Allergology International. 2014;63:421-442
DOI: 10.2332/allergolint.14-RAI-0771

REVIEW ARTICLE

# Japanese Guideline for Occupational Allergic Diseases 2014

Kunio Dobashi[1], Kazuo Akiyama[2], Atsushi Usami[3], Hiroo Yokozeki[4], Zenro Ikezawa[5], Naomi Tsurikisawa[6], Yoichi Nakamura[7], Kazuhiro Sato[8], Jiro Okumura[9], on behalf of Committee for Japanese Guideline for Diagnosis and Management of Occupational Allergic Diseases[10] and Japanese Society of Allergology

## ABSTRACT

In 2013, a guideline for occupational allergic diseases was published for the first time in Japan. Occupational allergic diseases are likely to worsen or become intractable as a result of continuous exposure to high concentrations of causative antigens, and are socioeconomically important diseases with which the patients might sometimes lose jobs due to work interruptions. Guidelines for occupational allergic diseases have been published in many countries. This guideline consists of six chapters about occupational asthma, occupational allergic rhinitis, occupational skin diseases, hypersensitivity pneumonitis and occupational anaphylaxis shock, and legal aspects of these diseases. The guideline is characterized with the following basic structure: Clinical Questions (CQs) are set with reference to Minds (Medical Information Network Distribution Service), statements by the committee are correspondingly listed, recommended grades and evidence levels are defined, and then descriptions and references are indicated.

## KEY WORDS

hypersensitivity pneumonitis, occupational allergic rhinitis, occupational anaphylaxis, occupational asthma, occupational skin diseases

## 1. Significance and Characteristics

A large number of case reports have been accumulated on occupational allergic diseases. In some cases, such as asthma caused by amorphophallus konjac or ascidian, improvement of working environment based on evidence from epidemiologic studies and analyses of antigens resulted in reduction in asthma cases at the workplace. However, because of the occupational features of the diseases, only case reports have been presented in many cases. Although guidelines for individual allergic diseases have been published by allergologic associations, the descriptions of occupational factors are generally minimal. In fact, guideline for diagnosis and management of occupational allergic diseases has not been developed.

If a worker with an occupational allergic disease doesn't consider it an occupational disease, or if an affected workers bear it and take no measures or treatment, extensive exposure at the workplace will persist, causing the disease to worsen or become intractable. Depending on the circumstances, patients

[1]Graduate School of Health Sciences, Gunma University, Gunma, [2]National Hospital Organization, Sagamihara National Hospital, [5]Department of Dermatology, Yokohama City University Hospital, [6]Department of Allergy and Respirology, National Hospital Organization, Sagamihara National Hospital, [7]Medical Center for Allergic and Immune Diseases, Yokohama City Minato Red Cross Hospital, Kanagawa, [3]Tohkai Research Institute for Pollinosis, Shizuoka, [4]Department of Dermatology, Tokyo Medical and Dental University, Tokyo, [8]Department of Environmental Health, Faculty of Medical Sciences, University of Fukui, Fukui, [9]Department of Environmental Medicine and Behavioural Science, Kinki University School of Medicine, Osaka, Japan and [10]Members listed at the end of the article.

Conflict of interest: KA received honoraria from GlaxoSmithKline, MSD, and research funding from Astellas Pharma. MA received honoraria from GlaxoSmithKline, Novartis Pharma, Astellas Pharma, Kyorin Pharmaceutical. KO received honoraria from GlaxoSmithKline, Kyorin Pharmaceutical, AstraZeneca, Boehringer Ingelheim, and research funding from MSD. MO received honoraria from MSD, GlaxoSmithKline, Sanofi, Kyowa Hakko Kirin, Mitsubishi Tanabe Pharma. YT received Kyorin Pharmaceutical, MSD, AstraZeneca. KN received honoraria from Mitsubishi Tanabe Pharma. The rest of the authors have no conflict of interest.

Correspondence: Kunio Dobashi, Graduate School of Health Sciences, Gunma University, 3–39–22 Showa-machi, Maebashi, Gunma 371–8511, Japan.
Email: dobashik@gunma-u.ac.jp

Received 24 March 2014.

might lose their job and therefore face economic difficulties. Therefore, it is extremely important to identify occupational allergic disease cases in their early stages and take appropriate preventive measures for the social lives of patients. In Europe and the USA, several guidelines for occupational allergic diseases have been published. It is extremely significant that the guideline for diagnosis and management of occupational allergic diseases have been published for the first time in Japan.[1]

This guideline is designed to assist healthcare professionals engaging in ordinary diagnosis and management of allergic diseases to practice early detection and treatment and early prevention in patients with allergic diseases induced and worsened by occupational factors. We hope that this guideline will be used for ordinary diagnosis and management of occupational allergic diseases and help the patients.

The guideline has a basic structure in which Clinical Questions (CQ) are set with reference to Minds (Medical Information Network Distribution Service), statements by the committee are listed, recommendation grades and evidence levels are defined, descriptions and references are indicated. Also, legal aspects are written in full.

As for occupational allergic diseases, because new substances have been continually produced due to technical innovation, and working environments have been changing due to changes in industrial structures, new occupational asthmas can always arise. In the future, we will continue to revise the guideline every three years, in order to maintain a high level of evidence for the guideline.

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

**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 |

## 2. Occupational Asthmas

### 2.1. Definitions and Classifications

CQ1: *What are the definitions and classifications of occupational asthmas? (Fig. 1)*

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 antigens 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. Work-aggravated (exacerbated) asthmas are those preexisted and aggravated by gas, cool air, or dust aspirated at the workplace.[2] In Japan, work-aggravated (exacerbated) asthmas are generally not included in OAs. [Minds Grade A]

### 2.2. Prevalence

CQ2: *What is the proportion of population-attributable risk of occupational factors in adult asthmas?*

The proportion of population-attributable risk of occupational factors in adult asthmas is approximately 15%.[3]

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

High prevalence rates are found in painters (isocy-

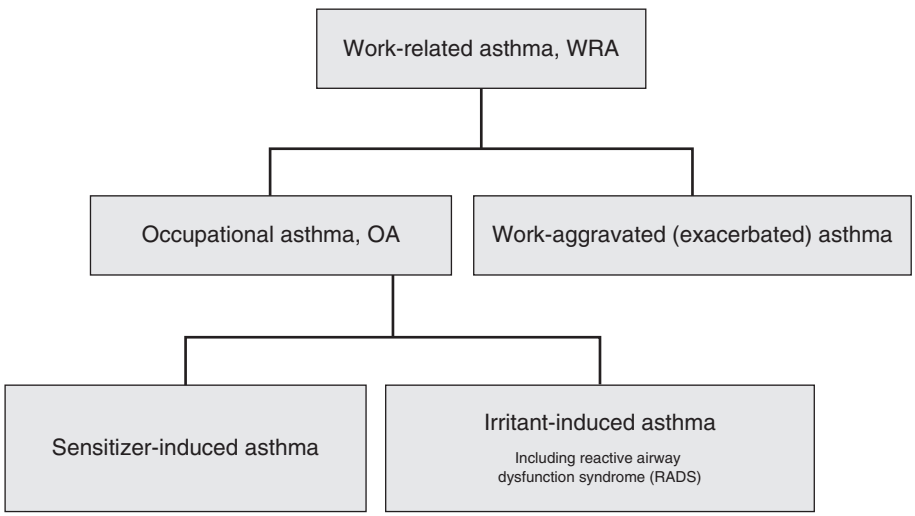


**Fig. 1** Work-related asthmas and their classifications. From reference 1.

**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 |

Adapted from reference 4.

**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) |

anate); 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. Antigens

CQ4: *What are causative antigens?*

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

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

For antigens 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 antigens in conventional OAs were most common?*

Substances derived from animals or plants. [C1]

CQ7: *What antigens have increased recently?*

Minerals and low molecular weight substances.[2,4] [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.[5] [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.[6] [A]

(3) Diagnosing it as early as possible.[7] [A]

CQ12: *Are questionnaires useful for definitive diagnoses?*

Although useful, the specificity of questionnaires is low.[8] [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.[9] [A]

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

**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<br>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 | (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)<br>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) |

(Continued)

**Table 4** (Continued)

| Aspirated substances inducing occupational asthmas | Occupation or other | Evidence levels | |
|---|---|---|---|
| | | Overseas | Japan |
| 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) |
| 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) |

(Continued)

**Table 4** (Continued)

| Aspirated substances inducing occupational asthmas | Occupation or other | Evidence levels | |
|---|---|---|---|
| | | Overseas | Japan |
| 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 and rabbit, 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) |
| C. Drugs and food | | | |
| 1. Drug powder dust | | | |
| Diastase, Gentian, Thyradin | Pharmacists | | (1) |
| Pancreatin | Pharmacists | | (3) |
| Matromycin, Sigmamycin | Pharmaceutical company employees | | (3) |
| 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) |

(Continued)

**Table 4** (Continued)

| Aspirated substances inducing occupational asthmas | Occupation or other | Evidence levels | |
|---|---|---|---|
| | | Overseas | Japan |
| *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) |
| Bacilus 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 | Polyurethane resin factory workers, Students making figurative objects with urethane resin, Orthopedists fixing plaster casts, House painters using coating reinforcement agents | (1) | (1) |
| Toluene diisocyanate (TDI), Methylene bisphenyl isocyanate (MDI), Hexamethylene diisocyanate (HDI) | | | |
| 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.

(1) It is the gold standard for diagnosing sensitizer-induced asthma, and is thus useful for identifying new antigens. [C1]
(2) Because it is risky, regardless of whether the antigen is new or known, it is not essential when diagnoses can be made with other methods. [C1]
CQ16: *Are immunological examinations useful?*
(1) They are useful for identifying high molecular weight antigens in sensitizer-induced asthma. [A]
(2) They are not useful for identifying low molecular weight antigens. [C2]

### 2.5. Treatment and Management

CQ17: *Are management methods by classification useful?*
This question is outlined in Table 5.[2,4,7] [B]
CQ18: *Is avoidance of causative antigens effective?*
Yes, it is effective. [B]
CQ19: *How does the drug treatment proceed?*
Treatment of asthma is conducted according to the guideline for diagnoses and management.[10] [B]
CQ20: *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 environ-

**Table 5** Dealing policies for occupational asthmas

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

From reference 1.

ment. [A]
(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]
CQ21: *Is antigen-specific immunotherapy effective?*
When subjects have sensitizer-induced asthma, it is effective for some causative agents. [B]
CQ22: *To confirm regarding symptoms or improvement in respiratory function after avoidance of exposure to an antigen, how long a follow-up period is necessary?*
Several years are necessary after avoidance of the causative agent.[11] [A]
CQ23: *What are conditions that facilitate symptom alleviation and enhance respiratory function after avoiding exposure to antigens?*
Those conditions include the respiratory function at the time of diagnosis, exposure period to a causative agent, and age at time of diagnosis.[12] [A]

### 2.6. Prevention

CQ24: *What is the highest priority in the management and prevention of hazardous working environments?*
Complete avoidance of inhaled antigens at the early stage is paramount. This can be achieved by changing to less sensitizing alternative agents or completely sealing off relevant areas.[2,4,13] [A]
CQ25: *Is it useful to reduce exposure to antigens by setting up ventilation devices at the workplace?*
Although it is effective, complete avoidance is more effective. [B]
CQ26: *Is it effective to substitute materials with lower antigenicity or without antigenicity?*
If materials with no or lower antigenicity can be used, it will be as effective as either a reduction or complete avoidance of exposure to antigens. [A]
CQ27: *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 antigens. [B]
CQ28: *Is it effective to inspect for the presence or absence of atopy before employees begin working?*
This might not always be effective.[12] [C1]
CQ29: *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]
CQ30: *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

### 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.[14]
(2) Antigens 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) Antigens 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%.[15]

### 3.4. Causes

CQ4: *What are causative antigens for occupational allergic rhinitis?*
Animals, plants, chemicals, and so forth.[16] [A]
CQ5: *What are the criteria for certifying causative antigens of occupational allergic rhinitis?*
It is diagnosed through a combination of doctor's questions, immunological examinations, and a nasal mucosa test.[16,17] [A]
CQ6: *Are causative antigens of occupational allergic rhinitis changing?*
Both type and incidence rates have been changing due to changes of industrial form and working environment.
CQ7: *What are problems related to chemical-induced occupational allergic rhinitis?*
Because specific IgE antibodies cannot be easily detected, diagnosis is difficult.[16] [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 antigen.
(2) Although essential differences in the mechanism have not been indicated, there are some cases of intense exposure to antigens 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 antigens for occupational allergic rhinitis?*
(1) Continuous exposure to antigens 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.[17] (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]
CQ12: *Is surgical therapy effective for occupational allergic rhinitis?*
It is effective. [C1]
CQ13: *Is treatment of occupational allergic rhinitis difficult?*
(1) Although avoiding antigens is a highly effective treatment, losing the job or natural endowment could occur. [C1]
(2) Continual exposure to an antigen at the workplace might cause allergic rhinitis to advance to asthma. [C1]
(3) It is difficult to specify a causative antigen in many cases. [C1]

### 3.6. Prevention

CQ14: *What is the highest priority in its prevention?*
To specify an inhaled antigen and completely eliminate it from the workplace. Complete avoidance of inhaled antigens 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.[16,18] [A]
CQ15: *Is it effective to reduce the concentration of exposed antigen 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 antigenicity?*
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 antigens. [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 antigens 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*

**Table 6** Types of occupational skin diseases

| Occupational skin diseases | Main causes |
|---|---|
| 1. Contact dermatitis<br>(1) Allergic contact dermatitis<br>(2) Irritant contact dermatitis<br>(3) Photocontact dermtitis | Metals (nickel, chrome etc.), epoxy resin, acrylic resin, rubber, agrichemicals, cutting oil, cleansers, plants<br>(1) Main acute irritant, erosive (including chemical burn) causative agents: hydrogen fluoride, cement, heating oil, hydrogen peroxide<br>(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)<br>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.

*an inspection tour through workplaces once or more per month?*
Refer to CQ31 of section 2.

## 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.[19]
CQ2: *How are occupational skin diseases classified?*
There are so many types of occupational skin diseases (Table 6).[19]
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.[20-22]

### 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.[19]

**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.

**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.

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, ani-

**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 (Vulcanisation 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 hydrolysates, 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.

mals, 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).[23]

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

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 1,830 definitive cases in Japan (1,750 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.[24]

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

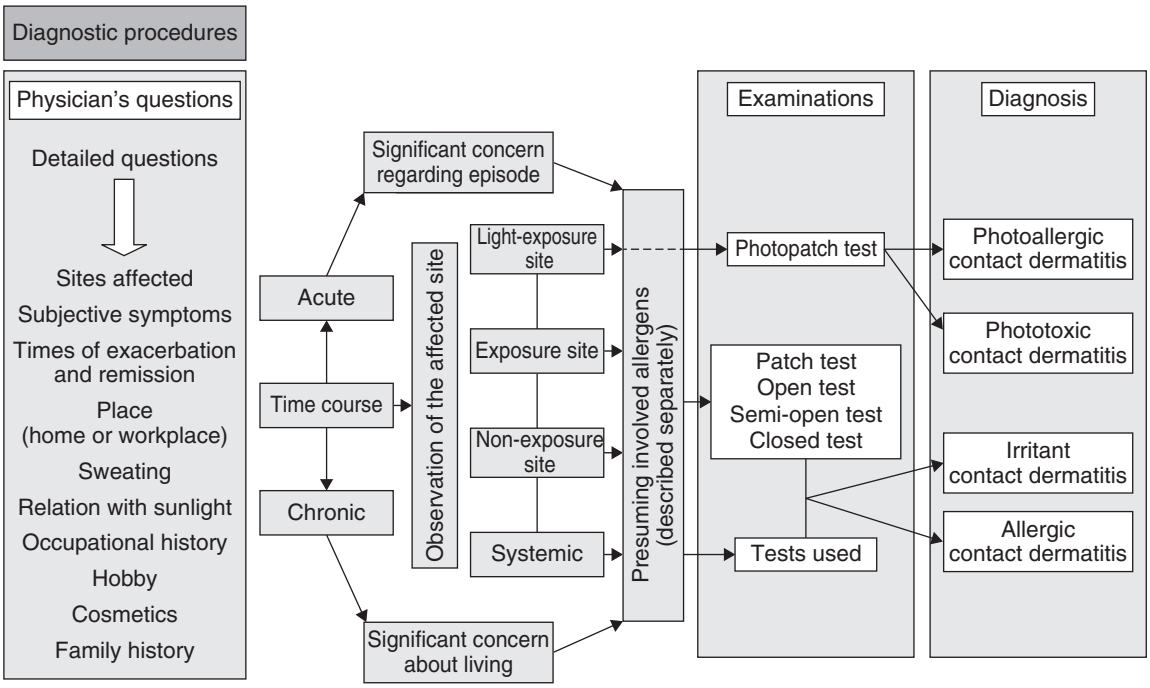


**Fig. 2** Procedures of diagnosis. From reference 1.

**Table 11** Evaluation criteria

| Criteria in Japan [29] | | 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 |

contained in cosmetics can become causative allergens for hairdressers, beauticians, as well as chefs. In the future, such allergies could increase.[25,26]

### 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.[27]
CQ19: *What is the procedure for the patch test? (Fig. 2)*
Allergens are presumed from occupation or contents of the work, and a photopatch test or patch test is then conducted.
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.[28]
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.

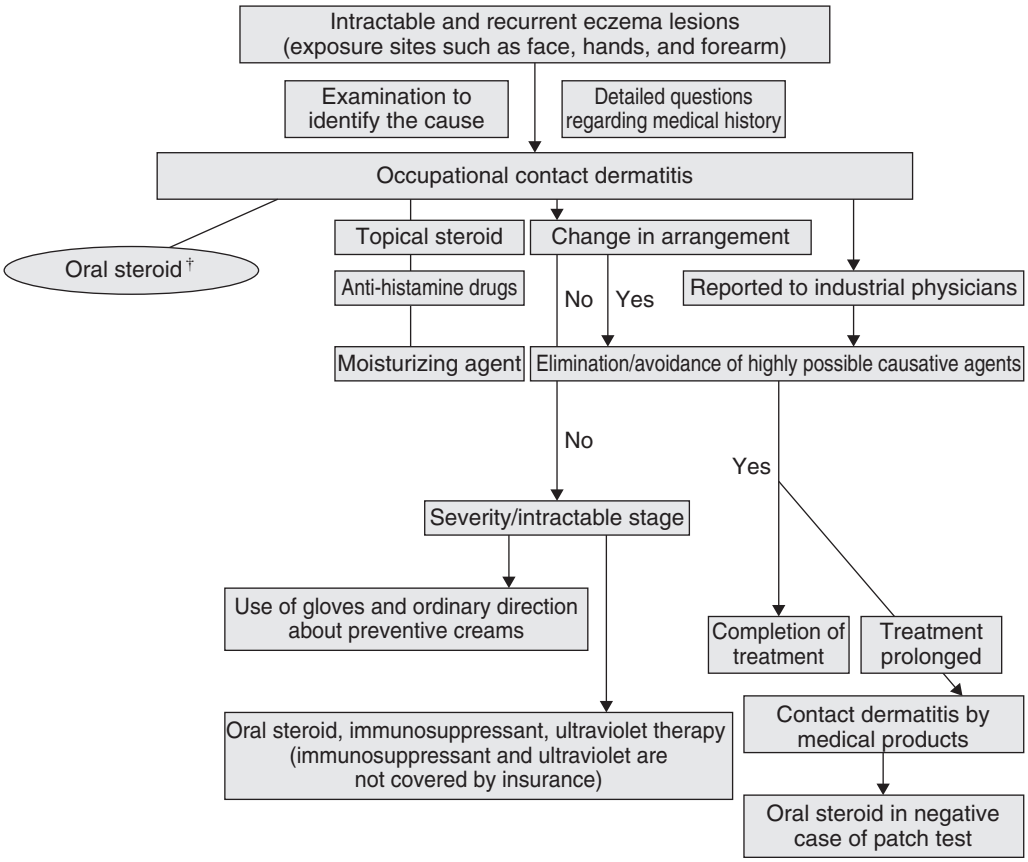


**Fig. 3** Algorism of treatment. From reference 1.
† Oral steroid is limited to severe cases. After elimination of the cause, 20-30 mg/day for about one week.

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?*
The criteria are the Japanese criteria[28,29] 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.[30]
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.[31]
CQ29: *What is the "as is prick test" using crude antigens?*
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 minutes. 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 antigen 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.[32]

CQ36: *What are drug therapies for occupational contact dermatitis?*[28] (Fig. 3)

(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.
  (4)-1 PUVA [A]
  (4)-2 NB-UVB [B]
(5) Barrier-cream gloves are effective for prevention.
  (5)-1 Irritant dermatitis [A]
  (5)-2 Contact dermatitis [B or C1]

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

Identifying and avoiding causative allergens.[28] [B]

### 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.[33] [A]

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

Gloves containing latex can be replaced with those with lower or no antigenicity.[34] [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.[35] [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?*

This is not prescribed as a duty.

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.[33] [A]

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

Refer to CQ30 from section 1.

## 5. Hypersensitive Pneumonitis

### 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 antigen 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%.[36]

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 antigens is high.

### 5.3. Causative Antigens

CQ6: *What are causative antigens?*

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 antigens of occupational hypersensitive pneumonitis?*

**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) |
| 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<br>Greenhouse rose cultivators | | (2) |
| 3. Bacteria, acid-fast bacillus, actinomycete | | | |
| *Saccharopolyspora rectivirgula (Micropolyspora faeni)* (Contaminated water) | Workers at humid working environments (humidifier lung, ventilator lung) | (1) | (1) |
| 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) |
| 6. Unconfirmed (candidate) | | | |
| Powder dust occurring at use of mobile bed disinfectant device | Assistant nurses | | (3) |

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

CQ8: *What are the causative antigens 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).

CQ9: *What are causative antigens 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?*

Antigen concentration, exposure period, exposure frequency, non-smoking, and so forth.[39]

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?*

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"[40] 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?*[41]

(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 antigens, measurement of antigen-specific antibody titer, lymphocyte proliferation test by addition of antigen, precipitation antibody test, challenge tests such as the antigen 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 antigen inhalation challenge test required for definitive diagnosis of occupational hypersensitive pneumonitis?*

It is useful for definitive diagnosis to identify antigens. 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.[42] [C1]

### 5.6. Treatment, Management, and Prognosis

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

The avoidance of antigens. Prednisolone as a sympto-

**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 37.

**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 38.

**Table 15** Clinical criteria for diagnosing anaphylaxis

| If one or more of the following three criteria are fulfilled, the probability of anaphylaxis is high. |
|---|
| 1. In addition of skin symptoms (systemic urticaria, itch, or flush) and/or mucosal symptoms (swelling of the lips, tongue, or uvula) occurring suddenly several minutes or hours later, the following complications: |
| Respiratory symptoms (dyspnea, wheezing, hypoxemia, etc.) |
| Hypotension, peripheral cardiovascular failure (faintness, impaired consciousness, or incontinence) |
| 2. Two or more following symptoms occurring suddenly several minutes or several hours after exposure to allergens or others (non-IgE allergens or non-allergic mast cell irritant factors): |
| Skin, mucosal symptoms (systemic urticarial, itch or flush, and swelling of the lips, tongue, and uvula) |
| Respiratory symptoms (dyspnea, wheezing, hypoxemia, etc) |
| Hypotension, peripheral cardiovascular failure (faintness, impaired consciousness, incontinence) |
| Persistent gastrointestinal symptoms (Spastic abdominal pain, vomiting) |
| 3. Hypotension occurring several minutes or several hours after an episode appeared to be exposed to known allergens (bee puncture or injection in specific immunotherapy) |
| In cases of infants/children, taking age into consideration, systolic arterial pressure decreases abnormally† or to less than 70% of normal pressure. |
| In adult cases, systolic pressure decreases to less than 90 mmHg or less than 70% of normal pressure. |

† Abnormal hypotension is less than 70 mmHg at one month to one year after birth, less than 70 mmHg + 2 × age at ages 1-10, less than 90 mmHg at ages 11-17. Normal heart rate is 80-140 times/min at ages 1-2, 80-120/min at age 3, and 70-115/min at age 4 or older. In infants, dyspnea rather than hypotension or shock often occurs, and tachycardia is a useful sign as a precursor to the shock.

Adapted from reference 1.

matic therapy is used for intermediate and severe cases of acute hypersensitive pneumonitis or cases of advancing chronic hypersensitive pneumonitis.[43,44] [A]

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

Avoidance of antigens is inevitably necessary and pathologic conditions after avoiding the antigen by leaving the job could progress.[43] [D]

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

Individuals with mild cases who avoid the antigen have a favorable prognosis. The prognosis is poor, however, in cases in which the antigen cannot be avoided or in chronic fibrotic cases that show poor response to treatment.[45]

### 5.7. Prevention

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

Complete elimination of causative antigens.[46] [A]

CQ23: *Is it effective to reduce exposure to antigens 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.[46] [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 antigens, 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 CQ30 from section 1.

## 6. Occupational Anaphylaxis (Shock)

### 6.1. Definition

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

It is an anaphylaxis that occurs or worsens because of exposure to a causative antigen at the workplace. [B]

### 6.2. Symptoms and Diagnosis of Anaphylaxis

CQ2: *What are diagnostic criteria for anaphylaxis?*

Although diagnostic criteria are nonexistent, clinical evaluation criteria based on the content of physician's questions and characteristic symptoms exist (Table 15).[47,48] [A]

### 6.3. Epidemiology of Anaphylaxis

CQ3: *What are the incidence and prevalence rates of anaphylaxis?*

The incidence is estimated to be 0.05-2.0% and tends to be increasing worldwide.[49] [C1]

CQ4: *What are main causes of anaphylaxis?*

**Table 16** Treatment of anaphylaxis at the acute stage

| |
|---|
| Items that must be executed first: |
| 1) Bring the written emergency protocol for recognizing and treating anaphylaxis and acquire proficiency in executing it. |
| 2) Eliminate known inducing factors (for example, if a contrast medium or drug is suspected, it must be discontinued). |
| 3) Conduct basic evaluations for first aid (vascular circulation, airway, respiration, consciousness condition, skin signs, body weight, etc.). |
| Treatments that must be conducted promptly: |
| 4) Call for help (for inpatients, the resuscitation team; for outpatients, the emergency and rescue team). |
| 5) When anaphylaxis is diagnosed, intramuscularly administer 0.1% adrenaline (0.01 mg/kg, the maximum dose is 0.5 mg in adults and 0.3 mg in children) at the anterior external side in the center of the femoral region.<br>Record the time of the injection and, when necessary, repeat the injection every 5-15 minutes. Usually, one or two injections is effective. |
| 6) Lay the patient down in supine position or, in case of dyspnea and/or vomiting, change the body position appropriately in accordance with the patient's condition. Uphold the lower limbs. Avoid standing up and coming to a sitting position too quickly. |
| Treatment should be conducted as needed: |
| 7) Administer oxygen at a high-flow volume (6-8 L/min.) through the nasotracheal airway using a facemask. |
| 8) Place a vascular needle or catheter (inner diameter 14-16 G), and administer 1-2 L of normal saline solution by drip infusion intravenously.<br>(In adults, for first 5-10 minutes, 5-10 mL/kg; in children, 10 mL/kg.) |
| 9) If needed, perform cardiopulmonary resuscitation by chest compression. |
| Continue to evaluate the situation. |
| 10) Regularly evaluate blood pressure, heart rate, respiratory condition, and oxygenation. If possible, monitor using a respiration/heart rate device. |

From reference 1.

**Table 17** 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<br>Wood dust: red cedar, lauan, Japanese clethra, mulberry tree<br>Cilia dust: sheep, cat, goat, horse, pig, scurf, mite, fungi, etc.<br>Other: sea squirt attaching to oyster shell, cocooning frame, drugs such as antibiotic, aspirin, sulfonamide, etc.<br>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, tar, cement, amine resin hardener (adhesive, condenser, coating compounds), glass fiber, rubber additive |

Adapted from reference 55.

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

### 6.4. Treatment of Anaphylaxis at the Acute Stage

CQ5: *What are the treatments at the acute stage?*
Those are shown in Table 16.[50] [A]

### 6.5. Causative Agents of Anaphylaxis

CQ6: *What are causes of occupational anaphylaxis?*
Foods (in children), drugs and insects (bees, etc.) (in adults) are reported as causes in many cases. Causes strongly associated with occupational exposure are bees and latex.[47,50] [B]

### 6.6. Anaphylaxis by Bee Puncture

CQ7: *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]
CQ8: *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]
CQ9: *What is the highest priority for prevention of anaphylaxis induced by bees?*
To avoid bee punctures by environmental arrangement. [A]
CQ10: *Is it effective to inspect for the presence or absence of atopic diathesis before employees begin working?*
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]
CQ11: *Is it effective to carry an adrenaline self-injection kit (EpiPen®) to treat anaphylaxis by bees?*
It is effective.[52] [A]
CQ12: *Is antigen-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]

### 6.7. Anaphylaxis by Latex

CQ13: *What occupations are susceptible to latex allergies?*
Medical workers and latex makers. [A]
CQ14: *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]
CQ15: *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]
CQ16: *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]

## 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 17).[55]

## Committee for Japanese Guideline for Diagnosis and Management of Occupational Allergic Diseases

Kunio Dobashi, Kazuo Akiyama, Atsushi Usami, Hiroo Yokozeki, Zenro Ikezawa, Naomi Tsurikisawa, Yoichi Nakamura, Kazuhiro Sato, Jiro Okumura, Mitsuru Adachi (Department of Clinical Research Center, International University of Health and Welfare/ Sanno Hospital, Tokyo), Kayoko Matsunaga (Department of Dermatology, Fujita Health University School of Medicine, Aichi), Kensei Naito (Department of Otolaryngology, Fujita Health University School of Medicine, Aichi), Tsugio Nakazawa (Gunma University, Gunma), Ken Ohta (National Hospital Organization, Tokyo National Hospital, Tokyo), Mitsuhiro Okano (Department of Otolaryngology - Head & Neck Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama), Kaoru Takayama (Department of Dermatology, Tokyo Medical and Dental University, Tokyo), Yuji Tohda (Department of Respiratory Medicine and Allergology, Kinki University School of Medicine, Osaka), Masanari Watanabe (Department of Respiratory Medicine and Rheumatology, Faculty of Medicine, Tottori University, Tottori), Masao Yamaguchi (Division of Respiratory Medicine and Allergology, Department of Medicine, Teikyo University School of Medicine, Tokyo, Japan).

## REFERENCES

1. Committee for Japanese Guideline for Diagnosis and Management of Occupational Allergic Diseases. *[Japanese Guideline for Diagnosis and Management of Occupational Allergic Diseases 2013]*. Tokyo: Kyowa Kikaku, 2013 (in Japanese).
2. Tarlo SM, Balmes J, Balkissoon R *et al*. Diagnosis and management of work-related asthma: American College of Chest Physicians Consensus Statement. *Chest* 2008; **134** (Suppl):1S-41.
3. Balmes J, Becklake M, Blanc P *et al*. American Thoracic Society statement: occupational contribution to the burden of airway disease. *Am J Respir Crit Care Med* 2003; **167**:787-97.
4. Mapp CE, Boschetto P, Maestrelli P, Fabbri LM. Occupational asthma. *Am J Respir Crit Care Med* 2005;**172**:280-305.
5. Malo JL, Chan-Yeung M. Agents causing occupational asthma. *J Allergy Clin Immunol* 2009;**123**:545-50.
6. Beach J, Russell K, Blitz S *et al*. A systematic review of the diagnosis of occupational asthma. *Chest* 2007;**131**: 569-78.
7. Nicholson PJ, Cullinan P, Taylor AJ, Burge PS, Boyle C. Evidence based guidelines for the prevention, identification, and management of occupational asthma. *Occup Environ Med* 2005;**62**:290-9.
8. Malo JL, Ghezzo H, L'Archieveque J, Lagier F, Perrin B, Cartier A. Is the clinical history a satisfactory means of diagnosing occupational asthma? *Am Rev Respir Dis* 1991; **143**:528-32.
9. Moore VC, Jaakkola MS, Burge PS. A systematic review of serial peak expiratory flow measurements in the diagnosis of occupational asthma. *Annals of Respiratory Medicine* 2010;**1**:31-44.
10. Japanese Society of Allergology. *[Asthma Prevention and Management Guideline 2012, Japan]*. Tokyo: Kyowa Kikaku, 2012 (in Japanese).
11. Rachiotis G, Savani R, Brant A *et al*. Outcome of occupational asthma after cessation of exposure: a systematic review. *Thorax* 2007;**62**:147-52.
12. Maestrelli P, Schlünssen V, Mason P, Sigsgaard T; ERS Task Force on the Management of Work-related Asthma. Contribution of host factors and workplace exposure to

the outcome of occupational asthma. *Eur Respir Rev* 2012;**21**:88-96.
13. Heederik D, Henneberger PK, Redlich CA; ERS Task Force on the Management of Work-related Asthma. Primary prevention: exposure reduction, skin exposure and respiratory protection. *Eur Respir Rev* 2012;**21**:112-24.
14. Nakamura S. [Definitions and positions of occupational allergies]. In: Nakamura S, Araki S, Usami A (eds). *[Occupational Allergy]*. Osaka: Nagai Shoten, 2011;3-5 (in Japanese).
15. Usami A. [From experiences with ninety cases of occupational allergies]. *[Journal of Japanese Society of Occupational and Environmental Allergy]* 2012;**9**:1-12 (in Japanese).
16. EAACI Task Force on Occupational Rhinitis, Moscato G, Vandenplas O, Gerth Van Wijk R *et al*. Occupational Rhinitis. *Allergy* 2008;**63**:969-80.
17. Committee for Practical Guideline for the Management of Allergic Rhinitis. *[Practical Guideline for the Management of Allergic Rhinitis in Japan]*, 7th edn. Tokyo: Life Science, 2013 (in Japanese).
18. Moscato G, Siracusa A. Rhinitis guidelines and implications for occupational rhinitis. *Curr Opin Allergy Clin Immunol* 2009;**9**:110-5.
19. Tokura Y. [Environmental dermatology—Practical knowledge for examining skin diseases caused by physicochemical stimulation and occupations—]. In: Tokura Y (ed). *[Environmental Dermatology—Skin Diseases from the Perspectives of the Environment and Occupations]*. Tokyo: Bunkodo, 2007 (in Japanese).
20. Hjorth N, Roed-Petersen J. Occupational protein contact dermatitis in food handlers. *Contact Dermatitis* 1976;**2**:28-42.
21. Tosti A, Guerra L, Morelli R, Bardazzi F, Fanti PA. Role of foods in pathogenesis of chronic paronychia. *J Am Acad Dermatol* 1992;**27**:706-10.
22. Kanerva L. Occupational protein contact dermatitis and paronychia from natural rubber latex. *J Eur Acad Dermatol Venereol* 2000;**14**:504-6.
23. Wagner S, Breiteneder H. The latex-fruit syndrome. *Biochem Soc Trans* 2002;**30**:935-40.
24. Burge PS, O'Brien IM, Harries MG, Pepys J. Occupational asthma due to inhaled carmine. *Clin Allergy* 1979;**9**:185-9.
25. Nicholson PJ, Llewellyn D, English JS; Guidelines Development Group. Evidence-based guidelines for the prevention, identification and management of occupational contact dermatitis and urticaria. *Contact Dermatitis* 2010;**63**:177-86.
26. Matsukura S, Aihara M, Ikezawa Z. [Pathogenesis of food allergy and percutaneous sensitization]. *[Allergology & Immunology]* 2011;**19**:46-55 (in Japanese).
27. Bourke J, Coulson I, English J; British Association of Dermatologists. Guidelines for care of contact dermatitis. *Br J Dermatol* 2001;**145**:877-85.
28. Committee for Guideline for Diagnosis of Contact Dermatitis. Japanese Dermatological Association. [Guideline for diagnosis of contact dermatitis]. *[Jpn J Dermatol]* 2009;**119**:1757-93 (in Japanese).
29. Mochitomi Y, Fukumaru R, Sakamoto K *et al*. [Results of routine patch testing for the past 5 years]. *[J Environ Dermatol]* 2002;**11**:38-46 (in Japanese).
30. Methodology of open (non-prick) testing, prick testing, and its variant. In: Lachapelle JM, Maibach HI (eds). *Patch Testing and Prick Testing*, 3rd edn. Heidelberg: Springer-Verlag, 2012;159-70.
31. Matsunaga K. [An encouragement of prick tests]. *[Journal of the Japan Organization of Clinical Dermatologists]* 2000;**63**:54-8 (in Japanese).
32. Akasawa A, Matsunaga K. *[Guideline for the Management of Latex Allergy]*. Tokyo: Kyowa Kikaku, 2009 (in Japanese).
33. Nicholson PJ, Llewellyn D, English JS, on behalf of the Guidelines Development Group. Evidencebased guidelines for the prevention, identification and management of occupational contact dermatitis and urticaria. *Contact Dermatitis* 2010;**63**:177-86.
34. Diepgen TL. Occupational skin diseases. *J Dtsch Dermatol Ges* 2012;**10**:297-313.
35. Wigger-Alberti W, Elsner P. Do Barrier creams and gloves prevent or provoke contact dermatitis? *Am J Contact Dermatitis* 1998;**9**:100-6.
36. Yoshizawa Y. [Hypersensitivity pneumonitis]. In: Sugimoto T, Yazaki Y (eds). *[Internal Medicine]*, 9th edn. Tokyo: Asakura Publishing, 2007;699 (in Japanese).
37. Suga M. [Summer-type hypersensitivity pneumonitis and its surroundings]. *[Jpn J Chest Dis]* 2003;**63**:97-106 (in Japanese).
38. Inase N, Yasui M, Unoura K *et al*. *[National Investigation of Chronic Hypersensitivity Pneumonitis. Annual Report of Research Project for Diffuse Pulmonary Disease, Research on Specific Diseases]*. Ministry of Health, Labour and Welfare, 2010;191-4 (in Japanese).
39. Agostini C, Trentin L, Facco M, Semenzato G. New aspects of hypersensitivity pneumonitis. *Curr Opin Pulm Med* 2004;**10**:378-82.
40. *[National Investigation of Chronic Hypersensitivity Pneumonitis. Annual Report of Research Project for Diffuse Pulmonary Disease, Research on Specific Diseases]*. Ministry of Health, Labour and Welfare, 1991;13 (in Japanese).
41. Patel AM, Ryu JH, Reed CE. Hypersensitivity pneumonitis: current oncepts and future questions. *J Allergy Clin Immunol* 2001;**108**:661-70.
42. Zacharisen MC, Fink JN. Hypersensitivity pneumonitis and related conditions in the work environment. *Immunol Allergy Clin North Am* 2011;**31**:769-86.
43. Bourke SJ, Dalphin JC, Boyd G, McSharry C, Baldwin CI, Calvert JE. Hypersensitivity pneumonitis: current concepts. *Eur Repir J* 2001;**18**:81s-92.
44. Yoshizawa Y. [Hypersensitivity pneumonitis]. In: Nukiwa T, Sugiyama Y, Kadota J (eds). *[Treatment of Patients Returning to Clinic for Respiratory Illnesses 2010-2012]*. Tokyo: Nankodo, 2010;342-5 (in Japanese).
45. Selman M, Pardo A, King TE Jr. Hypersensitivity pneumonitis: insights in diagnosis and pathobiology. *Am J Respir Crit Care Med* 2012;**186**:314-24.
46. Paul L, Lehrman SG, Aronow WS. Hypersensitivity pneumonitis: evaluation and management. *Comp Ther* 2009;**35**:177-87.
47. Sampson HA, Muñoz-Furlong A, Campbell RL *et al*. Second symposium on the definition and management of anaphylaxis: summary report Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;**117**:391-7.
48. Simons FE, Ardusso LR, Bilò MB *et al*; World Allergy Organization. World Allergy Organization anaphylaxis guidelines: summary. *J Allergy Clin Immunol* 2011;**127**:587-93.e1-22.
49. Lieberman P, Camargo CA Jr, Bohlke K *et al*. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Ana-

phylaxis Working Group. *Ann Allergy Asthma Immunol* 2006;**97**:596-602.
**50**. Lieberman P, Nicklas RA, Oppenheimer J *et al*. The diagnosis and management of anaphylaxispractice parameter: 2010 Update. *J Allergy Clin Immunol* 2010;**126**:477-80.
**51**. Matsuura M. [Ecology of bee and bee poison]. *Hifu* 1990; **32**:1-5 (in Japanese).
**52**. Hirata H, Hayashi Y, Fukuda T. [Epidemiological survey of employees]. In: Nakamura S, Araki S, Usami A (eds). *[Occupational Allergy]*. Osaka: Nagai Shoten, 2011;252-9 (in Japanese).
**53**. Bonifazi F, Jutel M, Biló BM *et al*, EAACI Interest Group on Insect Venom Hypersensitivity. Prevention and treatment of hymenoptera venom allergy: guidelines for clinical practice. *Allergy* 2005;**60**:1459-70.
**54**. Japanese Labor Standards Act; Article 75-Article 84 (in Japanese).
**55**. Ordinance for Enforcement of the Japanese Labor Standards Act; Article 35, Appended Table. [Paragraph 1-2 Illness in the course of employment under the provisions of Article 75.2 of Chapter VIII "Accident Compensation" of the Japanese Labor Standards Act, and Paragraph 2.2 (4) (d) and (e) of the same] (in Japanese).