JDA Japanese Dermatological Association
THE JOURNAL OF DERMATOLOGY
doi: 10.1111/1346-8138.15090
Journal of Dermatology 2019; ●●: 1–49

GUIDELINE

Clinical practice guidelines for the management of atopic dermatitis 2018

Norito KATOH,[1,*] Yukihiro OHYA,[2,*] Masanori IKEDA,[3] Tamotsu EBIHARA,[4] Ichiro KATAYAMA,[5] Hidehisa SAEKI,[6] Naoki SHIMOJO,[7] Akio TANAKA,[8] Takeshi NAKAHARA,[9] Mizuho NAGAO,[10] Michihiro HIDE,[8] Yuji FUJITA,[7] Takao FUJISAWA,[11] Masaki FUTAMURA,[12] Koji MASUDA,[1] Hiroyuki MUROTA,[13] Kiwako YAMAMOTO-HANADA[2]

[1]Department of Dermatology, Kyoto Prefectural University of Medicine Graduate School of Medical Science, Kyoto, [2]Allergy Center, National Center for Child Health and Development, Tokyo, [3]Department of Pediatric Acute Medicine, Okayama University Graduate School of Medicine, Dentistry, and Pharmacuetical Sciences, Okayama, [4]Department of Dermatology, Keio University School of Medicine, Tokyo, [5]Department of Dermatology, Graduate School of Medicine, Osaka University, Suita, [6]Department of Dermatology, Graduate School of Medicine, Nihon Medical School, Tokyo, [7]Department of Pediatrics, Graduate School of medicine, Chiba University, Chiba, [8]Department of Dermatology, Hiroshima University Graduate School of Biomedical Sciences, Hiroshima, [9]Division of Skin Surface Sensing, Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Divisions of [10]Clinical Research, [11]Allergy, National Hospital Organization Mie National Hospital, Tsu, [12]Division of Pediatrics, National Hospital Organization Nagoya Medical Center, Nagoya, [13]Department of Dermatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Download Clinical Guidelines

ABSTRACT

Atopic dermatitis (AD) is a disease characterized by relapsing eczema with pruritus as a primary lesion. The current strategies to treat AD in Japan from the perspective of evidence-based medicine consist of three primary measures: (i) the use of topical corticosteroids and tacrolimus ointment as the main treatment for the inflammation; (ii) topical application of emollients to treat the cutaneous barrier dysfunction; and (iii) avoidance of apparent exacerbating factors, psychological counseling and advice about daily life. The guidelines present recommendations to review clinical research articles, evaluate the balance between the advantages and disadvantages of medical activities, and optimize medical activity-related patient outcomes with respect to several important points requiring decision-making in clinical practice.

Key words: atopic dermatitis, clinical practice guidelines, clinical questions, evidence-based medicine, treatment.

CHAPTER I

Introduction

Atopic dermatitis (AD) is frequently encountered in clinical practice. There have been two clinical practice guidelines for the management of AD. Namely, one was published by the Japanese Dermatological Association (JDA), and was basically designed for dermatologists who treat patients in primary care to advanced specialty-required phases in the treatment of AD.[1–6] The other was published by the Japanese Society of Allergology (JSA) and research groups of the Japanese Ministry of Health, Labour and Welfare (MHLW), whose expected users were physicians, but not dermatologists, who are involved in management of allergic diseases.[7–13] The present guideline is a revised edition updated with novel findings (generally, manuscripts published by the end of December 2015 are reffered to) regarding AD published in Japan and abroad by physicians and healthcare professionals engaged in the treatment of patients with AD following the consolidation of two practical guidelines.

Descriptions regarding medical activities in the present guidelines reflect an aim and goal in the current strategies to treat AD in Japan from the perspective of evidence-based

Correspondence: Norito Katoh, M.D., Ph.D., Department of Dermatology, Kyoto Prefectural University of Medicine Graduate School of Medical Science, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan. Email: nkatoh@koto.kpu-m.ac.jp
*Norito Katoh and Yukihiro Ohya, Chairperson and Vice-Chairperson, respectively, of Committee for Clinical Practice Guidelines for the Management of Atopic Dermatitis 2018.
This is the English version of the original Japanese manuscript for Clinical Practice Guidelines for the Management of Atopic Dermatitis 2018, published in the Japanese Journal of Dermatology 128: 2431-2502, 2018.
Received 19 August 2019; accepted 21 August 2019.

medicine. They can be utilized as material for evaluations of decision-making in clinical practice. Attending physicians must make a final decision in cooperation with patients so that their values and preferences are reflected.

Disclaimer

If the contents of medical activities based on an individual's circumstances differ from those stated in the present guidelines, they may not be checked, or the experience of healthcare professionals may not be denied. In contrast, even if the contents stated in the present guidelines are not performed, the responsibilities of physicians may not be pursued. Use of these guidelines as a basis for use in medical disputes or in medical litigation deviates from their original purpose.

Some evidence (Japan, other countries)-based therapies with drugs that are not covered by health insurance (unapproved drugs) are described in the guidelines, with the grade of recommendation. The idea that drugs or therapies described in the guidelines are available in clinical practice is not correct. This also applies to the use of drugs of which contraindications or careful administration is described in the package inserts. Even if unapproved drugs are described in the guidelines, restrictions are not eliminated. Individual drugs should be managed based on the contents of the package insert or based on the latest information regarding safety.

Conflicts of interest

Each committee member declared the status of potential conflict of interest (COI) based on the standards of conflict of interest stipulated by their respective institute of affiliation (or The Japanese Association of Medical Sciences COI management guidelines [http://jams.med.or.jp/guideline/coi_guidelines.pdf]). The costs to develop these guidelines have been supported by: grants for research from the JDA; Grant-in-Aid for Scientific Research from the MHLW (as a Research Project on Measures for Intractable Diseases [Research on Allergic Disease and Immunology]). Committee members have not received any remuneration for developing the guidelines or attending related meetings. There has been no intervention by the JDA or JSA that may influence the contents of the guidelines. To avoid any influence by potential COIs, if any, on the guidelines, all recommendations were determined based on consensus voting, rather than on individual opinion, in reference to the opinions of the representatives of the JDA and JSA (public comment).

Members of the Committee for this guideline and their relatives defined within the first degree of consanguinity self-reported whether or not they had received some remuneration that corresponds to one of the following categories from companies or other bodies involved with the diagnosis or treatment of AD. The target period was between 1 April 2015 and 31 March 2017: (i) directors' or advisors' fees; (ii) shares of profit; (iii) royalties; (iv) lecture fees; (v) manuscript fees; (vi) research costs; (vii) scholarship donations; (viii) chairs donated by companies or other bodies; and (ix) relevant company/organization: travelling costs or gifts. Corresponding companies and bodies: Norito Katoh: Mitsubishi Tanabe Pharma Corporation (iv, vii), Maruho Co., Ltd. (iv, vii), Novartis Pharma K.K. (vi), Kyowa Hakko Kirin Co., Ltd.(iv, vi), Torii Pharmaceutical Co., Ltd. (iv), Taiho Pharma Co., Ltd. (iv, vii), Sanofi K.K. (vi), Mochida Healthcare Co., Ltd. (vi), Yukihiro Ohya: Maruho Co., Ltd. (iv), Hidehisa Saeki: Mitsubishi Tanabe Pharma Corporation (iv, vii), Maruho Co., Ltd. (iv, vii), Tokiwa Pharmaceutical Co., Ltd. (vii), Torii Pharmaceutical Co., Ltd. (vii), Eisai Co., Ltd. (vii), Taiho Pharma Co., Ltd. (iv), Kyowa Hakko Kirin Co., Ltd. (iv), Kyorin Pharmaceutical Co., Ltd. (iv), Sanofi K.K. (iv), Takao Fujisawa: Maruho Co., Ltd. (iv), Hiroyuki Murota: Maruho Co., Ltd. (iv), Mitsubishi Tanabe Pharma Corporation (iv), Taiho Pharma Co., Ltd. (iv), Sanofi K.K. (iv), Takeshi Nakahara: Maruho Co., Ltd. (viii), Naoki Shimojo: Torii Pharmaceutical Co., Ltd. (iv), Ichiro Katayama: Maruho Co., Ltd.(iv), Michihiro Hide: Mitsubishi Tanabe Pharma Corporation (iv, vii), Maruho Co., Ltd. (iv, vii), Novartis Pharma K.K. (iv, vi), Taiho Pharma Co., Ltd. (iv), Bathclin Corp. (vi), Sanofi K.K. (vi), Akio Tanaka: Sanofi K.K. (iv), Novartis Pharma K.K. (vi), Bathclin Corp. (vi), Sanofi K.K. (vi).

Definition, pathogenesis, epidemiology, diagnosis, severity

Definition of atopic dermatitis: Concept of disease

Atopic dermatitis is a pruritic eczematous dermatitis; its symptoms chronically fluctuate with remissions and relapses. Most individuals with AD have atopic diathesis (atopic diathesis).

AD is an eczematous skin disease characterized by symmetrical distribution, and the skin areas typically affected vary depending on age.[6,13] AD may develop during infancy or early childhood and may lead to remission during childhood; however, AD may become chronic in some cases with repeated relapses without remission, and present with characteristic eczematous lesions that persist until adulthood. (i) personal or family history (asthma, allergic rhinitis and/or conjunctivitis, and AD); and/or (ii) predisposition to overproduction of immunoglobulin (Ig)E antibodies. The presence of allergy is not always necessary for the definition of AD. This differs from allergic rhinitis for which the presence of allergy is mandatory for diagnosis.[14] Urticaria is not considered when investigating family and medical history. Total serum IgE levels and allergen-specific IgE antibody levels are considered as disease markers, as for the tendency to produce IgE antibodies. As total IgE level increases in response to disease activity, it is often low in patients with mild AD. In mild AD, the allergen-specific IgE antibody level can be a marker of disease.

Pathophysiology

Atopic dermatitis is a multifocal disease with multiple etiologies. Different etiologies are involved in the pathogenesis of AD within the context of atopic diathesis and hypersensitivity reactions of organs including skin that may be caused by causative factors (physical constitution) and the vulnerability of barrier functions. The fact that there is no hierarchy among those etiologies contributes to the diversity of symptoms or phenotypes of AD.

Skin hypersensitivity. Abnormalities of the horny cell layer: The horny cell layer is a thin membrane structure of 10 to 20 μm

located on the surface and outermost layer of the skin and is comprised of a dozen horny cells and intercellular lipids of the stratum corneum. The stratum corneum also forms a barrier contributing to the prevention of leakage of body fluids, retention of internal water within the cell layers, and contributes to biological defense (Figs 1 and 2). If the barrier function of the horny cell layer is dysfunctional, skin irritability to non-specific stimuli is enhanced, and allergen sensitization and inflammation are likely to occur.[13] Intercellular lipids of the stratum corneum are mainly composed of ceramide, cholesterol, and free fatty acids, and in the case of AD, the function of the intercellular lipids of the stratum corneum deteriorates due to an abnormal decrease of ceramide content, and the moisture retention capacity is impaired.[15,16] The horny cell layer consisting of keratin and filaggrin is structurally robust. Its external membrane is supported by a cornified cell envelope, which contributes to forming a strong barrier on the skin surface. Filaggrin loss-of-function mutation and filaggrin deficiency associated with inflammation have been observed in AD.[17,18]

Abnormallities of the epidermis: The epidermis also plays an important role in skin barrier function. The epidermis has an intercellular adhesion structure known as tight junctions (Fig. 1). In particular, tight junctions located in the granular layer regulate the movement of substances of from inside to outside the body. Decreased claudin-1 expression, which serves an important role in the formation of tight junctions and the presence of single nucleotide polymorphisms in the claudin-1 gene have been observed in patients with AD.[19,20]

Mechanisms involved in inflammation. A decline in skin barrier function may allow allergens to easily penetrate the skin (Fig. 2). Allergens, which are foreign (non-self) molecules, are eliminated by immunization and allergic reactions. Allergens, such as the dust mite allergen, as well as protein allergens, induce type 2 immune reactions through protease activity.[6] Helper T cells can be divided into Th1 and Th2 cells. Th1 cells have been demonstrated to be involved in cell-mediated immunity, while Th2 cells are mainly associated with allergic reactions. Interleukin (IL)-33, IL-25, and thymic stromal lymphopoietin (TSLP) produced by epidermal keratinocyte are

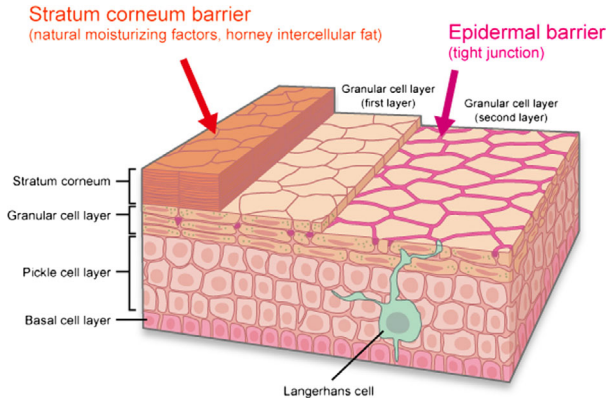

Figure 1. Construction for epidermal barrier.

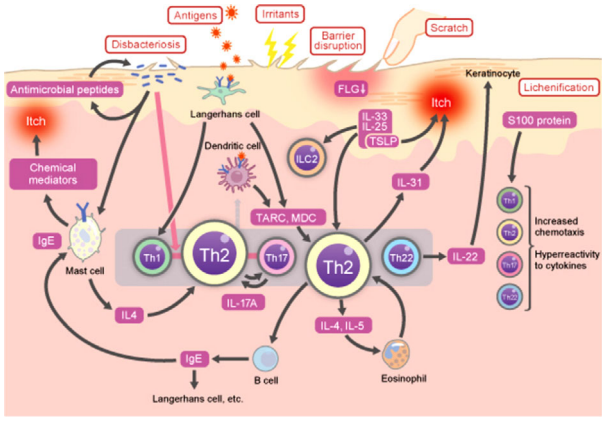

Figure 2. Pathogenesis of atopic dermatitis.

associated with Th2 cell migration to the lesion. Serum thymus and activation-regulated chemokine (TARC) levels are also used as a marker of short-term progression.[21,22] The type 2 immune response leads to allergen-specific induction of IgE antibodies. Langerhans cells and mast cells express the high affinity IgE receptor (FcεRI) and release cytokines and chemical transmitters (e.g. histamine) via binding of allergen-specific IgE to induce inflammation. Th22 cells produce IL-22 after migrating to the skin; likely, via regulation by activated cutaneous dendritic cells, which induces epidermal acanthosis.[23] S100 protein produced by epidermal damage further activates lymphocytes.[24]

Pruritus. Atopic dermatitis skin lesions release various substances (pruritogens), including cytokines and chemokines (e.g. IL-31, IL-4, and TSLP), and chemical mediators that induce pruritus. These substances act on nerves and thereby induce itching, which ultimately leads to scratching behavior. Scratching results in the further worsening of dermatitis. Skin hypersensibility can be observed in chronic inflammatory conditions such as AD. Hypersensibility may be partially caused by the extension of the cutaneous sensory nerve fibers to immediately below the horny cell layer of the skin surface due to dryness or inflammation.[25] An abnormal hypersensitivity reaction in which algesia or heat pain stimulation induces itching has also been reported for AD.[26–28] Besides dermatitis, visual and auditory stimulation suggestive of itching, such as the skin scratching sound, induces itching and becomes prominent in AD.[29,30] Imbalances between the sympathetic nerve system and the parasympathetic nerve system, emotional and psychogenic factors, and disturbances in life rhythm are associated with onset and worsening of itch.[31,32]

Genetic factors. Some genes have been described as candidate genes associated with AD: *CTLA4, IL18, TLR9, CD14, CARD4, PHF11, TLR2, SCCE, MCC, IL4R, GM-CSF, TIM1, CARD15, GSTT1, SPINK5, SCYA11, TGFβ1, IL-13, RANTES, IL4, and FCER1B*[13].In addition, 2q12 (*IL1RL1/IL18R1/IL18RAP*), 3q21.33 (*GLB1*), 3q13.2 (*CCDC80*), 6p21.3 (MHC region), 7p22

(*CARD11*), 10q21.2 (*ZNF365*), 11q15.4 (*OR10A3/NLRP10*), 20q13 (*CYP24A1/PFDN4*) have been reported to be an AD-related region based on genome-wide linkage analysis from Japanese samples.[33]

Factors involved in onset and exacerbation

When considering clinical pathology, factors associated with disease onset and worsening should be taken into account. In addition to adherence to treatment, exposure to environmental factors including allergens and stimuli in the work place and daily environment, lifestyle factors, and temperature, in addition to dysregulation of physiological changes in skin function are associated with maintenance and exacerbation of dermatitis. A feeling of warmth, sweating, wool fibers, psychological stress, food, alcohol drinking, and the common cold are considered to be particularly important as induction and exacerbating factors of itch in AD.[34] The details relative to onset and exacerbating factors and their specific measures will be discussed below.

Epidemiology

Prevalence of AD and its worldwide differences. An epidemiological survey of the prevalence of AD worldwide was conducted by the International Study of Asthma and Allergies in Childhood (ISAAC) from 1994 to 1996.[35] This was a large-scale questionnaire survey conducted across 56 countries. The results showed that the overall prevalence of AD among 6- to 7-year-old children was 7.3%, ranging from 1.1% in Iran to 18.4% in Sweden, and was 7.4% among children 13 to 14 years old, ranging from 0.8% in Albania to 17.7% in Nigeria. Overall, the prevalence rate was higher in Oceania and Northern Europe, while it was lower in Asian countries and Eastern Europe. The highest prevalence was observed in Sweden (18.4%, among children 6 to 7 years old; 14.5% among those 13 to 14 years old), followed by Finland (14.5% in children 13 to 14 years of age).

Another epidemiological survey was conducted from 2001 to 2003 by the ISAAC (Japan did not participate).[36] Some countries that had previously reported a higher prevalence among 13- to 14-year-old subjects in phase I of the study showed a decreased prevalence in phase III (e.g. United Kingdom, from 15.8% to 10.6%; New Zealand, from 12.7% to 8.8%).

Epidemiology of AD in Japan. Prevalence during childhood to early adolescence: AD generally has onset during infancy and childhood, and the number of newly diagnosed patients decreases with age. It is expected that some patients will shift to adult type AD. In an analysis of 14 studies, reporting the results of AD prevalence surveys conducted using dermatological medical examination data over a 10-year period (from 1992 to 2002) in Japan, the prevalence rates for different age groups varied and depended on the report. AD prevalence rates ranged from 6 to 32% in infants, 5 to 27% in pre-school children, 5 to 15% in school-age children, and 5 to 9% in university students, however, overall prevalence tended to decrease with increasing age.[37] A nationwide AD prevalence survey was conducted from 2000 to 2002 using medical examination records from public health centers and elementary schools as a part of the Health Labor Sciences Research initiative.[38,39] Base facilities were set in Hokkaido, the Shikoku-area, and in Kyushu; medical examinations were performed by specialists. Figure 3a shows the prevalence rates stratified according to age. National averages for prevalence rates based on medical examination were 12.8% (351/2744), 9.8% (631/6424), 10.6% (1185/11 230), and 8.2% (684/8317) in 4-month-old infants, 1.5-year-old children, sixth grade school children, and university students, respectively. Although the prevalence rate by district is believed to be higher in city areas and lower in suburban areas, no significant difference in the prevalence rates among school children was observed between city areas and suburban areas in this survey. Moreover, no differences in rates comparing boys and girls were also observed.

Prevalence rates in the adult population: Between 2006 and 2008, the Health Labor Sciences Research study, a prevalence survey of AD in adults, was conducted by medical examinations performed on 4826 university staff members of Tokyo University, Kinki (Kindai) University, and Asahikawa Medical University.[38] The prevalence rates of AD by age group were 10.2%, 8.3%, 4.1%, and 2.5% in adults in their 20s, 30s, 40s, and 50s to 60s, respectively (Fig. 3b). The prevalence rate stratified by sex was 5.4% and 8.4% in male and female participants, respectively, showing a higher prevalence in women, which was particularly higher in women in between the ages of 20 and 30 years. This medical examination survey among university staff can be considered reference data given the small sample size, and the geographic areas and occupations surveyed were also limited. Nonetheless, the results of this survey indicate that AD may be the most common cutaneous disease observed among young adults in their 20s and 30s as well as in children and adolescents.

Severity: Figure 4a shows the distribution of patients with AD by severity among individuals aged 1.5 years to university students in a nationwide epidemiological survey. The proportion of patients with moderate or severe AD according to age was 16%, 15%, 24%, 28%, and 27% for 1.5-year-old infants, 3-year-old children, first grade school children, sixth grade school children, and university students, respectively.[39] Based on these results, worse symptoms were generally more often exhibited in pre-school children than in school-aged children. The proportion of patients with more severe AD according to age was 1.7%, 2.2%, and 5.5% in first grade school children, sixth grade schoolchildren, and university students, respectively, showing a tendency of AD to increase in prevalence with age.

The distribution of AD according to severity based on the medical examination survey conducted among university staff of Tokyo university, Kindai University, and Asahikawa Medical University was 80.1%, 17.7%, 1.5%, and 0.6% for mild, moderate, severe, and most severe cases. The proportion of patients with moderate or severe AD was smaller for individuals in their 40s or older than in individuals in their 20s and 30s (Fig. 4b).[40]

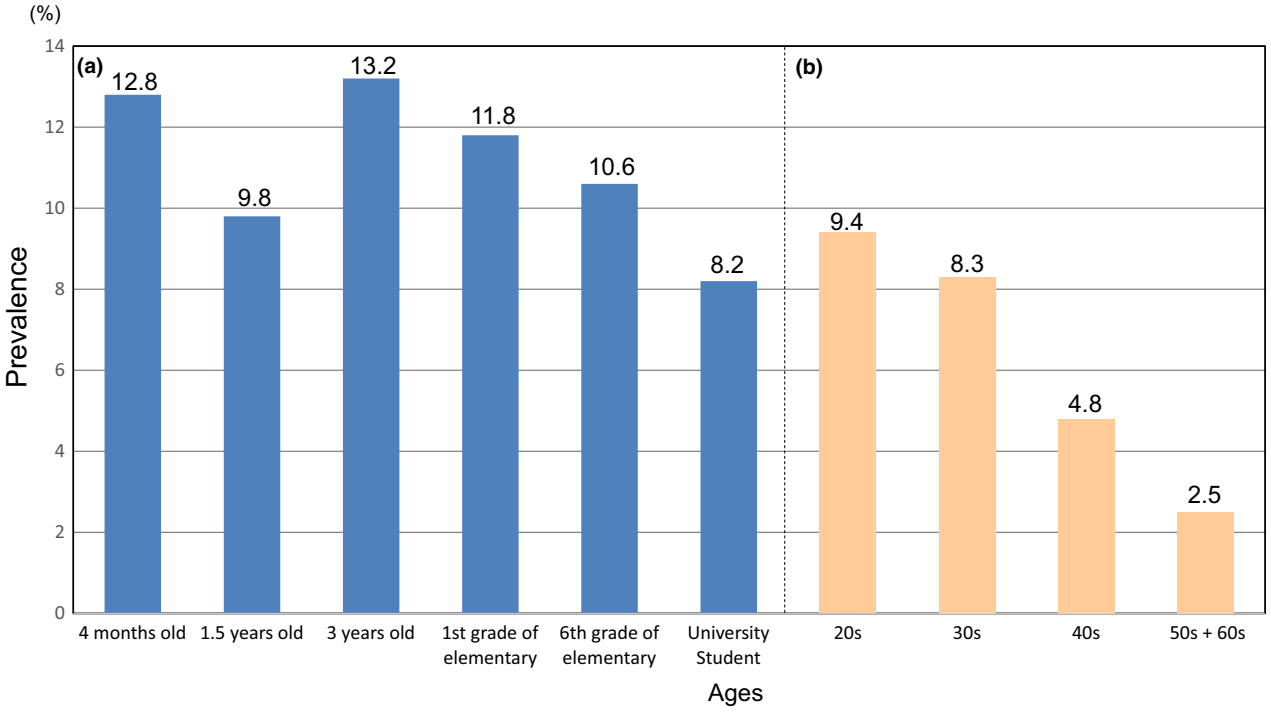

Figure 3. Prevalence of atopic dermatitis by age (Survey year a: fiscal year 2000–2002, b: fiscal year 2006–2008)[38–40] months old from: Hokkaido, Kanto, Chubu, Kinki, Chugoku, Shikoku, and Kyushu (seven districts, *n* = 2744). Children with 1.5 years old, 3 years old, 1st grade of elementary, 6th grade of elementary from: Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku, Shikoku, and Kyushu (eight districts, *n* = 6424). University students from: University of Tokyo, Kinki University, Hiroshima University (*n* = 8317). Adult (20s to 60s) from: Personnel of University of Tokyo and Kinki University (*n* = 2943). Modified from Ministry of Health and Welfare, Japan.[38–40]

Annual changes in prevalence: The number of patients affected by AD has been increasing. A survey of changes in prevalence over time of physician-diagnosed AD in the same geographical area was conducted in the Aichi prefecture. The results showed that AD prevalence was 2.8% among 3- to 15-year-old children in 1981, and increased in a stepwise fashion to 6.6% in 1992. After 1992, it reached a plateau, and the prevalence rate remained 6.6% in 1999, as well.[41]

According to the AD prevalence survey in infants conducted by the research project of child and maternal health of the MHLW, the prevalence of nationwide physician-diagnosed AD was 5.3% and 8.0% in 1.5-year-old children and in 3-year-old children, respectively, in 1992.[42] It should be noted that there was a slight difference in the survey method used between the nationwide survey conducted during the 2000 to 2002 period and the survey conducted in 1992, nonetheless, the number of infants reported with AD may have increased. In an allergic diseases prevalence survey conducted in elementary schoolchildren living in Western Japan, the prevalence rate of AD in 2002 was lower than that in 1992, although this was a questionnaire-based survey.[43] Conversely, in an epidemiologic study using ISAAC questionnaires on the prevalence of allergic diseases in schoolchildren (aged 7 to 15 years old) in Kyoto City, the prevalence of AD increased slightly from 4.2% (1996) to 5.6% (2006).[44]

Studies on the prognosis of AD. Studies abroad: In Italy, Ricci *et al*. followed-up 252 children diagnosed with AD, ranging in age from 6 months to 3 years, who were referred to specialized hospitals for an average of 16.9 years to evaluate their clinical course.[45] During the follow-up period, complete remission of AD was observed in 60.5% of children. Sensitization to egg was associated with a delay in remission. Illi *et al*. extracted data from 1314 of 7609 neonates born in six facilities across five cities in Germany in 1990 and followed up the children until age 7 years. Of these 1123 children (85.5%), 13.4% were diagnosed with AD before the age of 1 year, and the cumulative prevalence rate at 2 years of age was 21.5%.[46] Of the children diagnosed with AD before age 2 years, 43.2% were cured by age 3 without any evidence of eczema until age 7, although, eczema appeared until age 7 in 38.3% of children, and symptoms persisted in 18.7% of children. Poor prognostic factors included AD severity at age 2 years, allergen sensitization (particularly to wheat and soybean), a strong family history, and early wheezing complications.

While there are few studies on the prognosis of AD in children (from pre-adolescence to adulthood), in a report from Sweden that followed-up subjects who were 20 years old or older at the initial consultation for 25 to 38 years, symptoms persisted in the latter 12 months of follow-up in more than half of the subjects.[47]

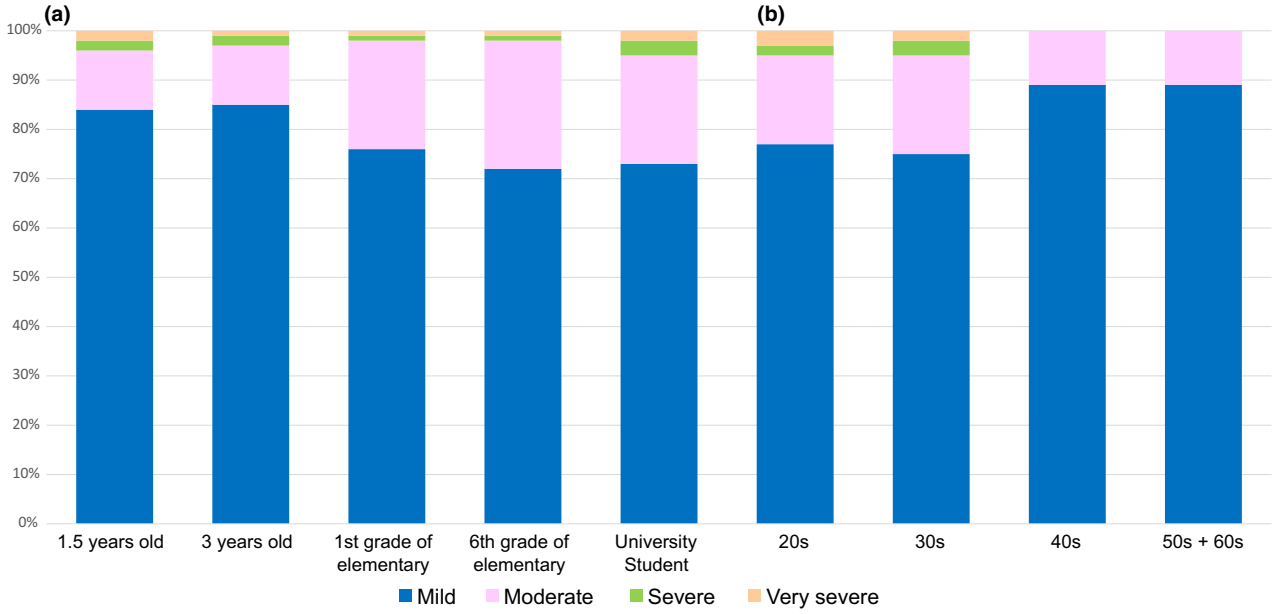

Figure 4. Atopic dermatitis by severity (Survey year a: fiscal year 2000–2002, b: fiscal year 2006–2008).[38–40]

Studies in Japan: Regarding onset and clinical course of AD during infancy, the Health Labor Sciences Research 2006–2008 study reported the results of a survey in which infants were followed-up from 4 months to 3 years of age using medical examination data obtained in Yokohama city, Chiba city, and Fukuoka city. According to this report, the onset of AD was observed in 16.2% of infants who participated in the 4-month medical examination (Fig. 5).[48] Interestingly, 70% of children diagnosed with AD within the 4-month period showed complete remission at 1.5 years of age. In this survey, the cumulative onset rate up to 3 years of age was over 30%, which is very similar to the rates reported in studies from abroad. Fukiwake *et al*. (Kyushu University) studied

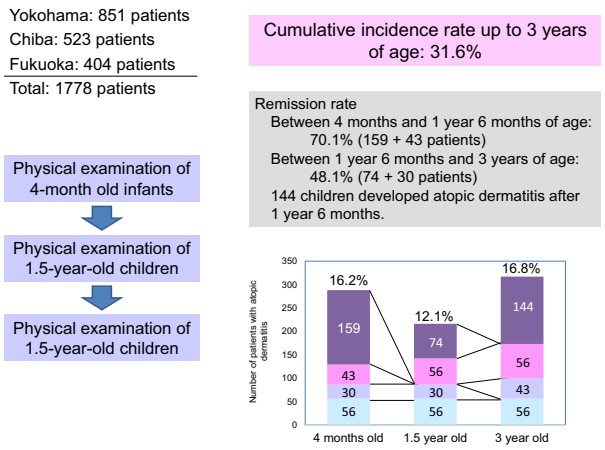

Figure 5. Onset and clinical course of atopic dermatitis based on individual follow-up study from 4 months after birth to 3 years of age (Survey year: fiscal year 2006–2008).[48]

kindergarten children in the Ishigaki Island for 4 years and reported that 53 of 74 (71.6%) children diagnosed with AD showed complete remission within 3 years, while 5.5% of children not previously diagnosed with AD, were eventually diagnosed with new onset AD within 3 years.[49]

Ohshima *et al*. followed-up 169 infants less than 1 year old diagnosed with AD by pediatric allergy specialists for 4 years and reported that symptoms improved and disappeared in 51% and 34%, respectively.[50] Anan *et al*. carried out a questionnaire survey among family members of patients considered to have achieved a spontaneous remission and reported that spontaneous remission was observed starting at 2 to 3 years of age, while 50% of the children achieved spontaneous remission at age 8 to 9 years. Approximately 90% of children achieved spontaneous remission after age 16 years.[51] Wakamori *et al*. reported that three-quarters of children who had AD at first grade of elementary school experienced remission before entering junior high school. The study surveyed the outcome of AD in elementary school children and junior high school children using dermatological medical examination data spanning more than 10 years in the mountainous areas of Kyoto prefecture.[52] In a study by Katoh *et al*. investigating the prognosis of AD in adulthood, the number of affected patients gradually decreased from a peak in subjects aged 20 to 30 years, and two-thirds of patients showed improvement to the level where they no longer need to visit the dermatological department by the age of 40.[53]

Diagnostic criteria

Based on the "Definition and Diagnostic Criteria for AD" prepared by the JDA, patients meeting three basic items are regarded as having AD regardless of the severity of symptoms: (i) pruritus; (ii) typical morphology and distribution of the

eczema; and (iii) chronic or chronically relapsing course (Table 1).[6] AD-suspected patients are regarded as having acute or chronic eczema, and diagnoses are made based on their age and courses. It is essential to differentiate the disorders which should be ruled out in diangnosis of AD and be familiar with the complications of AD. Internationally, the diagnostic criteria prepared by Hanifin and Rajka in 1980[54] and by the U. K. Working Party[55] are widely used.

Characteristics of eruption

Infancy (younger than 2 years of age). Eruptions usually initially develop on the cheek, forehead, or head (exposed area) appearing as skin dryness followed by flushing or papules during early infancy. With disease progression, flushing becomes more severe and is associated with the occurrence of itching, thus, eruptions will worsen by scratching and may lead to the formation of eczema and crusts. Concurrently, the eruption extends to the entire face including the ears, mouth, cheek, jaw, and their surrounding areas. With a slight delay after the occurrence of facial symptoms, exudative erythema develops in intertriginous zones such as the neck, axilla, cubital fossa, and the popliteal fossa, moreover, erythema and papules also develop on the thoracoabdominal region, back, and extremities (Figure S1).

Childhood/school-age (2–12 years old). From early childhood to school age, eruptions on the face decrease, instead, eruption is typically observed on the neck, axilla, cubital fossa, popliteal fossa, inguinal area, wrist, and ankle.[56] In severe cases, eruptions extend to the face and limbs, while repeated scratching leads to repeated erosions and blood crusts. Lichen papule and prurigo nodularis may develop on the elbows, knees, hands, and legs. Dry skin- or goose bump-like follicular papules may be observed on the trunk and extremities (Figure S2).

Adolescence/adulthood (13 years and older). After puberty, eruptions are more likely to develop on the upper body including the face, neck, chest, and back. In addition, a facial-type eruption that markedly develops on the face and neck may develop into a prurigo-type eruption in which papules with strong itching on the trunk and extremities. In severe cases, eruptions extend all over the body resulting in erythroderma (Figures S3 to S6).

Site of eruption. While eruptions can develop at any site of the body, eruptions develop more rapidly and intensely on regions where external factors are applied. Eruptions develop symmetrically, in principle.

Characteristics of eruption. The eruption presents morphological characteristics of both eczema and dermatitis. The manifestation can be divided into acute and chronic lesions. Patients with AD are likely to have dry skin (dried skin, xeroderma, dry skin, atopic skin) across all age groups. This characteristic is not visible in absence of inflammation of the skin; however, it is remarkable in the presence of dermatitis.

Table 1. Definition and diagnostic criteria for atopic dermatitis by the Japanese Dermatological Association

Definition

Atopic dermatitis is a pruritic, eczematous dermatitis; its symptoms chronically fluctuate with remissions and relapses. Most individuals with atopic dermatitis have atopic diathesis.

Atopic diathesis: (i) personal or family history (asthma, allergic rhinitis and/or conjunctivitis, and atopic dermatitis); and/or (ii) predisposition to overproduction of immunoglobulin E (IgE) antibodies.

Diagnostic criteria for atopic dermatitis

1. Pruritus.
2. Typical morphology and distribution.

(1) Diagnostic criteria for eczematous dermatitis
- Acute lesions: erythema, exudation, papules, vesiculopapules, scales and crusts
- Chronic lesions: infiltrated erythema, lichenification, prurigo, scales and crusts.

(2) Distribution
- Symmetrical.
- Predilection sites: forehead, periorbital area, perioral area, lips, periauricular area, neck, joint areas of limbs, trunk.
- Age-related characteristics
  - Infantile phase: starts on the scalp and face, often spreads to the trunk and extremities
  - Childhood phase: neck, the flexural surfaces of the arms and legs
  - Adolescent and adult phase: tendency to be severe on the upper half of body (face, neck, anterior chest and back).

(3) Chronic or chronically relapsing course (usually coexistence of old and new lesions)
- More than 2 months in infancy
- More than 6 months in childhood, adolescence and adulthood.

Definitive diagnosis of atopic dermatitis requires the presence of all three features without any consideration of severity.

Other cases should be evaluated on the basis of the age and clinical course with the tentative diagnosis of acute or chronic, non-specific eczema.

Differential diagnosis (association may occur):

Contact dermatitis, seborrheic dermatitis, prurigo simplex, scabies, miliaria, ichthyosis, xerotic eczema, hand dermatitis (non-atopic), cutaneous lymphoma, psoriasis, immunodeficiency diseases, collagen diseases (systemic lupus erythematosus, dermatomyositis), Netherton syndrome.

Diagnostic aids:

Family history (bronchial asthma, allergic rhinitis and/or conjunctivitis, atopic dermatitis), personal history (bronchial asthma, allergic rhinitis and/or conjunctivitis), follicular papules (goose skin), elevated serum IgE level.

Clinical types (not applicable to the infantile phase):

Flexural surface type, extensor surface type, dry form in childhood, head/face/neck/upper chest/back type, prurigo type, erythroderma type, combinations of various types are common.

Significant complications:

Ocular complication (cataract and/or retinal detachment): especially in patients with severe facial lesions, Kaposi's varicelliform eruption, molluscum contagiosum, impetigo contagiosa.

Acute lesions occur at the initial onset of eruption or at acute progression of eruption in the chronic phase. Eruptions immediately after acute onset, present with erythema and papules. Some may have vesicles in the epidermis, which is considered eczema erythema, and may include serous papules. When the epidermis is damaged due to disease progression or scratching, exudative fluid leaks from the lesion leading to the formation of crusts.

Chronic lesions are eruptions that have transitioned mainly due scratching. Repeated scratching results in thickened skin caused by mechanical irritation forming lichenified lesions and prurigo nodularis.

Differential diagnosis

The following is a description of the main differential diagnostic criteria to consider when distinguishing diseases from AD. These diseases may occur in association with AD.

Contact dermatitis. In this disease, eczema develops on a site on where an allergen has come into contact with an individual sensitized to that antigen, and eruptions are often well-circumscribed. Various substances such as cosmetics, metals, and topical drugs can act as potential allergens. It is important to be suspicious of contact dermatitis in cases in which eruptions are localized only on the face or other regions and are refractory to treatment or when a localized eczema lesion is asymmetrical (Figure S7).

Seborrheic dermatitis. Erythema and scales develop on seborrheic sites (i.e., the scalp, eyebrows, mesophryon, forehead, sulcus nasolabialis, pinna and back pinna, axilla, anterior chest anterior chest, umbilical region, and genitals, etc.). Itching is generally mild. Lipophilic fungi such as *Malassezia furfur* normally present on the skin appear to be associated with the pathophysiology. During infancy, scaly erythema with yellow crusts is observed at 1 month after birth (Figure S8) and thereafter, it often naturally resolves within 1 to 2 months. When it develops in adults (especially after middle age), chronic pale erythema and scales are observed during the clinical course (Figure S9). Whether an eczematous lesion or dry skin can be observed on the trunk or limbs, as well as the presence of eruption on the seborrheic site such as sulcus nasolabialis is the differential diagnosis point (if present, it is highly likely to be AD).

Prurigo simplex. Papules or small nodules develop with a strong itch. Generally, uniform sized papules or small nodules often develop and spread. Insect bite may be one of the causes. A prurigo eruption frequently develops as a type of AD eruption. The presence and clinical course of eczematous lesions or dry skin other than prurigo and the presence of a history of atopy can be of some help in diagnosis (Figure S10).

Scabies. Scabies is caused by *Sarcoptes scabiei* infestation on the skin, and infection usually occurs following long-term contact with patient's skin, bedding, or clothes. Papules accompanied by severing itching are observed on the body trunk and limbs (Figure S11) and linear scaling is observed on the palmar or interdigital area (so-called scabious tunnel). As infections are often observed in elderly care facilities or hospitals, opportunistic infections should be considered. Scales should be dissolved with potassium hydroxide (KOH) solution to be observed microscopically. If insect mites or eggs are detected, the diagnosis can be confirmed.

Miliaria. Red papules often develop due to the occlusion of the eccrine sweat glands, milaria is often observed in neonates and in individuals affected by excessive perspiration. It is commonly called a "heat eruption". Red papules of 1 to 2 mm in size accompanied by itching occur frequently and are often observed on the body trunk, the flexion side of the limbs, neck, and axilla. The presence of the eruption on other sites, observation of its characteristics and medical interview on clinical course are useful to differentiate from this lesion from AD.

Ichthyosis. The skin across the entire body becomes dry and rough and develops fish-like scales. Ichthyosis vulgaris is an autosomal dominant cutaneous disorder with onset during infancy. It resolves during summer. It may be complicated by AD. The presence of an eczematous lesion is the differential diagnostic point.

Xerotic eczema. Xerotic eczema is caused by dry skin and is often observed in the winter season among the elderly. It often occurs on the extension side of the lower leg. Skin dryness can be observed even on sites without eczema in many cases. Patients with AD can also develop eczema due to dry skin, which often progresses during winter season; however, xerotic eczema can be differentiated from AD by its clinical course and the distribution and properties of the eruption.

Hand dermatitis (differential diagnosis to distinguish hand dermatitis from AD). Eczema occurs on the hands due to physical and chemical stimulation or allergy, and is commonly referred to as "damaged hands". It is often observed in individuals with occupations requiring substantial exposure to water, such as hairstylists, cooks, healthcare professionals, and housewives. Eczema occurring on the hands is a symptom of AD, thus the presence of eruption on sites other than the hands or the clinical course can be used for differential diagnosis.

Cutaneous lymphoma. Malignant lymphoma primarily develops on the skin, and its representative diseases are mycosis fungoides and Sézary syndrome (Figure S12A,B). Mycosis fungoides is a T-cell lymphoma with a chronically progressive clinical course. It typically worsens from an erythematous stage, in which various sizes of erythema are observed on the body trunk and limbs, evolving to the plaque stage (infiltrative stage) and a tumor phase after a prolonged clinical course. In the erythema stage, a light red to brownish-red erythema is often observed with mild scales. Differentiating from eruption due to AD is sometimes clinically challenging when making a diagnosis. When diagnosis is uncertain, it is important to

perform a skin biopsy to examine the pathological findings (e.g. the presence of lymphocyte infiltration on the epidermis). Sézary syndrome is characterized by three features: erythroderma, superficial lymph node swelling, and the presence of atypical lymphocytes in the peripheral blood, and is often accompanied by intense itching. To differentiate from AD presenting with erythroderma, peripheral blood smears and dermatohistopathological findings are important.

Psoriasis. Psoriasis is an inflammatory keratosis presenting with well-circumscribed red plaques with thickened scales. It commonly appears on sites susceptible to external stimuli such as the elbow, knee, and scalp while the eruption can appear all over the body including palmar and plantar region. Scales can be described as silvery white. Various types of eruptions such as serous papules, and eczema erythema observed in patients with AD are generally not present in psoriasis. Pathological differential diagnosis based a skin biopsy is useful.

Immune deficiency diseases. Wiskott-Aldrich syndrome: It is an X-linked recessive inheritance disease caused by an abnormality of the *WASP* gene, and is characterized by immunodeficiency (T-cell dysfunction), thrombopenia, and refractory eczema. Eczema similar to AD occurs on the face and the flexion side of the limbs by 6 months of age. Purpura due to thrombopenia is also observed. It causes repeated infections such as impetigo contagiosa, herpes simplex, and candidiasis.

Hyper IgE syndrome: Hyper IgE syndrome (HIES) is characterized by skin abscesses (cold abscess) and pneumonia (pulmonary cyst) caused by bacteria such as *Staphylococcus aureus* (*S. aureus*), AD-like eczema lesion, and high serum IgE levels. A definitive diagnosis can be made based on the clinical scoring system developed by the National Institute of Health (NIH)[57] and genetic testing (*STAT3*, *TYK2*, *DOCK* gene, etc.). Differentiating eruptions found in HIES from those found in AD is not clinically easy.

Collagen diseases (systemic lupus erythematosus, dermatomyositis). Systemic lupus erythematosus: Systemic lupus erythematosus is an autoimmune disease with inflammatory lesions in multiple organs and commonly appears in young women. The representative cutaneous symptoms include a malar eruption and a discoid erythema. A malar eruption is also called butterfly eruption and manifests as a symmetrical edematous erythema on both cheeks and involves the bridge of the nose. The discoid erythema is a well-circumscribed erythema commonly appearing on the site exposed to light such as the face, lips, and pinna. It has a chronic clinical course and gradually progresses to an atrophic scar plaque. Differential diagnosis can be made based on the characteristic eruption, systemic symptoms, and the presence of abnormalities in blood tests such as anti-nuclear antibody, anti-DNA antibodies.

Dermatomyositis: It is an autoimmune disease affecting the skin and muscles. A characteristic eruption and muscle weakness starting at proximal muscles are the clinical features. The representative skin lesions include edematous purple-red plaques (heliotrope eruption) on the face, particularly on the eyelids, and erythema keratodes (Gottron's sign) on the back of the wrist joint. Edematous erythema consistent with scratch scars can sometimes be observed on the body trunk or shoulder. The characteristic eruption, muscle weakness, and blood test findings can help to make a differential diagnosis (Figure S13A,B).

Netherton's syndrome. Netherton's syndrome is an autosomal recessive disorder caused by alterations in the gene coding serine protease inhibitor (*SPINK5*). It causes an AD-like eruption. Trichorrhexis nodosa (Bamboo hair) appears on the head and hair is short and brakes easily.

Severity assessment

Precise severity assessment is essential for appropriate selection of treatment. While overall severity is assessed, assessment of the severity of the local lesion (i.e. individual eruption) is also important to select the topical drug to be applied locally.

Overall assessment of severity. There are several methods proposed for severity assessment. The easiest method is to use the "Severity index" as outlined in the "Guidelines for the Treatment of Atopic Dermatitis" developed by the MHLW Research Group. According to this "Severity index", the severity of eruption is categorized into mild eruption and eruption with severe inflammation, and is further subclassified into mild, moderate, severe, and most severe depending on relative proportion of the lesions to the body surface area. If there is an eruption associated with strong inflammation, even partially, it is classified as moderate or severe (Table 2). It is a simple and easy-to-use index for guiding treatment.

Severity classification methods with verified statistical reliability and validity include the Atopic Dermatitis Severity Classification[58,59] developed by the JDA, the Severity Scoring of Atopic Dermatitis (SCORAD) index,[60] and the Eczema Area and Severity Index (EASI).[61] The SCORAD index and the EASI are used internationally. The SCORAD index has been reported in many English language papers and has been frequently used

Table 2. Severity index

Mild: Only mild eruptions are observed irrespective of the area.
Moderate: Eruptions with severe inflammation are observed in less than 10% of the body surface area.
Severe: Eruptions with severe inflammation are observed in ≥10% to <30% of the body surface area.
Most severe: Eruptions with severe inflammation are observed in ≥30% of the body surface area.
Mild eruption: Lesions are seen chiefly with mild erythema, dry skin, or desquamation.
Eruption with severe inflammation: Lesion with erythema, papule, erosion, infiltration, lichenification, etc.
Modified from Ministry of Health and Welfare, Japan. [Guidelines for the Treatment of Atopic Dermatitis 2008] (in Japanese).

in clinical research and trials. The maximum score of the SCORAD Index is 103, and its score can be calculated using a dedicated website (http://adserver.sante.univ-nantes.fr/Scorad.html). The EASI is recommended by the Harmonising Outcome Measures for Eczema (HOME), an international multi-professional group dedicated to standardizing AD clinical research outcomes (http://www.homeforeczema.org/index.aspx). The EASI score chart can be downloaded from the dedicated website (http://www.homeforeczema.org/resources.aspx), and assessment training is available online. Either of the above methods can be selected, however, it is recommended that the simple "Severity index" be used for routine clinical practice and the international EASI or SCORAD index for clinical research or trials.

Assessment of eruption severity. Selection of topical steroids, a key treatment, depends on "the severity of individual eruption".[6,62] That is, a sufficiently potent topical therapy is selected for severe eruption even though the affected area is limited, while a potent topical therapy is not necessary for a milder eruption even if effects are more extensive. The severity of the eruption is categorized into 2 to 3 levels according to the abovementioned assessment methods.

Assessment of pruritus. Itching is the most important feature of AD. As it is difficult to assess itching objectively, the visual analogue scale (VAS) and the numeric rating scale (NRS) are often used to obtain a patient's subjective assessment.[63–66] In VAS, patients are instructed to mark one point on a 100-mm long horizontal line in accordance with the degree of pruritus, and the distance (mm) from the left end to the marked point is evaluated as the pruritus scale score, regarding the left end "no itch" as 0 and the right end "the worst imaginable itch" as 100.

For the NRS, patients are instructed to rate verbally their itch using an 11-point scale from 0 ("no itching") to 10 ("the worst imaginable itch"). Subjective itch and insomnia due to itching can be assessed using the SCORAD index, and neither VAS nor NRS are suitable indexes. A good correlation of these methods with itching has been reported.[66]

Assessment by patients. The Patient Oriented Eczema Measure (POEM) is a severity scale, which was specifically designed to measure severity by the patient and/or patient's caregiver using a questionnaire (For adults, https://www.nottingham.ac.uk/research/groups/cebd/documents/methodological-resources/poem-for-self-completion.pdf; for children, https://www.nottingham.ac.uk/research/groups/cebd/documents/methodological-resources/poem-for-proxy-completion.pdf).[67–69] It is useful in sharing treatment goals between the physician and patient as has been shown to correlate with assessment by physicians. A self-administered patient-oriented SCORAD index (PO-SCORAD) has also been reported.[70]

Assessment of quality of life. The quality of life (QOL) of patients with AD is tends to decrease because of itching, issues regarding appearance, and burden of treatment, among others. To provide QOL-conscious treatment, a QOL assessment questionnaire, which is verified to be statistically valid, is used.

For adult patients, the Skindex-16 and DLQI can be used as QOL assessment questionnaires for cutaneous diseases including AD[71–73]; their Japanese versions are currently available.

A Japanese version of the Children's Dermatology Life Quality Index (CDLQI) is available for children.[74,75] For younger children, a caregiver, often the mother is the main provider of treatment in many cases. As the burden borne by the caregiver is substantial, questionnaires evaluating "Quality of life in Primary Caregivers of children with Atopic Dermatitis" (QPCAD) (19 items)[76] and its abbreviated version QP9 (9 items)[77] have been specifically developed to evaluate the QOL of primary caregivers. The Japanese Culturally Modified Version of the CADIS (JCMV-CADIS),[79] a modified and translated version of the Childhood Atopic Dermatitis Impact Scale,[78] in which the caregiver responds to questions regarding the QOL of both the affected children and the caregiver, adapted to Japanese patients, is also useful.

Useful biomarkers for diagnosis and severity assessment (Table 3)

Serum IgE levels. A high serum total IgE level is observed in patients with allergic diseases, however, a clear cut-off cannot be established because its distribution greatly overlaps with that of healthy individuals. In patients with AD, a total serum IgE level of 500 IU/mL or higher is commonly observed.[80] Serum total IgE level may represent allergic diathesis rather than short-term disease activity in AD. However, it can be an indicator of long-term response in severe cases as the high serum total IgE level decreases after several months of follow-up.

In addition, patients with AD are often sensitized to multiple allergens including mites, house dust, pollen, fungi, and food. These allergens can be detected by specific serum IgE antibody tests and the skin prick test, however, it should be noted that non-specific sensitization is often observed, that is, the presence of positive specific IgE antibodies is not always causally related to the exacerbation of symptoms. In examining the causal relation between allergens and symptoms, an adequate medical interview is a fundamental approach.

Peripheral eosinophil count. Peripheral eosinophilia is more significant in patients with AD compared to other allergic diseases such as bronchial asthma or allergic rhinitis. As the peripheral eosinophil count increases with disease severity, it can be a marker for disease progression.

Serum lactate dehydrogenase level. Serum lactate dehydrogenase (LDH) level increases in more severe cases, thus, it acts as a marker of disease progression. An increase in LDH levels may reflect tissue damage caused by skin inflammation, and it returns to normal level when eruption is resolved. Nonetheless, in cases in which LDH levels remain elevated, complications

Table 3. Biomarkers for diagnosis of atopic dermatitis and disease progression

Marker	Mechanism of increase	Reference level (upper limit)	Clinical implications
Serum IgE level	Immune state with excessive Th2 activity (high IL-4 levels) causes an increase.	No definitive reference level is available. A high level (500 IU or higher) is often observed in patients with AD.	It indicates allergic diathesis and reflects disease progression of AD during a prolonged clinical course.
Specific IgE levels	Allergen-specific antibody produced via the same mechanism indicated above.	If an allergen is detected, it means that the allergen is responsible for sensitization.	Sensitization is not always related to causes. A detailed medical interview is necessary for identification of causal allergens.
Peripheral eosinophil count	It is produced and induced from bone marrow by IL-5.	No definitive reference level is available, and the cut-off levels used as an endpoint in clinical studies varies (e.g. more than 300/mm^3)	It reflects disease progression of AD.
Serum LDH level	It is isolated through cell damage. It is released by skin cells in patients with AD.	Age 0–2 years: <400 IU/L, Age 2–6 years: <300 IU/L Age 6–12 years: <270 IU/L Age 13 years: <250 IU/L	It reflects disease progression of AD.
Serum TARC level	It is produced by chemokine dendritic cells, and induces Th2 cell migration.	Age: 6 months to <12 months: <1367 pg/mL Age between 1 and 2 years: <998 pg/mL Age between 2 and 15 years: <743 pg/mL Adults: <450 mg/mL	It reflects disease progression of AD more than eosinophil count or LDH level. It is covered by national health insurance as a marker for AD.
Serum SCCA2 level	It is produced by epithelial cells activated by Th2 cytokines.	<1.93 ng/mL	It sharply reflects disease progression of AD (under application for regulatory approval).

due to other diseases leading to tissue damage should be suspected and a differential diagnosis should be considered.

Serum thymus and activation-regulated chemokine level. Thymus and activation-regulated chemokine (TARC: CCL17) is a ligand of the chemokine receptor CCR4 and induces Th2 cell migration.[81] Serum TARC in patients with AD increases consistently with severity, and testing for TARC levels is covered by the national insurance as it reflects disease progression more strongly than either serum IgE levels, LDH levels, or peripheral eosinophil counts.[82,83] Moreover, patient education and treatment can be reviewed using serum TARC levels as an index.[84] However, test values should be carefully interpreted because TARC levels are generally higher in younger children, especially in children under 2 years of age.[85] The reference levels according to age are shown in Table 3.

Serum squamous cell carcinoma antigen 2 level. Squamous cell carcinoma antigen 1 (SCCA1) and SCCA2 are proteins belonging to a family of serine protease inhibitors produced by epithelial cells, and were initially used as markers of cervical cancer. They have been demonstrated to be induced by IL-4 and IL-13, a Th2 cytokine, and increases in the serum of patients with AD, hence its current interest. Particularly, serum SCCA2 is reported to be a sensitive marker of disease progression of AD.[86] SCCA2 does not show any variations based on age, unlike TARC, and therefore, it is expected to be a more useful marker in clinical practice (pending regulatory approval).

Treatment approaches

Goal of treatment

The goal of treatment is to reach and maintain a state in which symptoms are absent or mild without being disturbed in daily activities by the disease and drug therapy is not required. Even when this level is not reached, the objective is to maintain a state in which symptoms are mild without rapid exacerbations that affect daily activities.

Treatment measures

Treatment measures for AD basically consist of drug therapy, skin care for physiological abnormalities in the skin and investigations/elimination of exacerbating factors based on its pathogenesis. These measures are important, and are adequately combined for individual patients based on the grade of symptoms and background.

Atopic dermatitis is a multifactorial disease involving genetic predispositions. There is currently no treatment that can completely cure this disease. However, in the lesion site, a further inflammation-related reduction in skin barrier function, enhanced irritability and scratching-related stimuli deteriorate eczema, leading to viscious cycle of inflammation. Therefore, controlling inflammation by drug therapy will also reduce AD-exacerbating factors.

Drug treatment

Topical anti-inflammatory drugs. Currently, these agents are used to provide adequate attenuation of inflammation in AD. The efficacy and safety of topical corticosteroids (TCS) and tacrolimus ointments (topical calcineurin inhibitor) have been examined in numerous clinical studies.

Hydrocortisone was the first TCS developed in 1952 and has been used as topical drug therapy for AD for over 60 years.[87] Efficacy and safety of TCS have been examined in many clinical studies.[88] TCS are often used as a first-line anti-inflammatory topical agent for both children and adults.

Tacrolimus ointment is an inhibitor of calcineurin. Protopic ointment 0.1% was approved and introduced as a second-line anti-inflammatory topical drug in 1999, and Protopic ointment 0.03% was approved and introduced for use in children in 2003. Both are now approved and marketed in over 75 countries.

Other topical agents include non-steroidal anti-inflammatory drugs (NSAIDs), which have an extremely weak anti-inflammatory effect and are not an uncommon cause of contact dermatitis; indications for their application is narrow. It is important to promptly and effectively attenuate inflammation in AD; thus, combination strategies of TCS and tacrolimus ointments should be considered as a basis of treatment. The extent of inflammation should be appropriately understood by inspection and to adequately apply these agents to a sufficient degree.

Topical corticosteroids (TCS): TCS are used as a basic drug in treatment of AD (CQ1: Recommendation grade 1, evidence level: A), and its intensity (rank) should be fully comprehended in order to select the most appropriate TCS, based on the severity of the individual lesions and to use different dosage forms of topical steroids according to the features and site of lesions in order to maximize their anti-inflammatory effects. Adequate instructions and education should be given to patients to improve adherence.

If eruption is maintained stable with suitable treatment, AD can be expected to achieve remission. It is important to use appropriate TCS, to promptly proceed with remission induction therapy to reduce inflammation and itching, and to maintain remission by concurrent use of moisturizing agents. Cases showing no improvement in eruption even after a 4-week treatment with topical drugs or severe cases should be referred to a dermatologist.

a) Use of TCS

Selection of rank

In Japan, TCS are generally classified into five ranks: strongest (Group 1), very strong (Group 2), strong (Group 3), medium (Group 4), and weak (Group 5). (Table 4) It is important to adequately select drugs at a rank that matches the severity of each eruption and use them at the required volume for the required period (Table 5).

Severe cases: primarily acute and progressive severe inflammatory lesions, retractable lesions such as lichenification, erythema, multiple papules, multiple scratch scars, or prurigo nodularis are observed. Use of a very strong or strong class TCS is the first-line treatment (Figures S14–19).

Table 4. Rank of topical corticosteroids

Strongest
0.05% clobetasol propionate
0.05% diflorasone diacetate
Very strong
0.1% mometasone furoate
0.05% betamethasone butyrate propionate
0.05% fluocinonide
0.064% betamethasone dipropionate
0.05% difluprednate
0.1% amcinonide
0.1% diflucortolone valerate
0.1% hydrocortisone butyrate propionate
Strong
0.3% deprodone propionate
0.1% dexamethasone propionate
0.12% dexamethasone valerate
0.1% halcinonide
0.12% betamethasone valerate
0.025% fluocinolone acetonide
Medium
0.3% prednisolone valerate acetate
0.1% triamcinolone acetonide
0.1% alclometasone dipropionate
0.05 clobetasone butyrate
0.1% hydrocortisone butyrate
0.1% dexamethasone
Weak
0.5% prednisolone

As of September 2016. Cited from Ref. [1] with modification. In the guidelines adopted in the USA, corticosteroids are classified into seven ranks (I, very high potency; II, high potency; III–IV, medium potency; V, lower-medium potency; VI, low potency; VII, lowest potency).[62] In Europe, they are classified into four ranks (very potent, potent, moderately, mild).[90] When referring to international clinical trial data, it must be considered that the rank classification of topical corticosteroids differs from that in Japan.

Moderate cases: primarily inflammatory findings of moderate or less severe erythema, scales, and a few papules, and scratch scar are observed. Use of a strong or medium classes of TCS is the first-line drug treatment (Figure S20).

Mild cases: primarily mild-dry skin, mild erythema, and scales are observed, and the use of medium class or weak rank TCS is the first-line drug treatment[1] (Figure S21).

Slight cases: Primarily dryness with negligible inflammation are observed. Use of a emollient is the first-line drug treatment (Figure S22).

Although there is no need to decrease the rank because of age, for infants and children the duration of use should be carefully monitored, as efficacy is likely to appear in a short time in these age groups.

Selection of vehicles

Vehicles, such as ointment, cream, lotion and tape preparations, need to be selected based on lesion characteristics/sites. Ointment should be basically selected in order to treat this disease, which involves dryness. On the other hand, when

Table 5. Severity of eruption and topical corticosteroid (TCS) application

Severity	Eruption	TCS application
Severe	Primarily severe swelling/edema/infiltration or erythema with lichenification, multiple papules, severe scales, crusts, vesicles, erosion, multiple excoriations and pruriginous nodules	Use of very strong or strong rank TCS is the first-line treatment. Strongest rank TCS are also available for refractory pruriginous nodules if sufficient effects are not achieved by applying very strong rank TCS
Moderate	Primarily moderate erythema, scales, a few papules and excoriations	Use of strong or medium rank TCS is the first-line treatment
Mild	Primarily dryness, mild erythema and scales	Use of medium or weak rank TCS is the first-line treatment
Slight	Primarily dryness with negligible inflammation	Topical application of medicines other than TCS (emollients)

Cited from Ref. [1] TCS, topical corticosteroid.

the oily sensation of ointment use reduces adherence to topical preparations (e.g. summer), a cream base is sometimes selected while avoiding the erosive surface or scratching marks. Lotion base is basically used for scalp lesion. Use of tape preparations would be considered for pruriginous lesions and lichenified lesions.

Way of application

Volume: A volume (~0.5 g) measuring 5 mm in diameter that is pushed out from a tube to an area between the tip and first joint of the second finger is appropriate for two palms of British adults, that is, approximately 2% of the body surface area of adults (fingertip unit)[91,92] (Table 6). This may be adopted as a reference, considering the physical status of Japanese individuals and the tube size of topical corticosteroids available in Japan. On the other hand, the adpprpriate volume would change according to some factors including skin constion and vehicle of topicas agent.

Frequency of application: As a rule, TCS should be applied twice a day (morning and evening: after bathing) in cases of acute exacerbation. When inflammation is reduced, the frequency of applications should be decreased to once a day to induce remission. Further evidence needs to be accumulated in order to determine whether efficacy differs between twice-a-day and once-a-day applications. However, several randomized controlled studies and systematic reviews reported no significant difference in efficacy between twice-a-day and once-a-day applications.[93,94] It is generally recognized that even a once-a-day application exhibits potent effects. If the number of applications is low, the incidence of adverse reactions may be low, thereby improving adherence. Therefore, topical corticosteroids should be applied twice a day to control acutely exacerbated eruptions for an early recovery. When the condition subsides, topical corticosteroids should be applied once a day to achieve remission (CQ2: Recommendation grade 1, Evidence level: B).

b) Consideration for the use of TCS

Regions of application

The absorption rate of topical steroids by skin region is 13.0 on the cheek, 6.0 on the neck and 42.0 on the scrotum, with the extensor surface of forearm defined as having a rate of 1.0.[95] Such skin regions having a high drug absorption rate require attentive monitoring for the development of local side effects due to TCS treatment, and prolonged use should be avoided. For the face, medium class or lower raked TCS are generally used, while drugs consistent with the severity rank are used for severe dermatitis to introduce prompt remission, and then, drugs are gradually tapered or administered intermittently. Moreover, an effort to transition from TCS to tacrolimus ointments is made.

Discontinuation of topical drug treatment

When attenuation of inflammation symptoms is achieved, TCS should not be discontinued abruptly, they should be gradually tapered or administered intermittently while maintaining remission. Topical drugs can be discontinued, if possible, however, proactive therapy, as discussed below, should be considered for patients with repeated relapses.

Table 6. Appropriate volume of topical corticosteroids (FTU)[13,92,93]

Dose of topical drugs –FTU (1FTU = 0.5 g)					
Children	Face & neck	One arm	One leg	Trunk (front)	Trunk (back)
3 to 6 months old	1 (0.5 g)	1 (0.5 g)	1.5 (0.75 g)	1 (0.5 g)	1.5 (0.75 g)
1 to 2 years old	1.5 (0.75 g)	1.5 (0.75 g)	2 (1 g)	2 (1 g)	3 (1.5 g)
3 to 5 years old	1.5 (0.75 g)	2 (1 g)	3 (1.5 g)	3 (1.5 g)	3.5 (1.75 g)
6 to 10 years old	2 (1 g)	2.5 (1.25 g)	4.5 (2.2 g)	3.5 (1.75 g)	5 (2.5 g)
Adults	Face & neck	One arm & hand	One leg & foot	Trunk (front)	Trunk (back)
	2.5 (1.25 g)	3+1 (2 g)	6+2 (4 g)	7 (3.5 g)	7 (3.5 g)

If TCS are suddenly discontinued in adult patients after prolonged use on the face or genitals, erythema, flushing, edema, papules, and pustules may appear and worsen.[96] In such cases, the patient should be referred to a dermatologist.

Proactive therapy

Proactive therapy is a form of maintenance treatment, whereby subsequent to the use of TCS or tacrolimus ointments to promptly reduce inflammation, TCS or topical tacrolimus are regularly applied (e.g. twice a week) to repeatedly relapsed eruptions in order to maintain remission (Fig. 6). In addition, skin care is provided using moisturizing topical drugs (CQ8: Recommendation grade 2, evidence level: A) (See Proactive therapy section).

In AD, inflammatory cells are still identifiable histologically in normal-appearing skin; recurrence of inflammation is highly possible.[97] Potential relapse of inflammation can be prevented by regular application of anti-inflammatory topical drugs such as TCS or tacrolimus.[98] However, it is important to transition from successful treatment with daily anti-inflammatory topical drugs to proactive treatment only after dermatitis has fully improved. The application range, timing of transfer from continuous application to intermittent application, and when to interrupt treatment should be determined comprehensively considering cutaneous symptoms, clinical course, and laboratory data for each individual case.

c) Side effects of TCS

Systemic side effects

While adrenal function suppression has been reported in some cases after the use of strong TCS,[99,100] adrenal function suppression and growth disorders have not been observed with the use of weak rank TCS.[101,102] If these drugs are used appropriately, less systemic side effects and higher safety can be expected.

Local side effects

Skin atrophy, capillary dilatation, steroidal acne, steroid flushing, trichosis, and progression of microbes/fungi and viral skin infection can occur in some cases, however, they can also be resolved with drug discontinuation or appropriate treatment. Skin atrophy has been reported after the long-term use of the very strong class of TCS, when compared to similar use in healthy subjects. There are no reports of serious side effects after prolonged use of TCS, thus, most side effects are transient and can be resolved with reduced frequency of topical application, with the exception of lineae atrophicae of the skin. Rosacea-like dermatitis is a TCS-induced side effect presenting erythema, capillary dilatation, follicular papules, and pustules, and is mainly observed on the face of adult patients after prolonged use of TCS. If the TCS is stopped abruptly, erythema and edema may worsen.[96] If these symptoms are observed, the patient should promptly be referred to a dermatologist.

Adverse reactions to TCS in the eyes

Adverse reactions to TCS for lesions around the eyes include cataracts and glaucoma (CQ3: Evidence level: B, cataract [the risk is not increased]; C, glaucoma [the risk is increased]). The periocular application of TCS in patients with AD is not considered to increase the risk of cataracts.[103–105] The exacerbation of facial eruption, habitual percussion and AD-related inflammation are considered to be risk factors for cataracts. The risk of glaucoma may be low if weak, low-dose TCS are applied.[106] However, not a few patients have been reported to develop glaucoma following TCS therapy; therefore, the volume and application period of TCS (especially strong TCS) must be carefully established when applying them around the eyes or to the palpebral skin, and switching to tacrolimus ointment should also be considered. If these ocular complications are suspected, patients should be referred to a department of ophthalmology at an appropriate time.

d) How should anxiety to steroids and inappropriate treatment be addressed? Because of misconceptions about treatment with TCS (i.e., side effects of oral steroids and progression of AD are often confused, as the latter is often considered a side effect of the former), patients tend to have unwarranted fears and avoid the use TCS altogether. Thus, the expected beneficial effects are not achieved in many cases due a decline in adherence. In addition, patients may develop doubts on efficacy of treatment, as they do not experience any improvement likely due to inappropriate use of TCS. To resolve these misconceptions, patients should be educated and instructed by adequate consultation. Prolongation of symptoms in children due to underuse of topical drugs should be avoided, thus, sufficient education and instruction should ensure the guardian's understanding.

Concern has been raised as to whether low reactivity of TCS, similar to that reported for systemic steroids, or rapid

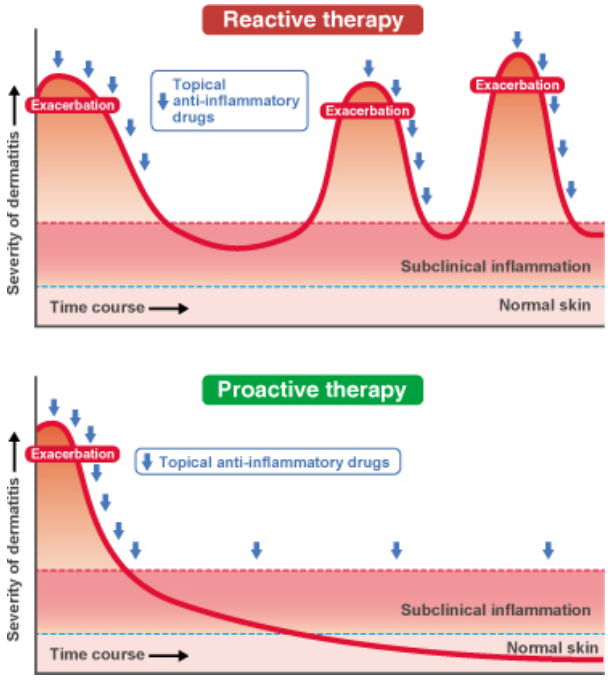

Figure 6. Reactive therapy and proactive therapy.

decrease in efficacy (tachyphylaxis) are observed in patients treated with TCS. In the AD guidelines issued by the American Academy of Dermatology, experts indicated that although there is possibility of tachyphylaxis occurring with TCS, there is no current research or proof to support the statement.[107] Indeed, the presence of tachyphylaxis in AD has not been fully elucidated, although, there are reports of experiments in animal models in which the vasoconstrictive activity of steroids has ben observed.[108,109] These studies examined the effects of successive local application of TCS on vasodilatation, in animal models of histamine-induced or irritant dermatitis.[108,109] The results showed that vasoconstriction induced by TCS was attenuated and a reduced efficacy was observed on Day 14 of TCS administration in the histamine treated group and in the early phase of steroid use in the irritant dermatitis group, thus, the presence of tachyphylaxis cannot be fully denied. Conversely, experimentally-induced vasodilatation was inhibited by TCS treatment in these experimental conditions; however, these results cannot be extrapolated to a multifactorial condition such as AD. If the expected efficacy has not been achieved during treatment with TCS, the rank and usage of the TCS, adherence to the treatment, and possibility of contact dermatitis associated with TCS should be confirmed, as well as the potential involvement of exacerbating factors including persistent exposure to allergens, before suspecting the presence of tachyphylaxis.

Tacrolimus. Tacrolimus inhibits the activity of intracellular calcineurin. It reduces inflammation via an action mechanism that differs from that of corticosteroids. Tacrolimus ointment can be expected to show a high level of effectiveness for AD-related eruption, which was difficult to treat with topical corticosteroids, considering adverse reactions (CQ5: Recommendation grade 1, Evidence level: A).

The efficacy of this drug depends on drug absorption: the site of application and barrier function. It is recognized as a drug to be frequently indicated for the eruption on the face and neck. However, there are restrictions for its application that differ from topical corticosteroids: tacrolimus ointment cannot be applied to erosive or ulcerative surfaces, and its drug efficacy is limited. This drug must be administrated according to the "Guidance for the Application of Tacrolimus Ointment in Patients with Atopic Dermatitis".[110] Tacrolimus ointment is available at the following concentrations: 0.1% for adults and 0.03% for children. It cannot be selected for children aged 1 year or younger as its safety has not yet been established for this age group. Its application should also be avoided in lactating women.

a) Volume

A volume of 0.1 g (corresponding to a volume squeezed by 1 cm from a 5-g tube commercially available in Japan) is appropriate for a 10-cm square. Based on the findings of a long-term observational study involving adults, the upper limit of the volume of a 0.1% ointment per session for adults was established as 5 g to avoid an increase in its blood concentration and maintain its safety. In accordance with the physical status, the maximum volume of a 0.03% ointment per use was established as 1 g for children aged 2–5 years (bodyweight <20 kg), 2–4 g for those aged 6–12 years (bodyweight 20–50 kg) and a maximum of 5 g for those aged 13 years or older (bodyweight ≥50 kg). The target volume of this ointment per area measuring 10 cm 9 10 cm is 0.1 g (1-cm volume pushed out from the 5-g tube commercially available in Japan).

b) Way of application

Irritative symptoms, such as a transient burning sensation and hot flushes, often appear at the site of application. However, these symptoms appear at the start of treatment, and most symptoms disappear with improvements in eruption. This should be explained to patients before the start of treatment. This ointment is very effective for the face and neck, in which its percutaneous absorption is favorable. This ointment should be indicated when conventional therapy with TCS is ineffective (e.g. sites in which local adverse reactions to TCS are observed) or when physicians hesitate to administrate TCS due to adverse reactions.

The efficacy of this ointment (0.1% for adults) for the trunk and limbs may be similar to that of strong class topical corticosteroids.[110] When treating the site of severe eruption, which requires potent drug efficacy, very strong class or stronger TCS should initially be used to reduce eruption, as a rule. The regimen should then be switched to tacrolimus ointment. The volume of TCS can be decreased in many cases by combining them with this ointment. If an improvement in eruption is achieved by this ointment, the interval of application should be prolonged at an appropriate time.

This ointment should not be used in sites/eruption areas in which blood transfer of this drug may increase and enhance irritability, that is, mucosa/genital areas and erosive/ulcerative surfaces. Occlusive dressing technique and superposition methods should not be adopted because they may increase the blood transfer of this drug. When erosive/ulcerative surfaces are markedly affected, the application of this ointment should be started after the amelioration of the eruption using other topical drugs.

c) Adverse reactions

A burning sensation, pruritus and erythema have been identified as local adverse events. These symptoms decrease or disappear with improvements in eruption in many cases. Furthermore, the appearance of infectious diseases of the skin, such as secondary skin infections with bacteria and viral infections (e.g. herpes simplex, molluscum contagiosum and verruca), must be considered. Skin atrophy, which is observed with the long-term use of TCS, has not been confirmed. Tacrolimus is detected in the blood following its topical application. Individual differences have been reported in blood levels of tacrolimus due to differences in percutaneous absorption (application of 0.1% tacrolimus: ≤1 ng/mL). Neither systemic adverse events nor toxicity related to blood transfer has been confirmed. We should explain patients about precautions for use written in its package insert, and should obtain their consents.

Risk of carcinogenesis

Evidence to show that the use of tacrolimus ointment does not increase the risk of skin cancer or lymphoma is increasing (CQ6: Evidence level: B).

Although previous studies reported the development of lymphoma during treatments with tacrolimus ointment, these were retrospective in nature. Limitations have been associated with the accuracy of lymphoma diagnoses, and lesions evaluated as AD-related eruption before the use of this ointment may have been lymphoma.[111,112] In addition, a previous study indicated that severe AD increased the risk of lymphoma. Therefore, AD may increase the incidence of lymphoma. An interim report was published in Japan on the safety of applying tacrolimus ointment (for children) in children with AD over a long period,[113] in which the onset of malignant neoplasms was not identified as an adverse event during a maximum follow-up period (7 years). However, a large sample size and long-term follow-up are needed for a carcinogenetic analysis. In the future, the relationship between the volume of tacrolimus ointment/application period and the development of malignant neoplasms must be analyzed through a long-term follow-up.

Non-steroidal anti-inflammatory drugs. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the cyclooxygenase enzyme of the arachidonate cascade and exert anti-inflammatory activity by inhibiting prostaglandin production. The anti-inflammatory effects of NSAIDs are extremely weak compared to those of TCS, thus, there is no evidence to support their efficacy in AD. There is no inclusion of NSAIDs treatment in the Guidelines for Management of Atopic Dermatitis in Western countries.[89,114] NSAIDs side effects include contact dermatitis and potential exacerbation of eczema. In particular, the use of bufexamac is associated with a potentially high risk of causing contact dermatitis; therefore, the European Medicines Agency (EMA) has recommended discontinuing marketing of bufexamac across Europe. In response to this recommendation, Japan also banned the sale of all bufexamac-based preparations. Benefits from NSAIDs for treatment of AD are poor, thus, the use of NSAIDs is not recommended in light of the potential side effects.

Proactive therapy. Proactive therapy is used to maintain remission via the application of topical steroids or intermittent topical tacrolimus (e.g. twice a week) to recurrently relapsed eruptions, in addition following treatment in the acute phase, skin care with moisturizing topical drugs is also introduced after remission (CQ8: Recommendation grade 2, evidence level: A). In contrast, reactive therapy is used to control inflammation with anti-inflammatory topical drugs on relapse (Figure S29).

In AD, histological evidence of inflammatory cells is still present despite the normal appearing skin following the resolution of inflammation; inflammation can easily relapse due to external or internal factors.[115,116] In such cases, markers indicating disease progression, such as TARC, do not decrease to normal levels in many cases. During this latent inflammation stage, proactive treatment with anti-inflammatory topical drugs including TCS or topical tacrolimus may prevent relapse of inflammation.[98] However, it is important to transition from successive application of anti-inflammatory topical drugs to proactive treatment based on laboratory data indicative of disease progression, such as TARC levels, after the dermatitis has fully improved and there is no evidence of itching or erythema, and in absence of any slight elevation of skin on palpation. Moreover, dose, application range, and the time to complete the treatment of topical drugs should be determined individually for each patient. Development of side effects should be also carefully monitored. Proactive treatment should be performed in collaboration with a physician experienced in the evaluation of cutaneous symptoms of AD or in the evaluation of cutaneous symptoms in general. During proactive treatment, continuation of daily skin care with moisturizing topical drugs is recommended.

Antihistamines. Atopic dermatitis is defined as a disease characterized by itching eczema as the main lesion. Itching results in a reduction of the QOL and an exacerbation of cutaneous symptoms due to scratching, and serves as a trigger for complications such as skin infections, eye symptoms, and progression of clinical features. Thus, controlling pruritus is important treatment approach.

Antihistamines are widely used in treatment of pruritus in AD in Japan and abroad. Efficacy of antihistamines has been examined in combination with anti-inflammatory topical drugs such as TCS, tacrolimus ointments, and moisturizing drugs, and beneficial effects on reducing itch have been reported in 75% of 26 randomized clinical trials (RCTs) conducted in Japan and abroad. These RCTs studied the efficacy of antihistamines in relieving itching as a primary endpoint, and some studies reported improvement of cutaneous symptoms, dose reduction of TCS, lowered drug rank, and improvement of sIL-2R and TARC levels. Therefore, the use of antihistamines is recommended as an adjuvant therapy to anti-inflammatory topical therapy for AD (CQ7: Recommendation grade 1, evidence level B). There is no reliable evidence for the efficacy of antihistamines alone in the treatment of AD, therefore, use of antihistamines alone without combination with anti-inflammatory topical drugs is not recommended.

Antihistamines which may be prescribed for AD are shown in Table 7. Antihistamines include sedative antihistamines (first-generation) with relatively strong anticholinergic and sedative effects and non-sedative antihistamines (second-generation) causing less drowsiness and impaired performance (impaired concentration, judgment, and reduced operating efficiency without subjective sleepiness) and anticholinergic activity with less fatigue. Based on the extent these central effects, of histamine H1 receptor occupancy in the brain, antihistamines have been divided into three groups: sedative, 50% or more occupancy; mildly sedative, 50–20%, and non-sedative, 20% or less; the H1 receptor occupancy of almost second-generation antihistamines has been demonstrated to be 30% or less.[117–121] Currently, H1 receptor occupancy is a pharmacological index in clinical practice. As there is no difference in treatment efficacy between sedative and non-sedative antihistamines, it is recommended that a non-sedative antihistamine be selected.[118,122,123]

According to the package insert of the antihistamine ketotifen, this agent is contraindicated in patients with epilepsy or a

Table 7. Antihistamines and anti-allergic drugs used for atopic dermatitis

First-generation antihistamines
Diphenylpyraline hydrochloride
Diphenhydramine hydrochloride
Cyproheptadine hydrochloride
Triprolidine hydrochloride
Hydroxyzine hydrochloride
Promethazine hydrochloride
Homochlorcyclizine hydrochloride
Alimezine tartrate
Diphenhydramine tannate
dl-Chlorpheniramine maleate
d-Chlorpheniramine maleate
Diphenylpyraline teoclate
Hydroxyzine pamoate
Clemastine fumarate
Second-generation antihistamines
Ebastine
Azelastine hydrochloride
Epinastine hydrochloride
Olopatadine hydrochloride
Cetirizine hydrochloride
Fexofenadine hydrochloride
Oxatomide
Emedastine difumarate
Ketotifen fumarate
Bepotastine besilate
Mequitazine
Loratadine
Bilastine
Desloratadine
Anti-allergic drugs without antihistamine effect
Sodium cromoglicate
Tranilast
Suplatast tosilate

As of December 2016. Cited from Ref. [117] with modification.

history of epilepsy, and careful administration of clemastine, hydroxyzine, cetirizine, and levocetirizine is indicated for patients with convulsive disorders. Convulsions are reported as a serious side effect of chlorpheniramine, cyproheptadine, and loratadine treatment. Thus, special attention is needed when administrating these agents to children.

The mechanism by which pruritus is mediated in AD varies and involves cytokines such as IL-31,[124–126] Epas1,[125] abnormal distribution of nerve C-fibers transmitting itching sensations,[127] substance-P (SP), and nerve peptides such as nerve growth factor (NGF), and histamine have been reported. It has also been reported that the severity of AD is correlated with levels of serum SP and NGF,[128] while SP levels in the epidermis are significantly higher in regions with eruption than in areas without eruption.[129] Inhibitory effects of antihistamine on itch vary depending on the individual patient's severity and clinical features; hence, it is desirable to judge the need for adjuvant therapy with oral antihistamines in addition to topical therapy with anti-inflammatory topical drugs and moisturizing agents, and to evaluate the efficacy on itching once the treatment is initiated.

Cyclosporin. The efficacy of cyclosporin for AD has been demonstrated in many countries in Europe and the USA.[130] It has been approved for use by patients with AD (CQ12: Recommendation grade 2, Evidence level: A). The use of cyclosporin was approved for patients with severe adult AD who do not respond to conventional treatments, showing eruption with marked inflammation involving 30% or more of the body surface area.[131]

This drug is also effective for patients with refractory erythema on the face or erythroderma. Because the severity of pruritus promptly decreases after its administration, cyclosporin is also useful for improving the QOL of patients with marked pruritus-related eruption or scratching. The initial dose of this drug is 3 mg/kg per day. It should be increased or decreased in accordance with symptoms, but in such a manner that it does not exceed 5 mg/kg per day. Its administration should be completed in 8–12 weeks. Factors such as nephropathy, hypertension and infection must be considered during therapy with cyclosporin. As the safety of its long-term administration has not yet been established, it is important to promptly switch cyclosporin therapy to conventional topical treatment after the amelioration of symptoms. Intermittent administration involving a 2-week or much longer period of discontinuation should be performed if long-term administration is necessary.

Cyclosporin is administrated p.o. after meals twice a day. However, a pharmacokinetic study involving patients with psoriasis showed that the blood concentration of this drug was higher when administrated before eating once a day.[132] Therefore, the therapeutic effects of once-a-day administration before meals may be more prominent than those of twice-a-day administration after meals.

Oral corticosteroids. A double-blind randomized controlled study has not yet been conducted to investigate the effects of oral corticosteroids on AD. However, these drugs have sometimes been used to induce the remission of acute exacerbation or severe/the most severe conditions. Although they are known to be effective, long-term oral corticosteroid therapy induces various serious systemic adverse reactions; therefore, long-term AD control with oral corticosteroids is not recommended. If necessary, administration should be completed in a short period.

Traditional Chinese medicine. It is undeniable that Chinese herbal medicine in combination with other drugs or as an adjuvant therapy may be useful in some cases. However, most clinical studies examining the efficacy of Chinese herbal medicines for AD to date have been case series conducted in small populations (several dozens of subjects). There have been only two double-blind randomized comparative studies of "Shofu-san"[133] and "Hochu-ekki-to",[134] which are Chinese medicines that can be prescribed in general dermatology clinics in Japan (CQ13: Recommendation grade 2, evidence level: B). The former was administered to patients with eruption which was not resolved with anti-inflammatory topical drugs such as steroids, while the latter

was administered in combination with conventional anti-inflammatory topical drugs such as steroid in patients regarded as having a delicate constitution based on a questionnaire score (such as easy fatigability or lack of perseverance). For Shofu-san, a significant improvement of eruption was observed, and reduction of the requirement for TCS was achieved with Hochu-ekki-to. The efficacy of Zemaphyte was reported in a double-blind randomized comparative study conducted abroad,[135,136] while another research group reported negative results.[137] Thus, a definitive statement regarding the efficacy of a typical agent, for example, "Chinese medicine A is suitable for AD", cannot be established at this time. Careful examination of Chinese medicines, as well as evaluation of selective Chinese medicines for eruption based on eruption features are necessary in the future. In addition, side effects of Chinese medicines, for example, pseudoaldosteronism due to liquorice-containing agents (Kanzo), and interstitial pneumonia, hepatic dysfunction, and jaundice due to Hochu-ekki-to have also been reported, Chinese medicine therapy should be implemented under the attentive surveillance of a physician proficient in the use of Chinese herbal medicines.

Considerations regarding pregnant or breastfeeding mothers. Dietary restrictions (elimination of food allergens) for pregnant or breastfeeding mothers to prevent the onset of AD cannot be recommended. There is the possibility that AD may be exacerbated and transferred to the infant after ingestion of food allergens such as eggs through breast milk, however, these infants should be carefully diagnosed based on the results of food elimination and food challenge tests (via breast milk).[138]

Administration of antihistamines during pregnancy which is considered safe can be administered if it is deemed therapeutically beneficial. Most antihistamines that have been demonstrated not to increase the risk of congenital anomalies based on epidemiological observational studies and meta-analyses belong to first-generation agents. Among the second-generation antihistamines, loratadine and cetirizine have been reported not to be associated with congenital anomalies in epidemiology studies.[139–141] However, it is important to use these agents according to the information on package inserts and the latest reports on safety.

As for administration of these drugs during breastfeeding, only a minimal amount of drug will be transferred to breast milk. However, second-generation antihistamines are recommended considering the potential for irritability and drowsiness in infants caused by first-generation sedative antihistamines. With regard to individual drugs, careful consideration of the contents of package inserts and the latest information on safety profiles is also necessary.

During both pregnancy and breastfeeding, topical steroids are considered safe, so they can be used without any concern about effects on the fetus or infant. Although long-term use of high doses of higher ranked topical steroids (300 g or more) may result in lower birth weight, complications are unlikely to occur with normal use.[139]

Standard TCS therapy shows low-level absorption in systemic circulation, and neither congenital anomalies nor the influence on fetal growth has been raised as an issue. However, we cannot rule out the possibility that birthweight may be decreased by the massive application of TCS classified as potent/very potent (in Europe, TCS are classified into four ranks (very potent, potent, moderately, mild).[90]) groups according to the classification used in Europe (especially 300 g or more). Therefore, attention should be paid to the volume of TCS used and fetal growth. Furthermore, it is important to favorably control dermatitis before pregnancy in order to avoid this anxiety. If the application of TCS to the breasts of lactating women is necessary, care must be taken to prevent infants from directly ingesting TCS.

Skin care

Topical moisturizers. In AD, the skin barrier functions and moisturizing factors are impaired. Moisture content in the stratum corneum decreases resulting in characteristically dry skin. Therefore, skin itching is likely to occur due to non-specific stimulation, and various allergens can easily penetrate into the skin to induce dermatitis. The use of moisturizer products (moisturizing drugs and skin protective agents) improve moisture content in the stratum corneum, which is decreased due to AD, and leads to the prevention of allergen invasion and relapse of dermatitis, as well as suppression of itching by recovering and maintaining skin barrier functions[142–144] (CQ9: Recommendation grade 1, evidence level: A). Moreover, skin care with moisturizers immediately after birth and thereafter, decreases the risk of onset of AD.[145,146]

An essential aim of skin care for dry skin is topical administration of hydrophilic ointments (oil in water, O/W) with a high moisture-retaining property or water-absorbing ointments (water in oil, W/O) to supplement the reduction of the moisture-retaining properties on the skin surface. Hydrophilic ointments with a high moisture-retaining property and water-absorbing ointments include heparin-containing preparations and urea preparations. To complement and reinforce the barrier functions of damaged skin, oleaginous ointments with protective action on the skin such as white petrolatum and zinc oxide ointment are applied topically.

Moisturizing efficacy is higher following twice-daily topical applications (morning and evening) than once-daily applications,[147] and it is recommended to apply moisturizers immediately after bathing in either applications. To determine the amount of agent to apply, a fingertip unit is helpful. The amount extruded from the tube (5 mm in a diameter) from the length of the tip of the second finger to the first joint (approximately 0.5 g) (fingertip unit) is the adequate dose for two adult palmars in the United Kingdom, that is, about 2% of adult body surface area.[91,92,148] Generally, transepidermal water loss (TEWL) is often found in the skin of patients with AD and not only in the lesion, but also in normal appearing areas representative of the dry skin.[149] Therefore, topical moisturizers should be applied all over the body including sites that appear to be normal. Topical products with anti-inflammatory activity are

used for dermatitis lesions. Continuous use of moisturizer products even after achieving remission of dermatitis with topical anti-inflammatory drugs is also useful to maintain the remission.[150] If relapse of dermatitis is observed during remission, maintenance therapy with topical moisturizers, and topical steroids or topical tacrolimus are used depending on the severity of inflammation, with the intention of early attenuation of inflammation and return to maintenance therapy. Differential diagnosis of contact dermatitis from relapse of AD is also important because contact dermatitis often occurs as a side effect of topical moisturizers in rare cases.

Combining two or more topical products, such as a topical steroid and a moisturizer, should not be done without careful consideration, as this may alter stability and percutaneous absorption of drugs.

Bathing, showering and washing. In AD, besides the adhesion of topical drugs and body fluids (e.g. sweat) to the lesions, sebum and colonization of infectious pathogens such as *S. aureus* may also adhere, and may act as exacerbating factors of cutaneous symptoms. Therefore, keeping the skin clean is important to maintain the skin's physiological functions. In general, bathing and showering are encouraged to clean skin and appropriate moisturizing and skin protective agents and anti-inflammatory topical drugs are used if necessary. The optimal bathing and cleaning procedure in AD varies depending on the individual patient, season, and symptoms in the same patient. The following points should be considered:

Temperature: The temperature of hot water in bathing/showering should be set at about 38–40°C because the itching response is induced at a skin temperature of 42°C or higher, while 36–40°C is the optimum temperature for recovery of skin barrier functions.[151–153] Water is diffused and evaporated from the skin surface immediately after bathing resulting in dry skin, thus, the skin should not be left without the application of a moisturizing agent for an extended time after bathing. When sweating or hot flashes have subsided, a moisturizing agent should be applied to minimize water evaporation and diffusion, and favor water retention to prevent the skin from getting dry.

Soap and/or detergent: Although there is no high quality evidence demonstrating the efficacy of using soap or detergent for AD, symptoms have been shown to improve without experiencing exacerbation in patients who did not use soap with prolonged bathing in a case series study of commonly used soap preparations.[154,155] As the major component of soap and/or detergent is surfactants, excessive abuse of these products may exacerbate skin dryness. Moreover, additives contained in detergent, such as pigment and perfume, are believed to irritate the skin. Based on the above, the use of soap and/or detergent may be useful to keep the skin clean, however, skin conditions that vary according to age, site, and season, type and usage of soap or detergent should be considered. As sebum generally melts at approximately 30°C,[156] it can be removed in lukewarm water to some extent from the skin. Thus, the use of soap should be limited to a minimum in patients with severe cases, during dry seasons, and in those sensitive to strong irritation by soap or detergents. In contrast, soap and detergents should be used aggressively in patients with oily skin or for seborrheic skin, in sites where ointment is applied every day, and in sites exhibiting recurrent skin infections to avoid exacerbating factors. There is no evidence of superiority between solid soap or detergents and liquid detergents (that use synthetic surfactants, etc.). It is important to choose an appropriate cleanser that satisfies the following conditions: its base composition is mildly-irritating/hypoallergenic, additives such as pigments and perfume are reduced as much as possible, and the usability is favorable without irritation, while detergents that exacerbate dry skin after washing should be avoided. Likewise, soap and/or detergents should be thoroughly rinsed to protect the skin from damage. Residues on the skin should be removed using a minimal degree of mechanical irritation, and adequate rinsing of the skin in necessary to remove residual detergent is also important.

Search for exacerbating factors and measures

Non-specific irritation. Non-specific irritation present in daily life such as contact with saliva, sweat, hair, and friction against clothes may exacerbate AD. Saliva or sweat should be washed away or wiped off with soft wet gauze. As even minor stimulation, including irritation from the rough texture of clothes, such as from wool, and contact from the tip of the hair can induce itchiness on sensitive skin due to skin dryness or eczema, appropriate measures should be taken, for example, choosing suitable nonirritating clothing, cutting hair short, or tying up hair.

Washing the skin with stiff materials such as a nylon towel leads to a decline in the skin barrier function and progression of eczema due to physical irritation. In addition, the residues from shampoo, conditioner, and soap or excessive use of these agents may induce irritant dermatitis, thus, providing instructions on appropriate cleansing methods is important. Makeup removal products may also cause irritation to the skin.

Irritation from scratching is extremely important as an exacerbation factor of AD. In addition to dermatitis treatment to reduce itch, cutting nails short, and wearing gloves, long sleeves and long pants while sleeping, if necessary, so that scratching does not cause skin damage, may be helpful in some cases.

Contact allergy. Contact allergy to topical drugs, cosmetics, perfume, metal, shampoo, hair conditioners, and disinfectants may case progression of eczema.[157–159] When expected treatment efficacy for AD cannot be achieved, the distribution of eczema is not typical. In cases in which AD onset or progression has occurred recently in an adult patient, complications due to contact allergy should be suspected. In such cases, observe whether the eczema can be resolved by avoiding contact with a potential causal agent, and confirm the diagnosis by a patch test. It is important avoid contact with causative agents of contact allergy defined in the diagnosis (see contact dermatitis guidelines[160] for details).

Food allergens. Food allergens may be present in patients with AD pathology, especially during infancy. However, a systematic

review has reported that there is only weak evidence of the efficacy of an allergen elimination diet in treating AD in children and adults without any clear involvement of food allergy.[161] The allergen elimination diet presents nutritional issues associated with potential growth and development impairment when undertaken during childhood; thus, allergen elimination therapy should be provided under the close surveillance of physicians. Except for cases in which progression of AD due to a certain food is confirmed, the elimination of a specific food because it is likely to become an allergen is not recommended (CQ15: Recommendation grade: 1, evidence level: B). In order to eliminate a specific food from the diet, an allergen elimination test should be conducted after adequate anti-inflammatory therapy for AD. If no improvement is achieved in cutaneous symptoms even after anti-inflammatory therapy with appropriate intensity and sufficient doses of TCS, food allergens causing progression of eczema should be identified. If AD is poorly controlled because of inadequate topical therapy, making a definitive diagnosis will be difficult.

The involvement of food allergens should be determined with reference to the results of interview to obtain detailed previous medical history, skin tests, and blood tests, as well as the oral challenge test after eliminating causal food. For example, clinical symptoms alone or positive results to a specific IgE antibody alone should not be used as a basis for diagnosis. If ingestion of certain food is restricted because it is perceived to be a likely allergen, it can be considered useful treatment for AD. AD is multifactorial, and elimination of food allergens is an adjuvant therapy to drug therapy, thus, it should be recognized that complete remission is not to be expected with elimination of food allergens even after clarifying the involvement of food allergens.

The American Academy of Pediatrics recommends the allergen elimination diet for pregnant women in 2000. However, a systematic review of randomized comparative studies of allergen elimination diets in pregnant or breastfeeding mothers conducted between 2006 and 2012[162] reported that dietary restrictions with the aim of eliminating allergens these women did not show any efficacy in preventing the onset of AD in neonates or in infants up to 18 months of age. Furthermore, dietary restrictions may have a role in limiting adequate weight gain during pregnancy and may worsen nutritional status among children leading an increased risk of immature births. Based on the above, dietary restrictions (allergen elimination) in pregnant or breastfeeding mothers may not be useful to prevent the onset of AD in children (CQ16: evidence level: A).

Inhaled allergens. Atopic dermatitis after infancy may experience progression due to the presence of environmental allergens such as mites, house dust, pollen, and pet hair.[163] Whether these allergens are to be considered exacerbating factors for eruption should be carefully evaluated by comprehensively considering medical history, environmental changes, and changes in eruption features, and should include results of elimination tests and challenge tests, if possible, rather be based on judgment of clinical symptoms alone, or by specific IgE antibody titer, or skin prick test results. Similar to handling of food allergens, eliminating environmental allergens is an adjuvant therapy to pharmacotherapy and skin care; thus, it should be noted that complete remission cannot be expected by eliminating these allergens alone.

Useful specific IgE antibodies to inhaled allergens. Mites and pollen (from cedar, cypress, white birch, *Alnus japonica*, *Anthoxanthum odoratum*, cocksfoot, and pollen includes ragweed), animals (from pets including dogs, cats, other mammals, birds, and hamsters), and fungi (from aspergillus and malassezia).

Measures for avoiding exposure to mites: Vacuum futons (Japanese-style bedding, bed, or covers), use anti-mite sheets, prohibit stuffed toys on beds, etc.

Pets: Give up pet(s), wash pet(s), prohibit pet(s) in the bedroom.

Pollen: Brush off all pollen on clothes when arriving home, wash face. Use protective glasses and masks against pollens. Use oral antihistamines, eye drops, and nasal sprays.

Sweating. Disturbances in perspiration as well as excess sweat remaining on the skin surface exposed to high temperatures and humidity may worsen symptoms of AD. Sweating influences AD symptoms in both positive and negative ways. Therefore, education on the fundamentals of sweating should be provided in function of the individual patient's lifestyle.

Sweat mainly consists of electrolytes (sodium chloride, potassium, etc.), sodium bicarbonate (HCO_3^-), urea, pyruvic acid, lactic acid, bactericidal peptides, proteases, and protease inhibitors. Urea and lactic acid act to retain water in the horny cell layer as a natural moisturizing factor. Sodium lactate derived from sweating acts as a natural moisturizing factor and may be involved in moisturizing the skin surface, as much of the sodium lactate is mostly contained within the horny cell layer.[164,165] Urea concentration in sweat is similar to that found in plasma, and functions to maintain persistent moisture within the horny cell layer as well as to regulate exfoliation.[164]

Moreover, the inhibitory effects of sweating on cysteine and serine proteases inactivates mite allergens (Derf1) and the kiwi fruit allergen (actinidin), cysteine protease allergens, and likely restores the vulnerability of the horny cell layer to excessive protease activity.[166–168] Bactericidal peptides contained in sweat are also involved in defending the skin surface from infection.[169–172]

The benefits of sweating deteriorate with time. Malassezia-derived allergens found in sweat residues on the skin surface that have not evaporated may lead to worsening of symptoms.[173] High temperatures and humidity on the skin surface occludes sweat pores and induces perspiration.[174] To protect the skin surface from having excessive sweat, an undergarment made of breathable and low hygroscopic fabric should be worn to avoid high temperatures and humidity, and appropriate measures such as showering, rinsing using running water, wiping with wet towels, and changing wet clothes after sweating should be adopted.

Among patients with AD, some sweat normally, while others produce moderate amounts (scanty sweat).[175–179] Inspection and palpation are helpful in determining whether a patient's

sweating is normal. Significant dryness of the skin, flushing, and heat sensations are important findings indicating poor perspiration. Dermatitis, histamine release, and anxiety (personalities prone to anxiety) are potential factors causing reduced sweating.[178,180,181] The effects of sweat-inducing activities including exercise and bathing on AD symptoms should be examined in future studies. However, there is no evidence that guidance on how to avoid sweating may improve symptoms, thus, such guidance is not necessary, and rather, patients should focus on the appropriate measures to be taken after sweating. Stimulation of sweating responses is a goal in patients with poor perspiration.[182]

Bacteria and fungi. It is known that *S. aureus* is often detected in the lesion of patients with AD, and *S. aureus* may be an exacerbating factor of AD. Treatment with povidone iodine solution and hypochlorous acid (bleach bath therapy) has been suggested with the aim of sterilization and bacteriostasis. The role of bacteria in AD is largely unknown, however, bacterial flora analysis of the skin has recently revealed its involvement in clinical conditions. On the skin of children with AD, it has been reported that the diversity of the bacterial flora of the skin decreases in the exacerbation phase, and the proportion of *S. aureus* increases.[183] The results of studies in animal models have shown that abnormal bacterial flora including the presence of *S. aureus* may induce AD-like dermatitis, and maintenance of normal bacterial flora with antibiotic treatment can inhibit the occurrence of dermatitis.[184] However, the relationship between the bacterial flora of the skin and clinical conditions of AD has not been fully examined, and additional future research is required.

There have been no reports suggesting that administration of oral antibiotics is effective for AD in the absence of infection, thus, administration of oral antibiotics is not recommended.[185] There is a lack of sufficient medical evidence to actively recommend the use of povidone iodine solution. Although povidone iodine solution is occasionally considered as an adjuvant therapy for patients with potential skin infections, it should not be implemented without careful consideration, as there is a potential for dermatitis progression due to irritation on the eroded surface, allergic contact dermatitis, and anaphylaxis, as well as potential effects on thyroid function.

Bleach bath therapy is widely practiced, mainly in the US and other countries, and there are reports showing its efficacy. Use of this therapy is recommended for patients in whom there is a suspicion that skin infections are potentially involved. However, its effects have not been fully validated, and there are no established recommendations in Japan, hence, future verification of its effects on AD are warranted.

The potential involvement of fungi on the pathology and worsening of AD has been suggested based on the results of measuring specific IgE antibodies levels to candida or malassezia and skin prick test results in patients with AD.[186] However, a clear correlation with the clinical conditions is still unknown. While there are some reports showing that oral antifungal drugs are effective for AD,[187] topical antifungal drugs have been shown to be effective for eruptions on the head and neck,[188] there have been no large-scale studies to date, thus, careful use is recommended.

Psychosomatic involvement

It is well known empirically that AD can be worsened by stress, and Alexander had addressed AD as one of seven representative psychosomatic diseases (the so-called holy seven) including bronchial asthma. AD is known to be associated with concomitant developmental disorders such as attention deficit hyperactivity disorder; however, such diagnosis is not helpful for treatment. When AD is poorly controlled, psychological burden or secondary cognitive abnormalities can occur, however, these patients should not be perceived as "special" by clinicians, and comprehensive treatment should be provided to all patients with specific attention to psychosomatic interaction.

Verification of drug therapy and patient adherence. Clinical features of AD mainly consist of a reduction of epidermal barrier functions and allergic inflammation, to which scratching contributes to induce a vicious circle of these symptoms; this cycle cannot be interrupted without the elimination of itching through appropriate drug therapy and improvement in treatment adherence. As persistence of itching is a trigger of various secondary physical or mental disorders and behavior abnormalities, intense medical treatment and patient education on specific procedures and implementation schedules are required. Careful patient education is essential for prevention and to overcome misconceptions associated with steroid treatment.

Understanding of stressor effects as exacerbating factors. Adolescents often experience progression of skin conditions due to tension before school exams and lack of sleep. They also often experience progression of skin exacerbation when affected by the flu or flu-like illnesses or sweating caused by fever or high temparature. Such stressors are unavoidable factors; however, these may be surmounted by stress management and behavior modification, including changes in lifestyle habits, and relaxation training.

Habitual scratching behavior. In situations where gain from illness can be obtained through scratching behavior, habitual scratching is likely to occur because of operant conditioning. When parents attempt to interrupt their child's scratching behavior or in situations in which a conflict exists among siblings, this can represent a potent instrument to draw parental affection or attention from the rival. In severe patients, anxiety and feelings of hopelessness regarding prognosis and treatment are respondently conditioned through the repeated paired presentation with the perception of a itching sensation, thus, patients are conditioned to instigate scratching behavior as a result of a stimulus induced by anxiety, even in the absence of a conscious itching sensation.

Patient education. Psychosomatic interventions with verified efficacy in RCTs have reported results limited to behavioral science approaches, such as behavioral therapy and cognitive

behavioral therapy,[189] while the efficacy of psychoanalysis and counseling with attentive listening have not been demonstrated. Implementing a comprehensive approach to patient education using behavioral science techniques such as appropriate drug therapy, supportive stress-reduction training, including relaxation training and cognitive behavioral therapy, behavioral therapy to stop habitual scratching, coaching to improve therapy adherence, and motivational interviewing[190] are important.

Complications: allergic diseases

Atopic dermatitis often complicates allergic diseases such as food allergies, bronchial asthma, allergic rhinitis, and allergic conjunctivitis. Allergic diseases are closely related; thus, consultation by a clinical team consisting of a pediatrician, dermatologist, otolaryngologist, and ophthalmologist is necessary to implement comprehensive management of the patient.

Food allergy. Numerous studies examining the relationship between AD and food allergy have been conducted. In 2003, Lack *et al*. reported that the development of peanut allergy was associated with the presence of inflamed skin and use of skin care products containing peanut oil; thus, suggesting that sensitization to allergens could occur through the skin (or via epicutaneous sensitization).[191] The concept of the "dual allergen exposure hypothesis" proposed by Lack *et al*. in 2008 indicated the importance of "cutaneous sensitization" and "oral tolerance" in the development of food allergies.[192]

The fact that AD occurring during infancy is associated with a higher risk of developing food allergies[191,193] supports the concept of "epicutaneous sensitization" in which exposure to food allergens via the skin may induce sensitization. Conversely, it has been reported that early prevention of the onset of AD through appropriate skin care in children may be beneficial for children at high risk of allergies,[145,146] however, studies have not demonstrated a preventive effect on food allergen sensitization. Further studies are necessary to address these issues in the future.

In children with AD, it is known that children who ingest eggs at a later age are at higher risk of developing egg allergy. Oya *et al*. conducted a study in infants with AD and showed that egg intake immediately after weaning was associated with a reduced risk of developing egg allergy at age 1 year after inducing remission of AD. In other words, this study indicated the importance of inducing oral tolerance to allergens to prevent the onset of food allergy during infancy.[194]

In relation to the above studies, the Japanese Society of Pediatric Allergy and Clinical Immunology released their "Recommendations for the prevention of the development of egg allergy" in 2017.[195] According to these recommendations, the Society clearly specified that allergen elimination on the sole grounds of avoiding sensitization to eggs not be recommended without careful consideration. Furthermore, these recommendations underlined the importance of treatment of AD before commencing baby food, and provided suggestions regarding timing and amount of egg intake.

Food causes an exacerbation of AD in some cases during infancy. According to the Japanese Pediatric Guidelines for Food Allergy 2016, this condition is clinically classified as AD during infancy associated with food allergy.[138] Please refer to the guidelines for a detailed description of medical procedures.

Bronchial asthma. The incidence of bronchial asthma in children with AD is 1.8 times higher than that of the general population.[196] When bronchial asthma is suspected to occur in combination with AD, intervention by a clinical team of dermatologsts, pediatricians, and specialists in internal medicine should collectively provide treatment. Systemic steroids are often administered during a bronchial asthma attack, and consequently, AD may show a transient improvement. Appropriate skin care should be continued during treatment for bronchial asthma attack, as cutaneous symptoms are likely to worsen on discontinuation of treatment with systemic steroids.

Allergic rhinitis. Allergic rhinitis often occurs in association with AD, and extra caution is warranted during the cedar pollen scattering period in Japan. For patients with allergic rhinitis sensitive to cedar pollen, contact with cedar pollen may worsen AD.[197] Abroad, the exacerbation of cutaneous symptoms due to the presence of other pollens has been reported.[198] Symptoms may extend to the entire body, and not only to exposed skin areas such as the face. In addition, external stimuli, including nose blowing and scratching the nose to address nasal discharge and itching sensations, may worsen perirhinal cutaneous symptoms. When allergic rhinitis is intractable, patients should be managed in collaboration with an otolaryngologist.

Allergic conjunctivitis. Concurrent allergic conjunctivitis is an exacerbation of cutaneous symptoms on the eyelids. The extension of inflammation to the eyelids due to conjunctivitis and scratching the eyelids make cutaneous symptoms on the eyelids obstinate. Frequently opening and closing of the eyes due to itchiness also serves as chronic stimulation and may make the symptoms refractory. Long-term eyelid scratching behavior may result in eye complications such as cataracts. When allergic conjunctivitis occurs in combination with AD or eyelid cutaneous symptoms are refractory to treatment, patients should be managed in collaboration with an ophthalmologist.

Diagnosis of infectious disease and its treatment. Atopic dermatitis is likely to occur with microbes, fungi, and viral infections due to decreased skin barrier functions and decreased skin immune activity. Bacterial infections include impetigo contagiosa, erysipelas, and cellulitis while virus infections include Kaposi's varicelliform eruption, and molluscum contagiosum.

Impetigo contagiosa is caused by *S. aureus* or *Streptococcus*. In the cases of impetigo contagiosa attributable to *S. aureus*, bullae frequently appear and are easily broken expanding redness peripherally. In the cases of *Streptococcus*, especially the Group A *Streptococcus*, pustules rapidly appear with systemic symptoms such as fever followed by significant crust

formation. Cephem-based oral antibiotics and penicillin are administered for bullous impetigo and crusted impetigo, respectively. Showering to keep lesions clean, use of topical antibiotic ointment, and protection of the lesions with gauzes is recommended.

Erysipelas is a dermal infectious disease mainly caused by Group A *Streptococcus*. It is accompanied by chills and fever, and well-circumscribed glossy red plaques with heat sensation and a strong pressing pain on the face (unilaterally in the early stages). Penicillin- or cephem-based systemic antibiotics are required.

Cellulitis is an acute suppurative inflammation extending from the dermal deep layer to the hypodermis. It is mainly caused by *S. aureus* while Group A *Streptococcus* is a potential cause. Cellulitis is accompanied by local heat sensations and pain on the lower limbs, in addition to well-circumscribed erythema and swelling. Systemic administration of cephem-based antibiotics and rest are required.

Kaposi's varicelliform eruption occurs caused by primary infection or reactivation of herpes simplex virus. In contrast to typical herpes simplex, many vesicles and pustules appear on the eczema lesions mainly on the face and neck and extend peripherally. This eruption is accompanied by fever and lymph node enlargement. Oral administration of antiviral drugs, acyclovir, and valacyclovir or intravenous infusion of acyclovir are required. It may also be associated with a secondary infection to bacteria making a differential diagnosis from impetigo difficult in some cases.

Although molluscum contagiosum is a poxvirus infection originally observed in children, it can be observed in adult patients with AD. Lesions are glossy skin color to yellow papules of about 2 to 5 mm in diameter with a central umbilication, and can be treated by the complete expulsion of the white vesicle using trachoma tweezers.

Since these infectious diseases occur often and becomes severe in patients with uncontrolled AD, it is important to maintain the skin condition well with basic treatments.

Ocular diseases. Eyelid dermatitis, keratoconjunctivitis, keratoconus, cataracts and retinal detachment frequently develop when skin symptoms in the face are severe. It is important to promote regular ophthalmological consultations, instruct patients not to rub/hit their eyes and control eruptions.

Ultraviolet irradiation therapy

Ultraviolet (UV) therapy is considered for non-responders to treatments with topical anti-inflammatory drugs, antihistamines or moisturizers, as well as for patients with adverse reactions to conventional treatments.[6,199] Narrow-band ultraviolet B (NB-UVB) irradiation therapy emitting light with a peak around 311 nm has been demonstrated to be effective in the treatment of AD.[200,201] A protocol of UV therapy should be established in the future for patients with AD. When administrating UV therapy, it is important to initially consider whether it should be indicated, and it should also be carefully performed by UV therapy-skilled physicians who sufficiently understand the action mechanism, radiation dose, acute skin disorders, deterioration of concomitant infectious diseases, various long-term adverse reactions, including skin cancer, and management methods. Ultraviolet irradiation therapy can be used for children with psoriasis beginning at 10 years of age and older, but is not recommended for children younger than 10 years of age.[202]

Hospital care

The goal of basic drug therapy for AD is to achieve early remission using TCS or tacrolimus ointment and then maintain it using the minimum amount of drugs. However, it is difficult to induce remission in some severe patients in whom the area of eruption is extensive. Hospital care is indicated for such patients. Some severe patients exhibit acute exacerbation, whereas severe dermatitis is chronically protracted in others. Both types of patients should be admitted, with hospital care being more significant for the latter.

In patients with chronically protracted severe dermatitis, there are problems regarding disease activity (enlargement of eruption related to inflammation with strong activity or scratching), patient adherence (insufficient understanding of the pathogenesis of AD or treatment methods, no goal of treatment in the absence of experience at the level of remission, experience-based misunderstanding of topical therapy and insufficient understanding of the significance of topical therapy or its methods) and aggravation factors (environmental/lifestyle related factors and overworking) as background factors. In many cases, these problems become deadlocked through interactions. Hospital care may make it possible to thoroughly perform intensive topical therapy with isolation from the daily environment, establish a healthcare professional–patient relationship of mutual trust, review triggering factors/application methods/skin care and overcome these problems in the early phase. Several hospitals reported that such therapeutic interventions improved long-term prognoses after patient discharge.[203,204] In addition, it is often the case that patients cannot continue the drug treatment appropriately, resulting in unexpected effects. For such patients with moderate to severe AD, hospital care would be considered as required. Because continuous topical treatment is required after the discharge of severe patients for whom hospital care is indicated, it is essential to understand their conditions and treatment methods. Therefore, the goal of hospital care is to achieve the early remission of dermatitis by intensive topical therapy and improve adherence through educational guidance.

Special considerations for children

Clinical presentation. It should be noted that eczematous lesions are subject to change in function of a child's growth and development. The definition of chronic also differs and is defined as a disease persisting for 2 months or longer and 6 months or longer in infants and older children, respectively. It is not always the case that a child with severe disease during infancy will experience more severe disease as the child grows older, and many children achieve near remission at 1 to 1.5 years of age. There are two types of pre-school children:

those with persistent disease from infancy and those with new onset the disease at around 3 years of age.

During infancy, erythema and infiltrative erythema initially appear on the face, specifically on the cheek, and then extend to the neck and peripheral sites, body trunk, and limbs on disease progression. Eruptions on the face gradually stabilize with a peak at 4 to 6 months and transition to the lesions on the neck and joints of limbs. Eczematous lesions occurring during pre-school to school ages mainly appear on the neck and joints of limbs. After adolescence, eruptions tend to appear on the upper body including the head, neck, chest, and back similarly to adults.

Exacerbating factors. During infancy, "food allergy-related infant AD" is the predominant form of AD, however, this does not mean that food allergy always causes AD. Infants with severe AD are likely to have already been sensitized to food allergens (in the order of egg, milk, and wheat) before ingestion of these foods. Thus, these causal foods that the mother has ingested may cause exacerbation of eruptions via breast milk. However, this is not always observed in all cases; thus, a food challenge test (through breast milk) should be conducted to make a definitive diagnosis. Hence, the suspected food is eliminated from mother's diet, and if any improvement of the symptoms is observed, the mother should resume intake of the food and after breastfeeding her child, she should observe whether the symptoms worsen. Even though sensitization is present in the child, elimination of the allergen from the mother's diet is not necessary in many cases.

In older pre-school or school-aged children, the contribution of inhaled allergens intensifies. As for mites, special attention is required to allergens derived from animals such as dogs and cats, the patient should be questioned on potential exposure to pet(s) during the medical interview. Eruptions may worsen mainly on the face during the cedar pollen scattering period. As the development of cedar pollen allergy has been observed in children of younger ages in recent years, particular attention should be taken for pre-school-aged children.

Atopic dermatitis is likely to worsen in the summer period because of sunburns and sweating, and patients tend to have difficulties in school activities. AD can be improved with appropriate management including showering at school. AD is likely to worsen due to dryness of skin during the winter period, and special attention is required in relation to school activities. Stress is also an important exacerbating factor. Special attention is necessary, as younger patients are likely to fall into a vicious circle if they are discriminated against because of AD or they are the objects of bullying.

Laboratory testing. The normal upper limit of total serum IgE level declines with age. Thus, it cannot be used as a marker of AD activity. In the allergen-specific IgE antibody test, food allergen sensitization (egg, milk, and wheat) can be observed in many cases during infancy. Sensitization to mite and pollen is observed more often in the pre-school phase. Food allergen sensitization does not always require elimination of causal allergens, and making a careful diagnosis is necessary through medical interview or the oral challenge test. Please refer to the "Japanese Pediatric Guidelines for Food Allergy 2016.[138]

The serum eosinophil count increases in correlation with severity, and a markedly high value can be detected during infancy. Levels improve promptly with the improvement of the lesions. As serum TARC levels correlated well with AD severity, it is useful as a marker of disease progression, however, it should be noted TARC levels are generally higher in younger children.

Biochemistry tests during infancy are required for more severe cases because hypoalbuminemia, hyponatremia, hypoproteinemia may occur concomitantly.

Treatment. The basic treatment approach is the same as that of adult patients; however, remission can be achieved in a relatively shorter period during childhood, providing appropriate treatment is given according to disease severity. Although mild class TCS (VI) are often instinctively administered to children because of their age, upper ranked TCS should be used when the improvement of eruption is poor. In contrast, if the symptoms improve following treatment with a very strong TCS (II) alone, it is recommended to follow-up disease control under the surveillance of a specialist, as additional exacerbating factors of eruption may be present.

Specific baby bathing products may be used when bathing babies for several months after birth. Caution is needed because inflammation may worsen by washing with baby bathing products alone without soap in some cases.

Antihistamines are occasionally used to control itching. When eruptions improve, itching also rapidly improves especially during infancy. Sedative antihistamines, likely to have central activity, should be avoided. Ketotifen is contraindicated in patients with epilepsy, thus, it is administered cautiously for convulsive disorders. If special considerations regarding convulsive disorder are warranted, such as in the case of positive medical history of febrile convulsions, non-sedative antihistamines are recommended (Table 7). However, appropriate measures should be taken when treating patient and attention should be paid to the information present on the package insert and with reference to the most recent data regarding safety.

Only TCS are used, in practice, and the use of systemic steroids is not necessary for the treatment of AD in children. Oral steroids are reserved for the treatment of asthma attacks (complication) or as an adjuvant therapy in case of anaphylaxis symptoms, and this often leads to a transient improvement of the eczema; nonetheless, concern of adverse effects is minimal as systemic steroids are only used for a limited period of time.

Change in the key caregivers of treatment. Although the parent's or caregiver's understanding of the disease and provision of topical therapy are important during infancy and early childhood, education on disease of both patients and parent/caregivers is necessary for school-aged children. Support from kindergarten, nursery school, and school personnel should be asked for support and these facilities should provide measures to protect children from potential exacerbating factors (sweat,

dryness). Patients or caregivers should be provided with specific instructions, for example, to wipe with a wet towel when sweating or to shower, if possible, and to use a topical moisturizer when dryness is severe during winter. An information sheet describing allergic disease management may also be helpful. It provides details on the patient's current treatment, severity, and considerations to be taken at school. As this information sheet is completed by the healthcare facility, it contributes to foster an effective culture of collaboration. The key caregiver of treatment will be the patient him/herself after adolescence; however, the patient may have not have a full understanding of his/her own disease and treatment; thus if the disease continues from early childhood, whether the patient understands his/her treatment, for example, who is responsible for applying topical treatment, should be confirmed.

Complications. During childhood, other allergic diseases (food allergy, allergic rhinitis, and bronchial asthma) may occur concomitantly in many cases. While food allergy due to cutaneous sensitization is observed during infancy, prevention of the development or induction of rapid remission of food allergy by controlling dermatitis is recommended; thus, appropriate continuous skin care is an important concern.

The development of allergies to pollen, such as cedar pollen allergy, during early childhood has been increasingly diagnosed recently, and progression of eruptions is prominent, as well as the presence of eye and nasal symptoms in some cases. When inflammation in the nose persists, allergic rhinitis should be suspected when making a differential diagnosis of infection.

The risk of developing asthma in children with AD is higher than in the general population. When symptoms suggesting airway hyperresponsiveness are observed, for example, prolonged coughing after infection, coughing after sustained laughing or crying, the clinical course should be observed for frequency and severity.

Differential diagnosis. Neonate acne is an acne-like eruption observed mainly on the face and occurs approximately 2 weeks after birth, and transiently improves thereafter. Seborrheic dermatitis during infancy is an eczematous lesion presenting as erythema with yellow desquamation at seborrheic sites (head and face during infancy), and is often observed around one month after birth. There is no itching, and if any, it is minor in degree and may improve by washing the face thoroughly with soap. If effusion is observed from lesions, it may be resolved by applying a mild class TCS, and recurrence is unlikely when the TCS is stopped as in AD. Conversely, in some cases seborrheic dermatitis during infancy can transition to AD despite improvement. This is because it is difficult to determine a definite diagnosis of AD at 1 month after birth, despite having already showed signs of development. To distinguish AD in the early stages, the presence of itching is an important sign. Whether an infant rubs his/her cheek due to itching when lifted, shows scratching behavior on the body when undressed, or if a scratching scar is observed at a reachable site for the infant are potential signs to be observed.

In addition, a differential diagnosis of diaper dermatitis is also necessary during infancy. Diaper dermatitis is an erythema appearing on sites in direct contact with the diaper, and it follows that a dermatitis appearing in this region may also be accompanied by skin eruptions. If an eruption is observed elsewhere on the body, either diaper dermatitis may have either occurred concomitantly with AD or AD may have worsened due to stimulus by the diaper.

Contact dermatitis may occur due to daily use of soap, baby bathing products, and detergents used for washing clothes. Commercially available fabric softeners or detergents for clothes that are not apparently harmful are recommended.

If an AD-specific eruption is ruled out, or enough improvement is obtained following treatment with TCS, differential diagnosis from other congenital cutaneous diseases such as congenital ichthyosis, Netherton syndrome, xeroderma pigmentosum is necessary and a referral to a dermatologist should be considered (see Differential Diagnosis section).

Patient education

For AD mainly treated by topical therapy at outpatient clinics, patients and their families have a key role in treatment. It is essential that the patient's family properly understands the patient's clinical conditions and the treatment required in order to improve adherence and achieve successful treatment (see Adherence section).

In Japan and abroad, various methods for patient education have been attempted, and each has been reported to be effective in decreasing the severity of eczema and improving QOL. Different approaches have been successful in many studies regarding children, specifically, education by a multidisciplinary medical team, group work by a specialized nurse, educational hospital-stay for a short period of time, and education using online videos.[205–209] Other than above, websites and leaflets for young patients have been developed and have been used as educational tools for patients with AD in Japan.[210,211]

In clinical practice, the above tools should be selected as effective and feasible educational methods taking into consideration the individual patient's characteristics and medical care system provided at the treating facility. Confirmation on the use of topical drugs is important and appropriate instructions should be provided before changing treatment, not only during the treatment introduction phase, but also when the expected efficacy of the therapy cannot be obtained.

Other: probiotics, and other agents

Enterobacteria have an important role in the immune response *in vivo* and have been reported to be associated with various diseases. There are many studies indicating a relationship with allergic diseases such as AD, and prevention of AD development and use of enterobacteria in treatment. Comparing enterobacteria composition of children with allergic diseases and that of healthy children, children with allergic diseases have been reported to have significantly less lactic acid bacteria present.[212,213] Ito *et al*. studied the relationship between pediatric AD and enterobacteria and reported that a significant

decrease of bifidobacteria was observed in infants with severe AD.[214] The effects of intervention by enterobacteria in the prevention of the development of allergic diseases or treatment after development have been examined in many studies. Probiotics (live micro-organisms yield useful effects on the host), prebiotics (food ingredients promoting growth of micro-organism useful for the host), and synbiotics (a combination of probiotics and prebiotics) are the representative preparations. In a recent meta-analysis on probiotics, administration of probiotics to pregnant mothers, and subsequently to the infant after birth was shown to prevent the development of AD.[215] Numerous studies have been conducted on the treatment effects of probiotics on AD after its development, and their results indicated that probiotics significantly improved the eruption score according to the SCORAD index in children older than 1 year of age and in adults.[216] Although there have been only a few studies on prebiotics, a meta-analysis showed these preparations do not have any preventive effects on the development of AD.[217] Synbiotics have been reported to be effective for AD in children over the age of 1 year in a meta-analysis, however, no preventive effect on AD development was observed.[218] The efficacy of probiotics, prebiotics, and synbiotics vary depending on different factors, including type, combination, dose-timing, living environment, dietary habits, and race; thus, further investigation is required.

Complementary and alternative medicine for atopic dermatitis

Complementary and alternative medicine means care other than standard medical treatment implemented by physician at a healthcare facility, and is a collective term for care whose precise mechanism of action has not been scientifically validated in most cases. Alternative therapy is used as a substitute for standard guideline medical care and often complementary therapy supplements standard medical care. There is much publicity or information relative to complementary and alternative medicine for AD in so-called health magazines and available on the internet and it represents a controversial industry.

In a survey conducted in Hiroshima, 67.4% of patients with AD have tried alternative medicine.[219] In a questionnaire survey of guardians of children with AD at their first visit to medical facilities conducted in Tokyo, those with steroid phobia had more frequent experience with alternative medicine than those without steroid phobia (22.2% vs. 13.0%, $P = 0.013$).[220] In patients hospitalized for exacerbation of AD or aggravation due to complications, in 44% of patients these complications were caused by inappropriate treatment using alternative medicine.[221] As a result of excessive reliance on alternative medicine, adherence to standard medical care decreases and the worsening of symptoms has been the main concern.

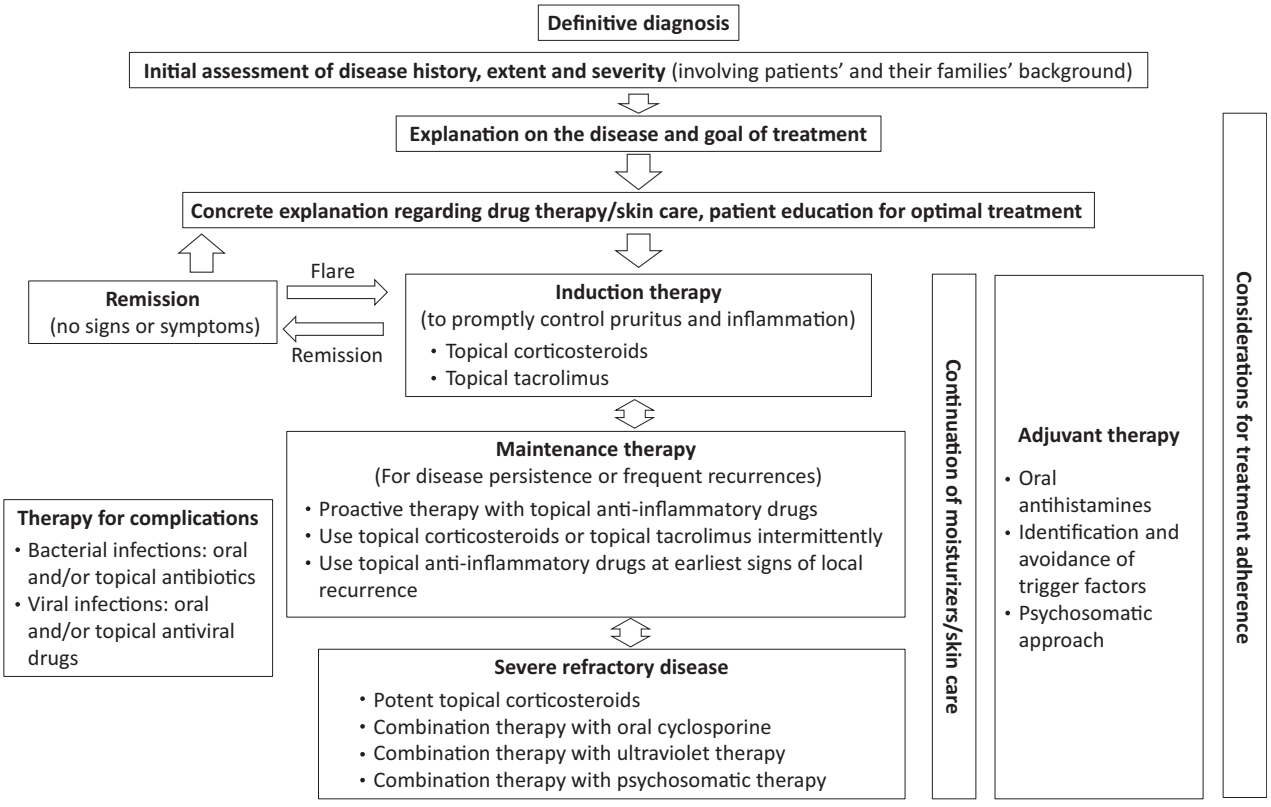

Figure 7. Algorithm for treatment of atopic dermatitis.

Several RCTs investigating the efficacy of complementary and alternative medicine have been reported. Although one study reported the efficacy of acupuncture in improving itching, the study size was small, and the quality of study was not good.[222] In an RCT evaluating the efficacy of a homeopathy, no significant differences in improvement were observed compared to the placebo group.[223] There is no adequate scientific evidence in the efficacy of complementary and alternative medicine.

Treatment adherence

In medical care for AD, a chronic disease, it is important for patients and their parents to understand their condition/the significance of treatments, positively participate in the selection of therapeutic strategies, accomplish treatments according to these strategies, and improve the will to continue treatments, that is, adherence to treatments. Treatment adherence-associated factors include patient-/disease-/treatment-/healthcare professional-related and socioeconomic factors.[224] Patient-related factors include the pressure of business and belief in medical practice/drug therapy. As treatment-related factors, complex treatment methods, those with a high incidence of adverse reactions and expensive procedures lead to a reduction in adherence. It is important to explain the merits and demerits of treatment with TCS in order to improve adherence. As factors related to healthcare professionals, their relationships with patients, explanations of the disease and treatment methods, and continuous information provision/support contribute to improvements in adherence. It is important to explain the necessity of drug therapy/skin care to patients and motivate them. Socioeconomic factors include a family's cooperation and human support by babysitters. To improve adherence, healthcare professionals should initially try to achieve factors that they can perform.[225–227]

Referral to a specialist

When no improvement of eczema is observed even after implementing treatment in accordance with the present clinical practice guidelines for a period of about 1 month, referral to a specialist or to a specialized facility should be considered.[13] When prominent erythema, scars from scratching, erosion, lichenification, or prurigo is observed, or a wide range of erythema like erythroderma is observed, referral to specialist should be considered. In addition, when infection by bacteria or virus is concomitantly observed, or a detailed examination of the exacerbating factors including food allergies and contact allergy is necessary, referral to specialist should also be considered.

Treatment procedures

Treatment procedures for AD are shown in Figure 7. After making an accurate diagnosis and evaluating its severity, appropriate treatment methods should be combined in accordance with the state of eruption. In the initial consultation, it is important to explain the condition of AD and treatment methods to patients and have a common understanding with them.

REFERENCES

1 Kawashima M, Takigawa M, Nakagawa H *et al*. Guidelines for management of atopic dermatitis. *Jpn J Dermatol* 2000; **110**: 1099–1104.
2 Furue M, Furukawa F, Hide M, Takehara K, Japanese Dermatological Association. Guidelines for therapy for atopic dermatitis 2003. *Jpn J Dermatol* 2003; **113**: 451–457.
3 Furue M, Furukawa F, Hide M, Takehara K. Japanese Dermatological Association Guidelines for therapy of atopic dermatitis 2004. *Jpn J Dermatol* 2004; **114**: 135–142.
4 Furue M, Saeki H, Furukawa F *et al*. Guidelines for therapy of atopic dermatitis. *Jpn J Dermatol* 2008; **118**: 325–342.
5 Furue M, Saeki H, Furukawa F *et al*. Guidelines for therapy of atopic dermatitis. *Jpn J Dermatol* 2009; **119**: 1515–1534.
6 Katoh N, Saeki H, Nakahara T *et al*. Guidelines for therapy of atopic dermatitis 2016. *Jpn J Dermatol* 2016; **126**: 121–155.
7 Kohno Y, Yamamoto S, The study group for Research on Allergic Disease and Immunology by Ministry of Health, Labour and Welfare of Japan. *Guidelines for the treatment of atopic dermatitis 1999*. (In Japanese.)
8 Furue M, Yamamoto S, The study group for Research on Allergic Disease and Immunology by Ministry of Health, Labour and Welfare of Japan. *Guidelines for the treatment of atopic dermatitis 2001*. (In Japanese.)
9 Kohno Y, Yamamoto S, The study group for Research on Allergic Disease and Immunology by Ministry of Health, Labour and Welfare of Japan. *Guidelines for the treatment of atopic dermatitis 2005*. (In Japanese).
10 Kohno Y, Yamamoto S, The study group for Research on Allergic Disease and Immunology by Ministry of Health, Labour and Welfare of Japan. *Guidelines for the treatment of atopic dermatitis 2006*. (In Japanese).
11 Katayama I, Kohno Y, Japanese Society of Allergology. *Japanese Guideline for Atopic Dermatitis 2009*. Tokyo: Kyowa Kikaku, 2009. (In Japanese).
12 Katayama I, Kohno Y, Japanese Society of Allergology. *Japanese Guideline for Atopic Dermatitis 2012*. Tokyo: Kyowa Kikaku, 2012. (In Japanese).
13 Katayama I, Kohno Y, Japanese Society of Allergology. *Japanese Guideline for Atopic Dermatitis 2015*. Tokyo: Kyowa Kikaku, 2015. (In Japanese).
14 Committee for Nasal Allergy Guidelines. *Nasal Allergy Guidelines 2016*. Tokyo: Life Science, 2016. (In Japanese).
15 Elias PM. Stratum corneum defensive functions: an integrated view. *J Invest Dermatol* 2005; **125**: 183–200.
16 Melnik B, Hollmann J, Plewig G. Decreased stratum corneum ceramides in atopic individuals–a pathobiochemical factor in xerosis? *Br J Dermatol* 1988; **119**(4): 547–549.
17 Cabanillas B, Novak N. Atopic dermatitis and filaggrin. *Curr Opin Immunol* 2016; **42**: 1–8.
18 Kono M, Nomura T, Ohguchi Y *et al*. Comprehensive screening for a complete set of Japanese-population-specific filaggrin gene mutations. *Allergy* 2014; **69**: 537–540.
19 De Benedetto A, Rafaels NM, McGirt LY *et al*. Tight junction defects in patients with atopic dermatitis. *J Allergy Clin Immunol* 2011; **127**: 773–786.
20 Tokumasu R, Yamaga K, Yamazaki Y *et al*. Dose-dependent role of claudin-1 *in vivo* inorchestrating features of atopic dermatitis. *Proc Natl Acad Sci U S A* 2016; **113**(28): E4061–E4068.
21 Vestergaard C, Bang K, Gesser B, Yoneyama H, Matsushima K, Larsen CG. A Th2 chemokine, TARC, produced by keratinocytes may recruit CLA+CCR21 + lymphocytes into lesional atopic dermatitis skin. *J Invest Dermatol* 2000; **115**: 640–646.
22 Nakamura K. TARC (thymus and activation regulated chemokine). *Jpn J Clin Med* 2010; **68**: 41–45. (In Japanese).
23 Fujita H, Nograles KE, Kikuchi T, Gonzalez J, Carucci JA, Krueger JG. Human Langerhans cells induce distinct IL-22-producing

CD4 + T cells lacking IL-17 production. *Proc Natl Acad Sci U S A* 2009; **106**: 21795–21800.
24 Hammad H, Lambrecht BN. Barrier epithelial cells and the control of type 2 immunity. *Immunity* 2015; **43**: 29–40.
25 Tominaga M, Takamori K. Itch and nerve fibers with special reference to atopicdermatitis: therapeutic implications. *J Dermatol* 2014; **41**: 205–212.
26 Murota H, Izumi M, Abd El-Latif MI. Artemin causes hypersensitivity to warm sensation, mimicking warmth-provoked pruritus in atopic dermatitis. *J Allergy Clin Immunol* 2012; **130**: 671–682.
27 Ikoma A, Fartasch M, Heyer G *et al*. Painful stimuli evoke itch in patients with chronic pruritus: central sensitization for itch. *Neurology* 2004; **27**: 212–217.
28 Murota H, Katayama I. Evolving understanding on the aetiology of thermally provoked itch. *Eur J Pain* 2016; **20**: 47–50.
29 Parsad D, Saini R. The sound of scratching: an unusual cause of neurotic excoriations. *Dermatology* 1997; **195**: 74.
30 Schut C, Grossman S, Gieler U, Kupfer J, Yosipovitch G. Contagious itch: what we know and what we would like to know. *Front Hum Neurosci* 2015; **9**: 57.
31 Lavery MJ, Stull C, Kinney MO, Yosipovitch G. Nocturnal pruritus: the battle for a peaceful night's sleep. *Int J Mol Sci* 2016; **17**: 425.
32 Gotoh Y, Omori Y, Andoh T, Kuraishi Y. Tonic inhibition of allergic itch signaling by the descending noradrenergic system in mice. *J Pharmacol Sci* 2011; **115**: 417–420.
33 Hirota T, Takahashi A, Kubo M *et al*. Genome-wide association study identifies eight new susceptibility loci for atopic dermatitis in the Japanese population. *Nat Genet* 2012; **44**: 1222–1226.
34 Wahlgren CF. Itch and atopic dermatitis: clinical and experimental studies. *Acta Derm Venereol Suppl (Stockh)* 1991; **165**: 1–53.
35 Williams H, Robertson C, Stewart A *et al*. Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *J Allergy Clin Immunol* 1999; **103**: 125–138.
36 Williams H, Stewart A, von Mutius E *et al*. Is eczema really on the increase worldwide? *J Allergy Clin Immunol* 2008; **121**: 947–954.
37 Morita E. *Analysis of Prevalence and Identification of Causative and Exacerbation Factors of Atopic Dermatitis and Studies for Improvement of Living Environment to Prevent the Development and Exacerbation of Symptoms. Reports of Research on Allergic Disease and Immunology by Ministry of Health, Labour and Welfare of Japan. Part*, Vol. **2**. Japanese)(In: 2002:; 184–186.
38 Yamamoto S. [*Identification of Causative and Exacerbation Factors of Atopic Dermatitis and Studies for Improvement of Living Environment to Prevent the Development and Exacerbation of Symptoms*. Reports of Research on Allergic Disease and Immunology by Ministry of Health, Labour and Welfare of Japan. Part 1, 2003: 71–77]. (In Japanese).
39 Saeki H, Iizuka H, Mori Y *et al*. Prevalence of atopic dermatitis in Japanese elementary schoolchildren. *Br J Dermatol* 2005; **152**: 110–114.
40 Saeki H, Oiso N, Honma M *et al*. Prevalence of atopic dermatitis in Japanese adults and community validation of the U.K. diagnostic criteria. *J Dermatol Sci* 2009; **55**: 140–141.
41 Ueda H. Epidemiology of atopic dermatitis. *Jpn J Ped Med* 2000; **32**: 986–992. (In Japanese).
42 Mikawa H. *Epidemiological Research of atopic dermatitis*. Reports of Research on Allergic Disease and Immunology by Ministry of Health, Labour and Welfare of Japan. 1995: 247–251. (In Japanese).
43 Ohta K, Oka N, Okazaki K *et al*. Prevalecen of atopic dermatitis in elementary schoolsin western Japan-Comparison between 1992 and 2002. *Jpn J Pediatr Allergy Clin Immunol* 2003; **17**: 255–268. (In Japanese).
44 Kusunoki T, Morimoto T, Nishikomori R *et al*. Changing prevalence and severity of childhood allergic diseases in Kyoto, Japan, from 1996 to 2006. *Allergol Int* 2009; **58**: 543–548.
45 Ricci G, Patrizi A, Baldi E *et al*. Long-term followup of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic diseases. *J Am Acad Dermatol* 2006; **55**: 765–771.
46 Illi S, von Mutius E, Lau S *et al*. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004; **113**: 925–931.
47 Sandström MH, Faergemann J. Prognosis and prognostic factors in adult patients with atopic dermatitis: a long-term follow-up questionnaire study. *Br J Dermatol* 2004; **150**: 103–110.
48 Kohno Y. *Identification of Causative and Exacerbation Factors of Atopic Dermatitis and Studies for Improvement of Living Environment to Prevent the Development and Exacerbation of Symptoms*. Reports of Research on Allergic Disease and Immunology by Ministry of Health, Labour and Welfare of Japan. Reports of Research on Allergic Disease and Immunology by Ministry of Health, Labour and Welfare of Japan. 2009: 1–11. (In Japanese).
49 Fukiwake N, Furusyo N, Kubo N *et al*. Incidence of atopic dermatitis in nursery school children –a follow-up study from 2001 to 2004, Kyushu University Ishigaki Atopic Dermatitis Study (KIDS). *Eur J Dermatol* 2006; **16**: 416–419.
50 Ohshima Y, Yamada A, Hiraoka M *et al*. Early sensitization to house dust mite is a major risk factor for subsequent development of bronchial asthma in Japanese infants with atopic dermatitis: results of a 4-year followup study. *Ann Allergy Asthma Immunol* 2002; **89**: 265–270.
51 Anan S, Yamamoto N. Natural remission of atopic dermatitis. *Skin Res* 1996; **38**(Suppl. 18): 13–16. (In Japanese).
52 Wakamori T, Katoh N, Hirano S *et al*. Atopic dermatitis, dry skin and serum IgE in children in a community in Japan. *Int Arch Allergy Immunol* 2009; **149**: 103–110.
53 Katoh N, Hirano S, Kishimoto S. Prognostic factor of adult patients with atopic dermatitis. *J Dermatol* 2008; **35**: 477–483.
54 Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm-Venereol (Stockh)* 1980; **92**(Suppl): 44–47.
55 Williams HC, Burney PGJ, Pembroke AC, Hay RJ. The UK Working Party's Diagnostic criteria for atopic dermatitis. III. Independent hospital validation. *Br J Dermatol* 1994; **131**: 406–416.
56 Aoki T, Fukuzumi J, Adachi J *et al*. Re-evaluation of skin lesion distribution in atopic dermatitis. *Acta Derm Venereol (Stockh)* 1992; **176**(Suppl): 19–23.
57 Hsu AP, Davis J, Puck JM, Holland SM, Freeman AF. *Autosomal Dominant Hyper IgE Syndrome*. http://www.ncbi.nlm.nih.gov/books/NBK25507/
58 Aoki T. The second report from the Advisory Committee for Atopic Dermatitis Severity Classification. *Jpn J Dermatol* 2001; **111**: 2023–2033. (In Japanese).
59 Yoshida H. Interim report from the Advisory Committee for Atopic Dermatitis Severity Classification. *Jpn J Dermatol* 1998; **108**: 1491–1496. (In Japanese.).
60 Severity scoring of atopic dermatitis: the SCORAD index. Consensus report of the European Task Force on atopic dermatitis. *Dermatology* 1993; **186**: 23–31.
61 Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol* 2001; **10**: 11–18.
62 Eichenfield LF, Tom WL, Berger TG *et al*. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol* 2014; **71**: 116–132.
63 Yamada H, Noda T, Matsukura M, Sugihara K, Yudate T, Tezuka T. Evaluation of itching by visual analogue scale (VAS). *Skin Res* 1996; **38**(Suppl 18): 71–77. (In Japanese with English abstract.).
64 Kido-Nakahara M, Katoh N, Saeki H *et al*. Comparative cut-off value setting of pruritus intensity in visual analogue scale and verbal rating scale. *Acta Derm Venereol* 2015; **95**: 345–346.
65 Furue M, Ebata T, Ikoma A *et al*. Verbalizing extremes of the visual analogue scale for pruritus: a consensus statement. *Acta Derm Venereol* 2013; **93**: 214–215.

66 Phan NQ, Blome C, Fritz F *et al*. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. *Acta Derm Venereol* 2012; **92**: 502–507.

67 Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Arch Dermatol* 2004; **140**: 1513–1519.

68 Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. *Br J Dermatol* 2013; **169**: 1326–1332.

69 Gaunt DM, Metcalfe C, Ridd M. The Patient-Oriented Eczema Measure in young children: responsiveness and minimal clinically important difference. *Allergy* 2016; **71**: 1620–1625.

70 Stalder JF, Barbarot S, Wollenberg A *et al*. Patient-Oriented SCORAD (PO-SCORAD): a new self-assessment scale in atopic dermatitis validated in Europe. *Allergy* 2011; **66**: 1114–1121.

71 Takahashi N, Suzukamo Y, Nakamura M *et al*. Japanese version of the Dermatology Life Quality Index: validity and reliability in patients with acne. *Health Qual Life Outcomes* 2006; **4**: 46.

72 Fukuhara S, Suzukamo Y. Japanese version of DLQI and Skindex-29. *Allergy Pract* 2007; **358**: 23–27. (In Japanese).

73 Higaki Y, Kawamoto K, Kamo T, Horikawa N, Kawashima M, Chren MM. The Japanese version of Skindex-16: a brief quality-of-life measure for patients with skin diseases. *J Dermatol* 2002; **29**: 693–698.

74 Ohya Y, Sasaki R, Matsumoto M *et al*. Development of Japanese Version of Children's Dermatology Life Quality Index (CDLQI). *Jap J Allergol* 2002; **51**: 265. (In Japanese).

75 Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *Br J Dermatol* 1995; **132**: 942–949.

76 Kondo-Endo K, Ohashi Y, Nakagawa H *et al*. Development and validation of a questionnaire measuring quality of life in primary caregivers of children with atopic dermatitis (QPCAD). *Br J Dermatol* 2009; **161**: 617–625.

77 Katsunuma T, Tan A, Ohya Y. Short verstion of quality of life questionnaire in primarycaregivers of children with atopic dermatitis (QPCAD): development and validation of QP9. *Jap J Allergol* 2013; **62**: 33–46. (In Japanese with English abstract.).

78 Chamlin SL, Cella D, Frieden IJ *et al*. Development of the Childhood Atopic Dermatitis Impact Scale: initial validation of a quality-of-life measure for young children with atopic dermatitis and their families. *J Invest Dermatol* 2005; **125**: 1106–1111.

79 Yamaguchi C, Futamura M, Chamlin SL, Ohya Y, Asano M. Development of a Japanese Culturally Modified Version of the Childhood Atopic Dermatitis Impact Scale (JCMV-CADIS). *Allergol Int* 2016; **65**: 312–319.

80 Smith PH, Ownby DR. Clinical significance of immunoglobulin E. In: Adkinson NF Jr, Bochner BS, Burks AW *et al*., eds. *Middleton's Allergy, Principles and Practice*. Philadelphia: Mosby, 2014; 1108–1119.

81 Saeki H, Tamaki K. Thymus and activation regulated chemokine (TARC)/CCL17 and skin diseases. *J Dermatol Sci* 2006; **43**: 75–84.

82 Tamaki K, Saeki H, Kadono T *et al*. Serum TARC/CCL17 levels as a disease marker of atopic dermatitis. *Jpn J Dermatol* 2006; **116**: 27–39. (In Japanese with English abstract.).

83 Fujisawa T, Nagao M, Noma Y *et al*. Clinical Utility serum TARC/CCL17 for monitoring clinical couse of atopic dermatitis in children. *Jpn J Pediatr Allergy Clin Immunol* 2005; **19**: 744–757. (In Japanese with English abstract.).

84 Kataoka Y. Thymus and activation-regulated chemokine as a clinical biomarker in atopic dermatitis. *J Dermatol* 2014; **41**: 221–229.

85 Fujisawa T, Nagao M, Hiraguchi Y *et al*. Serum measurement of thymus and activation-regulated chemokine/CCL17 in children with atopic dermatitis: elevated normal levels in infancy and age-specific analysis in atopic dermatitis. *Pediatr Allergy Immunol* 2009; **20**: 633–641.

86 Nagao M, Inagaki S, Kawano T *et al*. SCCA2 is a reliable biomarker for evaluating pediatric atopic dermatitis. *J Allergy Clin Immunol* 2018; **141**: 1934–1936.e11.

87 Hepburn DJ, Aeling JL, Weston WL. A reappraisal of topical steroid potency. *Pediatr Dermatol* 1996; **13**: 239–245.

88 Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000; **4**: 1–191.

89 Eichenfield LF, Tom WL, Berger TG *et al*. Guideline of care for the management of atopic dermatitis. Section2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol* 2014; **71**: 116–132.

90 https://www.nice.org.uk/guidance/ta81/chapter/Appendix-D-Topical-corticosteroids-for-the-treatment-of-atopic-eczema-grouped-by-potency

91 Long CC, Finlay AY. The finger-tip unit-a new practical measure. *Clin Exp Dermatol* 1991; **16**: 444–447.

92 Long CC, Finlay AY, Averill RW. The rule of hand: 4hand area = 2 FTU = 1 g. *Arch Dermatol* 1992; **128**: 1129–1130.

93 Green C, Colquitt JL, Kirby J, Davidson P. Topical corticosteroids for atopic eczema: clinical and cost effectiveness of once-daily vs. more frequent use. *Br J Dermatol* 2005; **152**: 130–141.

94 Green C, Colquitt JL, Kirby J, Davidson P, Payne E. Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation. *Health Technol Assess* 2004; **8**: 1–120.

95 Feldman RJ, Maibach HI. Regional variation in percutaneous penetration of 14C cortisol in man. *J Invst Dermatol* 1967; **48**: 181–183.

96 Hajar T, Lesham YA, Hanifin JM *et al*. A systematic review of topical corticosteroid withdrawal ("steroid addiction") in patients with atopic dermatitis and other dermatoses. *J Am Acad Dermatol* 2015; **72**: 541–549.

97 Tang TS, Bieber T, Williams HC. Are the concepts of induction of remission and treatment of subclinical inflammation in atopic dermatitis clinically useful? *J Allergy Clin Immunol* 2014; **133**: 1615–1625.

98 Schmitt J, von Kobyletzki L, Svensson Å, Apfelbacher C. Efficacy and tolerability of proactive treatment with topical corticosteroids and calcineurin inhibitors for atopic eczema: systematic review and meta-analysis of randomized controlled trials. *Br J Dermatol* 2011; **164**: 415–428.

99 Ellison JA, Patel L, Ray DW, David TJ, Clayton PE. Hypothalamic-pituitary-adrenal function and glucocorticoid sensitivity in atopic dermatitis. *Pediatrics* 2000; **105**: 794–799.

100 Schlessinger J, Miller B, Gilbert RD, Plott RT, Vanos Study Group. An open-label adrenal suppression study of 0.1% fluocinonide cream in pediatric patients with atopic dermatitis. *Arch Dermatol* 2006; **142**: 1568–1572.

101 Friedlander SF, Hebert AA, Allen DB, Fluticasone Pediatrics Safety Study Group. Safety of fluticasone propionate cream 0.05% for the treatment of severe and extensive atopic dermatitis in children as young as 3 months. *J Am Acad Dermatol* 2002; **46**: 387–393.

102 Hebert AA, Friedlander SF, Allen DB. Topical fluticasone propionate lotion does not cause HPA axis suppression. *J Pediatr* 2006; **149**: 378–382.

103 Hirano S, Katoh N, Yasuno H. A retrospective analysis of the severity of atopic dermatitis. *Jpn J Dermatol* 1995; **105**: 1309–1315. (In Japanese with English abstract.).

104 Nakagawa N, Tsukahara Y, Tetsumoto K. Statistical analysis of clinical risk factors associated with atopic cataract occurrence. *J Eye* 2000; **17**: 1679–1684. (in Japanese).

105 Furue M, Kawashima M, Furukawa F *et al*. Clinical epidemiology: a prospective questionnaire study for atopic dermatitis patients (part 2). *Jpn J Clin Dermatol* 2001; **65**: 83–92. (in Japanese).

106 Arikawa J, Higaki Y, Takamura E, Kawashima M. A study of intraocular pressure in patients with atopic Dermatitis and topical steroid treatment on the face. *Jpn J Dermatol* 2002; **112**: 1107–1110. (In Japanese with English abstract.).

107 Work group of guidelines of care for the management of atopic dermatitis Guidelines of care for the management of atopic dermatitis: Section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol* 2014; **71**: 116–132.

108 Singh S, Gupta A, Pandey SS, Singh G. Tachyphylaxis to histamine-induced wheal suppression by topical 0.05% clobetasol propionate in normal versus croton oil-induced dermatitis skin. *Dermatology* 1996; **193**: 121–123.

109 Singh G, Singh PK. Tachyphylaxis to topical steroid measured by histamine-induced wheal suppression. *Int J Dermatol* 1966; **25**: 324–326.

110 Japanese FK 506 Ointment Study Group. Clinical guidance for treatment of patients with atopic dermatitis by tacrolimus ointment 0.1% and 0.03%. *Jpn J Clin Dermatol* 2003; **57**: 1217–1234. (In Japanese with English abstract).

111 Arellano FM, Wentworth CE, Arana A, Fernández C, Paul CF. Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. *J Invest Dermatol* 2007; **127**: 808–816.

112 Schneeweiss S, Doherty M, Zhu S *et al*. Topical treatments with pimecrolimus, tacrolimus and medium-to high-potency corticosteroids, and risk of lymphoma. *Dermatology* 2009; **219**: 7–21.

113 Ohtsuki M, Shiragasawa C, So M, Nakagawa H. The long-term safety and effectiveness of 0.03% Tacrolimus ointment in the treatment of pediatric patients with atopic dermatitis-interim report of long-term special drug use –results survey. *J Pediatr Dermatol* 2013; **32**: 127–137. (In Japanese with English abstract).

114 Ring J, Alomar A, Bieber T *et al*. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. *J Eur Acad Dermatol Venereol* 2012; **26**: 1176–1193.

115 Caproni M, Torchia D, Antiga E *et al*. The comparative effects of tacrolimus and hydrocortisone in adult atopic dermatitis: an immunohistochemical study. *Br J Dermatol* 2007; **156**: 312–319.

116 Simon D, Vassina E, Yousefi S, Kozlowski E, Braathen LR, Simon HU. Reduced dermal infiltration of cytokine-expressing inflammatory cells in atopic dermatitis after short-term topical tacrolimus treatment. *J Allergy Clin Immunol* 2004; **114**: 887–895.

117 Yanai K, Yoshikawa T, Yanai A *et al*. The clinical pharmacology of non-sedating antihistamines. *Pharmacol Ther* 2017; **178**: 148–156.

118 Yanai K, Zhang D, Tashiro M *et al*. Positron emission tomography evaluation of sedative properties of antihistamines. *Expert Opin Drug Saf* 2011; **10**: 613–622.

119 Yanai K, Tashiro M, Okamura N *et al*. Non-sedating second-generation antihistamines: the penetration through blood-brain barrier by PET. *Nishinihon J Dermatol* 2009; **71**: 3–6. (In Japanese.).

120 Okamura N, Yanai K, Higuchi M *et al*. Functional neuroimaging of cognition impaired by a classical antihistamine, d-chlorpheniramine. *Br J Pharmacol* 2000; **129**: 115–123.

121 McDonald K, Trick L, Boyle J *et al*. Sedation and antihistamines: an update. Review of inter-drug difference using proportional impairment ratios. *Hum Psychopharmacol* 2008; **23**: 555–570.

122 Kawashima M, Furue M, Hide M *et al*. A comparative study of antipruritic effects and the occurrence of drowsiness between sedating and non-sedating antihistamines (ACROSS trial). *J Clin Therap Med* 2011; **27**: 563–573. (In Japanese).

123 Hiraoka K, Tashiro M, Grobosch T *et al*. Brain histamine H1 receptor occupancy measured by PET after oral administration of levocetirizine, a non-sedating antihistamine. *Expert Opin Drug Saf* 2015; **14**: 199–206.

124 Dillon SR, Sprecher C, Hammond A *et al*. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat Immunol* 2004; **5**: 752–760.

125 Yamamura K, Uruno T, Fukui Y *et al*. The transcription factor EPAS1 links DOCK8 deficiency to atopic skin inflammation via IL-31 induction. *Nat Commun* 2017; **8**: 13946.

126 Ruzicka T, Hanifin JM, Kabashima K *et al*. Anti–Interleukin-31 Receptor antibody for atopic dermatitis. *N Engl J Med* 2017; **376**: 826–835.

127 Tominaga M, Takamori K. Itch and nerve fibers with special reference to atopic dermatitis: therapeutic implications. *J Dermatol* 2014; **41**: 205–212.

128 Toyoda M, Nakamura M, Morohashi M *et al*. Nerve growth factor and substance P are useful plasma markers of disease activity in atopic dermatitis. *Br J Dermatol* 2002; **147**: 71–79.

129 Pincelli C, Fantini F, Giannetti A *et al*. Neuropeptides in skin from patients with atopic dermatitis: an immunohistochemical study. *Br J Dermatol* 1990 Jun; **122**: 745–750.

130 Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema-a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2007; **21**: 606–619.

131 Study Group of Neoral® Treatment for Atopic Dermatitis. Treatment: Safety and efficacy of intermittent cyclosporin MEPC therapy in patients with severe adult atopic dermatitis: multicenter, openlabel, long-term clinical trial. *Jpn J Clin Dermatol* 2009; **63**: 163–171. (in Japanese).

132 Hashizume H, Ito T, Yagi H *et al*. Efficacy and safety of preprandial versus postprandial administration of lowdose cyclosporin microemulsion (Neoral)in patients with psoriasis vulgaris. *J Dermatol* 2007; **34**: 430–434.

133 Cheng HM, Chiang LC, Jan YM, Chen GW, Li TC. The efficacy and safety of a Chinese herbal product (Xiao-Feng-San)for the treatment of refractory atopic dermatitis: a randomized, double-blind, placebo-controlled trial. *Int Arch Allergy Immunol* 2011; **155**: 141–148.

134 Kobayashi H, Ishii M, Takeuchi S *et al*. Efficacy and safety of a traditional herbal medicine, Hochu-ekki-to in the long-term management of Kikyo (delicate constitution)patients with atopic dermatitis: a 6-month, multicenter, double-blind, randomized, placebo-controlled study. *Evid Based Complement Alternat Med* 2010; **7**: 367–373.

135 Sheehan MP, Atherton DJ. A controlled trial of traditional Chinese medicinal plants in widespread non-exudative atopic eczema. *Br J Dermatol* 1992; **126**: 179–184.

136 Sheehan MP, Rustin MHA, Atherton DJ *et al*. Efficacy of traditional Chinese herbal therapy in adult atopic dermatitis. *Lancet* 1992; **340**: 13–17.

137 Fung AY, Look PC, Chong LY, But PP, Wong E. A controlled trial of traditional Chinese herbal medicine in Chinese patients with recalcitrant atopic dermatitis. *Int J Dermatol* 1999; **38**: 387–392.

138 Japanese Society for Pediatric Allergy and Clinical Immunogy. *Japanese pediatric guideline for food allergy 2016*. Tokyo: Kyowa Kikaku, 2016. (In Japanese).

139 Murase JE, Heller MM, Butler DC. Safety of dermatologic medications in pregnancy and lactation: Part I. Pregnancy. *J Am Acad Dermatol* 2014; **70**(401): pp. e1–14; quiz 15.

140 Butler DC, Heller MM, Murase JE. Safety of dermatologic medications in pregnancy and lactation: Part II. Lactation. *J Am Acad Dermatol* 2014; **70**: 417. e1-10; quiz 27.

141 Chi CC, Kirtschig G, Aberer W *et al*. Evidence-based (S3)guideline on topical corticosteroids in pregnancy. *Br J Dermatol* 2011; **165**: 943–952.

142 Loden M, Andersson AC, Andersson C *et al*. A double-blind study comparing the effect of glycerin and urea on dry, eczematous skin in atopic patients. *Acta Derm Venereol* 2002; **82**: 45–47.

143 Kawashima M, Numano K, Ishizaki C. Usefulness of moisturizers for dermato-physiological dysfunction in patients with atopic dermatitis. *Jpn J Dermatol* 2007; **117**: 969–977. (In Japanese with English abstract.).

144 van Zuuren EJ, Fedorowicz Z, Christensen R *et al*. Emollients andmoisturisers for eczema (Review). *Cochrane Database Sys Rev* 2016; **2**: CD012119.

145 Simpson EL, Chalmers JR, Hanifin JM *et al*. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol* 2014; **134**: 818–823.

146 Horimukai K, Morita K, Narita M *et al*. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol* 2014; **134**: 824–830.

147 Ohatani M, Ohtani M, Nozawa A *et al*. A study of the influence of the volume and frequency of application on the efficacy of moisturizers. *Jpn J Dermatol* 2012; **122**: 39–43. (In Japanese).
148 Nakamura M, Uemura K, Nemoto O, Miyachi Y. Evaluation of an optimal method for topical application of moisturizer. *Skin Res* 2006; **5**: 311–316. (In Japanese with English Abstract).
149 Werner Y, Lindberg M. Transepidermal water loss in dry and clinically normal skin in patients with atopic dermatitis. *Acta Derm Venereol* 1985; **65**: 102–105.
150 Kawashima M, Hayashi N, Nogita T, Yanagisawa K, Mizuno A. The usefulness of moisturizers for maintenance of remission in atopic dermatitis. *Jpn J Dermatol* 2007; **117**: 1139–1145. (In Japanese with English abstract.).
151 Murota H, Izumi M, Abd El-Latif MI *et al*. Artemin causes hypersensitivity to warm sensation, mimicking warmth-provoked pruritus in atopic dermatitis. *J Allergy Clin Immunol* 2012; **130**: 671–682.
152 Denda M, Sokabe T, Fukumi-Tominaga T, Tominaga M. Effects of skin surface temperature on epidermal permeability barrier homeostasis. *J Invest Dermatol* 2007; **127**: 654–659.
153 Cheng X, Jin J, Hu L *et al*. TRP channel regulates EGFR signaling in hair morphogenesis and skin barrier formation. *Cell* 2010; **141**: 331–343.
154 Uehara M, Takada K. Use of soap in the management of atopic dermatitis. *Clin Exp Dermatol* 1985; **10**: 419–425.
155 Uehara M. Use of soap in bathing for atopic dermatitis. *Rinsho Derma (Tokyo)* 1981; **23**: 1049–1052. (In Japanese).
156 Nicolaides N. Skin lipids. IV: Biochemistry and function. *J Am Oil Chem Soc* 1965; **42**: 708–712.
157 Fonacier LS, Aquino MR. The role of contact allergy in atopic dermatitis. *Immunol Allergy Clin North Am* 2010; **30**: 337–350.
158 Giordano-Labadie F, Rance F, Pellegrin F, Bazex J, Dutau G, Schwarze HP. Frequency of contact allergy in children with atopic dermatitis: results of a prospective study of 137 cases. *Contact Dermatitis* 1999; **40**: 192–195.
159 Tamagawa-Mineoka R, Masuda K, Ueda S *et al*. Contact sensitivity in patients with recalcitrant atopic dermatitis. *J Dermatol* 2015; **42**: 720–722.
160 Takayama K, Yokozaki H, Matsunaga K *et al*. The guidelines for the management of contact dermatitis. *Jpn J Dermatol* 2009; **119**: 1757–1793. (in Japanese).
161 Bath-Hextall F, Delamere FM, Williams HC. Dietary exclusions for established atopic eczema. *Cochrane Database Syst Rev* 2008; (1): CD005203.
162 Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database Syst Rev* 2012; (19): Cd000133.
163 Schafer T, Heinrich J, Wjst M, Adam H, Ring J, Wichmann HE. Association between severity of atopic eczema and degree of sensitization to aeroallergens in schoolchildren. *J Allergy Clin Immunol* 1999; **104**: 1280–1284.
164 Sato K, Kang WH, Saga K, Sato KT. Biology of sweat glands and their disorders. I. Normal sweat gland function. *J Am Acad Dermatol* 1989; **20**: 537–563.
165 Watabe A, Sugawara T, Kikuchi K, Yamasaki K, Sakai S, Aiba S. Sweat constitutes several natural moisturizing factors, lactate, urea, sodium, and potassium. *J Dermatol Sci* 2013; **72**: 177–182.
166 Yokozeki H, Hibino T, Takemura T, Sato K. Cysteine proteinase inhibitor in eccrine sweat is derived from sweat gland. *Am J Physiol* 1991; **260**: R314–R320.
167 Komatsu N, Takata M, Otsuki N *et al*. Expression and localization of tissue kallikrein mRNAs in human epidermis and appendages. *J Invest Dermatol* 2003; **121**: 542–549.
168 Eissa A, Amodeo V, Smith CR, Diamandis EP. Kallikrein-related peptidase-8 (KLK8)is an active serine protease in human epidermis and sweat and is involved in a skin barrier proteolytic cascade. *J Biol Chem* 2011; **286**: 687–706.
169 Murakami M, Ohtake T, Dorschner RA, Schittek B, Garbe C, Gallo RL. Cathelicidin anti-microbial peptide expression in sweat, an innate defense system for the skin. *J Invest Dermatol* 2002; **119**: 1090–1095.
170 López-García B, Lee PH, Yamasaki K, Gallo RL. Anti-fungal activity of cathelicidins and their potential role in Candida albicans skin infection. *J Invest Dermatol* 2005; **125**: 108–115.
171 Schittek B, Hipfel R, Sauer B *et al*. Dermcidin: a novel human antibiotic peptide secreted by sweat glands. *Nat Immunol* 2001; **2**: 1133–1137.
172 Imayama S, Shimozono Y, Hoashi M *et al*. Reduced secretion of IgA to skin surface of patients with atopic dermatitis. *J Allergy Clin Immunol* 1994; **94**: 195–200.
173 Hiragun T, Ishii K, Hiragun M *et al*. Fungal protein MGL_1304 in sweat is an allergen for atopic dermatitis patients. *J Allergy Clin Immunol* 2013; **132**: 608–615.
174 Griffin T, Sulzberger MB. Miliaria and anhidrosis. *J Invest Dermatol* 1967; **49**: 379–385.
175 Shiohara T, Doi T, Hayakawa J. Defective sweating responses in atopic dermatitis. *Curr Probl Dermatol* 2011; **41**: 68–79.
176 Papa C, Kligman A. Mechanism of eccrine anhidrosis. *J Invest Dermatol* 1966; **47**: 1–9.
177 Eishi K, Lee JB, Bae SJ, Takenaka M, Katayama I. Impaired sweating function in adult atopic dermatitis: results of the quantitative sudomotor axon reflex test. *Br J Dermatol* 2002; **147**: 683–688.
178 Kijima A, Murota H, Matsui S *et al*. Abnormal axon reflex-mediated sweating correlates with high state of anxiety in atopic dermatitis. *Allergol Int* 2012; **61**: 469–473.
179 Takahashi A, Murota H, Matsui S *et al*. Decreased sudomotor function is involved in the formation of atopic eczema in the cubital fossa. *Allergol Int* 2013; **62**: 473–478.
180 Matsui S, Murota H *et al*. Dynamic analysis of histamine-mediated attenuation of acethylcholine-iduced sweating via GSK3b activation. *J Invest Dermatol* 2013; **134**: 326–334.
181 Matsui S, Murota H, Ono E, Kikuta J, Ishii M, Katayama I. Olopatadine hydrochloride restores histamine-induced impaired sweating. *J Dermatol Sci* 2014; **74**: 260–261.
182 Murota H, Matsui S, Ono E, Kijima A *et al*. Sweat, the driving force behind the normal skin: an emerging perspective on functional biology and regulatory mechanisms. *J Dermatol Sci* 2015; **77**: 3–10.
183 Kong HH, Oh J, Deming C *et al*. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res* 2012; **22**: 850–859.
184 Kobayashi T, Glatz M, Horiuchi K *et al*. Dysbiosis and staphylococcus aureus colonization drives inflammation in atopic dermatitis. *Immunity* 2015; **42**: 756–766.
185 Bath-Hextall FJ, Birnie AJ, Ravenscroft JC *et al*. Interventions to reduce Staphylococcus aureus in the management of atopic eczema: an updated Cochrane revies. *Br J Dermatol* 2010; **163**: 12–26.
186 Savolainen J, Lammintausta K, Kalimo K, Viander M. Candida albicans and atopic dermatitis. *Clin Exp Allergy* 1993; **23**: 332–339.
187 Takechi M. Minimum effective dosage in the treatment of chronic atopic dermatitis with itraconazole. *J Int Med Res* 2005; **33**: 273–283.
188 Mayser P, Kupfer J, Nemetz D *et al*. Treatment of head and neck dermatitis with ciclopiroxolamine cream—results of a double-blind, placebo-controlled study. *Skin Pharmacol Physiol* 2006; **19**: 153–158.
189 Ehlers A, Stangier U, Gieler U. Treatment of atopic dermatitis: a comparison of psychological and dermatological approaches to relapse prevention. *J Consult Clin Psychol* 1995; **63**: 624–635.
190 Steven J, Cowdell F, Latter S *et al*. Psychological and educational interventions for atopic eczema in children. *Cochrane Database Syst Rev* 2014; (1): CD004054.
191 Lack G, Fox D, Northstone K *et al*. Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 2003; **348**: 977–985.
192 Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol* 2008; **122**: 984–991.

193 Tsakok T, Marrs T, Mohsin M *et al*. Does atopic dermatitis cause food allergy? A systematic review *J Allergy Clin Immunol* 2016; **137**: 1071–1078.
194 Natsume O, Kabashima S, Ohya Y. Two-step Egg Introduction for preventing egg allergy in High-risk Infants with eczema (PETIT study): a double-blind, placebo-controlled, parallel-group randomized clinical trial. *Lancet* 2017; **389**: 276–286.
195 Fukuie T, Ohya Y, Ebisawa M *et al*. *Proposal for prevention of hen's egg allergy*. Japanese Society for Pediatric Allergy and Clinical Immunology. (June 16, 2017.). (In Japanese)
196 Ohta K, Oka N, Okazaki K *et al*. Prevalecen of atopic dermatitis in elementary schoolsin western Japan-Comparison between 1992 and 2002. *Jpn J Pediatr Allergy Clin Immunol* 2003; **17**: 255–268. (In Japanese).
197 Iikura Y, Odasima Y, Kitabayashi T *et al*. Relationship between cedar pollen and some allergic symptoms. *Allergol Immunol* 2002; **9**: 343–349. (In Japanese).
198 Werfel T, Heratizadeh A, Niebuhr M *et al*. Exacerbation of atopic dermatitis on grass pollen exposure in an environmental challenge chamber. *J Allergy Clin Immunol* 2015; **136**: 96–103.
199 Sidbury R, Davis DM, Cohen DE *et al*. Guidelines of care for the management of atopic dermatitis. Section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol* 2014; **71**: 327–349.
200 Morita A. Phototherapy by using new wave lengths -narrow-band UVB, UVA1, 308 nm excimer blue light. In: Tamaki K, Iiduka H, Shimizu H, Tomita Y, Miyachi Y, Hashimoto K, Furue M, eds. *Comprehensive Handbook of Clinical Dermatology 2008-2009*. Tokyo: Nakayama Shoten, 2008; 55–64. (In Japanese)
201 Garritsen FM, Brouwer MW, Limpens J, Spuls PI. Photo (chemo) therapy in the management of atopic dermatitis: an updated systematic review with implications for practice and research. *Br J Dermatol* 2014; **170**: 501–513.
202 Morita A, Etoh T, Torii H, *et al*. Guidelines for phototerapy in psoriasis. *Jpn J Dermatol* 2016; **126**: 1239–1262. (In Japanese).
203 Mukai H, Fukuda H, Suzuki T, Saotome A, Hayade E. Usefulness of inpatient care for atopic dermatitis: a questionnaire survey in patients with a history of hospitalization. *Skin Res* 2012; **11**(Suppl 18): 43–47. (In Japanese with English Abstract).
204 Kataoka Y. Consideration of quality Index in clinical practice of atopic dermatitis. *J Visual Dermatol* 2014; **13**: 1094–1097. (In Japanese).
205 Staab D, Diepgen TL, Fartasch M *et al*. Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: multicentre, randomised controlled trial. *BMJ* 2006; **332**: 933–938.
206 Moore EJ, Williams A, Manias E, Varigos G, Donath S. Eczema workshops reduce severity of childhood atopic eczema. *Australas J Dermatol* 2009; **50**: 100–106.
207 Futamura M, Masuko I, Hayashi K, Ohya Y, Ito K. Effects of a short-term parental education program on childhood atopic dermatitis: a randomized controlled trial. *Pediatr Dermatol* 2013; **30**: 438–443.
208 Armstrong AW, Kim RH, Idriss NZ, Larsen LN, Lio PA. Online video improves clinical outcomes in adults with atopic dermatitis: a randomized controlled trial. *J Am Acad Dermatol* 2011; **64**: 502–507.
209 Ersser SJ, Cowdell F, Latter S *et al*. Psychological and educational interventions for atopic eczema in children. *Cochrane Database Syst Rev* 2014; CD004054.
210 Department of Dermatology, Kyushu University. *Standard therapy for atopic dermatitis*. http://www.kyudai-derm.org/atopy_care/index.html.2010. (In Japanese)
211 Environmental Restoration and Conservation Agency. *Handbook of pediatric atopic dermatitis Prevention for exacerbation of asthma*. (In Japanese). https://www.erca.go.jp/yobou/pamphlet/form/00/archives_1028.html. 2009.
212 Sepp E, Julge K, Vasar M *et al*. Intestinal microflora of Estonian and Swedish infants. *Acta Paediatr* 1997; **86**: 956–961.
213 Bjorksten B, Naaber P, Sepp E *et al*. The intestinal microflora in allergic Estonian and Swedish 2-year-old children. *Clin Exp Allergy* 1999; **29**: 342–346.
214 Itoh H. Pediatric allerc diseases and probiotics. *Jpn J Pediatr* 2006; **59**: 1511–1521. (In Japanese).
215 Panduru M, Panduru NM, Sălävästru CM *et al*. Probiotics and primary prevention of atopic dermatitis: a meta-analysis of randomized controlled studies. *J Eur Acad Dermatol Venereol* 2015; **29**: 232–242.
216 Kim SO, Ah YM, Yu YM *et al*. Effects of probiotics for the treatment of atopic dermatitits: a meta-analysis of randomized controlled trials. *Ann Allergy Asthma Immunol* 2014; **113**: 217–226.
217 Cuello-Garcia CA, Fiocchi A, Pawankar R *et al*. World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Prebiotics. *World Allergy Organ J* 2016; **9**: 10.
218 Chang YS, Trivedi MK, Jha A, Lin YF *et al*. Synbiotics for prevention and treatment of atopic dermatitis: a meta-analysis of randomized clinical trials. *JAMA Pediatr* 2016; **170**: 236–242.
219 Hide M, Yamamura Y, Morita E, Kohro O, Yamamoto S. Alternative treatments for atopic dermatitis : classification of the treatments and a questionnaire study. *Nishinihon J Dermatol* 2000; **62**: 83–88. (In Japanese with English Abstract).
220 Kojima R, Fujiwara T, Matsuda A *et al*. Factors associated with steroid phobia in caregivers of children with atopic dermatitis. *Pediatr Dermatol* 2013; **30**: 29–35.
221 Takehara K, Iiduka H, Itoh M *et al*. Survey of health damage caused by inadequate treatment for atopic dermatitis. *Jap J Dermatol* 2000; **110**: 1095. (In Japanese).
222 Pfab F, Huss-Marp J, Gatti A *et al*. Influence of acupuncture on type I hypersensitivity itch and the wheal and flare response in adults with atopic eczema-a blinded, randomized, placebo-controlled, crossover trial. *Allergy* 2010; **65**: 903–910.
223 Siebenwirth J, Luedtke R, Remy W, Rakoski J, Borelli S, Ring J. Effectiveness of a classical homeopathic treatment in atopic eczema. A randomised placebo-controlled double-blind clinical trial. *Forsch Komplementmed* 2006; **2009**(16): 315–323.
224 World Health Organization. *Adherence to long-term therapies-evidence for action*, 2003; http://whqlibdoc.who.int/publications/2003/9241545992.pdf
225 *Ascertaining barriers for compliance: policies for safe, effective and costeffective use of medicines in Europe*. Final report of the ABC project, 2012; Available at: http://www.ABCproject.eu
226 Ou HT, Feldman SR, Balkrishnan R. Understanding and improving treatment adherence in pediatric patients. *Semin Cutan Med Surg* 2010; **29**: 137–140.
227 Masuko I. *Introduction, Japanese Society of Pediatric Intractble Asthma and Allergic Diseases: Pediatric Allergy Educator Text*. Practice Part. Tokyo: Shindan To Chiryo Sha Inc, 2013; 1–24. (In Japanese)

CHAPTER II: EBMS FOR ATOPIC DERMATITIS

In Chapter II, to optimize the patient outcome by medical interventions, reports of clinical research are reviewed, balance between benefits and harm of medical interventions is evaluated, and recommendation grades and evidence levels are shown concerning 26 important points that require decisions in clinical settings (Clinical Questions; CQs) including matters that could not be presented in the text of the Guidelines in Chapter I. Recommendations, recommendation grades, and their explanations concerning CQs are shown.

PubMed, *Japana Centra Vevuo Medicina*, and Cochrane Library were searched for the relevant literature (including the literature in electronic media) published by the end of December 2015, in principle. In setting out the Clinical Questions, entries were extracted from those used publically on the internet between October 27, 2015 and November 6, 2015, and

then, 26 issues were selected on November 10, 2015 after having discussions with committee members on the individual entries (Table 8).

The evidence levels and recommendation grades in the present Guidelines were determined by referring to the evidence levels and strength of recommendations used in the GRADE Minds handbook for clinical practice guideline development 2014,[228] and clinical guidelines for infusion therapy in advanced cancer patients 2013[229] and JDA clinical practice guidelines for the management of atopic dermatitis.[230]

The evidence level was an eventual judgment concerning the "quality of evidence" based on evidence concerning important outcomes reached as a consensus of the committee by comprehensive evaluation of the design and quality of research, whether or not the results were coherent/consistent, and whether or not the subjects, intervention, and outcome of the study were consistent with the assumed situations. The evidence levels range from A to C, of which A is for "The results are nearly established and are unlikely to be changed markedly by future studies," B is for "There are studies that support the results, but as they are insufficient, they may be changed markedly by future studies," and C is for "There is no high quality studies that support the results." (Table 9) The research design was used as a starting point for the determination of the evidence level and was distinguished as in Table 10.[230]

Recommendations were comprehensively evaluated on the basis of the magnitude of benefits expected from the recommended treatments and balance between the benefits and harm or burdens that may be caused by the treatments in consideration of the evidence level, clinical experience, balance between benefits and harms, values, and wishes for treatment. The committee members discussed whether they considered each recommendation to be "1: strong" or "2: weak", and if opinions about the strength of recommendation were divided, the recommendation was considered "not to be strong enough for experts to reach an agreement" and presented as "a weak recommendation", in principle.

However, even if the evidence level was "low" or "very low", if the members unanimously judged the recommendation to be "1: strong", this judgment was reflected.

"Strong recommendation" means that, from the evidence obtained and clinical experience, the benefits obtained by the recommended treatment are judged to be large and to surpass the harm or burdens caused by the treatment (Table 11). In this event, it is desirable for the physician to propose the recommended treatment according to the patient's values, preferences, and wishes. "Weak recommendation" means that, from the evidence obtained and clinical experience, the magnitude of the benefits obtained by the recommended treatment is uncertain, or the benefits and harm or burdens that may result from the treatment are considered nearly equal (Table 8). In this event, the physician is required to hold careful counsel

Table 8. Clinical questions

CQ1. Is the use of topical steroids recommended for treatment of AD?
CQ2. When topical steroids are to be continued after adequate improvement of eruption is achieved, which is better: decreasing application frequency or reduction of rank (intensity)?
CQ3. Does the periocular use of topical steroids increase a risk of complication to the eyes?
CQ4. Is the use of antibacterial topical drugs recommended to improve symptoms of AD?
CQ5. Is the use of tacrolimus ointments recommended for treatment of AD?
CQ6. Does the use of topical tacrolimus ointments increase the risk of developing skin cancer or lymphoma?
CQ7. Is the use of antihistamines recommended for the treatment of AD?
CQ8. Is proactive therapy effective in maintaining remission of repeatedly relapsed eczema lesions in AD?
CQ9. Is the use of topical moisturizers recommended for the treatment of AD?
CQ10. Is showering effective for AD?
CQ11. Is the serum TARC level effective as a disease progression marker for AD?
CQ12. Is oral ciclosporin recommended for the treatment of severe AD?
CQ13. Is Chinese medicine effective for the treatment of AD?
CQ14. Is elimination of mite allergens from the environment recommended for the treatment of AD?
CQ15. Is the allergen elimination diet effective for the treatment of AD?
CQ16. Is the use of dietary restriction during pregnancy and breastfeeding effective for preventing the onset of AD in children?
CQ17. Is the administration of probiotics recommended to improve the symptoms of AD during infancy?
CQ18. Can remission of AD be expected with age?
CQ19. Is the use of antihistamines safe during pregnancy and breastfeeding?
CQ20. Is the use of topical steroids safe during pregnancy and breastfeeding?
CQ21. Is the use of detergents including soap effective for the management of AD?
CQ22. Is baby bathing effective for eczema during infancy?
CQ23. Is the use of povidone iodine solution recommended for treatment of AD?
CQ24. Is bleach bath therapy recommended for the treatment of AD?
CQ25. Is the use of sunscreen recommended for the prevention of progression of AD?
CQ26. Are instructions to avoid keeping pets or contact with animals effective to prevent the development of AD or to improve symptoms?

Table 9. Evidence level

A. High: The results are nearly established and unlikely to be changed markedly by future studies.
B. Low: There are studies that support the results, but the results are insufficient and may be changed markedly by future studies.
C. Very low: There are no high-quality studies that support

Table 10. Designs of studies used as references for the determination of the evidence level

A. A large number of randomized controlled trials with high quality and consistent results
Meta-analyses of randomized controlled trials
B. Randomized controlled trials with inconsistent results
Randomized controlled trials of questionable quality or the presence of a few randomized controlled trials
Non-randomized controlled trials†
Many controlled before-and-after trials or observational studies‡ with consistent results
C. A few controlled before-and-after trials or observational studies, case reports and expert opinions

†Including controlled crossover study. ‡Including estimation of results of active treatment group, or placebo-controlled group, in randomized controlled trials as before-and-after trials or observational studies.

Table 11. Clinical significance of the recommendation grade and evidence level

1A	The evidence level is high, and the benefits obtained by the treatment are large and considered to surpass the harm or burdens that may be caused by the treatment. Therefore, the physician is advised to perform the recommended treatment.
1B/1C	Although the evidence level is low (B) or very low (C), the benefits obtained by the treatment are large and considered to surpass the harm and burdens that may be caused by the treatment. Therefore, the physician is advised to perform the recommended treatment with the understanding that the evidence is insufficient.
2A/2B/2C	The magnitude of the benefits obtained by the recommended treatment is uncertain, or the benefits are considered to be nearly equal to the harm or burdens caused by the treatment. The evidence level is high (A), low (B), or very low (C). Therefore, the physician is advised to select and propose the treatment and to confer with the patient about whether the treatment should be performed.

with the patient about whether or not the recommended treatment should be performed by taking the patient's values, preferences, and wishes into consideration. CQs that were difficult to give a recommendation grade were rated with the evidence level alone. As explained above, in the present Guidelines, there are recommendations of the combinations shown in Table 19 based on the strength of recommendation and evidence level.

REFERENCES

228 Fukui T, Yamaguchi N, supervisors. Morizane T , Yoshida M, Kojimahara N, eds. *Minds Handbook for Clinical Practice Guideline Development 2014*. Tokyo: Igaku-Shoin Ltd, 2014. (In Japanese)

229 Japanese Society for Palliative Medicine. *Clinical Guidelines for Infusion Therapy in Advanced Cancer Patients 2013*. Tokyo: Kanehara & Co., Ltd, 2013. (In Japanese).

230 Saeki H, Nakahara T, Tanaka A *et al*. Clinical practice guidelines for the management of atopic dermatitis 2016. *J Dermatol* 2016; **43**: 1117–1145.

CQ1 IS THE USE OF TOPICAL STEROIDS RECOMMENDED FOR THE TREATMENT OF AD?

Recommendation

Topical steroids appear to be effective for AD, thus, they are recommended when used appropriately and potential side effects are considered.

Recommendation grade: 1, *evidence level*: A

Comments: A number of studies, but not all, have shown a significantly higher efficacy of topical steroids than placebo regardless of age, thus, TCS appear to be effective for AD. In studies that did not show any significant differences, weak steroids such as 1% hydrocortisone classified into the class V (lowest potency) were examined, hence, prescription of TCS with appropriate strength is desired.

For side effects due to a long-term use, there are less systemic side effects if appropriately used, thus, the safety profile is favorable. For local side effects, skin thinning has been reported due to the use of potent TCS such as 0.05% clobetasol propionate classified into the class I (very high potency)*, or 0.1% betamethasone valerate or 0.1% mometasone furoate classified into the class III to IV*. Moreover, skin thinning has been reported compared to healthy adults controls, however, no serious side effects were observed during a several-month observation period after successive application of mometasone or fluticasone twice a week for several weeks in patients with AD. Skin atrophy was rarely observed. Therefore, side effects can be reduced by limiting the application frequency of topical steroids in accordance with the resolution of the eruption.

For topical application frequency, no significant difference was observed between once-a-day use and multiple daily administration of potent steroids such as 0.1% halcinonide, classified as class II (high potency),* or 0.05% fluticasone propionate, classified as class III to IV*, however, a significant difference was observed in the remission rate in 0.01% hydrocortisone butyrate classified as class V (lower-medium potency)*. While twice-a-day use is recommended in the acute phase, efficacy can also be expected in once-a-day use.

*In the guidelines adopted in the USA, TCS are classified into seven ranks (I, very high potency; II, high potency; III–IV, medium potency; V, lower-medium potency; VI, low potency; VII, lowest potency). Eichenfield LF, Tom WL, Berger TG, et al.: Guideline of care for the management of atopic dermatitis. Section2. Management and treatment of atopic dermatitis with topical therapies, J Am Acad Dermatol, 2014; 71: 116-132.

REFERENCES

231 Gehring W, Gloor M. Treatment of the atopic dermatitis with a water-in-oil emulsion with or without the addition of

hydrocortisone-results of a controlled double-blind randomized study using clinical evaluation and bioengineering methods. *Z Hautkr* 1996; **71**: 554–560.
232 Sears HW, Bailer JW, Yeadon A. Efficacy and safety of hydrocortisone buteprate 0.1% cream in patients with atopic dermatitis. *Clin Ther* 1997; **19**: 710–719.
233 Lupton ES, Abbrecht MM, Brandon ML. Short-term topical corticosteroid therapy (halcinonide ointment)in the management of atopic dermatitis. *Cutis* 1982; **30**: 671–675.
234 Sudilovsky A, Muir JG, Bocobo FC. A comparison of single and multiple application of halcinonide cream. *Int J Dermatol* 1981; **20**: 609–613.
235 Wahlgren CF, Hägermark O, Bergström R, Hedin B. Evaluation of new method of assessing pruritus and antipruritic drugs. *Skin Pharmacol* 1988; **1**: 3–13.
236 Lebwohl M. Efficacy and safety of fluticasone propionate ointment, 0.005%, in the treatment of eczema. *Cutis* 1996; **57**(2 Suppl): 62–68.
237 Breneman D, Fleischer AB Jr, Kaplan D *et al*. Clobetasol propionate 0.05% lotion in the treatment of moderate to severe atopic dermatitis: a randomized evaluation versus clobetasol propionate emollient cream. *J Drugs Dermatol* 2005; **4**: 330–336.
238 Matheson R, Kempers S, Breneman D *et al*. Hydrocortisone butyrate 0.1% lotion in the treatment of atopic dermatitis in pediatric subjects. *J Drugs Dermatol* 2008; **7**: 266–271.
239 Kimball AB, Gold MH, Zib B *et al*. Clobetasol propionate emulsion formulation foam 0.05%: review of phase II randomized controlled trials in steroid-responsive dermatoses in adults and adolescents. *J Am Acad Dermatol* 2008; **59**(3): 448–454.

CQ2. WHEN TOPICAL STEROIDS ARE TO BE CONTINUED AFTER ADEQUATE IMPROVEMENT OF ERUPTION IS ACHIEVED, WHICH IS BETTER; DECREASING APPLICATION FREQUENCY OR REDUCTION OF RANK (INTENSITY)?

Recommendation

It is desirable to reduce the application frequency of topical steroids and shift to a moisturizer after the disappearance of eruption in patients with moderate to severe AD who may experience relapses.

Evidence level: C

Comments: In patients with mild AD, application of topical steroids should be stopped after adequate improvement of eruption is achieved. Conversely, continuous application of topical steroids is an option for some patients with moderate to severe AD who repeatedly experience relapses. When application is continued, either should be chosen. The frequency of application per week should be reduced, or a lower ranked topical steroid should be used, after achieving adequate improvement to avoid side effects of topical steroids. However, there is no clinical report comparing these two treatment methods.

The effects of intermittent application of strong class (group III) topical steroids for reduction of application frequency on prevention of eczema relapse during the remission maintenance phase in patients with moderate to severe AD has been demonstrated in some studies.[1] In these studies, no increase in the risk of side effects was suggested after application of topical steroids twice to three times a week for a certain period. That is, continuous application of topical steroids with reduced frequency (once a week) is recommended for relapse prevention and safety.

However, there are no currently available clinical studies that have examined the efficacy of successive application of lower ranked topical steroids. There are more studies describing side effects of a long-term use of higher-potency topical steroids, however, there are some reports also on side effects of lower-potency topical steroids.[7] Therefore, the efficacy of successive application of reduced-rank topical steroids is still unknown, and attention should be paid to the potential side effects of topical steroids in this treatment.

As efficacy varies greatly depending on the individual patient's severity or adherence in any of these treatments strategies, it is not necessarily appropriate to determine which treatment is better. Instead, based on available evidence, it is preferable to reduce the frequency of application of a strong class topical steroid if the use of topical steroids is to be continued, and shift to a moisturizer.

REFERENCES

240 Berth-Jones J, Damstra RJ, Golsch S *et al*. Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. *BMJ (Clinical research ed)* 2003; **326**: 1367.
241 Glazenburg EJ, Wolkerstorfer A, Gerretsen AL, Mulder PG, Oranje AP. Efficacy and safety of fluticasone propionate 0.005% ointment in the long-term maintenance treatment of children with atopic dermatitis: differences between boys and girls? *Pediatr Allergy Immunol* 2009; **20**: 59–66.
242 Hanifin J, Gupta AK, Rajagopalan R. Intermittent dosing of fluticasone propionate cream for reducing the risk of relapse in atopic dermatitis patients. *Br J Dermatol* 2002; **147**: 528–537.
243 Peserico A, Stadtler G, Sebastian M, Fernandez RS, Vick K, Bieber T. Reduction of relapses of atopic dermatitis with methylprednisolone aceponate cream twice weekly in addition to maintenance treatment with emollient: a multicentre, randomized, double-blind, controlled study. *Br J Dermatol* 2008; **158**: 801–807.
244 Van Der Meer JB, Glazenburg EJ, Mulder PG, Eggink HF, Coenraads PJ. The management of moderate to severe atopic dermatitis in adults with topical fluticasone propionate. The Netherlands Adult Atopic DermatitisStudy Group. *Br J Dermatol* 1999; **140**: 1114–1121.

CQ3. DOES THE PERIOCULAR USE OF TOPICAL STEROIDS INCREASE THE RISK OF COMPLICATIONS TO THE EYES?

Recommendation

Although the periocular use of topical steroids does not increase risk of cataract in patients with AD, it may increase the risk of glaucoma.

Cataract: evidence level B (no increased risk)

Glaucoma: evidence level C (increased risk)

Comments: The periocular use of topical steroids in patients with AD causes eye complications such as cataracts and glaucoma. The periocular use of topical steroids may not appear to increase the risk of cataract. Cataract formation may be induced by worsening of eruptions on the face and repeated rubbing, that is, not due to inflammation by AD itself.[1–3] A

number of cases of glaucoma after treatment with topical steroids have been reported, thus, periocular use of topical steroids is highly likely to increase risk of glaucoma; however, the risk with the use of a small volume of lower-ranked steroids may be low.[4] However, there is not enough evidence to refute the risk, thus, future case series analyses are required. Nonetheless, collaboration with an ophthalmologist is important.

REFERENCES

245 Uchiyama M, Sugiura H, Uehara M, Nakamura J, Kani K. Atopic cataract: recent occurrence and inducing factor of cataract. *Hifuka-No-Rinsho* 1996; **38**: 61–64. (In Japanese).

246 Taniguchi H, Ohki O, Yokozeki H *et al*. Cataract and retinal detachment in patients with severe atopic dermatitis who were withdrawn from the use of topical corticosteroid. *J Dermatol* 1999; **26**: 658–665.

CQ4. IS THE USE OF ANTIBACTERIAL TOPICAL DRUGS RECOMMENDED TO IMPROVE SYMPTOMS OF AD?

Recommendation

The use of topical steroids containing antibacterial or antifungal drugs is not recommended because the efficacy from their use to improve cutaneous symptoms of AD is not superior to the use of steroids topical drugs alone.

Evidence level: A

Comments: Four articles (3 clinical study reports and 1 systematic review) comparing topical steroids containing antibacterial/antifungal drug and only steroid topical drugs have been reported. In three clinical studies, the efficacies of tetracycline[248] and mupirocin[249] as antibacterial drugs and miconazole as an antifungal drug[250] were examined, and the results showed no superiority of the addition of antibacterial/antifungal drugs to steroids treatment. In the systematic review, nine RCTs were analyzed from the 2002–2008 database.[251] In the results of meta-analysis with the improvement of cutaneous symptoms as endpoint, no superiority of addition of antibacterial drugs was observed. Based on above, the efficacy of adding an antibacterial drug to topical steroids treatment to improve cutaneous symptoms of AD is not superior to that of topical drugs consisiting of steroids alone.

REFERENCES

247 Wong AW, Hon EK, Zee B. Is topical antimycotic treatment useful as adjuvant therapy for flexural atopic dermatitis: randomized, double-blind, controlled trial using one side of the elbow or knee as a control. *Int J Dermatol* 2008; **47**: 187–191.

248 Schuttelaar ML, Coenraads PJ. A randomized, double-blind study to assess the efficacy of addition of tetracycline to triamcinolone acetonide in the treatment of moderate to severe atopic dermatitis. *J Eur Acad Dermatol Venereol* 2008; **22**: 1076–1082.

249 Canpolat F, Erkoçoğlu M, Tezer H, Kocabaş CN, Kandi B. Hydrocortisone acetate alone or combined with mupirocin for atopic dermatitis in infants under two years of age-a randomized double blind pilot trial. *Eur Rev Med Pharmacol Sci* 2012; **16**: 1989–1993.

250 Birnie Andrew J, Bath-Hextall Fiona J, Ravenscroft JC, Williams HC. Interventions to reduce Staphylococcus aureus in the management of atopic eczema. *Cochrane Database Syst Rev* 2008; **3**: CD003871.

CQ5. IS TOPICAL TACROLIMUSRECOMMENDED FOR THE TREATMENT OF AD?

Recommendation

Topical tacrolimus is recommended for AD patients aged 2 years or older.

Recommendation grade: 1, *Evidence level*: A

Comments: Tacrolimus inhibits T lymphocyte function through a mechanism differing from that of corticosteroids. Its efficacy and safety have been confirmed in clinical studies using a vehicle or topical corticosteroid as a control agent. In clinical studies establishing an improvement in symptoms of AD as a primary endpoint, 0.03 or 0.1% tacrolimus ointment was more advantageous than a base or weak topical steroid, and the efficacy of 0.1% tacrolimus ointment was similar to that of medium to strong topical corticosteroids.[252,253] The more potent efficacy of tacrolimus ointment was confirmed in children or adults with mild/moderate to severe AD. In particular, it was more marked in mild-status patients.[254,255] Tacrolimus ointment is indicated for AD patients aged 2 years or older. Concerning the concentration of tacrolimus, 0.03% ointment is selected for children (2–15 years), and 0.1% ointment for adults (16 years or older). After the short-term (approximately 3 week) application of tacrolimus ointment in children (2–15 years), there was no difference in the efficacy between 0.03 and 0.1% ointments.[253] For local adverse reactions, a burning sensation, pruritus, and erythema were confirmed.[256] These symptoms are reduced during continuous application, or promptly disappear after discontinuation in many cases. With respect to infectious diseases of the skin, secondary skin infection with bacterial and viral infection (herpes simplex, molluscum contagiosum, and viral warts) must be considered.[256] Skin atrophy, which has been reported as an adverse reaction due to the long-term use of topical corticosteroids, has not been confirmed in patients treated with tacrolimus ointment. Concerning tumor development, refer to CQ6. Based on these findings, we recommend tacrolimus ointment for the treatment of AD in patients aged 2 years or older, if it is adequately used.

REFERENCES

251 Doss N, Kamoun MR, Dubertret L, et al. Efficacy of tacrolimus 0.03% ointment as second-line treatment for children with moderate-to-severe atopic dermatitis: evidence from a randomized, double-blind non-inferiority trial vs. fluticasone 0.005% ointment. *Pediatr Allergy Immunol* 2010; **21**: 321–329.

252 Ashcroft DM, Dimmock P, Garside R, Stein K, Williams HC. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomized controlled trials. *BMJ* 2005; **350**: 516–522.

253 El-Batawy MM, Bosseila MA, Mashaly HM, Hafez VS. Topical calcineurin inhibitors in atopic dermatitis: a systematic review and meta-analysis. *J Dermatol Sci* 2009; **54**: 76–87.

254 Svesson A, Chambers C, Gånemo A, Mitchell SA. A systematic review of tacrolimus ointment compared with corticosteroids in the treatment of atopic dermatitis. *Curr Med Res Opin* 2011; **27**: 1395–1406.
255 Callen J, Chamlin S, Eichenfield LF, et al. A systematic review of the safety of topical therapies for atopic dermatitis. *Br J Dermatol* 2007; **156**: 203–221.

CQ6. DOES THE USE OF TACROLIMUS OINTMENT INCREASE THE RISK OF SKIN CANCER OR LYMPHOMA?

Recommendation

The use of tacrolimus ointment may not increase the risk of skin cancer or lymphoma.

Evidence level: B

Comments: According to eight of nine original articles in Japan and other countries, there is no evidence that tacrolimus ointment increases the risk of skin cancer or lymphoma.[111–113,257–,259] In addition, there is no evidence that tacrolimus ointment increases the risk of lymphoma in two systematic reviews.[260,261]

On the other hand, a retrospective cohort analysis showed that the incidence of T cell lymphoma in patients treated with tacrolimus ointment was higher than in non-tacrolimus-treated patients.[262] However, this survey method had a limitation regarding the accuracy of AD/lymphoma diagnosis. In addition, a study reported that severe AD increased the risk of lymphoma. Based on this, the FDA (US Food and Drug Administration) indicated that the above finding did not provide evidence that tacrolimus ointment increases the risk of T cell lymphoma (May 10, 2011). Briefly, currently, tacrolimus ointment may not be involved in the risk of skin cancer or lymphoma. However, in the future, the sample size should be increased, or meta-analysis based on long-term follow-up must be conducted to clarify the relationship between dose or administration period of this ointment and the development of malignant tumors. Therefore, it is important to comply with the limits of application dose.

REFERENCES

256 Margolis DJ, Hoffstad O, Bilker W. Lack of association between exposure to topical calcineurin inhibitors and skin cancer in adults. *Dermatology* 2007; **214**: 289–295.
257 Reitamo S, Rustin M, Harper J *et al*. A 4-year follow-up study of atopic dermatitis therapy with 0.1% tacrolimus ointment in children and adult patients. *Br J Dermatol* 2008; **159**: 942–951.
258 Arellano FM, Arana A, Wentworth CE *et al*. Lymphoma among patients with atopic dermatitis and/or treated with topical immunosuppressants in the United Kingdom. *J Allergy Clin Immunol* 2009; **123**: 1111–1116.
259 Legendre L, Barnetche T, Mazereeuw-Hautier J *et al*. Risk of lymphoma in patients with atopic dermatitis and the role of topical treatment: a systematic review and meta-analysis. *J Am Acad Dermatol* 2015; **72**: 992–1002.
260 Cury Martins J, Martins C, Aoki V *et al*. Topical tacrolimus for atopic dermatitis. *Cochrane Database Syst Rev* 2015; **7**: CD009864.
261 Hui RL, Lide W, Chan J *et al*. Association between exposure to topical tacrolimus or pimecrolimus and cancers. *Ann Pharmacother* 2009; **43**: 1956–1963.

CQ7. IS THE USE OF ANTIHISTAMINES RECOMMENDED FOR THE TREATMENT OF AD?

Recommendation

Antihistamines may reduce itching symptoms when used in combination with anti-inflammatory topical drugs and topical moisturizing drugs, thus, their use is recommended as an adjuvant therapy to topical therapy with antihistamines. A non-sedative antihistamine is recommended.

Recommendation grade: 1, *evidence level*: B

Comments: Antihistamines are used for treatment of itching in AD in clinical practice in Japan and abroad. The efficacy of antihistamines has been studied in 26 RCTs (12 RCTs in Japan and 14 RCTs in abroad). Of these, 19 RCTs reported positive results,[263–281] while the results of 6 RCTs were negative,[282–287] and 1 RCT[288] reported the efficacy observed in some patients (52%).

There is no evidence of treatment efficacy of antihistamine monotherapy verified by quality RCTs as only 1 RCT studied the efficacy of monotherapy of antihistamine without using anti-inflammatory topical drugs.[274] All the other 25 RCTs studied the efficacy of antihistamines in combination with anti-inflammatory topical drugs including steroids and tacrolimus. All of these studies set the primary endpoint as improvements of itch, and some RCTs reported improvement of cutaneous symptoms, reduction of topical steroids and potency rank, and decrease of serum soluble IL-2 receptor and TARC levels. Antihistamines have not been fully positioned in the current guidelines in Europe and the United States because of the few large-scale studies among the abovementioned RCTs and the efficacy of antihistamines was not observed in a meta-analysis performed in abroad.

Conversely, the efficacy of non-sedative second-generation antihistamines was shown in a high evidence level RCT[271] conducted in Japan (this RCT is not included in the abovementioned meta-analysis), therefore, the use of oral antihistamines (non-sedative second-generation) is recommended as an adjuvant therapy to anti-inflammatory topical therapy and moisturizing topical products.

There is ample variability in the mechanisms involved the itching observed in AD, and the effects of antihistamines on inhibiting itching vary depending on the individual patient's severity and clinical conditions. Therefore, it is recommended to determine whether adjuvant therapy with antihistamines in addition to topical therapy is required on an individual patient basis as well as to evaluate the effect on itching after the start of therapy.

REFERENCES

262 Study Group of Adult Atopic Dermatitis. Studies on usefulness of antiallergic agent for adult type atopic dermatitis. Comparative studies between single external use of steroid and combined use with oxatomide. Nishinihon. *J Dermatol* 1989; **51**: 995–1002. (In Japanese).
263 Hamada T, Ishii M, Nakagawa K *et al*. Evaluation of the clinical effect of terfenadine in patients with atopic dermatitis. A

comparison of strong topical corticosteroid therapy to mild topical corticosteroid combined with terfenadine administration therapy. *Skin Res* 1996; **38**: 97–103. (In Japanese with English abstract).
264 Hashizume H, Takigawa M. Clinical efficacy of loratadine for the pruritus associated with atopic dermatitis. *Allergy Pract* 2004; **24**: 1105–1111. (In Japanese).
265 Kimura Y, Matuba S, Chikenji T *et al*. Usefulness of TARC in serum as treatment marker and combination treatment with loratadine and steroid ointment for atopic dermatitis. *Skin Res* 2009; **8**: 125–131. (In Japanese with English Abstract).
266 Ohtani T, Kanauchi H, Ishii T *et al*. Usefulness of anti-histamine drugs in treatment of facial atopic dermatitis -their effect on the dose-reduction maintenance of tacrolimus ointments used for facial lesions-. *Skin Res* 2004; **3**: 316–322. (In Japanese with English Abstract).
267 Kuniyuki S, Suzuki S, Murakami K *et al*. A study of the effect and safety of olopatadine hydrochloride in patients with atopic dermatitis. *J New Rem Clin* 2005; **54**: 1602–1613. (In Japanese).
268 Sugai J, Kakurai M, Ohtsuki M, Nakagawa H. Study of combination effect of tacrolimusointment and cetirizine hydrochloride for face and neck eruptions of atopic dermatitis. *Pract Dermatol* 2008; **30**: 201–206. (In Japanese).
269 Kawashima M, Harada S. A study of the effect on itch and quality of life of atopic dermatitis patients treated by standard therapy with anti-allergic drug. *Jpn J Clin Dermatol* 2006; **60**: 661–667. (In Japanese).
270 Kawashima M, Tango T, Noguchi T *et al*. Addition of fexofenadine to a topical corticosteroid reduces the pruritus associated with atopic dermatitis in a 1-week randomized, multicentre, double-blind, placebo-controlled, parallel-group study. *Br J Dermatol* 2003; **148**: 1212–1221.
271 Diepgen TL, Early Treatment of the Atopic Child Study Group. Long-term treatment with cetirizine of infants with atopic dermatitis: a multi-country, double-blind, randomized, placebo-controlled trial (the ETAC trial)over 18 months. *Pediatr Allergy Immunol* 2002; **13**: 278–286.
272 Toyoda M, Nakamura M, Nakagawa H. Distribution to the skin of epinastine hydrochloride in atopic dermatitis patients. *Eur J Dermatol* 2007; **17**: 33–36.
273 Yamanaka K, Motomura E, Noro Y *et al*. Olopatadine, a non-sedating H1 antihistamine, decreases the nocturnal scratching without affecting sleep quality in atopic dermatitis. *Exp Dermatol* 2015; **24**: 227–229.
274 Doherty V, Sylvester DG, Kennedy CT *et al*. Treatment of itching in atopic eczema with antihistamines with a low sedative profile. *BMJ* 1989; **298**: 96.
275 Yoshida H, Niimura M, Ueda H *et al*. Clinical evaluation of ketotifen syrup on atopic dermatitis: a comparative multicenter double-blind study of ketotifen and clemastine. *Ann Allergy* 1989; **62**: 507–512.
276 Monroe EW. Relative efficacy and safety of loratadine, hydroxyzine, and placebo in chronic idiopathic urticaria and atopic dermatitis. *Clin Ther* 1992; **14**: 17–21.
277 Falk ES. Ketotifen in the treatment of atopic dermatitis. Results of a double blind study. *Riv Eur Sci Med Farmacol* 1993; **15**: 63–66.
278 Hannuksela M, Kalimo K, Lammintausta K *et al*. Dose ranging study: cetirizine in the treatment of atopic dermatitis in adults. *Ann Allergy* 1993; **70**: 127–133.
279 La Rosa M, Ranno C, Musarra I *et al*. Double-blind study of cetirizine in atopic eczema in children. *Ann Allergy* 1994; **73**: 117–122.
280 Langeland T, Fagertun HE, Larsen S. Therapeutic effect of loratadine on pruritus in patients with atopic dermatitis. A multi-cross-over-designed study. *Allergy* 1994; **49**: 22–26.
281 Chunharas A, Wisuthsarewong W, Wananukul S, Viravan S. Therapeutic efficacy and safety of loratadine syrup in childhood atopic dermatitis treated with mometasone furoate 0.1 per cent cream. *J Med Assoc Thai* 2002; **85**: 482–487.
282 Munday J, Bloomfield R, Goldman M *et al*. Chlorpheniramine is no more effective than placebo in relieving the symptoms of childhood atopic dermatitis with a nocturnal itching and scratching component. *Dermatology* 2002; **205**: 40–45.
283 Berth-Jones J, Graham-Brown RA. Failure of terfenadine in relieving the pruritus of atopic dermatitis. *Br J Dermatol* 1989; **121**: 635–637.
284 Wahlgren CF, Hägermark O, Bergström R. The antipruritic effect of a sedative and a non-sedative antihistamine in atopic dermatitis. *Br J Dermatol* 1990; **122**: 545–551.
285 Savin JA, Dow R, Harlow BJ *et al*. The effect of a new non-sedative h1-receptor antagonist (In 2974) on the itching and scratching of patients with atopic eczema. *Clin Exp Dermatol* 1986; **11**: 600–602.
286 Frosch PJ, Schwanitz HJ, Macher E. A double blined trial of h1 and h2 receptor antagonists in the treatment of atopic dermatitis. *Arch Dermatol Res* 1984; **276**: 36–40.
287 Hjorth N. Terfenadine in the treatment of chronic idiopathic urticaria and atopic dermatitis. *Cutis* 1988; **42**: 29–30.

CQ8. IS PROACTIVE THERAPY EFFECTIVE IN MAINTAINING REMISSION OF REPEATEDLY RELAPSED ECZEMA LESIONS IN AD?

Recommendation

Proactive therapy is effective treatment to maintain remission of eczema lesions and is relatively safe treatment. Proactive therapy has been increasingly used as a measure to reduce the frequency of relapse.

Recommendation grade: 1, *evidence level:* B

Comments: Proactive therapy is a treatment in which a TCS or tacrolimus ointment is applied to the skin, where there is no inflammation after acute-phase treatment, twice a week, to prevent the recurrence of dermatitis. Recently, it has commonly been selected as a strategy for maintaining the remission of AD. Eleven RCTs[289–299] and 1 systematic review indicated that proactive therapy was useful for maintaining remission.[98] Proactive therapy with TCS or tacrolimus ointment is useful for preventing the recurrence of eczema (Evidence level: A). Concerning its safety, many studies reported that there was no difference in the incidence of adverse events between a vehicle and TCS/tacrolimus during a 16-week/1-year follow-up; proactive therapy may be relatively safe. However, no study has examined the safety of proactive therapy, with a longer period of follow-up. With respect to the appearance of adverse reactions, careful observation is necessary. Furthermore, it must be considered that proactive therapy is not a treatment method for patients without a marked improvement in dermatitis. In addition, the extent of application required, timing of switching daily administration to intermittent application, and timing of completion should be determined in accordance with individual patients. Therefore, proactive therapy should be performed by physicians specializing in the assessment of AD-related skin symptoms or in cooperation with physicians specializing in the assessment of skin symptoms.

REFERENCES

288 Peserico A *et al*. Reduction of relapses of atopic derma titis with methylprednisolone aceponate cream twice weekly in addition to maintenance treatment with emollient: a multicentre, randomized, double-blind, controlled study. *Br J Dermatol* 2008; **158**: 801–807.

289 Hanifin J *et al*. Intermittent dosing of fluticasone propionate cream for reducing the risk of relapse in atopic dermatitis patients. *Br J Dermatol* 2002; **147**: 528–537.
290 Berth-Jones J *et al*. Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. *BMJ* 2003; **326**: 1367.
291 Glazenburg EJ *et al*. Efficacy and safety of fluticasone propionate 0.005% ointment in the long-term maintenance treatment of children with atopic dermatitis: differences between boys and girls? *Pediatr Allergy Immunol* 2009; **20**: 59–66.
292 Van Der Meer JB *et al*. The management of moderate to severe atopic dermatitis in adults with topical fluticasone propionate. The Netherlands Adult Atopic Dermatitis Study Group. *Br J Dermatol* 1999; **140**: 1114–1121.
293 Chung BY *et al*. The proactive treatment of atopic dermatitis with tacrolimus ointment in Korean patients: a comparative study between once-weekly and thrice-weekly applications. *Br J Dermatol* 2013; **168**: 908–910.
294 Poole CD *et al*. Health-related utility among adults with atopic dermatitis treated with 0.1% tacrolimus ointment as maintenance therapy over the long term: findings from the Protopic CONTROL study. *Br J Dermatol* 2009; **161**: 1335–1340.
295 Thaçi D *et al*. Proactive disease management with 0.03% tacrolimus ointment for children with atopic dermatitis: results of a randomized, multicentre, comparative study. *Br J Dermatol* 2008; **159**: 1348–1356.
296 Wollenberg A *et al*. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. *Allergy* 2008; **63**: 742–750.
297 Breneman D *et al*. Intermittent therapy for flare prevention and long-term disease control in stabilized atopic dermatitis: a randomized comparison of 3-times-weekly applications of tacrolimus ointment versus vehicle. *J Am Acad Dermatol* 2008; **58**: 990–999.
298 Fukuie T, Hirakawa S, Narita M *et al*. Potential preventive effects of proactive therapy on sensitization in moderate to severe childhood atopic dermatitis: a randomized, investigator-blinded, controlled study. *J Dermatol* 2016; **43**: 1283–1292.

CQ9. IS THE USE OF TOPICAL MOISTURIZERS RECOMMENDED FOR THE TREATMENT OF AD?

Recommendation

The use of topical moisturizing agents is recommended for dermatitis in combination with topical steroids or topical tacrolimus. The continuous use of a topical moisturizer is recommended even after reducing symptoms of dermatitis during the acute phase.

Recommendation grade: 1, *evidence level*: A

Comments: Skin dryness is a major symptom of AD and is considered a reason for the reduction of the epidermal barrier function. The use of a topical moisturizer restores the reduction of water content in the stratum corneum and reduces symptoms and itching caused by skin dryness.[142–305] Moreover, providing skin care using a moisturizer immediately after birth is reported to reduce onset risk of AD in infants in some studies.[145,146] Any direct effects on dermatitis itself cannot be expected, however, the moisturizer improved symptoms of dryness and itching when used in conjunction with topical steroids with anti-inflammatory activity and is effective in maintaining remission of dermatitis after symptoms were resolved.[306] Continuous use of moisturizer agents even after achieving remission of dermatitis is effective to prevent relapses of dermatitis and maintain mitigated itching.[150] However, it should be noted that adverse events such as contact dermatitis might occur due to the use of a moisturizing agent.

REFERENCES

299 Wilhelm KP, Scholermann A. Efficacy and tolerability of a topical preparation containing 10% urea in patients with atopic dermatitis. *Aktuel Dermatol* 1998; **24**: 37–38.
300 Loden M, Andersson AC, Andersson C *et al*. Instrumental and dermatologist evaluation of the effect of glycerine and urea on dry skin in atopic dermatitis. *Skin Res Technol* 2001; **7**: 209–213.
301 Boralevi F, Saint Aroman M, Delarue A *et al*. Long-term emollient therapy improves xerosis in children with atopic dermatitis. *J Eur Acad Dermatol Venereol* 2014; **28**: 1456–1462.
302 Kawashima M, Numano K, Ishizaki C. Usefulness of moisturizers for dermato-physiological dysfunction in patients with atopic dermatitis. *Jpn J Dermatol* 2007; **117**: 969–977. (In Japanese with English abstract.).
303 Hamada M, Gyoutoku T, Sato S *et al*. The usefulness of camellia oil spray for treatment of atopic dermatitis. *Nishinihon J Dermatol* 2008; **70**: 213–218. (In Japanese).
304 Matsunaka H, Abe Y, Ooe M, Nishigori C, Miyachi Y. Clinical evaluation of OLIGOMARINE on atopic dry skin. *Skin Res* 2004; **3**: 73–83. (In Japanese with English abstract).
305 Szczepanowska J, Reich A, Szepietowski LC. Emollients improve treatment results with topical corticosteroids in childhood atopic dermatitis: a randomized comparative study. *Pediatr Allergy Immunol* 2008; **19**: 614–618.
306 Wiren K, Nohlgard C, Nyberg F *et al*. Treatment with a barrier-strengthening moisturizing cream delays relapse of atopic dermatitis: a prospective and randomized controlled clinical trial. *J Eur Acad Dermatol Venereol* 2009; **23**: 1267–1272.

CQ10. IS SHOWERING USEFUL FOR REDUCING SYMPTOMS OF AD?

Recommendation comments

Showering is useful for reducing symptoms of AD.

Recommendation grade: 1, *Evidence level*: B

Comments: In Japan, three school tap water showering intervention studies, involving children with AD, were conducted.[308–310] Showering significantly reduced symptoms of AD. Its effects may be more marked in seasons with an increase in sweat volume. There were no adverse events. Based on these results, tap water showering at school may be useful for reducing symptoms of childhood AD.

REFERENCES

307 Kameyoshi Y, Tanaka T, Mochizuki M *et al*. Taking showers at the school is beneficial for the children with severe atopic dermatitis. *Jpn J Allergol* 2008; **57**: 130–137. (in Japanese with English abstract).
308 Mochizuki H, Muramatsu R, Tadaki H, Mizuno T, Arakawa H, Morikawa A. Effects of skin care with shower therapy on children with atopic dermatitis in elementary schools. *Pediatr Dermatol* 2009; **26**: 223–225.
309 Murota H, Takahashi A, Nishioka M *et al*. Showering reduces atopic dermatitis in elementary school students. *Eur J Dermatol* 2010; **20**: 410–411.

CQ11. IS THE SERUM TARC LEVEL EFFECTIVE AS A DISEASE PROGRESSION MARKER FOR AD?

Recommendation

Measurement of serum TARC levels may be useful as a disease progression marker for pediatric and adult AD.

Recommendation grade: 2, *evidence level*: B

Comments: There are 37 reports (original papers, systematic reviews were excluded) studying the efficacy of measuring serum TARC levels as a disease progression marker of AD in Japan and abroad, and 35 of 37 articles indicated that measuring the serum TARC level was useful. In Japanese articles, Tamaki et al. studied 128 patients with AD aged 18 years old or older, and reported a significant correlation between the serum TARC level and the SCORAD index, which indicates the degree of cutaneous symptoms. There is a stronger correlation with the changes in the SCORAD index after treatment for AD with serum TARC levels than with serum LDH levels or peripheral eosinophil count.[82] Fujisawa et al. studied 65 pediatric patients with AD aged 6 months or older and younger than 15 years of age and reported a significant correlation between serum TARC levels and the SCORAD index; serum TARC levels corresponded well to changes (improvement) after treatment.[83] Maeda et al. measured the changes in serum TARC level over time in 93 adult patients with severe AD. Comparing total IgE levels, LDH levels, and the peripheral eosinophil count, the strongest correlation was observed between serum TARC levels and the EASI, a cutaneous symptom score. When eruptions improved after treatment, the serum TARC level also decreased. Provision of patient education and application of topical steroids can be based on serum TARC levels as an index, and in addition, the serum TARC level can be used as a tool to obtain a favorable outcome.[311] Kakinuma et al. measured the serum TARC levels in 40 patients with AD and reported a significant correlation between serum TARC level and the SCORAD index. Furthermore, when eruptions improved after treatment, the serum TARC level also decreased.[312] Hijnen et al. studied 276 patients with AD and reported that the serum TARC level was significantly correlated with the Leicester Sign Score (LSS), a cutaneous symptom score, and the serum TARC level decreased with improvement of the eruption after treatment.[313] Fujisawa et al. examined 45 patients with AD and reported that serum TARC levels increased with decreasing age and were significantly correlated with the SCORAD index in all three age groups (0–1, 2–5, and 6 years of age or older). The extent of the decrease of the SCORAD index and serum TARC levels was also correlated.[85] Moreover, Thijis et al. performed a systematic review and meta-analysis of 115 biomarkers of AD described in 222 articles and reported that the most reliable biomarker to reflect disease progression of AD was TARC.[314]

Based on the above, the serum TARC level appears to be the most reliable biomarker that strongly reflects disease progression compared to other available biomarkers, including serum IgE level, LDH level, and peripheral eosinophil count, in pediatric and adult patients with AD. In addition, provision of patient education and application of topical steroids can be reviewed using serum TARC level as an index. However, it should be noted that the reference level varies depending on age as serum TARC levels increase with decreasing age during childhood. Caution is required because serum TARC level increases in other cutaneous diseases besides AD, such as in bullous pemphigoid and mycosis fungoides.[81]

REFERENCES

310 Maeda N, Yoshida N, Nishino H, Kataoka Y. The clinical significance of serum TARC as a biomarker for severe adult atopic dermatitis. *J Environ Dermatol Cutan Allergol* 2011; **5**: 27–35. (In Japanese with Engish Abstract).

311 Kakinuma T, Nakamura K, Wakugawa M *et al*. Thymus and activation-regulated chemokine in atopic dermatitis: Serum thymus and activation-regulated chemokine level is closely related with disease activity. *J Allergy Clin Immunol* 2001; **107**: 535–541.

312 Hijnen D, De Bruin-Weller M, Oosting B *et al*. Serum thymus and activation-regulated chemokine (TARC)and cutaneous T cell-attracting chemokine (CTACK)levels in allergic diseases: TARC and CTACK are disease-specific markers for atopic dermatitis. *J Allergy Clin Immunol* 2004; **113**: 334–340.

313 Thijs J, Krastev T, Weidinger S *et al*. Biomarkers for atopic dermatitis: a systemic review and meta-analysis. *Curr Opin Allergy Clin Immunol* 2015; **15**: 453–460.

CQ12. IS THE ORAL ADMINISTRATION OF CYCLOSPORIN RECOMMENDED FOR THE TREATMENT OF SEVERE AD?

Recommendation comments

For patients with AD in whom control is difficult, despite the application of TCS/tacrolimus, skin care and elimination of triggering factors, cyclosporin therapy may be selected.

Recommendation grade: 2, *Evidence level*: A

Comments: The results of previous clinical studies in Japan and other countries demonstrate the efficacy of cyclosporin therapy for AD.[130] In a clinical study involving Japanese adults (aged 16 years or older) with severe AD, an initial dose was established as 3 mg/kg per day (if necessary, it was increased or decreased in accordance with symptoms so that it did not exceed 5 mg/kg per day), while reviewing the efficacy and adverse events. The authors concluded that treatment involving the discontinuation period is effective and safe when administration is completed in 8–12 weeks, or continued.[131] However, neither the efficacy nor safety of long-term administration has been established; therefore, cyclosporin should be used after explaining its efficacy and safety to patients. In addition to safety-related problems, the drug price is high. When selecting cyclosporin therapy for severe patients who do not respond to conventional treatment, it is important to promptly switch it to topical therapy, as standard, after symptom relief. The combination group with topica anti-inflammatory agents and oral cyclosporine had a shorter median time to response and a longer time to relapse than the monotherapy group with cyclosporine.[319] In children, the efficacy was investigated, but the safety of long-term treatment was not

sufficiently examined. In Japan, cyclosporin therapy for childhood AD has not been approved.

REFERENCES

314 Sowden JM, Berth-Jones J, Ross JS *et al*. Double-blind, controlled, crossover study of cyclosporin in adults with severe refractory atopic dermatitis. *Lancet* 1991; **338**(8760): 137–140.
315 Harper JI, Ahmed I, Barclay G *et al*. Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy. *Br J Dermatol* 2000; **142**: 52–58.
316 Czech W, Bräutigam M, Weidinger G *et al*. A body-weight-independent dosing regimen of cyclosporine microemulsion is effective in severe atopic dermatitis and improves the quality of life. *J Am Acad Dermatol* 2000; **42**: 653–659.
317 Study Group of Neoral®. Treatment for Atopic Dermatitis: cyclosporine MEPC versus placebo for treating patients with severe adult atopic dermatitis: a multicenter, randomized, double-blind, placebo-controlled study. *Jpn J Clin Dermatol* 2009; **63**: 73–82. (In Japanese).
318 Kim JE, Shin JM, Ko JY *et al*. Importance of concomitant topical therapy in moderate-to-severe atopic dermatitis treated with cyclosporine. *Dermatol Ther* 2016; **29**: 120–125.
319 Tan HY, Zhang AL, Chen D, Xue CC, Lenon GB. Chinese herbal medicine for atopic dermatitis: a systematic review. *J Am Acad Dermatol* 2013; **69**: 295–304.

CQ13. IS CHINESE MEDICINE EFFECTIVE FOR THE TREATMENT OF AD?

Recommendation comments

For patients with AD who do not respond to topical anti-inflammatory drugs, such as TCS or tacrolimus, oral antihistamines, skin care, or strategies against triggering factors, combination therapy with traditional Chinese herbal medicines may be considered.

Recommendation grade: 2, *Evidence level*: B

Comments: Explanation: Most clinical studies examining the usefulness of traditional Chinese herbal medicine for AD were case series studies involving approximately 20 to 30 patients. There were seven double-blind RCTs.[133–137] Of these, concerning preparations that can be prescribed at general dermatological clinics in Japan, there were only two studies using Xiao-Feng-San[133] and Hochu-ekki-to.[134] The former involved patients in whom treatment with topical anti-inflammatory drugs, such as corticosteroids, did not reduce eruption, and the latter involved those with Kikyo (easy fatigability or lack of perseverance) based on the results of a questionnaire survey. Both studies were conducted, while simultaneously performing conventional treatment with topical anti-inflammatory drugs, such as TCS. The former showed a significant improvement in eruption in the prescription-treated group in comparison with the placebo group. The latter indicated that the doses of topical corticosteroids could be decreased. An international, double-blind, RCT using Zemaphyte reported its efficacy,[135,136] whereas another study group reported against it.[137]

The basis of Chinese herbal medicine is "zuisho therapy", in which the best suitable treatment is selected based on patient's symptoms considering them as a "pattern" of Yin/Yang and Kyo/Jitsu (xu/shi). In Chinese herbal medicine for AD, the individual patient's constitution is considered a systemic "pattern" while eruption is considered a local "pattern", thus, treatment is provided as a combination of root treatment (with the aim to improve the patient's constitution) and symptomatic treatment (with the aim to improve symptoms). In this respect, the efficacy of stereotypical treatment such as "Drug A is the best for AD" is questionable. With respect to the usefulness of traditional Chinese herbal medicine for the treatment of AD, many issues, including the usefulness of selecting prescriptions based on the properties of eruption and adequacy of evidence assessment using simple methods, such as a questionnaire, must be examined. In the future, the results of multicenter, double-blind, RCTs, of which the accuracy is high, should be accumulated for careful examination. Furthermore, the adverse events related to Kampo preparations must be considered, such as pseudohyperaldosteronism related to licorice-containing preparations, which may occur.

REFERENCES

320 Hon KL, Leung TF, Ng PC *et al*. Efficacy and tolerability of a Chinese herbal medicine concoction for treatment of atopic dermatitis: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2007; **157**: 357–363.
321 Huang YQ, Chen DC, Mo XM. Clinical observation of the treatment of spleen deficiency childhood atopic dermatitis with Jean Pi Shen Shi granules. *Shan Xi Zhong Yi* 2004; **5**: 396–398.

CQ14. SHOULD ENVIRONMENTAL MITE ANTIGENS BE ELIMINATED FOR THE TREATMENT OF AD?

Recommendation comments

Strategies to decrease the mite antigen level in a living environment may be considered for patients in whom the results of an inquiry or blood test suggest the involvement of mite antigens in the aggravation of eruption.

Recommendation grade: 2, *Evidence level*: B

Comments: In many patients with AD, IgE antibodies against mites are detected by blood test, or skin test with mite antigens showing a positive reaction. We have sometimes encountered patients in whom symptoms subsided with environmental arrangements to reduce exposure to mite allergens, e.g. in an environment such as a bedroom, while there is often no improvement in eruption in clinical practice even when guidance for standardized strategies to eliminate mite antigens is performed for patients with a high anti-mite IgE antibody titer or a positive reaction on a skin test. In RCTs involving mite antigen avoidance using a bed cover that does not allow mite allergens to pass, the relief of AD-related eruption was achieved in addition to a decrease in the level of mite antigens in bedclothes.[323–327] On the other hand, according to some studies, such a strategy against mite antigens decreased the antigen level, but there were no effects on eruption.[328,329] High quality long-term trials of single, easy-to-administer house dust mite reduction or avoidance measures are worth pursuing.[330]

The characteristics of patients in whom mite antigen avoidance leads to an improvement in AD-related eruption are

unclear. Evaluation should not thus be performed based on clinical symptoms or hematological data alone. When eruption deteriorates or reduces with environmental changes, such as visits to a dusty place and travelling, in the presence of strong sensitization with mite allergen on blood or skin prick tests, mite avoidance strategies, such as ventilation, frequent bedroom/living room cleaning (every 3 days or more), bedclothes cleaning with a vacuum cleaner (for 20 to 30 s/m^2, once a week), sun drying, and sheet washing,[331] should be conducted to review whether or not eruption reduces.

REFERENCES

322 Holm L, Bengtsson A, van Hage-Hamsten M, Ohman S, Scheynius A. Effectiveness of occlusive bedding in the treatment of atopic dermatitis–a placebo-controlled trial of 12 months' duration. *Allergy* 2001; **56**: 152–158.
323 Ricci G, Patrizi A, Specchia F *et al*. Effect of house dust mite avoidance measures in children with atopic dermatitis. *Br J Dermatol* 2000; **143**: 379–384.
324 Friedmann PS, Tan BB. Mite elimination–clinical effect on eczema. *Allergy* 1998; **53**(48 Suppl): 97–100.
325 Tan BB, Weald D, Strickland I, Friedmann PS. Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. *Lancet* 1996; **347**: 15–18.
326 Sanda T, Yasue T, Oohashi M, Yasue A. Effectiveness of house dust-mite allergen avoidance through clean room therapy in patients with atopic dermatitis. *J Allergy Clin Immunol* 1992; **89**: 653–657.
327 Oosting AJ, de Bruin-Weller MS, Terreehorst I *et al*. Effect of mattress encasings on atopic dermatitis outcome measures in a double-blind, placebo-controlled study: the Dutch mite avoidance study. *J Allergy Clin Immunol* 2002; **110**: 500–506.
328 Gutgesell C, Heise S, Seubert S *et al*. Double-blind placebo-controlled house dust mite control measures in adult patients with atopic dermatitis. *Br J Dermatol* 2001; **145**: 70–74.
329 Nankervis H, Pynn EV, Boyle RJ *et al*. House dust mite reduction and avoidance measures for treating eczema. *Cochrane Database Syst Rev* 2015; **1**: CD008426.
330 Nanbu M. Indoor allergen avoidance for allergic children. *Jpn J Pediatr Allergy Clin Immunol* 2010; **24**: 203–216. (In Japanese with English abstract).

CQ15. IS THE ALLERGEN ELIMINATION DIET EFFECTIVE FOR THE TREATMENT OF AD?

Recommendation

Unless progression of AD is confirmed to be caused by a specific food, eliminating the specific food is not recommended solely for the reason that the specific food is suspected to be an allergen.

Evidence level: B

Comments: A systematic review[161] containing 9 RCTs was reported in the Cochrane Collaboration 2008.[332–340] Overall, the quality of those RCTs was poor, thus, their evidence level was determined to be low.

Conversely, strict dietary restriction carries a high risk of inducing adverse health effects including weight loss and nutritional insufficiency. Food allergens are involved in AD in some cases; however, an allergen elimination test should be performed after adequate treatment with anti-inflammatory topical drugs for AD before eliminating the suspected food from the diet. Limiting food only because it is likely to be an allergen appears not to be effective for AD.

REFERENCES

331 Atherton DJ, Sewell M, Soothill JF, Wells RS, Chilvers CE. A double-blind controlled crossover trial of an antigen-avoidance diet in atopic eczema. *Lancet* 1978; **1**: 401–403.
332 Neild VS, Marsden RA, Bailes JA, Bland JM. Egg and milk exclusion diets in atopic eczema. *Br J Dermatol* 1986; **114**: 117–123.
333 Cant AJ, Bailes JA, Marsden RA, Hewitt D. Effect of maternal dietary exclusion on breast fed infants with eczema: two controlled studies. *Br Med J (Clin Res Ed)* 1986; **293**: 231–233.
334 Lever R, MacDonald C, Waugh P, Aitchison T. Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. *Pediatr Allergy Immunol* 1998; **9**: 13–19.
335 Niggemann B, Binder C, Dupont C, Hadji S, Arvola T, Isolauri E. Prospective, controlled, multi-center study on the effect of an amino-acid-based formula in infants with cow's milk allergy/intolerance and atopic dermatitis. *Pediatr Allergy Immunol* 2001; **12**: 78–82.
336 Isolauri E, Sutas Y, Makinen-Kiljunen S, Oja SS, Isosomppi R, Turjanmaa K. Efficacy and safety of hydrolyzed cow milk and amino acid-derived formulas in infants with cow milk allergy. *J Pediatr* 1995; **127**: 550–557.
337 Mabin DC, Sykes AE, David TJ. Controlled trial of a few foods diet in severe atopic dermatitis. *Arch Dis Child* 1995; **73**: 202–207.
338 Munkvad M, Danielsen L, Hoj L *et al*. Antigen-free diet in adult patients with atopic dermatitis. A double-blind controlled study. *Acta Derm-Venereol* 1984; **64**: 524–528.
339 Leung TF, Ma KC, Cheung LT *et al*. A randomized, single-blind and crossover study of an amino acid-based milk formula in treating young children with atopic dermatitism. *Pediatr Allergy Immunol* 2004; **15**: 558–561.

CQ16. IS THE USE OF DIETARY RESTRICTIONS DURING PREGNANCY AND BREASTFEEDING EFFECTIVE FOR PREVENTING THE DEVELOPMENT OF AD IN CHILDREN?

Recommendation

Maternal dietary restriction during pregnancy and breastfeeding is not useful to prevent AD development in children.

Evidence level: A

Comments: A child's exposure to allergens may be associated with the onset of AD. Food ingested by the mother may have effects on the child's immune system through the placenta and breast milk; however, the association with the development of allergic diseases has not been clarified.

The American Academy of Pediatrics recommended to refrain from the consumption of peanuts during pregnancy as a preventive measure for peanut allergy in 2000, however, no inhibiting effect on the development of peanut allergy was observed.[341–343] Thus, the recommendation was waived in 2008, and the Academy decided not to recommend dietary restriction during pregnancy. In the Cochrane systematic review summarizing the results of five RCTs (952 cases in total), allergen elimination in pregnant women was not useful in preventing AD development in their children up to 18 months of age. In the same review, it was also reported that dietary

restriction during pregnancy was likely to impair fetal growth. Based on above, dietary restriction during pregnancy is not useful to prevent the onset of AD, thus, it is not recommended.[162]

Dietary restriction in breastfeeding mothers was also reported not to be useful for preventing the development of AD in their children similarly to during pregnancy in the abovementioned Cochrane systematic review.[341] A measure was taken for indoor mites, whereby allergen elimination occurred concomitantly with dietary restriction during breastfeeding, and as a result, the rate of AD development was reported to decrease in some cases. However, the efficacy of dietary restriction alone has not been elucidated. For all these reasons, dietary restriction during breastfeeding is not useful to prevent the development of AD, thus, it is not recommended.[341,346–348]

The excessive intake of a specific food during pregnancy may promote the onset of food allergy as a frequent intake of peanuts during pregnancy is also reported to be associated with sensitization to peanuts in their infants.[349,350]

There is not sufficient evidence to actively recommend dietary restriction during pregnancy and breastfeeding to prevent the development of AD in children, thus, it can be concluded that dietary restriction is not useful.

REFERENCES

340 Lack G, Fox D, Northstone K, Golding J. Factors associated with the developmentof peanut allergy in childhood. *N Engl J Med* 2003; **348**: 977–985.

341 Hourihane JO, Aiken R, Briggs R *et al*. The impact of government advice to pregnant mothers regarding peanut avoidance on the prevalence of peanut allergy in United Kingdom children at school entry. *J Allergy Clin Immunol* 2007; **119**: 1197–1202.

342 Dean T, Venter C, Pereira B, Grundy J, Clayton CB, Higgins B. Government advice on peanut avoidance during pregnancyeis it followed correctly and what is the impact on sensitization? *J Hum Nutr Diet* 2007; **20**: 95–99.

343 Herrmann ME, Dannemann A, Gruters A *et al*. Prospective study on the atopy preventive effect of maternal avoidance of milk and eggs during pregnancy and lactation. *Eur J Pediatr* 1996; **155**: 770–774.

344 Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 1995; **95**: 1179–1190.

345 Chandra RK, Puri S, Hamed A. Influence of maternal diet during lactation and use of formula feeds on development of atopic eczema in high risk infants. *BMJ* 1989; **299**: 228–230. rectraction BMJ 2015; 351: h5682.

346 Hattevig G, Sigurs N, Kjellman B. Effects of maternal dietary avoidance during lactation on allergy in children at 10 years of age. *Acta Paediatr* 1999; **88**: 7–12.

347 Arshad SH, Bateman B, Sadeghnejad A, Gant C, Matthews SM. Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight prevention study. *J Allergy Clin Immunol* 2007; **119**: 307–313.

348 Frank L, Marian A, Visser M, Weinberg E, Potter PC. Exposure to peanuts *in utero* and in infancy and the development of sensitization to peanut allergens in young children. *Pediatr Allergy Immunol* 1999; **10**: 27–32.

349 Sicherer SH, Wood RA, Stablein D *et al*. Maternal consumption of peanut during pregnancy is associated with peanut sensitization in atopic infants. *J Allergy Clin Immunol* 2010; **126**: 1191–1197.

CQ17. IS THE ADMINISTRATION OF PROBIOTICS RECOMMENDED TO IMPROVE THE SYMPTOMS OF AD DURING INFANCY?

Recommendation

Probiotics are not recommended to improve symptoms of infant AD at the present moment.

Evidence level: B

Comments: Boyle et al. reported a systematic review[351] consisting of two RCTs conducted in children younger than 2 years of age[352,353] in the Cochrane Collaboration. In the meta-analysis, a superior efficacy of probiotics in treating AD was not shown when compared to placebo. Moreover, in a meta-analysis reported by Kim et al.,[354] a significant improvement in the SCORAD index was observed in children younger than 1 year old, thus, the authors concluded that there was no efficacy due to probiotics. Therefore, the use of probiotics is not recommended to improve symptoms in infant AD at the current time.

REFERENCES

350 Boyle RJ, Bath-Hextall FJ, Leonardi-Bee J, Murrell DF, Tang ML. Probiotics for treating eczema. *Cochrane Database Syst Rev* 2008; **4**: CD006135.

351 Weston S, Halbert A, Richmond P, Prescott SL. Effects of probiotics on atopic dermatitis: a randomised controlled trial. *Arch Dis Child* 2005; **90**: 892–897.

352 Gruber C, Wendt M, Sulser C *et al*. Randomized, placebo-controlled trial of Lactobacillus rhamnosus GG as treatment of atopic dermatitis in infancy. *Allergy* 2007; **62**: 1270–1276.

CQ18. CAN REMISSION OF AD BE EXPECTED WITH AGE?

Recommendation

AD can be expected to show a certain level of remission with age. However, the remission rate varies depending on the degree of symptoms.

Evidence level: B

Comments: There are 21 articles (original articles) regarding remission of AD with age in Japan and abroad, and all articles reported that AD showed a certain degree of remission with age. In the articles published in Japanese language, Okano et al. reported the results of a school physical examination study performed between 1992 and 2002 in Hiroshima. Among the 121 children who were diagnosed with AD in their first year in primary school, 60 children (49.6%) who were followed-up again in the 6th grade still presented AD while symptoms were resolved in 22 children.[353] Arima et al. started a follow-up cohort study in 2003 in 1778 infants who underwent a 4-month medical examination in three regions (Chiba, Yokohama, and Fukuoka). The results showed that about 70% of the 4-month-old children with AD experienced complete remission (or disappearance) at the age of 1.5 years, and about 50% of the infant aged 1.5 years with AD experienced complete remission by age 3 years.[354] In English language articles, Fukiwake et al. conducted annual medical examinations in nursery school

children aged 5 years or younger in Ishigaki Island of the Okinawa prefecture between 2001 and 2004 and reported that symptoms disappeared within 3 years in 53 of 74 (71.6%) children who were diagnosed with AD at their initial medical examination.[49] Hua et al. followed-up 1404 children for 8 years born between 1996 and 2000 in Taiwan who had developed AD before the age of 2 years, and reported that 19.4%, 48.7%, and 69.8% of children experienced remission within 1, 4, and 8 years, respectively.[355] A study by von Kobyletzki et al. followed the clinical course for 5 years of 894 children aged 1 to 3 years who were diagnosed with AD in 2000 in Sweden. They reported that remission was achieved in 52% of children. The authors also reported mild AD, older onset age, no eruption on flexion sides, no food allergies, and living in suburban areas as factors of high remission rate.[356,357]

Based on studies, AD may be expected to show a degree of remission with age. However, the remission rate may vary depending on the extent of symptoms. Generally, remission rates were higher for mild AD following medical examination not peformed in a hospital setting. The remission rate was likely to be higher in children with AD without any food allergies than in children with AD with food allergies.

REFERENCES

353 Okano S, Takahasi H, Yano T *et al*. Member posted first grade school children after five years of skin lesions, including atopic dermatitis with prognosis Survey: Study in Hiroshima Prefecture Asa district. *J Jpn Med Assoc* 2006; **135**: 97–103. (In Japanese).

354 Arima T, Kohno Y. The present study about the prevalence of atopic dermatitis in Japan. *The Allergy in Practice* 2009; **29**: 581–587. (In Japanese).

355 Hua TC, Hwang CY, Chen YJ *et al*. The natural course of early-onset atopic dermatitis in Taiwan: a population-based cohort study. *Br J Dermatol* 2014; **170**: 130–135.

356 von Kobyletzki LB, Bomehag CG, Breeze E *et al*. Factors associated with remission of eczema in children: a population-based follow-up study. *Acta Derm Venereol* 2014; **94**: 179–184.

CQ19. IS THE USE OF ANTIHISTAMINES DURING PREGNANCY AND BREASTFEEDING SAFE?

Recommendation

Administration of antihistamines during pregnancy can be considered mostly safe, thus, antihistamines with verified safety can be administered if clinical benefit is substantial. It should be noted that most antihistamines, not associated with congenital anomalies through epidemiological observation studies and meta-analysis are first-generation antihistamines, while there are only a few reports regarding second-generation antihistamines. Informed consent should be obtained after discussing the risks of congenital anomalies in comparison with the background rate (2–3%).

Administration of antihistamines appears to be safe even during breastfeeding. The amount of the drug transferred into breast milk is very small. However, second-generation antihistamines are recommended given the potential for irritability or somnolent in infants caused by sedative first-generation antihistamines.

With regard to individual drugs, careful consideration of the contents of package inserts and the latest information on safety profiles is also necessary.

Evidence level: B

Comments: A meta-analysis (case-control study or prospective cohort study) consisting of more than 200 000 subjects who received first-generation antihistamines showed there was no increase in congenital malformations.[358] A placebo-controlled intervention study of first-line antihistamines administered for hyperemesis was recently conducted and the results confirmed the absence of teratogenic risk of these agents.[359]

Most studies regarding second-generation antihistamines were conducted using loratadine, and many failed to show any relationship between antihistamine treatment and the development of congenital malformations. Loratadine had once been reported to be a risk factor for hypospadias, although this was refuted by a meta-analysis conducted in 2694 boys exposed to loratadine and in 450 413 boys in the control group.[360] Many studies have failed to show a correlation between cetirizine use and the risk of congenital malformations, and a recent prospective cohort study has also denied the hypothesis that cetirizine causes adverse events in unborn children.[361] There are no reports on levocetirizine; however, the safety profile of this drug is considered similar to that of cetirizine because it is the R-enantiomer (optical isomer) of cetirizine, a racemic mixture. Although there are no reports available on fexofenadine, an active metabolite of terfenadine (a discontinued product because of side effects involving QT prolongation), the teratogenic potential of terfenadine has not been demonstrated. Further studies are expected as there are currently no reports available on other second-generation antihistamines.

In a telephone survey of first-generation antihistamines administered during breastfeeding, irritability or somnolentia was observed in a small group of infants, however, none showed symptoms sufficiently severe to warrant a visit to a medical facility.[362] In a study examining drug passage into breast milk after a single dose of loratadine, four times that of the recommended dose, the assumed maximum dose transferred to the infant was 1.1% of mother's general daily dose considering the infant's degree of sucking.[363] A similar pharmacokinetic study was conducted for fexofenadine, and it suggested that the assumed maximum dose transferred to the infant was 0.45% of the mother's general daily dose.[364] The results of both studies suggested that second-generation antihistamines transferred into breast milk were unlikely to have any effects on infants.

In conclusion, administration of antihistamines during pregnancy and lactation is mostly safe. If clinically required (i.e., when severe itching interferes with the mother's QOL and inhibits the performance of daily activities), administration of these drugs with verified safety can be administered. With regard to individual drugs, careful consideration of the contents of package inserts and the latest information on safety profiles is also necessary.

REFERENCES

357 Seto A, Einarson T, Koren G. Pregnancy outcome following first trimester exposure to antihistamines: meta-analysis. *Am J Perinatol* 1997; **14**: 119–124.

358 Koren G, Clark S, Hankins GD *et al*. Maternal safety of the delayed-release doxylamine and pyridoxine combination for nausea and vomiting of pregnancy; a randomized placebo controlled trial. *BMC Pregnancy Childbirth* 2015; **15**: 59.

359 Schwarz EB, Moretti ME, Nayak S, Koren G. Risk of hypospadias in offspring of women using loratadine during pregnancy: a systematic review and meta-analysis. *Drug Saf* 2008; **31**: 775–788.

360 Weber-Schoendorfer C, Schaefer C. The safety of cetirizine during pregnancy. A prospective observational cohort study. *Reprod Toxicol* 2008; **26**: 19–23.

361 Ito S, Blajchman A, Stephenson M, Eliopoulos C, Koren G. Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication. *Am J Obstet Gynecol* 1993; **168**: 1393–1399.

362 Hilbert J, Radwanski E, Affrime MB, Perentesis G, Symchowicz S, Zampaglione N. Excretion of loratadine in human breast milk. *J Clin Pharmacol* 1988; **28**: 234–239.

363 Lucas BD Jr, Purdy CY, Scarim SK, Benjamin S, Abel SR, Hilleman DE. Terfenadine pharmacokinetics in breast milk in lactating women. *Clin Pharmacol Ther* 1995; **57**: 398–402.

CQ20. IS THE USE OF TOPICAL STEROIDS DURING PREGNANCY AND BREASTFEEDING SAFE?

Recommendation

Topical steroid therapy during pregnancy and breastfeeding, and can be used without worrying about its effects on the fetus/infant if standard application methods are adopted. However, the use of high-dose potent topical steroids for extended periods should be avoided because these may cause low weight at birth.

Evidence level: B

Comments: No interventional studies have been performed to date, because the study population is pregnant women. Both a large-scale case-control study and a prospective cohort study[365,366] and the relative meta-analysis[367] reported that the use of topical steroids was not associated with xmlstyle of delivery at birthing, congenital malformations (including cleft lip palate and hypospadias), low birth weight, preterm delivery, fetal death, abnormal delivery, or low Apgar score. Even in the stratified analysis (light to moderate use, heavy to heaviest use), no changes were observed in risk of cleft lip palate or preterm delivery, and low Apgar score. Based on theoretical evidence that the systemic absorption of steroids used in topical therapy is generally very small, it can be assumed that steroids almost never have any effect on the fetus.

However, it has been shown that the use of high-dose potent or very potent (in Europe, TCS are classified into four ranks (very potent, potent, moderately, mild).[90]) topical steroids (Especially 300 g or more) was likely to cause low weight at a birth in a large-scale study conducted in the United Kingdom.[368–370] Although the systemic absorption of the drugs evaluated varied depending on their individual properties and the overall condition and range of eruptions, it is recommended that the use of potent or stronger topical steroids for a prolonged period should be avoided. Eczema should be adequately controlled before getting pregnant.

Based on the theoretical evidence that systemic absorption of topical steroids is limited during breastfeeding, the use of topical steroids appears to be safe. However, topical use of steroids directly on the breasts should be avoided immediately before breastfeeding, and instructions should be given to the patient to adequately to wipe the treated areas before breastfeeding.

REFERENCES

364 Mygind H, Thulstrup AM, Pedersen L, Larsen H. Risk of intrauterine growth retardation, malformations and other birth outcomes in children after topical use of corticosteroid in pregnancy. *Acta Obstet Gynecol Scand* 2002; **81**: 234–239.

365 Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. *Teratology* 1997; **56**: 335–340.

366 Chi CC, Wang SH, Wojnarowska F, Kirtschig G, Davies E, Bennett C. Safety of topical corticosteroids in pregnancy. *Cochrane Database Syst Rev* 2015; **10**: CD007346.

367 Chi CC, Mayon-White RT, Wojnarowska FT. Safety of topical corticosteroids in pregnancy: a population-based cohort study. *J Invest Dermatol* 2011; **131**: 884–891.

368 Chi CC, Wang SH, Mayon-White R, Wojnarowska F. Pregnancy outcomes after maternal exposure to topical corticosteroids, a UK population-based cohort study. *JAMA Dermatol* 2013; **149**: 1274–1280.

369 Chi CC, Kirtschig G, Aberer W *et al*. Updated evidence-based (S2e)European Dermatology Forum guideline on topical corticosteroids in pregnancy. *J Eur Acad Dermatol Venereol* 2017; **31**: 761–773.

CQ21. IS THE USE OF DETERGENTS INCLUDING SOAP EFFECTIVE FOR THE MANAGEMENT OF AD?

Recommendation

The use of soap and detergents may be useful for management of AD if specific skin conditions, type of soap and detergent, and cleaning methods are considered.

Recommendation grade: 1, *evidence level*: C

Comments: Dirt on the skin surface mainly consists of sebum, however, some substances from the environment can also be present. In addition to sebum, topical drugs, adhesion of body fluids and colonization of infectious pathogens such as *S. aureus* can be observed in AD, and these may become exacerbating factors for cutaneous symptoms. Therefore, keeping the skin clean using detergent is important to maintain the physiological functions of the skin. Although there is no quality evidence about the efficacy of soap and/or detergent in the treatment of AD, the result of a case series study evaluating the use of general soap conducted in patients who do not use soap, but rather prolonged bathing showed there was an improvement of symptoms without any evidence of exacerbation.[371,372]

As the major component of soap and/or detergent is surfactants, excessive abuse of these products may worsen skin dryness by dissolving lipids on the skin surface or intercellular

lipids present in the stratum corneum. Transient pH elevation after the use of soap causes a temporary decrease in barrier functions.[373,374] Moreover, additives contained in detergent, such as pigments and perfumes, are believe to cause irritation of the skin. Based on the above, the use of soap and/or detergent may be useful to keep the skin clean, however, skin conditions change in function of age, site, and season; thus, the type of soap and/or detergent product and cleansing approaches to be used should be carefully considered.

In other words, the use of soap should be limited to a minimum and should be thoroughly rinsed using hot water (approximately, 38–40°C). If patients exhibit severely dry skin or exhibit specific skin areas with severe dryness, or show severe irritation caused by soaps and/or detergents, or if the climate is seasonally dry, cleansing products with extremely low degreasing power should be selected. For oily skin or seborrheic areas, areas in which ointment is applied daily, and areas presenting reccurent skin infections, the active use of soaps and/or detergents can be considered in order to circumvent exacerbating factors. There is no evidence currently available regarding the superiority of the type of product (soap [solid] or detergent [liquid using synthetic surfactant]) to be used. It is important to select appropriate detergents, for example, detergents with basic chemical properties ensuring low irritability and low allergic properties; detergents containing the fewest possible additives, such as pigments, and perfumes; detergents with favorable usability and without irritability; and the use of detergents leading to dry skin after cleansing. Likewise, it is also important that the detergent produces sufficient foam so as not to damage the skin, and allows removal of dirt from the skin in the least irritating way. Patients should also be cautious of residual detergent remaining on the skin.

REFERENCES

370 Uehara M, Takada K. Use of soap in the management of atopic dermatitis. *Clin Exp Dermatol* 1985; **10**: 419–425.

371 Uehara M. Use of soap in bathing for atopic dermatitis. *Rinsho Derma (Tokyo)* 1981; **23**: 1049–1052. (In Japanese).

372 White MI, Jenkinson DM, Lloyd DH. The effect of washing on the thickness of the stratum corneum in normal and atopic individuals. *Br J Dermatol* 1987; **116**: 525–530.

373 Ananthapadmanabhan KP, Moore DJ, Subramanyan K, Misra M, Meyer F. Cleansing without compromise: the impact of cleansers on the skin barrier and the technology of mild cleansing. *Dermatol Ther* 2004; **17**(Suppl 1): 16–25.

CQ22. IS BABY BATHING EFFECTIVE FOR ECZEMA DURING INFANCY?

Recommendation

There is no evidence that the use of baby bathing products clearly improves eruptions. However, these do not cause any adverse effects, as some baby bathing products also include moisturizing activity, unless contact dermatitis occurs.

Evidence level: C

Comments: The ingredients contained in baby bathing products vary by product. For example, baby bathing agent S contains guaiazulene, reduced lanolin, cetanol, paraben, chlorhexidine gluconate, perfume, and tocopherol (vitamin E), while ingredients of baby bathing agent B contains mineral oil, ceteth-13, steareth-15, stearyl alcohol, sorbitan stearate, sorbitan isostearate, natural horse oil, glycyrrhizic acid 2K, natural loquat leaf extract, natural peach leaf extract, organic palmarosa oil, BG, phenoxyethanol, and Na benzonate. There is reduced potential of causing inflammation if these products are not completely rinsed from the skin surface of healthy patients as these agents have weaker surfactant activity,[375–379] however, attention is needed for patients with eczema as these may induce a strong irritation. If rinsing is inadequate, residual sebum may lead to worsening of eczema. Although it is believed that these baby bathing products have a mild moisturizing activity, there is no clear evidence suggesting they improve eruption.

Seventeen articles were retrieved in using the search term “baby bathing agent” in the Japan Medical Abstracts database, however, there was no article reported the effects of baby bathing agents on improving dermatitis. A PubMed search with the key words “eczema”, “baby”, and “bath” produced 34 articles however, none described any effects of the baby bathing agent on eczema.

Although it is not required that the baby bathing agents be rinsed after use, contact dermatitis may occur due to the presence of paraben, and as such it is not recommended for children with eczema.

REFERENCES

374 Ikezawa S, Takei Y, Tanabe M *et al*. Comparison of several bath additives. *Jap J Midwives* 1976; **30**: 357–361. (In Japanese).

375 Yamaguchi N. Drug therapy in perinatal period. *Perinat Med (Tokyo)* 1995; **25**: 405–407. (In Japanese).

376 Takahashi E, Suzuki H, Yamamoto H. Skin care from pediatricians: comparison between liquid bath additives and soap in newborn. *J Pediatr Dermatol* 1990; **9**: 204–212. (In Japanese).

377 Nashiro M, Chiba M, Nakata T, Ishibashi H, Masuda S, Zenke T. *Effects of Bath Additives on Prevention of Dry Skin: Measuring Water Content of Statum Corneum after Whole Body and Feet Bathing with Bath Additives and Hot Wateeruptioni*. Ashi 2007; 149–151. (In Japanese).

378 Lavender T, Bedwell C, Roberts SA *et al*. Randomized, controlled trial evaluating a baby wash product on skin barrier function in healthy, term neonates. *J Obstet Gynecol Neonatal Nurs* 2013; **42**: 203–214.

CQ23. IS THE USE OF POVIDONE IODINE SOLUTION RECOMMENDED FOR THE TREATMENT OF AD?

Recommendation

There is no medical evidence to actively recommend the use of povidone iodine solution. It may be considered as an adjuvant therapy for patients who are difficult to treat using first-lineTCS due to the presence of infection; however, povidone iodine should not be implemented without careful consideration if there are concerns regarding safety.

Evidence level: C

Comments: It is known that *S. aureus* is more frequently isolated on skin lesions in patients with AD than in the healthy population and has been considered a well known exacerbation factor of AD for some time.[380]

Therefore, eradication of *S. aureus* using disinfectants (e.g. povidone iodine solution, hypochlorous acid) has been attempted for treatment of AD.

In Japan, povidone iodine solution is often used as a disinfectant, and a study has reported the potential efficacy of some disinfectants in AD.[381] However, no comparative study using a control group has been conducted, thus, its efficacy is limited to empirical evidence. A study reported that the effect of povidone iodine solution on eradiation of *S. aureus* was similar to that of soap.[382] Side effects may include progression of dermatitis caused by irritation on the eroded surface, allergic contact dermatitis, anaphylaxis, and effects on thyroid function.[383,384]

Based on the above, the use of povidone iodine solution is poorly supported by medical evidence to be recommended for AD treatment, thus, this solution not recommended for general use. Povidone iodine solution may be considered as an adjuvant therapy for patients who are difficult to treat with first-line treatment with TCS and topical moisturizers and whose comcomitant skin infection would lead to additional difficulty in controlling the eczema.

REFERENCES

379 Rudikoff D, Lebwohl M. Atopic dermatitis. *Lancet* 1998; **351**: 1715–1721.

380 Sugimoto K, Kuroki H, Kanazawa M *et al*. New successful treatment with disinfectant for atopic dermatitis. *Dermatology* 1997; **195**(Suppl2): 62–68.

381 Uenishi T, Uehara M. Evaluation of popidone-iodine antiseptic solution. *Rinsho Derma (Tokyo)* 1998; **40**(Suppl 38): 984–987. (In Japanese).

382 Iijima S, Kuramochi M. Irritant contact dermatitis caused by 10% povidone-iodine solution after an operation. *Jpn J Dermatol* 1999; **109**: 1029–1041. (In Japanese with Engish Abstract).

383 Pedrosa C, Costa H, Oliveira G, Romariz J, Praca F. Anaphylaxis to povidone in a child. *Pediatr Allergy Immunol* 2005; **16**: 361–362.

CQ24. IS BLEACH BATH THERAPY RECOMMENDED FOR THE TREATMENT OF AD?

Recommendation

Bleach bath therapy is not currently recommended (the efficacy of bleach bath therapy has not been evaluated in Japan as there is no product available for use in humans).

Evidence level: B

Comments: It is known that *S. aureus* is more frequently isolated on the skin lesion in patients with AD than in the healthy population and has been considered a well known exacerbation factor of AD for some time.[380]

Therefore, eradication of *S. aureus* using disinfectants (e.g. povidone iodine solution, hypochlorous acid) has been attempted for treatment of AD.

Hypochlorous acid has been used as a disinfectant for a longer period of time in the United States and other countries, and the efficacy of bleach bath therapy, in which patients are take a bath with hypochlorous acid dissolved in water, has been reported in recent years.[385–387] The Cochrane Review has discussed the different approaches for the eradication of *S. aureus* as a treatment for AD. The results showed that improvement of disease was observed only with the use of bleach bath therapy.[388] The American Academy of Dermatology announced in 2014 that bleach bath therapy should be recommended as a treatment option for patients with moderate to severe AD and possible presence of infection.[6] Conversely, there have been some studies reporting that bleach bath therapy did not have better effects on skin barrier functions compared to the control group.[389,390]

There are no practical guidelines available for this approach in Japan, thus, future research and discussion are expected.

REFERENCES

384 Su-ming WON, Ting Guan NG, Roshidah BABA. Efficacy and safety of sodium hypochlorite (bleach)baths in patients with moderate to severe atopic dermatitis in Malaysia. *J Dermatol* 2013; **40**: 874–880.

385 Ryan C, Shaw RE, Cockerell CJ, Hand S, Ghali FE. Novel sodium hypochlorite cleanser shows clinical response and excellent acceptability in the treatment of atopic dermatitis. *Pediatr Dermatol* 2013; **30**: 308–315.

386 Huang JT, Abrams M, Tlougan B, Rademaker A, Paller AS. Treatment of Staphylococcus aureus colonization in atopic dermatitis decreases disease severity. *Pediatrics* 2009; **123**: e808–e814.

387 *Eczema: Bleach Bath Therapy*, www.aad.org. Accessed September, 20, 2015.

388 Hon KL, Tsang YC, Lee VW *et al*. Efficacy of sodium hypochlorite (bleach)baths to reduce Staphylococcus aureus colonization in childhood onset moderate-to-severe eczema: a randomized, placebo-controlled cross-over trial. *J Dermatolog Treat* 2016; **27**: 156–162.

389 Shi VY, Foolad N, Ornelas JN *et al*. Comparing the effect of bleach and water baths on skin barrier function in atopic dermatitis: a split-body randomized controlled trial. *Br J Dermatol* 2016; **175**: 212–214.

CQ25. IS THE USE OF SUNSCREEN RECOMMENDED FOR THE PREVENTION OF PROGRESSION OF AD?

Recommendation

As excessive exposure to sunlight is an exacerbating factor of eruption in AD, using sunscreen products that do not contain an ultraviolet (UV) absorbing agent should be considered when spending extended periods of time outdoors during seasons and periods of the day when exposure to ultraviolet light may be more intense.

Recommendation grade: 2, *evidence level*: C

Comments: There are only a few clinical studies examining the worsening, protective or treatment effects of sunscreen on eruption in AD (sunscreen, UV cut).[391]

Ultraviolet light has an inhibitor effect on immune-related cells of the skin, thus, improvement of eruption in AD can be

expected.[392,393] Indeed, UV light therapy is occasionally performed under the surveillance of doctor to improve eruption and itching in AD.

Conversely, given that high temperatures on the skin surface and sweating, due to the action of infrared radiation, a part of sunlight, may worsen erythema or itching of the eczematous lesion, and ultraviolet light may cause decrease in skin barrier functions,[394,395] an excessive exposure to sunlight may be an exacerbating factor for eruption in AD.[392,396]

As AD is not known to be photosensitive, strict protection from sunlight is not necessary. However, precautions are recommended, for example, wearing a hat and walking in shadows as much as possible when outdoors between May and August under intense UV light, especially between 10 to 14 o'clock when the amount of UV light is at its maximum. The use of sunscreen is recommended when exposure to UV light is prolonged. Recommended sunscreens are as those that have the following characteristics: are easy to apply, have a certain degree of protection from UV light (SPF and PA are the indexes), without chemical ultraviolet absorbing agents (non-chemical), and containing an UV scattering agent.[397] However, sunscreens should not be used on weeping and moist lesions or scared lesions resulting from severe scratching. If possible, a sample of the product should be tested in a small area on the arm for several days to confirm there are no contraindicating issues.

REFERENCES

390 Uchida M, Miki K, Mitsui T *et al*. *In vitro* and clinical evaluation of SSP UV-care cream for children with atopic dermatitis. *J Pediatr Dermtol* 2003; **22**: 132–137. (In Japanese).

391 Moriwaki S. Point of daily life guidance about ultraviolet light exposure for patients with atopic dermatitis. In: Katoh N, ed. *Q&A55 Atopic Dermatitis Answered by Experts*. Tokyo: Sindan To Chiryo Sha, 2014; 121–123. (In Japanese)

392 Juzeniene A, Moan J. Beneficial effects of UV radiation other than via vitamin D production. *Dermatoendocrinol* 2012; **4**: 109–117.

393 Biniek K, Levi K, Dauskardt RH. Solar UV radiation reduces the barrier function of human skin. *Proc Natl Acad Sci U S A* 2012; **109**: 17111–17116.

394 Nin M, Katoh N, Kokueruptionanda O, Yoshikawa T, Kishimoto S. Dichotomous effect of ultraviolet B on the expression of corneodesmosomal enzymes in human epidermal keratinocytes. *J Dermatol Sci* 2009; **54**: 17–24.

395 Deguchi H, Danno K, Sugiura H, Uehara M. Sun exposure is an aggravating factor responsible for the recalcitrant facial erythema in adult patients with atopic dermatitis. *Dermatology* 2002; **204**: 23–28.

396 Uchida M, Miki K, Mitsui T *et al*. *In vitro* and clinical evaluation of SSP UV-care cream for children with atopic dermatitis. *J Pediatr Dermtol* 2013; **22**: 179–185.

CQ26. ARE INSTRUCTIONS TO AVOID KEEPING PETS OR TO AVOID CONTACT WITH ANIMALS EFFECTIVE TO PREVENT THE DEVELOPMENT OF AD OR TO IMPROVE SYMPTOMS?

Recommendation

As a history of keeping a pet and history of contact with animals in childhood do not always lead to an increased risk of developing AD. Thus, instructions to avoid contact with animals cannot be recommended for all patients.

After careful consideration of the association between worsening of eruption and contact with animals in patients whose symptoms may be worsened by contact with animals and have tested positive to animal-derived specific IgE allergens, avoidance should be considered if it is felt that this would lead to an improvement of the patient's QOL.

Evidence level: C

Comments: Based on 26 reports from 21 birth cohort studies, the results of meta-analysis examining the effects of keeping a pet and contact with animals during pregnancy, infancy, and childhood indicate there is a higher risk of developing AD. According to the results, a history of keeping a pet dog decreased the risk of developing AD, while a history of keeping a pet cat did not have any effect on the risk of developing AD.[398] Some studies have reported that contact with animals including pets during childhood (especially before 1 year of age) stimulated the development of the immune system and lead to the prevention of the onset of AD.[399–401] In particular, a history of keeping a pet dog may have more preferable effects.[400,401]

Conversely, in a postal questionnaire survey on children's allergies involving parents in Sweden who have children aged 1 to 6 years old, the relationship between pet allergy and asthma, allergic rhinitis, and eczema was identified.[402] In a self-administered questionnaire survey on allergy conducted in primary school children aged 6 to 12 years old in the United Arab Emirates, children having birds or cats as pets were associated with an increased morbidity due to allergic diseases.[403]

Animal allergens may be involved in the exacerbation of symptoms in AD [404]. Patients with animal allergen-specific IgE are considered to potentially experience worsening of their symptoms due to contact with the relevant animal. In recent years, the number of patients positive to cat-specific IgE has been increasing despite not having a cat as a pet, while testing for animal allergies is often positive.

Based on the above, avoidance of keeping a pet or any contact with animals during childhood may not always be necessary, however, it should be kept in mind that there are contrasting opinions. Although patients positive to animal-specific IgE are considered to be subjected to worsening of dermatitis following exposure to pets, the pet may be deeply involved in mental stability of the patient. Therefore, it is desirable to provide appropriate instructions on keeping pets or contact with animals after having carefully considered the relationship between exacerbation of eruption and contact with the animal giving the highest priority to the patient's QOL.

REFERENCES

397 Pelucchi C, Galeone C, Bach JF, La Vecchia C, Chatenoud L. Pet exposure and risk of atopic dermatitis at the pediatric age: a meta-analysis of birth cohort studies. *J Allergy Clin Immunol* 2013; **132**: 616–622.

398 Dharmage SC, Lodge CL, Matheson MC, Campbell B, Lowe AJ. Exposure to cats: update on risks for sensitization and allergic diseases. *Curr Allergy Asthma Rep* 2012; **12**: 413–423.

399 Bufford JD, Reardon CL, Li Z *et al*. Effects of dog ownership in early childhood on immune development and atopic diseases. *Clin Exp Allergy* 2008; **38**: 1635–1643.
400 Zirngibl A, Franke K, Gehring U *et al*. GINI study group: exposure to pets and atopic dermatitis during the first two years of life. A cohort study. *Pediatr Allergy Immunol* 2002; **13**: 394–401.
401 Bröms K, Norbäck D, Eriksson M, Sundelin C, Svärdsudd K. Prevalence and co-occurrence of parentally reported possible asthma and allergic manifestations in pre-school children. *BMC Public Health* 2013; **13**: 764.
402 Bener A, Galadari I, Naser KA. Pets, allergy and respiratory symptoms in children living in a desert country. *Allerg Immunol (Paris)* 1995; **27**: 190–195.
403 Schäfer T, Heinrich J, Wjst M *et al*. Indoor risk factors for atopic eczema in school children from East Germany. *Environ Res* 1999; **81**: 151–158.

ACKNOWLEDGMENTS: This study was supported by Grant-in-Aid for Scientific Research from the Ministry of Health, Labour and Welfare, Japan (as a Research Project on Measures for Intractable Diseases [Research on Allergic Disease and Immunology]).

CONFLICT OF INTEREST: None declared.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Facial eruption in an infant.
Figure S2. Lichenified eruption in a child.
Figure S3. Erythematous eruption on the face and neck in adult/adolescent patients.
Figure S4. Erythematous eruption on the trunk in an adult/adolescent patient.
Figure S5. Lichenified eruption in an adult/adolescent patient.
Figure S6. Pruriginous papules in an adult/adolescent patient.
Figure S7. Contact dermatitis.
Figure S8. Seborrheic dermatitis (infant).
Figure S9. Seborrheic dermatitis (adult).
Figure S10. Prurigo simplex.
Figure S11. Scabies.
Figure S12. Cutaneous lymphoma, A: mycosis fungoides, B: Sézary syndrome.
Figure S13. A, B: Dermatomyositis in a child.
Figure S14. severe swelling/edema/infiltration or erythema and multiple papules (Severe).
Figure S15. Severe erythema with lichenification and multiple papules (Severe).
Figure S16. Severe scales and crusts (Severe).
Figure S17. Vesicles and erosion (Severe).
Figure S18. Multiple excoriations (Severe).
Figure S19. Pruriginous nodules (Severe).
Figure S20. Moderate erythema, scales, a few papules and excoriations (Moderate).
Figure S21. Dryness, mild erythema and scales (Mild).
Figure S22. Dryness with negligible inflammation (Slight).