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REVIEW

Irritant and asphyxiant gases

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ABSTRACT:

Both irritant and asphyxiant gases are hazardous substances that, when inhaled, can cause a spectrum of respiratory complications, ranging from mild irritation to life-threatening respiratory failure. These gases are classified into three main categories based on their mechanisms of toxicity: pulmonary irritants, simple asphyxiants, and chemical asphyxiants. Pulmonary irritants, such as chlorine, phosgene, and ammonia, cause direct injury to the respiratory mucosa, leading to inflammation, bronchospasm, and pulmonary edema. Simple asphyxiants, including nitrogen, methane, and carbon dioxide, displace oxygen in the environment, resulting in hypoxia and potentially fatal respiratory depression. Chemical asphyxiants, such as carbon monoxide, hydrogen cyanide, and hydrogen sulfide, interfere with oxygen transport or cellular respiration, causing systemic hypoxia at the mitochondrial level.

Diagnosis of the gas exposure relies on a detailed history of exposure, clinical symptoms, and laboratory investigations, including arterial blood gas analysis, pulse oximetry, and carboxyhemoglobin or methemoglobin levels. Management involves immediate removal from the toxic environment, decontamination, oxygen supplementation, and supportive treatment. Specific antidotes, such as hydroxocobalamin for cyanide poisoning and methylene blue for methemoglobinemia, may be required in severe cases. Given the potential for rapid deterioration, early recognition and prompt intervention are essential in preventing morbidity and mortality. This review provides an in-depth analysis of the toxicology, pathophysiology, and management strategies associated with asphyxiant gas exposure.

Keywords: Asphyxiants; Carbon monoxide; Cyanide; Hydrogen sulfide; Methemoglobinemia; Respiratory irritants

INTRODUCTION

Irritant and asphyxiant gas refers to a gas or vapor that, when inhaled, can cause varying degrees of respiratory distress. These effects range from respiratory irritation to immediate death by asphyxiation, which may occur through mechanisms such as acute upper airway inflammation, delayed pulmonary edema, respiratory muscle dysfunction, or a combination of these conditions [1].

This gas can be divided into 3 main categories by its mechanism.

1. Pulmonary irritants: Directly irritated the respiratory system mucous membranes. (e.g., chlorine gas, phosgene, ammonia, sulfur dioxide).
2. Simple Asphyxiants: Displace oxygen in the air (e.g., nitrogen, methane, carbon dioxide).
3. Chemical Asphyxiants: Interfere with oxygen transport or cellular respiration (e.g., carbon monoxide, hydrogen cyanide).

RESPIRATORY IRRITANTS

Respiratory irritants are a group of chemical compounds that are typically water-soluble and cause direct injury to the respiratory mucosa by generating acids, alkalis, or other reactive substances. The symptoms caused by these irritants vary depending on their concentration, duration of exposure, and chemical solubility.

Respiratory irritants can be classified into three categories based on their water solubility:

1. High water solubility: Includes ammonia, hydrogen chloride, sulfur dioxide, and formaldehyde
2. Intermediate water solubility: Includes chlorine and isocyanates
3. Low water solubility: Includes nitrogen oxides and phosgene

Highly water-soluble compounds predominantly affect the upper airway, leading to symptoms such as skin irritation, dyspnea, wheezing, chest tightness, and laryngospasm. In contrast, poorly soluble compounds can penetrate deeper into the pulmonary parenchyma, potentially causing exertional dyspnea and even permanent lung fibrosis. Intermediate-solubility compounds pose the greatest risk, as they can injure both the upper airway and the lung parenchyma [2,3]. In addition, exposure to these irritants may provoke allergic responses in susceptible individuals, particularly those with asthma, hypersensitivity pneumonitis, or chronic obstructive pulmonary disease (COPD).

KEY MESSAGES:

- Irritant and asphyxiant gases are categorized into three main types:
  a. Pulmonary Irritants
  (e.g., chlorine, ammonia, phosgene)
  b. Simple Asphyxiants
  (e.g., nitrogen, methane, carbon dioxide)
  c. Chemical Asphyxiants
  (e.g., carbon monoxide, hydrogen cyanide, hydrogen sulfide).
- The gases cause harm through airway irritation, oxygen displacement, or inhibition of cellular respiration, leading to severe hypoxia, metabolic acidosis, and multi-organ dysfunction.
- A thorough exposure history, recognition of characteristic symptoms, and laboratory tests (e.g., blood gas analysis, carboxyhemoglobin/methemoglobin levels) are crucial for early diagnosis.
- Treatment involves immediate removal from exposure, oxygen therapy, supportive care, and specific antidotes where applicable
  (e.g., hydroxocobalamin for cyanide poisoning, methylene blue for methemoglobinemia).
- Delays in recognition and treatment can lead to fatal outcomes. Rapid assessment and targeted therapy are essential to reducing morbidity and mortality associated with asphyxiant gas exposure.

Diagnosis and treatment

The most important clue to diagnosis is a relevant history of exposure, including concentration and duration of exposure. Basic laboratory investigation and initial chest x-ray, pulse oximetry, and arterial blood gas may be useful to evaluate the degree of respiratory injuries. The mainstay of treatment is removing patients from the environment, decontamination, and supportive treatment with hydration and oxygen therapy.

Ammonia Gas (NH_3)

Ammonia is a colorless, alkaline, corrosive gas with a very pungent odor of drying urine. After dissolution of ammonia in water generating ammonium hydroxide, a basic compound, causing irritation. Generally, ammonia is a byproduct of human catabolism of amino acids, urea hydrolysis by urease-producing organisms in the colon, breakdown of purine nucleotide, and hydrolysis of glutamine in the proximal renal tubular cells [4]. Due to its highly toxic nature, it was quickly metabolized into urea by the liver and excreted through the kidneys [4,5]. However, ammonia can be found in external source in difference methods as it was widely used as refrigerant in ice plant, raw material in plastic and explosive productions, chemical fertilizer or as animal feeds. Gas leaks, exposure to high concentrations of ammonia levels in fertilized soil, household and industrial cleaners, and exposure to decaying manure are the main risks of inhalation.

The odor threshold of ammonia is 5 parts per million (ppm). Ammonia concentrations in the air are generally tolerable at levels up to 100 ppm for several hours without significant health effects. However, at 1700 ppm, symptoms such as coughing and laryngospasm begin to manifest. Concentrations of 2500 to 4500 ppm can be fatal within 30 minutes, while levels exceeding 5000 ppm typically result in rapid respiratory arrest [6-8].

There is no systemic antidote for ammonia poisoning. Removal of the victim and decontamination are mainstays of treatment. Supportive treatment with humidified oxygen, restrictive fluid resuscitation to avoid further pulmonary edema, and bronchodilators is suggested [7]. Asymptomatic patients should be observed for upper airway irritation for at least 6-12 hours [9,10].

Chlorine gas (Cl_2)

Chlorine is a yellow-green, noncombustible gas that is heavier than air with an irritating odor. The gas was a strong oxidizing agent and can react explosively. Chlorine gas was used as a disinfecting agent at swimming pools, formed by mixing household products that contain hydrochloric acid (HCl) found in bathroom cleaner with sodium hypochlorite (NaOCl) found in bleach or as an industrial solvent, and in the production of bleached paper products and plastics such as PVC [11-13].

Chlorine inhalation causes airway injury through multiple mechanisms. Hydration of chlorine gas forms hydrochloric acid (HCl) and hypochlorous acid (HOCl), both of which react with airway lining components.

Reactive oxygen species (ROS) are generated through recruited neutrophils and secondary mitochondrial dysfunction. Neutrophil myeloperoxidase can produce additional HOCl, while inducible nitric oxide synthase (iNOS) generates nitric oxide and peroxynitrite ($ONOO^-$). These reactive species collectively contribute to further airway injury [11].

Symptoms can vary depending on the concentration of exposure. Humans can detect the odor of gas at a level of 0.1-0.3 ppm. Exposure to a low level of 1–30 ppm for up to one hour results in mucous membrane irritation, whereas higher exposure of more than 30 ppm causes chest pain, dyspnea, and cough. Acute pulmonary edema typically develops at 40–60 ppm. Concentrations above 400 ppm are usually fatal over 30 minutes, whereas levels above 1000 ppm are typically fatal within minutes [11,14,15]. Long-term effects of chlorine gas exposure may contribute to cardiovascular complications, including myocardial infarction and biventricular heart failure [14] .

Treatment was primarily supportive with humidified oxygen and bronchodilators as needed. Nebulized sodium bicarbonate as a neutralizing therapy may improve pulmonary function during the initial 4 hours of treatment, however, long-term benefits are unproven [16,17]. Steroid therapy also shows improvement in airway resistance and arterial oxygenation but shows no improvement in the outcome with severe lung injury [18]. Asymptomatic patients may be discharged after 4 hours of observation [12,19].

Phosgene gas ($COCl_2$)

Historically, phosgene was used in World War I by the German forces and estimated to have caused nearly 85% of gas-related fatalities. Nowadays, phosgene gas is an industrial chemical used to make plastics and pesticides. The gas is colorless or a white to pale yellow cloud and nonflammable. When soluble, phosgene decay to hydrochloric acid (HCl) and carbon dioxide (CO_2). A small amount of phosgene of 1 ppm may cause little irritation, however, if exposed for hours, it may cause severe pulmonary edema. The lethal dose of phosgene is 500 ppm in 1 minute or 3 ppm for 170 minutes and is equal to 30 ppm for 17 minutes [20]. Due to low water solubility, onset of symptoms could be delayed after 2 - 72 hours of exposure [21,22].

After immediate exposure, phosgene contributes to the necrosis of club cells and ciliated epithelial cells. Uncontrolled inflammatory responses leading to cytokine storms activate cascade-like inflammatory reactions that result in secondary biological attacks [23,24]. Supportive treatment was suggested. Phosgene exposure patients should be observed for 48 hours [22].

SIMPLE ASPHYXIANTS

Simple asphyxiants are gases or vapors, e.g., Inert gas, carbon dioxide, propane, methane, and nitrogen displace oxygen in the inspired air, leading to normal alveolar–arterial gradient hypoxemic respiratory failure. Symptoms depend on the level and duration of exposure and the level of inspired oxygen concentration. The occupational Safety and Health Administration defines the minimum safe level of oxygen as 19.5% at sea level. At FiO_2 16 to 19.5%, workers with exertion can become symptomatic[25]. When the fraction of inspired oxygen (FiO_2) falls below 16%, victims experience tachypnea with hypocarbia and decreased mental status. Loss of consciousness and coma occur if FiO_2 falls below 10%, and death if FiO_2 less than 6% [2].

Rapid removal of victims away from asphyxiants is the most important treatment, however, rescuers can become second victims. Prevention of further hypoxemia with supportive treatment involving oxygen and ventilation is required for a better outcome.

CHEMICAL ASPHYXIANTS

These are substances that interfere with oxygen delivery to the cells. Either binding to hemoglobin, leading to dyshemoglobinemias, resulting in reduced oxygen delivery to tissue cells (e.g., carbon monoxide (CO) or methemoglobin inducers) and cellular asphyxiants (e.g., hydrogen cyanide (HCN) and hydrogen sulfide (H_2S)) blocking oxygen utilization in cells.

Carbon monoxide (CO)

Carbon monoxide is a colorless, odorless gas produced by incomplete combustion of fuel. Carbon-based fuel and household fires are the main sources of the gas [26]. Another source of CO poisoning is hepatic transformation of methylene chloride, the chemical used as a solvent in paint and varnish strippers and in degreasing agents [27]. In critically ill patients, sepsis and hemolytic anemia also account for endogenous sources of CO production [28].

There are three main mechanisms of CO toxicity. First, CO causes tissue hypoxemia secondary to the formation of carboxyhemoglobin (COHb) since CO binds to hemoglobin with 200–250 times greater affinity than oxygen, causing a left shift of the oxygen-hemoglobin dissociation curve, leading to decreased oxygen binding capacity and transportation to cells. The second mechanism is direct CO-mediated damage at the cellular level. CO can bind to cytochrome C oxidase (CCO), impairing mitochondrial function, contributing to more hypoxia, and leading to oxidative stress by reactive oxygen species (ROS) formation. The third mechanism is the binding of CO to heme-containing proteins in platelets and neutrophils, leading to the production of nitric oxide (NO) and its interaction with superoxide to form peroxynitrite ($ONOO^-$), which causes further compromise in mitochondrial function and promotes platelet activation. The platelet activation can induce oxidative burst via neutrophil activation, degranulation, and releasing of myeloperoxidase (MPO), proteases, and ROS, which further damage endothelial cells and neuronal tissues [29-32].

Diagnosis of CO poisoning required a clinical triad.

1. Symptoms consistent with CO poisoning
2. History of recent CO exposure
3. Elevated COHb levels [33]

Symptoms of acute CO poisoning vary on blood carboxyhemoglobin level. In a healthy adult non-smoker, the level of CO is around 0.5-1.5%, the level is higher if the patient is a smoker. Up to 10% of COHb levels can be found in heavy smokers without clinical symptoms. In acute CO poisoning, a COHb level of 10% can cause headache, and 10-20% can cause dyspnea on exertion, lethargy, tension

headache, and nausea. A level of 20-30% can cause vision disturbance and vertigo. A 40-50% COHb leads to severe headache, confusion, and collapse. A level up to 60% can cause syncope, Cheyne-stroke breathing pattern, coma, respiratory failure, and death. Physical examination might reveal a cherry-pink color of the skin, nails, and mucosa. Bright red retinal veins, flame-shaped retinal hemorrhages, or papilledema, and in severe intoxication, can lead to hypotension, bradycardia, bradypnea, and noncardiogenic pulmonary edema [26,32,33].

Long-term exposure to CO may lead to increasing the risk of myocardial infarction. Due to decreasing oxygen delivery, cardiac contractility and oxygen extraction increase as compensatory mechanisms until exhausted and lead to myocardial ischemia. Inhibition of adequate aerobic metabolism also alters calcium gradients, as its increase in intracellular calcium concentration results in a hyperadrenergic stage and interferes with intracellular sodium levels. Both electrolyte imbalances increase arrhythmia risk [2]. The most common ECG change in CO poisoning is prolongation of QT. Long-term neurologic sequalae are also found, as CO-poisoned patients show white matter hyperintensities (WMH), especially around the periventricular area, and hippocampal atrophy. CO toxicity impairs brain oxygen delivery and directly damages neuronal mitochondria, resulting in ischemic and anoxic brain injury. This occurs through the release of glutamate, which activates N-methyl-D-aspartate (NMDA) receptors, ultimately exacerbating neurologic damage [32].

For decades, doctors have been looking for cherry-red skin colorings of patients with suspected CO poisoning, as COHb appears brighter than oxyhemoglobin, however, it could be misinterpreted with the patient's skin color [33]. To measure COHb level, a conventional pulse oximeter with two wavelengths of light cannot be used since it cannot distinguish the different wavelengths of oxyhemoglobin and carboxyhemoglobin, causing significant misses of COHb levels and profound hypoxemia. Nowadays, pulse CO oximetry is available and can measure not only COHb but also methemoglobin by using readings at eight different wavelengths of light [2,26]. Another bedside method to help diagnose COHb quicker is to mix 1 milliliter (ml) of the patient's blood with 10 mL of distilled water and 1 ml of 5% sodium hydroxide (NaOH). After mixing, if the color remains pink, it can be interpreted that COHb is more than 20%, in contrast, if the mixing solution yields a straw yellow color, it indicates COHb is less than 20% [2].

Current therapy for CO poisoning, like for another toxic gas exposure, is to remove victims from the scene. Gold standard therapy is to provide 100% normobaric oxygen (NBO) or hyperbaric oxygen (HBO) (2.5-3 atmospheres (atm)) to prevent long-term neurocognitive sequelae. The normal half-life for CO elimination is 3–4 hours while breathing room air. CO levels reduce faster within 60 minutes if breathing 100% NBO, and with 100% HBO at 2.5–2.8 atm, it takes only 15–23 minutes to decay [26,33,34]. HBO should be considered for all cases of serious acute CO poisoning, including loss of consciousness, myocardial ischemia, neurological deficits, significant metabolic acidosis, or COHb greater than 25% [26]. In house fires, CO poisoning is commonly found with cyanide poisoning thus, specific treatment for cyanide poisoning might also be needed for empirical treatment.

Apart from external sources of CO production, endogenous production of CO is increased, especially in sepsis and hemolytic anemia. When hemoglobin breaks down, it produces biliverdin, which later converts to bilirubin, free iron, which is later stored as ferritin, and lastly, carbon monoxide. There is a retrospective study suggesting that carboxyhemoglobin is a reliable diagnostic biomarker of hemolysis and was better using carboxyhemoglobin compared with LDH and unconjugated bilirubin [28].

Methemoglobinemia

Methemoglobinemia is a condition when iron in the hemoglobin (Hb) within red blood cells is oxidized from the ferrous (2^+) form to the ferric (3^+) form. The human hemoglobin molecule consists of four globin chains, and each chain attaches to a heme group containing iron in ferric (Fe^{2+}) form. When sharing an electron with oxygen, it becomes oxyhemoglobin, which delivers oxygen to tissues. When Hb molecules loses its electron and become oxidized to ferric form (Fe^{3+}) or methemoglobin (MetHb) results in the increase of oxygen affinity of hemes and leftward shift of the oxyhemoglobin dissociation curve led to functional anemia and inadequate oxygen delivery. Normally, MetHb levels are maintained at less than 1% with two important mechanisms. The first mechanism is the hexose monophosphate shunt pathway, which utilizes glutathione for the reduction of MetHb, and the second pathway is through enzymes that utilize NADH and NADPH, for example, cytochrome B5 reductase (CYB5R, also known as NADH-dependent MetHb reductase or diaphorase I) and flavin-reductases (biliverdin reductase B [BLVRB], nicotinamide adenine dinucleotide phosphate (NADPH) MetHb reductase, and NADPH MetHb diaphorase) convert the MetHb back to Hb. The diaphorase I pathway is responsible for the reduction of 95–99% of normally produced methemoglobin. With these enzyme deficiencies or dysfunctions, red blood cells cannot reduce MetHb back to normal-functioning hemoglobin [2,35,36].

Increased levels of MetHb can result from congenital or acquired processes. However, the acquired form is the most common and mainly due to exposure to specific medication or agents that account for transforming to MetHb [37]. Occupational and household exposure of product containing nitrate, nitrite and drug exposure is the main source. Common medications that produce methemoglobin are vasodilator drugs such as nitroglycerine, isosorbide dinitrate, amyl nitrite, sodium nitroprusside, and inhaled nitric oxide, which is commonly used for the treatment of pulmonary hypertension. Other possible drug causing MetHb are antimicrobial such as cotrimoxazole, dapsone, nitrofurantoin and sulfonamides, antimalarial drugs such as quinine, chloroquine and primaquine, rifampicin, anticonvulsant such as phenytoin, phenobarbitone and sodium valproate, and local anesthetics such as lidocaine and bupivacaine [2]. Patients within intensive care receiving

this medication might need further investigation if hypoxia occurs, as MetHb accounts for one of the causes for hypoxia.

Blood containing MetHb appears chocolate or dark brown. Two bedside methods can be used to distinguish MetHb from deoxyhemoglobin. First, 100% oxygen can be bubbled through a tube to draw blood. In methemoglobinemia, the blood remains dark despite the oxygen exposure. Another method is to place one to two drops of blood on a white paper and blow oxygen over it. Deoxygenated Hb changes to bright red, while MetHb remains brown [2]. The presence of an oxygen saturation gap may raise suspicion of Met-Hb. Pulse oximetry shows low oxygen saturation ($SpO_{2)}$, which is falsely low due to the dark coloration of chocolate blood. Meanwhile, partial pressure of oxygen in arterial blood gas (PaO_2) is high reflecting high plasma oxygen content but not the oxygen binding capacity. CO oximetry with a wider range of wavelength detection is also used to detect MetHb [38].

Clinical signs and symptoms of methemoglobinemia are associated with blood level. MetHb less than 3% is usually asymptomatic. A level of 3-10% may present as blue or slate gray skin change. Chocolate-brown blood can be observed if the level is 10-20%. A level of 20-50% shows headache, tachycardia, breathlessness, and syncope. Coma, seizures, arrhythmias, lactic acidosis, CNS depression, and dysrhythmias are associated with the level of 50-70%. A level of more than 70% results in death due to profound hypoxia [37,38].

The mainstay treatment of methemoglobinemia is methylene blue solution accompanied by supplemental oxygen. For methemoglobinemia caused primarily by drug exposure, after removal of the culprit drug, methylene blue infusion is used typically when methemoglobin levels are 30% for asymptomatic and 20% for symptomatic patients. If the patient has underlying anemia or cardiac or pulmonary diseases, lower thresholds of methemoglobin levels should be considered [38-40]. The active ingredient, methylene blue trihydrate (3,7-bis(dimethylamino) phenazathionium chloride trihydrate), functions as a prodrug and is converted into leucomethylene blue by flavin reductase in erythrocytes, enabling it to act as an electron donor. This conversion process requires NADPH as an electron acceptor. Leucomethylene blue reduces methemoglobin (MetHb) back to hemoglobin (Hb) while simultaneously being oxidized back to methylene blue, allowing it to be recycled for subsequent MetHb reduction. However, in G6PD deficiency patients, methylene blue seems to be ineffective due to insufficient NADPH to form leukomethylene blue since the G6PD enzyme is responsible for the production of NADPH in the pentose phosphate pathway [35,36].

Methylene blue 1 to 2 mg/kg infused intravenously over 3-5 minutes. The maximum effect appears at 30 minutes. Additional doses may be given after 1 hour if the response is inadequate. Methylene blue can be given orally, but absorption is variable, ranging from 53% to 97%. After administration, it is eliminated in bile, feces, and urine as the metabolite leukomethylene blue (blue-green color). However, the long half-life of culprit medications, such as dapsone, and the short half-life of methylene blue usually lead to rebound increases in Met-Hb levels up to 12 hours after the initial administration of methylene blue, therefore, patients may require repeat dosing every 6–8 h for up to 2–3 days or may be given a continuous IV infusion of 0.10–0.25 mg/kg/hr [2,37,39]. Furthermore, high doses (7 mg/kg) can lead to hemolysis and a paradoxical rise in Met-Hb levels of up to 10%. For those G6PD patients, exchange transfusion and hyperbaric oxygen therapy might be used to improve hypoxemia [2]. Another treatment included ascorbic acid and N-acetylcysteine. Ascorbic acid can directly reduce Met-Hb, however, the reaction rate is very slow and requires multiple doses. Ascorbic acid is a treatment of choice when methylene blue is not available. Meanwhile, N-acetylcysteine is believed to act as a cofactor of reducing intracellular glutathione, thereby reducing Met-Hb. Nevertheless, the 2023 American Heart Association Focused Update on the Management of Patients with Cardiac Arrest or Life-Threatening Toxicity Due to Poisoning did not recommend both ascorbic acid and N-acetylcysteine treatment due to non-effectiveness during resuscitation [40].

Hydrogen cyanide (HCN)

Cyanide gas poisoning may result from various exposures. Most HCN was used as an intermediate chemical agent in producing nylons, plastics, and fumigants. Apart from chemical agents, Exposures to HCN may result from combustion of synthetic polymers, wool and silk after household fires [41]. Prolonged use of certain drugs like sodium nitroprusside, used to treat hypertension, can also break down into nonionized HCN [42].

Once absorbed into systemic circulation, cyanide inhibits cellular aerobic respiration by shutting down ATP synthesis with reversible binding to ferric iron in cytochrome oxidase three within mitochondria, leading to malfunction of the electron transport chain. Metabolic acidosis occurs not only from lactate production by anaerobic respiration but also from the accumulation of hydrogen ions after oxidative phosphorylation is ceased. Cyanide toxicity most affects the ATP-dependent organs like the heart and brain.

Symptoms of cyanide toxicity depend on the route of exposure, dosage, and duration of exposure [43]. Gaseous exposure yields the most rapid symptoms, followed by ingested soluble cyanide salt, insoluble salt, and cyanogen. Exposure to low-dose cyanide can cause anxiety and vertigo with a bitter almond odor, while exposure to higher concentrations may result in loss of consciousness within 30 seconds. After 30-45 seconds, patients exhibit convulsions. After 3-5 minutes, respiratory arrest occurs, and hypotension with cardiac arrest occurs after 5-8 minutes of exposure. Chronic exposure to sublethal doses of cyanide might present with tobacco amblyopia, a progressive loss of visual function in those who smoke cigarettes, and konzo, a sudden and symmetrical spastic paralysis of legs found in those who ingest insufficiently processed cassava. Orally administered HCN to adults has a lethal dose estimated to be 50–100 mg, and for KCN, about 150–250 mg [2]. Pulse oximetry shows normal saturation (SpO_2). Arterial blood gas analysis shows normal PaO_2 and high lactate with wide

anion gap metabolic acidosis due to lactate production. A plasma lactate concentration of more than 8 mmol/L was found to be 94% sensitive and 70% specific in predicting a blood cyanide concentration of more than 1.0 mg/L [44]. Venous blood gas reveals high venous oxygen saturation, or the term "arterialization," due to inhibition of cellular oxygen uptake. Quantitative cyanide level in whole blood may be used for confirmation. Blood cyanide levels of more than 3 mg/L are often related to sudden death. Another more specific test is to measure thiocyanate in urine.

Removal from the environment and decontamination of victims are important steps in the treatment of cyanide poisoning, along with administering supplemental oxygen therapy and airway protection. The antidote for cyanide should be provided as soon as possible. Current FDA-approved treatment for cyanide poisoning was classified into 3 groups:

1. MetHb generators and nitric oxide donors (sodium nitrite, amyl nitrite, and dimethyl aminophenol)
2. Sulfur donors (sodium thiosulfate and glutathione),
3. Direct binding agents (hydroxocobalamin and dicobalt edetate) [43]

    a. Hydroxocobalamin (vitamin B12) scavenges cyanide to form nontoxic cyanocobalamin. Using hydroxocobalamin is the preferred option due to its rapid onset and simple use. Hydroxocobalamine 5 grams infused via intravenous for 15 minutes is used and may be repeated at half dose if needed. Common side effects are transient hypertension, skin discoloration, and rash [40].

    b. Cobalt compound, by giving Dicobalt edetate 300 mg (in 20% dextrose 20ml) intravenously, and can be repeated for two doses if necessary. However, cardiovascular toxicity and angioedema should be a concern.

Amyl nitrite and sodium nitrite act as methemoglobin generators, helping unload cyanide from cellular cytochrome oxidase, restoring mitochondrial aerobic energy production, and generating cyanomethemoglobin. After the formation, sodium thiosulfate, acting as a sulfur donor, helps transfer cyanide from a stable form to thiocyanate, which is an excretable molecule via renal [40,45,46].

Normally, amyl nitrite is given with 0.3 ml (1 ampule) inhaled for 15 seconds and may be repeated every 3-5 minutes until an intravenous route is established. Once the intravenous route is available, sodium nitrite is given with a dose of 300 mg (10 ml of 3% solution) or 10 mg/kg intravenous drip in 3-5 minutes (2.5-5 ml/min). Dimethyl aminophenol (4-DMAP) at a dosage of 3-5 mg/kg intravenously can also be given. Methemoglobin generator may cause hypotension and methemoglobin formation, which may worsen oxygen-carrying capacity, especially in patients with concomitant carbon monoxide poisoning from smoke inhalation. Sodium thiosulfate is given as 12.5 g (ampule) in 50 ml of intravenous saline for 30 minutes [2].

In life-threatening cyanide intoxication, 2023 American Heart Association Focused Update on the Management of Patients with Cardiac Arrest or Life-Threatening Toxicity Due to poisoning, we recommend treatment with hydroxocobalamin or sodium nitrite if the first one is not available. Sodium thiosulfate is suggested for additional treatment after the first two drugs are given. Administration of 100% oxygen during resuscitation [40]. Asymptomatic patients without metabolic acidosis can be discharged after 6 hours of observation [47].

In a situation of enclosed-space fire, HCN poisoning can be found together with CO poisoning. Diagnosis and treatment must therefore consider both conditions together, especially in patients presenting with neurological changes, hypotension, or metabolic acidosis accompanied by elevated lactate levels. A lactate level ≥10 mmol/L is associated with cyanide levels ≥1 mg/L, and carboxyhemoglobin levels >10% are often found alongside elevated cyanide concentrations [48]. However, before sodium nitrite administration in smoke inhalation victims, additional data are needed regarding its effects on oxygen delivery and the formation of cyanomethemoglobin, as it carries the risk of hypotension and elevated methemoglobin levels, which can be particularly dangerous when combined with carbon monoxide poisoning [49].

Hydrogen sulfide (H_2S)

Hydrogen sulfide is a colorless chalcogen-hydride gas that is poisonous, corrosive, and flammable with a foul rotten egg odor. It's heavier than air, so most of the gases accumulate and concentrate near the floors. Normally trace amounts can be found in the ambient atmosphere. The toxic gas can be found in sewage, swamps, and manure gas after the decomposition of organic substances containing sulfur. Another exogenous source of H_2S can be found at hot springs, geysers, and volcanoes.

Most commonly H_2S enters through inhalation, due to high lipid solubility, it's spread quickly to tissue. Acute exposures, defined as exposure to high doses of chemicals once or multiple times for less than 24 hours, result in both immediate and delayed effects. Doses of 3-5 ppm often yield a "rotten egg smell," and 10-20 ppm causing eye irritation, and exposure to doses of 50-100 ppm can cause conjunctivitis. At a concentration of 100-150 ppm, there is olfactory fatigue, and patients may no longer smell the unpleasant odor. Higher concentrations around 150-250 ppm cause nausea, headaches, and vomiting. Respiratory irritation with acute lung injury and pulmonary edema occurs at concentrations of 250-500 ppm. At a dosage of 500-1000 ppm, patients experience CNS stimulation effects like seizures, hyperpnea, apnea, and coma. Doses higher than 1000 ppm usually result in intermediate knockdown and death [50]. The acute toxidrome of H_2S poisoning is characterized by "knockdown" (sudden collapse), acute lung injury, pulmonary edema, conjunctivitis, and olfactory paralysis. The higher the concentration exposed, the more symptoms exhibit [51].

Central nervous system–related symptoms of acute H_2S poisoning include interference with olfactory sensations, persistent headache, fainting, ataxia, anxiety, insomnia, knockdown, seizures, coma, and respiratory arrest. The knockdown may easily be fatal if prolonged exposure is at a high concentration, but if exposure is transient, it may also reverse. However, H_2S toxicity

on neurons is suspected from hypoxia, hypotension, and ischemia; by inhibition of cellular metabolism, it enhances cell apoptosis via increasing oxidative stress and protein modification [50]. Chronic sublethal exposure to hydrogen sulfide can lead to neurotoxicity and chronic brain injury. Anoxic brain damage may damage basal ganglia, resulting in movement disorder [51]. Peripheral neuropathy, not often found but has been reported, is present as paresthesia and mononeuritis.

The main mechanism of injury is that hydrogen sulfide inhibits the cytochrome C oxidase IV enzyme in mitochondria resulting in less ATP production from aerobic cellular respiration, therefor, cellular hypoxia and lactate accumulation occur as a result of anaerobic respiration [52]. After inhalation of the gas, hydrogen sulfide penetrates deeply to alveoli due to low solubility, leading to acute pulmonary edema.

Rapid removal from the exposure and decontamination is the mainstay for treatment. Rescuers must protect themselves and utilize personal protective equipment lest they become second victims. Clothing should be removed and double-bagged to prevent it from emitting further gases. An oxygen supplement is needed. All patients who have experienced a fall, especially those who experience knockdown symptoms, should be evaluated for signs of trauma. Supportive care with prevention of life-threatening conditions is important; for example, intubation for airway protection or bronchodilators for relief of bronchospasm and ventilation support for acute lung injury and pulmonary edema. Nowadays, there is no FDA-approved antidote for H_2S. One possible antidotal therapy is the induction of methemoglobinemia by nitrates, which allows the formation of ferric iron to bind with H_2S, leaving cytochrome C oxidase back to normal function. Sodium nitrite can be given to enhance the mentioned process; however, hypotension, a side effect of sodium nitrite, should be noted. Unlike cyanide poisoning, thiosulfate is not useful. Hydroxocobalamin is a possible antidote since it has a high affinity for sulfides. Hyperbaric oxygen therapy may be useful, but current evidence does not demonstrate a clear benefit of

SUMMARIZE TABLE FOR CHEMICAL ASPHYXIANTS

	Methemoglobinemia	Carbon Monoxide	Cyanide	Hydrogen Sulfide
Mechanism	Oxidized iron (Fe^{3+}) case left shift in Hb-oxygen dissociation curve led to functional anemia and inadequate oxygen delivery.	Left shift of the Hb-oxygen dissociation curve	Reversibly binding to ferric iron in cytochrome oxidase inhibit cellular aerobic respiration	Inhibits cellular aerobic respiration by binging to cytochrome C oxidase IV enzyme
Cyanosis	Present (Blue lips, Chocolate colored blood)	No (Cherry red lips)	No	No
Common culprits' source	Nitroglycerine, ISDN, amyl nitrite, sodium nitroprusside, inhale nitric oxide dapsone, primaquine, rifampicin, lidocaine	Incomplete combustion Endogenous production from hemolytic anemia	Sodium nitroprusside Household fires	H_2S gas
Pulse oximetry	Low SpO_2 Falsely low due to hemoglobinopathy	High SpO_2 Falsely high due to pulse oximetry cannot differentiate Carboayhemoglobin from oxyhemoglobin	Normal SpO_2	Normal SpO_2
PaO_2	High/Normal PaO_2 (normal plasma O_2 content)	Low PaO_2	Normal PaO_2	Normal PaO_2
A-a gradient	Low	High	Normal	Normal
Saturation gap	Present	Present	Absent	Absent
Lactic acidosis	Present	Present	Present	Present
Venous hyperoxia (high $ScvO_2$)	+	+	+++	+++
Definite diagnosis	Methemoglobin level	Carboxyhemoglobin level	Cyanide level	Sulfide ion levels
Treatment	Removal of the exposure Oxygen supplement Methylene blue Ascorbic acid N-acetylcysteine	Removal of the exposure HBO or 100%FiO_2	Removal of the exposure Oxygen supplement Sodium nitrite Sodium thiosulfate Hydroxocobalamin	Removal of the exposure Oxygen supplement Sodium nitrite

this treatment [53]. Asymptomatic patients without metabolic acidosis, pulmonary edema, or signs of respiratory or eye irritation may be discharged after 4 to 6 hours of observation with advice to observe for respiratory symptoms and dermal and mucosal irritation for 24 hours [54].

CONCLUSION

An asphyxiant gas is a gas or vapor that can cause different levels of respiratory distress when inhaled. Physicians should raise awareness on rapid detection, especially in patients admitted to the intensive care unit receiving various medications. Rapid detection and diagnosis prompt adequate management for the best outcome.

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