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Invited Review Article

Japanese guidelines for occupational allergic diseases 2020☆

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ABSTRACT

Occupational allergic diseases are likely to worsen or become intractable as a result of continuous exposure to high concentrations of causative allergens. These are socioeconomically important diseases that can lead to work interruptions for patients and potentially job loss. We published the first guideline for managing occupational allergic diseases in Japan. The original document was published in Japanese in 2013, and the following year (2014) it was published in English. This guideline consists of six chapters about occupational asthma, occupational allergic rhinitis, occupational skin diseases, hypersensitivity pneumonitis, occupational anaphylaxis shock, and the legal aspects of these diseases. Providing general doctors with the knowledge to make evidence-based diagnoses and to understand the occupational allergic disease treatment policies, was a breakthrough in allergic disease treatment.

Due to the discovery of new occupational allergens and the accumulation of additional evidence, we published a revised version of our original article in 2016, and it was published in English in 2017. In addition to including new knowledge of allergens and evidence, the 2016 revision contains a "Flowchart to Diagnosis" for the convenience of general doctors.

We report the essence of the revised guidelines in this paper.

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1. Significance and characteristics

The "Japanese guideline for diagnosis and management of occupational allergic diseases 2013" contained the first clinical practice guidelines for occupational allergic diseases in Japan. Traditionally, only doctors with specialized knowledge of occupational allergic diseases were able to diagnose and treat affected patients. The 2013 guidelines were a breakthrough in patient care because they provided general doctors (not only specialists) with the knowledge to diagnose and treat patients with occupational allergic diseases. Including occupational allergic disease guidelines in a single volume with information from several departments was also uncommon internationally.

The discovery of new occupational allergens and the accumulation of additional evidence necessitated a new version of the 2013 guidelines. The Japanese Society of Occupational and Environmental Allergy organized the Committee for Japanese Guideline for Diagnosis and Management of Occupational Allergic Diseases, which published a revision titled "Japanese guideline for diagnosis and management of occupational allergic diseases 2016." The 2016 version included new knowledge and evidence, and a "Flowchart to Diagnosis" for the convenience of healthcare professionals.[1]

☆ This article is an updated version of "Japanese guidelines for occupational allergic diseases 2017" published in Allergol Int 2017:66:265-80.

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[1] The members of Japanese Guideline for Diagnosis and Management of Occupational Allergic Disease are listed at Appendix A section.

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Similar to the 2013 guidelines, the 2016 version is designed to assist healthcare professionals that practice ordinary diagnosis and management of allergic diseases with transitioning to early prevention, diagnosis, and treatment practices in patients with occupational allergic diseases. We hope that these guidelines will improve the care of patients with occupational allergic diseases.

The guideline has a basic structure in which clinical questions (CQ) are answered by referencing the Medical Information Network Distribution Service (MINDS), statements by the committee are listed, recommendation grades and evidence levels are defined, descriptions and references are indicated, and legal aspects are written in full.

Technical innovation and changing work environments provide opportunities for new occupational asthmas to arise. We will continue to revise the guideline every three years in order to maintain relevant evidence.

In this paper, recommended grades are written in parentheses following each statement, as shown in Table 1.

2. Occupational asthmas (Fig. 1)

2.1. Definitions and classifications

CQ1: *What are the definitions and classifications of occupational asthmas?*

Asthmas related to occupations are called "work-related asthmas (WRAs)." These can be classified into "occupational asthmas (OAs)" and "work-aggravated (exacerbated) asthmas." OAs are those related to occupations and caused by allergens existing in the workplace. OAs can be further divided into "sensitizer-induced asthmas," which are associated with an immunological and allergic mechanism, and "irritant-induced asthmas," which occur due to aspiration of a large quantity of an irritant at the workplace. Irritant-induced asthma: IIA is classified into acute-onset IIA, Probable IIA and Possible IIA.[2] Work-aggravated (exacerbated) asthmas are those preexisted and aggravated by gas, cool air, or dust aspirated at the workplace.[3] In Japan, work-aggravated (exacerbated) asthmas are generally not included in OAs [Minds Grade A].

2.2. Prevalence

CQ2: *What is the population attributable risk for occupational factors in adult asthmas?*

The proportion of population-attributable risk of occupational factors in adult asthmas is approximately 15%.[4]

CQ3: *How does the prevalence by occupation group in cross-sectional studies?*

High prevalence rates are found in painters (isocyanate); bread and needle makers; nurses; those who work with chemicals; animal handlers; welders; those working in food-processing, and lumbering; and so forth (Table 2).

2.3. Allergens

CQ4: *What are causative allergens?*

Causative allergens are divided into allergens of high molecular weight, such as those derived from animals and plants, and allergens of low molecular weight, such as chemicals and metals [A].

Table 1
Recommended grades.

Grades	Meaning
A	Strongly recommended to apply
B	Recommended to apply
C1	Should apply
C2	Should not apply
D	Recommended not to apply

CQ5: *What is the standard for a causative allergen designation?*

For allergens reported in Japan, the evidence levels are defined as shown in Table 3 and are written as individual causative substances (Table 4). As for epidemiologic studies, cases that the prevalence in specific occupational group is reported were made "Present."

CQ6: *What types of allergens in conventional OAs were most common?*

Substances derived from animals or plants [C1].

CQ7: *What allergens have increased recently?*

Minerals and low molecular weight substances[3,5] [C1].

CQ8: *What are the problems in OAs caused by chemicals?*

Because the specific immunoglobulin E (IgE) antibody cannot be easily detected, diagnosis is difficult[6] [A].

CQ9: *What is the influence of genetics?*

The disease occurs as a result of some interaction between multiple genetic factors and environmental factors. It can be expected that understanding molecular pathologic conditions of OAs will advance by identifying genetic factors and that preventive measures such as setting environmental exposure limits according to individual onset risks will be practiced [C1].

CQ10: *What are risk factors?*

Heredity, exposure to high concentrations of causative substances with high frequency, atopic diathesis, and smoking [C1].

2.4. Diagnosis

CQ11: *What is the most important factor in diagnosis?*

(1) Suspecting an OA. Questioning the patient is most important [A].
(2) In diagnosis of sensitizer-induced asthma, the diagnosis rate increases with the combination of multiple examinations as well as medical history[7] [A].
(3) Diagnosing it as early as possible[8] [A].

CQ12: *Are questionnaires useful for definitive diagnoses?*

Although useful, the specificity of questionnaires is low[9] [A].

CQ13: *Is peak flow useful for definitive diagnosis?*

It is useful. The daily continuous peak flow measurement has a high sensitivity and specificity in the diagnosis of OA, and is thus the most useful method[10] [A]. However, because accurate peak expiratory flow rate monitoring depends on patient effort, the reliability of the data should be considered.

CQ14: *Is the non-specific airway hypersensitivity test useful for diagnosis?*

(1) Airway hypersensitivity changes associated with occupations are helpful for diagnosis [B].
(2) It is desirable that, in the same patient, the standard method test is conducted at the same facility [B].

CQ15: *Are changes in eosinophils and neutrophils in induced sputum useful for diagnosis of occupational asthma?*

Changes in eosinophils and neutrophils in induced sputum are useful for the diagnosis of occupational asthma [B].[11]

CQ16: *Is the allergen inhalation challenge test necessary for definitive diagnosis?*

(1) It is the gold standard for diagnosing sensitizer-induced asthma, and is thus useful for identifying new allergens [C1].
(2) Because it is risky, use of the allergen inhalation challenge is not essential when diagnoses can be made with other methods [C1].

CQ17: *Are immunological examinations useful?*

(1) They are useful for identifying high molecular weight allergens in sensitizer-induced asthma [A].
(2) They are not useful for identifying low molecular weight allergens [C2].

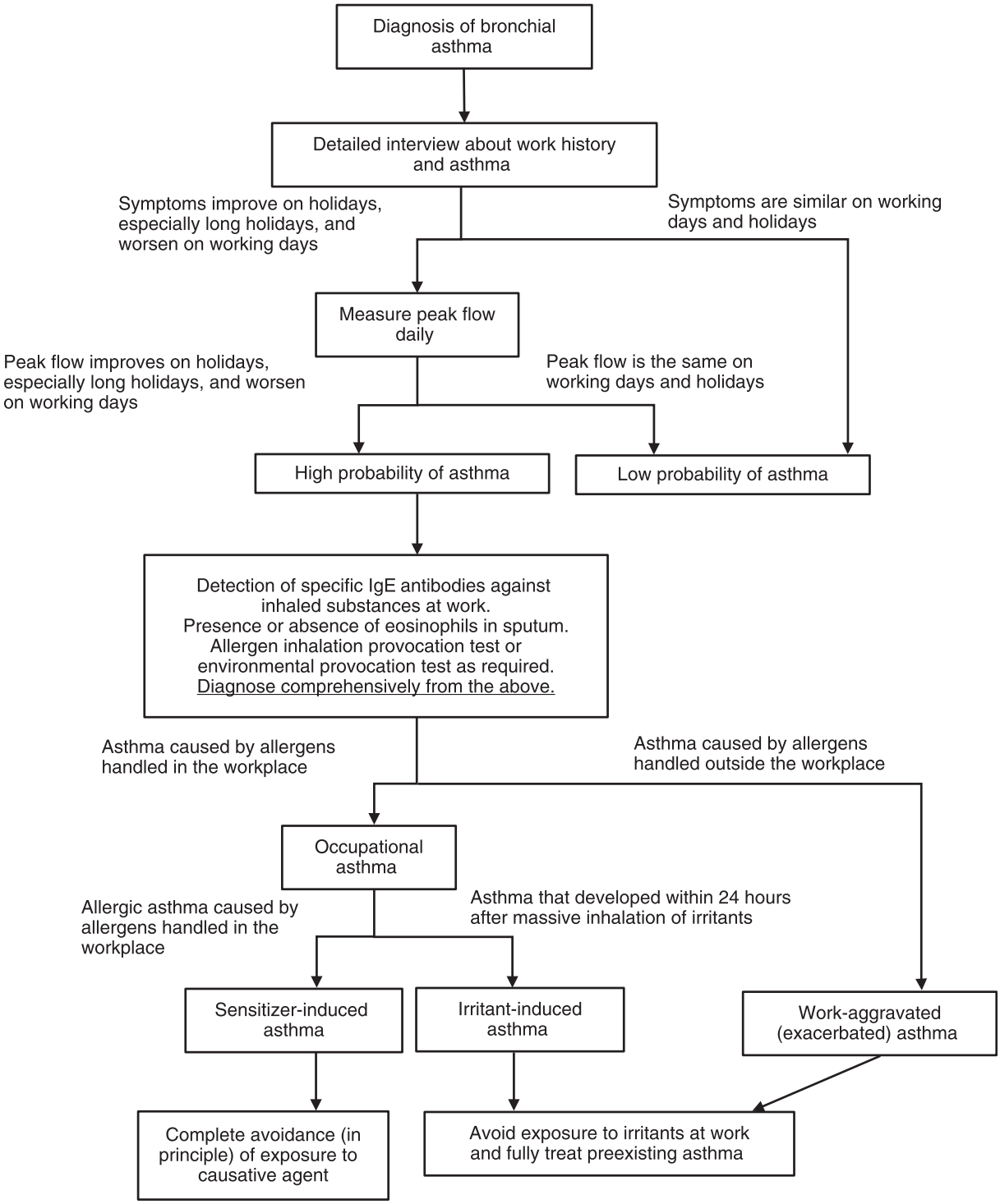

Fig. 1. Work-related asthma diagnostic flowchart.
From reference.[1]

2.5. *Treatment and management*

CQ18: *Are management methods by classification useful?*
This question is outlined in Table 5[3,5,8] [B].

CQ19: *Is avoidance of causative allergens effective?*
Yes, it is effective [B].

CQ20: *How does the drug treatment proceed?*

Treatment of asthma is conducted according to the Asthma Prevention and Management Guidelines regarding diagnosis and management[12] [B].

CQ21: *Can one continue working if a drug treatment is conducted?*

(1) It is not recommended to conduct the drug treatment alone without changing the working environment [A].

Table 2
Incidence of occupational asthmas in main occupational groups according to cross-sectional studies.

Occupation/exposed antigen	Number of cases	Incidence (%)	Country
Snow crab processors	303	15.6	Canada
Guar gum (natural polysaccharide)	151	3.0	Canada
Painters (isocyanate)	730	7.1 (All subjects were non-smokers.)	Italy
Poultry workers	134	11.0	South Africa
Rats allergens	113	4.4	France
Natural rubber latex (health care workers in general hospital)	196	7.1	Italy
Florists	128	14.1	USA
Supermarket bakery workers	66	9.0	UK
Strawberry growing industry workers	43	4.7	Japan
Oyster shucker (Sea squirt)	250–417	18.0–36.0	Japan
Nurse	4634	10.7	Japan

Adapted from reference.[5]

Table 3
Classification of evidence levels.

Panel Consensus	Evidence levels	
	Overseas	Japan
Epidemiologic studies and analyses of antigens have been published	(1)	(1)
Multiple case reports have been presented	(2)	(2)
One case is reported	(3)	(3)

(2) For irritant-induced asthma or work-aggravated asthma, another consideration is that when asthma control is done through drug treatment, the same work might be continued with reduced exposure to the causative agent [C1].

CQ22: *Is allergen-specific immunotherapy effective?*

When subjects have sensitizer-induced asthma, it is effective for some causative agents [B].

CQ23: *To confirm regarding symptoms or improvement in respiratory function after avoidance of exposure to an allergen, how long a follow-up period is necessary?*

Several years are necessary after avoidance of the causative agent[13] [A].

CQ24: *What are conditions that facilitate symptom alleviation and enhance respiratory function after avoiding exposure to allergens?*

Those conditions include the respiratory function at the time of diagnosis, exposure period to a causative agent, and age at time of diagnosis[14] [A].

2.6. Prevention

CQ25: *What is the highest priority in the management and prevention of hazardous working environments?*

Complete avoidance of inhaled allergens at the early stage is paramount. This can be achieved by changing to less sensitizing alternative agents or completely sealing off relevant areas[3,5,15] [A].

CQ26: *Is it useful to reduce exposure to allergens by setting up ventilation devices at the workplace?*

Although it is effective, complete avoidance is more effective [B].

CQ27: *Is it effective to substitute materials with lower allergenicity or without allergenicity?*

If materials with no or lower allergenicity can be used, it will be as effective as either a reduction or complete avoidance of exposure to allergens [A].

CQ28: *Is the risk assessment of chemicals provided in the Safety Data Sheet (SDS) important?*

Risk assessment of chemicals is important [A].

CQ29: *Is it effective to wear a gas protection mask, dust protective masks, protective clothing, and so forth at the workplace?*

It is effective for avoiding and reducing exposure to allergens [B].

CQ30: *Is it effective to inspect for the presence or absence of atopy before employees begin working?*

This might not always be effective[14] [C1].

CQ31: *Is education on occupational health effective as a preventative measure?*

It is effective to educate about the symptoms of OA, exacerbation factors, protective tools, treatment, and so forth [B].

CQ32: *Is it effective for industrial physicians to conduct an inspection tour through workplaces once or more per month?*

It is effective that industrial physicians conduct a tour inspection through workplaces, evaluate management of working environment at workplaces and management of works, and advise and recommend business owners at a health and safety committee meeting [C1].

3. Occupational allergic rhinitis (Fig. 2)

3.1. Definition

CQ1: *What is the definition of occupational allergic rhinitis?*

(1) Occupational allergic rhinitis is defined as allergic rhinitis induced, caused and worsened by inhaling work-derived agents into the nasal cavity.[16]
(2) Allergens are not limited to workplace-specific substances.
(3) Allergic rhinitis is an allergic disease with three main symptoms—sneezing, watery rhinorrhea, and nasal stuffiness—which are mediated by IgE.
(4) In Japan, it will also be necessary to make efforts to deal with occupational rhinitis under a broader definition, which includes occupational non-allergic rhinitis.

3.2. Classification

CQ2: *How is occupational allergic rhinitis classified?*

(1) Type I in the Coombs & Gell Classification has been reported, and types IV and III are possible.
(2) Allergens are not limited to the workplace; they might exist in the general public.
(3) There are classifications of severity and disease type, which are important for treatment.

3.3. Epidemiology

CQ3: *What is the prevalence of occupational allergic rhinitis?*

Overseas, the prevalence has been reported to range from 0.2% to 16.1% according to exposed allergens in individual occupations. In Japan, the incidence rate of occupational allergic rhinitis among all allergic rhinitis cases is reported to be 0.6–3.0%.[17]

3.4. Causes

CQ4: *What are causative allergens for occupational allergic rhinitis?*

Animals, plants, chemicals, and so forth[18] [A].

CQ5: *What are the criteria for certifying causative allergens of occupational allergic rhinitis?*

It is diagnosed through a combination of doctor's questions, immunological examinations, and a nasal mucosa test[18,19] [A].

CQ6: *Are causative allergens of occupational allergic rhinitis changing?*

Both type and incidence rates have been changing due to changes of industrial form and working environment.

Table 4
Aspirated substances and occupations assumed to induce occupational asthma.

Aspirated substances inducing occupational asthmas	Occupation or other	Evidence levels	
		Overseas	Japan
A. Plant-derived			
I. Powder dust			
1. Grain dust			
Konjac flour	Makers of konjac	(3)	(1)
Buckwheat flour	Soba noodle business Soba noodle makers and distributors	(1)	(1)
Wheat flour	Baking industry, noodle makers, rice millers	(1)	(1)
Barley flour	Workers for milling factories	(1)	(1)
Animal feed dust	Animal feed business		(3)
Rice	Families of rice millers	(2)	(3)
Rice bran	Rice millers		(2)
Rice straw	Rice farmers, tatami mat makers	(1)	(3)
2. Wood dust			
Red cedar	Red cedar wood industry	(1)	(1)
Clethra	Woodworkers		(2)
Zelkova	Woodworkers		(1)
Mulberry tree	Furniture makers		(3)
Magnolia	Wood industry		(3)
White birch	Disposable chopsticks makers	(1)	(3)
Lauan	Wood industry		(1)
Chinese quince	Furniture makers		(1)
Rosewood	Furniture makers		(1)
Paulownia	Lumber/wood industry		(1)
Japanese oak	Oak lumber producers		(3)
Yellow pine/other pines	Carpenters	(1)	(2)
Box	Furnishing producers		(3)
Japanese cedars	Wood processors, paper processors	(1)	(3)
Ayous	Carpenters	(2)	(3)
White ash	Furniture workers/carpenters	(2)	(3)
Sengon laut	Furniture workers/carpenters		(3)
3. Other powder dust			
Unseasoned Japanese angelica tree sap dust	*Taranome* producers		(3)
Cotton dust	Drop curtain/flag makers	(1)	(2)
Coffee bean dust	Traders handling these beans	(1)	(1)
Chinese sesame non-oil ingredients	Quality inspection workers	(1)	(3)
Powder dust of sunflower seeds, Lenovatole (cosmetics containing sunflower seeds)	Confectioners handling sunflower seeds, beauticians using lenovate essence containing sunflower seeds	(3)	(3)
Shoot of tea, downy hair of new leaves	Tea-picking workers		(2)
Tea packing business (overseas), green tea components (Japan)	Tea makers	(1)	(1)
Downy hair and pollen of mum	Mum planters in plastic greenhouses		(3)
Components of statice flowers	Statice planters	(3)	(3)
Tomato stems	Planters in plastic greenhouses	(1)	
Lettuce leaves	Planters in plastic greenhouses	(1)	(2)
Stems and pollen of Japanese butterbur	Intake of Japanese butterbur		(3)
Mellon crusty trichome	Planters in plastic greenhouses	(2)	(2)
Pepper	Food processors	(1)	(3)
Indian rice flour	*Kamakura-bori* workers (Indian rice users)		(3)
Smoke of tabaco	Resort hotel workers		(3)
II. Pollens and spores			
1. Occupational pollinosis			
Sugar beet pollen	Staff in sugar beet research institutes	(1)	(3)
Rose pollen	Staffs in rose research institutes		(3)
Hogweed pollen	Hogweed pollen researchers	(1)	(1)
Cocksfoot pollen	Commercial growers of cocksfoot for cow feed	(1)	(1)
Italian ryegrass pollen	Cattle breeders	(2)	(2)
Strawberry pollen	Strawberry growers in plastic greenhouses	(1)	(2)
Peach pollen	Flower pickers at peach fields	(1)	(2)
Pear pollen	Pear growers (flower picking, anther release, artificial mating)		(1)
Apple pollen	Hand pollinators	(1)	(1)
Cosmea pollen	Florists handling cosmeas		(3)
Mum pollen	Mum growers with electric illumination in plastic greenhouses, Buddhist monks frequently handling mums at temples	(2)	(2)
Insect flower pollen	Insect flower growers on the Setonaikai coast		(2)
Grape pollen	Workers growing grapes in plastic greenhouses and shaking shelves to spread the pollen		(2)

(*continued on next page*)

Table 4 (*continued*)

Aspirated substances inducing occupational asthmas	Occupation or other	Evidence levels	
		Overseas	Japan
Umbrella pine pollen	Distributors of umbrella pine for gifts at Koyasan		(3)
Green pepper pollen	Green pepper quick growers in plastic greenhouses	(1)	(3)
Cedar pollen	Workers of electric companies who conduct inspections and look around of transformer stations located at cedar forests		(1)
Corn pollen	Dairy farmers who raise corn as feed	(1)	(3)
Cape marigold pollen	Cape marigold growers in plastic greenhouses		(3)
Gloriosa pollen	Gloriosa growers in plastic greenhouses	(3)	(3)
China grass pollen	Sellers of diagnostic products for the China grass pollinosis		(1)
Fennel, blue lace, lace flower	Flower arrangement specialists using umbelliferae		(3)
Rice pollen	Personnel at rice cropping test organizations	(1)	(2)
Tomato pollen	Tomato growers in plastic greenhouses	(3)	(2)
Strelitzia reginae pollen	*Strelitzia reginae* growers for ornamental use in plastic greenhouses		(3)
2. Spores			
Shiitake mushroom spore	Shiitake mushroom growers in plastic greenhouses	(1)	(1)
Club moss spore	Dental technicians using lycopodium for making artificial teeth	(2)	(3)
	Policemen using lycopodium for collecting fingerprints		
Wheat smut fungus spore	Farmers growing wheat (crop season)		(3)
3. Fungus			
Trichophyton (fungus)	Judo bonesetter coming into contact with tinea patients	(1)	(3)
B. Animal-derived			
1. Arthropod, insects			
Sericultural industry			
Mature silkworm urine	Sericulturists using mabushi		(1)
Scary hair of moth of silkworm	Sericulturists		(1)
Carp food	Carp growers		(2)
Dried pupas	Silk handlers	(1)	(1)
Bee poison	Silk sericin	(1)	(3)
Trichopteran powder dust	Fishing gear business capturing Trichopteran as fishing food	(1)	(1)
House dust mite antigen	Researchers working toward the separation and purification of house dust mite antigens	(1)	(1)
Tetranychidae, mandarin orange spider mite	Workers cultivating *yuzu*	(1)	(1)
Pupas of arrowhead Coccoidea	Workers who clip mandarin orange trees		(3)
2. Fish			
Ricinus lees, fish lees powder dust	Farmers using mixed feed		(3)
Shrimp powder dust	Dried shrimp makers	(1)	(3)
Sardine powder dust	Dried sardine makers	(1)	(3)
3. Birds			
Chicken farming			
Chick feathers	Chick hatching stations		(2)
Poultry manure and chicken feathers	Poultry dealers	(2)	(3)
4. Mammals			
Human dander	Persons in charge of cosmetic at the cosmetic companies, hairdressers	(1)	(3)
Pig stool powder dust	Pig industry	(2)	(3)
Dog skin	Managers of animal hospitals		(3)
Cat skin	Managers of animal hospitals		(3)
Cow hair	Cattle farmers	(2)	(3)
Cow hair/furfur	Horse-riders, family of people who work in stables	(1)	(3)
Animal hair	Hair pencil makers		(2)
Japanese deer hair	Persons handling deer hair	(3)	(2)
Sheep wool	Persons handling sheep wool	(3)	(3)
Furfur of guinea pig, rabbit, mouse, dog, rat and body components of frogs	Personnel raising animals in university laboratories, researchers who experiment on frogs	(1)	(1)
5. Other			
Body components of ascidian	Oyster shuckers		(1)
Soft coral denronephthytia nipponica	Crawfish fishermen		(1)
Shell powder dust	Shell polishers	(1)	(3)
Pearl powder dust	Workers who form necklace holes at peal processing factories		(2)
Plumularia filicaulis var. japonica	Seaweed culturing workers		(1)
C. Drugs and food			
1. Drug powder dust			
Diastase, gentian, thyradin	Pharmacists		(1)
Pancreatin	Pharmacists		(3)
Matromycin, sigmamycin	Pharmaceutical company employees		(3)

Table 4 (*continued*)

Aspirated substances inducing occupational asthmas	Occupation or other	Evidence levels	
		Overseas	Japan
Penicillin	Person in charge of experiments at the pharmaceutical company	(2)	(3)
Kallikrein	Pharmaceutical factory employees		(2)
Gastropylore	Pharmacists		(3)
INAH	Pharmacists preparing isoniazid	(3)	(3)
Trapidil, ticlopidine	Pharmacists		(3)
Cetraxate hydrochloride pantothenic acid	Pharmaceutical factory employees		(2)
2. Foods			
Stevia powder	Traders adding stevia to sucrose		(3)
Galacto-oligosaccharide	Traders of oysters removed from their shells		(1)
Glycyrrhiza powder dust	Workers extracting pigment from glycyrrhiza	(3)	(3)
Dokusogan ingredients such as glycyrrhiza and smilax glabra	Person in charge of manufacturing at the pharmaceutical company		(3)
Honey	Families of apiary workers	(1)	(3)
Royal jerry	Traders dividing royal jerry into sacks		(3)
Bacillus subtilis (enzyme-containing cleanser)	Cleaning business using enzyme-containing cleansers	(1)	(1)
Oxygen products containing amylase as a main component (diastatic enzyme products for making alcohol)	Sake brewers		(3)
Milk-curdling enzyme rennin (for making cheeses)	Cheese plant employees	(1)	(3)
Lysozyme, glycine, glucono delta lactone	Food preservative manufacturers	(3)	(2)
Food additive powder dust (pearl meat F, FR powder) (main component: egg white)	Employees handling food additives at meat processing factories	(3)	(2)
D. Metals and chemicals			
1. Chemicals			
Dyestuffs			
Dyestuff intermediates, chicago red, pyrazolone derivatives	Employees of dye-stuff factories	(3)	(3)
Reactive dyestuffs, Reactive Orange 7	Employees of dye-stuff factories		(3)
Arabian rubber powder dust	Printing factory workers	(2)	(3)
Isocyanate			
Toluene diisocyanate (TDI), methylene bisphenyl isocyanate (MDI), hexamethylene diisocyanate (HDI)	Polyurethane resin factory workers, students making figurative objects with urethane resin, orthopedists fixing plaster casts, house painters using coating reinforcement agents	(1)	(1)
Cyanoacrylate adhesives (Aron Alpha®), Cyanon	Makers of ear pieces for acoustic aid, plate makers	(2)	(2)
Anhydrous pyromellitic acid	Traders handling anhydrous pyromellitic acid as a raw material for heat-resistant resin synthetics	(1)	(3)
Stimulation of anti-rust oil	Welders aspirating smoke of anti-rust oil at the time of welding	(2)	(3)
2. Metals			
Chrome			
Chrome in cement	Cement factory workers	(3)	(1)
Bichromate of soda, etc.	Metal factory workers, coating factory workers	(1)	(3)
Chloroplatinic acid	Makers of platinum oxygen sensors (automobile internal combustion)	(1)	(1)
Tungsten, etc.	Workers at factories making cemented carbide tools		(1)
Cobalt	Workers at factories making cemented carbide tools	(1)	(3)

Adapted from reference.[1]

CQ7: *What are problems related to chemical-induced occupational allergic rhinitis?*

Because specific IgE antibodies cannot be easily detected, diagnosis is difficult[18] [A].

CQ8: *What are the mechanisms for the occurrence of occupational allergic rhinitis?*

(1) It is a disease whose allergic immunologic mechanism and process are most clearly defined, and is only a precious human model of pure allergic disease induced by single allergen.
(2) Although essential differences in the mechanism have not been indicated, there are some cases of intense exposure to allergens at the workplace that are substantially different from ordinary situations.
(3) Some cases have reported a genetic predisposition in which biophylactic reaction symptoms are mediated by an IgE antibody.

3.5. Treatment

CQ9: *What are characteristic problems for the avoidance of allergens for occupational allergic rhinitis?*

(1) Continuous exposure to allergens at workplaces leads allergic rhinitis to develop asthma, which is a severe airway disease [C1].
(2) Continuing work might become difficult [C1].
(3) The disease restricts the patient and brings about issues such as a reduction in productivity [C1].

CQ10: *Are drug therapies effective for occupational allergic rhinitis?*

(1) They are effective[19][C1].
(2) It is desirable to avoid asthma advancement by continuously working in the same environment [C1].

CQ11: *Is specific immunotherapy effective for occupational allergic rhinitis?*

It is effective [C1].

Table 5
Dealing policies for occupational asthmas.

Dealing policies for occupational asthmas	Dealing policies for work-aggravated (exacerbated) asthmas
1. Sensitizers Avoidance of exposure to sensitizers Depending on situation, reducing exposure and antigen-specific immune-therapy are taken into consideration. Exposed workers are inspected. 2. Irritants Reduction of exposure to irritants 3. Sensitizers and irritants Appropriate treatment of asthma Follow-up of patients; career change to prevent worsening asthma Aid for economic compensation for patients Consideration of preventing onset in other workers	1. Appropriate treatment of asthma 2. Reduction of asthma-exacerbating factors inside and outside workplace 3. Follow-up of patients; career change to prevent worsening asthma 4. Consideration of economic compensation 5. Consideration of preventing onset in other workers

From reference.[1]

CQ12: *Is surgical therapy effective for occupational allergic rhinitis?*

It is effective [C1].

CQ13: *Is treatment of occupational allergic rhinitis difficult?*

(1) Although avoiding allergens is a highly effective treatment, losing the job or natural endowment could occur [C1].
(2) Continual exposure to an allergen at the workplace might cause allergic rhinitis to advance to asthma [C1].
(3) It is difficult to specify a causative allergen in many cases [C1].

3.6. Prevention

CQ14: *What is the highest priority in its prevention?*

To specify an inhaled allergen and completely eliminate it from the workplace. Complete avoidance of inhaled allergens at the early stage is important, which will be achieved by changing to alternative agents without a sensitizing nature or completely sealing off relevant areas[18,20] [A].

CQ15: *Is it effective to reduce the concentration of exposed allergen by setting up ventilation devices at the workplace?*

Although it is effective to reduce inhalation by utilizing full ventilation or local ventilators, such as push–pull ventilation, complete avoidance is more effective [B].

CQ16: *Is it effective to substitute materials without a allergenicity?*

If materials without a sensitizing nature or with a less sensitizing can be used, it will be as effective as either a reduction or complete avoidance of exposure to inhaled allergens [B].

CQ17: *Is it effective to wear respiratory protective tools, such as dust or gas protective masks, at the workplace?*

It is effective to avoid and reduce exposure to allergens by appropriately using protective tools [B].

CQ18: *Is it effective to inspect for the presence or absence of atopic diathesis before employees begin working?*

This might not always be effective [C1].

CQ19: *Is education on labor hygiene effective as preventive measure?*

It is effective to educate about the symptoms, exacerbation factors, protective tools, treatments, and so forth related to occupational allergic rhinitis [B].

CQ20: *Is it effective for industrial physicians to conduct an inspection tour through workplaces once or more per month?*

Refer to CQ31 of Section 2.6.

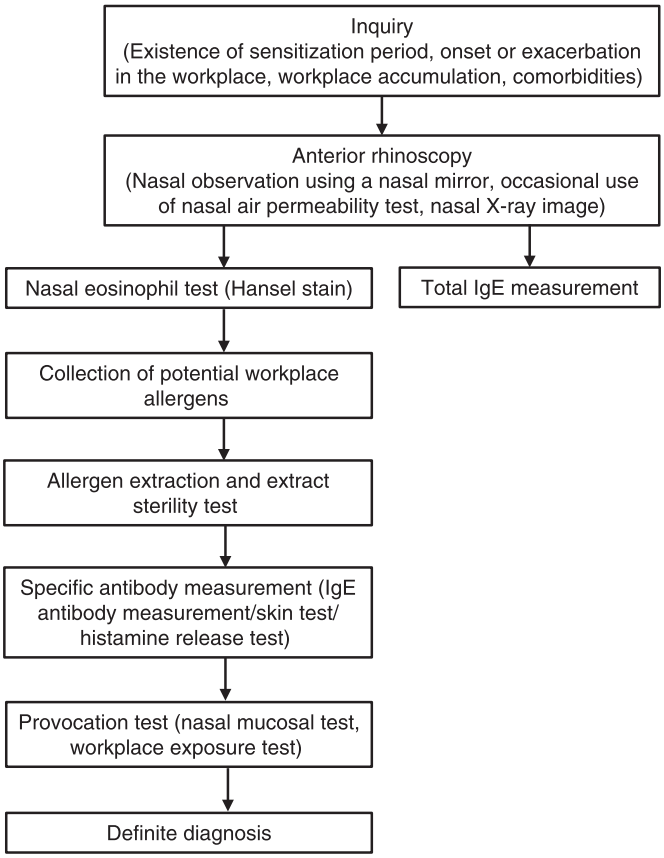

Fig. 2. Occupational allergic rhinitis diagnostic flowchart. In the interview, it is important to confirm the existence of the latency period and the workplace aggregation, which are characteristic of occupational allergies, as well as workplace-specific onset. The causal allergen identification method is divided into testing for specific IgE antibodies and provocation testing. The nasal provocation test is a gold standard for diagnosing occupational rhinitis. From reference.[1]

4. Occupational skin diseases

4.1. Definition and classification

CQ1: *What is the definition of occupational skin diseases?*

Diseases closely related to occupation are called occupational diseases and skin-related diseases at the workplaces are called occupational skin diseases.[21]

CQ2: *How are occupational skin diseases classified?*

There are so many types of occupational skin diseases (Table 6).[21]

CQ3: *What is occupational irritant contact dermatitis?*

It is defined as "non-immunological local inflammation characterized by erythema, edema, and erosion occurring after a single or repetitive exposure to certain skin sites."

CQ4: *What is occupational allergic contact dermatitis?*

The disease occurs in certain individuals and sensitization reaction involving an immunological mechanism is required.

CQ5: *What is occupational urticaria? What is occupational contact urticaria?*

Urticaria in which there is an apparent causal association with occupation is called occupational urticaria in a broad sense. Contact urticaria in which there is an apparent causal association with occupation is called occupational contact urticaria.

CQ6: *What is occupational protein contact dermatitis (PCD)?*

The disease refers to repeated recurrent allergic contact dermatitis occurring at contact sites in which protein becomes a

causative allergen. The pathogenesis of this dermatitis is assumed to be different from that of type IV allergic contact dermatitis in which hapten, a chemical, becomes a causative allergen.[22–24]

4.2. Epidemiology

CQ7: *What is the prevalence of occupational skin diseases?*

There are more than 57,000 types of chemicals used in the industrial sector in Japan. More than 500 kinds are introduced into workplace annually. Thus, it is difficult to evaluate the prevalence.

CQ8: *What is the prevalence of occupational contact dermatitis?*

It is very high.

CQ9: *What is the prevalence of occupational urticaria and occupational contact urticaria?*

The prevalence of these diseases, other than latex allergy, has not been reported accurately in Japan.

4.3. Causative agents

CQ10: *What are the causative agents of occupational irritant contact dermatitis?*

Chemical burn, which is an extreme type of acute irritant contact dermatitis, is caused by acid/alkali, hydrogen fluoride, cement, heating oil, and so forth.[21]

CQ11: *What are the causative agents of occupational allergic contact dermatitis?*

These are presented in Table 7–9.

CQ12: *What are the causative allergens for occupational urticaria (occupational contact urticaria)?*

Main causative proteins include foods, plants, animals, wheat, crops, natural rubber products, and so forth. The causes of non-allergic urticarial include chemicals such as fragrances or preservatives (Table 10).

CQ13: *Can latex allergy induced by rubber glove become a cause of food allergy onset?*

Some patients with latex allergies have an immediate allergic reaction to certain kinds of plant foods (latex fruit syndrome).[25]

CQ14: *Are there food allergies induced by soaps, shampoos, and pack agents containing food components such as hydrolyzate?*

There have been wheat allergy cases in which patients using soaps containing hydrolyzed wheat powder were percutaneous-mucosally sensitized by hydrolyzed wheat powder. By March 26, 2013, there had been 1830 definitive cases in Japan (1750 female cases [95.8%] and 76 male cases [4.2%]) caused by soaps. Approximately half of these cases were life-threatening cases, such as anaphylaxis (Japanese Society of Allergology: "Special Committee for Safety of Protein Hydrolysates in Cosmetics" Head: Kayoko Matsunaga).

CQ15: *What is cochineal allergy?*

It is an acute immediate allergy reaction induced by intake of drinks/confectionery and use of cosmetics containing a cochineal pigment as an additive. The allergy is assumed to increase in the future.[26]

CQ16: *Which workplaces have high incidences of contact urticaria?*

The food processing industry, bread makers, chefs, agricultural workers, beauticians/hairdressers, and medical-care workers who handle protein allergens. Non-allergic contact dermatitis has been occurring in food processing industry as well as among beauticians/hairdressers and medical care workers who handle food preservatives, fragrances, and disinfectants.

CQ17: *What is occupation in which occupational contact urticaria associated with food allergens might be more likely to occur? What are causative allergens?*

There have been reports that food-related proteins contained in cosmetics can become causative allergens for hairdressers, beauticians, as well as chefs. In the future, such allergies could increase.[27,28]

4.4. Diagnosis

CQ18: *Is the patch test useful for diagnosis?*

It is required to evaluate for the presence or absence of irritability in agents or identify causative agents for allergic contact dermatitis.[29]

CQ19: *What is the procedure for the patch test?* (Fig. 3)

Allergens are presumed from occupation or contents of the work, and a photopatch test or patch test is then conducted.

Table 6
Types of occupational skin diseases.

Occupational skin diseases	Main causes
1. Contact dermatitis (1) Allergic contact dermatitis (2) Irritant contact dermatitis (3) Photocontact dermtitis	Metals (nickel, chrome etc.), epoxy resin, acrylic resin, rubber, agrichemicals, cutting oil, cleansers, plants (1) Main acute irritant, erosive (including chemical burn) causative agents: hydrogen fluoride, cement, heating oil, hydrogen peroxide (2) Irritant reactive causative agents: surfactants, disinfectants, cosmetics, epoxy resin
2. Ultraviolet hazards	Acute lesions (sunburn, suntan), chronic lesions (optical aging, skin cancer)
3. Urticaria	Contact urticaria: wheat
4. Acne	Oil acne, chloracne, taracne
5. Pigmentary abnormality	Absence of the pigment (hydroquinone, phenylphenol, alkyl phenol) Pigmentation (ultraviolet light, tar and pitch, arsenic)
6. Radiodermatitis	Acute radiodermatitis, chronic radiodermatitis
7. Tar and pitch dermatopathy	Pigmentation, acne, Bowen's disease, squamous cell cancer
8. Aresevic dematopathy	Keratosis, cutaneous melanosis, Bowen's disease, squamous cell cancer
9. Heat injury	Electric damage, chemical burn
10. Cold injury	
11. Skin cancer	Bowen's disease, squamous cell cancer
12. Skin circulatory disorder	
13. Infection/insect sting	

From reference.[1]

Table 7
Highly frequent allergens causing occupational contact dermatitis.

Causative agents	Symptoms and summary
Metals (nickel, cobalt, chrome)	Contact dermatitis syndrome expanding beyond the contact site or systemic metal allergy may occur. In many cases, it occurs through contact with agents containing metals (leather, coating materials, etc.).
Resin, epoxy resin, acryl resin	Dermatitis occurs not only at the hands, but also at the face. Airborne micro-powder induces symptoms. Besides factory workers, it can occur in dental hygienists.
Rubber (MBT, TMTD)	At workplaces, rubber gloves and boots might cause frequent problems.
Agrichemicals (herbicides, antibacterial agents)	Erythema, lichen, or cracks might occur at the face/neck or hands if exposed. Repetitive contact induces a chronic condition in many cases. Photocontact dermatitis can also occur.
Cutting oil, machine oil	Acne may occur. Various substances are contained in cutting oil and it is difficult to specify the cause.
Plants	Refer to Table 8.

From reference.[1]

CQ20: *What is the effect of the patch test?*

Clarification of the causative contact allergen will lead to radical cure of intractable/recurrent allergic contact dermatitis.

CQ21: *What types of patch test units are recommended?*

The International Contact Dermatitis Research Group (ICDRG) recommends Finn Chamber® on Scanpor tape (Alpharma AS, Oslo, Norway).

CQ22: *What are allergens for patch tests?*

There are 25 kinds of Japanese standard allergens.[30]

CQ23: *What are precautions for conducting the patch test?*

They include preservation method of allergens, application sites, pregnant women, and a combination with oral medicines.

CQ24: *What are the procedures for the patch test (simple closure test)?*

Preparation of unit, cloth-application method, removal of the unit, and evaluation time are prescribed.

CQ25: *Are there other patch test methods?*

The open test, photopatch test, and repeated open application test (ROAT).

CQ26: *How is the patch test evaluated?*

Table 8
Plants causing contact dermatitis.

Disease type	Representative plants	Main causative substances	Symptoms and summary
Irritant contact dermatitis (mechanical irritation)	Rose, *Aralia elata*, cactus		
	Aloe arborescens, kiwi fruit, pineapple, Araceae	Calcium oxalate (needle-like crystal)	Needle-like crystal becomes mechanical irritant. Dermatitis caused by aloe is reported to be an irritant inflammatory reaction similar to an allergic reaction.
Irritant contact dermatitis (chemical irritation)	Nettle	Histamine, acetylcholine, serotonin	Pedicles and leaves of urticaceae have many nettling hairs. Touching them causes urticaria. Dried types change to non-irritant anemonin.
	Ranunculus glaber, *Clematis terniflora*	Protoanemonin	
Allergic contact dermatitis	Anacardiaceae (poison oak, poison ivy, *Toxicodendron trichocarpum*, *Toxicodendron sylvestre*, Japanese wax tree)	Urushiol	Anacardiaceae grow in the wild. If one makes contact, 2–3 days later strong itchiness occurs, edematous erythema or water blisters occur and arrange linearly.
	Ginkgo (outer seed coat), maidenhair tree	Ginkgolic acid, bilobol (easily crossed with Urushiol)	Outer seed coat of ginkgo has an antigenic substance, and the leaves also contain trace amounts.
	Primula	Primine	Primula without primine has recently been commercialized.
	Compositae (mum, Margaret, sunflower, dahlia, Artemisia, lettuce, etc.)	Sesquiterpene lactones (alantolactone, Arteglasin A)	Compositae has several variations.
	Araliaceae (Dendropanx trifidus trees, fatsia, rhombea)	Falcarinol	
	Liliaceae (tulip)	Tulipalin A	The bulb contains the antigenic substance.
	Labiatae (beefsteak plant)	Perillaldehyde, perillalchol	The oil component contains the antigenic substance.
Photocontact dermatitis	Umbelliferae (celery, parsley), Rutaceae (lime, lemon), Moraceae	Furocoumarin is the cause substance. It is the psoralen-allied substance.	After touching the fruit juice or leaf juice, if sunlight reaches the site(s), dermatitis occurs.

From reference.[1]

Table 9
Causes of contact dermatitis by occupations.

Job type	Contact dermatitis	Causes
Agriculture	Acute irritant dermatitis	Agrichemicals (organic phosphates, herbicides), farm products
	Chronic irritant dermatitis/Allergic contact dermatitis	Agrichemicals, fertilizer, farm products, grass pollen, surfactant
Industrial	Acute irritant dermatitis	Rust-preventive agents, heating oil, cutting oil, tar, phenol
	Chronic irritant dermatitis/Allergic contact dermatitis	Coating agents, metals (nickel, cobalt, chrome), surfactant, epoxy resin, rubber agents, cutting oil
Beauticians	Irritant dermatitis	Hair, surfactant (Cocamidopropyl betaine: CAPB), permanent wave solution (Ammonium thioglycolate [ATG])
	Allergic contact dermatitis	Surfactant (Paraphenylenediamine [PPD]), permanent wave solution, fragrances, bleach agents (ammonium persulfate, scissors [metals]), rubber gloves (vulcanizing accelerator, latex), disinfecting antiseptic agent (caisson CG)
Medical workers	Irritant dermatitis	Hand cleansers, disinfectants (povidone iodine, benzalkonium chloride, chlorhexidine gluconate)
	Allergic contact dermatitis	Disinfectants, materials for dental case (resin), rubber gloves (Vulcanization accelerators, latex; contact urticaria, latex)
Clerical workers	Allergic contact dermatitis	Deskmat (2, 3, 5, 6-tetrachloro-4-metylsulfonyl pyridine [TCMSP])

Table 10
Causative allergens for contact urticaria other than latex that have been reported in Japan.

Type	Causative allergens
Food related	Crustacea, fish and shellfish, fruits and vegetables (red-leaved chicory, chicory, avocado, garlic, cotton seed), rice, wheat, eggs, cow's milk, buckwheat, gelatin
Animal related	Chironomid larva (feeds for breeding), silk, house dust mites, skin fragments
Antibacterial drugs	Cefotiam, cefoperazone, streptomycin, piperacillin, pentoxifylline
Chemicals	Henna (hair dye), para-aminophenol, para-phenylendiamine, para-toluenediamine, meta-aminophenol, orthoaminophenol (hair dye), Ammonium persulphate (hair bleaching agent), methylparaben (cosmetics, shampoo, toothpaste, etc.), polyoxyethylene alkyl ether (cleanser), polyethylene glycol (cleanser), benzalkonium chloride, chlorhexidine gluconate, formalin
Others (enzymes and protein hydrolyzates, etc.)	Papain (proteolytic enzyme, cleansers and face-washes), hydrolyzed collagen (cosmetics), gelatin (hair care product), Glupearl (hydrolyzed wheat, face-washes, hair care products, cosmetics)

From reference.[1]

The criteria are the Japanese criteria[30,31] and those from the International Contact Dermatitis Research Group (ICDRG) (Table 11).

CQ27: *What is required for diagnosis of occupational urticaria (occupational contact urticarial)?*

The prick test is listed as a highly sensitive and specific test method that is accessible at many facilities.[32]

CQ28: *What are the procedures for the prick test? What is the nature of the practice and what are the precautions?*

We must always have adrenaline preparations ready for emergency, and must exercise caution against pseudo-negative and pseudo-positive results.[33]

CQ29: *What is the "as is prick test" using crude allergens?*

It means a test using fruits or vegetables as subjects. It is appropriate to use the "prick by prick test."

CQ30: *How are allergens used in the prick test adjusted?*

Because adjustment methods are different between agents, in cases of fresh vegetables and fruits, using those themselves is useful. As for latex, extracted fluid is prepared.

CQ31: *How is the prick test evaluated?*

The diameter of the urticarial lesion (the mean level of the vertical diameter at the middle point with the maximum length diameter in mm) is measured after 15 min. The evaluation is conducted by comparing with the control.

CQ32: *Is the measurement of allergen-specific IgE antibody titer by molecular allergology (MA) useful for the diagnosis of occupational urticaria (occupational contact urticaria)?*

It is useful for diagnosis that the allergen-specific IgE test using purified allergen is conducted to understand the sensitized condition [A].

CQ33: *What sites are likely to have occupational contact urticaria?*

As with occupational contact dermatitis, it appears that the hands are most likely, followed by contact hand joints, upper arm, and face.

4.5. Treatment and management

CQ34: *How do they deal with the onset of occupational contact dermatitis?*

In cases in which the causal association between the cause and the work (work-originated) is apparent, the event is notified to industrial physicians and personnel in charge of health and safety in the place of business to which the patient belongs.

CQ35: *How do they deal with the onset of occupational contact urticaria?*

It is most important to identify a causative allergen and then to avoid/eliminate it. Because it is likely to be comorbid with atopic dermatitis or irritant dermatitis, which is an etiology for skin barrier impairment, alleviating these symptoms is necessary.[34]

CQ36: *What are drug therapies for occupational contact dermatitis?*[30] (Fig. 4)

(1) Oral steroids and topical steroids are effective [A].
(2) Anti-histamine drugs are effective [B].
(3) Immunosuppressors are effective [C1].
(4) For chronic hand eczema, ultraviolet is effective.
    a) PUVA [A]
    b) NB-UVB [B]
(5) Barrier-cream gloves are effective for prevention.
    a) Irritant dermatitis [A]
    b) Contact dermatitis [B or C1]

CQ37: *What are basic treatment procedures for occupational contact urticaria?*

Identifying and avoiding causative allergens[30] [B].

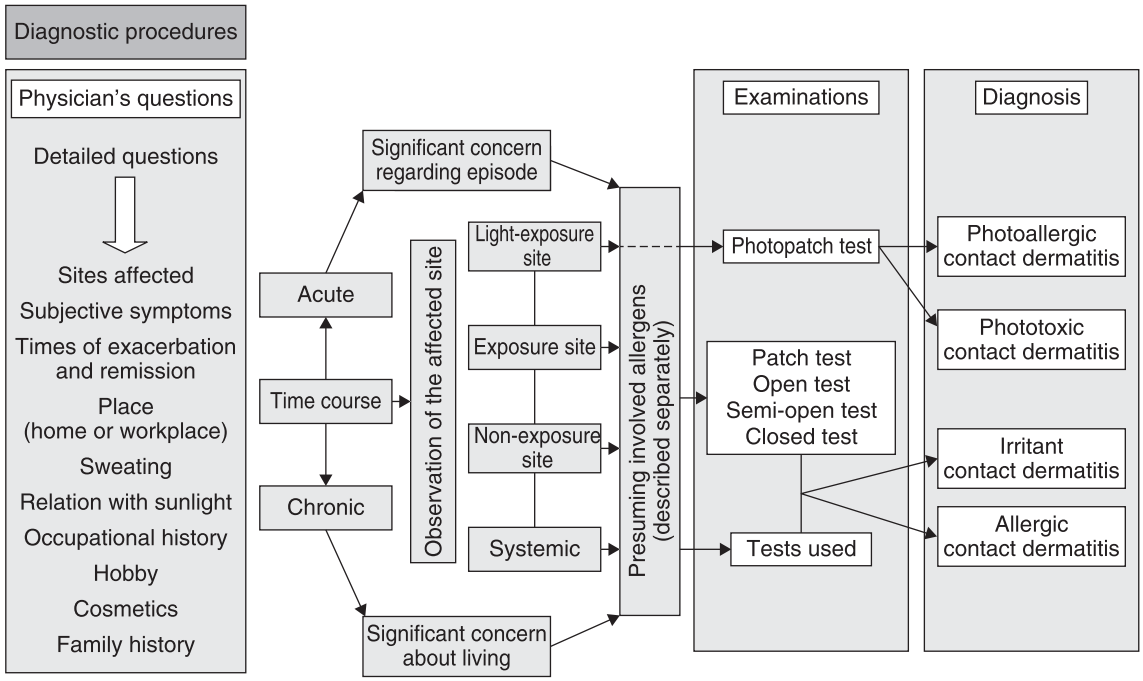

Fig. 3. Procedures of diagnosis.
From reference.[1]

Table 11
Evaluation criteria.

Criteria in Japan[31]		ICDRG criteria	
Positive reaction: ++ or more	Reaction	Positive reaction: + or more	Reaction
−	No reaction	−	No reaction
±	Mild erythema	+?	Only erythema
+	Erythema	+	Erythema + infiltration, papula
++	Erythema + edema, papula	++	Erythema + infiltration + papula + small water blister
+++	Erythema + edema + papula + small water blister	+++	Large water blister
++++	Large water blister	IR	Irritant reaction
		NT	Not conducted

4.6. Prevention

CQ38: *How is occupational contact dermatitis prevented?*

Avoiding contact with relevant chemicals and reducing harmful work as much as possible.

CQ39: *How can occupational contact urticaria be prevented?*

(1) Use of rubber gloves, vinyl gloves, mask, protective cloth, and so forth, are recommended for avoiding causative allergens [C1].
(2) Because antecedent pathologies such as atopic dermatitis or irritant contact dermatitis are often comorbid, use of moisturizing agents and preventive creams can be preventative against the worsening of symptoms [C2].

CQ40: *What is the highest priority for prevention?*

Complete elimination of causative allergens and irritants from the workplace[27] [A].

CQ41: *Is it effective to substitute materials with a low allergenicity or without an allergenicity?*

Gloves containing latex can be replaced with those with lower or no allergenicity[35] [B].

CQ42: *Is it effective to wear gas or dust protective masks and respiratory protective tools at the workplace?*

For prevention of dermatitis, protection of the skin is the highest priority.

CQ43: *Is it effective to wear gloves at the workplace for prevention?*

If used appropriately, they are effective. However, caution is required[36] [B].

CQ44: *Is it effective to apply cream?*

Although applying barrier (protective) cream before work is not recommended, applying moisturizing agents after work are effective.

CQ45: *Is it effective to inspect for the presence or absence of atopic diathesis before employees begin working?*

To prevent occupational contact dermatitis, inspecting employees for the presence or absence of atopic diathesis before they begin working is effective [C1].

CQ46: *Is education on labor hygiene effective as preventive measure?*

Specialized education regarding skin diseases and skin care is effective for preventing occupational contact dermatitis[27] [A].

CQ47: *Is it effective for industrial physicians to conduct an inspection tour through workplaces once or more per month?*

Refer to CQ32 from Section 2.6.

5. Hypersensitive pneumonitis (Fig. 5)

5.1. Identification and classification

CQ1: *What is the definition of occupational hypersensitive pneumonitis?*

Repetitive inhalation of fungus and bacteria floating within the work environment, excretory substances and body constituent of animals, and other organic/inorganic chemicals induced to establish per-airway sensitization, causing pulmonary alveolitis [A].

CQ2: *What is the classification of occupational hypersensitive pneumonitis?*

Those are classified into acute type, sub-acute type, and chronic type according to manner of onset.

5.2. Epidemiology

CQ3: *What is the prevalence of occupational hypersensitive pneumonitis?*

Because it is influenced by the type of allergen and nature of exposure, it is difficult to conduct definitive epidemiologic evaluations at present. It is reported in Japan that the incidence of farmer's lung is 5.8% and bird breeder's disease among pigeon breeders is 10.4%.[37]

CQ4: *What is the mortality of occupational hypersensitive pneumonitis?*

Generally, the mortality is believed to be low. The mortality increases in cases of chronic types with pulmonary fibrosis.

CQ5: *What are the regional and seasonal characteristics in occupational hypersensitive pneumonitis?*

Pneumonitis occurs at a high rate in regions and seasons in which the probability of exposure to causative allergens is high.

5.3. Causative allergens

CQ6: *What are causative allergens?*

Plant powder dust, body constituent and excretory substances of animals, insects, fungi, bacteria, drugs, organic chemicals, and so on [A].

CQ7: *What are the criteria to certify causative allergens of occupational hypersensitive pneumonitis?*

Evidence levels of causative allergens are defined according to Table 3 and allergens are listed in Table 12. Only causative allergens reported in Japan are listed.

CQ8: *What are the causative allergens with high incidence in occupational hypersensitive pneumonitis?*

Farmer's lung has been decreasing. Reports on various causes have been increasing because of the recognition of diseases and consequent increase in diagnostic rates (Table 13, 14).[38,39]

CQ9: *What are causative allergens that have been increasing recently in occupational hypersensitive pneumonitis?*

Low molecular weight chemicals.

5.4. Risk factors for onset

CQ10: *What are environmental factors that might predispose one to be at risk for occupational hypersensitive pneumonitis?*

Allergen concentration, exposure period, exposure frequency, non-smoking, and so forth.[40]

CQ11: *What are genetic factors that might be a risk factor for occupational hypersensitive pneumonitis?*

Specific genetic factors have not been sufficiently elucidated.

5.5. Diagnosis

CQ12: *What are diagnostic criteria for occupational hypersensitive pneumonitis?*

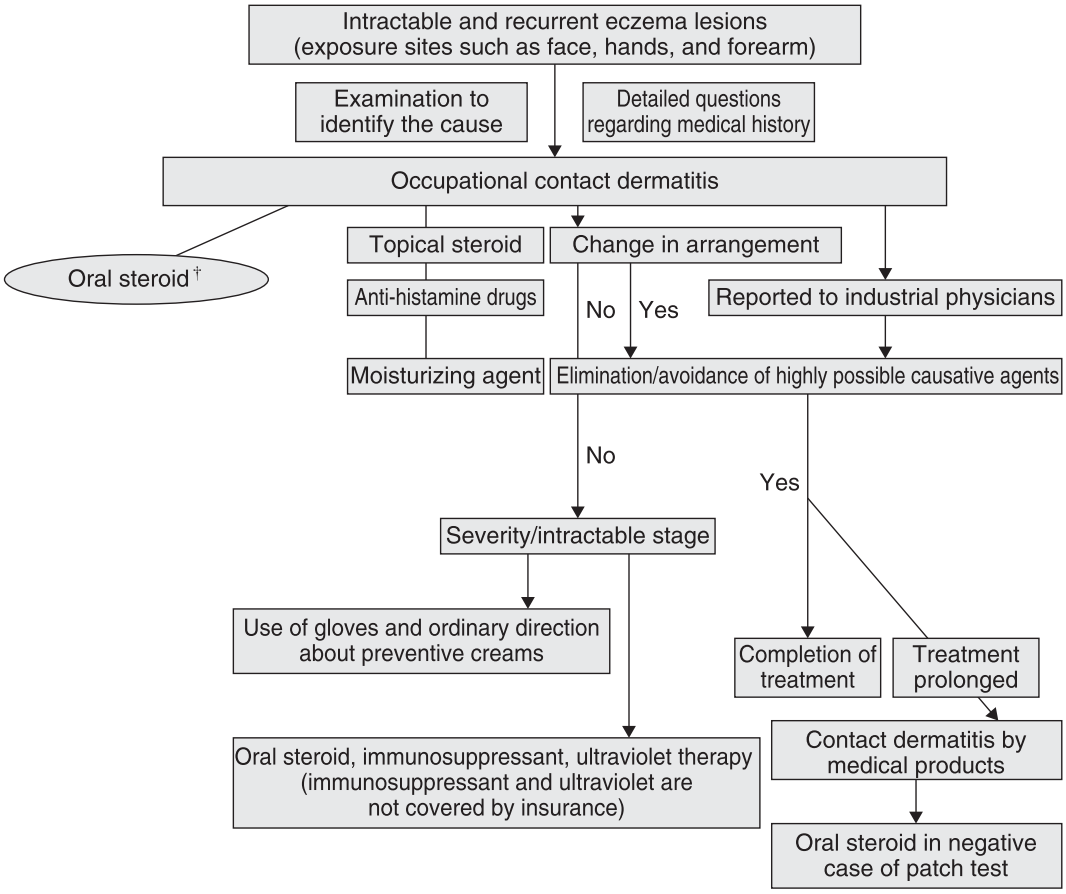

Fig. 4. Algorism of treatment. From reference.[1] †Oral steroid is limited to severe cases. After elimination of the cause, 20–30 mg/day for about one week.

There are no independent diagnostic criteria for occupational hypersensitive pneumonitis. The diagnosis is made based on the "Guideline for Diagnosis and Treatment of Hypersensitive Pneumonitis"[41] prepared in 1990 by the Investigation and Research Group of Specific Diseases and Diffuse Diseases of Ministry of Health, Labour and Welfare, Japan [A].

CQ13: *What are differential diagnoses for which caution must be exercised in occupational hypersensitive pneumonitis?*

Other interstitial lung diseases such as idiopathic interstitial pneumonitis and occupational asthmas [A].

CQ14: *What is the most important point in diagnosing occupational hypersensitive pneumonitis?*

Physician questions are the most important. In particular, a detailed occupational history is required [A].

CQ15: *What examination methods are used for occupational hypersensitive pneumonitis?*[42]

(1) General blood examinations, imaging (X-ray and CT), examination of respiratory function, bronchoalveolar lavage (BAL), and tracheobronchial lung biopsy (TBLB) [A].
(2) To identify causative allergens, measurement of allergen-specific antibody titer, lymphocyte proliferation test by addition of allergen, precipitation antibody test, challenge tests such as the allergen inhalation challenge test, and the environmental challenge test are listed [A].

CQ16: *Is tissue diagnosis required for definitive diagnosis of occupational hypersensitive pneumonitis?*

Tissue diagnosis is not always required [C1].

CQ17: *Is the allergen inhalation challenge test required for definitive diagnosis of occupational hypersensitive pneumonitis?*

It is useful for definitive diagnosis to identify allergens. Because it is accompanied by the risk of exacerbation of hypersensitive pneumonitis, it is not essential [C1].

CQ18: *Are immunological examinations useful for definitive diagnosis of occupational hypersensitive pneumonitis?*

They are useful for indirect diagnosis[43] [C1].

5.6. Treatment, management, and prognosis

CQ19: *What are treatments for occupational hypersensitive pneumonitis?*

The avoidance of allergens. Prednisolone as a symptomatic therapy is used for intermediate and severe cases of acute hypersensitive pneumonitis or cases of advancing chronic hypersensitive pneumonitis[44,45] [A].

CQ20: *Is it possible for patients with occupational hypersensitive pneumonitis to continue working only through drug treatment?*

Avoidance of allergens is inevitably necessary and pathologic conditions after avoiding the allergen by leaving the job could progress[44] [D].

CQ21: *What is the prognosis for occupational hypersensitive pneumonitis?*

Individuals with mild cases who avoid the allergen have a favorable prognosis. The prognosis is poor, however, in cases in which the allergen cannot be avoided or in chronic fibrotic cases that show poor response to treatment.[46]

5.7. Prevention

CQ22: *What is the highest priority in management of the working environment?*

Complete elimination of causative allergens[47] [A].

CQ23: *Is it effective to reduce exposure to allergens by setting up ventilation devices at the workplace?*

It is effective [C1].

CQ24: *Is it effective to wear dust or gas protective masks at the workplace as a preventative measure?*

It is effective[47] [B].

CQ25: *Is it effective to inspect for the presence or absence of atopy before employees begin working?*

This might not be effective [C2].

CQ26: *Is education on labor hygiene effective as preventive measure?*

It is effective in educating workers regarding symptoms of occupational hypersensitive pneumonitis, the avoidance of allergens, and the correct uses of protective tools [C1].

CQ27: *Is it effective for industrial physicians to conduct an inspection tour through workplaces once or more per month?*

Refer to CQ32 from Section 2.6.

6. Occupational anaphylaxis (shock)

6.1. Definition

CQ1: *What is the definition of occupational anaphylaxis?*

It is an anaphylaxis that occurs because of exposure to a causative allergen that is present in a certain workplace [B].

6.2. Pathogenesis of occupational anaphylaxis

CQ2: *Is the pathogenesis of occupational anaphylaxis usually an immediate allergy?*

Anaphylaxis induced by exposure to a causative allergen at the workplace is usually IgE-dependent, but it could also be a non-allergic reaction. In both cases, the method of evaluation and assessment is the same.

6.3. Symptoms and diagnosis of occupational anaphylaxis

CQ3: *What are diagnostic criteria for occupational anaphylaxis?*

Generally, anaphylaxis is suspected when skin and mucous symptoms occur and are complicated by respiratory, persistent digestive, and hypotension-induced symptoms. Occupational anaphylaxis is similarly suspected. The details of the diagnostic criteria for anaphylaxis according to inquiries and characteristic symptoms are described in reference. [48] [A].

6.4. Epidemiology of anaphylaxis

CQ4: *What are the incidence and prevalence rates of anaphylaxis?*

The incidence is estimated to be 0.1–2.4%[49] [C1].

CQ5: *What are main causes of anaphylaxis?*

The number of annual deaths in Japan is approximately 60. Two major causes are pharmaceutical drugs (increasing) and bee punctures (decreasing) [C1] (Table 15).

6.5. Emergency management

CQ6: *What are emergency management?*

Intramuscular adrenaline injection, high-flow oxygen, and intravenous fluids are the most important for emergency management. Further details on emergency management are described in Ref. 48 [A].

6.6. Causative agents of anaphylaxis

CQ7: *What are allergens of occupational anaphylaxis?*

Allergens that can cause occupational anaphylaxis include food, drugs, insect bites and stings, snake and mammal bites, latex, and chemicals[50] [B].

6.7. Prevention of anaphylaxis

CQ 8: *How is occupational anaphylaxis prevented?*

Methods for primary and secondary prevention of occupational anaphylaxis include reducing exposure to allergens and risk reduction by workers. Tertiary prevention occurs through identifying and removing allergens.

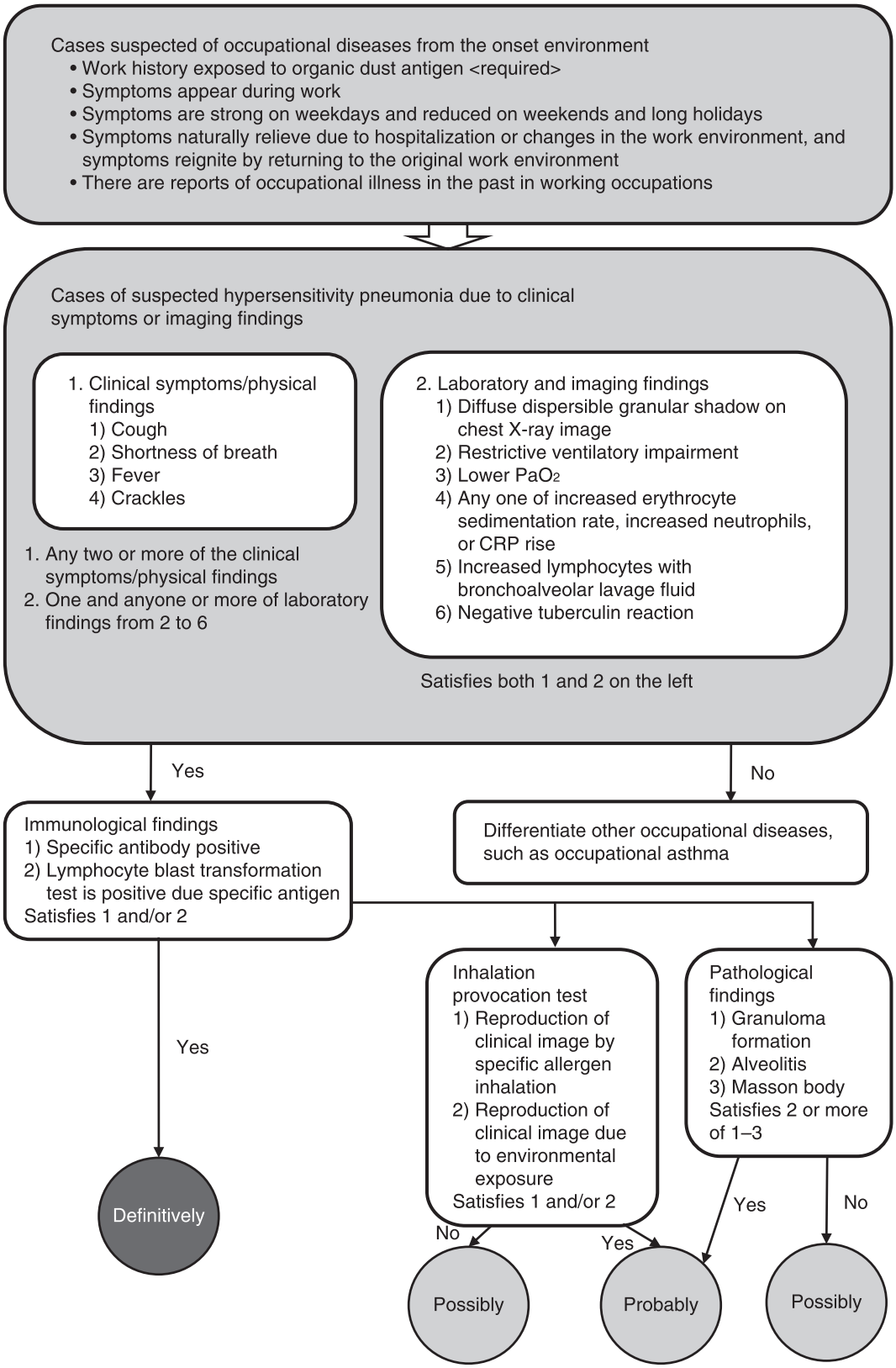

Fig. 5. Occupational hypersensitivity pneumonia diagnostic flowchart.
From reference.[1]

Table 12
Inhaled agent inducing occupational hypersensitive pneumonitis.

Inhaled agent inducing occupational hypersensitive pneumonitis	Occupations (disease name)	Evidence level	
		Overseas/Japan	
1. Plant antigens			
Wheat	Confectionery making (wheat flour lung)	(2)	(3)
Green tea	Green tea manufacturers		(3)
2. Fungi/yeast			
Aspergillus niger	Dairy farming (farmer lung)		(3)
Aspergillus oryzae	Miso and soy sauce makers		(3)
Shiitake mushroom spores	Cultivation of shiitake mushrooms		(2)
Nameko mushroom spores	Cultivation of nameko mushrooms		(2)
Trichosporon cutaneum	Cultivation of nameko mushrooms		(3)
Shimeji mushroom spores	Cultivation of shimeji mushrooms		(1)
King trumpet mushroom spores	Cultivation of king trumpet mushrooms		(2)
Polypore mushroom spores	Cultivation of polypore mushrooms		(2)
Penicillium citrinum	Cultivation of enoki mushrooms		(2)
Fungi mixed and growing *Saccharopolyspora rectivirgula* (*Micropolyspora faeni*)	Lungs of persons cultivating mushrooms		(3)
Fungi attaching to rush	Tatami mat makers		(3)
Contaminated water	Workers in humid working environments (humidifier lung, ventilator lung)		(2)
Aspergillus fumigatus	Orchid planters		(3)
Aspergillus fumigatus	Vegetables planters in plastic greenhouse, vegetable planters (compost lung)	(2)	(3)
Aspergillus spp., Penicillium sp., Paecilomyces sp.	Mandarin orange planters		(2)
Penicilliun spp.	Wooden pulp workers, greenhouse rose cultivators		(2)
Aspergillus oryzae	Rice cake makers		(3)
Aspergillus niger	Onion farmers		(3)
3. Bacteria, acid-fast bacillus, actinomycete			
Saccharopolyspora rectivirgula (*Micropolyspora faeni*) (contaminated water)	Workers at humid working environments (humidifier lung, ventilator lung)	(1)	(1)
Pseudomonas sp.	Estheticians		(3)
4. Other organics			
Shellfish powder dust	Nuclear processing traders for pearl aquafarming		(3)
Marine univalve shell	Mollusk shell HP	(2)	(2)
Pearl oyster powder dust	Shellworkers		(2)
Freshwater shellfish powder dust	Pearl nuclear processing traders		(3)
Makomozumi (Makomozumi makers, Ustilago esculenta spores)	Traditional craftwork workers lung		(3)
5. Chemicals (metals, drugs, inorganics, etc.)			
Isocyanate (toluene diisocyanate [TDI], methylene diisocyanate [MDI], hexamethylene diisocyanate [HDI], etc.)	Paint applicator lung, automobile mechanics, casting metal workers, piano mechanics (use of polyurethane)	(1)	(2)
Cobalt	Hard metal disease	(2)	(2)
Dichloromethane	Cleaning company employees		(3)
6. Unconfirmed (candidate)			
Powder dust occurring at use of mobile bed disinfectant device	Assistant nurses		(3)

Table 13
National epidemiologic surveys on acute hypersensitive pneumonitis.

Disease name	1980–1989		1990–1999	
	Number of patients	(%)	Number of patients	(%)
Summer-type hypersensitive pneumonitis	621	(74.4)	624	(69.8)
Farmer's lung	68	(8.1)	39	(4.4)
Ventilator lung	36	(4.3)	53	(5.9)
Bird breeder's lung	34	(4.1)	36	(4.0)
Other hypersensitive pneumonitis	19	(2.3)	68	(7.6)
Unknown cause	57	(6.8)	74	(8.3)
Total	835	(100.0)	894	(100.0)

Adapted from reference.[38]

6.8. Anaphylaxis by bee puncture

CQ9: *In what occupations is anaphylaxis caused by bee puncture most likely to occur?*

The forest industry, apiculture, agriculture, landscaping, and so forth are listed[51] [A].

CQ10: *How is bee allergy diagnosed?*

Although screening is conducted with a bee toxin-specific IgE antibody, the specificity is insufficient and medical history is most important for diagnosis [B].

CQ11: *What is the highest priority for prevention of anaphylaxis induced by bees?*

To avoid bee punctures by environmental arrangement [A].

CQ12: *Is it effective to inspect for the presence or absence of atopic diathesis before employees begin working?*

Table 14
National epidemiologic surveys of chronic hypersensitive pneumonitis.

1989–1998			2001–2010		
Disease name	Number of patients (%)		Disease name	Number of patients (%)	
Summer-type hypersensitive pneumonitis	10	(27.8)	Summer-type hypersensitive pneumonitis	33	(20)
Bird breeder's lung	7	(19.4)	Hypersensitive pneumonitis associated with birds	86	(52.1)
Isocyanate induced	5	(13.3)	Isocyanate induced	1	(0.6)
Hypersensitive pneumonitis associated with houses	5	(13.9)	Hypersensitive pneumonitis associated with houses	26	(15.8)
Farmer's lung	4	(11.1)	Humidifier lung	2	(1.2)
Other hypersensitive pneumonitis	5	(13.9)			
Unknown cause			Unknown cause	17	(10.3)
Total	36	(100.0)	Total	165	(100.0)

Adapted from reference.[39]

Table 15
Diseases related to occupations and causative agents.

Bronchial asthma, rhinitis	Protease, wood dust, animal hair dust, fluorine, vinyl chloride, synthetized resins such as acrylic resin
	Wood dust: red cedar, lauan, Japanese clethra, mulberry tree
	Cilia dust: sheep, cat, goat, horse, pig, scurf, mite, fungi, etc.
	Other: sea squirt attaching to oyster shell, cocooning frame, drugs such as antibiotic, aspirin, sulfonamide, etc.
	Occupations: lumber and wood processing, hair pencil maker, veterinarian, farmer, handling experimental animals, drug manufacturer, medical work, drug preparation at pharmacy
Skin disease/dermatitis	(In addition to agents associated with bronchial asthma and rhinitis), soot (black printing ink, artificial coal), mineral oil (lubricant oil, electric insulator), Japanese lacquer, turpentine, tar, cement, amine resin hardener (adhesive, condenser, coating compounds), glass fiber, rubber additive

Adapted from reference.[55]

The more medical history of allergies one has, the higher the incidence of systemic symptoms by bee punctures, and the higher the risk of anaphylaxis [C1].

CQ13: *Is it effective to carry an adrenaline self-injection kit (Epi-Pen®) to treat anaphylaxis by bees?*

It is effective[52] [A].

CQ14: *Is allergen-specific immune-therapy for bee allergies useful?*

Although its use is desirable due to its high effectiveness, the therapy is not covered by insurance in Japan[53] [B].

6.9. Anaphylaxis by latex

CQ15: *What occupations are susceptible to latex allergies?*

Medical workers and latex makers [A].

CQ16: *Is specific IgE antibody test useful for diagnosis of latex allergies?*

Although it is important as a screening examination, its sensitivity is not 100% [B].

CQ17: *Is the prick test useful for diagnosis of latex allergy?*

The test is conducted for the specific IgE antibodies negative cases in which latex allergy is suspected[49] [B].

CQ18: *What are preventive measures against anaphylaxis by latex?*

Complete elimination of agents containing latex must be implemented in all medical practices for individuals with a medical history of latex allergy [B].

6.10. Occupational anaphylaxis induced by allergens other than bee venom or latex

CQ19: *What occupational anaphylaxis is induced by food allergens?*

Occupational anaphylaxis induced by food allergens is not very common. It is possible that patients are not diagnosed with an anaphylaxis when they have anaphylactic reactions in locations unrelated to the workplace.

CQ20: *What occupational anaphylaxis is induced by drugs?*

Patients with occupational anaphylaxes induced by drugs are usually sensitized through the airway or skin. High-risk occupations include nurses, pharmacists, and others working in the drug industry.

CQ 21: *What occupational anaphylaxis is induced by animals?*

Other than tick bites related to animal breeding, occupational anaphylaxes can occur in forest workers and farmers from caterpillar bites and in individuals who work in the basic medical sciences from mosquito, fly, and animal bites.

CQ 22: *Are there occupational anaphylaxes induced by snake venom?*

People who work with venomous snakes are sensitized by inhalation or through contact with dried snake venom.

7. Legal aspects

CQ1: *Who is responsible?*

For occupational diseases, it is prescribed that, except for the case of gross negligence in employees, employers are responsible. The employer is responsible for indemnifying the employees for cure, cessation of work, disturbances, bereaved family, and so forth.[54]

CQ2: *Is it covered by workman's compensation?*

Certain causes (exposure conditions) and symptoms have been prescribed administratively as subjects for cure, cessation of work, disturbances, compensation for bereaved families (accident compensation by employers based on the Labor Standard Act) and workers' accident compensation (payment according to Workmen's Accident Compensation Insurance Act). Occupational allergic diseases such as relevant asthmas, skin diseases, and rhinitis are regarded as occupation-related diseases (Table 15).[55]

Appendix A. Committee for Japanese Guideline for Diagnosis and Management of Occupational Allergic Diseases

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Conflict of interest

The authors have no conflict of interest to declare.

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