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Review Article

Irritant-Induced Asthma: A Literature Review

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ABSTRACT

One of occupational illnesses is irritant-induced asthma (IIA), which IIA is a phenotype of asthma caused by the inhalation of irritant agents. The incidence of IIA is reported as 5-18% of occupational asthma cases. In some cases, it is challenging to differentiate IIA from work-exacerbated asthma (WEA) because no specific diagnostic tests can determine whether a person has asthma caused by exposure to irritants. In any case of suspected IIA, the diagnosis of asthma should be confirmed by spirometry demonstrating airflow limitation with significant bronchodilator response or nonspecific bronchial hyperresponsiveness (NSBHR) to methacholine/histamine. IIA Management is similar to asthma management, including bronchodilator therapy and inhaled and/or systemic corticosteroids. Several studies recommend treating asthma in adults and adolescents with short-acting beta-agonists (SABA), adding a controller in the form of inhaled corticosteroids (ICS) as needed to reduce the risk of severe exacerbations and to control symptoms. This type of controller can be given regularly every day, or ICS-formoterol can be given as needed to relieve symptoms in mild asthma. Prevention that can be done at IIA includes health promotion, special protection, early diagnosis and early treatment, limitation of disabilities, and rehabilitation.

Keywords: Asthma, Bronchodilator, Health risk, Irritant exposure, Irritant-induced asthma, Occupational illness.

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INTRODUCTION

Rapid technological advances and industrial growth have helped boost many countries' economies. However, the industrial revolution that started in the 18th century also significantly impacted the development of occupational illness (OI) [1]. OI is a disease caused by the influence of the work environment and factors at work [2]. Workers are a high-risk group for various health problems caused by work processes, work environment, and worker behavior, so they have the potential to experience OI [3]. Various kinds of particles in the workplace can cause disease instead. Lungs and respiratory tract are the organs and systems most susceptible to exposure to these materials [4]. One of OIs is work-related asthma [5,6]. Work-related asthma (WRA) includes occupational asthma (OA) and work-exacerbated asthma (WEA) [7,8]. Furthermore, OA is grouped into sensitizer-induced asthma (SIA) and irritant-induced asthma (IIA) [9]. Diagnosis of IIA is relatively tricky, even though prompt diagnosis and early management are key factors influencing disease prognosis and socioeconomic consequences [9,10]. Therefore, this literature review would discuss IIA more.

Epidemiology

According to the International Labor Organization (ILO), every year, no less than 250 million accidents occur in the workplace and nearly 160 million workers become sick due to exposure to hazards in the workplace. Furthermore, 1.2 million workers die from workplace accidents [11]. WRA often occurs in the community, but there are difficulties in diagnosis. According to The National Institute for Occupational Safety and Health (NIOSH), approximately 17-25% of asthma in adults is work-related asthma [10,12]. Based on surveillance studies for 15 years, WRA was reported to reach 42 per million population [13]. In addition, WRA is mainly found in women, around 60% [10,14]. Meanwhile, WEA occurs in about 22% of WRA, but some studies reported the prevalence could be up to 58% [13,15]. The differences are due to the methodology as well as the type and opportunity of employment [16], in which SIA accounts for 90% of OA incidence[9,10] and IIA incidence for 5-18% of OA incidence [7,9]. Workers may develop asthma due to a history of exposure to single high levels of cleaning products, diisocyanates, reactive chemicals, wheat flour production, animal protein and latex rubber [7,17].

Definition

Experts use the term WRA for all asthma-related occupational agent exposure incidents. WRA is divided into two group, namely (1) occupational asthma (OA), asthma caused by specific workplace agents and work exacerbated asthma (WEA), asthma that is preexisting but is aggravated by exposure to nonspecific stimuli at work. The distribution of WRA can be seen in Figure 1 [16].

In contrast to OA, WEA is a state of exacerbation of asthma due to conditions at work. The diagnosis of WEA must fulfil 4 criteria, namely (1) worsening of preexisting asthma from exposure and/or unique environment at work, (2) there is a unique condition and/or exposure in the work environment that can cause asthma exacerbation, (3) the worker is exposed to the specific exposure and/or environment before his asthma worsened, (4) the exacerbation event is not included in other diagnostic criteria for occupational asthma [18].

Based on the pathogenesis, OA is divided into two groups. The first is substance sensitizer-induced OA (SIA), also known as 'immunological OA', 'allergic OA' or 'OA with a latent period'. IgE mediates the

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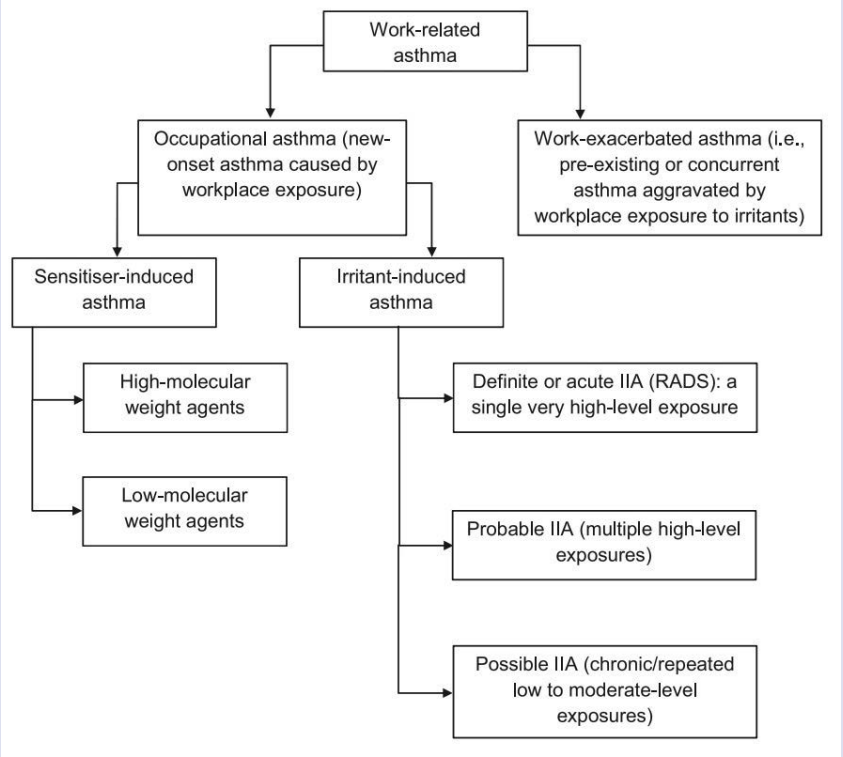

Figure 1. WRA categories [16].

immunological reactions that occur. High molecular weight (HMW) agents, including glycol, vegetable or animal protein and low molecular weight (LMW) agents, including chemicals, metals, and wood dust. The second is IIA, also known as 'OA without a latent period' or 'non-immunological OA', arising from exposure to irritant agents, either following accidental acute inhalation exposure or after repeated exposure [16].

IIA is a clinical form of asthma associated with occupational exposure to irritants. A temporal relationship between the onset of asthma symptoms and single or multiple high levels of exposure to irritants can demonstrate the relationship between irritant exposure and the development of asthma. In contrast, this relationship can only be inferred from epidemiological data for workers chronically exposed to moderate irritants. The spectrum of IIA is comprehensive, and therefore phenotype must be distinguished: (i) definite IIA, namely IIA with acute onset characterized by the rapid onset of asthma within a few hours after a single exposure to very high levels of irritants; (ii) probable IIA, namely asthma developed in workers exposed to high levels of multiple irritants; and (iii) possible IIA, i.e. asthma that occurs with a late onset after chronic exposure to moderate levels of irritants [19]. Definite IIA is also called acute IIA or reactive airways dysfunction syndrome (RADS), namely, occupational asthma without a latency period caused by a single exposure to very high levels of irritants in the form of massive aerosols, gases, vapors, or smoke without immunological sensitization [10,16,20].

Pathophysiology

The mechanism of IIA still needs to be better understood and its mechanisms still need to be fully explained and are largely speculative [16,19,21]. Inhaled irritants injure the lung epithelium and trigger an inflammatory response. Several factors can affect the lungs' response to irritants, namely the intensity of exposure, the nature of the irritant, such as vapor pressure and solubility, and chemical reactivity. Water-soluble irritants with a diameter of more than 5 μm precipitate predominantly in the upper respiratory tract. Substances that are insoluble in water and particles 0.5-5 μm can reach the distal airways and alveoli [19,22].

Irritant inhalation causes bronchial epithelial damage, produces a proinflammatory response, induces the release of reactive oxygen and alarmin, neurogenic inflammation, increased lung permeability, and airway epithelial remodeling [19]. Alarmin, secreted by epithelial, leukocytes and necrotic cells, promotes the activation of innate immune cells and antigen-presenting cells (APCs) involved in tissue repair and host defence via Toll-like receptors. Inhaled irritants can also activate the Transient Receptor Potential (TRP) channel, expressed by epithelial cells and inflammatory cells in the respiratory tract and triggers local inflammation [10].

Furthermore, irritants also activate vanilloid-1 (TRPV1) and the cation channel subfamily A (TRPA1). TRPV1 and TRPA1 are the most commonly expressed TRP channels in the respiratory tract. The TRPV1 channel can respond to capsaicin, extreme temperatures (>42^{0}C), low pH (<5.9), and hydrogen and arachidonic acid lipoxygenase products. TRPA1 is activated by cinnamaldehyde, allicin, and allyl isothiocyanate. TRPA1 acts as the primary irritant detector because it can also be activated by environmental irritants such as acrolein, tear gas, vehicle exhaust, nicotine, ozone, hydrogen peroxide and hypochlorite [19,23].

Oxidative stress is one mechanism that causes epithelial damage [19]. Oxidative stress can result in the production of interleukins such as interleukin-8 and chemokines such as monocyte chemoattractant protein-1 (MCP-1), which cause changes in neutrophilic inflammatory cells [21]. Genetic factors are also thought to play a role in IIA, as shown by the discovery of genetic polymorphisms with genes that play a role in inflammation through the NF-kappaB pathway [18].

Epithelial damage is the keyword. This damage affects the intrinsic function of the epithelium; for example, loss of cilia decreases neutral endopeptidase activity, decreases the ability of the epithelium to produce relaxant factors and initiates the release of inflammatory

mediators through activation of noncholinergic nerves, neurokinin A, neurokinin B and substance P. These effects not only cause changes in microvascular permeability but also increased mucus cell secretion, subepithelial fibrosis, structural changes of mucous glands, smooth muscle, and changes related to remodeling can be found [24].

In RADS, the produced alarmin migrates into the extracellular space as damage-associated molecular patterns (DAMPs) triggering an innate immune response. Subsequently, intracellular alarmin enters the extracellular space to trigger cellular repair and tissue healing propagated through DAMPs through mechanisms of nonallergic innate immunity. Throughout the repair process, various mediators and regulatory agents, chemokines and cytokines, arachidonic acid products, growth factors, prostaglandins, lung macrophages, and matrix components are involved [25]. The pathophysiological mechanism of RADS is shown in Figure 2 [24].

In addition to the cells above, mast cells respond to various stimuli through IL-6 and IL-8 after exposure to ionomycin. Environmental irritants can indirectly activate mast cells. Mast cells do not affect the epithelial barrier function upon environmental exposure [26]. A study on bronchoalveolar fluid IIA in mice showed an increase in the number of neutrophils compared to SIA. In mice that did not have the Nrf2- and CysLTr1 genes, they show prolonged neutrophilic inflammation and airway hyperresponsiveness. This was due to the loss of the antioxidant protective effect of Nrf2-dependent enzymes that might play a role in the pathogenesis of IIA [16,27].

From the PA results, the bronchial biopsy of IIA patients show typical epithelial desquamation, inflammation with lymphocyte predominance, airway remodeling, and collagen deposition in the bronchial walls. Although the histological changes are similar in IIA and SIA, the thickness of the basement membrane (sub-epithelial fibrosis) appears to be more extensive in IIA than in SIA [10,28]. Overall, in IIA, the pathological changes observed during the acute phase are consistent with acute toxic injury, whereas the long-term phase is similar to SIA. Bronchial biopsies in mice exposed to chlorine showed denuded epithelium with evidence of regeneration and increased smooth muscle mass [16]. The most significant difference in tissue morphometry was the increase in basement membrane thickness in subjects with IIA compared with healthy controls and subjects with mild asthma (Figure 3) [28,29].

Risk Factor

The risk factors for IIA are still largely unknown. Indirect evidence suggests that the risk of acute IIA/RADS depends on the severity of the exposure. Gas-exposed pulp mill workers are more likely to develop nonspecific bronchial hyperresponsiveness (NSBHR). It is very easy for firefighters in the World Trade Center (WTC), New York, USA attacks who are exposed to high intensity and long duration to experience asthma. Occurrences of NSBHR have also been reported in workers exposed to acetic acid spills. In both cases, atopy and smoking were not associated with the development of IIA [7,16]. A study found that workers who inhaled fire smoke or other chemicals had three times the risk of

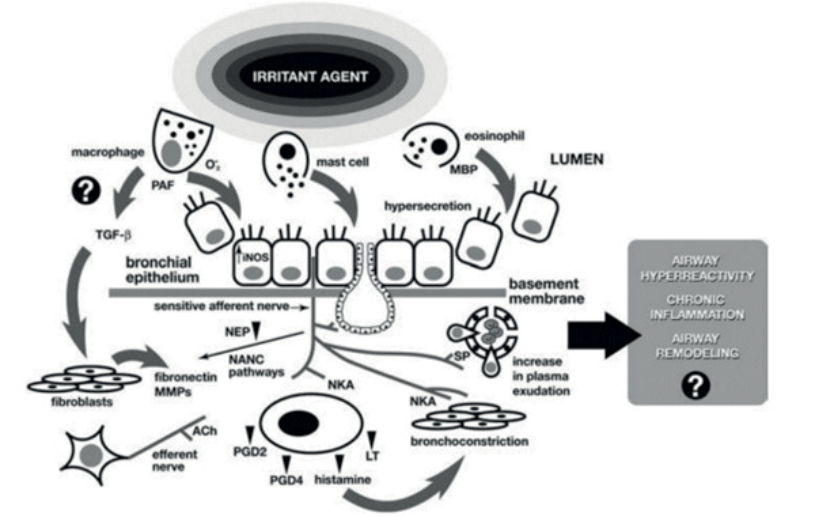

Figure 2. RADS pathophysiology hypothesis [24].

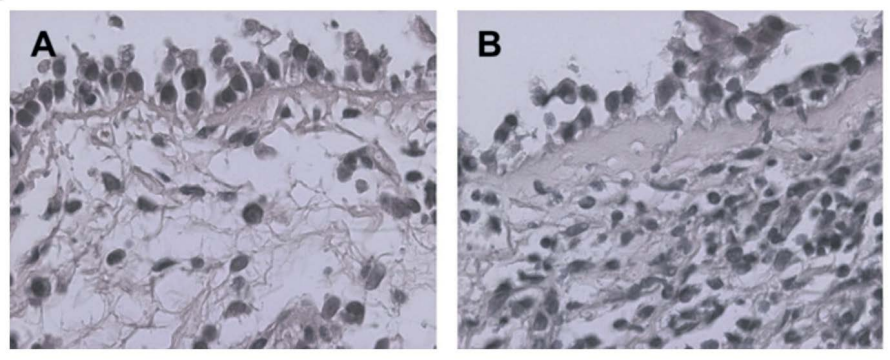

Figure 3. Representative examples of hematoxylin and eosin staining in bronchial biopsies from healthy subjects (A) and subjects with RADS (B) [28].

developing asthma. The most common agents known to cause IIA are summarized in Table 1 [10].

Diagnosis

The diagnosis of IIA is essential because this condition has health consequences and socioeconomic impacts on workers, employers, and society. Misdiagnosis of occupational asthma can lead to continued exposure and progressive worsening of asthma [30]. The European Association of Allergy and Clinical Immunology has divided the IIA phenotype into three. The first is definite/acute IIA associated with acute-onset IIA as manifested by the rapid onset of asthma within 24 hours of a very high-intensity exposure to an irritant. One example of acute IIA is classic RADS. The following two groups are probable IIA or asthma which occurs after moderate-high level irritant exposure; and possible IIA, relatively late onset of asthma after chronic and/or repeated exposure to low–moderate levels of irritants [16,19].

In any case of suspected IIA, the diagnosis of asthma should be confirmed by spirometry demonstrating airflow limitation with significant bronchodilator response or NSBHR to methacholine or histamine. The IIA diagnosis algorithm is based on the pattern of symptom onset, "acute" and "delayed/insidious", and the characteristics of irritant exposure which are categorized into "single high-level", "multiple high-level", and "chronic moderate" [19]. The diagnosis of acute onset IIA/RADS can be made based on retrospective documentation of a close temporal relationship between the incidence of inhalation and the acute onset of asthma symptoms (Table 2 [24] and Figure 4 [19]). Numerous reports describe an association between upper and lower airway symptoms following accidental exposure, leading to reactive upper airway dysfunction syndrome (RUDS) or acute irritant-induced rhinitis. Several cases of WTC events demonstrated that symptoms leading to a diagnosis of asthma could be delayed in onset for up to several months after high-level acute exposure [7,19]. The diagnosis of "probable" IIA requires some evidence of irritant symptoms at high levels of exposure. Reports can confirm peak exposure to these symptoms in the first aid unit at work, medical records of visits to general practitioners or emergency departments, and similar conditions in fellow workers [19,31].

Several clinical features differentiate acute and probable IIA from SIA. IIA subjects induced by high levels of exposure do not develop WRA after re-exposure to lower concentrations of irritants because they are not 'sensitized' to the causative agent. However, sometimes, SIA occurs due to a single exposure to the LMW agent. Specific inhalation challenges with the suspected agent may help differentiate IIA from SIA in such cases. Of note, patients with acute onset IIA may experience an exacerbation of asthma symptoms at work because newly acquired NSBHR makes them more susceptible to various irritant stimuli at work (or outside of work). Finally, unlike SIA, acute IIA does not require a latency period before the onset of asthma. Nonetheless, asymptomatic latency periods may occur when IIA occurs after multiple exposures to high levels of irritants [16,19].

In some cases, it is challenging to distinguish possible IIA from WEA because no specific diagnostic test can determine whether a person has asthma caused by irritant exposure. In patients who report steadily worsening asthma symptoms at work, workplace roles can be documented by assessing symptoms, lung function and use of medications during work and holidays or temporary removal from work. In these patients, specific inhalation challenges in the laboratory or workplace can be used to differentiate IIA, WEA, and SIA, although irritant challenge tests are poorly standardized [16,19].

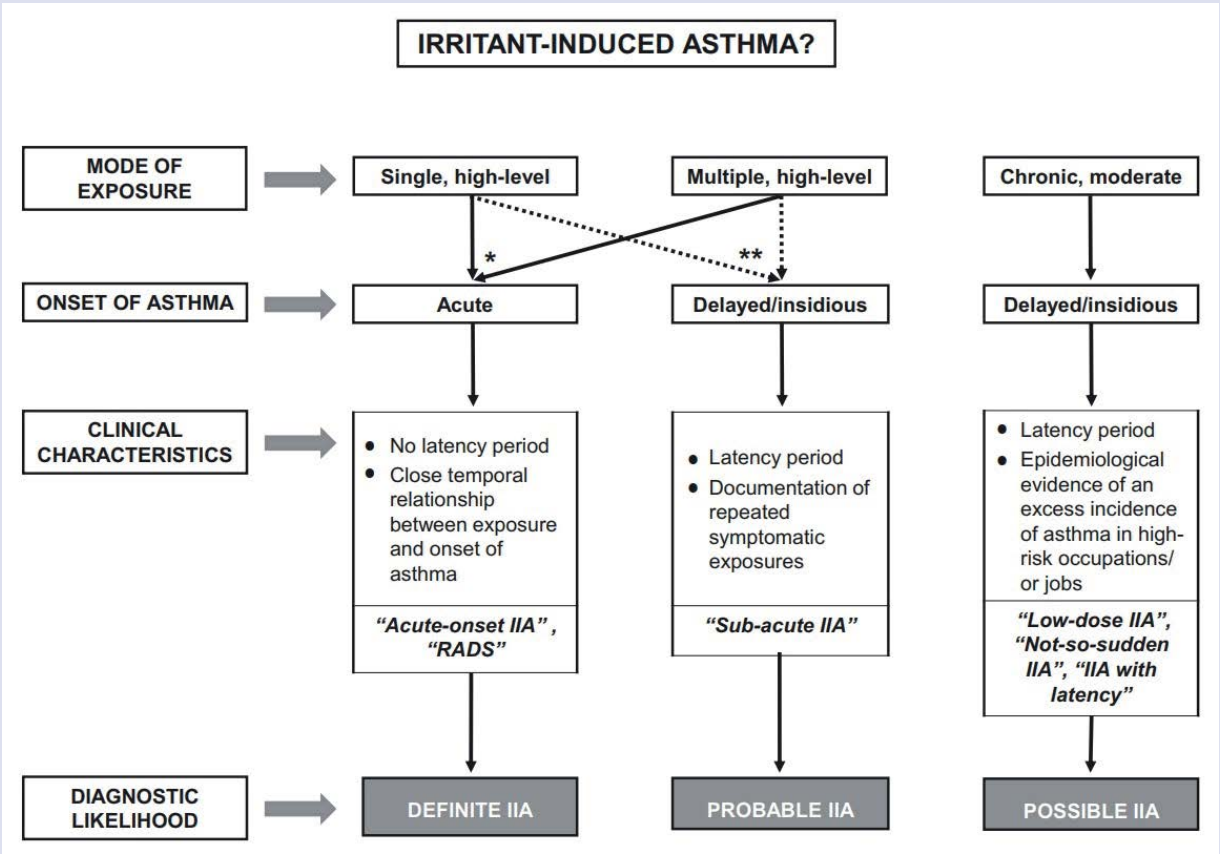

Figure 4. Proposed diagnostic algorithm to identify various IIA phenotypes. *Onset of asthma symptoms often follows a single incident of high-level exposure. **There is some evidence that asthma may develop within days to weeks after an incident of high-level acute exposure [19].

Table 1. The most frequent causative agent for IIA causes[10].

Exposure type	Examples of Irritant Agents
Acute/Definite IIA	
Gas	Chlorine (e.g., released by mixing sodium hypochlorite with acids), chloramines (released by mixing sodium hypochlorite with ammonia), sulphur dioxide, nitrogen oxides, dimethyl sulphate
Acid	Acetic, hydrochloric, hydrofluoric, and hydrobromic acids
Alkali	Ammonia, calcium oxide (lime), hydrazine
Biocide	Formalin, ethylene oxide, fumigating agents, insecticides (sodium diethyldithiocarbamate, dichlorvos)
Halogen derivatives	Bromochlorodifluoromethane (fire extinguisher), trifluoromethane, chlorofluorocarbons (CFC, thermal degradation products of freons), uranium hexafluoride, hydrogen and carbonyl fluoride
Solvent	Perchloroethylene
Steam	Diesel exhaust, paint fumes, urea fumes, fire smoke, iodine compounds (iodine and aluminium iodide, hydrogen iodide), dimethylaminoethanol (corrosion inhibitor)
Spray agent	Paints (not specified), floor sealant (aromatic hydrocarbons)
Dust	World Trade Center New York, USA alkaline dust, calcium oxide (lime)
Potential sensitizers	Isocyanates, phthalic anhydride
Subacute/Probable IIA	
Gas	Chlorine, Sulfur Dioxide (SO2), Ozone
Chronic/Possible IIA	
Cleaning agent	Bleach, ammonia, disinfectant
Pesticide	Organophosphates, methyl carbamates
Dust	Wood dust
Gas	SO2 in sulfurization or aluminium smelting, Fluorides in welding and aluminium smelting

Table 2. RADS Diagnostic Criteria[24].

Absence of previous respiratory complaints suggestive of asthma, history of asthma or asthma in remission.
The onset of symptoms occurs after a single and specific exposure, in very high concentrations and has irritant properties.
The onset of asthma symptoms occurs within minutes to hours and always <24 hours after exposure.
The exposure is gas, smoke, exhaust gas or vapor. Less often if the exposure is dust.
A positive methacholine test finding (≤8 mg/mL) after exposure indicates NSBHR.
Pulmonary function tests may show airflow obstruction.
Other pulmonary disorders causing asthma-like symptoms should be excluded (such as vocal cord dysfunction).

As a differential diagnosis, vocal cord dysfunction, hyperventilation syndrome, and multiple chemical sensitivity syndrome should be considered because they have asthma-related complaints. In patients with sinonasal symptoms, anterior rhinoscopy and nasal endoscopy should be considered to evaluate changes in the nasal mucosa that may be due to irritant exposure [16,19].

Management

Published data on the management of IIA are scarce. However, workers exposed to irritants require treatment according to clinical practice guidelines. Patients with IIA who are not-sensitized to irritants can continue to work in the same environment with appropriate asthma management and exposure prevention measures. If IIA becomes out of control, they should change their workplace [19]. Several case reports indicate that the treatment of acute IIA is almost similar to that of treatment of acute exacerbations of asthma [7,16]. Cautious administration of supplemental oxygen and montelukast (a CysLT1 antagonist frequently used in the treatment of asthma) requires caution because animal studies have reported increased lung injury and reduced inflammatory markers and airway hyperresponsiveness (AHR) [16,29].

Long-term treatment of IIA is similar to that of regular asthma. Unlike SIA patients, IIA patients can return to work in the workplace with adequate asthma management. Interestingly, at least 75% of acute IIA patients still have evidence of persistent AHR several years after exposure. Only about 17% of acute IIA patients have normal spirometry [7,16]. The Global Initiative for Asthma (GINA) no longer recommends treating asthma in adults and adolescents with short-acting beta-agonists (SABAs) alone. Controller therapy containing inhaled corticosteroids (ICS) is necessary to reduce the risk of severe exacerbations and to control symptoms. This type of controller can be given daily regularly, or in mild asthma, ICS-formoterol is given as needed for relief of symptoms [32].

RADS patients who do not respond to drug agents respond well to lidocaine nebulization therapy because it suppresses neurogenic inflammation and reflex bronchial hyperactivity. Lidocaine nebulization is an effective and safe therapy in subjects with refractory cough and mild to moderate asthma in adults and children. Other studies have shown that nebulized lidocaine functions as an anti-inflammatory and is an alternative to glucocorticoids. However, lidocaine can also cause reflex bronchoconstriction in asthmatic patients, so caution is needed, especially for the first use. It is not recommended to eat and drink for 1 hour after nebulization because of the anesthetic effect. A safe dose for nebulization is between 100 and 200 mg per dose [33].

Prevention

Various preventive measures need to be taken to prevent or reduce the disease rate. Five general levels of prevention are:

1) Health Promotion

The initial prevention step is introducing the work environment so that workers can know the hazards in their work environment and take precautions.

a. Company doctors must make a mitigation (risk matrix) of exposure the work area, work place modification, and inform workers about agents that can cause lung disease.

b. Establishing an educational program on protection and care that includes information on healthy lungs and work-related lung diseases.

c. Providing self-introduction about lung disease and the use of protective procedures.

d. Organizing recreation to a place with excellent air quality so that the lungs of the workforce are not always exposed to the agent.

e. Placing proper and sufficient ventilation positions when the workplace is closed.

2) Specific Protection

a. Creating good working conditions and good sanitation.

b. Health checks are carried out before placement and periodically, at intervals of 6 months to 2 years, depending on the workplace exposure level.

c. Workers must wear masks and are prohibited from smoking.

d. Isolating the source so as not to emit dust in the workspace with or without a water sprayer on the chimney.

e. Substituting dust-generating devices.

f. The wet method with floor sprinkling and wet drilling.

3) Early diagnosis and prompt treatment

a. Recruiting workers who do not have the risk of lung disease.

b. Checking lung function to obtain an overview of the development of the workforce's health.

c. Completing medical history, including occupational and environmental exposure history

d. Investigations include a complete blood count, electrocardiography, chest X-ray, spirometry, single breath diffusing capacity, CT scan of thorax, bronchoalveolar lavage, and others.

4) Disability limitation

a. Appropriate therapy to stop the disease and prevent complications and disability.

b. Preventing progression and anticipate complications such as smoking cessation and tuberculosis prophylaxis in silica workers.

c. Provision of facilities to limit disability and prevent death

d. Providing time off or leave for employees who are sick for treatment.

5) Rehabilitation

a. Placing workers with lung disease in places with no risk of worsening their lung conditions.

b. If they cannot be transferred, workers with lung disease are given extra protection, such as wearing unique masks and giving a relatively short time to avoid prolonged exposure to agents that cause lung disease and worsening lung conditions.

Providing extra protection in places that are at risk of causing lung disease [34].

CONCLUSION

One of the occupational lung diseases that need attention is occupational asthma, especially the OA-IIA type. Forms of asthma associated with exposure to irritants at work. Inhaled irritants injure the lung epithelium, triggering an inflammatory response characterized by neurogenic inflammation, increased lung permeability, and airway epithelial remodeling. The diagnosis of IIA is crucial because workers with IIA still have the possibility of working in that place as long as they use sound prevention principles and adequate asthma management. Management of IIA is similar to that of asthma, including bronchodilator therapy and inhaled and/or systemic corticosteroids. Finding the risk factors underlying the OA-IIA mechanism is a common challenge. Linking the genes involved in injury processes in the epithelium could uncover the pathogenesis of IIA.

AUTHOR CONTRIBUTION

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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CONFLICTS OF INTEREST

Yoni Frista Vendarani and Wiwin Is Effendi declare that they have no conflict of interest.

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