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18.14.11 Toxic gases and aerosols 4267 have been noted, and might be useful in monitoring the activity and progression of the disease. Treatment Etidronate, a bisphosphonate, reduces the formation of calcium hydroxyapatite crystals and has led to clinical and radiological im- provement in some cases, particularly in childhood, but seems to be ineffective in adults with advanced disease. Lung transplantation is the main treatment option to be con- sidered in advanced stage disease and has improved the prog- nosis and quality of life for the small number of patients with pulmonary alveolar microlithiasis who have undergone this pro- cedure. Transplant surgery can be difficult if there are severe ad- hesions between the lungs and the chest wall. Deaths post lung transplantation have been due to complications of transplantation such as obliterative bronchiolitis, and there has been no evi- dence of recurrence of alveolar microlithiasis up to 15 years post-transplantation. Prognosis The severity of the disease and prognosis are variable, and this may be influenced by the specific type of gene mutation. Survival of 10–20 years from the onset of symptoms is typical. At death, ex- tensive areas of the chest radiograph show a dense ‘whiteout’ ap- pearance due to the considerable accumulation of calcium. At post-mortem examination, the lungs are difficult to cut and are heavy and sink in water. FURTHER READING Castellana G, Castellana G, Gentile M, Castellana R, Resta O (2015). Pulmonary alveolar microlithiasis: review of the 1022 cases reported worldwide. Eur Respir Rev, 24, 607–20. Francisco FA, et al. (2013). Pulmonary alveolar microlithiasis. State-of-the-art review. Resp Med, 107, 1–9. Harbitz F (1918). Extensive calcification of the lungs as a distinct disease. Arch Int Med, XXI, 139–46. Huqun SI, et al. (2007). Mutations in the SLC34A2 gene are associated with pulmonary alveolar microlithiasis. Am J Respir Crit Care Med, 175, 263–8. Jonsson AL, et al. (2012). Pulmonary alveolar microlithiasis: two case reports and review of the literature. Eur Resp Rev, 21, 249–56. Jonsson AL, et al. (2012). SLC34A2 gene mutation may explain comorbidity of pulmonary alveolar microlithiasis and aortic valve sclerosis. Am J Respir Crit Care Med, 185, 464. Ozcelik U, et al. (2010). Long-term results of disodium etidronate treatment in pulmonary alveolar microlithiasis. Pediatr Pulmonol, 45, 514–17. Saito A, McCormack FX (2016). Pulmonary alveolar microlithiasis. Clin Chest Med, 37, 441–8. Shigemura N, et al. (2010). Lung transplantation for pulmonary al- veolar microlithiasis. J Thorac Cardiovasc Surgery, 139, e50–2. Zhang XD, et al. (2018). Pulmonary alveolar microlithiasis: a case

re- port and review of the literature. Exp Ther Med, 15, 831–7. 18.14.11 Toxic gases and aerosols Chris Stenton ESSENTIALS Acute exposure to noxious agents causes pulmonary effects that are determined by the size of aerosol particles and by the solubility of gases. Large particles (>10 um) and soluble agents such as CS gas, am- monia, or sulphur dioxide affect primarily the upper respiratory tract, causing lacrimation, blepharospasm, rhinitis, cough, and breath- lessness. Nitrogen oxides, ozone, and other agents of low solubility affect mainly the lungs, with pneumonitis and pulmonary oedema that can develop 24 hours or more after exposure. Smoke inhalation, intermediate solubility gases such as chlorine, and overwhelming ex- posures have effects throughout the respiratory tract. Some inhaled gases such as carbon monoxide and methane act as simple asphyxi- ants. Other reactions occur, such as metal fume fever with zinc and cadmium, and pulmonary haemorrhage with crack cocaine. Management is essentially supportive. Carboxyhaemoglobin and lactate levels should be measured with smoke inhalation. Consideration should be given to the possibility of delayed pul- monary oedema even if the patient is well initially. Chronic effects such as asthma, pulmonary fibrosis, and bronchi- ectasis can follow acute inhalation injuries. These can occur without any obvious acute injury, and may be difficult to detect as the radio- logical and lung function abnormalities are subtle. Introduction The inhalation of toxic chemicals following accidents or through routine use is one of the commonest forms of workplace injury. There has been a resurgence of military and paramilitary exposure to toxic substances such as sulphur mustard in recent decades. Long term effects of these and other exposures is increasingly recognized, with disease of the small airways (constrictive bronchiolitis) the commonest outcome. Smoke inhalation from domestic fires in- volves exposure to numerous toxic agents and remains common. Acute toxic injury to the respiratory tract The acute effects of inhaled gases are determined largely by their solubility in water (Table 18.14.11.1). Soluble gases such as am- monia or sulphur dioxide dissolve in the secretions lining the upper respiratory tract and cause acute irritant effects there. The symptoms usually force the affected individual to withdraw from exposure and that limits adverse effects. Poorly soluble gases such as nitrogen oxides and ozone have little or no effect in the upper airways but penetrate to the alveoli and cause pneumonitis and pulmonary oedema, which often becomes apparent only several hours after exposure. The effect of aerosols (airborne suspensions of substances that are normally solid or fluid) is largely determined by their particle size. Particles of more than 10 μm diameter are deposited chiefly in

 the nose and oropharynx. Smaller particles penetrate to the alveoli. Gases of intermediate solubility such as chlorine, massive exposures, or mixed exposures (e.g. with smoke inhalation), are likely to have effects at all levels of the respiratory tract. Clinical features Acute airway effects Soluble irritant gases Aerosols of the riot control and antipersonnel agents CS ‘gas’ (2-chlorobenzylidene malononitrile), mace (CN; 2-chloroaceto phenone), and pepper (capsaicin) are employed because of their acute irritant effects on the eyes and upper respiratory tract. Exposures to soluble irritant gases and other large particle aerosols cause similar symptoms. A burning sensation develops in the eyes, nose, throat, and large airways within seconds, usually with lacrimation, blepharospasm, rhinitis, cough, and breathlessness. Symptoms generally settle within 30 minutes, although some effects may persist for up to 24 hours. With more marked exposure there may be laryngeal oedema and upper airway obstruction with progressive coughing, wheezing, and stridor. Full recovery remains the rule, but acute bronchospasm can be fatal and tracheobronchitis can lead to secondary infection. If consciousness is lost then there is likely to be greater penetration to the alveoli, and pulmonary oedema may develop. Some individuals are left with asthma that persists for months, or even indefinitely. The

latter is known as acute irritant asthma or the reactive airways dysfunction syndrome. Sulphur mustard Sulphur mustard (C4H8Cl2S) caused injury to many Iranians during the 1980–1988 Iran–Iraq war. It affects mainly the skin, eyes, nose, and upper respiratory tract. Symptoms progress over several hours to days with lacrimation, rhinorrhoea, and coughing. Airway oedema and inflammation can lead to the development of pseudomembranes that can slough and cause airflow obstruc- tion. Pulmonary oedema, and secondary infection is common. Pulmonary problems are the principal cause of mortality within the first few weeks of exposure. Burns Between 20% and 30% of burn victims suffer from pulmonary com- plications. Improvements in the treatment of shock and sepsis have rendered inhalation injury the main cause of mortality. Thermal in- jury affects the upper airways causing oedema and narrowing. Soot particulates and toxic gases including ammonia, sulphur dioxide, chlorine, phosgene, nitrogen dioxide, aldehydes affect all levels of the respiratory tract. Carbon monoxide and hydrogen cyanide act as chemical asphyxiants. If fat or oil is involved, a lipoid pneumonia may ensue, particularly if combustion (or explosion) leads to oil nebulization (see Chapter 18.14.9). Acute pneumonitis/ pulmonary oedema Gases of low solubility such as oxides of nitrogen, ozone, or phos- gene have little if any effect in the upper airways. They penetrate readily to the gas-exchanging tissues, where they cause pneumon- itis and pulmonary oedema. The effects are exemplified by nitrogen dioxide generated by stored grain. Farm workers can develop silo- filler's lung when they enter or decap a contaminated silo. Typically breathlessness caused by pulmonary oedema develops several hours after exposure though presentation may be delayed for 24 hours or more. Nitrogen dioxide can also be generated by thermal oxidation of nitrogen in air when welding is carried out in poorly ventilated areas, and from the combustion of nitrogen-containing substances such as nitrocellulose. A wide range of other chemical agents can cause acute pneumon- itis. Household waterproofing and dirt repellent sprays often con- tain fluorocarbon polymers. When used in confined spaces they can cause acute chemical pneumonitis (Fig. 18.14.11.1) that on oc- casions has been fatal. Exposure to cadmium fumes from welding metal alloys can also cause acute and potentially fatal chemical pneumonitis. Mercury vapour and less commonly antimony, man- ganese, beryllium, vanadium, cobalt, tributyl tin, and halide salts have all been reported to cause similar problems. Acid anhydrides Table 18.14.11.1 The effects of gases and vapours on the airways and lungs Highly soluble gases and vapours with upper airway effects Hydrogen chloride Ammonia Formaldehyde Acrolein Sulphur dioxide Intermediate solubility gases causing upper airway effects and pneumonitis Chlorine Hydrogen sulphide Low solubility gases causing pneumonitis Nitrogen oxides Ozone Phosgene Fig. 18.14.11.1 Acute lung injury following the use of a waterproofing spray in an enclosed area. Lung biopsy showed a desquamative interstitial pneumonia pattern. From Nakazawa A, et al. (2014). Surgically proven desquamative interstitial pneumonia induced by waterproofing spray. Intern Med, 53, 2107–10.

18.14.11 Toxic gases and aerosols 4269 used as cross-linking agents in the production of epoxy resins cause pneumonitis with prominent alveolar haemorrhage and haemo- lytic anaemia. Smoking crack cocaine can also cause diffuse alveolar damage with alveolar haemorrhage that presents up to 48 hours after exposure. Nonpulmonary effects Asphyxiants Gases other than oxygen can act as asphyxiants by displacing oxygen from inhaled air. The most commonly encountered are CO2 and methane produced by decomposing vegetable material. The accumulation of oxygen-deficient air from soil in wells during periods of low barometric pressure has led to asphyxiation of those climbing into them. Blackdamp in coal mines arises from the slow combustion of coal. Occasionally deoxygenated air can escape from disused mines and enter

cellars of overlying houses posing a risk to unsuspecting residents. Chemical asphyxiants such as carbon monoxide and hydrogen cyanide act by blocking oxygen uptake by haemoglobin or by inhibiting intracellular oxygen utilization. They are important considerations in the case of smoke inhalation as they may be associated with tissue hypoxaemia despite apparently normal ar- terial oxygen saturation and pO2 measurements. On rare occasions they may require specific treatment such as hyperbaric oxygen for carbon monoxide intoxication or dicobalt edetate for cyanide poisoning. Metal and polymer fume fevers Metal fume fever and polymer fume fever are acute self-limiting conditions characterized by influenza-like symptoms with fever, myalgia, headache, malaise, cough, and mild breathlessness, begin- ning within 6 hours of exposure and resolving fully within 24 hours. They are distinguished from inhalation injuries by the greater prom- inence of systemic features and by the absence of chest radiograph abnormalities or hypoxaemia. Metal fume fever is most commonly caused by exposure to zinc from welding galvanized (i.e. zinc-coated) steel, but can also be caused by copper, magnesium, and other metal fumes. Polymer fume fever is caused by exposure to heated fluoropolymers. Over heated frying pans, and fluoropolymer particles from sealant tape transferred from plumbers' hands onto cigarettes are recognized causes. Tachyphylaxis leads to progressively milder responses with repeated exposures, similar to the 'Monday fever' described in cotton workers. Assessment and management Supportive care The initial treatment of acute inhalation injuries is essentially sup- portive. The affected individual should be moved to a safe area and potentially contaminated clothing removed to avoid secondary ex- posure. Carers should wear appropriate protective clothing to en- sure that they themselves do not become contaminated. Oxygen saturation should be monitored and oxygen admin- istered if the patient is hypoxaemic or if there has been possible exposure to carbon monoxide or cyanide (e.g. from fires). Carboxyhaemoglobin, methaemoglobin, and lactate levels should be measured following smoke inhalation. Nebulized bronchodilators should be administered if there is bronchospasm, and oral cortico- steroids considered. Early intubation may be necessary if there is evidence of laryngeal oedema. Bronchoscopy is occasionally neces- sary to remove excessive airway secretions. Other issues A detailed history of the circumstances of the exposure will provide important information to guide further management, such as the likelihood of exposure to a poorly soluble gas and the risk of de- layed pulmonary oedema or systemic toxicity. Unconscious victims are likely to have received particularly heavy exposures. The circum- stances of the exposure may have been psychologically traumatic and panic with psychogenic hyperventilation may need to be iden- tified and managed. A chest radiograph is essential, but an initially normal film does not rule out the later development of pneumonitis and pulmonary oedema. Patients with significant inhalation injury should be moni- tored for at least 24 hours. Even if they are well, they should be ad- vised of the risk of delayed pulmonary oedema developing over the next few days, particularly if there has been exposure to low solu- bility gases such as nitrogen oxides. Recurrent episodes of pulmonary oedema 1–3 weeks after the initial exposure have been reported following exposure to nitrogen oxides, although the underlying mechanism is obscure. Severe pulmonary oedema should be managed as for the acute respiratory distress syndrome. There is no established role for corticosteroids, but they may help prevent the development of late pulmonary oe- dema after nitrogen dioxide exposure. Subacute toxic injury to the respiratory tract Acute inhalation injuries can give rise to persisting lung damage. Tracheal stenosis, bronchiectasis, asthma, and pulmonary fibrosis have all been reported, but more recently it has become clear that constrictive bronchiolitis is the commonest outcome. Fibrous tissue proliferation with narrowing and obliteration of the small periph- eral airways develops as a consequence of respiratory epithelial and basement membrane damage caused by the toxic

exposure. Chronic diseases such as chronic obstructive pulmonary disease (COPD) and pneumoconiosis may arise through other ‘toxic’ or ‘irritant’ mechanisms (see Chapters 18.8 and 18.13). Clinical features Constrictive bronchiolitis following acute inhalation injury Chronic respiratory symptoms were common in World War I veterans who were exposed to chemical warfare agents, but the underling pathophysiology was poorly characterized. A 10-year follow-up study of those exposed to sulphur mustard in the Iran– Iraq war revealed persisting abnormalities of lung function in al- most 50% of subjects. Features of constrictive bronchiolitis were found in two-thirds of a small group of patients who underwent lung biopsy. The Bhopal disaster of 1984 involved the release of 40 tonnes of methyl isocyanate gas, with at least 3800 immediate deaths. A high proportion of survivors reported ongoing respiratory symptoms and had impaired lung function, probably caused by bronchiolitis.

section 18 Respiratory disorders 4270 Persisting constrictive bronchiolitis is also described following acute exposure to other irritant gases including nitrogen oxides, sul- phur dioxide, bromine compounds, ammonia, fly ash, and smoke inhalation. The 2001 destruction of the New York World Trade Centre gave rise to a dense dust cloud of very alkaline pH that caused acute airway and eye irritation and inflammation. 14 000 firefighters were involved, all of whom had pre-exposure lung function meas- urements. They had a mean fall of FEV1 of 440 ml within the first year of exposure, with little recovery over the subsequent 6 years. The pathological process has been poorly characterized, but biopsy studies have suggested that bronchiolitis is an important mech- anism. A range of other outcomes has been reported, including asthma, bronchitis, and sarcoidosis, but a causal relationship with the exposure has not always been clear. Constrictive bronchiolitis without an antecedent acute injury Early studies of silo fillers exposed to nitrogen dioxide suggested that some individuals developed insidious-onset constrictive bron- chiolitis. A cluster of cases of constrictive bronchiolitis was reported in US military personnel who served in Iraq and Afghanistan and developed persisting breathlessness and exercise limitation. The diagnosis was confirmed by lung biopsy in 38 cases. The commonest association was with proximity to a mine fire that produced high ambient air levels of sulphur dioxide, but one-third of those affected reported no unusual exposures. Severe constrictive bronchiolitis was identified in eight former workers of a popcorn factory in 2000. Four required lung transplant- ation. All had handled the butter-flavouring agent 2,3-butanedione (diacetyl), and none had reported work-related symptoms to raise the suspicion of an occupational cause. A subsequent survey of 20 flavouring manufacturing companies identified abnormal lung function in 23% of workers, suggesting a high prevalence of ‘pop- corn workers lung’ (Fig. 18.14.11.2). The disease generally presents insidiously with cough, breathlessness and (in some cases) eye, nose, and throat, and skin irritation. Similar conditions have been re- ported in other industries with flavouring exposures such as cookie manufacture and coffee processing. Severe constrictive bronchiolitis has also been described in workers exposed to glass fibre, resins, accelerating agents, and other chemicals when making fibreglass-reinforced boats. Other subacute lung disease arising from toxic exposures Outbreaks of respiratory disease have been caused by the inhalation of nylon fragments in the nylon flock industry. Affected workers developed a restrictive ventilatory abnormality with reduced gas diffusion, and interstitial shadowing on chest radiographs or CT scans. Biopsies generally showed a distinctive lymphocytic bron- chiolitis and peribronchiolitis with lymphoid hyperplasia and aggregates. The Ardystil syndrome resulted from an apparently minor change in the formulation of sprayed printing dyes in textile factories. Approximately 10% of exposed workers developed lung disease and 5 of the original case series of 14 patients died. Affected individ- uals reported breathlessness, cough, and prominent epistaxis. The radiological and pathological appearances

were those of organizing pneumonia. Respiratory problems have been identified in up to 20% of workers exposed to indium in the manufacture of electronic display screens. Radiological abnormalities have often mimicked those of pulmonary alveolar proteinosis, with ground-glass shadowing and superimposed ‘crazy paving’ interlobular septal thickening. Biopsies showed granular eosinophilic and intra-alveolar exudates typical of pulmonary alveolar proteinosis together with diffuse lung fibrosis. Diagnosis and management The recognition of chronic respiratory disease caused by an acute inhalational injury is generally straightforward, but there may be difficulties distinguishing persisting effects of exposure from antecedent lung disease such as asthma or COPD. Disease arising without an acute episode is much more difficult to attribute to the causative exposure. Often effects have been recognized only when a cluster of cases has presented to the same hospital clinic or though detailed epidemiological investigation. Constrictive bronchiolitis is a particularly difficult diagnosis to es- tablish and is easily mistaken for asthma or COPD. Lung function tests typically show airflow obstruction, but there may be an equal re- duction in forced expiratory volume (FEV) and forced vital capacity (FVC) associated with gas trapping and an elevated residual volume. The transfer factor may be normal or impaired. The plain chest radio- graph is often normal. High-resolution CT (HRCT) findings may also be subtle, with patchy areas of decreased lung density that are en- hanced on expiratory images. Lung biopsies have identified symptom- atic disease in the presence of normal HRCT scans and lung function. Constrictive bronchiolitis generally stabilizes following the ces- sation of exposure, but there is no clear evidence of benefit from therapy. Those exposed to sulphur mustard have been reported to respond to bronchodilators, inhaled glucocorticoids, oral N- acetylcysteine, and interferon-γ. Popcorn worker’s lung does not respond to oral corticosteroids or cyclophosphamide. A high pro- portion of those with occupationally-induced constrictive bron- chiolitis have required lung transplantation. Importantly, the identification of a sentinel case of possibly work- related disease should prompt a survey of fellow workers and a re- view of the occupational exposures (see Chapter 10.2.1). Worker education and appropriate surveillance schemes are also important 3.5 3 FEV1 (ltr) 2.5 2 1.5 1 0.5 0 0 5 10 15 20 25 30 Months since start of work Acute exposure 35 40 Fig. 18.14.11.2 Lung function in a flavouring manufacturer before and after exposure to diacetyl. Acute irreversible reduction of FEV caused by constrictive bronchiolitis. Adapted from Hendrick DJ (2008). ‘Popcorn worker’s lung’ in Britain in a man making potato crisp flavouring. Thorax, 63, 267–268.

Revision #1
Created 2026-01-22 16:40:09 UTC by Omar Ayman
Updated 2026-01-22 16:40:09 UTC by Omar Ayman