

Acute Inhalation Injury

Akut İnhalyasyon Hasarı

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Abstract

Inhaled substances may cause injury in pulmonary epithelium at various levels of respiratory tract, leading from simple symptoms to severe disease. Acute inhalation injury (AI) is not uncommon condition. There are certain high risk groups but AI may occur at various places including home or workplace. Environmental exposure is also possible. In addition to individual susceptibility, the characteristics of inhaled substances such as water solubility, size of substances and chemical properties may affect disease severity as well as its location. Although AI cases may recover in a few days but AI may cause long-term complications, even death.

We aimed to discuss the effects of short-term exposures (minutes to hours) to toxic substances on the lungs.

Key Words: Acute inhalation injury, Diagnosis, Epidemiology, Lung, Prognosis, Treatment

Özet

Solunan maddeler, solunum yollarında farklı seviyelerde pulmoner epitelde hasara yol açabilir. Bu hasar basit semptomlardan ağır hastalık tablosuna kadar farklı şekilde klinik tablo oluşumuna yol açabilir. Akut inhalasyon hasarı (AIH), çok nadir görülen bir durum değildir. Bazı özel risk grupları olmasına rağmen ev, işyeri gibi farklı yerlerde ortaya çıkabilir. Çevresel maruziyet de söz konusudur. Bireysel duyarlılık yanı sıra, solunan maddenin özelliği, örneğin suda çözünürlüğü, çapı veya kimyasal özelliği hastalığın şiddetini ve lokalizasyonunu etkileyebilir. AIH birkaç gün içerisinde düzelmesine rağmen uzun dönemde komplikasyonlar hatta ölüme yol açabilir.

Akciğerlerin toksik maddelere kısa süreli maruziyetinin (dakika-saat) etkilerini tartışmayı amaçladık.

Anahtar Kelimeler: Akciğer, Akut inhalasyon hasarı, Epidemiyoloji, Tanı, Tedavi, Prognoz

Introduction

Toxic exposures are most likely to occur via inhalation, direct contact with the skin or eyes, and/or ingestion, for which inhalation with associated fatalities is the most commonly reported. Gases and vapors are the most frequently inhaled substances; nevertheless, liquids and solids can also be inhaled in the form of finely divided mists, aerosols, or dusts.

Inhaled substances may directly injure the pulmonary epithelium at various levels of the respiratory tract, leading to a wide range of disorders from tracheitis and bronchiolitis to pulmonary edema. They may also be absorbed, resulting in systemic toxicity. Strikingly, under many exposure situations, both routes may be common. Thus, determining the mechanism of respiratory insufficiency, whether it is a result of direct injury of respiratory tract or systemic toxicity, is difficult. Accordingly, it is best to classify inhaled agents as airway irritants and systemic toxins.

By direct exposure to the epithelial surface, the airway irritants often lead to symptoms related to upper airways, such as rhinitis, eye irritation, and conjunctivitis and respiratory symptoms such as tracheitis, bronchitis, bronchiolitis, and alveolitis. Systemic toxins comprise asphyxiants, the substances that interfere with oxygen delivery or utilization as well as other toxins with primary effects on distant organ systems. The respiratory tract also may also be injured when the unconscious or convulsing patient vomits and aspirates gastric contents into the lungs because of depressed airway protective reflexes, which may then cause further pulmonary insult. To exemplify, pulmonary aspiration of an ingested hydrocarbon can cause a particularly severe pneumonitis due to the irritating action of these

chemicals on lung tissue with a tendency to spread over a wide surface area. In addition, acute inhalation injury may also be associated with burns because many agents or conditions causing burns also affect the airways as can occur in smoke inhalation without burn [1-5].

In the acute pulmonary responses, the lungs are primarily affected by toxicity. Thus, this chapter discusses the effects of short-term exposures (minutes to hours) to toxic substances on the lungs.

Epidemiology

Inhalation of a number of gases, mists, aerosols, fumes or dusts may cause irritant lung injury, asphyxiation, or other systemic effects. The use of industrial chemicals with potential toxicity has been on the rise. Accidental spills, explosions, and fires can result in complex exposures to such substances, the health consequences of which are not well-known. Therefore, the potential degree of the health effects produced by inhaled agents is not easy to estimate. According to the National Occupational Exposure Survey (NOES 1981-1983), more than one million workers in US are estimated to be under the risk of exposure to respiratory irritants annually; however, data from poison control centers suggest that inhalation injuries occur more frequently in the home environment than in the workplace [6]. The number of people affected varies depending on the environment and may be as high as tens of millions in case of air pollution reaching hazardous levels, for example, due to ozone depletion.

Unfortunately, no definitive data on the rate of inhalation injury have been acquired for Turkey to date. According to the data presented by the Social Security System, occupational accidents occurred most commonly among metal industry and mining workers

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in 2003 (n:83,830) reaching a rate of 1.24 per 100 workers in 2004 [7]. However, the rate for inhalation exposure is unclear.

Handling chemicals, working in inadequately ventilated areas, or entering areas of exposure with improper or no protective equipment are generally the reasons for occupational injuries [8, 9]. In general environment, random exposures may occur such as mixing household chemicals by mistake, for example bleach and hydrochloric acid mixture, or a gas leak at home, for example carbon monoxide, or smoke containing irritant chemicals, for example pyrolysis products made of synthetic materials when used during a house-fired. The list of substances that can cause lung damage continues to expand in both occupational and environmental setting. An increasing number of chemicals that have been used in the flavoring industries are now being recognized as potential causes of lung disease (e.g., popcorn worker's lung) with an increase in litigation directed to these industries. Chemicals are used in manufacturing of polyurethane foam, molding, insulation, synthetic rubber, and packaging materials and can induce lung cell injury when inhaled. Chemical toxins and chemical warfare agents, such as tabun, sarin, soman, cyclosarin, VX nerve gas, sulfur mustard, chlorine, phosgene, and diphosgene, can cause life-threatening lung disease [1, 5, 10, 11].

Pathogenesis

Inhaled substances may affect respiratory system at various levels according to various factors, such as the characteristics of substances, environment and host factors, and sometimes can be absorbed into systemic circulation, causing toxicity to various organ systems.

Highly water-soluble gases and vapors and larger mist or dust particles (greater than 10 microns in diameter) generally are deposited in the upper airways (Figure 1). Less soluble gases and vapors and smaller particles can be inhaled more deeply into the respiratory tract. However, many factors such as concentration of inhaled toxin, duration of exposure, whether exposure occurred in an enclosed space, determine the degree of injury after acute inhalation exposure as well as particle size and water solubility. The degree of injury also affected by multiple host factors; elderly or younger patients, allergic or nonallergic bronchospastic response, exertional state or metabolic rate of the victim, history of smoking and those with underlying lung debilitating illness, particularly

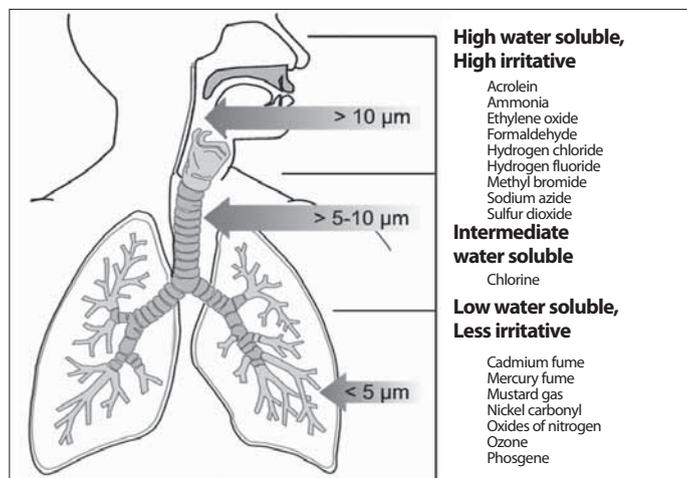


Figure 1. Distribution of the irritant gases and the site of injury in the respiratory tract according to their particle size and water solubility

underlying reactive airway disease or lung disease that impairs host defense mechanisms, typically fare worse [1-4, 12].

Important environmental factors include intensity and duration of exposure as well as the quality of ventilation in the space in which exposure occurs. In general, greater exposure dose (simply defined as the product of the concentration of exposure and duration of exposure) is associated with greater potential harm. Even if the duration of exposure to an unscheduled chemical release may be brief, the chemical concentration may be high. Despite their high toxicity, some chemicals may not pose a risk of illness with brief exposure or low concentration. On the other hand, exposures to high concentration of even mildly toxic substances can prove dangerous [1-4, 12].

When an individual is exposed to agents with particle diameters greater than 10 μm or that are highly water-soluble, the substance is deposited in the upper airways. This is followed by rapidly developing signs of upper airway irritation that are accompanied by eye and mucous membrane irritation. In severe exposures, progressive coughing, wheezing, or stridor may result in upper airway obstruction. Inhaled toxins of smaller particle size or lower solubility such as phosgene, ozone, fluorine, or oxides of nitrogen reach the lower respiratory tract, resulting in delayed onset of the symptoms. Following mild exposure, gases with intermediate solubility (e.g. chlorine) may lead to early irritating symptoms, and after massive exposure, they may even cause delayed pulmonary edema. In massive exposure, upper airway obstruction related death may rapidly follow due to massive alveolar destruction or asphyxiation [1-4, 12].

High Risk Groups and Specific Exposures

Inhalation exposure and injury are related to the major environmental risk factors and not to host. Chemical irritants, asphyxiants, toxic metals, products of fires and combustion, and many other substances have been reported to cause acute inhalation injury. Some cases of acute inhalation injury may involve more than one substance or mechanism.

1. Common Chemical Irritants

Chemical irritants in occupational and environmental areas are usually the cause of acute inhalation toxicity. The characteristics, effects, and sources of the most commonly encountered chemical irritants have been summarized in Table 1.

a. Chlorine (Cl_2)

Chlorine gas is one of the most common agents for single-irritant inhalation exposures in occupational and environmental areas. Also produced when sodium hypochlorite comes in contact with an acid, chlorine gas alone can severely damage airway mucosa. Its intermediate water solubility that liberates hydrogen chloride (HCl) and oxygen free radicals (hypochlorous, HOCl) when it has contact with water comprises the mechanism that causes acute damage in the upper and lower respiratory tract. Hydrochloric acid, which is highly soluble in water, predominantly targets the epithelia of the ocular conjunctivae and upper respiratory mucus membranes. Similarly, hypochlorous acid is highly water soluble and has an injury pattern similar to hydrochloric acid, which may account for the toxicity of elemental chlorine and hydrochloric acid to the human body [13-15].

Acute inflammation of the conjunctivae, nose, pharynx, larynx, trachea, and bronchi are some of the immediate effects of chlorine gas toxicity. Local edema secondary to active arterial and capillary hyperemia develops due to irritation of the airway mucosa. Then, with the plasma secretion, the alveoli are filled with edema fluid,

Table 1. Some chemical irritants causing acute inhalation injury: their effects and sources of exposure

Agent	Characteristics	Effects	Source of Exposure
Ammonia	Highly water soluble; colorless; sharp, pungent odor	Highly irritating to eyes and upper airways; upper airway obstruction, such as laryngeal edema, bronchospasm and noncardiogenic pulmonary edema may occur	Agriculture (mostly fertilizers); plastics, pesticides, explosives and detergents manufacture; refrigerants, home cleaning products
Hydrogen chloride	Highly water soluble; colorless to slightly yellow; pungent odor	Laryngeal edema, tracheobronchitis	Dyes, fertilizers, textiles, rubber manufacture; metal ore refining; meat wrappers
Hydrogen sulfide	Slightly water soluble; colorless; rotten egg odor (sewer or swamp gas)	Airway irritant and chemical asphyxiant	Decaying organic matter, in sewer and barns; petroleum refining, viscose rayon, rubber and mining industries; hot-asphalt paving
Hydrogen fluoride	Highly water soluble; colorless; pungent odor; corrosive	Chemical pneumonitis; can cause clinically important hypocalcemia	Phosphate fertilizer, metal refining and etching, glass and ceramic etching, microelectronic, masonry, pharmaceuticals, chemical manufacture; rust removal agents
Sulfur dioxide	Highly water soluble; colorless; pungent odor	Bronchoconstriction, airway edema, asthma, bacterial pneumonitis, bronchiolitis obliterans	Airway pollution, burning of oil and coal, smelting, power plants, wineries, paper manufacture, chemical manufacture, food preparation
Chlorine	Intermediate water solubility; greenish yellow noncombustible gas	Tracheobronchitis, acute respiratory distress syndrome	Household cleaners (household accidents involving the inappropriate mixing of hypochlorite cleaning solutions with acidic agents), paper production, sewage treatment, swimming pool maintenance, chemical manufacture, disinfection, chemical warfare
Oxides of nitrogen	Low water solubility; nearly colorless; a sharp sweet smelling (nitric oxide), strong harsh odor (nitrogen dioxide)	Bronchoconstriction, airway edema, asthma, bronchiolitis obliterans	Agriculture (Silo filler's disease); manufacture of dyes, lacquers and fertilizer; firefighters; welding, air pollution, hockey rinks
Phosgene	Low water solubility; colorless; musty odor at room temperature	Mild upper airway irritation, noncardiogenic pulmonary edema	Firefighters, welding, paint strippers, chemical warfare; Phosgene is used in the manufacture of dyes, insecticides, plastics and pharmaceuticals; household substances such as solvents, paint removers and dry cleaning fluid can produce phosgene when exposed to heat or fire

resulting in pulmonary congestion and dose-dependent epithelial cell injury. The upper airways and eyes irritated at low levels of exposure. As the levels of exposure increase, the nasopharynx and larynx are injured. Pulmonary edema develops within 6 to 24 hours of higher exposures [15, 16].

Pulmonary injury presents nonspecific pathological findings, such as severe pulmonary edema, pneumonia, hyaline membrane formation, multiple pulmonary thromboses, and ulcerative tracheobronchitis. The most important sign of pulmonary injury associated with chlorine toxicity is pulmonary edema, manifested as hypoxia. Noncardiogenic pulmonary edema may occur in a loss of pulmonary capillary integrity and subsequent transudation of fluid into the alveolus. The onset may be within minutes or hours, after the exposure, depending on the severity of exposure. Persistent hypoxemia is associated with a higher mortality rate due to airflow obstruction and air trapping, typical findings of pulmonary function tests. Reversibility and nonspecific provocation tests may be positive [15-18].

Beta-agonists, which should be considered a first-line agent in the setting of chlorine gas exposure and respiratory symptoms or signs, have been widely used for supportive clinical management of respiratory symptoms in chlorine gas exposure. Despite negative physical examination and laboratory tests, symptomatic individuals must be observed for at least 6 hours since there is always the potential for a delay in the onset of significant airway toxicity. Corticosteroids may improve persistent symptoms [19]. In one of our recent studies, nebulized sodium bicarbonate presented some advantages in the earlier period with respect to pulmonary function test and quality of life in the cases who had reactive airway dysfunction syndrome (RADS) caused by chlorine exposure [20].

b. Hydrogen chloride (HCl)

Hydrogen chloride, a colorless to slightly yellow gas with a pungent odor, is used for cleaning, pickling, and electroplating metals; in refining mineral ores; in petroleum well extraction; in leather tan-

ning; and in the refining of fats, soaps, and edible oils as well as in producing polymers and plastics, rubber, fertilizers, dyes, dyestuffs, and pigments. It can be formed during combustion of many plastics. Inhalation is an important route of exposure to HCl, which is highly water soluble and highly irritating to the mucous membranes of the nose, throat, and respiratory tract because of its acidity. Mucous membrane irritation can occur in acute exposure of as low as 5 to 10 parts per million (ppm), while brief exposure to 35 ppm causes throat irritation, and levels of 50 to 100 ppm are barely tolerable for 1 hour. Massive exposures may cause an accumulation of fluid in the lungs. Another outcome of exposure to HCl can be RADS [1-4].

c. Ammonia (NH₃)

Ammonia, a colorless, water-soluble, highly irritating gas with a sharp, suffocating odor, is easily compressed. It forms a clear, colorless liquid under pressure. Since it is highly dissolvable in water to form caustic solutions, nearly 80% is used in fertilizers. In liquid form, it may be involved in many accidents while being transferred from tanks to farm equipment, producing rapid onset of eye, nose and throat irritation; coughing; and bronchospasm even at fairly low concentrations. Its low odor threshold, however, creates an early warning of its presence. Still, olfactory fatigue or adaptation may occur and render its presence less detectable [4, 8, 21-23].

Ammonia reacts with water in mucosa; thus forming a strong alkali, ammonium hydroxide (NH₄OH), also a common commercial form of ammonia. Severe clinical signs that result in upper airway obstruction include immediate laryngospasm and laryngeal edema. Laryngeal edema without other obvious clinical signs of burns may develop. However, in the presence of skin burns, inhalation injury is likely. Individuals who may be severely exposed to this chemical may develop noncardiogenic pulmonary edema within hours to a few days of exposure. Even when they survive, they often suffer residual chronic lung disease, such as persistent bronchitis, bronchiectasis, airflow obstruction, interstitial fibrosis and impaired gas exchange. Supportive treatment involves bronchodilators, oxygen therapy, and observation for need for airway protection for 6 to 12 hours as well as early intubation, which may be required to defend the airway from acute laryngeal obstruction. Cricothyroidotomy may be required in more severe cases [4, 8, 21-23].

d. Hydrogen fluoride (HF) and hydrofluoric acid

Hydrogen fluoride (HF), a colorless, highly irritating gas with a pungent odor, easily dissolves in water to form hydrofluoric acid. When compared to most other mineral acids, hydrofluoric acid is weak, but it still can produce serious health effects through any route of exposure, most of which occur by cutaneous contact with hydrofluoric acid. The fluoride ion penetrates tissues deeply; thus, it can cause both local cellular destruction and systemic toxicity. It has respiratory effects as well as skin effects. Nevertheless, in the lungs, the effects have a very rapid onset. Consequently, patients present with acute respiratory distress [1, 3, 4].

Exposure to both HF gas and fumes arising from concentrated HF liquid create inhalation hazards. Airborne concentrations of HF, even at fairly low levels, lead to rapid onset of eye, nose, and throat irritation because of its water solubility. It still may result in chemical pneumonitis, delayed onset pulmonary edema and death [1, 3, 4].

e. Sulfur dioxide (SO₂)

The source of Sulphur dioxide (SO₂) is either volcanoes or various industrial processes. Poor-quality coal and petroleum in particular contain sulfur compounds and generate sulfur dioxide when burned.

Being one of the most common causes of air pollution at peak levels, SO₂ contributes to respiratory illness, particularly in children and the elderly and aggravate preexisting heart and lung diseases, especially asthma. Injury to larynx, trachea, bronchi and alveoli occur with high exposures (above 50 ppm), response to this substance varies in a wide range, with atopic and asthmatic subjects being the most susceptible. In addition, prior exposure to ozone may intensify the effect of sulfur dioxide in asthmatic subjects. Classical signs include rapid onset of a burning of the eyes, nose, and throat (with associated cough, chest pain, chest tightness, and dyspnea), accompanied by conjunctivitis, corneal burns, and pharyngeal edema that may be followed hours later by pulmonary edema. Bronchiolitis obliterans can develop 2 to 3 weeks after exposure [1, 3, 4].

Symptomatic treatment is the treatment modality. Systemic corticosteroids may be beneficial in acute toxicity. Removal from the exposure area may reverse bronchospasm in asthmatic patients spontaneously, or administration of bronchodilators and inhaled corticosteroids may be needed [1, 3, 4].

f. Oxides of nitrogen (NO_x)

The oxides of nitrogen, i.e. nitrogen oxides, are composed of a mixture of nitrogen and oxygen type of gases. The most toxicologic nitrogen oxides are nitric oxide (NO) and nitrogen dioxide (NO₂), both of which are nonflammable and colorless to brown at room temperature. Millions of workers face fatal respiratory injury when they are exposed to NO_x or any of these gases. The damages to the lungs attributed to NO_x have been explained in as follows: [1] it is converted to nitric (HNO₃) and nitrous (HNO₂) acids in the distal airways, directly damaging certain structural and functional cells; [2] it initiates free radical generation, resulting in protein oxidation, lipid peroxidation and cell membrane damage; and [3] it reduces resistance to infection by altering macrophage and immune function [1, 3, 4, 24].

Farmers who work near silos, firefighters, coal miners after firing of explosives, welders who work with acetylene torches in confined spaces, military personnel, hockey rink workers, and chemical workers who may be exposed to byproduct fumes in the manufacture of dyes and lacquers constitute some of the occupations at risk.

The lower respiratory tract, which is the primary site of toxicity of NO_x may be irritated even at low concentrations (15 to 25 ppm), and this may initially cause mild shortness of breath and cough. After a period of hours to days, victim may suffer bronchospasm and pulmonary edema. Toxic pneumonitis and bronchiolitis can develop at exposure levels of 25 to 100 ppm, often with a smothering sensation and dyspnea. Exposures above 150 ppm are usually fatal due to bronchiolitis obliterans, chemical pneumonitis, and pulmonary edema. With their greatest degree of toxicity, nitric oxide and nitrogen dioxide lead to pulmonary edema and subsequent bronchiolitis obliterans. Warnings include delayed symptom onset and relapses that can occur 3 to 6 weeks after initial exposure, with symptoms of cough, chills, fever, and shortness of breath [1, 3, 4, 24].

Despite suggestions of high-dose corticosteroids for use in the treatment of pulmonary manifestations, data on their prophylactic use after NO_x exposure are anecdotal.

Silo Fillers' Disease: Silo fillers' disease (SFD), an occupational disease that results from pulmonary exposure to NO_x forms rapidly in farm silos that are filled with fresh organic material (e.g., corn, grains). Because SFD is a preventable occupational hazard, it can be eliminated by proper work practices. The greatest risk is in the first weeks after the silo is filled. Toxic and lethal levels of nitrogen dioxide, which is heavier than air, form on top of the silage hours after

the organic material is stored. The duration of exposure and the concentration of gas determine the clinical presentation of SFD. If farm workers enter a silo or work near the open hatches during the first 10 days after filling (without proper precautions), they may experience various degrees of exposure. Although most symptomatic exposures are mild and self-limiting, some cause sudden death from asphyxiation, pulmonary edema, or, weeks later, bronchiolitis obliterans. Nitrogen dioxide at low concentrations may cause cough, dyspnea, fatigue, and upper airway and ocular irritation. Increased concentration and duration cause symptoms such as cyanosis, vomiting, vertigo, and a loss of consciousness. In individuals with more severe exposure, acute respiratory distress syndrome (ARDS), an acute lung injury pattern, laryngeal spasm, bronchiolar spasm, reflex respiratory arrest, or asphyxia, may develop, resulting in death [25].

g. Phosgene (COCl₂)

Phosgene, a highly toxic gas and also known as carbonyl chloride, carbon oxychloride, carbonyl dichloride, chloroformyl chloride and green cross, was used in combination with chlorine gas during World War I. Since phosgene is an intermediate product in the manufacture of isocyanates, pesticides, dyes and pharmaceuticals, it is widely used in the household substances (Table 1). Although it is colorless and has an odor similar to that of green corn or newly mown hay at low concentrations, which may seem innocent, it has a sharp and suffocating odor at high concentrations [9, 26, 27].

Inhalation is the major route of phosgene toxicity. Despite providing sufficient warning of dangerous concentration, Phosgene's odor has a mild or delayed irritating quality, which may allow persons to be exposed for a prolonged interval. Phosgene is poorly water-soluble and its hydrolysis tends to be slow. Thus, it causes only mild airway and eye irritation symptoms at low concentrations, and deposits distally in the lung where it hydrolyzes to form hydrochloric acid, leading to epithelial damage and cellular necrosis in the bronchi and small bronchioles, and carbon dioxide [9, 26, 27].

Symptoms including dryness and burning of the throat and cough develop due to mild airway irritation. However, these symptoms may cease when the patient is removed from exposure, but it should be kept in mind that after an asymptomatic interval of 30 minutes to a few hours, chest pain, bronchospasm, hypoventilation, and bradycardia can develop. Profound damage such as dyspnea, hypoxemia, and/or severe transudative (noncardiogenic) pulmonary edema may develop as late as 24 hours after the exposure. Hemolysis in pulmonary circulation can cause capillary plugging that leads to cor pulmonale and death [1, 26, 27].

Supportive management of phosgene toxicity includes oxygen, corticosteroids (inhaled, systemic), leukotriene inhibitors, IV fluids, and prophylactic antibiotics. Treatment of hypotension, bradycardia, and renal failure may require the use of pressor agents [1, 26, 27].

h. Hydrogen sulfide (H₂S)

Hydrogen sulfide is produced naturally by decaying organic matter and by certain industrial processes. It is a colorless, highly flammable and explosive gas. Being a respiratory irritant and asphyxiant, also known as "sewer or swamp gas" with its "rotten egg" odor that is detectable at concentrations as low as 0.5 ppm, it may not provide adequate warning of hazardous concentrations since the victim may suffer olfactory fatigue [28-30].

The major route of hydrogen sulfide exposure is inhalation. Slightly heavier than air, the gas is rapidly absorbed by the lungs. By accumulating in enclosed, poorly ventilated, and low-lying areas, it causes poisoning during oil drilling and wastewater treatment and

as a result of natural gas field leaks. Inhalation of hydrogen sulfide primarily affects the lower respiratory tract with symptoms of cough, shortness of breath, and bronchial or lung hemorrhage. At higher concentrations, it can cause bronchitis and accumulation of fluid in the lungs, which may be immediate or delayed for up to 72 hours. Pulmonary edema can occur at concentrations of 250 ppm. Systemic and neurologic effects develop at higher concentrations, with sudden loss of consciousness and even death due to asphyxia above 700 ppm and 1000 ppm, respectively [28-30].

With prompt endotracheal intubation and mechanical ventilation for severe cases of intoxication, management is generally supportive, involving immediate inhalation of amyl nitrite, injections of sodium nitrite (3%), inhalation of pure oxygen because oxygen enhances sulfide metabolism, administration of bronchodilators to overcome eventual bronchospasm and in some cases hyperbaric oxygen therapy [28-30].

II. Asphyxiants

Unlike chemical irritants, asphyxiant has a different mechanism. However, some asphyxiants such as hydrogen sulfide may also have a chemical irritation effect. Based on their effects, asphyxiants can be divided into two groups: simple asphyxiants which act by displacing oxygen from inspired air resulting in a reduced fraction of inspired oxygen and subsequent hypoxemia, and chemical asphyxiants, such as carbon monoxide and hydrogen cyanide, which act by interfering with oxygen delivery or utilization. However, any gas in high concentration can act as an asphyxiant. Although, for example, methane, ethane, argon, and helium are more innocent at low concentrations, at high exposure levels they can displace oxygen or block the reaction of cytochrome oxidase or hemoglobin, impairing cellular respiration and oxygen transport [1, 3].

III. Burns and Smoke Inhalation

Exposure to heat, particulate matter, and toxic gases are considered the exposure to smoke. Closed-space fires and conditions that cause unconsciousness are often the reason for inhalation injuries. Between 20% and 30% of burn victims suffer from pulmonary complications, with an incidence rate correlating with the severity of the burn and a history of being in enclosed space. Tracheobronchial damage and pulmonary complications, which are common and an important cause of morbidity and mortality, may be accompanied by infection, shock, and the consequences of therapy, including overhydration. The improvements in the treatment of burn shock and sepsis has rendered inhalation injury the main cause of mortality in the burn patients [31, 32].

"Smoke inhalation" is a generic term that refers to a potential exposure to a wide variety of substances because of the complex chemistry of heat decomposition and pyrolysis. Both firefighters (both urban and wildland) and non-occupational victims can be exposed to substantial numbers of irritants. Thermal injuries typically limited to upper airways; however, those below the vocal cords occur only with steam inhalation. The entire respiratory tract can be affected by smoke inhalation from fires. Smoke contains particulate matter which is formed from incomplete combustion of an organic material, usually less than 0.5 μm in size. Thus, small particles can easily reach the terminal bronchioles and here they can initiate an inflammatory reaction, leading to bronchospasm [33, 34].

IV. Chemical Warfare and Riot Control Agents

Chemical Warfare and Riot Control Agents of the past, especially during World War I and II, were gases such as mustard gas, phosgene

and chloropicrin. Today, chemical warfare armamentarium includes systemic toxins derived from organophosphate pesticides. Besides being highly lethal neurotoxins, they also have important respiratory effects, such as bronchorrhea and bronchospasm, which occur via muscarinic receptor stimulation [1, 4].

Riot control agents (crowd control agents, tear gases) aim to incapacitate persons via immediate mucous membrane irritation. Chloroacetophenone and orthochlorobenzamalonitrile are the most common agents worldwide. They have been reported to have mucous membrane effects as well as causing lower respiratory injury. Contrary to tear gases, zinc chloride, which is the primary component of smoke bombs, is a potent lower respiratory tract irritant and may cause severe pulmonary edema [1, 4].

V. Toxic Metals and Inhalation Fever

Cadmium and mercury are the most common metals causing inhalation injury. Welding, brazing, or flame cutting metal under poor ventilation are the typical conditions for cadmium exposure typically, while heated metal reclamation processes involve potential mercury exposure risks. Metals or their compounds such as antimony, manganese, beryllium, vanadium and tributyltin rarely cause inhalation injury. Through the inhalation of fumes or vapors of the certain metals, acute pneumonitis may develop. Heavy metal pneumonitis has been accounted for by the inhibition of enzymatic and other critical cellular functions. In such cases, chelation treatment may be considered [4, 35].

Inhalation fever includes metal fume fever, polymer fume fever, and organic dust toxic syndrome, all of which share similar clinical findings and prognosis. Exposure to zinc fume and sometimes to copper and magnesium fume causes metal fume fever. Exposure to heated fluoropolymers and high amounts of endotoxin leads to polymer fume fever and organic dust toxic syndrome, respectively, which are characterized with chills, fever, malaise, and myalgia with onset 4 to 8 hours after intense inhalation of fumes or dust. Common respiratory complaints include cough or mild dyspnea. Nevertheless, findings of chest radiographic infiltrates or hypoxemia are inconsistent with this disorder. Self-limited clinical manifestations resolve within 12 to 48 hours. In the presence of clinical lung disease, the clinical syndrome should be regarded as inhalation injury and not inhalation fever [36].

VI. Complex Exposures

Individuals who suffer inhalation injuries are frequently exposed to complex mixtures of toxic compounds, not just a single agent. Though poorly characterized, such mixtures may contain admixtures of combustion products, pyrolysis products, metals, particulates, and gas. Such mixtures have been shown to have the potential to produce a range of airway and diffuse interstitial lung lesions.

Clinical Findings and Diagnosis

Symptoms and Signs

Highly soluble substances or substances with a larger particle size cause severe burning in the eyes, nose, throat, windpipe and large airways within minutes of exposure. They also often lead to upper respiratory tract symptoms including lacrimation, rhinitis, epistaxis, pharyngitis and cough as well as retching and shortness of breath [1-4].

The mucous membranes of the eyes, nose, pharynx, and skin should be the focus of physical examination. Inspection of upper airway for evidence of singed nasal hair, soot in the oropharynx,

facial or oropharyngeal burns, erythema or parching of mucous membranes, stridor, hoarseness, dysphagia, cough, carbonaceous sputum, tachypnea, retractions, accessory muscle use, wheezing, rales, diaphoresis, or cyanosis is essential [1-4].

In physical examination, conjunctivitis, pharyngitis, laryngotracheitis, and expiratory wheezing are detected. Edema may also be seen in the nose, posterior pharynx and larynx. Patients report hoarseness and difficulty in speaking with more severe laryngeal injury and sometimes exhibit stridor on physical examination. Careful auscultation of the lungs is required to detect the stridor, wheezing, and crackles. A careful ophthalmological examination with a slit-lamp for corneal burns should be performed for patients with ocular symptoms [1-4].

Headache and dizziness accompanied with chest pains and emesis suggest systemic poisons, such as cyanide or hydrogen sulfide. Unconscious victims found in confined spaces are thought to have received longer inhalation exposures than conscious ones because of the unprotected airways and concentrated exposures [1-4].

Laboratory and Imaging Studies

The basis of clinical evaluation for inhalation lung injury consists of multiple steps: obtaining a thorough exposure history, focusing on nature of the compound inhaled, estimating the probable circumstances of exposure (including the magnitude and duration of exposure), determining the water solubility of the inhaled agent, and determining whether the individual was exposed to multiple irritants and asphyxiants simultaneously as in the case of firefighters or other subjects exposed to smoke inhalation. Thus, the causative agent can be accurately determined and mixed exposures can be ruled out [1-4].

Laboratory studies include arterial blood gas analysis with carboxyhemoglobin, methemoglobin, and lactate levels; RBC cyanide levels if persistent acidosis occurs; electrocardiographic (ECG) monitoring; and chest x-ray. For severe inhalation exposure or suspected pulmonary aspiration, chest radiography and arterial blood gas analysis are strictly recommended. The presence of hypoxemia despite a normal arterial partial pressure of oxygen suggests carbon monoxide toxicity. Carboxyhemoglobin levels should be obtained for all fire and explosion victims. Metabolic acidosis may indicate cyanide or hydrogen sulfide intoxication. Pulmonary edema, atelectasis or infiltrates may be detected on chest radiographs [1-4].

As the final step, baseline pulmonary function should be determined through pulmonary function tests. Flow-volume loops are the most sensitive noninvasive indicators of upper and lower airway obstruction. On the other hand, the efficiency of diagnostic bronchoscopy for inhaled toxin exposure remains controversial.

In individuals with persistent symptoms months after exposure, bronchial provocation tests with methacholine may help assess the presence of any RADS. Computed tomography may help determine possible permanent fibrotic changes.

Differential Diagnosis

Thermal injuries and infections, especially epiglottitis if severe laryngeal symptoms are present, constitute the basis for the differential diagnosis of upper airway symptoms and compromise. Another entity, anaphylactic reactions, could also mimic inhalation exposure, except when edema is more prominent. The lower respiratory tree to inhalation injury reacts in the form of diffuse alveolar damage (DAD), the same pathology found in acute respiratory distress syndrome (ARDS).

Complications

Individuals who are accidentally exposed to toxic gases usually recover completely. However, sometimes acute life threatening or chronic severe complications may develop. Acute respiratory failure death is the most feared complications. It may be caused by both severe laryngeal injury and noncardiogenic pulmonary edema. In addition, a wide variety of chronic pulmonary complications may occur; however, they occur in less than 10% of all exposed victims.

Reactive Airway Disease Syndrome (RADS)

RADS, sudden onset of asthma like symptoms and persistence of airway reactivity, is a form of occupational asthma that may develop in individuals who are acutely exposed to high concentrations of an irritant product. Exposure victims develop respiratory symptoms in the minutes or hours that follow and persistent bronchial hyperresponsiveness after the inhalation incident. Repeated exposures may cause similar pathology [14, 37-40].

RADS, as the most common sequel of acute inhalation lung injury, has been reported in the cases exposed to a large variety of irritants. Following the acute inhalation, it creates an asthma-like illness with episodic dyspnea, cough, and wheezing that persist for months to years. Some patients may permanently suffer from clinical and physiological abnormalities. Significant bronchodilator responsiveness on spirometry and/or bronchial hyperresponsiveness are demonstrated on methacholine challenge testing. Avoidance of further irritant exposure is the key for the treatment that has the same guidelines as those for the treatment of asthma [38-40]. Although on pulmonary function test, especially on FEV₁, sodium bicarbonate (NaHCO₃) treatment has been shown to be beneficial in such patients in the earlier period, this is not based on long-term data [20, 41].

Bronchiolitis Obliterans (BO)

Bronchiolitis obliterans, also known as obliterative bronchiolitis or constrictive bronchiolitis, is a rare complication, which has been reported most frequently following exposure to oxides of nitrogen (e.g., silo gas) or sulfur dioxide. Occupational or environmental exposures to chlorine, ammonia, and phosgene have been reported as some other causes of BO [3, 42, 43].

In patients who present with symptoms of progressive dyspnea on exertion months to years after exposure, the findings of airflow obstruction are typical in pulmonary function tests, and hyperinflation is detected on chest radiographs [3, 42, 43].

Oral corticosteroids have been advocated for the treatment; however, controlled trials are needed. The patients who develop BO within weeks of exposure are more likely to benefit from steroids because they have a more proliferative type of bronchiolitis unlike scarring or constrictive bronchiolitis [3, 42, 43].

Cryptogenic Organizing Pneumonia (COP)

COP, which is also known as Bronchiolitis Obliterans with Organizing Pneumonia (BOOP), rarely occurs after inhalation injury. Exposure to oxides of nitrogen has been reported as the primary cause. The findings in victims presenting within weeks of exposure include dyspnea on exertion, multifocal pulmonary consolidation on chest radiograph, and a restrictive pattern on pulmonary function testing. Similar treatment as that in idiopathic BOOP is used [3, 42, 43].

Bronchiectasis

Bronchiectasis is a rare complication, reported primarily after high dose ammonia exposure. It has the identical clinical findings and treatment to those of bronchiectasis secondary to other causes [3].

Treatment

Utmost care should be paid to prevent exposure when handling gases and chemicals. One way is to have gas masks with their own air supply available in case of accidental spillage in workplaces or farmers should be made aware of the dangers of accidental exposure to toxic gases in silos, including its fatality.

After an exposure to certain agents, decontamination may be required. However, in many inhalation exposures without skin or eye irritation, it is not required. It should be kept in mind that victims with skin or clothing grossly contaminated with condensed vapor may contaminate health care personnel by off-gassing vapor.

Acute irritant-induced lung injury requires largely supportive treatment, which follows the basic approach to resuscitation focusing on airway protection, support of breathing, and maintenance of circulation. Removal from source, application of 100 percent oxygen, humidification for irritating symptoms, and inhaled bronchodilators for bronchospasm constitute general management of the patients with toxic inhalation injury [1-4].

In the presence of upper respiratory tract symptoms and a history of exposure to only highly soluble agents, patients should be observed for approximately 6 hours unless symptoms are severe. Severe laryngeal injury may indicate the need for early intubation. Hazardous agents that can cause delayed onset pulmonary edema (e.g., phosgene and nitrogen oxides, such as nitric oxide and nitrogen dioxide) are poorly soluble in water. Thus, they produce slow onset of airway irritation or respiratory distress contrary to soluble irritants, such as ammonia or hydrogen chloride, which act rapidly. Because delayed-onset noncardiogenic pulmonary edema may develop until 12 to 72 hours later, longer observation period has been recommended for people with significant exposure to low solubility agents [1-4].

Oxygen is the basis of treatment in inhalation injury cases. When the lungs are severely damaged, the patient may need mechanical ventilation. If intubation is necessary, ventilation should be performed using tidal volumes of 6 mL/kg, aiming to protect the lungs [1-4].

The use of digoxin, morphine, afterload reduction, or diuretics has not been beneficial to patients with noncardiogenic edema. Noncardiogenic pulmonary edema can be managed by the use of positive end-expiratory pressure or bilevel positive airway pressure (BiPAP). Some cases who are exposed to hydrogen sulfide and unresponsive to nitrites may require hyperbaric oxygen therapy. In addition, bronchodilator therapy, intravenous fluid replacement, steroids and antibiotics may be beneficial. However, the patients with burns and inhalation injury in particular should receive fluid resuscitation to avoid exacerbating pulmonary edema because almost half of intubated burn patients admitted to burn centers develop acute respiratory distress syndrome, and ventricular dysrhythmias may be provoked in some patients with exposure to certain types of hydrocarbons by bronchodilators. For patients with evidence of significant airflow obstruction, supplemental therapy with corticosteroids is recommended to reduce inflammation, but it has not been studied for patients with noncardiogenic pulmonary edema. Antibiotics should be used only in patients with clinical evidence of infection. Pulmonary aspiration that may occur in patients with depressed mental status can sometimes be prevented by inserting a cuffed endotracheal tube into the airway or by placing the patient in a head down, left side position and using suction immediately if vomiting occurs [3, 4, 44].

Prognosis

Irritant-induced inhalation lung injury usually has an excellent prognosis. More than 90% of individuals who suffer from inhalation

injury recover completely, returning to normal health, while only about 5-6% may develop any of a variety of long-term complications.

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