and tongue when deoxygenated hemoglobin reaches a concentration of 5 g/dL in capillary blood. This corresponds to 3.5 g/dL of deoxygenated hemoglobin in arterial blood, or oxygen saturation of 73–78%.¹ Discoloration due to hypoxia is termed "cyanosis." Cyanosis is increasingly perceptible as the concentration of deoxyhemoglobin rises.

Any patient who appears unexpectedly blue should be quickly evaluated with pulse oximetry and/or arterial blood analysis, to determine if life-threatening hypoxemia is the cause. Those hypoxemia tests must be conducted even if the patient is otherwise asymptomatic, because some patients do not feel short of breath despite hypoxemia. Decreased sensitivity to hypoxemia is found in chronically hypoxemic individuals, such as residents of high altitude and patients with congenital right-to-left cardiac shunt, and in some patients with chronic lung disease or obesity hypoventilation syndrome.²⁻⁵ Additionally, altered mental status prevents patients from reporting shortness of breath. Therefore, even patients who don't feel short of breath but appear blue should have their oxygenation assessed.

Cyanosis is an unreliable sign of hypoxemia. One reason is that total hemoglobin concentration affects the level of deoxygenated hemoglobin, so cyanosis appears sooner in patients with polycythemia, and may not appear at all in patients with anemia.⁴ Second, cyanosis might be harder to detect in darker-skinned individuals,^{6,7} though data to support that hypothesis are lacking.

Pulse oximetry is the most convenient way to assess oxygenation, because it is noninvasive and readily available. Pulse oximetry may overestimate oxygen saturation in dark-skinned individuals, but this effect is most marked with a low oxygen level,⁸ at which point arterial blood gases should be measured. A normal oxygen saturation is reassuring that a patient's bluish tint is not due to hypoxemia.

The distribution of bluish discoloration can provide clues to the etiology. Central cyanosis, or discoloration visible first on the lips and tongue, indicates systemic hypoxemia. In contrast, cyanosis visible first on the extremities (pe-

Table 1. Common Drugs and Toxins That May Precipitate Methemoglobinemia

Drugs
Anesthetics
Benzocaine
Lidocaine
Prilocaine
Chloroquin
Dapsone
Metoclopramide
Nitrites
Amyl nitrite
Nitroprusside
Nitroglycerin
Nitric or nitrous oxide
Phenazopyridine
Primaquin
Sulfamethoxazole
Toxins
Aniline dyes
Benzene derivatives
Nitrates or nitrites in foods or well water
Paraquat

ripheral or acral cyanosis) occurs when deoxygenated blood accumulates in a specific region of the body. This occurs when oxygen demand outstrips supply, and may result from reduced cardiac output (as in heart failure), peripheral vasoconstriction (as in hypothermia or Raynaud syndrome), or regional ischemia (as in arterial thrombosis).⁹ In patients with only peripheral cyanosis, the pulse oximetry value may be low if measured on an affected limb, but the arterial blood will have a normal oxygen level.

Bluish coloring may also result from abnormal forms of hemoglobin, such as methemoglobin. Methemoglobin is hemoglobin in which the iron moiety is in the ferric form, rather than the normal ferrous form. Methemoglobin cannot bind oxygen, so if too much of a patient's hemoglobin is converted to methemoglobin, tissue oxygenation is impaired. Furthermore, methemoglobin shifts the oxygen-dissociation curve to the left, which further impairs tissue oxygenation.^{10,11} Normal individuals have less than 1–2% methemoglobin. Elevated methemoglobin may result from congenital enzyme defects or certain toxins and medications in susceptible individuals (Table 1).^{10,12} The blue discoloration appears when methemoglobin is at least 10–20% of total hemoglobin.^{10,13} Once methemoglobin reaches 20% the patient may have symptoms of headache, tachycardia, dyspnea, and nausea. Altered mental status, arrhythmia, seizure, and death may occur if methemoglobin is greater than 50%.¹⁰⁻¹²

When a substantial amount of methemoglobin is present, the blood appears chocolate-brown or brown-black in the syringe. The blood will not turn bright red when exposed

Table 2. Differential Diagnosis of Blue-Gray Skin Discoloration

Medical conditions
Hemochromatosis
Addison's disease
Disseminated melanoma
Wilson's disease
Drugs
Chlorpromazine
Amiodarone
Minocycline
Anti-malarials
Metals
Silver
Gold
Mercury
Bismuth
Arsenic

to oxygen, as normal blood will.¹³ This can be an important clue to check the methemoglobin level in an apparently cyanotic patient. Our patient's blood was not noted to be abnormally colored, and methemoglobin level was not checked.

Our patient's above-normal oxygen content in arterial blood excluded hypoxemia as the problem, and the normal pulse oximetry reading ruled out substantial methemoglobinemia.¹⁴ Once hypoxemia and abnormal hemoglobins are eliminated as the cause of bluish discoloration, the clinician should consider processes that affect the skin, rather than the underlying capillary blood. These include skin staining caused by metals and certain drugs, and various chronic medical conditions (Table 2).¹⁵⁻¹⁷ Based on our patient's history of colloidal silver ingestion, silver toxicity became the primary concern.

Silver has been used medicinally for centuries. In the 19th and early 20th centuries silver was frequently used to prevent wound infections and to treat sinus infections, colds, and syphilis. Absorption of silver, whether by ingestion, inhalation, or through the skin, can cause blue-gray skin discoloration, known as argyria, or "false cyanosis." Silver particles are deposited in the skin, which causes a permanent stain and increases melanin production.

The medical use of silver declined once the association between silver-containing medications and argyria became apparent. Although no longer routinely prescribed by physicians, colloidal silver is still available over the counter in some countries, and is sold as an unregulated "dietary supplement" in the United States. It is marketed as a therapy for many conditions, including cancer, acquired immune deficiency syndrome, respiratory infections, and aging. Several reports of argyria due to these unregulated products have appeared in recent years.¹⁵⁻¹⁹ Silver can also be absorbed from standard medical therapies, such as sil-

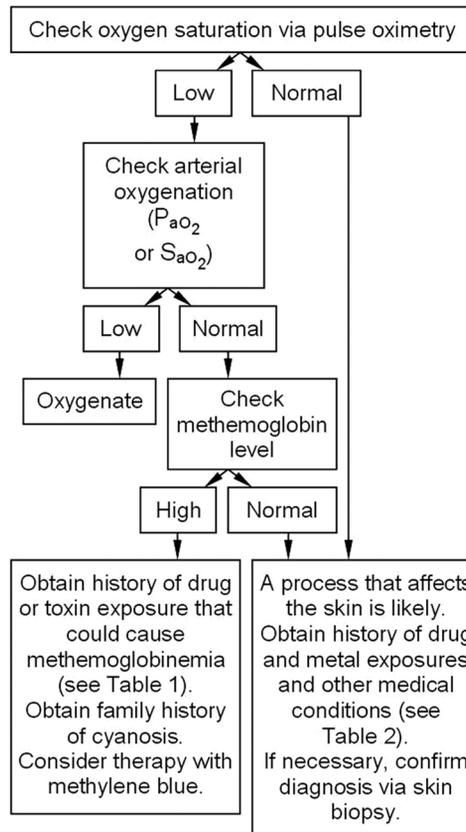


Fig. 2. Diagnostic approach to a patient who appears blue.

ver sulfadiazine cream and other wound-care products, and from implanted medical devices that contain silver, such as catheters, bone cements, orthopedic pins, and artificial heart valves, but these have not been associated with generalized argyria.^{20,21} Workers may be exposed in photography, jewelry, and mining occupations.²⁰

Toxicity to other body systems is rare,²¹ but the skin staining is unfortunately irreversible. Argyria can be severely embarrassing and cause withdrawal from normal activities.^{19,22} It may also be mistaken for true cyanosis and lead to unnecessary medical care.^{18,23-25}

Teaching Points

A bluish patient may have life-threatening hypoxia or methemoglobinemia. Both conditions may be chronic or acute, symptomatic or not. If hypoxia or methemoglobinemia are excluded by normal oxygen saturation, arterial blood gas analysis, and/or methemoglobin assay, if indicated, rarer chronic conditions that affect the skin should be suspected. The diagnosis can then be pursued based on history, physical examination, disease-specific tests, and/or skin biopsy (Fig. 2).

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