

## Lung Damaging Agents (Choking Agents)

### GENERAL

#### Introduction

Lung damaging agents are chemical agents, which produce a toxic inhalational injury – they attack lung tissue and primarily cause pulmonary oedema. Whether produced for military or industrial use, these chemical agents pose a very real threat to military personnel.

The term choking agents has been traditionally applied to the use of certain lung damaging agents as chemical weapons, and includes phosgene (CG), diphosgene (DP), chlorine (CL), and chloropicrin (PS). Phosgene accounted for 80% of all chemical fatalities in World War I, but at least 14 different respiratory agents were used, as well as obscurants (smokes), harassing agents (chloracetone), and vesicants (mustard) that could cause pulmonary injury.

Today, only a handful of such pulmonary toxicants still exist in stockpiles around the world. Several however, such as chlorine and phosgene, are currently produced in large quantities for industrial purposes; other toxic industrial chemicals which may cause toxic inhalational injury include ammonia, isocyanates, mineral acids etc.

Other lung damaging materials – although not likely to be used as CW agents – are still likely to be encountered on the battlefield. Perfluoroisobutylene (PFIB) is a toxic pyrolysis product of tetrafluoroethylene polymers encountered in military materiel (e.g., Teflon®, found in the interior of many military vehicles). The oxides of nitrogen (NO<sub>x</sub>) are components of blast weapons or may be toxic decomposition products. Smokes (e.g. HC) contain toxic compounds that cause the same effects as phosgene. Similar substances encountered in fires, e.g. PFIB, isocyanates, phosgene, and HCl may also produce lung damage. Chemical fire extinguishers containing carbon dioxide should not be used in confined spaces to extinguish thermite or magnesium types of incendiaries – carbon tetrachloride in contact with flame or hot metal produces a mixture of phosgene, chlorine, carbon monoxide and hydrochloric acid.

#### Physical and Chemical Properties

Choking agents are usually true gases in field environments, and stored and transported as a liquid under pressure. Other less volatile

lung damaging materials injury such as those in smoke or products of combustion may cause toxic inhalational injury following the generation of particulate aerosols.

Military dispersion of phosgene during World War I followed the explosion of liquid filled shells with subsequent rapid evaporation and formation of a white cloud due to its slight solubility in an aqueous environment. It spontaneously converted to a colourless, low-lying gas four times as dense as air. Because of its relatively low boiling point (7.5°C), phosgene was often mixed with other substances. Chlorine was released from pressurised cylinders to form a pungent greenish-yellow gas that was heavier than air.

#### Detection

Although field-detection equipment for classical choking agents is currently employed by some nations, and various commercial industrial detectors are available for the wider of lung damaging agents, there are no automatic detectors in service. The characteristic odour of some lung damaging agents may be unreliable as a sure means of detection. For example, in low concentration phosgene has a smell resembling new mown hay, but the odour may be faint or lost after accommodation. There is also considerable variation in the sense of smell between individuals.

Similarly the eye irritation, coughing, sneezing, hoarseness, and other central respiratory effects seen after exposure to high concentrations of some pulmonary toxicants are also unreliable indicators of exposure, as these may be transient or entirely absent at lower but still potentially lethal concentrations. This is particularly true in the case of phosgene.

#### Protection

The activated charcoal in the canister of the chemical protective mask adsorbs phosgene, and in-service respirators afford full protection from this and other choking agents. However, only limited or temporary protection against toxic products of combustion or smoke can be assumed, and may be complicated in addition by the presence of oxygen-depleted air.

#### Decontamination

No decontamination is required following exposure to classic choking agents or other lung damaging agents in gas or vapour form.



Fig 26. Phosgene induced injury to pig lungs.

### Mechanism of Action

Chemicals that are highly reactive and/or highly soluble in aqueous solutions tend to act in the conducting, or central compartment of the respiratory tract. Centrally-acting irritants such as sulphur mustard, ammonia, and hydrochloric acid, cause pronounced irritation of the epithelial cells lining the upper airway. Additionally, at low concentrations, centrally-acting compounds are essentially consumed by deposition and reaction in the conducting airways before they reach the peripheral portion of the respiratory tract.

In contrast, most of the pulmonary agents, such as phosgene, oxides of nitrogen, and PFIB, are relatively insoluble and nonreactive, readily penetrating to the level of the respiratory bronchioles and the alveoli. There they undergo acylation reactions and are essentially consumed at that site, causing the damage that may eventually lead to pulmonary oedema.

Chemically induced, acute lung injury by these peripherally-acting agents involves a permeability defect in the blood-air barrier (the alveolar-capillary membrane); however, the precise mechanisms of toxicity remain largely unknown. Leakage of fluid from capillaries into the pulmonary interstitium is normally compensated by lymphatic drainage from the parenchyma, but as the fluid leakage increases, normal drainage mechanisms become progressively overwhelmed. After an asymptomatic or latent period of 20 min to 24 h (depending on the exposed dose), fluid leakage into the pulmonary interstitium decreases compliance producing a stiff lung and increasing complaint of tight chest, shortness of breath, and dyspnoea. Fluid eventually invades the alveoli and produces clinically evident pulmonary oedema.

The distinction between centrally and peripherally acting agents is not strict.

Following exposure to high concentrations of centrally acting irritants, sufficient agent may penetrate into the peripheral lung to cause pulmonary oedema. Similarly, high concentrations of peripherally-acting agents can release enough hydrochloric acid to cause significant central airway irritation and epithelial damage. Because chlorine is intermediate in its solubility and reactivity, chlorine-exposed soldiers in World War I usually exhibited both central airway damage and pulmonary oedema, even from moderate concentrations of the gas. Phosgene is only slightly soluble in water and aqueous solutions; once dissolved, it rapidly hydrolyses to form carbon dioxide and hydrochloric acid. The early-onset ocular, nasopharyngeal, and central airway irritation from high concentrations of phosgene appears to result from the release of hydrochloric acid during phosgene hydrolysis by water in the upper airways.

### Toxicity

The odour threshold for phosgene is about  $1.5 \text{ mg/m}^3$ , and phosgene irritates mucous membranes at  $4 \text{ mg/m}^3$ . The LC<sub>50</sub> of phosgene is approximately  $3200 \text{ mg}\cdot\text{min}\cdot\text{m}^{-3}$ , which is half the LC<sub>50</sub> ( $6,000 \text{ mg}\cdot\text{min}\cdot\text{m}^{-3}$ ) of chlorine, the first gas used on a large scale in World War I. Phosgene is twice as toxic as chlorine; although it is less potent than almost all of the subsequently developed chemical warfare agents, this should not lead to an underestimation of its danger - deaths have occurred after the inhalation of only a few breaths of high concentrations of phosgene. Perfluoroisobutylene (PFIB) is said to be ten times more toxic than phosgene.

## CLINICAL-PATHOLOGICAL EFFECTS

### Pathology

The outstanding feature of acute lung injury caused by lung damaging agents is massive pulmonary oedema. This is preceded by damage to the bronchiolar epithelium, development of patchy areas of emphysema, partial atelectasis, and oedema of the perivascular connective tissue. The trachea and bronchi are usually normal in appearance. This contrasts with the findings in chlorine and chloropicrin poisoning in which both structures may show serious damage to the epithelial lining with desquamation. The lungs are large, oedematous and darkly congested. Oedema fluid, usually frothy, pours from the bronchi and may be seen escaping from the mouth and nostrils (Figure 26). With exposure to very high concentrations, death may occur within several hours; in most fatal cases pulmonary oedema reaches a maximum in

12h, followed by death in 24 to 48h. If the casualty survives, resolution commences within 48h and, in the absence of complicating infection, there may be little or no residual damage.

### Clinical Effects

Exposure to high concentrations of lung damaging agent may irritate moist mucous membranes, depending on their reactivity and solubility in water. Transient burning sensation in the eyes with lacrimation may coexist with early onset cough and a substernal ache with a sensation of pressure. Irritation of the larynx by very large concentrations of the agent may lead to sudden laryngeal spasm and death.

Pulmonary oedema follows a clinically latent period of variable length that depends primarily on the intensity of exposure (i.e., the Ct), but also partly on the physical activity of the exposed individual. This is particularly true for phosgene. After the latent period, the patient experiences worsening respiratory distress that at first is unaccompanied by objectively verifiable signs of pulmonary damage, but may progress relentlessly to pulmonary oedema and death.

The most prominent symptom following the clinical latent period is dyspnoea, perceived as shortness of breath, with or without chest tightness, and in the initial stages there may be no objectively verifiable signs of pulmonary damage. These sensations reflect hypoxemia, increased ventilatory drive, and decreased lung compliance, all of which result from the accumulation of fluid in the pulmonary interstitium and peripheral airways. Fine crackles appear at the lung bases, but these may not be clearly audible unless auscultation is conducted after a forced expiration. Later, auscultation reveals coarse crackles and râles in all lung fields, and increasing quantities of thin, watery secretions are noted. The build-up of fluid in the lungs has two clinically pertinent effects.

1. Developing pulmonary oedema interferes with oxygen delivery to alveolar capillaries and may lead to hypoxemia. If a sufficient percentage of haemoglobin is unoxygenated, cyanosis will become apparent.
2. The sequestration of plasma-derived fluid in the lungs (up to one litre per hour) may lead to hypovolemia and hypotension. Death results from respiratory failure, hypoxemia, hypovolemia, or a combination of these factors. Hypoxia and hypotension may progress particularly rapidly and suggest a poor prognosis.

The development of symptoms and signs of pulmonary oedema within four hours of exposure is an especially accurate indicator of a poor prognosis; in the absence of immediately available intensive medical

support, such patients are at high risk of death. Complications include infection of damaged lungs and delayed deaths following such respiratory infections.

### Condition of Exposed Tissues

Pre-existing airway damage (such as that caused by prior exposure to a lung damaging agent) may seriously compromise the respiratory system's normal protection and clearance mechanisms. Cigarette smoking may severely compromise airway function with respect to both airway patency and clearance mechanisms. Hyper-reactive airways (asthma in varying degrees) are seen in up to 15% of the adult population. Exposures to pulmonary intoxicants may trigger bronchospasm in these individuals. This bronchospasm may delay the clearance of the agent, interfering further with gas transport. The development of an acute interstitial process (e.g. phosgene-related pulmonary oedema) may also trigger bronchospasm. Individuals with any of the following characteristics should be considered likely to develop bronchospasm as the result of a exposure to lung damaging agents:

- Prior history of asthma or hay fever (even as a child).
- Prior history of eczema.
- Family history of asthma, hay fever, or eczema.
- History of chronic sinusitis or seasonal rhinitis.

Individuals with hyper-reactive airways will benefit from bronchodilator therapy and possibly from steroids after exposure to a lung damager. This statement, however, does not constitute an endorsement for routine steroid use in all toxic inhalational injuries.

### Differential Diagnosis

*Phosgene* is distinguished by its odour, its generalised mucous membrane irritation in high concentrations, dyspnoea, and pulmonary oedema of delayed onset.

*Riot-control agents* produce tearing along with burning and pain sensation predominantly in the eyes, upper airways, mucous membranes and skin. This irritation is typically more intense than that caused by phosgene and is unaccompanied by the distinctive odour of phosgene.

*Nerve agents* induce the production of watery secretions as well as respiratory distress; however, their other characteristic effects (e.g. muscle twitching, miosis) distinguish nerve agent toxicity from organohalide inhalation injury.

*Vesicants* usually produce a delayed respiratory toxicity associated predominantly with the central, rather than the peripheral airways. Vesicant inhalation severe enough to cause dyspnoea typically causes signs of airway necrosis, often with pseudomembrane

formation and partial or complete upper airway obstruction. Finally, pulmonary parenchymal damage following vesicant exposure usually manifests itself as haemorrhage rather than pulmonary oedema.

### Clinical Investigations

Sophisticated laboratory studies are of limited value in the immediate care of an exposed, injured individual. The following studies are of some predictive value in determining the severity of exposure and the likely outcome.

#### *Chest Radiograph*

The presence of hyperinflation suggests toxic injury of the smaller airways, which results in air being diffusely trapped in the alveoli. The presence of "batwing" infiltrates suggests pulmonary oedema secondary to toxic alveolar-capillary membrane damage. Atelectasis is often seen with more-central-toxic inhalant exposures. As radiological changes may lag behind clinical changes by hours to days, the chest radiograph may be of limited value, particularly if normal.

#### *Arterial Blood Gases*

Hypoxia often results from exposure to lung damaging materials such as chlorine. Measurement of the partial pressure of oxygen ( $PO_2$ ) is a sensitive but non-specific tool in this setting; both the central and peripheral effects of pulmonary intoxicants may produce hypoxia. Arterial blood gases may show a low  $PaO_2$  or  $PaCO_2$ , which are early, nonspecific warnings of increased interstitial fluid in the lung. At 4 to 6h, normal arterial blood gas values are a strong indication that a particular exposure has little likelihood of producing a lethal effect. Typically, carbon dioxide elevation is seen in individuals with underlying hyper-reactive airways; in this circumstance, it is thought that bronchospasm is triggered by exposure to the chemical.

#### *Haematocrit*

An increase in the hematocrit may reflect the hemoconcentration induced by transudation of fluid into the pulmonary parenchyma.

#### *Pulmonary Function Tests*

Peak expiratory flow rate may decrease soon after a massive exposure. This non-specific test helps to assess the degree of airway damage and the effect of bronchodilator therapy. Decreased lung compliance and carbon dioxide diffusing capacity are particularly sensitive indicators of interstitial fluid volume in the lung, but are complex tests for hospital use only. Ventilation/perfusion ratio (V/Q) scanning is very sensitive but is nonspecific and for hospital use only.

## TREATMENT OF TOXIC INHALATIONAL INJURY

### Medical Management

*Terminate exposure as a vital first measure.* This may be accomplished by physically removing the casualty from the hazard environment or by protecting with a properly fitting respirator. Decontamination of liquid agent on clothing or skin terminates exposure from that source.

*Execute the ABCs of resuscitation as required.* Establishing an airway is especially crucial in a patient exhibiting hoarseness or stridor; such individuals may face impending laryngeal spasm and require intubation. Establishing a clear airway also aids in interpretation of auscultatory findings. Steps to minimise the work of breathing must be taken. Because of the danger of hypotension induced by pulmonary oedema or positive airway pressure, accurate determination of the casualty's circulatory status is vital, not just initially, but also at regularly repeated intervals and whenever indicated by the clinical situation. Carefully replace intravascular volume as required to maintain hemodynamic stability.

*Enforce rest.* Even minimal physical exertion may shorten the clinical latent period and increase the severity of respiratory symptoms and signs in an organohalide casualty. Physical activity in a symptomatic patient may precipitate acute clinical deterioration and even death. Strict limitation of activity (i.e. forced bed rest) and litter evacuation are mandatory for patients suspected of having inhaled any agent that might cause pulmonary oedema. This is true whether or not the patient has respiratory symptoms and whether or not objective evidence of pulmonary oedema is present.

*Manage airway secretions and prevent/treat bronchospasm.* Unless super-infection is present, secretions present in the airways of phosgene casualties are usually copious and watery. They may serve as an index to the degree of pulmonary oedema and do not require specific therapy apart from suction and drainage. Antibiotics should be reserved for those patients with an infectious process documented by sputum gram-staining and culture. An elevation of the partial pressure of carbon dioxide ( $PCO_2$ ) greater than 45 mm Hg suggests that bronchospasm is the most likely cause of hypercarbia, therefore bronchodilators should be used aggressively. Bronchospasm may occur in individuals with reactive airways, and these patients should receive beta-adrenergic bronchodilators. Steroid therapy is also indicated for bronchospasm. Parenteral administration is the preferred route of steroid administration as inhaled routes may result in inadequate distribution to damaged airways. Methylprednisolone, 700-1000 mg or its equivalent, may be given intravenously in divided doses

during the first day and then tapered during the duration of the clinical illness. The increased susceptibility to bacterial infection during steroid therapy mandates careful surveillance of the patient. No human studies have shown any benefit from steroids, thus steroids are not recommended in individuals without evidence of overt or latent reactive airway disease.

*Prevent/treat pulmonary oedema.* Positive airway pressure provides some control over the clinical complications of pulmonary oedema. Early use of a positive pressure mask may be beneficial. Positive airway pressure may exacerbate hypotension by decreasing thoracic venous return, necessitating intravenous fluid administration and perhaps judicious use of the pneumatic anti-shock garment. Pulmonary oedema noted after a toxic inhalant exposure should be treated similarly to adult respiratory distress syndrome (ARDS) or "noncardiac" pulmonary oedema. The early application of PEEP is desirable, possibly delaying or reducing the severity of pulmonary oedema. Diuretics are of limited value; however, if diuretics are used, it is useful to monitor their effect by means of the pulmonary artery wedge pressure measurement because excessive diuretics may predispose the patient to hypotension if PEEP or positive-pressure ventilation is applied.

*Prevent/treat hypoxia.* Oxygen therapy is definitely indicated and may require supplemental positive airway pressure administered via one of several available devices for generating intermittent or continuous positive pressure. Intubation with or without ventilatory assistance may be required, and positive pressure may need to be applied during at least the end-expiratory phase of the ventilator cycle.

*Prevent/treat hypotension.* Sequestration of plasma-derived fluid in the lungs may cause hypotension that may be exacerbated by positive airway pressure. Urgent intravenous administration of either crystalloid or colloid (which in this situation appear equally effective) may need to be supplemented by the judicious application of the pneumatic anti-shock garment. The use of vasopressors is a temporary measure until fluids can be replaced.

### Steroid Therapy

Systemic steroid therapy has been considered for use in certain toxic inhalational exposures. Human evidence of benefit from steroids in phosgene exposure is scanty. There is some support in the literature for steroid use in exposure to zinc/zinc oxide and oxides of nitrogen. However, there is no other strong support in the literature for the treatment of other specific toxic inhalations with systemic steroids.

A significant percentage of the population

has a degree of airway irritability or hypersensitivity, as exemplified by persons with asthma. These individuals are likely to display heightened sensitivity or even bronchospasm, non-specifically after an inhalational exposure. The use of systemic steroids would be indicated in this population if their bronchospasm was not readily controlled with more routine bronchodilators. If used in this setting, systemic steroids may be required for prolonged periods, particularly if superinfection should supervene. Inhaled steroids may be less effective than systemic steroids in circumstances of acute exposure, especially if later infected. Inhaled steroids appear most useful as an adjunct to the gradual reduction or weaning or both from a systemic steroid use.

### Combined Injuries

Acute lung injury may complicate resuscitation and aggravate hypovolaemic shock associated with traumatic injury. In such cases the latent period between exposure and the development of pulmonary oedema may also be shortened

### Triage

*Patients seen within 12 h of exposure.* A patient with pulmonary oedema only is classified **immediate** if intensive pulmonary care is immediately available. In general, a shorter latent period portends a more serious illness. A **delayed** patient is dyspnoeic without objective signs and should be observed closely and re-triaged hourly. An asymptomatic patient with known exposure should be classified **minimal** and observed and re-triaged every two hours. If the patient remains asymptomatic 24 h after exposure, discharge the patient. If exposure is doubtful and the patient remains asymptomatic 12 h following putative exposure, consider discharge. An **expectant** patient presents with pulmonary oedema, cyanosis and hypotension. A casualty who presents with these signs within 6 h of exposure generally will not survive; a casualty with the onset of these signs 4 h or longer after exposure may survive with immediate, intensive medical care.

*Patients seen more than 12 h after exposure.* A patient with pulmonary oedema is classified **immediate** provided he will receive intensive care within several hours. If cyanosis and hypotension are also present, triage the patient as **expectant**. A **delayed** patient is dyspnoeic and should be observed closely and re-triaged every 2 h. If the patient is recovering, discharge 24 h after exposure. An asymptomatic patient or patient with resolving dyspnoea is classified **minimal**. If the patient is asymptomatic 24 h after exposure, he is fit for discharge. A patient with persistent hypotension despite intensive medical care is **expectant**.

**Further Reading**

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