Metal Allergy and the Lungs

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41.1 Introduction

About 91 of the 118 elements in the periodic table are metals or metalloids. Some metals are ubiquitous in the environment of human life. The most significant exposure to metals occurs in industrial use. In certain occupations, exposure to dusts and aerosols containing metals is particularly important. Metal salts are widely used in electroplating processes, metal alloys, pigments, tanning of leather, and production of many chemicals. Significant exposure to metals takes place also during welding processes, construction, grinding, and metalworking [1]. Soluble metallic salts may penetrate the airways and be transported as metal ions into lung tissues. Exposure to metals is not confined to the work environment. Hobbies and domestic activities may lead to clinical sensitivity in susceptible individuals.

The role of metals in the induction of skin allergy (allergic contact dermatitis) has been well known for many years. It is generally recognized that some metals may have allergenic properties (e.g., nickel, chromium, cobalt). Other metals (e.g., lead, cadmium) do not show such activity, even at high concentrations. So far, the reasons for this difference have not been fully explained. It is also not clear why sensitization occurs only in some exposed persons and what factors predispose to allergy to metals.

41.2 Impact of Metals on the Immune System

At high concentrations, metals are usually immunosuppressive, whereas at low concentrations, they are often immunostimulative. For many years it was believed that, like other haptens, metal ions are recognized by T cells as complexes with major histocompatibility complex (MHC) molecules or as complexes with peptides presented by MHC molecules. Specific metal-binding sites in enzymatic proteins seem to play a role in the pathogenesis of metal-related allergic reactions. Thus far, however, researchers have failed to demonstrate "metal-peptide" connections recognized by specific T cells. Metal ion particles are smaller than those of other allergens and do not form stable covalent linkages. Therefore, the activation of immune cells by metal ions likely differs from that of classic haptens [2]. Some metal ions can alter the structure of Langerhans cells and thus lead to changes in the peptides presented by these cells via three possible mechanisms: oxidation of the side chains of amino acids, the formation of coordination complexes that modify the structure of proteins, and nonenzymatic hydrolysis of amide bonds. Changes in the polypeptide chain of

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J.K. Chen, J.P. Thyssen (eds.), *Metal Allergy*, https://doi.org/10.1007/978-3-319-58503-1_41

proteins may affect the process of antigen presentation. The role of humoral responses in allergy to metals is even less understood. Allergen-specific IgE (a-s IgE) to some metals (nickel, chromium, cobalt, platinum) has been identified in exposed workers, but their role in the pathogenesis of metal-induced asthma (MIA), except platinum-induced asthma, has not been elucidated. Therefore, the pathophysiological mechanism of MIA is still poorly recognized. The role of immediate and delayed type allergy (and/or other mechanisms, such as immunotoxic mechanisms) in this disease is unclear.

A new interesting and yet unexplored issue is the impact of metal nanoparticles on the immune system. Gas metal arc welding processes are able to generate significant levels of nanoparticles [3]. Ding et al. described the effect of metallic (tungsten carbide/cobalt) nanoparticles on the production of free radicals and the activation of cell signaling pathways in murine epidermal cells. Metal particles may activate the transcription factors, AP-1 and NF-κB, with stimulation of mitogen-activated protein kinase (MAPK) signaling pathways [4]. Copper oxide nanoparticles aggravated the development of asthma and increased inflammatory cell infiltration into the lung, as well as mucus secretion, in asthmatic mice via MAPK phosphorylation [5]. Also, zinc oxide nanoparticles induced eosinophilic inflammation in mice [6]. The influence of silver nanoparticles on allergic airway inflammation was investigated by Park et al. The authors showed these particles caused airway hyperresponsiveness, increased levels of IL-4, IL-5, and IL-13, and increased NF-κB levels in the lungs after ovalbumin inhalation [7].

41.3 Metals and Airway Diseases

Several forms of pulmonary toxicity or immunologic conditions (including acute and chronic obstructive syndromes) have been noted after exposure to metals. Inhalation of fumes or dusts containing various metallic salts may cause many airway diseases (Table 41.1). Some of them may mimic asthma and should be taken into consideration in the differential diagnosis.

Table 41.1 Lung diseases due to exposure to metals

Disease	Etiologic factors
Chemical tracheobronchitis	Many metals at high concentrations
Chemical pneumonitis/ adult respiratory distress syndrome (ARDS)	Many metals at high concentrations
Chronic obstructive pulmonary disease/ pulmonary emphysema	Cobalt, aluminum, manganese, titanium dioxide, beryllium, cadmium (chronic exposure)
Metal fume fever	Zinc, copper, magnesium, cadmium, aluminum, antimony, iron, manganese, mercury, nickel
Chronic beryllium lung diseases	Beryllium
Hard metal disease (cobalt lung)	Cobalt
Immunological asthma	Platinum, nickel, chromium, cobalt
Nonimmunological asthma (reactive airways dysfunction syndrome (RADS))	Many metals in high concentrations
Pneumoconioses (collagenous and non-collagenous)	Aluminum, tin, barium, iron
Cancer	Beryllium, chromium, cadmium, nickel

Workers are rarely exposed to pure metals, while their exposure to metal salts (sulfides, oxides, carbides, hydrides, and others) is quite common. Metals also form coordination complexes with ligands (sulfur molecules, ammonia, cyanogen, organic nitrogen). Bioavailability of such compounds and complexes is an important determinant of the possible effects on the respiratory system resulting from exposure to metals.

41.4 Metal Allergy in Asthma

Occupational asthma-like symptoms induced by inhalation exposure to metals were first described by Georgius Agricola, who published *De Re*

Metallica in 1556 [8]. Although the number of reported cases of MIA and metal-induced allergic rhinitis is relatively small, reports concerning the importance of metals as inhalant allergens are growing steadily [9, 10]. Almost all reported cases have been related to occupational exposure. However, some data indicate an association between environmental exposure to ambient metals (manganese, nickel, chromium, lead) and the development of asthma [11, 12]. There are very few epidemiological studies on the prevalence of airway allergy to metals. According to the program Surveillance of Occupational Respiratory Diseases in South Africa (SORDSA), platinum was the third most common agent causing occupational asthma in South Africa (12.3%) [13]. Because of the fact that occupational exposure to metals affects a large number of employees, it is likely that the disease may be underdiagnosed, especially when we remember that the diagnostic capabilities for airway allergy to metals are limited.

Occupational asthma from sensitization due to inhalation of metal-containing fumes or aerosols has been reported mainly in electroplaters, welders, construction workers, and metalworkers exposed to metalworking fluids. Asthma has been reported in workers exposed to various metals. The main metals which may cause MIA belong to the group of "transitional metals" located between group IIA and III in the periodic table (Table 41.2), although not all asthmogenic metals belong to that group. The biological activity and impact of transitional metals are predicated on their abilities to change oxidation states by oxidation (loss of electrons) and reduction (gain of electrons). As transition metals are electrically stable in more than one oxidation state, they play important roles in the catalysis of biologic oxidation reactions [1].

Table 41.2 Transitional metals that can induce asthma

Group of transitional metals	Metals that can trigger asthma
I ("iron group")	Vanadium, chromium, cobalt, manganese, nickel, zinc
II ("palladium group")	Ruthenium, rhodium, palladium
III ("platinum group")	Platinum, iridium

41.5 Diagnostic Challenges for Metal-Induced Asthma

Metals may exhibit different biological activities. Distinguishing between nonspecific (irritant) and specific (allergenic) effects of metals on the respiratory system is difficult. Most of the dust and aerosols containing these elements at high concentrations may cause irritant effects. Only a few metals may cause asthma via an immunologic mechanism. Therefore, asthma induced by metals could be immunologically mediated, or due to irritation (nonimmunological irritant-induced asthma; reactive airways dysfunction syndrome (RADS)). Moreover, in many workplaces there is exposure to a wide variety of metals. There are few workplaces where irritant-induced asthma due to metal compounds has been described in the absence of other irritants. Therefore, in some cases it is unknown which of these is the causative agent. For this reason, occupational asthma due to metals is characterized by significant diagnostic difficulties, especially for medical certification purposes. The incidence of this form of asthma may also be underestimated. Specific diagnostic difficulties relate to welders. Welding processes produce fumes consisting of gaseous and aerosol by-products composed of metals, metal oxides, and volatile chemical compounds. Stainless steel and mild steel are the most common wire types used in welding. In addition to exposure to dust and fumes containing various metals, welders are exposed to coating materials. These coverings have been known to contain epoxy resins, acrylics, phenol, formaldehyde, isocyanates, polyvinyl chloride, and various nanoparticles [14].

In most publications (epidemiological studies and case reports) the diagnosis of occupational asthma due to metals was based on questionnaire and spirometry examinations or bronchial challenge tests [15–18]. Such methodology is not

able to exclude nonspecific irritant effects. Much more reliable diagnoses are based on the clinical response to placebo-controlled specific challenge tests with metals at small concentrations (0.1% aqueous solutions or less) and concomitant evaluation of the accompanying changes (influx of inflammatory cells such as eosinophils and basophils) in the biological material (induced sputum and nasal or bronchial lavage fluid). The placebo-controlled specific inhalation challenge is generally regarded as the gold standard in the diagnosis of occupational asthma. The presence of metal-specific IgE in the serum or skin does not by itself indicate clinical response to the allergen and could be only a biomarker of exposure [1, 19].

41.6 Metals Causing Immunologic Occupational Asthma

41.6.1 Platinum

Platinum salts are among the most prominent allergens that cause immunologic occupational asthma and allergic rhinoconjunctivitis. Exposure to platinum is limited to certain industries (precious metal refineries, automobile exhaust catalyst production) and countries (mainly the Republic of South Africa). Platinum salt allergy is a considerable health problem in some chemical plants, with high cumulative risks for sensitization. In bronchial challenges with platinum salt, immediate or dual responses have been observed. Laboratory tests aiming to identify a-s IgE (such as skin prick testing (SPT)) are a useful technique for surveillance and early detection of platinum salt-sensitized workers with asthma. A direct comparison between SPT and bronchial challenges has revealed that SPT has high sensitivity and specificity [20]. Radioallergosorbent test (RAST) procedures with platinum salts conjugated to different proteins or anion-exchange resin have been also used for the detection of platinum sensitivity (presence of a-s IgE in serum); however it is suggested that serum-specific IgE assays are less efficient than SPT [21, 22]. There are few reports on the natural history of platinum-induced asthma. According to Merget et al., 17 of 24 workers with this kind of asthma (71%) still reported symptoms 2 years after exposure cessation. SPT reverted to negative in three subjects, but this was not accompanied by reduced bronchial responsiveness to methacholine and platinum salts [23]. It has been suspected that persistence of platinum-induced asthma could be due to continued contact with platinum of former platinum workers, who retain small amounts of the metal on their clothing [24].

41.6.2 Chromium

Of particular importance are hexavalent chromium compounds, found in many workplaces, for example, in the construction industry (cement). They may have an elevated allergenic potential because they are more soluble and presumably have easier access into body tissues. The first supposed case of chromium-induced occupational asthma was described in 1931 by Smith in a worker exposed to ammonium bichromate [25]. The diagnosis in this patient was based upon a positive patch test. The case of an electroplater with asthma, rhinoconjunctivitis, and dermatitis, and positive reaction after scratch testing with potassium bichromate has been described by Joules [26]. Card published a case report of a female polisher in an electroplating shop with asthma and dermatitis. About 2 hours after intradermal testing with potassium dichromate, she developed a severe asthmatic reaction [27]. In five subjects with occupational asthma described by Olaguibel [28], positive bronchial challenges with chromium salt were observed. A case series of four subjects with suspected chromium-induced occupational asthma showed positive bronchial challenges [29]. Two of them demonstrated positive SPT with chromium sulfate. A cement floorer with work-related asthma and dermatitis to chromium was presented by De Raeve et al. [30]. The patient developed a severe bronchial reaction after the challenge; SPT was negative. Eosinophilia was demonstrated in bronchoalveolar lavage fluid after the challenge. Cases of chromium-induced occupational asthma

and allergic rhinitis were reported also by other authors, demonstrating that bronchoconstriction can be experimentally induced by inhalation of chromium containing aerosol [31, 32]. Some authors have reported serum-specific IgE antibodies to chromium [33, 34].

41.6.3 Nickel

Despite the large number of workers exposed to nickel salts, the occurrence of asthma induced by this exposure is uncommon. Most occupational asthma cases caused by nickel have been single case reports. Relatively few cases of nickel-induced asthma have been associated with or preceded by contact dermatitis, a frequent outcome of nickel sensitization [35]. No conclusions can be drawn regarding the association of nickel dermatitis and asthma due to the low number of reported cases. It has been shown that nickel ions bind to human serum albumin (HSA). Specific IgE antibodies to nickel HSA were demonstrated in a nickel-sensitized subject [36]. Many studies described positive SPT with nickel salt solutions in exposed subjects with asthma/allergic rhinitis symptoms [1]. Bronchial challenge (mainly with nickel sulfate) produced immediate-type, dual, or isolated late responses. Several of these patients also manifested an increase in bronchial hyperresponsiveness for varying periods after the nickel sulfate challenge. Employees are often exposed to nickel and chromium at the same time, and thus asthma to both metals has been described by a number of authors. Cross-reactivity to nickel and cobalt has also been suggested [31, 33, 37–39].

41.6.4 Cobalt

Asthma due to cobalt has been reported mostly in hard metal workers and diamond polishers. Cobalt interacts with oxygen to produce activated toxic oxygen species which may be important in the pathogenesis of airway changes. Kusaka et al. observed that 5% of hard metal workers had work-related asthma and reported 19 cases of occupational asthma due to cobalt. These patients developed positive bronchial challenge reactions to cobalt chloride (dual, immediate, or late reactions), but only two subjects showed positive patch test results [40]. Twenty-two cases of cobalt asthma were described in a cobalt plant in Finland. The diagnosis was based on inhalation challenge testing. SPT with cobalt chloride was negative [41]. Shirakawa et al. have described two case series of cobalt-induced asthma in the hard metal industry, showing positive bronchial reactions with cobalt chloride. The authors did not perform SPT but instead carried out intradermal testing with the same cobalt salt which showed positive reactions in six of eight cases. Patch testing was positive in two cases, and cobalt-specific antibodies were demonstrated in 11 of 12 cases [42, 43]. Kusaka et al. observed that the patients who had specific IgE antibodies to cobalt also exhibited lymphocyte proliferation responses when their peripheral blood lymphocytes were incubated with either free cobalt or a cobalt-HSA conjugate. Bronchoalveolar lavage fluid examination revealed an increase in T lymphocytes with an inverted CD4+/CD8+ ratio [44, 45]. These results suggest that cobalt-sensitized lymphocytes may play a role in the immunopathogenesis of some hard metal asthma cases. However, it should be noted that some asthmatic patients did not demonstrate either cobalt-specific IgE or sensitized lymphocytes.

We have published a case of airborne cobalt-induced anaphylaxis, contact urticaria, bronchial obstruction, and delayed skin allergy in a ceramic decorator. In this patient, positive results of SPT and patch testing with cobalt chloride were obtained. Cobalt-specific IgE was also detected in the serum [46].

Cobalt is also likely to cause hard metal disease (HMD, cobalt lung)—an interstitial pneumonia with clinical presentations resembling hypersensitivity pneumonitis and with the potential to evolve to irreversible fibrosis. Workers presenting with both HMD and asthma have been described. We described the case of a female dental technician with the simultaneous presence of cobalt-induced asthma and interstitial changes suggesting HMD [47].

41.6.5 Manganese

The first report of manganese-induced occupational asthma was described by Saakadze et al. in 1977 in the former USSR [48]. An in-depth analysis of that report revealed some issues that may have produced a false conclusion from the study. Authors used a 20% solution of manganese chloride for the provocation test, which seems to be too hypertonic for the inhalation test. It is plausible that such a solution could produce bronchial spasm due to its hypertonicity rather than an allergic reaction. Moreover, no placebo control had been performed which could confirm the specific nature of the bronchoconstriction. In 2008, we identified the first well-documented case of manganese-induced occupational asthma in a welder. Our diagnosis was based on the clinical response to a placebo-controlled specific challenge (with 0.1% manganese chloride solution) and the accompanying changes in induced sputum (an increase in the proportion of eosinophils, from 0% to 10%, and basophils, from 0% to 3%, in 24 h after challenge) [49].

41.6.6 Other Metals

There has been only one case report regarding iridium-induced occupational asthma, in a worker exposed to iridium chloride in an electrochemical factory manufacturing titanium anodes [50]. SPT with iridium chloride showed a positive reaction, but a specific challenge test was not performed. There has also been only one case report regarding asthma due to palladium salt. An exposed worker exhibited positive SPT to tetraamminepalladium chloride as well as a positive bronchial provocation test [51]. A case study of occupational asthma due to rhodium salt in an electroplater has been described. This patient showed positive SPT reactions and positive bronchial immediate-type reactions separately with rhodium and platinum salts. Sensitivity to rhodium was much higher than to platinum salt. Reaction to platinum was interpreted as co- or cross-reactivity [52]. There have been two case reports of occupational asthma due to zinc in electroplaters. Both patients showed positive SPT and bronchial reactions (but only immediate type) to zinc sulfate, with increased bronchial hyperresponsiveness after the exposure [53]. Although positive immediate tests were demonstrated in these cases, it is not certain that IgE-mediated mechanisms were involved.

41.7 Metal-Related Asthma of Unknown Immunologic Mechanism

Because of irritant properties, exposure to high concentrations of metal-containing aerosols or fumes may cause irritant-induced nonimmunological asthma without a latency period. This form of asthma is referred to as "reactive airways dysfunction syndrome" (RADS) [54]. In many cases, it is difficult to determine whether the bronchoconstriction is caused by irritation or sensitization. Therefore, diagnosis is difficult, and the resultant epidemiological data are not reliable.

The form of occupational asthma occurring in aluminum smelter workers is known as "potroom asthma." The components of the potroom environment include various substances: fluorides particularly in gaseous forms, aluminum, dust containing cryolite, sulfur dioxide, oxides of carbon, and particulate organic matter. Airway inflammation is a central feature of potroom asthma, but the causative agent and pathomechanism of this condition remain unknown [55–57].

Aluminum was documented as causing occupational asthma by Vandenplas et al. [58]. They described the case of a welder with work-related asthmatic symptoms reported to occur specifically on days he was welding aluminum. The diagnosis was based on a specific inhalation challenge that (according to the authors) excluded the role of irritant gases and other constituents. An immunologic mechanism, however, has not been confirmed.

Information about vanadium-induced asthma is available only from case reports [59]. The cases associated with the cleaning of oil tanks were called "boilermaker's bronchitis/asthma." Occupational exposure to vanadium pentoxide is

primarily an inhalation hazard causing irritation of the respiratory tract. Positive SPT results or any other immunological findings have not been described. There are no reports of controlled laboratory challenges to vanadium.

41.8 Prevention of Metal-Induced Asthma

Personal protective equipment (masks) and appropriate ventilation can prevent the penetration of metal particles into the airways. While exposure reduction may be a rational approach to the management of subjects with irritant-induced asthma due to metals, this is rarely effective for workers with occupational asthma caused by a sensitizer. A smoking habit has been shown to increase the risk of lung function impairment in workers chronically exposed to metal fumes (e.g., welders). A tobacco smoking habit has been demonstrated to play a role in airway allergy to platinum [60, 61]. Therefore, platinum-exposed workers should be encouraged to stop smoking. The effectiveness of secondary prevention by medical surveillance programs in metal-exposed workers (at precious metal refineries) has been demonstrated. It has been shown in platinum salt-exposed workers that immediate removal from exposure after SPT conversion from negative to positive resulted in a good prognosis and positive-to-negative SPT reversion [62].

Although MIA is relatively rare, it should prompt occupational health and safety services to improve diagnostic and medical certification procedures and health risk management (prevention).

41.9 Other Manifestations of Metal-Induced Lung Diseases

41.9.1 Beryllium

Beryllium is a steel gray, lightweight metal which, due to its physical properties, has several important industrial applications. Beryllium is used mainly in alloys with aluminum, copper, iron, and nickel. Workplaces with potential sources of beryllium exposure include fluorescent lamp and neon sign manufacturing, the aerospace industry, automotive parts, the defense and weapon (including nuclear) industry, electronics, telecommunication, foundries, and beryllium extraction plants. Historical data suggest that daily-weighted average beryllium exposure levels could sum up to >50 μg/m^3 during the mid-1960s and to >30 μg/m^3 during the mid-1970s. At present the time-weighted average concentrations are in the range of 0.01–1 μg/m^3. Exposure to beryllium is mostly hazardous via the cutaneous and inhalation routes as this metal and its compounds are poorly absorbed from the gastrointestinal tract. In general, inhalation exposure to beryllium compounds results in long-term storage of appreciable amounts of beryllium in lung tissue, particularly in the pulmonary lymph nodes and in the skeleton. Exposure to beryllium may induce several clinical manifestations ranging from skin changes (edematous, erythematous, and papulovesicular dermatitis, granulomatous necrotic changes, and ulcerations), acute toxicity (irritation of the skin, eye, nose, and throat, inflammation, and pneumonitis), beryllium sensitization (BeS), and chronic beryllium disease (CBD) [63].

Several epidemiological studies showed that the prevalence of BeS ranged from 1.0 to 16.2% of workers exposed to beryllium, and 0.0 to 11.0% of subjects developed CBD [64]. The risk of developing BeS/CBD is dependent on genetic predisposition, with major histocompatibility complex human leukocyte antigen (HLA)-DPB1 Glu69 and Glu71 known to be significant risk factors (odds ratio > 10). The proportion of BeS that progresses into CBD varies from 10% to 100%. It seems that the risk of progression of BeS into CBD is the highest in the early years; however, there are cases of CBD diagnosed 10 to even 40 years after the first exposure [65]. Duration of exposure and the threshold values for beryllium are of course important risk factors. More cases of BeS/CBD were reported in the 1970s and 1980s, times of high occupational exposure, and a significant decrease in BeS was found after comprehensive preventive programs were introduced [64].

The immunopathology of BeS/CBD includes several steps. After the inhalation of beryllium, antigen-presenting cells expressing MHC molecule HLA DP Glu69 or Glu71 present beryllium (probably bound to albumins as a typical hapten) to naïve CD4+ T cells, which results in the activation, proliferation, and production of several Th1-type cytokines, including IFN-γ, IL-2, and TNF-α. This cytokine mixture promotes macrophage accumulation, activation, and aggregation, which induce the development of typical noncaseating granulomas, similar to those found in sarcoidosis. The distribution of granulomas within the lung tissue mimics the pattern seen in sarcoidosis, including the subpleural areas, bronchovascular bundles, and interlobular septa. In some cases, fibrosis may develop. Beryllium-containing particles can be demonstrated within granulomas; however, this is not necessary for the diagnosis.

The primary diagnostic tool is the beryllium lymphocyte proliferation test (BeLPT). This test should be performed in experienced centers. Mononuclear cells isolated from peripheral blood or bronchoalveolar lavage (BAL) fluid are cultured in the presence of different concentrations of beryllium salts. A positive test result confirms beryllium sensitivity (BeS). Of note, it has been suggested that beryllium patch testing may not be recommended as a diagnostic tool, as this may lead to sensitization in beryllium-naïve individuals [64].

The typical clinical manifestation of lung pathology in workers exposed to beryllium includes chronic beryllium disease (CBD) in a form of granulomatous lung disease sharing several similarities to sarcoidosis (Table 41.3). The natural history of CBD is variable. In most described cases, mild airflow limitations and a slow decline in diffusing capacity are seen. Clinical symptoms comprise dyspnea, cough, and decreased exercise tolerance.

Table 41.3 Characteristics of sarcoidosis and chronic beryllium disease

Characteristic	Sarcoidosis	Chronic beryllium disease
Triggering factor	Unknown	Beryllium exposure
Primary diagnostic tools	Clinical picture, radiological picture, lung or other tissue biopsy	Beryllium lymphocyte proliferation test
Beryllium lymphocyte proliferation test	Normal	Abnormal
Onset	Acute (Löfgren's syndrome) or insidious	Insidious
Isolated hilar lymphadenopathy	Common	Rare
Extrapulmonary manifestations without pulmonary involvement	Common	None
Ophthalmologic manifestations	Conjunctivitis, uveitis, retinal involvement	Conjunctivitis only
Erythema nodosum	Yes	No
Lupus pernio	Yes	No
Neurologic involvement	Central or peripheral nervous system	None
Cardiac involvement	Occasional	Rare
Hepatic involvement	Common	Occasional
ACE (angiotensin-converting enzyme)	Increased in serum	Increased in 22–75% of patients
BAL (bronchoalveolar lavage)	Lymphocytosis common (>20%)	
First-line therapy	Systemic corticosteroids (20–40 mg/daily) only in progressive disease	
Other therapies	Steroid-sparing agents may be considered (methotrexate, azathioprine, cyclophosphamide, infliximab(?))	
Prevention	Unknown	Possible (personal protective equipment, ventilation, workplace control of exposure)

Rarely, rapid progression, including fulminant pneumonitis, or slow but irreversible advancement into fibrosis and a restrictive pattern in lung function are reported. Diagnostic criteria for CBD include confirmation of an immune response to beryllium (BeLPT) and granulomatous lung inflammation on lung biopsy. Radiographic findings are similar to those found in sarcoidosis; however, hilar or mediastinal lymphadenopathy (very typical for sarcoidosis) is rare in CBD. It is recommended that all patients with a clinical and radiographic picture of sarcoidosis are carefully questioned for potential occupational exposure to beryllium. Additional workup includes bronchoscopy with BAL and transbronchial (ultrasound-guided) biopsies.

Patients with BeS/CBD should be followed up at experienced clinical centers. In progressive cases (based on lung function or radiology), immunosuppression with systemic corticosteroids (prednisone 20–40 mg daily) is the first-line therapy; however, this recommendation is likely based on experience from sarcoid patients as no clinical trials in this cohort of patients were published. Steroid-sparing agents, similar to other interstitial lung diseases, may be of use in some cases. Prevention programs to control exposure to beryllium should be considered in all facilities where this metal is in use, with the goal of limiting inhalational and skin exposures with elimination, substitution, engineering control, personal protective equipment, and other measures. The reduction of exposure to beryllium has been proven to reduce the incidence of BeS and, as a consequence, likely CBD [64].

41.9.2 Copper Sulfate

Several cases of vineyard sprayer's lung disease have been identified and described in vineyard workers who used the "Bordeaux mixture" containing copper sulfate and slaked lime. The mixture is used as a fungicide to prevent infestation of downy mildew or powdery mildew in vineyards. The Bordeaux mixture may induce several forms of lung disease, with the most typical being hypersensitivity pneumonitis and foreign body-type granulomas [65].

41.9.3 Other Metals

Occupational exposure to other metals may induce several manifestations of lung pathology. Zirconium alloys are used in electronic industries, as a powder for polishing, and in ceramic factories. Zirconium may cause granulomatous skin disease, and some reports of granulomatous pulmonary hypersensitivity, allergic alveolitis, granulomatous pneumonia, and a disease similar to sarcoidosis/chronic beryllium disease with the confirmed presence of zirconium particles within granulomas have been published [65]. Similarly, single cases of granulomatous lung disease have been found in workers exposed to titanium and aluminum. Indium, a soft metal, is mainly used nowadays as indium oxide or indium tin oxide as a conductive coating in electroluminescent panels. A few cases of interstitial lung disease and pulmonary alveolar proteinosis (PAP) have been reported in workers involved in the production of plasma TV and monitors. Pulmonary alveolar proteinosis is characterized by accumulation of pulmonary surfactant within alveoli, interfering with gas exchange and resulting in significant restriction, reduced diffusing capacity, and a typical "crazy paving pattern" on CT scans. In sporadic cases, whole-lung lavage as a treatment is usually effective, which seems not to be the case with subjects exposed to indium. Based only on limited case reports, the role of autoantibodies against granulocyte-macrophage colony-stimulating factor (GM-CSF) remains unclear. The disease seems to progress despite limiting exposure to indium, and some fatalities have been reported [66].

Nowadays, there have been advances in science and nanotechnology implementing nanoparticles (defined as particles between 1 and 100 nanometers in size), with potential applications in electronics, optics, and medicine. Several

materials are used to create nanoparticles, including silicon, zinc oxide, carbon, gold, silver, titanium, and other metals. Physiochemical properties of nanoparticles, including small size, a high surface to volume ratio, high reactivity and catalytic properties, and the ability to pass through cell membranes, make them potentially harmful to biological systems. Several studies suggest that potential occupational exposure and nanoparticles as components of air pollution (e.g., automotive pollution produced by abrasion of catalyst materials in car exhaust systems) may be harmful to the health, although this has not been fully elucidated to date [67].

41.9.4 Hard Metal Lung Disease (HMLD)

Cobalt is a metal well known due to cobalt-based blue pigments used since ancient times in pottery manufacturing. Nowadays cobalt is mainly employed in the preparation of magnetic, wear-resistant, high-strength alloys. Cobalt sintered together with tungsten carbide is used for the grinding of other metals, including metal tools. Inhaled exposure to cobalt dust may lead to the development of a wide spectrum of lung disease, known as hard metal lung disease (HMLD). The typical clinical manifestation includes giant cell interstitial pneumonitis (GIP), with the most characteristic multinucleated giant cells engulfing other cells (macrophages and neutrophils) present in the air spaces and interstitium. These giant cells may be found in BAL or in histological lung tissue samples and are regarded as pathognomonic for GIP due to hard metal exposure. Other rare lung manifestations of cobalt exposure may present as desquamative interstitial pneumonia or bronchiolitis obliterans organizing pneumonia. Hard metal disease shares some similarities in clinical symptoms and radiology with chronic beryllium disease (CBD). In contrast to CBD, avoiding further exposure at the early stage of the disease may result in significant improvement or total remission; however, substantial fibrosis in advanced disease is not reversible [68].

Key Points

- Several metals with increasing industrial applications and thus potential occupational exposures may induce diseases of the upper and lower respiratory tract, with clinical presentations of asthma, rhinosinusitis, acute bronchitis, acute pneumonitis, carcinoma, and interstitial lung disease.
- Few metals may cause immunological asthma, and they all belong to transition metals of the fourth (chromium, cobalt, nickel, manganese, zinc), fifth (rhodium, palladium), and sixth (platinum, iridium) periods of the periodic table.
- The pathogenesis of airway allergy to metals is relatively poorly understood. The underlying immune and nonimmune mechanisms involved in asthma caused by metals or metal salts are various and have not yet been fully elucidated.
- Laboratory tests (skin and serological tests, lymphocyte proliferation test) have limited value in the diagnosis of metal-induced immunological asthma.
- Specific inhalation challenge tests play a key role in the diagnosis of metal-induced asthma.
- In the case of beryllium, the most common manifestations of allergy in the lung include beryllium sensitization and chronic granulomatous lung disease.
- Other metals such as indium, zirconium, titanium, cobalt, aluminum, and copper sulfate may sporadically induce lung pathology.
- New industrial applications and new formulations of metals, including nanoparticles, may in the near future result in unpredictable health hazards.

References

1. Merget R, Gautrin D. Metals. In: Malo JL, Chan-Yeung M, Bernstein DI, editors. Asthma in the workplace. 4th ed. London/New York: CRC Press/Taylor & Francis Group; 2013. p. 290–304.
2. Rice RH, Cohen DE. Toxic responses of the skin. In: Klassen CD, editor. Casarett and Doull's toxicol-

ogy, The basic science of poisons. New York, NY: McGraw-Hill; 1995. p. 529–46.
3. Zhang M, Jian L, Bin P, Xing M, Lou J, Cong L, Zou H. Workplace exposure to nanoparticles from gas metal arc welding process. J Nanopart Res. 2013;15:1–14.
4. Ding M, Kisin ER, Zhao J, Bowman L, Lu Y, Jiang B, Leonard S, Vallyathan V, Castranova V, Murray AR, Fadeel B, Shvediva AA. Size-dependent effects of tungsten carbide-cobalt particles on oxygen radical production and activation of cell signaling pathways in murine epidermal cells. Tox Appl Prarmacol. 2009;241:260–8.
5. Park JW, Lee IC, Shin NR, Jeon CM, Kwon OK, Ko JW, Kim JC, Oh SR, Shin J, Ahn KS. Copper oxide nanoparticles aggravate airway inflammation and mucus production in asthmatic mice via MAPK signaling. Nanotoxicology. 2016;10:445–52.
6. Huang KL, Lee YH, Chen HI, Liao HS, Chang BL, Cheng TJ. Zinc oxide nanoparticles induce eosinophil inflammation in mice. J Hazard Mater. 2015;297:304–12.
7. Park HS, Kim KH, Jang S, Park JW, Cha HR, Lee JE, Kim JO, Kim SY, Lee CS, Kim JP, Jung SS. Attenuation of allergic airway inflammation and hyperresponsiveness in a murine model of asthma by silver nanoparticles. Int J Nanomedicine. 2012;5:505–15.
8. Agricola G. De re metallica. In: Translated by Hoover HC, Hoover LH. The mining magazine. London: Mining Journal, Ltd.; 1912.
9. Brooks SM. Lung disorders resulting from the inhalation of metals. Clin Chest Med. 1981;2:235–54.
10. Malo JL. Occupational rhinitis and asthma due to metal salts. Allergy. 2005;60:138–9.
11. Farkhondeh T, Sarkhandian S, Sadikhara P. Lead exposure and asthma: an overview of observational and experimental studies. Toxin Rev. 2016;34:6–10.
12. Rosa MJ, Benedetti C, Pell IM, Filippo D, Nazarro M, Fedrighi C, Zoni S, Marcon A, Zimmermann N, Wright R, Lucchini R. Association between personal exposure to ambient metals and respiratory disease in Italian adolescents: a cross-sectional study. BMC Pulm Med. 2016;16:6.
13. Esterhuizen TM, Hnido E, Ress D. Occurrence and causes of occupational asthma in South Africa – results from SORDSA's occupational Astma registry, 1977–1999. S Afr Med J. 2001;91:509–13.
14. Wittczak T, Dudek W, Walusiak-Skorupa J, Swierczynska-Machura D, Cader W, Kowalczyk M, Pałczynski C. Metal-induced asthma and chest x-ray changes in welders. Int J Occup Environ Health. 2012;25:242–50.
15. Antonini JM, Taylor MD, Zimmer AT, Roberts JR. Pulmonary responses to welding fumes: role of metal constituents. J Toxicol Environ Health. 2004;67:233–49.
16. Huvinen M, Uitti J, Oksa P, Palmroos P, Laippala P. Respiratory health effects of long-term exposure to different chromium species in stainless steel production. Occup Med. 2002;52:203–12.
17. Rehfisch P, Anderson M, Berg P, Lampa E, Nordling Y, Swartengren M, Westberg H, Gunnarson LG. Lung function and respiratory symptoms in hard metal workers exposed to cobalt. J Occup Environ Med. 2012;54:409–13.
18. Venables KM, Dally MB, Burge PS, Pickering CA, Newman-Taylor AJ. Occupational asthma in a steel coating plant. Br J Ind Med. 1985;42:517–24.
19. Malo JL, Cartier A, Gagnon G. Isolated late asthmatic reaction due to nickel sulphate without antibodies to nickel. Clin Allergy. 1985;15:95–9.
20. Merget R, Schultze-Werninghaus G, Bode F. Quantitative skin prick and bronchial provocation tests with platinum salt. Br J Ind Med. 1991;48:830–7.
21. Merget R, Schultze-Werninghaus G, Muthorst T. Asthma due to complex salts of platinum – a cross sectional survey of workers in a platinum refinery. Clin Allergy. 1988;18:569–80.
22. Murdoch RD, Pepys J, Hughes EG. IgE antibody responses to platinum group metals: a large scale refinery survey. Br J Ind Med. 1986;43:37–43.
23. Merget R, Reineke M, Ruckmann A. Nonspecific and specific bronchial responsiveness in occupational asthma due to platinum salts after allergen avoidance. Am J Respir Crit Care Med. 1994;150:1146–9.
24. Biagini RE, Bernstein IL, Gallagher JS, Moorman WJ, Brecks S, Gann PH. The diversity of reaginic immune responses to platinum and palladium metallic salts. J Allergy Clin Immunol. 1985;76:794–802.
25. Smith AR. Chrome poisoning with manifestation of sensitization: report of a case. JAMA. 1931;97:95–8.
26. Joules H. Asthma from sensitization to chromium. Lancet. 1932;2:182–3.
27. Card WI. A case of asthma sensitivity to chromates. Lancet. 1935;229:1348–9.
28. Olaguibel JM, Basomba A. Occupational asthma induced by chromium salts. Allergol Immunopathol. 1989;17:133–6.
29. Park HS, Yu HJ, Jung KS. Occupational asthma caused by chromium. Clin Exp Allergy. 1994;24:676–81.
30. De Raeve H, Vandecasteele C, Demedts M, Nemery B. Dermal and respiratory sensitization to chromate in a cement floorer. Am J Ind Med. 1998;34:169–76.
31. Fernandez-Nieto M, Quirce S, Carnes J. Occupational asthma due to chromium and nickel salts. Int Arch Occup Environ Health. 2006;79:483–6.
32. Sastre J, Fernandez-Nieto M, Maranon F, Fernandez-Caldas E, Pelta R, Quirce S. Allergenic cross-reactivity between nickel and chromium salts in electroplating-induced asthma. J Allergy Clin Immunol. 2001;108:650–1.
33. Novey HS, Habib M, Wells ID. Asthma and IgE antibodies induced by chromium and nickel salts. J Allergy Clin Immunol. 1983;72:407–12.
34. Walters GI, Moore VC, Robertson AS, Burge CBSG, Vellore AD, Burge PS. An outbreak of occupational asthma due to chromium and cobalt. Occup Med. 2012;62:533–9.
35. Eastlander T, Kanerva L, Tupasela O, Keskinen H, Jolanki R. Immediate and delayed allergy to nickel

with contact urticaria, rhinitis, asthma and contact dermatitis. Clin Exp Allergy. 1993;23:306–10.
36. Dolovich J, Evans SL, Nieboer E. Occupational asthma from nickel sensitivity: human serum albumin in the antigenic determinant. Br J Ind Med. 1984;41:51–5.
37. Bright P, Burge PS, O' Hickey SP. Occupational asthma due to chrome and nickel electroplating. Thorax. 1997;52:28–32.
38. Cruz MJ, Costa R, Marquilles E. Occupational asthma caused by chromium and nickel. Arch Broncopneumol. 2006;42:302–6.
39. Leroyer C, Dewitte JD, Bassanets A. Occupational asthma due to chromium. Respiration. 1998;65:403–5.
40. Kusaka Y, Yokoyama K, Sera Y. Respiratory diseases in hard metal workers: an occupational hygiene study in a factory. Br J Ind Med. 1986;43:474–45.
41. Sauni R, Linna A, Oksa P. Cobalt asthma – a case series from a cobalt plant. Occup Med. 2010;60:301–6.
42. Shirakawa T, Kusaka Y, Fujimura N. Occupational asthma from cobalt sensitivity in workers exposed to hard metal dust. Chest. 1989;95:29–37.
43. Shirakawa T, Kusaka Y, Fujimura N, Goto S, Morimoto K. The existence of specific antibodies to cobalt in hard metal asthma. Clin Allergy. 1988;18:451–60.
44. Forni A. Bronchoalveolar lavage in the diagnosis of hard metal disease. Sci Tot Environ. 1994;150:69–76.
45. Kusaka Y, Nakano Y, Shirakawa T, Morimoto K. Lymphocyte transformation with cobalt in hard metal asthma. Ind Health. 1989;27:155–63.
46. Krecisz B, Kiec-Swierczynska M, Krawczyk P, Chomiczewska D, Pałczynski C. Cobalt-induced anaphylaxis, contact urticaria, and delayed allergy in a ceramics decorator. Contact Dermatitis. 2009;60:173–4.
47. Wittczak T, Walusiak J, Krakowiak A, Pałczyński C. Occupational asthma and interstitial cobalt-induced changes in a dental technician: a case report. Med Pr. 2003;54:159–64. Polish
48. Saakadze VP, Vasilov BG. Occupational bronchial asthma from exposure to manganese. Gig Tr Prof Zabol. 1977;6:19–23. Russian
49. Wittczak T, Dudek W, Krakowiak A, Walusiak J, Pałczynski C. Occupational asthma due to manganese exposure: a case report. Int J Occup Med Environ Health. 2008;21:81–3.
50. Bergman A, Svedberg U, Nilsson E. Contact urticaria with anaphylactic reactions caused by occupational exposure to iridium salt. Contact Dermatitis. 1995;32:14–7.
51. Daenen M, Rogiers P, Van der Walle C. Occupational asthma caused by palladium. Eur Respir J. 1999;13:213–6.
52. Merget R, Sander I, Van Kampen V. Occupational immediate-type asthma due to rhodium salts. Am J Ind Med. 2010;53:42–6.
53. Malo JL, Cartier A, Dolovich J. Occupational asthma due to zinc. Eur Respir J. 1993;6:447–50.
54. Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposures. Chest. 1985;88:376–84.
55. Sjaheim T, Halstensen TS, Lund MB. Airway inflammation in aluminium potroom asthma. Occup Environ Med. 2004;61:779–85.
56. Sorgdrager B, de Loof A, de Monchy J, Pal T, Dijk F. Factors affecting FEV1 in workers with potroom asthma after their removal from exposure. Int Arch Occup Environ Health. 2001;74:55–8.
57. Sorgdrager B, de Loof A, de Monchy J, Pal T, Dubois E, Rijcken B. Occurrence of occupational asthma in aluminium potroom workers in relation to preventive measures. Int Arch Occup Environ Health. 1998;71:53–9.
58. Vandenplas O, Delwiche JP, Vanbilsen ML. Occupational asthma caused by aluminium welding. Eur Respir J. 1998;11:1182–4.
59. Musk AW, Tees JG. Asthma caused by occupational exposure to vanadium compounds. Med J Aust. 1982;1:183–4.
60. Calverley AE, Rees D, Dowdeswell RJ. Platinum salt sensitivity in refinery workers: incidence and effects of smoking exposure. Occup Environ Med. 1995;52:661–6.
61. Venables KM, Dally MB, Nunn AJ, Stevens JV, Stephens R, Farrer N. Smoking and occupational allergy in workers in a platinum refinery. Br Med J. 1989;299:939–42.
62. Merget R, Caspari C, Dierkes-Globish A. Effectiveness of a medical surveiilance programme for the prevention of occupational asthma due to platinum salts. A nested case-control study. J Allergy Clin Immunol. 2001;107:707–12.
63. Jakubowski M, Palczynski C. Beryllium. In: Nordberg GF, Fowler BA, Nordberg M, editors. Handbook on the toxicology of metals, vol. 2. 4th ed. Amsterdam: Academic Press, Elsevier B.V; 2015. p. 635–53.
64. Balmes JR, Abraham JL, Dweik RA, Fireman E, Fontenot AP, Maier LA, Muller-Quernheim J, Ostiguy G, Pepper LD, Saltini C, Schuler CR, Takaro TK, Wambach PF, ATS Ad Hoc Committee on Beryllium Sensitivity and Chronic Beryllium Disease. An official American Thoracic Society statement: diagnosis and management of beryllium sensitivity and chronic beryllium disease. Am J Respir Crit Care Med. 2014;190(10):e34–59.
65. Mayer A, Hamzeh N. Beryllium and other metal-induced lung disease. Curr Opin Pulm Med. 2015;21:178–84.
66. Cummings KJ, Nakano M, Omae K, et al. Indium lung disease. Chest. 2012;13:1512–21.
67. Wilkinson KE, Palmberg L, Witasp E, Kupczyk M, Feliu N, Gerde P, Seisenbaeva GA, Fadeel B, Dahlen SE, Kessler VG. Solution-engineered palladium nanoparticles: model for health effect studies of automotive particulate pollution. ACS Nano. 2011;5(7):5312–24.
68. Nemery B, Verbeken EK, Demedts M. Giant cell interstitial pneumonia (hard metal lung disease, cobalt lung). Semin Respir Crit CareMed. 2001;22:435–48.