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GUIDELINES

English version of clinical practice guidelines for the management of atopic dermatitis 2024

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Abstract

This is the English version of the 2024 clinical practice guidelines for the management of atopic dermatitis (AD). AD is a disease characterized by relapsing eczema with pruritus as a primary lesion. A crucial aspect of AD treatment is the prompt induction of remission via the suppression of existing skin inflammation and pruritus. To achieve this, topical anti-inflammatory drugs, such as topical corticosteroids, tacrolimus ointment, delgocitinib ointment, and difamilast ointment, have been used. However, the following treatments should be considered in addition to topical therapy for patients with refractory moderate-to-severe AD: oral cyclosporine, subcutaneous injections of biologics (dupilumab, nemolizumab, tralokinumab), oral Janus kinase inhibitors (baricitinib, upadacitinib, abrocitinib), and phototherapy. In these revised guidelines, descriptions of five new drugs, namely, difamilast, nemolizumab, tralokinumab, upadacitinib, and abrocitinib, have been added. 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.

KEYWORDS
atopic dermatitis, clinical practice guidelines, decision-making, evidence-based medicine, treatment

1 | CHAPTER I

1.1 | Introduction

Atopic dermatitis (AD) is frequently encountered in clinical practice. Two clinical practice guidelines had been available for the management of AD in Japan. The first guideline was published by the Japanese Dermatological Association (JDA) and was designed for dermatologists who treat patients with AD from primary care to advanced specialty-required phases of treatment.[1–6] The second guideline was published by the Japanese Society of Allergology (JSA) and research groups of the Japanese Ministry of Health, Labour and

Junichi Furuta is the chairperson, and Yukihiro Ohya is the vice chairperson of the Committee for Clinical Practice Guidelines for the Management of Atopic Dermatitis 2024.

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For affiliations refer to page 55.

Welfare (MHLW), whose expected users were physicians, but not dermatologists, and who are involved in the management of allergic diseases.[7–13] In 2018, the clinical practice guidelines for all physicians and healthcare professionals engaged in medical care for patients with AD were published following the consolidation of the two practical guidelines.[14,15] The present guideline is a revised edition of clinical practice guidelines for the management of AD 2021,[16,17] which was a revised edition of the consolidated guideline 2018, updated with novel findings (generally, manuscripts published by the end of October 2023 are referred to) regarding AD published in Japan and other countries.

Descriptions regarding medical activities in the present guidelines reflect the goals in the current strategies to treat AD in Japan from the perspective of evidence-based medicine. They can be utilized as tools for the evaluation of decision-making in clinical practice. Attending physicians must make a final decision in cooperation with patients to reflect their values and preferences.

1.1.1 | 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. By contrast, even if the recommendations in the present guidelines are not performed, the responsibilities of physicians may not be pursued. The application of these guidelines as a basis for use in medical disputes or in medical litigation deviates from their original purpose.

Some evidence-based therapies (from Japan and other countries) 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 the latest information regarding safety.

1.1.2 | Conflict of interest

According to the criteria for conflicts of interest (COI) at the institutions of each committee member or the "COI management guidelines" and the "Guidance on eligibility for participation in the formulation of clinical practice guidelines" of the Japanese Association of Medical Sciences, the committee members of the present guidelines disclosed their COIs for the past 3 years until the inauguration, and for each year until the publication of the guidelines. The costs to develop the guidelines have been supported by research grants from the JDA and JSA. The members of this committee did not receive any rewards for the development of the guidelines or participation in related meetings. There has been no intervention by the JDA or JSA that could influence the contents of the guidelines. To avoid any influence by potential COIs on the guidelines, all recommendations were determined based on consensus voting, rather than on individual opinion. With respect to voting on clinical questions (CQs), committee members with financial, academic, or other COIs beyond the regulations were required to abstain from voting, although they could participate in the discussion. Concerning CQs regarded as non-specialty by each committee member, it was possible to choose to abstain from voting. Furthermore, the contents were polished with reference to the opinions of the representatives of the JDA and JSA (public comments).

Members of the committee for the guidelines and their relatives, defined as within the first degree of consanguinity, self-reported whether they received remuneration that corresponds to one of the following categories from companies or other bodies involved in the diagnosis or treatment of AD (the target period was between January 1, 2019, and December 31, 2023): (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) traveling costs or gifts relevant to a company/organization. For disclosure of COI and abstained CQs for each committee member, please refer to the JDA's website (https://www.dermatol.or.jp/modules/guideline/index.php?content_id=25).

1.2 | Definition, pathophysiology, epidemiology, diagnosis, and severity

1.2.1 | Definition of AD: Concept of disease

Atopic dermatitis is pruritic, eczematous dermatitis. Its symptoms chronically fluctuate with remissions and relapses. Most individuals with AD have atopic diathesis: (i) personal or family history (asthma, allergic rhinitis and/or conjunctivitis, and AD) and/or (ii) predisposition to overproduction of immunoglobulin (Ig) E antibodies.

Atopic dermatitis is an eczematous skin disease characterized by symmetrical distribution, and the skin areas typically affected vary depending on age.[16,17] 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. Adolescent-/adult-onset AD also occurs, but with low incidence.

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.[18] Urticaria is not considered when investigating family and medical history. Total serum IgE levels and allergen-specific IgE antibody levels are considered disease markers, for the tendency to produce IgE antibodies. As the 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 disease marker.

1.2.2 | 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 the skin, which may be caused by causative factors (physical constitution) and the vulnerability of barrier functions. The lack of hierarchy among those etiologies contributes to the diverse symptoms or phenotypes of AD.

Skin hypersensitivity: Abnormalities of the horny cell layer. The horny cell layer is a thin membrane structure of 10–20 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 (Figures 1 and 2). Dysfunction in the barrier of the horny cell layer results in enhanced cytokine production in the epidermis, activation of the Langerhans cells,[19] allergen sensitization, and inflammation. Furthermore, skin irritability to non-specific stimuli is also enhanced. 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 in ceramide content, and the moisture retention capacity is impaired.[20,21] 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 the formation of a strong barrier on the skin surface. Filaggrin loss-of-function mutation and filaggrin deficiency associated with inflammation have been observed in AD.[22,23]

Abnormalities of the epidermis. The epidermis also plays an important skin barrier function. The epidermis has an intercellular adhesion structure known as tight junctions (Figure 1). Specifically, the tight junctions located in the granular layer regulate the movement of substances from inside to outside the body. A 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.[24,25]

Mechanisms involved in inflammation. The application of various external stimuli to sensitive skin leads to the production and release of interleukin (IL)-33, IL-25, and thymic stromal lymphopoietin (TSLP) from the epidermal keratinocytes. The activation of type 2 innate lymphoid cells (ILC2) and T helper 2 (Th2) cells by these agents induces type 2 inflammation, leading to the production of IL-4, IL-5, IL-13, and IL-31 (Figure 2). A decline in skin barrier function may allow allergens to easily penetrate the skin. Allergens, which are foreign (non-self) molecules, are eliminated through immune responses and excessive immune responses induce allergic reactions. Allergens, such as the dust mite allergen, induce type 2 immune reactions through protease activity.[16,17] Type 2 immune responses lead 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. In addition, thymus and activation-regulated chemokine (TARC) is produced from the inflamed skin, promoting the infiltration of Th2 cells into the lesion site. Th22 cells produce IL-22 after migrating to the skin, likely via regulation by activated cutaneous dendritic cells, which induces epidermal acanthosis.[26] The involvement of basophils in the inflammation and the infiltration of other T-cell subsets (Th1 and Th17 cells) into the skin lesion have also been reported, but their roles in the pathogenesis remain to be elucidated.

Pruritus. Chronic pruritus, a key symptom of AD that is involved in its pathogenesis, significantly impairs the quality of life (QOL) of patients. Scratching in response to pruritus impairs the function of the skin barrier and exacerbates inflammation.

Chemical mediators such as histamine, cytokines, and chemokines involved in peripheral inflammation in AD induce pruritus.

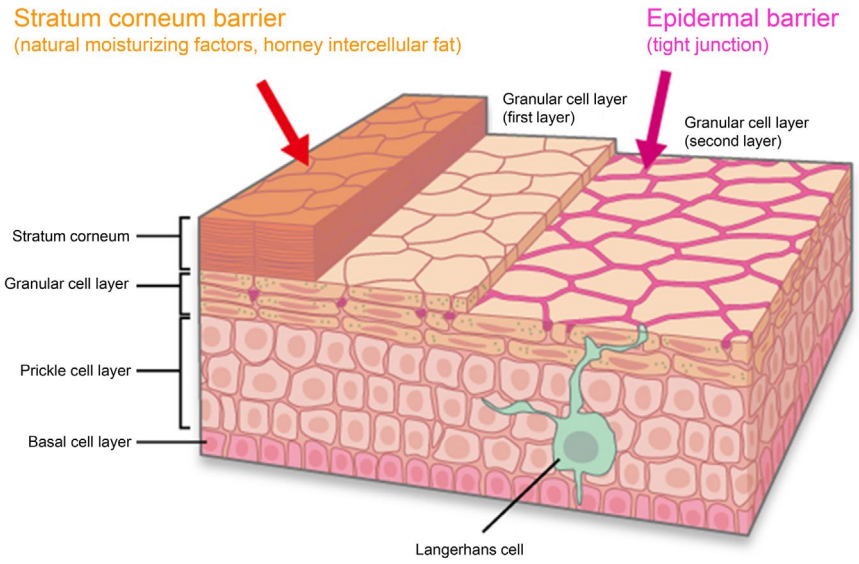


FIGURE 1 Construction of epidermal barrier.

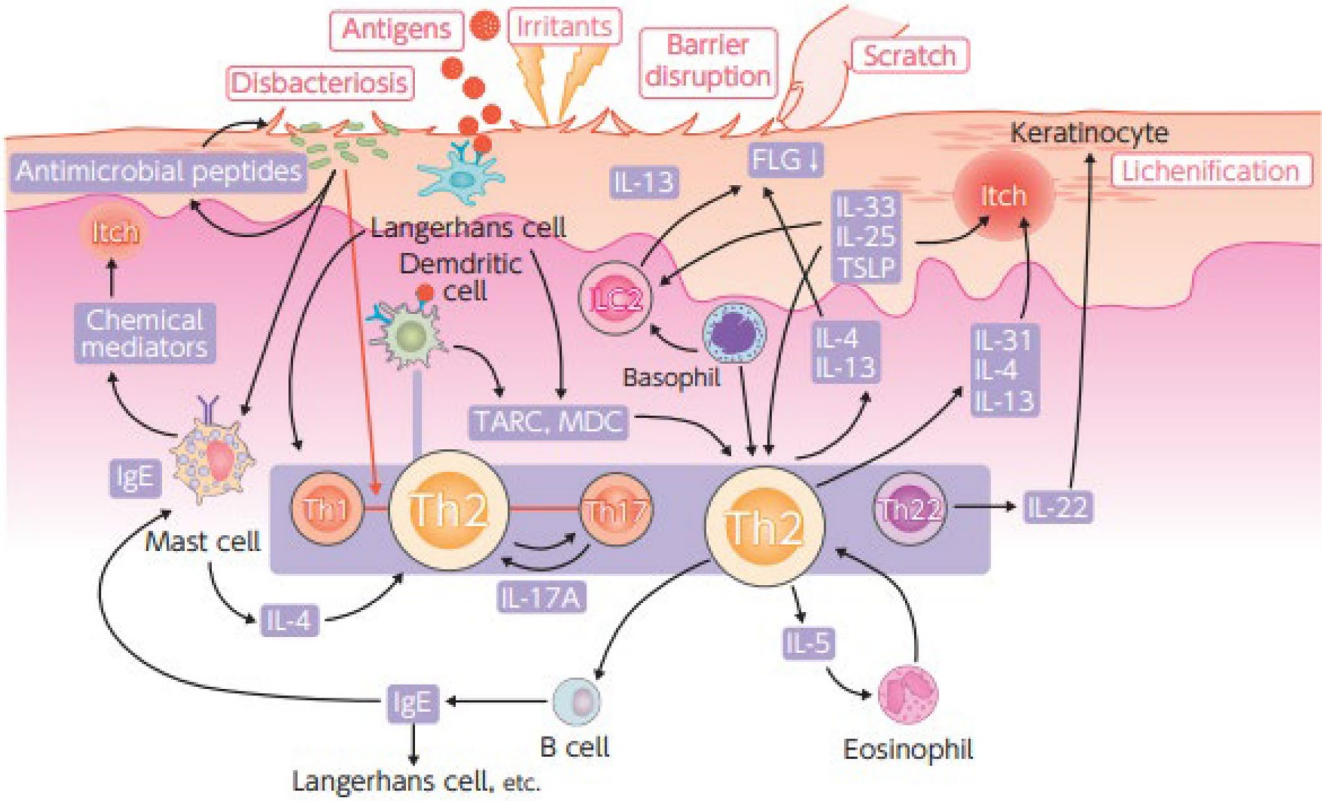


FIGURE 2 Pathogenesis of atopic dermatitis.

AD lesions are characterized by the presence of high levels of histamine,[27] an activated amine primarily released from resident mast cells in the tissues, and high concentrations of histamine are present in the tissues. Histamine activates histamine type 1 receptors (H1R) on the sensory neurons, inducing acute pruritus. The involvement of histamine in the pathogenesis of pruritus in AD is considered partial, and H1R antagonists are used to provide some relief from pruritus (CQ19).[28] Exposure to dryness, scratching, or chemical stimuli leads to the release of the cytokines TSLP and IL-33 from the epidermis. TSLP and IL-33 act as triggers for type 2 inflammation and induce pruritus by directly acting on the sensory neurons.[29,30] IL-31 has been identified as a substance that directly stimulates sensory neurons, leading to acute pruritus. Thus, it is a representative cytokine involved in the immune–neuronal correlation of pruritus.[31,32] IL-31 enhances the irritability of nerves in the skin.[33] High levels of IL-31 have been detected in the skin lesions of AD, with the serum levels of IL-31 showing a correlation with the disease activity.[34,35] Monoclonal antibodies against IL-31 receptor A have demonstrated efficacy in improving pruritus in patients with moderate-to-severe AD (CQ17).[36] IL-4 and IL-13 act on IL-4 receptor α (IL-4Rα). Accumulated evidence from anti-IL-4Rα monoclonal antibody therapy has confirmed the significance of IL-4 and IL-13 as effector molecules in patients with AD.[37–39] IL-4Rα is expressed on sensory neurons, and IL-4 and IL-13 directly activate these neurons in vitro.[40] In contrast to pruritogens, such as IL-31, which induce acute pruritus in vivo, IL-4 and IL-13 induce chronic pruritus by enhancing the sensitivity of sensory neurons to other pruritogens, such as histamine, IL-31, and TSLP.[40]

The central nervous system is thought to be involved in the induction of pruritus in patients with AD. The urge to scratch prompted by the visual/auditory stimuli to recall pruritus is induced by the central nervous system without the involvement of the skin. This urge is stronger and more pronounced in patients with AD than in healthy individuals.[41]

1.2.3 | Genetic factors

Some genes have been described as candidate genes associated with AD: *CTLA4*, *IL18*, *TLR9*, *CD14*, *CARD4*, *PHF11*, *TLR2*, *SCCE*, *MCC*, *IL4R*, *GMCSF*, *TIM1*, *CARD15*, *GSTT1*, *SPINK5*, *SCYA11*, *TGFβ1*, *IL13*, *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*), and 20q13 (*CYP24A1/PFDN4*) have been reported to be an AD-related region based on genome-wide linkage analysis from Japanese samples.[41]

1.2.4 | Factors involved in onset and exacerbation

Regarding clinical pathology, factors associated with disease onset and worsening should be considered. In addition to adherence to treatment, exposure to environmental factors including allergens and stimuli in the workplace and daily environment, lifestyle factors, and temperature, in addition to dysregulation of physiological changes in skin function are associated with the maintenance and exacerbation of dermatitis. A feeling of warmth, sweating, wool fibers, psychological stress, food, alcohol consumption, and common colds are considered particularly important as inducing and exacerbating factors of itch in AD.[43] Details regarding the onset and exacerbating factors and their specific measures will be discussed below.

1.2.5 | 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.[44] This was a large-scale questionnaire survey conducted across 56 countries. The results demonstrated 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 aged 13–14 years, ranging from 0.8% in Albania to 17.7% in Nigeria. Overall, the prevalence rate was higher in Oceania and Northern Europe, whereas it was lower in Asian countries and Eastern Europe. The highest prevalence was observed in Sweden (18.4%, among children aged 6–7 years; 14.5% among those aged 13–14 years), followed by Finland (14.5% in children aged 13–14 years).

Another epidemiological survey was conducted from 2001 to 2003 by ISAAC (Japan did not participate).[45] Some countries that had previously reported a higher prevalence among 13- to 14-year-old children in phase I of the study presented 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 cases decreases with age. Expectedly, 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 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%–32% in infants, 5%–27% in preschool children, 5%–15% in school-age children, and 5%–9% in university students; the overall prevalence tended to decrease with increasing age.[46] 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.[47,48] Base facilities were set-up in Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku, Shikoku, and Kyushu, and medical examinations were performed by specialists. Figure 3a exhibits 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), 13.2% (906/6868), 11.8% (1479/12489), 10.6% (1185/11230), and 8.2% (684/8317) in 4-month-old infants, 1.5-year-old children, 3-year-old children, first graders, sixth graders, and university students, respectively. Although the prevalence rate by district is believed to be higher in cities and lower in suburban areas, no significant difference in the prevalence rates among school children was observed between cities and suburban areas in this survey. Moreover, no differences in rates between boys and girls were 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 through medical examinations performed on 4826 university staff members of Tokyo University, Kinki (Kindai) University, and Asahikawa Medical University.[47] 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 (Figure 3b). The prevalence rates stratified by sex were 5.4% and 8.4% in male and female participants, respectively, indicating 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 presents the distribution of patients with AD by severity from individuals aged 1.5 years to university students in a nationwide epidemiological survey. The proportions of patients with moderate, severe, or very severe AD according to age were 16%, 15%, 24%, 28%, and 27% for 1.5-year-old infants, 3-year-old children, first graders, sixth graders, and university students, respectively.[47] Based on these results, worse symptoms were generally more often exhibited in school-aged children than in preschool children. The proportions of patients with severe or very severe AD according to age were 1.7%, 2.2%, and 5.5% in first graders, sixth graders, and university students, respectively, showing a tendency for AD to increase in prevalence with age.

The distributions of AD according to severity based on the medical examination survey conducted among university staff of Tokyo University, Kindai University, and Asahikawa Medical University were 80.1%, 17.7%, 1.5%, and 0.6% for mild, moderate, severe, and very severe cases, respectively. The proportion of patients with moderate, severe. or very severe AD was smaller in individuals in their 40s or older than in individuals in their 20s and 30s (Figure 4b).[49]

Annual changes in prevalence. The number of patients with 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. Accordingly, the AD prevalence was

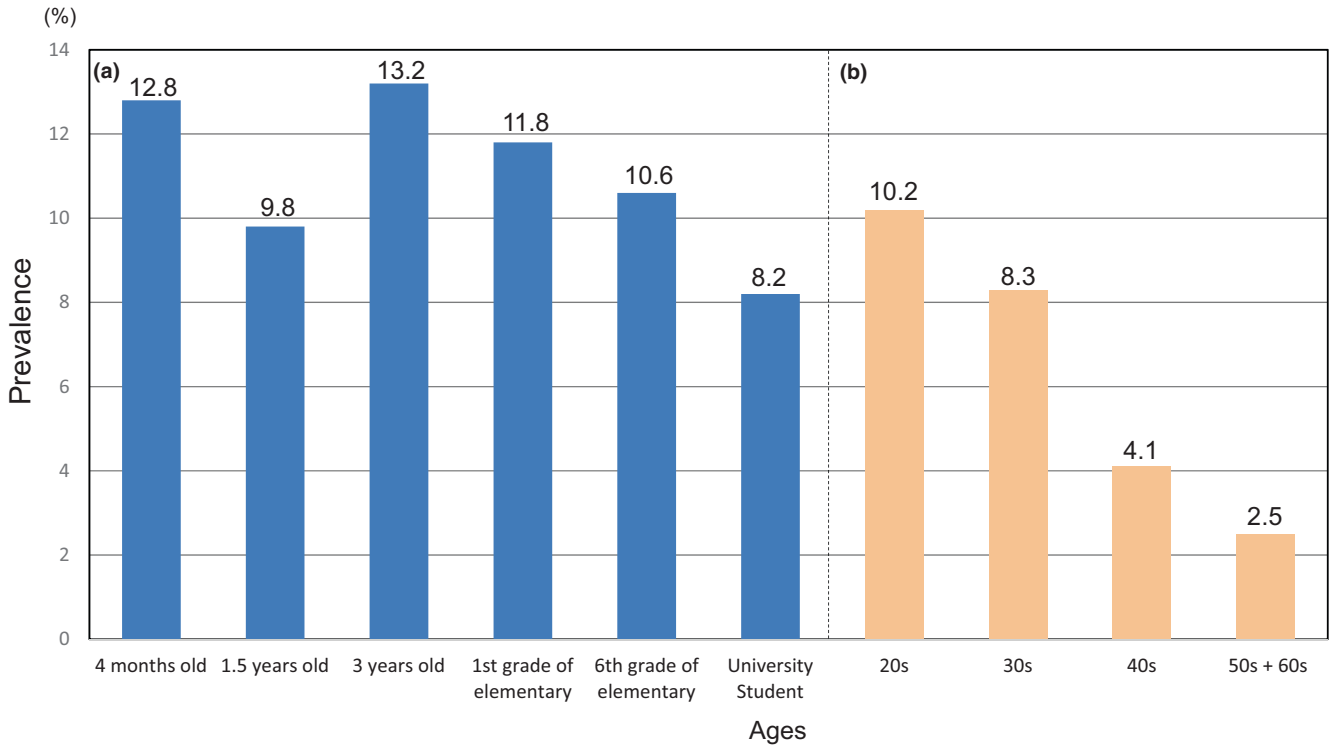


FIGURE 3 Prevalence of atopic dermatitis by age (survey year: [a] fiscal year 2000–2002 and [b] fiscal year 2006–2008).[40–42] Children aged 4 months from Hokkaido, Kanto, Chubu, Kinki, Chugoku, Shikoku, and Kyushu (seven districts, $n = 2744$). Children aged 1.5 years, 3 years, first graders, and sixth graders in elementary school from Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku, Shikoku, and Kyushu (eight districts, $n = 6424$). University students from the University of Tokyo, Kindai University, and Hiroshima University ($n = 8317$). Adults (20s–60s) were personnel of the University of Tokyo, Kindai University, and Asahikawa Medical University ($n = 2943$). Modified from the Ministry of Health and Welfare, Japan.[40–42]

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.[50]

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- and 3-year-old children respectively, in 1992.[51] A slight difference was found in the survey method used between the nationwide survey conducted during the 2000–2002 period and the survey conducted in 1992; nonetheless, the number of infants reported to have AD may have increased. In an allergic disease prevalence survey conducted in elementary-school children living in western Japan, the prevalence rate of AD in 2002 was lower than that in 1992, although this was a questionnaire-based survey.[52] Conversely, in an epidemiological study using ISAAC questionnaires on the prevalence of allergic diseases in schoolchildren (aged 7–15 years) in Kyoto City, the prevalence of AD increased slightly from 4.2% (1996) to 5.6% (2006).[53]

Studies on the prognosis of AD

Studies abroad. In Italy, Ricci et al.[54] 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. During the follow-up period, complete remission of AD was observed in 60.5% of children. Sensitization to eggs 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 age 1 year, and the cumulative prevalence rate at 2 years of age was 21.5%.[55] 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. In China, Zhang et al. followed 260 children who developed AD before age 2 years. The remission rates at 6 and 12 years were 50.8% and 70.3%, respectively. Factors such as severity, family history of asthma, and sensitization to food contributed to the persistence of AD.[56]

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 patients aged ≥20 years at the initial consultation for 25–38 years, symptoms persisted in the latter 12 months of follow-up in more than half of the patients.[57]

Studies in Japan. Regarding the onset and clinical course of AD during infancy, the Health Labor Sciences Research 2006–2008

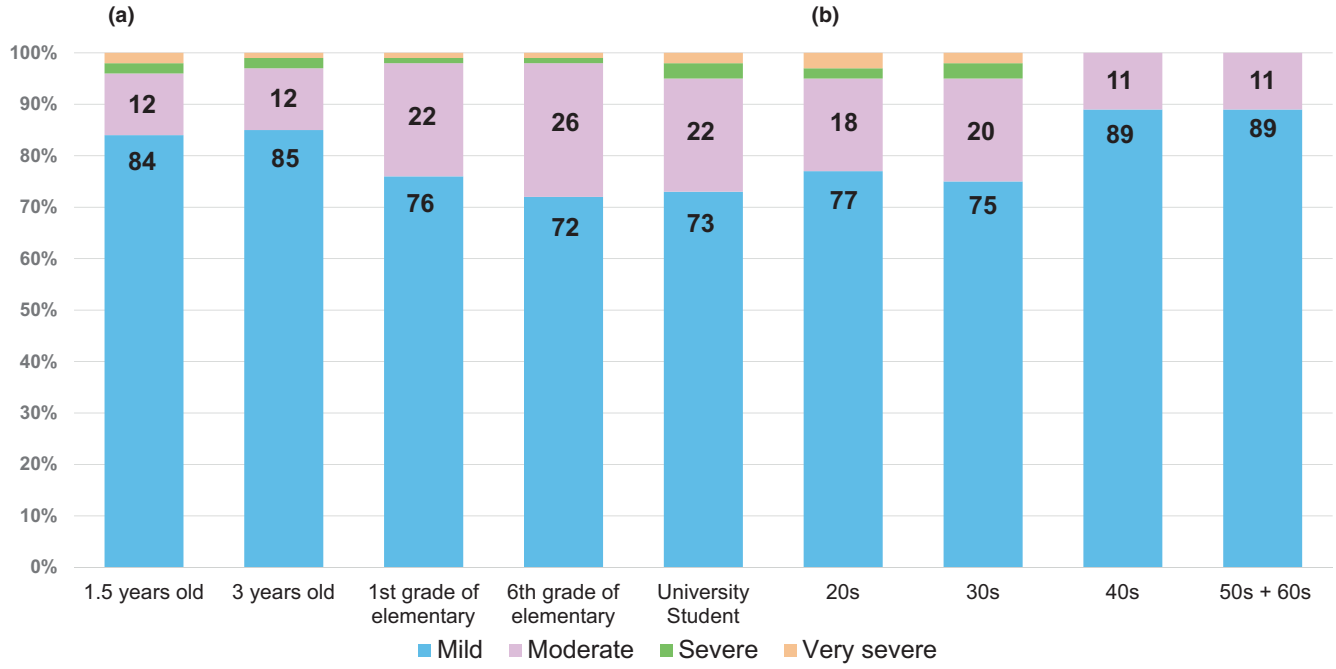


FIGURE 4 Atopic dermatitis by severity (survey year: [a] fiscal year 2000–2002 and [b] fiscal year 2006–2008).[40–42]

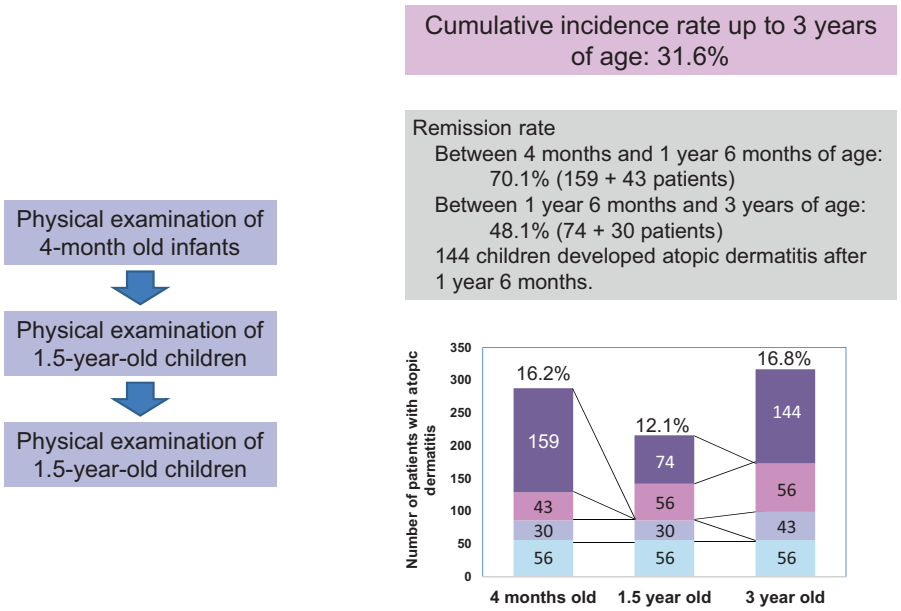


FIGURE 5 Onset and clinical course of atopic dermatitis based on an individual follow-up study from 4 months after birth to age 3 years (survey year: fiscal year 2006–2008).[50]

study reported the results of a survey in which infants were followed up from age 4 months to 3 years 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 (Figure 5).[58] Interestingly, 70% of the children diagnosed with AD within 4 months demonstrated complete remission at age 1.5 years. In this survey, the cumulative onset rate up to age 3 years was ≥30%, which is very similar to the rates reported in studies from abroad. Fukiwake et al.[59] (Kyushu University) examined kindergarten children in the Ishigaki Island for 4 years and reported that 53 of 74 (71.6%) children diagnosed with AD experienced complete remission within 3 years, whereas 5.5% of the children not previously diagnosed with AD, were eventually diagnosed with new-onset AD within 3 years.

Ohshima et al.[60] followed up 169 infants aged <1 year diagnosed with AD by pediatric allergy specialists for 4 years and reported that Symptoms imprroved in 51% and disappeared in 34 %, respectively. Shibuya and Saito[61] conducted a birth-cohort survey involving infants or children aged ≤4 years and reported that the remission of AD was achieved at age 4 years in 30 (75%) of 40 children diagnosed

with AD at age 1 year. Yamamoto-Hanada et al.[62] performed a birth-cohort study involving the general population (T-CHILD study) and confirmed that AD can be classified into four types (never/infrequent, 62.7%; early onset, 17.8%; late onset, 9.5%; persistent, 10.1%) based on the follow-up course for 9 years. Furthermore, they conducted a multicenter birth-cohort survey involving the general population (JECS cohort) and reported that the prevalence rates of AD symptoms at age 1, 2, and 3 years were 4.0%, 7.3%, and 6.0%, respectively.[63] Anan et al. conducted a questionnaire survey among family members of patients considered to have achieved a spontaneous remission and reported that spontaneous remission was observed starting at age 2–3 years, and 50% of the children achieved spontaneous remission at age 8–9 years. Approximately 90% of children achieved spontaneous remission after age 16 years.[64] Wakamori et al. reported that three-quarters of children who had AD at the first grade of elementary school experienced remission before entering junior high school. The study surveyed AD outcomes in elementary school children and junior high school children using dermatological medical examination data spanning over 10 years in the mountainous areas of Kyoto prefecture.[65] Katoh et al.[66] investigated the prognosis of AD in adulthood; the number of affected patients gradually decreased from a peak in patients aged 20–30 years, and by age 40, two-thirds of the patients experienced improvement to the level where they no longer needed to visit the dermatological department.

1.2.6 | 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, namely, (i) pruritus, (ii) typical morphology and distribution of eczema, and (iii) a chronic or chronically relapsing course (Table 1).[16,17] Patients suspected of AD are regarded as having acute or chronic eczema, and diagnoses are made based on their age and disease course. Thus, it is essential to differentiate the disorders that should be ruled out in the diagnosis of AD and be familiar with the complications of AD. Internationally, the diagnostic criteria prepared by Hanifin and Rajka in 1980[67] and by the UK Working Party[68] are widely used.

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. Symmetrical distribution.

Predilection sites: forehead, periorbital area, perioral area, lips, periauricular area, neck, joint areas of limbs, and 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: often 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 consideration of severity.
Other cases should be evaluated based on 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), and 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), and high serum total 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, and erythroderma type; combinations of types are common.

Significant complications:

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

Note: Cited from Ref. [16].

1.2.7 | Characteristics of eruption

Infancy (aged <2 years). 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 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 surrounding areas. With a slight delay following the occurrence of facial symptoms, exudative erythema develops in intertriginous zones such as the neck, cubital fossa, and popliteal fossa; moreover, erythema and papules develop on the thoraco-abdominal region, back, and extremities (Figure S1).

Childhood or school age (2–12 years old). From early childhood to school age, eruptions on the face decrease, but eruptions are

typically observed on the neck, cubital fossa, popliteal fossa, inguinal area, wrist, and ankle.[69] In severe cases, eruptions extend to the face and limbs, and 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 or adulthood (aged ≥13 years). After puberty, eruptions are more likely to develop on the upper body including the face, neck, chest, and back. In some cases, facial-type eruptions markedly affecting the face to neck or a prurigo-type eruption consisting of multiple papules of the trunk and extremities with strong itching is observed. In severe cases, eruptions extend throughout the body resulting in erythroderma (Figures S3–S6).

Site of eruption. While eruptions can develop in any body area, eruptions develop more rapidly and intensely in regions influenced by external factors. Generally, eruptions develop symmetrically.

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

Acute lesions occur at the initial onset or 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 are considered eczema erythema, and may include serous papules. When the epidermis is damaged by disease progression or scratching, exudative fluid leaks from the lesion, which leads to crust formation.

Chronic lesions are eruptions that have transitioned mainly due to scratching. Repeated scratching results in a thickened skin because of mechanical irritation forming lichenified lesions and prurigo nodularis.

1.2.8 | Differential diagnosis

The main differential diagnostic criteria to consider when distinguishing diseases from AD are presented below. These diseases may occur in association with AD.

Contact dermatitis. In this disease, eczema develops on a site where an allergen has come into contact with an individual sensitized to that antigen. 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 if eruptions are localized only on the face or other regions and are refractory to treatment, or if a localized eczema lesion is asymmetrical (Figure S7).

Seborrheic dermatitis. Erythema and scales develop on seborrheic sites (i.e., scalp, eyebrows, mesophryon, forehead, sulcus nasolabialis, pinna and back pinna, axilla, anterior chest, umbilical region, and genitals, etc.). Itching is generally mild. Lipophilic fungi such as *Malassezia furfur* that 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); thereafter, it often naturally resolves within 1–2 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 the sulcus nasolabialis, is a differential diagnosis point (if present, it is highly likely to be AD).

Prurigo simplex. Papules or small nodules develop with a strong itch. Generally, uniformly sized papules or small nodules often develop and spread. Insect bites 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 a history of atopy can help in the diagnosis (Figure S10).

Scabies. Scabies is caused by *Sarcoptes scabiei* infestation on the skin, and infection usually occurs following long-term contact with the skin, bedding, or clothes of the infected patients. Papules accompanied by severe 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 for microscopic observation. If mites or eggs are detected, the diagnosis can be confirmed.

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

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

Hand dermatitis (to distinguish hand dermatitis from AD). Eczema occurs on the hands following 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 stay-at-home parents. Eczema 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 in the 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 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. When making a diagnosis, differentiating from eruption due to AD is sometimes clinically challenging. When the diagnosis is uncertain, it is important to perform a skin biopsy to examine the pathological findings (e.g., presence of lymphocyte infiltration on the epidermis). Sézary syndrome is characterized by three features, namely, erythroderma, superficial lymph node swelling, and 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 dermato-histopathological 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 throughout the body including the palmar and plantar regions. Scales can be described as silvery white. Various eruptions, such as serous papules, and eczema erythema observed in patients with AD are generally not present in psoriasis. Pathological differential diagnosis based on a skin biopsy is useful.

Immune deficiency diseases

Wiskott-Aldrich syndrome. This is an X-linked recessive inherited 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 age 6 months. Purpura due to thrombopenia is also observed. It causes repeated infections such as impetigo contagiosa, herpes simplex, and candidiasis.

Hyper IgE syndrome (HIES). This syndrome is characterized by skin abscesses (cold abscess) and pneumonia (pulmonary cyst) caused by bacteria such as *S. aureus*, AD-like eczema lesion, and high serum total IgE levels. A definitive diagnosis can be made based on the clinical scoring system developed by the National Institute of Health (NIH)[70] 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 and dermatomyositis)

Systemic lupus erythematosus. This is an autoimmune disease with inflammatory lesions in multiple organs and commonly appears in young women. Representative cutaneous symptoms include a malar eruption and 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. A 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. The differential diagnosis can be made based on the characteristic eruption, systemic symptoms, and presence of abnormalities in blood tests such as anti-nuclear antibodies and anti-DNA antibodies.

Dermatomyositis. This is an autoimmune disease affecting the skin and muscles. Its clinical features are a characteristic eruption and muscle weakness starting at the proximal muscles. 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 trunk or shoulder. A characteristic eruption, muscle weakness, and blood test findings can help in the differential diagnosis (Figure S13A,B).

Netherton's syndrome. This 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 the hairs are short and break easily.

1.2.9 | Severity assessment

A precise severity assessment is essential for appropriate treatment selection. 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.

Assessment by doctors

Overall assessment of severity. Several methods are 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 the relative proportion of the lesions to the body surface area. Eruptions associated with severe inflammation, even partially, are classified as moderate or severe (Table 2). It is a simple and easy-to-use index for guiding treatment.

Severity classification methods with verified reliability and validity include the Atopic Dermatitis Severity Classification[71,72] developed by the JDA, the Severity Scoring of Atopic Dermatitis (SCORAD) index,[73] and the Eczema Area and Severity Index (EASI).[74] The SCORAD index and EASI are used internationally. The SCORAD index has been reported in many English language papers and is frequently used in clinical research and trials (Figure S14 in Japanese). The maximum score of the SCORAD index is 103, and

TABLE 2 Severity index.

Mild	Only mild eruptions[a] are observed irrespective of the area
Moderate	Eruptions with severe inflammation[b] are observed on less than 10% of the body surface area
Severe	Eruptions with severe inflammation are observed on ≥10% to <30% of the body surface area
Most severe	Eruptions with severe inflammation are observed on ≥30% of the body surface area

[a]Mild eruption: Lesions are seen chiefly with mild erythema, dry skin, or desquamation.
[b]Eruption with severe inflammation: Lesions with erythema, papule, erosion, infiltration, or lichenification.

its score can be calculated using a dedicated website (http://adserver.sante.univ-nantes.fr/Scorad.html). The EASI is recommended by the Harmonizing Outcome Measures for Eczema (HOME), an international multi-professional group dedicated to standardizing AD clinical research outcomes (http://www.homeforeczema.org/index.aspx) (Table S1 in Japanese). The EASI score chart can be downloaded from its dedicated website (http://www.homeforeczema.org/resources.aspx), and assessment training is available online. Either of the above methods can be selected; however, the simple "severity index" is recommended for routine clinical practice and the international EASI or SCORAD index for clinical research or trials. Furthermore, the Investigator's Global Assessment (IGA) of dermal lesions (0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe) is frequently used in clinical studies.

Assessment of eruption severity. The selection of topical steroids, a key treatment, depends on the "severity of individual eruptions."[16,17,75] That is, a sufficiently potent topical therapy is selected for severe eruption even though the affected area is limited, whereas a potent topical therapy is not necessary for milder eruptions even if the effects are more extensive. The severity of the eruption is categorized into 3–4 levels according to the above-mentioned assessment methods.

Assessment by patients

Assessment of pruritus. The degree of pruritus can be indirectly assessed by visually observing scratching behavior and its traces. When infants experience pruritus, they may attempt to scratch by rubbing their faces against the caregiver holding them. The accumulation of scales and bloody scabs along the edges of the nail are suggestive of scratching. The degree of pruritus can also be inferred from the frequency and extent of bleeding or exudates from the scratch marks adhered to the clothing or bedding.

Subjective assessment methods of the degree of pruritus include the numerical rating scale (NRS), visual analogue scale (VAS), behavioral rating scale for evaluating the degree of scratching behaviors and pruritus (Kawashima's criteria), and the 5D-itch scale.[76,77]

To evaluate the degree of pruritus objectively, the degree of nocturnal pruritus can be estimated by serially recording arm movement using a watch-type accelerator (ActiGraph®).[78] An application using the same principle, (e.g., the Itch Tracker®), facilitates the estimation of the degree of nocturnal pruritus by monitoring scratching behaviors during sleep with an accelerator installed in the Apple Watch®.[79]

A microphone-installed watch-type device for recording scratching sounds and evaluating the frequency of scratching behaviors and degree of pruritus is also reported.[80]

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

For adult patients, the Skindex-16 and Dermatology Life Quality Index (DLQI) can be used as QOL assessment questionnaires for cutaneous diseases including AD;[81–83] their Japanese versions are currently available (Tables S2 and S3, in Japanese).

A Japanese version of the Children's DLQI (CDLQI) is available for children (Table S4 in Japanese).[84,85] 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)[86] and its abbreviated version QP9 (9 items)[87] have been specifically developed to evaluate the QOL of primary caregivers (Table S5 in Japanese). The Japanese Culturally Modified Version of the Childhood Atopic Dermatitis Impact Scale (JCMV-CADIS),[88] a modified and translated version of the CADIS,[89] 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 (Table S6 in Japanese).

Other assessment. The Patient-Oriented Eczema Measure (POEM) is a severity scale, that 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/methodologicalresources/poem-for-self-completion.pdf; for children, https://www.nottingham.ac.uk/research/groups/cebd/documents/methodologicalresources/poem-for-proxy-completion.pdf) (Tables S7-1 and S7-2 in Japanese).[90–92] It is useful in sharing treatment goals between the physician and patient, and has been reported to correlate with the assessment by physicians. A self-administered patient-oriented SCORAD (PO-SCORAD) has also been reported.[93] Recently, validated, brief, and easily scored tools to comprehensively evaluate the state of AD control, such as the Recap of Atopic Eczema (RECAP) and Atopic Dermatitis Control Tool

TABLE 3 Biomarkers for the diagnosis of atopic dermatitis and disease progression.

Marker	Mechanism of increase	Reference level (upper limit)	Clinical implications
Serum total 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 level used as an outcome 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 keratinocytes 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	<1.6 ng/mL	It closely reflects disease progression of AD (approved as a diagnostic drug)

Abbreviations: AD, atopic dermatitis; IgE, immunoglobulin E; IL, interleukin; LDH, lactate dehydrogenase; SCCA, squamous cell carcinoma antigen; TARC, thymus and activation-regulated chemokine; Th2, T helper 2.

(ADCT), were developed[94,95] and recommended for evaluating long-term control by the HOME (http://www.homeforeczema.org/research/long-term-control.aspx).[96] A Japanese version of ADCT was created, with a score table being available for download on the website (https://www.adcontroltool.com/adct-downloads1). Similarly, Japanese versions of RECAP have been developed for adults and children.[97]

1.2.10 | 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 is commonly observed.[98] The 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, 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 relationship 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 with other allergic diseases such as bronchial asthma or allergic rhinitis. As the peripheral eosinophil count increases with disease severity, it can be a marker of disease progression.

Serum lactate dehydrogenase (LDH) level. Serum 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 a normal level when the eruption is resolved. Nonetheless, in cases in which LDH levels remain elevated, complications due to other diseases leading to tissue damage should be suspected and a differential diagnosis considered.

Serum TARC level. TARC (CCL17) is a ligand of the chemokine receptor CCR4 and induces Th2 cell migration.[99] The serum TARC level 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 serum total IgE levels, LDH levels, or peripheral eosinophil counts.[100,101] Moreover, patient education and treatment can be reviewed using serum TARC levels as an index.[102] However, test values should be carefully interpreted because TARC

levels are generally higher in younger children, especially in children aged <2 years.[103] The reference levels according to age are shown in Table 3. When treated with nemolizumab, serum TARC levels may transiently increase, exhibiting no correlation with the clinical symptoms; therefore, caution is required.[104]

Serum squamous cell carcinoma antigen (SCCA2) is a serine protease inhibitor that belongs to the serpin superfamily (serpin is derived from the SERine Protease INhibitor). It is classified into two proteins, SCCA1 and SCCA2, coded by the high-homology genes, *SERPINB3* and *SERPINB4*, respectively, which are located on chromosome 18q21.3.[105] They were first identified in patients with cervical carcinoma,[106] and they have been utilized for monitoring several squamous cell carcinomas.[96] Moreover, SCCA1 and SCCA2 are Th2-related molecules induced by IL-4 and IL-13,[107] and they play an important role in barrier dysfunction or skin inflammation in an AD animal model.[108] Thus, these proteins have also been clinically examined as important biomarkers in patients with AD. Particularly high serum SCCA2 levels have been observed in AD among individuals with pediatric allergic disorders,[109] showing a strong correlation with SCORAD and EASI and accurately reflecting treatment responsiveness.[110–112] Serum SCCA2 testing is covered by health insurance for children (aged ≤15 years). The reference range is unified regardless of age.[110]

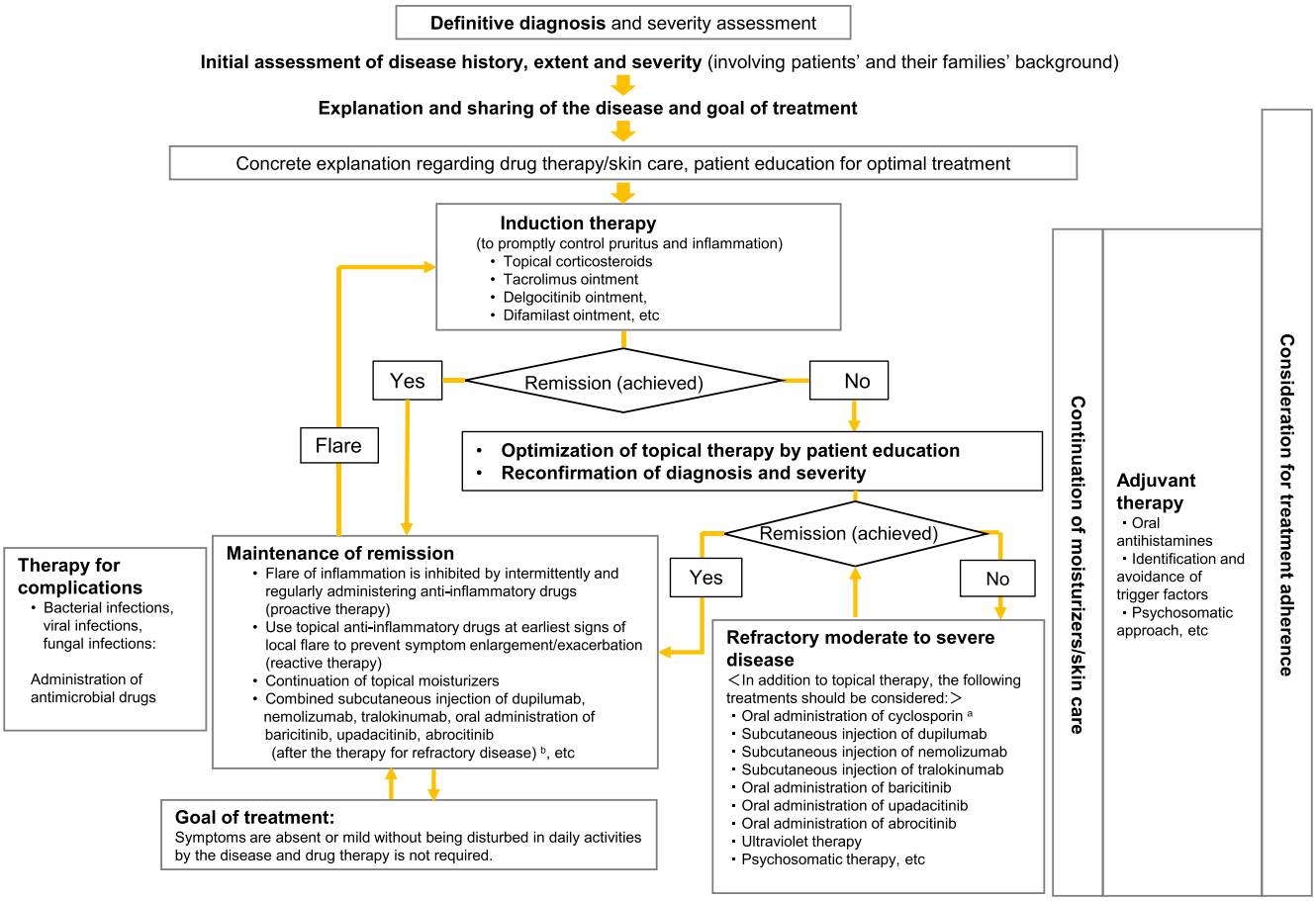
1.3 | Treatment approaches

1.3.1 | Goal of treatment

The goal of treatment is to reach and maintain a state in which symptoms are absent or mild without disturbance of daily activities 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.

1.3.2 | Treatment measures

Figure 6 illustrates the algorithm used for the management of AD. Making a definite diagnosis of AD and performing a severity assessment is the first essential step. The diagnosis of AD should be made



a: Administration should be completed in 8–12 weeks. Intermittent administration involving a 2-week or much longer period of discontinuation should be performed if longer-term administration is necessary.
b: If remission is maintained a specific period (6 months as a guide), the transient discontinuation of this drug should be considered after confirming the adequate use of topical anti-inflammatory drugs.

FIGURE 6 Algorithm for the management of atopic dermatitis.

in accordance with the definition and diagnostic criteria proposed by the JDA (Table 1). Furthermore, it is essential to accurately differentiate diagnoses to be excluded (although they may coexist). The overall severity of AD must be assessed based on criteria such as the "severity index" of AD (Table 2) after making the definitive diagnosis. Factors such as current medical history, past medical history, family history, and evaluation of the extent and severity of AD (including the social background of the patient and family) should be considered while making the definitive diagnosis and performing the severity assessment. In the treatment of AD, it is important to explain to the patient the disease and the goal of treatment and to share the goal with the patient. In addition, the patient must be provided with concrete explanations regarding drug therapy and skin care, and patient education for optimal treatment should be conducted. The prompt inducing of remission via the suppression of existing skin inflammation and pruritus is a crucial aspect of AD treatment. Topical anti-inflammatory drugs, such as topical corticosteroids (TCS), tacrolimus ointment, delgocitinib ointment, and difamilast ointment, are used to achieve remission. When the remission is achieved, it is important to maintain the remission. In cases where the inflammation is prone to flares, proactive therapy with regular intermittent administration of topical anti-inflammatory drugs can effectively suppress the flare of inflammation. Patients must continue skin care using moisturizers on days when topical anti-inflammatory drugs are not used. When there is minimal flare of inflammation, topical anti-inflammatory drugs must be used at the earliest signs of local flare to prevent the progression of symptoms and their exacerbation.

Topical therapy must be optimized via patient education if the remission cannot be achieved. A sufficient amount (referred to as finger-tip units) of an appropriate rank of topical anti-inflammatory drugs must be applied to the affected areas based on the severity of the eruption. In addition, the diagnosis of the severity of AD must be reconfirmed. A skin biopsy must be performed, if necessary, to exclude diagnoses such as cutaneous lymphoma. For patients with refractory moderate-to-severe AD, despite the confirmation of the diagnosis and optimization of topical therapy, the following treatments should be considered in addition to topical therapy: oral cyclosporine, subcutaneous injections of biologics (dupilumab, nemolizumab, and tralokinumab), oral Janus kinase (JAK) inhibitors (baricitinib, upadacitinib, and abrocitinib), phototherapy, and psychosomatic therapy. If the remission is achieved via the above-mentioned treatment strategies, the treatment goal should be aimed at maintaining the remission.

Atopic dermatitis is a multifactorial disease involving genetic predispositions. Currently, no treatment 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 a vicious cycle of inflammation. Therefore, controlling inflammation by drug therapy will also reduce AD-exacerbating factors.

1.3.3 | Drug treatment

Topical anti-inflammatory drugs. These drugs are used to provide adequate attenuation of inflammation in AD. The efficacy and safety of topical TCS, tacrolimus ointments (topical calcineurin inhibitor), delgocitinib ointments (JAK inhibitor), and difamilast ointments (phosphodiesterase 4 [PDE4] 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.[113] The efficacy and safety of TCS have been examined in many clinical studies.[114] TCS are often used as first-line anti-inflammatory topical agents for both children and adults.

Tacrolimus ointment is an inhibitor of calcineurin. Protopic ointment 0.1% was approved and introduced in 1999, and protopic ointment 0.03% was approved and introduced for use in children in 2003.

Delgocitinib ointment inhibits intracellular signal transduction (JAK). In 2020, CORECTIM® Ointment 0.5% was first approved and marketed in Japan.

Difamilast ointment inhibits the expression of PDE4. After receiving approval in 2021, Moizerto® Ointments 1% and 0.3% have been available in the market since 2022.

Other topical drugs 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 are narrow. It is important to promptly and effectively attenuate inflammation in AD; thus, combination strategies of TCS, tacrolimus ointments, and delgocitinib ointments should be considered a basis of treatment. The extent of inflammation should be appropriately understood by inspection and palpation to adequately apply these drugs to a sufficient degree.

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

If eruptions are stable with suitable treatment, AD can 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 4-week's treatment with topical drugs or severe cases, should be referred to a dermatologist.

Use of TCS

Selection of rank. A rank table of TCS, as a modification of Takeda's classification, is presented in Table 4.[16,17,75,115] 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). It is important to carefully 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).

TABLE 4 Rank of topical corticosteroids.

Strongest (Group 1)
0.05% clobetasol propionate
0.05% diflorasone diacetate
Very strong (Group 2)
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 (Group 3)
0.3% deprodone propionate
0.1% dexamethasone propionate
0.12% dexamethasone valerate
0.12% betamethasone valerate
0.025% fluocinolone acetonide
Medium (Group 4)
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 (Group 5)
0.5% prednisolone

Note: As of June 2023. Cited from Ref. [16] 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).[67] In Europe, they are classified into four ranks (very potent, potent, moderate potency, and mild potency).[104] When referring to international clinical trial data, it must be considered that the rank classification of topical corticosteroids differs from that in Japan.

Severe cases include primarily acute and progressive severe inflammatory lesions, retractable lesions such as lichenification, erythema, multiple papules, multiple scratch scars, or prurigo nodularis. The use of a very strong TCS is the first-line treatment (Figures S15–S20). When sufficient effects are not obtained from a very strong TCS, the strongest TCS is also available.

Moderate cases include primarily inflammatory findings of moderate or less severe erythema, scales, few papules, and scratch scar. The use of a strong or medium TCS is the first-line treatment (Figure S21).

Mild cases include primarily mild dry skin, mild erythema, and scales, and the use of a medium or weak TCS is the first-line treatment (Figures S22 and S23).[16,17]

Although there is no need to decrease the rank of the TCS 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, should be selected based on lesion characteristics or sites. Ointments should be the basic method selected to treat this disease, which involves dryness. On the other hand, when 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 preparations are basically used for scalp lesions. Tape preparations could 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)[16,17,116,117] (Table 6). This may be adopted as a reference, considering the physical status of Japanese individuals and the tube size of TCS available in Japan. On the other hand, the appropriate volume would change according to some factors including skin condition and vehicle of a topical drug.

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

	Severity of eruption	TCS application
Severe	Primarily severe swelling/edema/infiltration or erythema with lichenification, multiple papules, severe scales, crusts, vesicles, erosion, and multiple excoriations and pruriginous nodules	Use of very strong rank TCS with necessary and sufficient effects is the first-line treatment. Strongest rank TCS are sometimes selected/used for the site alone 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

Note: Cited from Ref. [16].

TABLE 6 Appropriate volume of topical corticosteroids (FTU).

Dose of topical drugs – FTU (1FTU = 0.5 g)					
Children	**Face and neck (g)**	**One arm (g)**	**One leg (g)**	**Trunk (front) (g)**	**Trunk (back) (g)**
3 to 6 months	1 (0.5)	1 (0.5)	1.5 (0.75)	1 (0.5)	1.5 (0.75)
1 to 2 years	1.5 (0.75)	1.5 (0.75)	2 (1)	2 (1)	3 (1.5)
3 to 5 years	1.5 (0.75)	2 (1)	3 (1.5)	3 (1.5)	3.5 (1.75)
6 to 10 old	2 (1)	2.5 (1.25)	4.5 (2.25)	3.5 (1.75)	5 (2.5)

Adults	**Face and neck (g)**	**One arm and hand (g)**	**One leg and foot (g)**	**Trunk (front) (g)**	**Trunk (back) (g)**
	2.5 (1.25)	3 + 1 (2)	6 + 2 (4)	7 (3.5)	7 (3.5)

Note: Cited from Ref. [16].

Abbreviation: FTU, fingertip unit.

Frequency of application. Generally, 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 is needed to determine whether efficacy differs between twice-a-day and once-a-day applications. However, several randomized controlled studies (RCTs) and systematic reviews have reported no significant difference in the efficacy between twice-a-day and once-a-day applications.[118,119] 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, TCS should be applied twice a day to control acutely exacerbated eruptions for an early recovery. When the condition subsides, TCS should be applied once a day to achieve remission.

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.[120] Such skin regions with a high drug absorption rate require attentive monitoring for the development of local side effects of TCS treatment; prolonged use should be avoided. For the face, medium or weak TCS are generally used, whereas drugs consistent with the severity rank are used for severe dermatitis to introduce prompt remission, and the drugs are then tapered gradually or administered intermittently. Moreover, an effort to transition from TCS to tacrolimus, delgocitinib, or difamilast ointment is made.

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

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.[121] In such cases, the patient should be referred to a dermatologist.

Side effects of TCS

Systemic side effects. The systemic side effects of TCS depend on the rank of steroids, application volume, and application period. The long-term massive-volume application of high-ranked TCS may induce such side effects.[122] Furthermore, they may often develop because of high level percutaneous absorption in a skin-barrier-reduced state such as erythroderma. In children, the percutaneous absorption rate is high, and the ratio of the body surface area to the bodyweight is also high; therefore, systemic side effects might occur.[122] They include suppression of the hypothalamus-pituitary–adrenal system, hypertension, hyperlipidemia, diabetes mellitus, moon face, and Cushing's syndrome.[122,123] Studies have suggested that TCS are not a risk factor for osteoporosis.[124–126]

However, such systemic effects may not occur in clinical practice for the following reasons. In skin lesions where the barrier function is reduced, the percutaneous absorption rate of steroids increases, and steroid application for extensive eruptions transiently suppresses the adrenal function. However, when barrier function recovery is achieved through anti-inflammatory effects, the percutaneous absorption rate of steroids rapidly decreases.[127,128] According to a study regarding the long-term use of very strong TCS, when starting at an initial dose of approximately 5 or 10 g/day in adults and gradually decreasing the dose in accordance with symptoms, there may be no irreversible systemic side effects even after 3 months of treatment, although transient, reversible adrenal function suppression may occur. A study reported that the occlusive dressing technique with a strong TCS, 0.12% betamethasone valerate ointment, at 10 g/day, or simple application at 20 g/day induced adrenal function suppression.[129] The percutaneous absorption rate after the simple application of the strongest TCS, (0.05% clobetasol propionate ointment, at 10 g/day) corresponds to that of betamethasone administered orally at 0.5 mg/day. The absorption rate after simple application at 40 g/day corresponds to that of betamethasone administered orally at ≤1 mg/day.[130]

However, it is highly exceptional to continue topical steroid therapy at such a large volume in clinical practice[127] because sufficient volume application promptly controls eczema lesions, leading to decreases in the TCS volume or extent of application and a reduction

in the steroid rank. Thus, if TCS are appropriately used, systemic side effects may not develop through standard application methods. Indeed, in a meta-analysis of studies regarding AD in children treated with steroids for ≥2 weeks, the rate of patients with suppression of the hypothalamus-pituitary–adrenal system was 3.8%, and there was no association with symptoms of adrenal failure. When stratifying the patients with respect to low-, medium-, and high-potency steroids, the rates of those with suppression were 2.0, 3.1, and 6.6%, respectively.[131]

We cannot conclude that TCS have no systemic side effects;[123] therefore, when administering massive TCS volume for a long period or when applying TCS to the lesions where the barrier function is reduced, sufficient examinations of systemic side effects, such as adrenal function suppression, must be periodically conducted. In such cases, adequate management, such as a combination of TCS therapy and systemic treatment other than oral steroid administration, should be considered to achieve a dose reduction of TCS.

Local side effects. Local side effects may develop through the immunosuppressive, cell-proliferation- or stroma-production-suppressing, and hormonal actions of steroids.[128] Local side effects of TCS include telangiectasia, skin atrophy, striae cutis (striae distensae and striae atrophicae), purpura, rosacea-like dermatitis or perioral dermatitis, hypertrichosis, depigmentation, delayed wound healing, contact dermatitis, acne or folliculitis, and cutaneous infection with bacteria, fungus, or viruses such as herpes simplex, molluscum contagiosum, tinea corporis, and scabies.[122,123,127,128,132–134]

Local side effects depend on the steroid rank, application period, application site, and patient age. They may occur when high-ranked steroids are used, steroids are used over a long period, they are applied to areas with high absorption rates, such as the face and genital area, and they are used in older people.[122,128] Such side effects are also influenced by the type of base. The percutaneous absorption rate of cream is higher than that of ointment.[128] Some are based on the specificity of the site, and rosacea-like dermatitis and perioral dermatitis are side effects on the face where the pilosebaceous system is developed.

Most local side effects resolve with the discontinuation of TCS or adequate treatment.[127,133] However, striae cutis is irreversible. The percutaneous absorption rate of steroids is high in the axilla, inguinal region, and genital area, often causing striae cutis.[127]

The incidence of the local side effects of TCS can be reduced by selecting an adequate rank and limiting the application period to a necessary one based on the grade or site of eruptions and age. When the skin condition improves, the steroid rank should be adequately reduced, or TCS may be intermittently used. Switching to tacrolimus, delgocitinib, or difamilast ointment after reducing inflammation with TCS is also a good method. A study suggested that the use of tacrolimus ointment reduced the dose of steroid ointment, markedly reducing the local side effects of TCS.[134]

The incidence of local side effects increases with age because the cumulative frequency of TCS usage increases. However, these side effects do not occur in all patients. Furthermore, the incidence of side effects in patients aged <2 years is low.[133] Therefore, the necessary TCS should be adequately used without getting excessively anxious, paying attention to the appearance of local side effects.

Pigmentation is sometimes observed after the use of TCS. However, this is post-inflammatory pigmentation related to persistent dermatitis, and it becomes apparent when TCS application leads to the disappearance of inflammation; such a pigmentation is not related to TCS.[127] Instead, to prevent pigmentation, topical anti-inflammatory medications, including TCS, should be used in the early stage for the dermatitis to sufficiently subside.

Adverse reactions to TCS in the eyes. The frequent application of high-ranked TCS may induce cataracts,[135,136] but it is not always associated.[137,138] On the contrary, AD itself is a risk factor for cataracts. It is also associated with facial eruptions, and the onset of cataracts may be related to eye-rubbing or scratching activities (CQ6).[138–143] Severe cataract occurrence was frequently observed in patients inadequately treated with drugs other than TCS, supporting its association with the severity of eruptions, but not with TCS.[144] Many case reports on TCS-related glaucoma have been published. The use of high-ranked TCS, frequent applications, or a prolonged application period increases the risk of such a glaucoma (CQ6).[135] Specifically, TCS use around the eyes may increase the intraocular pressure or risk of glaucoma.[135] When low-ranked TCS are used, the risk is low.[145]

Strong TCS should not be used around the eyes, unnecessarily and chronically for a long period. After improvement is achieved by TCS therapy, the condition should be maintained with tacrolimus ointment.[136,146]

How should anxiety about steroids be addressed?

Owing to the misconceptions about treatment with TCS, fears about TCS or avoidance often reduces adherence. Concretely, the side effects of orally administered steroids are wrongly regarded as those of TCS, or the deterioration of AD as the side effects of TCS. Furthermore, misusage makes it impossible for each patient to consider TCS effective, leading to a feeling of distrust for TCS in some cases. To resolve these misconceptions, patients should be educated and instructed by sufficient consultation. Furthermore, the presence of the side effects of TCS should be examined on consultation, and it is important to establish a strong relationship between the healthcare professional and patient by selecting TCS in accordance with symptoms and explaining the frequency of application.

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 demonstrate a high level of effectiveness for AD-related eruption, which was difficult to treat with TCS because of adverse reactions (CQ7: Recommendation grade 1, Evidence level: A).

The efficacy of this drug depends on its absorption, application site 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 TCS: tacrolimus ointment cannot be applied to erosive or ulcerative surfaces, and its drug efficacy is limited. This drug must be administered according to the

"Guidance for the Application of Tacrolimus Ointment in Patients with Atopic Dermatitis."[147] Tacrolimus ointment is available as 0.1% for adults and 0.03% for children. It cannot be selected for children aged ≤1 year as its safety has not yet been established for this age group. Its application should also be avoided in lactating women.

Volume of application. 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 an area 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 (bodyweight ≥50 kg).

Way of application. Irritative symptoms, such as a transient burning sensation and hot flushes, often appear at application sites. However, these symptoms appear at the start of treatment, and most symptoms disappear with improvements in eruptions. This should be explained to patients before the start of treatment. This ointment is very effective for the face and neck, and 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 administer TCS because of adverse reactions.

The efficacy of this ointment (0.1% for adults) for the trunk and limbs may be similar to that of strong TCS.[147] Generally, when treating the site of severe eruption, which requires potent drug efficacy, very strong or the strongest TCS should initially be used to reduce eruption. The regimen should then be switched to tacrolimus ointment. The TCS volume can be decreased in many cases by combining it with this ointment. If an improvement in eruption is achieved by this ointment, the interval of application should be prolonged at an appropriate time.

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

Adverse reactions. Burning sensation, pruritus, and erythema have been identified as local adverse events. These symptoms decrease or disappear with improvements in eruptions in many cases. Furthermore, the appearance of infectious diseases of the skin, such as secondary skin infections with bacteria and viruses (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 in blood levels of tacrolimus have been reported 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 to patients the precautions for use written in the package insert and should obtain their consent.

Risk of carcinogenesis. Evidence showing that the use of tacrolimus ointment does not increase the risk of skin cancer or lymphoma is increasing (CQ8: Evidence level: B). Although previous studies have 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 eruptions before the use of this ointment may have been lymphoma.[148,149] In addition, a previous study indicated that severe AD increased the risk of lymphoma. Therefore, AD may increase the incidence of lymphoma. Regarding the safety of the long-term use of tacrolimus ointment for children for the treatment of childhood AD, no malignant tumor was found as an adverse event based on the results of follow-up for 10 years maximum in Japan.[150] However, 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 or application period and the development of malignant neoplasms must be analyzed through a long-term follow-up.

Delgocitinib. Delgocitinib is a JAK inhibitor that is important for the signal transduction of various cytokines. It inhibits all types of JAK family kinases (JAK1, JAK2, JAK3, and tyrosine kinase 2), suppressing the activation of immune cells.[152] Some clinical studies involving patients with moderate to severe adult AD have reported significant improvement in the eruption score in the 0.5% delgocitinib ointment group in comparison with the vehicle group,[153,154] and a phase 3 trial targeting pediatric patients with AD aged 2–15 years demonstrated that delgocitinib at concentrations of 0.5% and 0.25% was more effective in improving eruptions than the vehicle.[155] As topical side effects, folliculitis, acne, Kaposi's varicelliform eruption, herpes simplex, and contact dermatitis have been reported.[153–155] Moreover, based on the results of a phase 3 trial (QBB4-2 study) evaluating the efficacy and safety of 0.25% and 0.5% delgocitinib ointment during a 52-week period of application in mild to severe patients with AD aged 6 months to less than 2 years, in an open-label, non-controlled design, delgocitinib became available for use for pediatric (infant and toddler) patients aged 6 months and older, starting from January 30, 2023.[156]

The administration of delgocitinib in excessive doses may induce systemic effects via the increased percutaneous absorption rate.[153–157] Thus, delgocitinib ointment should be used according to its administration method or usage: "for adults, twice a day, with a single application not exceeding 5 g;" "for children aged ≥6 months, twice a day, with a single application not exceeding 5 g based on the body size;" and "the application area should not exceed about 30% of body surface area." Application to erosive or mucosal surfaces, the occlusive dressing technique, and pasting a cloth on which zinc oxide ointment is spread increase percutaneous absorption; therefore, these should be avoided.[158] As delgocitinib ointment exhibits immunosuppressive actions, much attention must be paid to prevent its

application to the site of cutaneous infection. During administration, folliculitis, acne, and cutaneous infection, such as herpes virus infection, including Kaposi's varicelliform eruption, must be considered. If these occur, the application of this agent to the corresponding site should be discontinued and adequate infectious disease treatment must be performed. With respect to information on the safety of delgocitinib ointment and combination therapy with other treatment methods, please refer to the "Manual for the safe use of delgocitinib ointment (CORECTIM® Ointment 0.5%)."[158]

Difamilast. Difamilast exhibits selective inhibitory effects on PDE4, a member of the PDE family that is present in several immune cells. It can selectively resolve cyclic adenosine monophosphate (cAMP). Difamilast increases the intracellular cAMP levels in inflammatory cells and epithelial cells by inhibiting PDE4 and suppresses the inflammation of the skin by controlling the production of inflammatory cytokines and chemokines.[159]

Some clinical studies have reported significant improvement in the eruption and pruritus scores in patients in the difamilast ointment group in comparison with that in the vehicle group.[160,161] Hyperpigmentation, folliculitis, pruritus, impetigo, acne, and contact dermatitis have been reported as topical side effects of difamilast.[159]

Adults are instructed to apply 1% difamilast ointment twice daily, whereas children are instructed to apply an appropriate amount of 0.3% difamilast ointment to the affected area. The recommended application amount is approximately 1 g/0.1 m^2 of the eruption. Application on eroded surfaces, occlusive dressing, and pasting a cloth with zinc oxide ointment should be avoided as they increase percutaneous absorption.[162] There is minimal concern for an increase in clinically significant adverse events when using difamilast ointment with TCS, tacrolimus ointment, or delgocitinib ointment. Concurrent use of difamilast with these drugs is considered feasible; however, caution must be exercised as data regarding the application of these drugs to the same site are lacking.[162] For women of childbearing age, it is advisable to provide guidance on practicing appropriate contraception methods, during and for a certain period after, the administration of difamilast. The administration of this drug to pregnant women and those who may be pregnant is not recommended.[159] Please refer to the "Manual for the safe use of difamilast ointment (Moizerto® ointment 0.3% and 1%) for the safe use of this drug.[162] The use of difamilast in children aged ≥3 months (including infants) was approved from December 11, 2023.

NSAIDs. These drugs 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 with those of TCS; thus, no evidence can support their efficacy in AD. NSAIDs are not included in the Guidelines for Management of Atopic Dermatitis in Western countries.[146,164] Side effects of NSAIDs include contact dermatitis and potential exacerbation of eczema. Specifically, the use of bufexamac is associated with a potentially high-risk of contact dermatitis; therefore, the European Medicines Agency has recommended discontinuing the marketing of bufexamac across Europe. In response to this recommendation, Japan also banned the sale of all bufexamac-based preparations. Benefits from NSAIDs for the treatment of AD are poor; thus, NSAIDs are not recommended in light of the potential side effects.

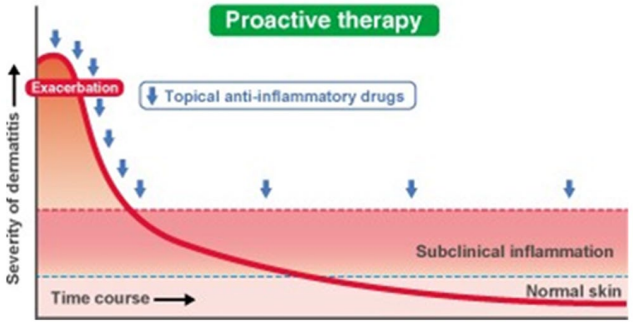


FIGURE 7 Reactive therapy and proactive therapy.

Proactive therapy. This therapy is used to maintain remission via the intermittent application of TCS or tacrolimus ointment (e.g., twice a week) to recurrently relapsing eruptions, in addition to skin care with moisturizing topical drugs, after obtaining remission with treatments in the acute phase (Figure 7, CQ11: Recommendation grade 1, Evidence level A). By contrast, reactive therapy is used to control inflammation with anti-inflammatory topical drugs on relapse. Reactive therapy should be used in areas less prone to relapse, as it is difficult to maintain remission in areas susceptible to relapse or where dermatitis has become chronic. Topical anti-inflammatory drugs should be applied to such areas intermittently to maintain remission.

In AD, histological evidence of inflammatory cells is still present despite the normally appearing skin following the resolution of inflammation; inflammation can easily relapse because of external or internal factors.[165,166] 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 tacrolimus ointment may prevent relapse of inflammation.[167] However, it is important to transit from the 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 any slight elevation of the skin on palpation. Moreover, the dose, application range, and time to complete the treatment of topical drugs should be determined individually for each patient. The development of side effects should also be carefully monitored. Proactive treatment is necessary for collaboration with a physician experienced in the evaluation of cutaneous symptoms of AD or cutaneous symptoms in general.

A previous study indicated that the improvement in AD induced by acute-phase treatment for 1–3 months had a positive impact on the condition the skin 1 year later.[168] When adopting proactive therapy, it is important to initially and promptly induce remission. During proactive therapy, daily skin care with moisturizing topical drugs should be continued.

Oral anti-inflammatory drugs

Cyclosporin. The efficacy of cyclosporin for AD has been demonstrated in many countries in Europe and USA.[169] It has been approved for use by patients with AD (CQ12: Recommendation grade 2, Evidence level A). In Japan, it was approved for very severe AD patients (eruptions with marked inflammation comprising ≥30% of the body surface area), aged ≥16 years, in whom sufficient effects are not obtained by conventional treatment, in October 2008.[170]

Notably, this drug has exhibited remarkable efficacy in the management of refractory erythema on the face and erythroderma. Furthermore, the prompt alleviation of pruritus achieved after the administration makes it useful for improving the QOL in patients with multiple prurigo and notable excoriations. The initial dose of this drug is 3 mg/kg/day. It should be increased or decreased in accordance with symptoms, but in a manner that does not exceed 5 mg/kg/day. The treatment should be completed in 8–12 weeks. During administration, the occurrence of nephropathy, hypertension, and infection must be considered, and the blood concentration of this drug (trough level) should be periodically measured. 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 for 2 weeks or a much longer discontinuation period should be implemented if long-term administration is necessary.

Cyclosporin is administered orally after meals twice a day. However, a pharmacokinetic study involving patients with psoriasis reported that the blood concentration of this drug was higher when administered before eating once a day.[171] Therefore, the therapeutic effects of once-a-day administration before meals may be more marked than those of twice-a-day administration after meals.

Oral JAK inhibitors.

Baricitinib. Baricitinib is a selective, reversible JAK1/JAK2 inhibitor. It suppresses inflammatory or immune responses by inhibiting the JAK1-/JAK2-mediated intracellular signal transduction of cytokines.[172,173]

Several clinical studies of baricitinib have demonstrated that it significantly reduced clinical symptoms, such as eruptions and pruritus, in comparison with a placebo, and improved the QOL, including sleep (CQ13).[174–177] Side effects include infectious diseases (inflammation of the upper airway, herpes simplex, including Kaposi's varicelliform eruption, herpes zoster, cellulitis, and pneumonia), cardiovascular events, and deep venous thrombosis (CQ13).[178,179] As this drug is highly effective, it is appropriate for inducing and maintaining remission.[174–177]

Baricitinib should be indicated for patients with AD in whom conventional treatment is ineffective and be administered orally to adults at 4 mg once a day. However, the dose should be decreased to 2 mg in accordance with the patient's condition, such as moderate renal dysfunction. Clinical studies have demonstrated that the effects of combination therapy with TCS are more potent than those of monotherapy. Thus, the application of topical anti-inflammatory drugs, such as TCS and moisturizers, should be continued along with the administration of this drug (CQ13).[175,176] Before the use of this drug, physicians must sufficiently understand and follow the "Guidelines for promoting optimal use: Baricitinib (trade name: Olumiant tablets 2 mg, 4 mg), -AD-"[180] prepared by the MHLW in cooperation with the Pharmaceuticals and Medical Devices Agency (PMDA), JDA, JSA, and Japan Organization of Clinical Dermatologists (JOCD).

Patients for whom baricitinib is indicated should be carefully selected, and whether its administration should be continued must be adequately evaluated. Furthermore, the management of side effects is necessary and institutions or patients where or to whom this drug is available are established in the above guidelines and described below.[180]

Concerning institutions where this drug is available, all of the following criteria: (i–iii) must be met.

(i) Institutions

A physician who is familiar with the pathogenesis, course, prognosis, diagnosis, and treatment of AD and has sufficient knowledge about this drug (who has accomplished clinical training for dermatological care for ≥5 years after the completion of initial training for 2 years after medical-license acquisition, or has a ≥6-year career of clinical experience after the completion of initial training for 2 years after medical-license acquisition [has accomplished clinical training for the treatment of allergic diseases, including AD, for ≥3 of the 6 years]) is deployed as a person responsible for treatment regarding this drug in the corresponding department.

As a post-marketing survey for evaluating the safety and efficacy of this drug after manufacturing or sales is necessary, the institution should be appropriate for conducting this survey adequately.

At the institution, it is possible to periodically perform tuberculosis or hepatitis B virus infection tests and measure the neutrophil count, lymphocyte count, hemoglobin level, transaminase level, renal function test parameters, and lipid levels in reference to the guidelines for promoting optimal use.

(ii) In-hospital drug information management system.

(iii) A system to manage pharmaceutical information, such as the efficacy or safety, from pharmaceutical companies and to manage or utilize drug information, including the adequate management of adverse events and prompt reporting, must be arranged.

(iv) Management of side effects

Requirements regarding the facility system. A system to provide admission management in accordance with serious side effects, such as serious infection, promptly obtain the results of examinations, such as computed tomography, necessary for the differentiation of side effects, and manage emergencies in the corresponding or affiliated institutions must be arranged.

Physicians who have specialized knowledge and experience regarding immunosuppressive therapy must monitor side effects.

A system to promptly provide adequate treatment in cooperation with specialists belonging to the corresponding or neighborhood medical institutions with respect to the following safety matters (important

specified risks:*, Herpes zoster, serious infectious diseases including tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, and opportunistic infection), gastrointestinal perforation, reactivation of hepatitis B virus, interstitial pneumonia, venous thromboembolism, neutropenia, lymphopenia, decreased hemoglobin level, and liver dysfunction and important latent risks**(Rhabdomyolysis, myopathy, malignant tumors, and cardiovascular events) described in the drug risk management protocol must be arranged.

Concerning patients to be treated, patients should meet both of the following criteria:

(i) Patients definitively diagnosed with AD in reference to the present guidelines.
(ii) Adults with AD in whom sufficient effects were not obtained by treatment with topical anti-inflammatory drugs (a), with a specific level or higher of disease activity (b), or those in whom treatment with topical anti-inflammatory drugs alone is difficult because of hypersensitivity to topical steroids or calcineurin inhibitors or marked topical or systemic side effects, with a specific level or higher of disease activity (b).
   a. Adequate treatment with TCS (strong class or higher) or calcineurin inhibitors, as recommended in accordance with the severity in the present guidelines, has been employed for the past ≥6 months.
   b. The condition should meet all of the following criteria:
      (i) IGA score ≥3
      (ii) EASI score ≥16 or having eruptions with marked inflammation involving an extensive area of the face (EASI score for the head and neck ≥2.4 as a guide)
      (iii) The rate of AD lesions as a percentage of the body surface area is ≥10%.

Based on these recommendations, the following contents must be written in the remarks column of certificates of medical remuneration.[181]

(i) An institution where a person responsible for the treatment using this drug meets one of the following requirements for physicians (should be described as "Institution requirement A" or "Institution requirement b").

   A: A physician who has accomplished clinical training for dermatological care for ≥5 years after the completion of initial training for 2 years after medical-license acquisition.
   B: A physician who has a clinical career of ≥6 years after the completion of initial training for 2 years after medical-license acquisition. For ≥3 of the 6 years, the physician has accomplished clinical training for the treatment of allergic diseases, including AD.

(ii) Status of treatment with topical anti-inflammatory drugs before the administration of this drug (should be described as "Pretreatment requirement A" or "Pretreatment requirement B").

   A: Adults with AD in whom adequate treatment with TCS (strong class or higher) or calcineurin inhibitors, as recommended in accordance with the severity in the present guidelines, has been performed for the past ≥6 months.
   B: Adults with AD in whom it is difficult to continue treatment with the topical anti-inflammatory drugs alone because of hypersensitivity to TCS or calcineurin inhibitors or marked topical or systemic side effects.

(iii) Values of all items described below as the state of disease activity:

   A: IGA score.
   B: EASI score for the whole body or head and neck.
   C: Rate of AD lesions as a percentage of the body surface area (%).

For continuous administration, information at the start of administration must be written in the remarks column of certificates of medical remuneration.

In the guidelines for promoting optimal use, the administration of this drug should be discontinued if there is no treatment response in 8 weeks after the start of administration with respect to the continuation of administration. Furthermore, dose reduction to a 2 mg once-a-day administration should be considered if a treatment response is achieved. In addition, if remission is maintained by combination therapy with topical steroids or calcineurin inhibitors for a specific period (6 months as a guide), the transient discontinuation of the administration of this drug should be considered after confirming the adequate use of these topical anti-inflammatory drugs or moisturizers. However, in many cases, the continuous administration of this drug may be required to maintain remission. In such cases, this drug may be continuously administered.

Upadacitinib. Upadacitinib is a selective, reversible JAK1 inhibitor. It suppresses inflammatory or immune responses by inhibiting the JAK1-mediated intracellular signal transduction of cytokines.[172,173]

Several clinical studies of upadacitinib have demonstrated that it significantly reduced clinical symptoms, such as eruptions and pruritus, in comparison with a placebo, and improved the QOL, including sleep (CQ14).[182–184] Side effects include infectious diseases (pneumonia, sepsis, opportunistic infections including fungal infections and tuberculosis), oral herpes, herpes zoster, acne, and increased creatine phosphokinase levels in the blood (CQ14).[185] As this drug is highly effective, it is appropriate for inducing and maintaining remission.[182–184]

This drug should be indicated for patients with AD in whom conventional treatment is ineffective and be administered orally to adults at 15 mg once a day. In accordance with the patient's condition, 30 mg of upadacitinib may be administered once a day. Upadacitinib can be administered orally to children aged ≥12 years weighing ≥30 kg once a day at a dose of 15 mg. Clinical studies have demonstrated that the effects of combination therapy with TCS are more potent than those of monotherapy (CQ14).[184,185] Thus, the application of

topical anti-inflammatory drugs such as TCS and moisturizers should be continued during the administration of this drug. Before the use of this drug, physicians must sufficiently understand and follow the "Guidelines for promoting optimal use before the use: Upadacitinib hydrate (Trade name: Rinvoq tablets 7.5 mg, 15 mg, 30 mg) -AD-"[185] prepared by the MHLW in cooperation with the PMDA, JDA, JSA, and JOCD.

Patients for whom upadacitinib is indicated should be carefully selected, and whether its administration should be continued must be adequately evaluated. Furthermore, the management of side effects is necessary, and institutions or patients where or to whom this drug is available are established in the above guidelines. Basically, it is the same as the content described in *baricitinib*. However, some differences are outlined below.

The following has been added to "A physician who is familiar with the pathogenesis, course, prognosis, diagnosis, and treatment of AD and has sufficient knowledge about this drug" in the case of administration to patients with childhood AD; (who has accomplished clinical training for dermatological care for ≥5 years after the completion of initial training for 2 years after medical-license acquisition, or has a ≥6-year career of clinical experience after the completion of initial training for 2 years after medical-license acquisition [has accomplished clinical training for the management of pediatric patients for ≥3 years of the 6 years and the treatment of allergic diseases, including AD, for ≥3 of the 6 years]).

The term "renal dysfunction" has been added to the category of "important latent risks."

The phrase "patients aged ≥12 years, children: body weight ≥30 kg" has been added to "patients to be treated."

The following criteria have been added to "the contents which must be written in the remarks column of certificates of medical remuneration":

(i) An institution where a person responsible for the treatment using this drug meets one of the following requirements for physicians (should be described as "Institution requirement A," "Institution requirement B," or "Institution requirement C).

A: A physician who has accomplished clinical training for dermatological care for ≥5 years after the completion of initial training for 2 years after medical-license acquisition in the case of administration to patients with adult or childhood AD.

B: A physician who has a clinical career of ≥6 years after the completion of initial training for 2 years after medical-license acquisition in the case of administration to adult patients with AD. For ≥3 of the 6 years, the physician has accomplished clinical training for the treatment of allergic diseases, including AD.

C: A physician who has a clinical career of ≥6 years after the completion of initial training for 2 years after medical-license acquisition in the case of administration to patients with childhood AD. The physician has accomplished clinical training for the management of pediatric patients for ≥3 years of the 6 years and the treatment of allergic diseases, including AD, for ≥3 of the 6 years.

(ii) Body weight, in the case of administration to patients with childhood AD.

The sentence "In the guidelines for promoting optimal use, the administration of this drug should be discontinued if there is no treatment response in 12 weeks after the start of administration with respect to the continuation of administration." has been added to "continuous administration."

Abrocitinib. Abrocitinib is a selective, reversible JAK1 inhibitor. It suppresses inflammatory or immune responses by inhibiting the JAK1-mediated intracellular signal transduction of cytokines.[172,173]

Several clinical studies of abrocitinib have demonstrated that it significantly reduced clinical symptoms, such as eruptions and pruritus, in comparison with a placebo, and improved the QOL, including sleep (CQ15).[187–190] Side effects include infectious diseases (pneumonia, sepsis, opportunistic infections including fungal infections and tuberculosis), nausea, oral herpes, acne, and thrombocytopenia (CQ15).[191] As this drug is highly effective, it is appropriate for inducing and maintaining remission.[187–190]

This drug should be indicated for patients with AD in whom conventional treatment is ineffective and be administered orally to adults and children aged ≥12 years at 100 mg once a day. In accordance with the patient's condition, 200 mg of abrocitinib may be administered once a day. Clinical studies have demonstrated that the effects of combination therapy with TCS are more potent than those of monotherapy (CQ15).[189,190] Thus, the application of topical anti-inflammatory drugs, such as TCS and moisturizers, should be continued during the administration of this drug. Before the use of this drug, physicians must sufficiently understand and follow the "Guidelines for promoting optimal use: Abrocitinib (Trade name: Cibinqo tablets 200 mg, 100 mg, 50 mg) -AD-"[191] prepared by the MHLW in cooperation with the PMDA, JDA, JSA, and JOCD. Basically, it is the same as the content described in *Upadacitinib*. However, some differences have been outlined below.[173,185,186]

The term "thrombocytopenia" has been added to the category of "important specified risks."

The term "renal dysfunction" has not been added to the category of "important latent risks."

The term "patients aged ≥12 years" has been added to "patients to be treated."

The sentence "(ii) Body weight in the case of administration to patients with childhood AD." has not been added to "the contents which must be written in the remarks column of certificates of medical remuneration."

Oral corticosteroids. No double-blind RCT has been conducted to investigate the effects of oral corticosteroids on AD. However, in some cases, these drugs have been used to induce remission of acute exacerbation or severe/most severe conditions. Despite their

known effectiveness, long-term oral corticosteroid therapy induces serious systemic adverse reactions; therefore, long-term AD control with oral corticosteroids is not recommended. If necessary, the administration should be completed in a short period.

Biologics

Dupilumab. Dupilumab is a recombinant human IgG4 monoclonal antibody that binds to IL-4 receptor α subunits (IL-4Rα) comprising IL-4 and IL-13 receptors, inhibiting signal transduction mediated by IL-4 and IL-13 as ligands.[193–195] IL-4- and IL-13-mediated signal transduction routes are involved in type 2 inflammatory responses, playing an important role in the pathogenesis of AD (see "Pathophysiology").[196–199]

Several clinical studies have reported that dupilumab significantly reduced clinical symptoms, such as eruptions and pruritus, in comparison with placebo, also improving the QOL, including sleep (CQ16).[37,39,200–205] Furthermore, not only does this drug suppress inflammation, but it also improves the barrier function of the skin.[206] The main side effects include conjunctivitis and injection site reactions (CQ16). This drug is highly effective, and its effects persist for a long period. The incidence of serious side effects is low, and this drug is highly safe; therefore, it is appropriate for inducing and maintaining remission.[205,207–209]

This drug should be indicated for patients with AD in whom conventional treatment is ineffective and subcutaneously administered to adults at an initial dose of 600 mg and 300 mg/injection every 2 weeks. Dupilumab can be administered subcutaneously to children aged ≥6 months according to their body weight: ≥5 kg and <15 kg, 200 mg every 4 weeks; ≥15 kg and <30 kg, 300 mg every 4 weeks; ≥30 kg and <60 kg, 400 mg (initial dose) and 200 mg every 2 weeks thereafter; and ≥60 kg, 600 mg (initial dose) and 300 mg every 2 weeks thereafter.

Before using dupilumab, physicians must sufficiently understand and follow the "Guidelines for promoting optimal use: Dupilumab (genetical recombination) -AD-."[210] prepared by the MHLW in cooperation with the PMDA, JDA, JSA, and JOCD.

Patients for whom dupilumab is indicated should be carefully selected, and whether administration should be continued must be adequately evaluated. Furthermore, side effects should be managed. Therefore, institutions or patients where or in whom this drug is available are established in the above guidelines, as described below[210]:

Concerning institutions where dupilumab is available, all of the following criteria must be met:

(i) Institutions:

Because the administration of this drug is intended for patients with AD who meet certain criteria, such as an IGA or EASI score, indicating a certain level of disease activity, it is crucial to be able to accurately assess the subjective and objective severity of AD. A physician familiar with the pathogenesis, course, prognosis, diagnosis, and treatment of AD who has sufficient knowledge about this drug (refer to *Upadacitinib*) is deployed as a person responsible for treatment regarding this drug in the corresponding department.

(ii) In-hospital drug information management system: the same as described in *baricitinib*.
(iii) Management of complications and side effects.

When administering this drug to patients with other allergic diseases, such as asthma, a system to receive guidance or support regarding disease control in cooperation with a physician responsible for the treatment of the allergic disease must be arranged.

Concerning the side effects described in the "Cautions for use," such as anaphylaxis, a system to promptly provide adequate treatment based on guidance or support regarding the diagnosis and management of side effects in cooperation with specialists belonging to the corresponding or neighborhood medical institutions must be arranged.

Concerning patients to be treated, patients with adults or children aged ≥6 months (body weight: ≥5 kg) should meet both of the following criteria:

(i) Patients definitively diagnosed with AD in reference to the present guidelines.
(ii) Patients with AD in whom sufficient effects were not obtained by treatment with topical anti-inflammatory drugs (a), with a specific level or higher of disease activity (b), or those in whom treatment with topical anti-inflammatory drugs alone is difficult because of hypersensitivity to topical steroids or calcineurin inhibitors or marked topical or systemic side effects, with a specific level or higher of disease activity (b).
   a. Adequate treatment with TCS (adults: strong class or higher, children: medium class or higher) or calcineurin inhibitors, as recommended in accordance with the severity in the present guidelines, has been employed for the past ≥6 months (infants aged <1 year: the past ≥3 months).
   b. The condition should meet all of the following criteria:
      (a) IGA score ≥3
      (b) EASI score ≥16 or having eruptions with marked inflammation involving an extensive area of the face (EASI score for the head and neck ≥2.4 and ≥4.8 for patients aged >7 years and ≤7 years, respectively, as a guide)
   c. The rate of AD lesions as a percentage of the body surface area is ≥10%.

Based on these, the following contents must be written in the remarks column of certificates of medical remuneration.[211–213]

(i) An institution where a person responsible for the treatment using this drug: the same as described in *Upadacitinib*.
(ii) Status of treatment with topical anti-inflammatory drugs before the administration of this drug (should be described as "Pretreatment requirement A," "Pretreatment requirement B or "Pretreatment requirement C").

A: Adults with AD in whom adequate treatment with TCS (strong class or higher) or calcineurin inhibitors, as recommended in accordance with the severity in the present guidelines, has been performed for the past ≥6 months.

B: Children with AD in whom adequate treatment with TCS (medium class or higher) or calcineurin inhibitors, as recommended in accordance with the severity in the present guidelines, has been performed for the past ≥6 months. Moreover, strong-class TCS should be considered in cases exhibiting insufficient response to medium-class TCS before initiating administration of this drug.

C: Adults or children with AD in whom it is difficult to continue treatment with the topical anti-inflammatory drugs alone because of hypersensitivity to TCS or calcineurin inhibitors or marked topical or systemic side effects.

(iii) Values of all items described below as the state of disease activity:

A: IGA score.

B: EASI score for the whole body or head and neck.

C: Rate of AD lesions as a percentage of the body surface area.

(iv) Body weight, in the case of administration to patients with childhood AD.

For continuous administration, information at the start of administration must be written in the remarks column of certificates of medical remuneration.

In the guidelines for promoting optimal use, the administration of this drug should be discontinued if there is no treatment response in 16 weeks after the start of administration. This is based on the timing of efficacy assessment in clinical studies of this drug with respect to the continuation of administration.[210] In addition, if remission is maintained by combination therapy with TCS or calcineurin inhibitors for a specific period (6 months as a guide), the transient discontinuation of administration should be considered after confirming the adequate use of these topical anti-inflammatory drugs or moisturizers.[210] However, in many cases, the continuous administration of dupilumab may be required to maintain remission. In such cases, this drug may be continuously administered.

As described in the guidelines for promoting optimal use, the application of topical anti-inflammatory drugs, such as TCS and moisturizers, should be continued during the administration of dupilumab. As described in CQ16, clinical studies on dupilumab also have demonstrated that the effects of combination therapy with TCS are more potent than those of monotherapy.

Self-administration is also approved,[214] and patient burden can be reduced by a lower frequency of hospital visits. After confirming that adequate self-injection can be accurately and safely conducted through sufficient education, guidance, and training for drug storage, cleaning operations, injection procedures, and waste handling, hospital injection should be switched to self-injection. It can be calculated as a home self-injection guidance and management fee. Before the introduction of self-injection at home, patients should have a sufficient period of education by physicians during admission or on ≥2 sessions of outpatient consultation.

Side effects involving the eyes. The incidence of conjunctivitis after treatment with dupilumab was significantly higher than after the administration of a placebo.[37,201,202,205,215] In patients with other diseases, such as asthma and sinusitis, no difference was found in the incidence of conjunctivitis in comparison with placebo; a dupilumab-related increase in the incidence of conjunctivitis is observed only in patients with AD.[135,216] In most cases, the severity of conjunctivitis is mild to moderate. It sometimes subsides during continuous administration of dupilumab; if conjunctivitis treatment is initiated, dupilumab administration can be continued; therefore, the onset of conjunctivitis in a few cases leads to discontinuation.[135,216] In patients with severe AD or those with a history of conjunctivitis, the incidence of dupilumab-related conjunctivitis increases.[135,216] Although several mechanisms have been reviewed, the pathogenesis remains to be clarified.[135,216] The International Eczema Council recommends administration of dupilumab, if necessary, even to patients with a history of conjunctivitis and continuation of dupilumab, if possible, based on the results of ophthalmological examination even when conjunctivitis develops newly during dupilumab treatment through an inquiry regarding ocular symptoms.[217]

Nemolizumab. Nemolizumab is a recombinant, humanized, IgG2 monoclonal antibody that binds to IL-31 receptor A (IL-31RA) comprising IL-31 receptors, inhibiting signal transduction mediated by IL-31 as ligands.[195,218] IL-31-mediated signal transduction routes are mainly involved in the induction of pruritus, playing an important role in the pathogenesis of AD (refer to "Pathophysiology").[34,219,220]

Clinical studies have reported that nemolizumab significantly improved pruritus in comparison with placeb.[104,221–223] Notably, the onset of efficacy on skin eruption was gradual,[104,221–223] and an improvement in the QOL, including sleep and work productivity, was also observed.[104,221,222,224,225] Side effects include skin infections (such as herpes infection, cellulitis, impetigo, and secondary infections), worsening of skin eruptions (including AD), and upper respiratory tract infections (CQ17). This drug is highly effective against pruritus, the incidence of serious side effects is low, and it is very safe; therefore, it is appropriate for inducing and maintaining remission.[104,221,222] Clinical laboratory tests have revealed a transient increase in the serum TARC levels that is inconsistent with the inflammatory symptoms of AD. This elevation is often observed during the early administration phase (4–8 weeks after initiation). The serum TARC levels gradually return to the pre-administration levels (by approximately 32 weeks). Thus, the serum TARC levels cannot be used as a short-term disease activity marker for AD during a certain period after the initiation of treatment.[226]

This drug should be indicated for AD pruritus in the cases which are refractory to conventional treatments, and subcutaneously

administered to adults and children aged ≥13 years every 4 weeks at the dose of 60 mg. Before using this drug, physicians must sufficiently understand and follow the "Guidelines for promoting optimal use: Nemolizumab (genetical recombination, trade name: Mitchga® S.C. Injection 60 mg syringes) -Pruritus due to AD-."[227] prepared by the MHLW in cooperation with the PMDA, JDA, JSA, Japanese Society of Pediatric Allergy and Clinical Immunology (JSPACI), Japan Pediatric Society (JPS), and JOCD.

Patients for whom nemolizumab is indicated should be carefully selected and whether administration should be continued must be adequately evaluated. Furthermore, side effects should be managed. Therefore, institutions or patients where or in whom this drug is available are established in the above guidelines, as described below:[227]

Concerning institutions where this drug is available, all of the following criteria must be met:

(i) Institutions:

A physician who is familiar with the pathogenesis, course, prognosis, diagnosis, and treatment of AD and has sufficient knowledge about this drug (refer to *Upadacitinib*) is deployed as a person responsible for treatment regarding this drug in the corresponding department.

As a post-marketing survey for evaluating the safety and efficacy of this drug after manufacturing or sales is necessary, the institution should be appropriate for conducting this survey adequately.

(ii) In-hospital drug information management system: the same as described in *baricitinib*.

(iii) Management of side effects:

Concerning the side effects listed in the package insert, such as serious hypersensitivity, a system to promptly provide adequate treatment based on guidance or support regarding the diagnosis and management of side effects in cooperation with specialists belonging to the corresponding or neighborhood medical institutions must be arranged.

Nemolizumab is intended to treat pruritus in AD; this should be explained to the patient, and their understanding should be confirmed before starting its administration. It is necessary to confirm that patients aged ≥13 years meet all of the following criteria while evaluating the necessity of its administration:

(i) Patients definitively diagnosed with AD in reference to the present guidelines.

(ii) Patients who have experienced persistent pruritus (VAS for pruritus ≥50, or NRS for pruritus ≥5, and pruritus scale ≥3) for 3 days from 2 days before commencing the administration of the drug, even if they were receiving TCS (strong-class or higher) or calcineurin inhibitors, as recommended by the present guidelines, for ≥4 weeks and receiving oral antihistamines or anti-allergic drugs for ≥2 weeks. However, the administration of these drugs is not necessary if treatment with TCS, calcineurin inhibitors, oral antihistamines, or anti-allergic drugs is inappropriate owing to hypersensitivity or contraindications.

(iii) EASI score ≥10

Based on these recommendations, the following contents must be written in the remarks column of certificates of medical remuneration.[228]

(i) An institution where a person responsible for the treatment using this drug: the same as described in *Upadacitinib*.

(ii) Status of treatment before commencing the administration of this drug

A: Duration of treatment with TCS (strong-class or higher) or topical calcineurin inhibitors for patients aged ≥13 years before starting the administration of this drug (the reason should be noted if <4 weeks).

B: Duration of treatment with oral antihistamines or anti-allergic drugs for patients with AD aged ≥13 years before starting the administration of this drug (the reason should be noted if <2 weeks).

(iii) Values of all items described below as the state of disease activity:

A: VAS for pruritus or NRS for pruritus.

B: Pruritus score.

C: EASI score.

For continuous administration, information at the start of administration must be written in the remarks column of certificates of medical remuneration.

In the guidelines for promoting optimal use, the administration of this drug should be discontinued if there is no treatment response in 16 weeks after the start of administration, and the effects during administration must be monitored.[210] In addition, if remission of pruritus is maintained by combination therapy with TCS, calcineurin inhibitors, oral antihistamines, and/or anti-allergic drugs for a specific period (6 months as a guide), the transient discontinuation of administration should be considered after confirming the adequate use of these drugs.[227] However, in many cases, the continuous administration of nemolizumab may be required to maintain remission. In such cases, this drug may be continuously administered.

As described in the guidelines for promoting optimal use, the application of topical anti-inflammatory drugs, such as TCS and moisturizers, should be continued during the administration of nemolizumab. As described in CQ17, the efficacy of this drug in the management of AD has only been confirmed in clinical trials when used in combination with TCS or tacrolimus ointment.[104,221,222] Nemolizumab exhibits a gradual onset of effectiveness against

eruption.[104,221–223] Thus, it is crucial to continue the use of topical anti-inflammatory drugs depending on the condition of the affected areas in AD.[227]

Self-administration is also approved,[229] and patient burden can be reduced by a lower frequency of hospital visits (refer to *Dupilumab* in detail).

Exacerbation of skin eruption as side effects. Clinical trials of nemolizumab revealed that the frequency of AD exacerbation, regardless of causality, was similar to that of placebo. However, the frequency of AD exacerbation with an undeniable causality was higher than that of placebo.[104] Cases reported as exacerbations of AD included skin eruptions that differ from the typical features of AD exacerbation.[226,227] In the event of exacerbation of skin eruptions, it is important to adequately differentiate between the exacerbation of AD itself and other skin eruptions, and implement appropriate management strategies (such as the use of topical anti-inflammatory drugs) according to the pathophysiology. If skin eruptions do not improve promptly, appropriate measures should be taken, such as discontinuing the use of nemolizumab.[226,227]

Tralokinumab. Tralokinumab is an antibody drug targeting IL-13 that can neutralize the activity of IL-13 by inhibiting the interaction between IL-13 and its receptor, IL-13Rα1. The signaling pathway mediated by IL-13 modulates type 2 inflammatory responses and plays a crucial role in the pathophysiology of AD (refer to "Pathophysiology").[194–199]

Several clinical trials have demonstrated that tralokinumab significantly improved eruption, pruritus, sleep disturbances, and QOL compared with placebo.[230,231] Tralokinumab has been used to achieve and maintain remission in patients with moderate-to-severe AD who failed to achieve remission with topical therapy. Tralokinumab has demonstrated high tolerability lasting up to 1 year in clinical trials, with no significant differences being observed between tralokinumab and the placebo in terms of the frequency of adverse events, including serious adverse events.[230–232] Similar to those of dupilumab, the main side effects include conjunctivitis and injection site reactions.[230–233] Thus, the measures taken to counter the onset of conjunctivitis due to administration of dupilumab must be taken following the administration of tralokinumab (refer to *Dupilumab* for further details).

Tralokinumab should be indicated for patients with AD in whom conventional treatment is ineffective and subcutaneously administered to adults at an initial dose of 600 mg, then 300 mg/injection every 2 weeks. Before using this drug, physicians must sufficiently understand and follow the "Guidelines for promoting optimal use: Tralokinumab (genetical recombination, trade name: Adtralza S.C. Injection 150 mg syringes) -AD-."[234] prepared by the MHLW in cooperation with the PMDA, JDA, JSA, and JOCD.

Patients for whom tralokinumab is indicated should be carefully selected, and whether administration should be continued must be adequately evaluated. Furthermore, side effects should be managed. Therefore, institutions or patients where or in whom this drug is available are established in the above guidelines, as described below[234]:

Concerning institutions where this drug is available, all of the following criteria must be met:

(i) Institutions:

A physician who is familiar with the pathogenesis, course, prognosis, diagnosis, and treatment of AD and has sufficient knowledge about this drug (refer to *baricitinib*) is deployed as a person responsible for treatment regarding this drug in the corresponding department.

As a post-marketing survey for evaluating the safety and efficacy of this drug after manufacturing or sales is necessary, the institution should be appropriate for conducting this survey adequately.

(ii) In-hospital drug information management system: the same as described in *baricitinib*.
(iii) Management of side effects

Concerning the side effects described in the "Cautions for use," such as anaphylaxis, a system to promptly provide adequate treatment based on guidance or support regarding the diagnosis and management of side effects in cooperation with specialists belonging to the corresponding or neighborhood medical institutions must be arranged.

Concerning patients to be treated, patients should meet the same criteria described in *baricitinib*.

Based on these, the same contents described in *baricitinib* must be written in the remarks column of certificates of medical remuneration.[235]

In the guidelines for promoting optimal use, the administration of this drug should be discontinued if there is no treatment response in 16 weeks after the start of administration.[234] In addition, if remission is maintained by combination therapy with TCS or calcineurin inhibitors for a specific period (6 months as a guide), the transient discontinuation of administration should be considered after confirming the adequate use of these topical anti-inflammatory drugs or moisturizers.[234] However, in many cases, the continuous administration of tralokinumab may be required to maintain remission. In such cases, this drug may be continuously administered.

As described in the guidelines for promoting optimal use, the application of topical anti-inflammatory drugs, such as TCS and moisturizers, should be continued during the administration of tralokinumab. As described in CQ18, clinical studies on tralokinumab also have demonstrated that the effects of combination therapy with TCS are more potent than those of monotherapy.

Other oral drugs

Antihistamines

Atopic dermatitis is defined as a disease characterized by itching eczema as the main lesion. Itching results in QOL reduction and 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 an important treatment approach.

Antihistamines are widely used in the treatment of pruritus in AD in Japan and abroad. A meta-analysis examining the therapeutic effects of adding TCS to antihistamines has revealed a synergistic effect in patients with AD associated pruritus.[236] In addition, 32 RCTs in Japan and other countries have investigated the usefulness of antihistamines in combination with anti-inflammatory topical drugs such as TCS, tacrolimus ointments, and moisturizing drugs. As primary endpoints, their efficacy for pruritus and safety were investigated. Some trials have also examined the interval until the initial flare. A meta-analysis involving 25 of the 32 RCTs was conducted. However, pooled data assessment was not performed because the treatment period, drug type, dose, combined topical drugs, and endpoints varied; three drugs were analyzed. Consequently, no clear evidence can support the efficacy of antihistamines as an additional treatment to topical drugs.[237] However, many studies of non-sedative, second-generation antihistamines in Japan indicated their efficacy. They can be safely used for a long period[238] and relieve symptoms of complications, such as allergic rhinitis or conjunctivitis and urticaria; therefore, the use of non-sedative second-generation antihistamines is proposed as "add-on" therapy for topical anti-inflammatory treatment for AD (CQ19: Recommendation grade 2, Evidence level B). However, a meta-analysis regarding the therapeutic effects of antihistamines alone did not provide reliable evidence;[239] therefore, antihistamines as monotherapy for AD without topical anti-inflammatory drugs is not recommended.

Antihistamines include sedative antihistamines (first-generation) with relatively strong anticholinergic and sedative effects and non-sedative antihistamines (second-generation) that cause less drowsiness and impaired performance (such as impaired concentration, judgment, and reduced operating efficiency without subjective sleepiness) and anticholinergic activity with less fatigue. Based on the extent of these central effects of histamine H1 receptor (H1R) occupancy on the brain, antihistamines have been divided into three groups: sedative, ≥50% occupancy; mildly sedative, 50%–20%, and non-sedative, ≤20% occupancy. The H1R occupancy of most second-generation antihistamines was ≤30%. Currently, H1R occupancy is a pharmacological index in clinical practice (Figure S24).[240] As the therapeutic effects of sedative antihistamines do not differ from those of non-sedative ones in the treatment of AD, non-sedative second-generation antihistamines should be selected (Table 7 and Table S8).

According to the package insert of the antihistamine ketotifen, this drug is contraindicated in patients with epilepsy or a history of epilepsy, and cetirizine and levocetirizine should be carefully administered in patients with convulsive disorders. Convulsions are reported as serious side effects of loratadine. Thus, special attention is needed when administering these agents to children. Furthermore, oxatomide is contraindicated for pregnant women or those who may be pregnant, and it is recommended that the administration of mequitazine, loratadine, desloratadine, or rupatadine be avoided. Concerning administration during breastfeeding, it is stated in the package inserts of most drugs that breastfeeding be avoided; thus, caution is needed.

TABLE 7 Second-generation antihistamines.

Mequitazine
Azelastine hydrochloride
Emedastine fumarate
Epinastine hydrochloride
Ebastine
Cetiridine hydrochloride
Bepotastine besilate
Fexofenadine hydrochloride
Olopatadine hydrochloride
Loratadine
Levocetirizine hydrochloride
Desloratadine
Bilastine
Rupatadine fumarate

It has been reported that the mechanism by which pruritus is mediated in AD varies and involves cytokines, such as IL-31, abnormal distribution of nerve C-fibers transmitting itching sensations, substance-P (SP), and nerve peptides such as nerve growth factor, and histamines. A recent study reported that fexofenadine reduced the serum IL-31 levels in patients with AD.[241] Furthermore, biologics, anti-IL-4/IL-13 receptor antibody, anti-IL-31 receptor antibody, and oral JAK inhibitors, also exhibited marked effects on pruritus. The inhibitory effects of antihistamine on pruritus vary depending on the clinical features and the severity of patient's condition. Thus, it is desirable to judge the need for adjuvant therapy with oral antihistamines in addition to the therapy with topical anti-inflammatory drugs and moisturizers and to evaluate the efficacy of treatment on pruritus.

Traditional Chinese medicine

Chinese herbal medicine in combination with other drugs or as an adjuvant therapy may be useful in some cases. However, to date, most clinical studies examining the efficacy of Chinese herbal medicines for AD have been case series conducted in small populations (several dozens of participants). There have been only two double-blind, randomized comparative studies of "Shofu-san"[242] and "Hochu-ekki-to",[243] which are Chinese medicines that can be prescribed in general dermatology clinics in Japan (CQ20: Recommendation grade 2, Evidence level B). The former was administered to patients with eruptions that did not resolve with topical anti-inflammatory drugs such as TCS, and the latter was administered in combination with conventional topical anti-inflammatory drugs, such as TCS, in patients having conditions such as easy fatigability or lack of perseverance, based on a questionnaire score. For Shofu-san, a significant improvement of eruption was observed, and a 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,[244,245] whereas another research group reported negative results.[246] 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 and evaluation

of selective Chinese medicines for eruption based on eruption features are necessary. Side effects of Chinese medicines, for example, pseudoaldosteronism due to licorice-containing agents (Kanzo) and interstitial pneumonia, hepatic dysfunction, and jaundice due to Hochu-ekki-to, have also been reported. Thus, it is desirable that Chinese medicine therapy is implemented under the attentive surveillance of a physician proficient in the use of Chinese herbal medicines.

Considerations regarding pregnancy or breastfeeding

Adequate AD control is important even during pregnancy or breastfeeding. Initially, there is no direct drug transfer from the mother to the fetus (all-or-none period) before week 4 of pregnancy (2 weeks after fertilization), when pregnancy is perceived, before implantation; there is no risk of drug therapy. Therefore, patients who may be pregnant should receive an explanation that it is unnecessary to abstain from treatment and that treatment should be properly continued. Regarding safety, a background malformation incidence of 2%–3% should be explained, and informed consent to understanding these risks must be obtained from the patient.

Concerning the use of TCS during pregnancy, large-scale, case-controlled or prospective cohort studies[247,248] and meta-analyses[249,250] did not find an association with the mode of delivery, congenital malformations (including cleft lip and palate and hypospadias), low birthweight, preterm birth, fetal death, abnormal delivery, or a low Apgar score. Several studies have suggested an association between the massive-dose (≥300 g) application of potent TCS during pregnancy and low birthweight.[251–253] However, adequate control is important before such a state is reached (CQ21). The use of TCS during breastfeeding may be safe because the systemic absorption rate is low, theoretically. However, application to the breast immediately before breastfeeding should be avoided, and patients must be instructed to clean the breast before breastfeeding.

Tacrolimus and cyclosporin were previously contraindicated, but their package inserts were revised in July 2018. In the "Contraindication" section, "pregnant women or those who may be pregnant" was deleted. In the "Administration to pregnant, parturient, or lactating women" section, the description was changed to "the agent may be administered only when its therapeutic advantage is considered to exceed its risk". Specifically, concerning tacrolimus ointment, which is used as a basic drug, theoretically, there is almost no systemic absorption; it may be safe. It is not contraindicated for breastfeeding women; however, the continuation or discontinuation of breastfeeding should be reviewed, considering the therapeutic advantage of this ointment and the benefits of breastfeeding, and this agent may transfer into breast milk in humans. Concerning the latter, an article from which this was quoted describes the oral administration of tacrolimus,[254] and there is almost no systemic transfer of topical preparations.

The administration of antihistamines during pregnancy may be safe. Second-generation drugs may be administered if they have greater therapeutic advantages (CQ:22). The volume of the drug secreted into breast milk is quite small; thus, its administration during breastfeeding is generally considered safe. However, first-generation antihistamines can cause irritability and drowsiness in infants owing to their sedative effect; thus, it is advisable to administer second-generation antihistamines to lactating women.

1.3.4 | Ultraviolet irradiation therapy

Ultraviolet (UV) irradiation therapy is considered for non-responders to treatments with topical anti-inflammatory drugs, antihistamines, or moisturizers, and patients with adverse reactions to conventional treatments.[16,17,255] In UV therapy for AD, many studies have reported the efficacy of UVA1 therapy at a wavelength of 340–400 nm and narrow-band UVB with a peak of 311 nm;[256–258] however, no protocol or guidelines of UV therapy involving patients with AD have been established. When administering UV therapy, it is important to initially consider whether it should be indicated, and it should 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. Because information on the safety of long-term treatment with UV in children is insufficient, UV irradiation therapy can be used for children with psoriasis aged ≥10 years, but it is not recommended for children aged <10 years.[259]

1.3.5 | Skin care

Topical moisturizers

In AD, the skin barrier functions and moisturizing factors are impaired. Moisture content in the stratum corneum decreases in AD, resulting in characteristically dry skin. Therefore, skin itching is likely to occur because of non-specific stimulation, and various allergens can easily penetrate the skin to induce dermatitis. The use of moisturizer products (moisturizing drugs and skin protective agents) improves moisture content in the stratum corneum, which is decreased because of AD and helps prevent allergen invasion, relapse of dermatitis, and suppression of itching by recovering and maintaining skin barrier functions[260–262] (CQ24: Recommendation grade 1, Evidence level A).

An essential point of skin care for dry skin is the topical administration of hydrophilic ointments (oil in water) with high moisture-retaining properties or water-absorbing ointments (water in oil) to supplement the reduced 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 the damaged skin, oleaginous ointments with protective action on the skin, such as white petrolatum and zinc oxide ointment, are applied topically (Table S9).

The moisturizing efficacy is higher with twice-daily topical applications (morning and evening) than once-daily applications,[263] and

it is recommended to apply moisturizers immediately after bathing in either application. To determine the amount of agent to apply, a fingertip unit is helpful. The amount extruded from the tube (5 mm in diameter) from the length of the tip of the second finger to the first joint (approximately 0.5 g) (finger-tip unit) is the adequate dose for two adult palmars in the United Kingdom, that is, approximately 2% of the adult body surface area.[116,117,264] Generally, TEWL is often found in the skin of patients with AD, not only in the lesion, but also in normally appearing areas representative of the dry skin.[265] Therefore, topical moisturizers should be applied throughout the body including normally appearing sites. Continuous use of moisturizers even after achieving remission of dermatitis with topical anti-inflammatory drugs is also useful to maintain remission.[266] If relapse of dermatitis is observed during remission, maintenance therapy with topical moisturizers, and TCS or topical tacrolimus is 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 AD relapse is also important because contact dermatitis may occur as a side effect of topical moisturizers in rare cases.

Combining two or more topical products, such as a TCS and a moisturizer, should be avoided without careful consideration, as this may alter the stability and percutaneous absorption of drugs.

Bathing, showering, and washing

In AD, besides the adhesion of 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. Generally, bathing and showering are encouraged to clean the 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 each patient, season, and symptoms in the same patient. The following points should be considered.

Water temperature

Concerning the water temperature during bathing or showering, the optimal temperature for skin barrier function recovery is 38°C–40°C.[267] A water temperature of ≥42°C is not recommended, because sebum or natural moisturizing factor elution and pruritus are induced.[267–270] After bathing, a moisturizer should be promptly applied to maintain the water-retaining capacity through the minimization of water transpiration or diffusion and prevent skin dryness.

Soap and/or detergent

As the major component of soap and/or detergent is surfactants, excessive abuse of these products may exacerbate skin dryness. Moreover, additives in detergents, such as pigment and perfume, are believed to irritate the skin. Thus, the use of soap and/or detergent may be important to keep the skin clean; however, in skin conditions that vary according to age, site, and season, the type and usage of soap or detergent should be considered. As sebum can generally be removed from the skin in lukewarm water, to some extent, the use of soap should be limited in patients with severe conditions, during dry seasons, and in those sensitive to strong irritation by soap or detergents. By contrast, soap and detergents should be used aggressively in patients with oily skin or for seborrheic skin and in sites exhibiting recurrent skin infections. No evidence supports the superiority of solid soap or detergents over liquid detergents (that use synthetic surfactants). An appropriate cleanser that satisfies the following conditions should be used: (i) its base composition is mildly irritating or hypoallergenic, (ii) additives such as pigments and perfume are reduced as much as possible, and (iii) the usability is favorable without irritation; detergents that exacerbate dry skin after washing should be avoided. Likewise, soap and/or detergents should be thoroughly rinsed off 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 is necessary to remove residual detergents. High-quality evidence demonstrating the efficacy of soap or detergent for AD is lacking; however, some studies have reported a reduction in the severity of dermatitis with the use of an appropriate detergent.[271,272]

Management of ointment residues

The residues of ointments containing oils and fats, such as Vaseline, as a base may not be removed with soap or detergents. In such cases, the application of olive oil to areas where ointment may remain is considered.

1.3.6 | 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 with the hair tip can induce itchiness on the sensitive skin due to skin dryness or eczema, appropriate measures should be taken, for example, choosing suitable non-irritating clothing, cutting hair short, or tying up hair.

Wiping the skin with stiff materials, such as a nylon towel, leads to a decline in the skin barrier function and progression of eczema because of 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 irritate the skin.

Irritation from scratching is an extremely important exacerbation factor of AD. In addition to dermatitis treatment to reduce itching, 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 cause progression of

eczema.[273–275] When the expected treatment efficacy for AD cannot be achieved, the distribution of eczema is not typical, or if AD onset or progression 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 to avoid contact with causative agents of contact allergy defined in the diagnosis (see contact dermatitis guidelines[276] for details).

Food allergens

Food allergens may be present in patients with AD, especially during infancy. However, a systematic review reported only weak evidence of the efficacy of an allergen elimination diet in treating AD in children and adults without a clear food allergy.[277] 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 AD progression due to a certain food is confirmed, the elimination of a specific food because it is likely to become an allergen is not recommended (CQ28: Evidence level B). To eliminate a specific food from the diet, an allergen elimination test should be conducted after adequate anti-inflammatory therapy for AD. If cutaneous symptoms did not improve even after anti-inflammatory therapy with appropriate intensity and sufficient doses of TCS, food allergens causing the progression of eczema should be identified. If AD is poorly controlled because of inadequate topical therapy, making a definitive diagnosis will be difficult.

Food allergens should be determined with reference to the results of an interview to obtain detailed medical history, skin tests, blood tests, and 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 the basis for diagnosis. If a certain food is restricted because it is likely an allergen, it cannot be considered a useful treatment for AD. AD is multifactorial, and elimination of food allergens is an adjuvant therapy to drug therapy; thus, complete remission is not to be expected with the elimination of food allergens alone, even after clarifying the involvement of food allergens.

In 2000, the American Academy of Pediatrics recommended an allergen elimination diet for pregnant women. However, in 2006 and 2012, a systematic review of RCTs of allergen elimination diets for pregnant or breastfeeding women was reported from the Cochrane Collaboration.[278] Dietary restrictions by allergen elimination in pregnant or breastfeeding women did not inhibit AD onset within 18 months after birth. Furthermore, dietary restrictions may play a role in limiting adequate weight gain during pregnancy and may worsen nutritional status among children, leading to an increased risk of preterm births. Thus, dietary restrictions (allergen elimination) in pregnant or breastfeeding women may not be useful for preventing the onset of childhood AD but is instead harmful (CQ29: Evidence level A).

Inhaled allergens

Atopic dermatitis after infancy may progress because of environmental allergens such as mites, house dust, pollen, and pet hair.[278] Whether these allergens are exacerbating factors for eruption should be carefully evaluated by comprehensively considering medical history, environmental changes, and changes in eruption features (e.g., eruptions and pruritus exacerbates in a place where the concentration of a suspected allergen is high and reduces after leaving), rather than based on judgment of clinical symptoms alone, specific IgE antibody titer, or skin prick test results. Eliminating environmental allergens is an adjuvant therapy to pharmacotherapy and skin care; thus, it is necessary to recognize that its effectiveness has limitations.

Measurement and measures of specific IgE antibodies against inhaled allergens[279]

The evaluation of allergen-specific IgE antibody levels is useful in determining the involvement of inhaled allergens in AD; however, a positive result does not necessarily indicate a causative factor for exacerbation. Measures against common exacerbating factors, such as dust mite allergens, pollen allergens (e.g., cedar, grasses, and weeds), and animal allergens (e.g., dogs, cats, and other hairy animals with which contact is possible) are described below.

Mites: The use of flooring, cleaning, or vacuuming futons (Japanese-style bedding, bed, or covers), and using anti-dust mite sheets.

Pets: Give up pet(s), wash pet(s), and prohibit pet(s) in the bedroom. In the case of cat allergy, female cats, in which antigen (Fel d 1) production is low, should be selected if possible.

Pollen: On coming in from outside, pollen should be brushed off from clothes before entering the house. After returning home, the patient should promptly wash the face or take a shower and change the clothes. Wearing pollen glasses (goggles) or masks is also recommended.

Sweating

Despite differences in the degree, patients with AD have a decreased sweat volume.[280–284] A decrease in the volume of sweat leads to an increase in skin temperature, skin dryness, and a decrease in antibacterial activity.[280–284] Etiological factors for a decrease in the sweat volume include sweat retention related to sweat pore occlusion, dermatitis-related sweat gland hypofunction, sweat leakage from the sweat glands into tissues, and neurosis (trait anxiety).[280,281,283,285] Many patients with AD exhibit type I allergic reaction to the Malassezia antigen present on the skin surface derived from sweat.[286] Specifically, sweat may markedly affect the joint flexion side and the cervical region where sweat tends to retain.[220] Furthermore, changes occur in the components of sweat (such as antimicrobial peptide, salt concentration, and glucose) in accordance with the severity of eruption in patients with AD; therefore, the merits of sweat may not be obtained in the patients with severe AD.[287–289] The decrease in the sweat volume and the abnormalities in sweat composition improve with the reduction in the severity of AD.[282,289]

In patients with AD who can sweat, if excess sweat on the surface of the skin is left for a long time, the stratum corneum softens and can be stripped away through minor friction (intertrigo). Allergens mixed with sweat can exacerbate inflammation. Therefore, it is advised to take preventive measures against sweating that is to the extent that the skin and clothing become wet. Concrete measures, such as wearing breathable clothes, showering, running water washing, blanket bathing with wet towels, and changing wet clothes, should be taken.[290]

Regarding arguments for and against sweating in patients with AD, no evidence confirms that avoiding sweating reduces symptoms; such guidance is not necessary. Guidance for sweat-removing strategies after sweating should instead be emphasized. In patients with a decreased sweat volume, becoming capable of sweating may be a goal of treatment.

Bacteria and fungi

S. aureus is often detected in the lesions 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 for sterilization and bacteriostasis. The role of bacteria in AD is largely unknown; however, analysis of the bacterial flora of the skin has recently revealed its involvement in clinical conditions. In children with AD, the diversity of the bacterial flora of the skin decreases in the exacerbation phase, and the proportion of *S. aureus* increases.[291] In addition, several studies have noted that a specific gene lineage type of *S. aureus* strain is frequently detected in patients with AD,[292] abnormally biased bacterial flora, including *S. aureus*, induced AD-like dermatitis in an animal model, and the onset of dermatitis can be prevented by correcting the abnormal bacterial flora by antimicrobial treatment.[293] However, the relationship between the bacterial flora of the skin and clinical conditions of AD has not been fully examined; thus, additional studies are necessary.

No report has suggested that oral administration of antibiotics is effective for AD in the absence of infection; thus, oral administration of antibiotics is not recommended.[294] Medical evidence is insufficient to actively recommend the use of povidone-iodine solution. Although povidone-iodine solution is occasionally considered 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, anaphylaxis, and potential effects on thyroid function.

Bleach bath therapy is widely practiced, mainly in the USA and other countries, and reports reveal its efficacy. This therapy is recommended for patients with suspected skin infections.[295,296] However, its effects have not been fully validated, and there are no established recommendations in Japan; thus, future verification of its effects on AD is warranted.

The potential involvement of fungi in the pathology and worsening of AD has been suggested based on the levels of specific IgE antibodies to *Candida* or *Malassezia* and skin prick test results in patients with AD.[297] However, a clear correlation with the clinical conditions is still unknown. Despite some reports that orally administered antifungal drugs are effective for AD,[298] and topically administered antifungal drugs are effective for eruptions on the head and neck,[299] no large-scale studies have been conducted to date; thus, careful use is recommended.

1.3.7 | Psychosomatic aspects

The psychosomatic aspects of AD were previously emphasized as a classic psychosomatic disease called "holy seven." Psychosomatic approaches are still important even after its immunological pathogenesis became clear.[300] For example, the risk of concomitant developmental disabilities such as attention-deficit/hyperactivity disorder (ADHD), is high in patients with AD;[301] this must be considered for patient education. In patients with a severe or poorly controlled disease, secondary psychological disorders often occur, and their background should be accurately understood. Thus, comprehensive treatment and management involving psychosomatic assessment and management are necessary for patients with AD.

Mental stressor

Advice or guidance should be given to the patients through an inquiry regarding stressors. Many factors such as being too busy at work, pre-examination tension, and personal relationships lead to deterioration. Initially, understanding these stressors is important, and communication alone reduces them in some cases. In addition, physicians can help the patient to coexist with stressors by concretely advising the patient to utilize methods to manage the stress-related deterioration of pruritus (refreshment, physical cooling, and sweat removal).

Habitual scratching behavior

In situations where relief from illness can be obtained through scratching behavior, habitual scratching is likely to occur because of operant conditioning. 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 patients with severe disease, anxiety and feelings of hopelessness regarding prognosis and treatment are conditioned through the repeated paired presentation with the perception of an itching sensation; thus, even in the absence of pruritus, scratching activities are sometimes induced by anxiety. In addition, scratching causes a scratching-related pleasant sensation through the activation of the reward system, such as the midbrain and striatum; therefore, it is difficult to stop scratching in some cases.[302] Because of the conditioning resulting in these scratching activities, physicians should search for conditions for withdrawal from scratching activities.

Concomitant development of psychiatric diseases

Atopic dermatitis increases the risk of developing depression, anxiety disorder, and suicidal ideation in children and adults.

Furthermore, AD has been associated with an increased incidence of introverted behavior, autism, behavioral disorder, and ADHD in pediatric patients. An increased incidence of schizophrenia, cognitive impairment, self-harm behaviors, alcohol consumption, adjustment disorders, attention-deficit disorder/ADHD, and personality disorders has been reported in adult patients with AD. Notably, the incidence of several mental health issues is correlated with the severity of AD.

Various mechanisms have been proposed to explain the association between AD and mental health disorders. Chronic nocturnal pruritus, which disrupts the sleep–wake cycle, is associated with the onset of psychological symptoms in adolescents. Decreased levels of melatonin have been associated with sleep disturbances and abnormal immune responses in patients with AD. Moreover, supplementation of melatonin has been reported to be effective in improving QOL and reducing time to sleep onset in patients with AD. Furthermore, repeated exacerbations of AD become chronic stressors, resulting in decreased responsiveness of the hypothalamus-pituitary–adrenal axis owing to the sustained activation of the sympathetic nerve-adrenal medullary system. This can lead to dysregulation of the catecholamine and cortisol levels, which can induce the onset of mental health problems.[303]

Concrete approaches

The presence of any comorbid mental disorders and the ease of communication with healthcare providers must be evaluated in difficult-to-treat cases. The treatment should proceed while collaborating with psychiatrists and psychotherapists in such cases.

The explanation of the disease should be adjusted according to the patient's level of understanding while communicating with patients who have some misconceptions about AD or have limited understanding. The treatment goals must be communicated clearly and simply. When treatment is difficult or when it is impossible to cope with a depressive state, both of which reduce adherence, the components of treatment should be simplified as much as possible. Furthermore, patients tend to apply topical drugs consciously before the date of the scheduled consultation at the outpatient clinic; therefore, an increasing number of consultations may be effective in improving adherence in some cases.

If stress exacerbates the condition, it should be overcome by lifestyle strategies or stress management, including relaxation training, to manage factors for deterioration.

The parents of children with habitual scratching activities should be instructed to ignore the scratching behavior and praise them when they do not scratch the skin. The following instructions are also effective in some cases: to prevent scratching at night, children should wear clothes or gloves such that the hands cannot directly scratch the skin, and their attention and concentration should be diverted to something other than scratching.

Patients who have had pruritus for many years and come to accept it as usual may not be able to imagine a state without pruritus or eczema. Thus, it is difficult for these patients to share treatment goals as they think "it is okay not to have complete control" or be motivated to continue treatment owing to distrust or resignation, thinking "it will just worsen soon." Stepping down of treatment after achieving sufficient improvement of symptoms in a short period through hospitalization or intensive treatment and obtaining a successful experience of "getting better if treated properly" should be considered in such cases.

1.3.8 | Treatment of complications (including 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 with a clinical team that includes a pediatrician, dermatologist, otolaryngologist, and ophthalmologist is necessary to implement comprehensive management.

Food allergy. Numerous studies have examined the relationship between AD and food allergy. In 2003, Lack et al.[304] reported that peanut allergy was associated with the presence of inflamed skin and the use of skin care products containing peanut oil, suggesting that sensitization to allergens could occur through the skin (or via epicutaneous sensitization). The "dual allergen exposure hypothesis" proposed by Lack,[305] indicated the importance of "cutaneous sensitization" and "oral tolerance" in the development of food allergies.

Atopic dermatitis development during infancy is associated with a higher risk of developing food allergies,[304,306,307] and this fact supports the concept of "epicutaneous sensitization" in which exposure to food allergens via the skin may induce sensitization. Observational studies demonstrated that early skincare intervention reduced the incidence of AD among high-risk children with a family history of allergies.[308,309] Furthermore, commencing an aggressive treatment strategy in the early stages of AD had a preventive effect on the development of food allergies in an RCT.[310]

Children with AD who ingest eggs at a later age are at higher risk of developing egg allergy. Natsume et al. reported that the start of egg ingestion at age 6 months, early after weaning, in infants with AD in whom the remission of AD was achieved with topical steroids reduced the incidence of egg allergy at age 1 year. Thus, this study supports the importance of inducing oral tolerance to allergens to prevent the onset of food allergy during infancy.[311]

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.[312] Accordingly, the society specified that allergen elimination on the sole grounds of avoiding sensitization to eggs should not be recommended without careful consideration. Furthermore, these recommendations underlined the importance of AD treatment before commencing baby food and provided suggestions regarding timing and amount of egg intake.

Food causes AD exacerbation 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.[313] Please refer to the guidelines for a detailed description of medical procedures.

Bronchial asthma. Approximately, 25% of patients with AD have bronchial asthma.[314] When bronchial asthma in combination with AD is suspected to occur, intervention by a clinical team of dermatologists, pediatricians, and internal medicine specialists should collectively provide treatment.

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 pollens, contact with cedar pollens may worsen AD.[315] Abroad, the exacerbation of cutaneous symptoms due to the presence of other pollens was reported.[316] Symptoms may extend to the entire body, not only to the exposed skin areas such as the face. In addition, external stimuli, including 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 factor of cutaneous symptoms on the eyelids. The spread of inflammation to the eyelids because of conjunctivitis and scratching the eyelids make cutaneous symptoms on the eyelids obstinate. Frequent 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. Collaborating with ophthalmologists is recommended in cases presenting with complications of allergic conjunctivitis or skin eruptions of the eyelids which are difficult to treat.

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

Impetigo contagiosa is caused by *S. aureus* or *Streptococci*. In cases of impetigo contagiosa attributable to *S. aureus*, bullae frequently appear and are easily ruptured, expanding redness peripherally. In cases of *Streptococci* infection, especially group A β-hemolytic *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 ointments, and protection of the lesions with gauzes are recommended.

Erysipelas is a dermal infectious disease mainly caused by β-hemolytic *Streptococcus*.[317] Chills, fever, well-circumscribed glossy red plaques with heat sensation, and marked pressure pain develop, frequently on the face. Initially, it appears on the unilateral side, extending to the contralateral side. The systemic administration of penicillin or cephem antibiotics is necessary.

Cellulitis is a bacterial infectious disease in the deep layer of the dermis and extends to the subcutaneous tissue. β-hemolytic *Streptococcus* is the most frequently detected causative bacteria, followed by Gram-negative bacteria and *S. aureus*.[318] The possibility of *S. aureus*, particularly community-acquired methicillin-resistant *S. aureus*, being the causative pathogen is higher in cases accompanied by purulent exudate.[319] Cellulitis is accompanied by local heat sensations and pain on the lower limbs, in addition to well-circumscribed erythema and swelling. The systemic administration of penicillin or cephem antibiotics and rest are necessary.

Kaposi's varicelliform eruption is caused by a primary infection or reactivation of the herpes simplex virus. In contrast to typical herpes simplex, many vesicles and pustules appear on the eczema lesions mainly on the face and neck. This eruption is accompanied by fever and lymph node enlargement. The administration of antiviral drugs (oral administration of aciclovir or valaciclovir and intravenous infusion of aciclovir) is necessary. 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 also observed in adult patients with AD. Lesions are glossy skin color to yellow papules of about 2–5 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 become severe in patients with uncontrolled AD, it is important to maintain the skin condition well with basic treatments.

Ocular diseases. Ocular complications related to AD other than allergic conjunctivitis include blepharitis, keratoconjunctivitis, keratoconus, cataract, glaucoma, retinal detachment, and bacterial or viral infection.[136,137,320,321] In AD patients with severe and refractory facial eruptions, ocular complications are likely to occur.[136,321] Furthermore, AD treatment causes ocular diseases in some cases (CQ6). Patients with AD may have ocular complications despite the absence of ophthalmological complaints. Such complications lead to irreversible visual impairment in some cases. Therefore, considering ocular complications, dermatologists should instruct patients to consult an ophthalmologist to maintain visual function.[135–137,320] Furthermore, sufficient control of facial eruptions is important, especially around the eyes, to prevent ocular complications.[135,136]

1.3.9 | Hospital care

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

In patients with chronically protracted severe dermatitis, problems are identified regarding disease activity (enlargement of

eruption related to inflammation with rigorous activity or scratching), patient adherence (insufficient understanding of the pathogenesis of AD or treatment methods, no treatment goal 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 (environment- or 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 and skin care and overcome these problems in the early phase. Several hospitals reported that such therapeutic interventions improved long-term prognoses after patient discharge.[322,323] In addition, patients often cannot continue the drug therapy 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 discharge of patients with severe AD for whom hospital care is indicated, it is essential to understand their conditions and treatment methods. Therefore, hospital care aims to achieve the early remission of dermatitis by intensive topical therapy and improve adherence through educational guidance.

1.3.10 | Patient education

For AD mainly treated by topical therapy at outpatient clinics, patients and their families have a key role in treatment. The patient's family should properly understand the clinical conditions and treatment of the patient to improve adherence and achieve successful treatment (see "Treatment adherence").

In Japan and abroad, various methods of 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 on children, specifically education by a multidisciplinary medical team, group work by a specialized nurse, a short education program during the hospital stay, and education using online videos.[324–328] In addition, websites and leaflets for young patients have been developed and used as educational tools for patients with AD in Japan.[329,330]

In clinical practice, the above tools should be selected as effective and feasible educational methods taking into account the characteristics of each patient and medical-care system provided at the treatment facility. Confirmation of 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 is not achievable.

1.3.11 | Probiotics/prebiotics

Enterobacteria play an important role in the immune response in vivo and have been reported to be associated with various diseases. Many studies have reported their association with allergic diseases such as AD. A study compared the intestinal flora between children with allergic diseases and healthy children and noted a significant decrease in the number of *Lactobacillus* sp. in the former.[331] Many studies have examined the effects of intervention by enterobacteria on preventing the development of allergic diseases or treatment after development. Probiotics (live microorganisms yield useful effects on the host), prebiotics (food ingredients promoting the growth of microorganisms useful for the host), and synbiotics (combination of probiotics and prebiotics) are the representative preparations.

Concerning the prevention of onset, meta-analyses concluded that continuous administration of probiotics to mothers during pregnancy and, subsequently, to infants after birth was effective in preventing the onset of allergic diseases.[332,333] However, the preventive effects of the administration of single-strain probiotics or administration to infants alone have not been confirmed.[333,334] Other meta-analyses did not find preventive effects of prebiotics and synbiotics against the onset of allergic diseases.[335,336] The preventive effects of probiotics may be obtained to some degree with certain bacteria in certain methods of administration. However, there is no evidence on specific species of bacteria or methods of administration that can be used practically. The present guidelines do not recommend probiotics as a preventive method (CQ38).

Several studies have examined the therapeutic effects of probiotics on AD. A meta-analysis revealed that probiotics significantly reduce the SCORAD index. However, there are RCTs that show no effect in pediatric patients (CQ37); thus, the results are not consistent.[333,337] Some RCTs have reported the efficacy of synbiotics, whereas others did not. Their meta-analysis demonstrated that synbiotics significantly reduced the SCORAD index in children aged ≥1 year and adults.[336] Some RCTs have noted the therapeutic effects of prebiotics, whereas others demonstrated their ineffectiveness (CQ37).[338–340] A meta-analysis of these RCTs has not been conducted.

The efficacy of probiotics, prebiotics, and synbiotics varies depending on various factors, such as species, combination, dose timing, living environment including dietary habits, and race. Thus, for practical use or clinical application, this must be further examined in the future.

1.3.12 | Complementary and alternative medicine

Complementary and alternative medicine means the provision of care other than standard medical treatment implemented by the physician at a healthcare facility, and it 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 and information relating to complementary and alternative medicine for AD in so-called health magazines and available on the internet and it represents a controversial industry.

According to a survey conducted in Hiroshima in 1997, 67.4% of patients with AD have tried alternative medicine.[341] According to another questionnaire survey involving the parents of children with AD at the time of initial consultation in Tokyo in 2003–2006, those with steroid phobia had more frequently received alternative medicine than those without it (22.2% vs 13.0%, $p=0.013$).[342] In patients hospitalized for exacerbation of AD or aggravation due to complications, in 44% of the patients, these complications were caused by inappropriate treatment using alternative medicine.[343] 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.

Several RCTs have investigated the efficacy of complementary and alternative medicine. Although one study reported the efficacy of acupuncture in improving itching, the sample size was small, and the quality of the study was not good.[344] In an RCT evaluating the efficacy of homeopathy, no significant differences in improvement were observed when compared with the placebo group.[345] No adequate scientific evidence supports the efficacy of complementary and alternative medicine.

1.3.13 | Treatment adherence

In medical care for AD, a chronic disease, patients and their parents/families must understand the condition or significance of treatments, positively participate in the selection of therapeutic strategies, accomplish treatments according to these strategies, and improve the will to continue treatments, i.e., adherence to treatments. Treatment adherence-associated factors include patient-, disease-, treatment-, healthcare professional-related, and socioeconomic factors.[346,347] Patient-related factors include the pressure of business and belief in medical care or drug therapy. In treatment-related factors, complex treatment methods, a high incidence of adverse reactions, and expensive procedures reduce treatment adherence. Thus, politely explaining the merits and demerits of respective treatment methods and concrete application methods for improving adherence is important. Regarding healthcare professional-related factors, their relationships with patients, explanations of the disease and treatment methods, and continuous provisions of information or support contribute to improvements in adherence. Moreover, the necessity of drug therapy or skin care must be explained to patients and thereby motivate them. The process of shared decision making, where patients and healthcare professionals share and discuss information and collaborate to make medical decisions, enhances patient treatment satisfaction and treatment adherence.[348,349] Socioeconomic factors include a family's cooperation and babysitter's support. To improve adherence, healthcare professionals should initially try to achieve factors that they can perform.[350–352]

1.3.14 | Referral to a specialist

When no improvement of eczema is observed even after implementing treatment in accordance with the present clinical practice guidelines (Figure 6) for a period of approximately 1 month, referral to a specialist or to a specialized facility should be considered.[16,17] When prominent erythema, scars from scratching, erosion, lichenification, prurigo, or a wide range of erythema-like erythroderma is observed, referral to a 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 a specialist should also be considered.

1.3.15 | Maintenance phase treatment using telemedicine

For AD treatment, it is important to maintain favorable control over a long period by adequate maintenance therapy after inducing remission. To achieve this, good adherence is necessary; however, the continuation of treatment is sometimes stressful for the patients. Specifically, regular hospital visits affect going to work or school for patients with AD, many of whom have social activities, reducing the QOL in some of these patients. However, low compliance with regular hospital visits easily leads to exacerbation. Therefore, telemedicine is one of the useful options for minimizing the stress level and continuing the treatment. Indeed, numerous studies have supported the usefulness of telemedicine for AD treatment.

In a randomized study of telemedicine and face-to-face medical care at a ratio of 1:1 involving 156 children and adults with AD who did not require systemic therapy, such as oral immunosuppressive drugs or phototherapy, the improvement rates for the POEM and IGA scores during the 12-month follow-up were comparable between the telemedicine and face-to-face medical care groups.[353] Similarly, improvement in the QOL, which was assessed based on the DLQI, CDLQI, and Short Form-12, was comparable between the two groups.[354]

From the viewpoint of cost-effectiveness, a study involving 199 patients diagnosed with AD on the initial consultation reported that outpatient follow-up with "e-health (online consultation)" between face-to-face consultations led to an improvement in the cost, while the QOL and disease severity were comparable with those receiving face-to-face medical care.[355] The e-health program includes the provision of materials for education and patient monitoring; therefore, it is not completely consistent with telemedicine in Japan. However, there may be a certain value from the viewpoint of cost-effectiveness.

To establish evidence in Japan, further examination is necessary. However, remission may be maintained through adherence support while minimizing the stress levels of the patients and their families by providing medical care in combination with telemedicine in patients with stable AD. For this purpose, medical fees must be adequately approved.

1.4 | Special considerations for children

1.4.1 | Clinical presentation

Eczematous lesions are subject to change during growth and development. The definition of "chronic" also differs, and it is defined as a disease persisting for ≥2 months and ≥6 months in infants and older children, respectively. During infancy, erythema and infiltrative erythema initially appear on the face, specifically on the cheek, and head, and then extend to the neck, trunk, and limbs on disease progression. Eruptions on the face gradually stabilize with a peak at 4–6 months and transition to the lesions on the neck and joints of limbs. Eczematous lesions occurring from preschool to school ages mainly appear on the neck and limb joints. After adolescence, eruptions tend to appear on the upper body including the head, neck, chest, and back similarly to adults.

It is not always the case that children with a severe disease during infancy will experience the same severe disease as they grow older, and many children achieve near remission at age 1–1.5 years. There are two types of AD-affected preschool children: those with persistent disease from infancy and those with new disease onset at around age 3 years.

1.4.2 | Exacerbating factors

During infancy, "food allergy-sensitized infant AD" is the predominant form of AD; however, this does not mean that food allergy causes AD. In infants with AD, sensitization with food allergens (in the order of egg, milk, and wheat) is established through percutaneous sensitization before ingestion, especially in severe cases. Thus, these causal foods that the mother has ingested may cause exacerbation of eruptions via breastmilk. However, this is not observed in all infants. After reducing symptoms through suspected food removal by the mother and maintaining remission by topical therapy for 1–2 months, the resumption of such food ingestion by the mother and breastfeeding results in the disappearance of symptom exacerbation in many cases. Therefore, even when sensitization is present, neither long-term food removal by the mother nor breastmilk discontinuation is necessary in many cases.

In older preschool or school age children, the contribution of inhaled allergens intensifies. Other than mites, special attention is necessary to allergens derived from animals such as dogs and cats. The patient should be questioned about potential exposure to pets 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 younger children in recent years, preschool-aged children should also receive particular attention.

Atopic dermatitis is likely to worsen in the summer because of sunburn and sweating, and patients tend to have difficulties in school activities. AD can be improved with appropriate management including showering at school (CQ26). AD is likely to worsen because of skin dryness during the winter, 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 cycle if they become indifferent or are bullied because of AD, further increasing the stress level.

1.4.3 | Laboratory testing

Concerning the serum total IgE level, the upper limit of the normal range is lower at a younger age. However, there is no definite cut-off value at respective ages. In severe AD, this level is markedly high, as described for adults. In the allergen-specific IgE antibody test, food allergen sensitization (such as egg, milk, and wheat) can be observed in many cases during infancy. Sensitization to mites and pollen is observed more often at preschool. Food allergen sensitization does not always require the elimination of causal allergens, and making a careful diagnosis is necessary through a medical interview or the oral challenge test. In particular, the specific IgE antibody level is high in patients with severe AD. A higher probability of symptom induction is estimated through the interpretation of a probability curve; thus, caution is needed (refer to "Japanese Pediatric Guidelines for Food Allergy 2021").[356]

The serum eosinophil count increases in correlation with severity, and during infancy sometimes a markedly high value can be detected. However, levels improve promptly with the improvement of the lesions. As serum TARC and SCCA2 levels correlate well with AD severity, they are useful as a marker of disease progression. The reference range of SCCA2 is unified.[97] However, in children, the TARC level is higher at a younger age, therefore, it is necessary to refer to its range with respect to age.[101] In infants with severe AD, hyponatremia or hypoproteinemia may develop,[357] and biochemical testing is also necessary.

1.4.4 | Treatment

To manage infants, schoolchildren or adolescents widely ranging in age, drugs to be used in each age group must be considered. The basic treatment approach is the same as that of adult patients; however, remission can be achieved in a relatively shorter period during childhood; appropriate treatment should be given according to disease severity. Even in younger children, therapy with medium (group 4) TCS should not be chronically continued.

When eruption reduction is not apparent, ranking up is necessary. A 0.03% tacrolimus ointment should be used in children. This drug is not indicated for infants. 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 (bodyweight ≥50 kg); caution is thus needed.

Children, especially infants, cannot understand that scratching the skin further promotes pruritus, exacerbating dermatitis, and, thus, they should stop scratching; therefore, for pruritus control, TCS are combined with oral antihistamines in many cases. First-generation antihistamines exhibit potent sedative actions, and second-generation antihistamines with low-level intracerebral transfer should be used in children. Specifically, these drugs should be carefully administered to infants or children with febrile convulsions or epilepsy.

The systemic administration of oral steroids has been recommended for the treatment of bronchial asthma attacks or anaphylaxis; however, its effectiveness in the treatment of AD is short-term, and rebound effects are observed following the discontinuation of treatment. Side effects such as growth retardation, osteoporosis, and increased susceptibility to infections, are common with the use of systemic steroids. Thus, their use is not recommended in children as the risk of side effects outweighs the treatment benefits. The administration of oral JAK inhibitors and biologics has commenced in refractory cases that do not improve with conventional treatment in recent years. The age when oral JAK inhibitors or biologics can be used is limited, and caution is needed when indicating these drugs.

The occurrence of eruption around the eyes may become refractory in some cases. Rapid induction therapy with TCS, following maintenance therapy with tacrolimus ointment, is recommended in refractory or recurrent cases. Anti-allergic eye drops for pruritus caused by allergic conjunctivitis may be used concurrently. However, steroid eye drops should be prescribed by ophthalmologists owing to the potential side effect of increased intraocular pressure.

1.4.5 | Change in key caregivers of treatment

Treatment for children is often given through parents or carers, and patient education is usually directed towards them. In particular, during infancy, topical therapy is conducted through the understanding of the disease by parents or carers. However, for children aged ≥2 years, it is possible to approach the patients themselves. It is important to perform topical application while praising the child so that it can be completed without causing discomfort or resistance and make it a habit. The children become somewhat capable of understanding the necessity of ongoing treatment by the time they reach school age. The key caregivers of treatment may shift from parents or carers to the patients themselves when the children reach the upper grades of elementary school. Thus, patient education is not only provided through parents or carers, but also requires the pathophysiology and necessity of treatment to be explained directly to the children in words tailored to their level of understanding. Kindergartens, nursery schools, and elementary schools use the school life guidance form for allergic diseases to ask for cooperation. It provides details on the patient's current treatment, severity, and factors to be considered while at school. As the guidance form is drawn up by family doctors, adequate cooperation may be obtained. As matters to be managed at school, concrete instructions, such as wiping the child's body with a wet towel after sweating, showering if possible, and application of a moisturizer when the air is very dry in winter, should be described.

After adolescence, the key caregiver of treatment will be the patients themself; however, the patient may not have a full understanding of their disease and treatment. It is also common for adolescents to enter a growth phase specific to puberty where they become less inclined to heed the words of parents or carers. This attitude is further compounded by feelings of shame, leading to decreased adherence to topical treatment, thereby potentially exacerbating the eruption. When treating adolescent patients, it is important to confirm who applies the topical drugs and whether they understand the treatment regimen themselves.

When continuing topical treatment beyond adolescence, it is necessary to ensure that patients have an awareness of "accepting the disease" and "managing it well," as the treatment may extend over a long period. To achieve this, it is important for patients to actively confront the disease, and transitional medical care that encourages patient independence is required. Providing transitional support that fosters patient independence from pre-adolescence, taking into account the shift in key caregivers of treatment, plays a crucial role in completing transitional treatment.

1.4.6 | Complications

During childhood, other allergic diseases (such as food allergy, allergic rhinitis, and bronchial asthma) may occur concomitantly in many cases. During infancy, prevention of the development or inducing of rapid remission of food allergy by controlling dermatitis is recommended; thus, appropriate continuous skin care is an important concern.

The prevalence of pollen allergies, represented by cedar pollen, among infants has been increasing in recent years. Some of these patients present with noticeable exacerbation of eruption, in addition to eye and nasal symptoms.

The risk of developing asthma in children with AD is higher than that in the general population. If symptoms suggestive of airway hypersensitivity, such as prolonged post-infection cough and frequent cough related to a loud laugh or inhalation of cold air, are observed, follow-up should be performed while paying attention to the severity. If there is no improvement, medical care should be provided in cooperation with a pediatrician and not by a dermatologist alone.

1.4.7 | Differential diagnosis

In children, AD is frequently observed as a skin disease. However, diseases to be excluded should be considered, as described in the diagnostic criteria. Diseases to be differentiated vary (refer to "Differential diagnosis"). They include neonatal acne, neonatal toxicoderma, seborrheic dermatitis, contact dermatitis, nummular dermatitis, miliaria, candidal intertrigo, and psoriasis vulgaris. Furthermore, AD-associated immunodeficiency syndromes include Wiskott–Aldrich syndrome, HIES, Omenn syndrome, and immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. Congenital skin diseases such as Netherton syndrome, hereditary ichthyosis syndrome (such as recessive X-linked ichthyosis syndrome), and peeling skin syndrome must be differentiated from AD. Extrinsic skin diseases such as scabies, tinea corporis, and insect bites (that secondarily deteriorate to eczema in some cases) must be differentiated from AD in some cases. Zinc or vitamin B deficiency and metabolic diseases, such as phenylketonuria, also cause eczema as a symptom; therefore, they should be differentiated. The above diseases may be complicated by AD; this must be considered for consultation.

Neonatal acne is an acne-like eruption observed mainly on the face, 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 1 month after birth. There is no itching, and if any, it is minor and may improve by washing the face thoroughly with soap. If effusion is observed from the lesions, it may be resolved by applying medium TCS (group 4), and recurrence is unlikely when the TCS are 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 it having exhibited signs of development. According to the criteria set forth by the UK Working Party, infants with AD exhibit decreased barrier function and increased markers of type 2 inflammation at the age of 1 month. Easily distinguishable methods should be developed using objective biomarkers in the future.[358] To distinguish AD in the early stages, the presence of itching is an important sign. If an infant rubs his or 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, these are potential signs to be observed.

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

Contact dermatitis may occur due to daily use of soap, baby bathing products, and detergents used for washing clothes. It is sometimes necessary to be careful about commercially available fabric softeners or detergents that appear harmless for clothes.

If an AD-specific eruption is excluded, or sufficient improvement is not obtained following treatment with TCS, differential diagnosis from other congenital skin diseases is necessary, and referral to a dermatologist should be considered.

1.4.8 | Death owing to medical neglect and complications

Atopic dermatitis is a chronic disease, but severe cases carry a higher risk of complications owing to eczema, sometimes leading to death. Severe AD can be accompanied by hypoalbuminemia and electrolyte imbalances, especially in infants; this can cause life-threatening emergencies.[359] A case of an infant who deteriorated into multiorgan dysfunction owing to the exacerbation of eczema resulting from avoidance of standard treatment with TCS, and who required requiring intensive care unit treatment, has been reported in Hong Kong.[360] Similarly, another case of a patient with AD where dietary therapy was commenced at a private facility to avoid treatment with TCS at the insistence of their caregivers resulting in malnutrition and death was reported in Japan.[361] A further case of an infant who died due to parental TCS phobia led to the arrest of the parents in Australia.[362] In childhood, especially in infancy, it is important to understand that there is a non-zero possibility of deterioration leading to "eczema death." Medical neglect in children refers to situations where, despite the child needing medical care, caregivers fail to provide appropriate medical attention. The MHLW defines medical neglect as situations where caregivers fail to provide necessary medical care to children. Medical neglect is deemed to have serious implications on the life and health of the child. Medical intervention is necessary to ensure the child's safety in such cases; however, consent from the guardian is required for medical institutions to perform these medical procedures. In other words, medical procedures cannot be performed if consent cannot be obtained from the guardian. When actions towards a child are deemed as medical neglect by caregivers, it is necessary for medical institutions or child welfare offices involved in treatment to take appropriate action.[363] Reports from domestic child welfare offices have documented fatalities due to AD resulting from medical neglect.[364]

In adults, there has been a case where a patient with severe AD refused treatment for years owing to TCS phobia. This patient developed infective endocarditis caused by methicillin-sensitive *S. aureus*, further complicated by disseminated intravascular coagulation, resulting in the death of the patient.[365] Large-scale epidemiological studies conducted overseas revealed that patients with severe AD had a significantly higher risk of mortality than healthy individuals. In addition, a significant increase in the risk of mortality associated with infectious diseases, respiratory diseases, and urinary tract diseases was also observed.[366] Similar to children, adults are also at an increased risk of developing various complications and mortality owing to deterioration of poorly controlled severe AD.

2 | CHAPTER II: EVIDENCE-BASED MEDICINES FOR ATOPIC DERMATITIS

In Chapter II, to optimize patient outcomes by medical interventions, reports of clinical research are reviewed, the balance between benefits and harm of medical interventions is evaluated, and recommendation grades and evidence levels are shown concerning 38 important points that require decisions in clinical settings (CQs) including matters that could not be presented in Chapter I. Recommendations, recommendation grades, and their explanations concerning CQs are shown in Table 8.

PubMed, Japana Centra Vevuo Medicina, and Cochrane Library databases were searched for relevant studies (including the literature in electronic media) published by the end of October 2023, in principle.

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,[367] the Clinical Guidelines for Infusion Therapy in Advanced Cancer Patients 2013,[368] and JDA Clinical Practice Guidelines for the Management of Atopic Dermatitis 2021.[16,17]

The evidence level was an eventual judgment concerning the "quality of evidence" based on evidence on (i) important outcomes reached as a consensus of the committee by comprehensive evaluation of the design and quality of research, (ii) whether the results were coherent or consistent, and (iii) whether the subjects, intervention, and outcome of the study were consistent with the assumed situations. The evidence levels range from A to C: (A) "The results are nearly established and are unlikely to be changed markedly by future studies." (B) "There are studies that support the results, but as they are insufficient, they may be changed markedly by future studies." (C) "There are 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 shown in Table 10.[16,17]

Recommendations were comprehensively evaluated based on 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 harm, values, and wishes for treatment. The committee members discussed whether they considered each recommendation to be "strong (1)" or "weak (2)". 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."

However, even if the evidence level was "low" or "very low," if the members unanimously judged the recommendation to be "strong (1)," 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 surpass the harm or burdens

TABLE 8 Clinical questions.

CQ1: Can remission of AD be expected with age?
CQ2: Is the serum TARC level effective as a disease progression marker of AD?
CQ3: Is the serum SCCA2 level effective as a disease progression marker of AD?
CQ4: Are TCS recommended for the treatment of AD?
CQ5: When TCS are to be continued after adequate improvement of eruption is achieved, which is better: Decreasing application frequency or reduction of rank (intensity)?
CQ6: Do AD and AD treatment increase the risk of ocular lesions?
CQ7: Is topical tacrolimus recommended for the treatment of AD?
CQ8: Does tacrolimus ointment increase the risk of skin cancer or lymphoma?
CQ9: Is delgocitinib ointment recommended for the treatment of AD?
CQ10: Is difamilast ointment recommended for the treatment of AD?
CQ11: Is proactive therapy effective in maintaining remission of repeatedly relapsed eczema lesions in AD?
CQ12: Is the oral administration of cyclosporin recommended for the treatment of refractory AD?
CQ13: Is the oral administration of baricitinib recommended for the treatment of refractory AD?
CQ14: Is the oral administration of upadacitinib recommended for the treatment of refractory AD?
CQ15: Is the oral administration of F recommended for the treatment of refractory AD?
CQ16: Is the subcutaneous injection of dupilumab recommended for the treatment of refractory AD?
CQ17: Is the subcutaneous injection of nemolizumab recommended for the treatment of refractory pruritus due to AD?
CQ18: Is the subcutaneous injection of tralokinumab recommended for the treatment of refractory AD?
CQ19: Are antihistamines recommended for the treatment of AD?
CQ20: Is Chinese medicine effective for the treatment of AD?
CQ21: Are TCS safe during pregnancy and breastfeeding?
CQ22: Are antihistamines safe during pregnancy and breastfeeding?
CQ23: Is phototherapy recommended for the treatment of refractory AD?
CQ24: Are topical moisturizers recommended for the treatment of AD?
CQ25: Is the application of moisturizers in neonates recommended for the prevention of AD onset?
CQ26: Is showering useful for reducing AD symptoms?
CQ27: Are soap and detergents effective for the management of AD?
CQ28: Is the allergen elimination diet effective for the treatment of AD during infancy?
CQ29: Are dietary restrictions during pregnancy and breastfeeding effective for preventing AD development in children?
CQ30: Should environmental mite antigens be eliminated for the treatment of AD?
CQ31: Are instructions to avoid keeping pets or to avoid contact with animals effective to prevent AD development or improve symptoms?
CQ32: Are antibacterial topical drugs recommended to improve AD symptoms?
CQ33: Is povidone-iodine solution effective for the treatment of AD?
CQ34: Is bleach bath therapy recommended for the treatment of AD?
CQ35: Is baby bathing effective for eczema during infancy?
CQ36: Is sunscreen recommended for the prevention of exacerbation of AD?
CQ37: Can probiotics or prebiotics improve AD symptoms?
CQ38: Are probiotics or prebiotics effective to prevent AD development?

Abbreviations: AD, atopic dermatitis; SSCA, serum squamous cell carcinoma antigen; TARC, thymus and activation-regulated chemokine: TCS, topical corticosteroids.

TABLE 9 Evidence level.

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

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[a] Many controlled before-and-after trials or observational studies[b] with consistent results
C	A few controlled before-and-after trials or observational studies, case reports, and expert opinions

[a]Including controlled crossover study.

[b]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 Recommendation grade.

1: Strong	The benefits obtained by the recommended treatment are judged to be large and surpass the harm or burdens caused by the treatment
2: Weak	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

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 11). In this event, the physician must carefully counsel 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.

2.1 | CQ1: Can remission of AD be expected with age?

Recommendation

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

Evidence level B

Comments: There are 28 original articles regarding remission of AD with age in Japan and abroad, and all studies have reported that AD showed a certain degree of remission with age. 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 elementary school, 60 (49.6%) who were followed up again in the 6th grade still presented AD, whereas symptoms were resolved in 22 children.[369] Arima et al. started a follow-up cohort study in 2003 on 1778 infants who underwent a 4-month medical examination in three regions (Chiba, Yokohama, and Fukuoka). Accordingly, approximately 70% of the 4-month-old children with AD experienced complete remission (or disappearance) at age 1.5 years, and approximately 50% of infants aged 1.5 years with AD experienced complete remission by age 3 years.[370] Shibuya et al. conducted a birth-cohort survey involving children aged ≤4 years and reported that the remission of AD was achieved at age 4 years in 30 (75%) of 40 children diagnosed with AD at age 1 year. In addition, the remission rate in AD children with food allergy was 57%, whereas the rate in those without it was 95%.[61] Fukiwake et al.[59] conducted annual medical examinations in nursery school children aged ≤5 years 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. Hua et al.[371] followed up 1404 children for 8 years born between 1996 and 2000 in Taiwan who had developed AD before age 2 years and reported that 19.4%, 48.7%, and 69.8% of children experienced remission within 1, 4, and 8 years, respectively. In 2000, von Kobyletzki et al. followed the clinical course for 5 years in 894 children aged 1–3 years who were diagnosed with AD 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.[372] Wan et al.[373] followed-up 8015 children with AD for up to 10 years and reported that the remission rate was higher in those who developed AD at an older age. Zhang et al. followed up 260 children who developed AD before age 2 years and reported remission rates of 50.8% and 70.3% at the ages of 6 and 12 years, respectively. Severe disease, family history of asthma, and sensitization to food have been identified as factors contributing to the persistence of AD.[56] In a recent epidemiological survey, Tanaka et al. conducted health examinations at elementary schools in Hiroshima prefecture between 2010 and 2019. Their study revealed that among the 87 children diagnosed with AD in their first year of elementary school, 51 (58.6%) had achieved remission by the sixth year.[374]

Based on studies, AD may be expected to present a certain level of remission with age. However, the remission rate may vary depending on the extent of symptoms. Factors for a high remission rate include the mild status, older age at the time of onset, and absence of food allergy.

2.2 | CQ2: Is the serum TARC level effective as a disease progression marker of AD?

Recommendation

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

Recommendation grade 2, Evidence level B

Comments: Thirty-nine studies (original papers, but systematic reviews were excluded) have examined the efficacy of measuring serum TARC levels as a disease progression marker of AD in Japan and abroad, and 39 of these 41 articles indicated the usefulness of measuring the serum TARC level. Tamaki et al. studied 128 patients with AD aged ≥18 years and reported a significant correlation between the serum TARC level and the SCORAD index. Changes in the SCORAD index after AD treatment showed a stronger correlation with serum TARC levels than with serum LDH levels or peripheral eosinophil count.[100] Fujisawa et al.[101] examined 65 patients with AD aged ≥6 months and <15 years and reported a significant correlation between serum TARC levels and the SCORAD index; serum TARC levels corresponded well to changes (improvement) after treatment. Maeda et al. measured changes in the serum TARC level over time in 93 adult patients with severe AD. Comparing total IgE levels, LDH levels, and peripheral eosinophil count, the strongest correlation was observed between serum TARC levels and the EASI score. When eruptions improved after treatment, the serum TARC level also decreased. Provision of patient education and TCS application can be based on serum TARC levels as an index; in addition, the serum TARC level can be used as a tool to obtain a favorable outcome.[375] Kakinuma et al. measured the serum TARC levels in 40 patients with AD and reported a significant correlation between the serum TARC level and the SCORAD index. Furthermore, when eruptions improved after treatment, the serum TARC level also decreased.[376] Hijnen et al.[377] studied 276 patients with AD and reported that the serum TARC level was significantly correlated with the Leicester Sign Score, a skin symptom score, and the serum TARC level decreased with the improvement of eruptions after treatment. 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). The extent of the decrease of the SCORAD index and serum TARC levels also correlated.[103] 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 level.[378]

Based on the above, the serum TARC level appears to be the most reliable biomarker that strongly reflects disease progression than other available biomarkers, including serum total IgE level, LDH level, and peripheral eosinophil count, in pediatric and adult patients with AD. In addition, the provision of patient education and application of anti-inflammatory drugs can be reviewed using the serum TARC level as an index. However, the reference level varies depending on age as serum TARC levels increase with decreasing age during childhood. Caution is required because the serum TARC level increases in other skin diseases besides AD, such as bullous pemphigoid and mycosis fungoides.[90] The administration of nemolizumab must be commenced with caution as the serum TARC levels may transiently increase without correlation to the clinical course of AD.[104]

2.3 | CQ3: Is the serum SCCA2 level effective as a disease progression marker of AD?

Recommendation

Measurement of serum SCCA2 levels may be useful as a disease progression marker for pediatric AD.

Recommendation grade 2, Evidence level B

Comments: SCCA exists as two types of proteins, SCCA1 and SCCA2, that are encoded by highly homologous genes known as *SERPINB3* and *SERPINB4*, which belong to the serpin (serine protease inhibitor) superfamily. SCCA was first identified in patients with cervical cancer, and it is highly expressed in tumor cells. Type 2 inflammatory cytokines, IL-4 and IL-13, as well as type 17 inflammatory cytokines, IL-22 and IL-17, induce the production of SCCA from epithelial cells. SCCA is a biomarker of AD, psoriasis, and asthma.[379]

The serum levels of SCCA2 and SCCA1 in children with AD are higher than those in healthy individuals, and these levels are closely correlated with the severity of disease.[109–111,380,381] Compared with SCCA1, SCCA2 shows a higher correlation with severity and treatment responsiveness.[109,111] Furthermore, SCCA2 exhibits a slightly higher diagnostic performance and correlation with severity than TARC.[109–111] The serum TARC levels are often elevated in patients with gastrointestinal allergy. Thus, the assessment is difficult when gastrointestinal allergy is accompanied by AD in infants. Notably, SCCA2 is not elevated in such cases.[382] Among respiratory allergies complicating pediatric AD, the SCCA2 levels rise with acute exacerbations of asthma;[383] however, its levels seldom rise during stable periods of asthma or allergic rhinitis.[109] The serum TARC levels are higher at a young age owing to physiological factors; consequently, age-specific reference values have been set for children. Although the serum SCCA2 levels show a similar trend, its diagnostic performance remains almost equivalent, even at a single cut-off value.[110] Therefore, the serum SCCA2 levels are useful as a marker of the severity of pediatric AD, although reports are limited to Japan.

Compared with that in healthy individuals, serum SCCA2 levels are elevated in adults with AD, reflecting the severity of AD.[112] However, the insurance coverage is limited to children (aged ≤15 years) at present. Notably, serum SCCA levels are also elevated in patients with diseases such as psoriasis, various types of SCC, mycosis fungoides, and Sézary syndrome.[384–387] Thus, SCC2 levels cannot be used to determine the differential diagnosis.

2.4 | CQ4: Are TCS recommended for the treatment of AD?

Recommendation

Topical corticosteroids are considered effective for the treatment of AD. When used appropriately, they have few side effects and are recommended.

Recommendation grade 1, Evidence level A

Comments: The efficacy of TCS was significantly higher than that of placebo regardless of age in several studies.[388–395] Thus, TCS appear to be effective in the management of AD.[75,396]

For topical application frequency, no significant difference was observed between once-a-day use and multiple daily administrations of potent steroids, such as 0.1% halcinonide,[390] classified as class II (high potency),* or 0.05% fluticasone propionate,[397] classified as class III–IV;* however, a significant difference was observed in the remission rate with 0.1% hydrocortisone butyrate[398] classified as class V (lower–medium potency).* While twice-a-day use is recommended in the acute phase, efficacy can also be expected with once-a-day use after the eruptions have subsided.[75]

In terms of safety, when used appropriately systemic side effects are rarely observed in most cases, even with long-term administration.[399]

For local side effects, several studies involving healthy adults have suggested that the use of class I (very high potency)* steroids,[400] such as 0.05% clobetasol propionate, or class III–IV* steroids,[401] such as 0.1% betamethasone valerate and 0.1% mometasone furoate, induced thinning of the skin in comparison with a base. However, in studies involving patients with AD, there was no serious side effect or skin atrophy during follow-up involving twice-a-week application for a few months following the daily application of mometasone[402] or fluticasone for a few weeks. A meta-analysis of pediatric patients revealed adrenal suppression in 3.8% of the patients receiving TCS; however, no clinical symptoms were noted, and the patients' recovery occurred after discontinuation of the administration of TCS.[131] Therefore, side effects can be reduced by limiting the application frequency of TCS in accordance with the resolution of the eruption.[75]

*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).[75]

2.5 | CQ5: When TCS 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 TCS and shift to a moisturizer after the disappearance of eruption in patients with moderate-to-severe AD who may experience relapses.

Recommendation grade 2, Evidence level C

Comments: In patients with mild AD, TCS application should be stopped after adequate improvement of eruption is achieved. Conversely, continuous TCS application is an option for some patients with moderate-to-severe AD who experience repeated relapses. When the application is continued, either should be chosen. The frequency of application per week should be reduced, or a lower-ranked TCS should be used, after achieving adequate improvement to avoid side effects of TCS.

Some studies have demonstrated the effects of the intermittent application of strong TCS (group 3) for the reduction of application frequency on the prevention of eczema relapse during the remission maintenance phase in patients with moderate-to-severe AD.[403–407] In these studies, no increase in the risk of side effects was suggested after TCS application twice to three times a week for a certain period.[167] Furthermore, a clinical study that targeted pediatric patients with moderate-to-severe AD compared the method of sequentially lowering the rank to medium TCS (group 4) with the method of intermittent application by reducing the frequency of administering very strong TCS (group 2) to twice a week after the improvement of eruption. Although no statistical significance was observed, the relapse rate after 4 weeks was slightly lower in the group receiving intermittent application.[408] That is, continuous TCS application with reduced frequency is recommended for relapse prevention and safety.

More studies describe the side effects of long-term use of higher-potency TCS; however, some also reported side effects of lower-potency TCS.[121] Caution should be exercised regarding the potential side effects when lowering the rank and applying TCS daily.

As efficacy varies greatly depending on the disease severity of each patient or adherence to any of these treatment 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 TCS (group 3) if their use is to be continued and shift to a moisturizer.

2.6 | CQ6: Do AD and AD treatment increase the risk of ocular lesions?

Recommendation

As ocular lesions may occur with AD and AD treatment, patients with severe AD, especially those with severe facial eruptions, should be instructed to consult an ophthalmologist at appropriate times. For the prevention of ocular complications, it is important to sufficiently control facial eruptions, especially those around the eyes, in the early phase.

Evidence level B

Comments: Main ocular complications related to AD include blepharitis, keratoconjunctivitis, keratoconus, cataracts, glaucoma, retinal detachment, and bacterial or viral infections.[136,137,320,321,409–411] The incidence of keratitis and conjunctivitis are high in patients with severe AD.[321] TCS may be a

risk factor for glaucoma and cataracts.[135,136] Long-term systemic administration of steroids may lead to the development of cataracts, but the risk also increases with frequent topical application of high-potency TCS.[135,136] However, TCS are not always associated with cataracts,[137,138] as cataracts were already observed in patients with AD before the development of TCS.[412] Cataracts are associated with facial eruptions or disease duration, and both AD-related inflammation and physical stimuli, such as rubbing or hitting the eyes, are involved in the pathogenesis.[138–145] Genetic predispositions also play a role in the development of cataracts.[135] Glaucoma is related to a steroid-associated increase in the intraocular pressure, but AD involvement is also suggested.[135] The use of TCS, especially around the eyes, increases the intraocular pressure or risk of glaucoma, but this does not apply to all patients.[135] When low-ranked TCS are used, this risk is low.[145] The risk of glaucoma is also influenced by a predisposition to glaucoma (corticosteroid responder); however, it is difficult to specify it in advance.[135] Retinal detachment is associated with physical stimuli to the eyes but not influenced by TCS.[135,143] The incidence of keratoconus is high in patients with severe AD,[321] and physical stimuli to the eyes is considered an important factor. However, the involvement of inflammation was also noted.[320] Furthermore, ocular infection with *S. aureus* or herpes simplex virus may occur in patients with AD.

Topical administration of calcineurin inhibitors does not induce skin atrophy, and the percutaneous absorption rate is low. It does not increase the intraocular pressure. Therefore, in adults and children, calcineurin inhibitors are highly safe for the eyes and can be safely used around the eyes.[135] Irritating sensations may occur in the initial phase after the start of the application. However, the continuous application reduces such sensations.[135] Similarly, cyclosporin does not affect the eyes.[135] Treatment with dupilumab increases the frequency of conjunctivitis.[37,201,202,215] In most cases, its severity is mild to moderate and subsides during continuous treatment with dupilumab in some cases, or the treatment of conjunctivitis facilitates the continuation of dupilumab therapy; there are few cases in which dupilumab is discontinued.[135,216] For phototherapy, UVB affects the corneal epithelium or endothelium; therefore, eye protection is necessary.[135] This therapy may induce photo-conjunctivitis or photo-keratoconjunctivitis in a short time, and long-term therapy may induce cataracts. Even UVA may cause cataracts if the treatment period is prolonged. Moisturizers are ophthalmologically safe.[135]

2.7 | CQ7: Is topical tacrolimus recommended for the treatment of AD?

Recommendation

Topical tacrolimus is recommended for patients with AD.

Recommendation grade 1, Evidence level A

Comments: Tacrolimus inhibits T lymphocyte function through a mechanism different from that of corticosteroids. Its efficacy and safety have been confirmed in clinical studies using a vehicle or TCS as a control agent. In clinical studies establishing an improvement in AD symptoms as a primary endpoint, 0.03% or 0.1% tacrolimus ointment was more advantageous than a base or weak TCS, and the efficacy of 0.1% tacrolimus ointment was similar to that of medium-to-strong TCS.[413,414] More potent efficacy of tacrolimus ointment was confirmed in children and adults with mild, moderate and severe AD. Specifically, it was more marked in patients with mild AD.[415,416] Tacrolimus ointment is indicated for patients with AD aged ≥2 years. Concerning the concentration of tacrolimus, 0.03% ointment is recommended for children (2–15 years) and 0.1% ointment for adults (≥16 years). After the short-term (approximately 3 weeks) application of tacrolimus ointment in children (2–15 years), no difference was found in the efficacy between 0.03% and 0.1% ointments.[414] For local adverse reactions, a burning sensation, pruritus, and erythema were confirmed.[417] These symptoms are reduced during continuous application or promptly disappear after discontinuation in many cases. With respect to infectious skin diseases, bacterial or viral infections (herpes simplex, molluscum contagiosum, and viral warts) must be considered.[417] Skin atrophy, which has been reported as an adverse reaction following long-term use of TCS, has not been confirmed in patients treated with tacrolimus ointment. Concerning tumor development, refer to CQ8. Based on these findings, we recommend tacrolimus ointment for the treatment of AD in patients aged ≥2 years, if it is carefully used.

2.8 | CQ8: Does 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 10 of 13 original articles in Japan and other countries, no evidence confirms that tacrolimus ointment increases the risk of skin cancer or lymphoma.[148,149,151,418–422] A long-term, large-scale, prospective cohort study, the APPLES trial, that followed up to 7954 pediatric patients for a maximum of 10 years revealed no significant difference between the group of patients using this drug and the standard group in terms of the risk of developing malignancies.[151] In addition, no evidence supports that tacrolimus ointment increases the risk of lymphoma in four systematic reviews.[423–426]

On the contrary, a retrospective cohort study reported that the incidence of lymphoma in the tacrolimus ointment-treated patients was higher than in TCS-treated patients.[427,428] Another study noted that the incidence of T cell lymphoma in the tacrolimus ointment-treated patients is higher than that in the non-tacrolimus-ointment-treated patients.[429] However, concerning the former, it is concluded that there is a low association between tacrolimus and cancer. Concerning the latter, this survey method was limited regarding the accuracy of AD or lymphoma diagnosis. A study also reported that

severe AD increased the risk of lymphoma. Based on this, the US Food and Drug Administration stated that the above finding did not provide evidence that tacrolimus ointment increases the risk of T cell lymphoma.[430]

Currently, tacrolimus ointment may not be involved in the risk of skin cancer or lymphoma. However, further studies should analyze a larger sample size, or meta-analysis based on long-term follow-up must be conducted to clarify the relationship between the dose or administration period of this ointment and the development of malignant tumors.

2.9 | CQ9: Is delgocitinib ointment recommended for the treatment of AD?

Recommendation

Delgocitinib ointment is recommended for patients with AD.

Recommendation grade 1, Evidence level A

Comments: Delgocitinib inhibits all kinases belonging to the JAK family (JAK1, JAK2, JAK3, and TYK2). It inhibits cytokine signaling, suppressing the activation of immune cells.[152] A phase III study involving patients with moderate-to-severe and mild-to-moderate AD aged ≥16 years in Japan demonstrated significant improvement in the eruption score in the delgocitinib 0.5% group in comparison with the placebo group.[153,154] A phase III study involving patients with pediatric AD aged 2–15 years in Japan also reported significant improvement in the eruption score in the delgocitinib 0.5% and 0.25% groups compared with that in the placebo group.[155] As topical side effects after application, folliculitis, acne, Kaposi's varicelliform eruption, herpes simplex, and contact dermatitis have been reported.[152–154] Furthermore, based on the results of a phase III trial (QBB4-2 trial) that investigated the efficacy and safety of delgocitinib ointment 0.25% and 0.5% for 52 weeks in patients with mild-to-severe AD aged 6 months to 2 years, in an open-label, non-controlled manner, the prescription of delgocitinib ointment became available for patients with AD aged ≥6 months in Japan on January 30, 2023.[156]

In clinical trials involving adults, the maximum application volume was 5 g/session (daily volume of 10 g). However, in the 1% and 3% groups, the frequency of delgocitinib detection in the blood increased in comparison with the 0.25% and 0.5% groups. Even in the 0.5% group, its blood concentration exceeded 10 ng/mL in some patients.[153,154,157] Clinical trials involving children revealed that delgocitinib was not detected in the blood of many patients (83.6%–95.1%) (detection limit 1.00 ng/mL); however, delgocitinib was detected in the blood of some patients.[155] The application at a volume of >5 g/session (daily volume of >10 g), application to erosive surfaces, combination therapy with this drug and classic topical drug attachment, or occlusive dressing therapy may further increase the blood concentration of this drug; therefore, these must be avoided.[158] The instructions in the package insert,[431] such as limiting the amount per application to 5 g based on the child's body size, aiming to apply up to 30% of the BSA, and considering switching from the ointment 0.5% to the 0.25% if the eruptions improve, must be adhered to. Concerning other oral JAK inhibitors, the appearance of malignant tumors, such as malignant lymphoma and solid cancer, was reported. A carcinogenicity study of this drug involving oral administration to rats revealed tumorous changes after massive-dose exposure.[158,432] The possibility of malignant tumors, when the blood concentration of this drug is maintained high, cannot be excluded; therefore, it is necessary to comply with cautions regarding the above application volume or method. With respect to the information on the safety or combination therapy with this drug and other treatments, refer to the "Manual for the safe use of delgocitinib ointment (CORECTIM® Ointment 0.5%)."[158]

2.10 | CQ10: Is difamilast ointment recommended for the treatment of AD?

Recommendation

Delgocitinib ointment is recommended for patients with AD.

Recommendation grade 1, Evidence level A

Comments: Difamilast exerts selective inhibitory effects on PDE4, a member of the PDE family, which is present in several immune cells and can selectively resolve cAMP. Difamilast increases the intracellular cAMP levels in inflammatory cells and epithelial cells by inhibiting PDE4 and suppresses the inflammatory reaction of the skin by controlling the production of inflammatory cytokines and chemokines.[159]

A phase III trial conducted in Japan that targeted patients with AD aged 15–70 years revealed that the proportion of IGA response (defined as IGA score of 0 or 1 and at least a 2-grade improvement) in the difamilast 1% group was significantly higher than that in the placebo group after twice-daily application for 4 weeks.[160] Another phase III trial conducted in Japan that targeted patients with AD aged 2–14 years revealed that the proportion of IGA response in the difamilast 0.3% and 1% groups was significantly higher than that in the placebo group after twice-daily application for 4 weeks. Notably, no statistically significant difference was observed between the 0.3% and 1% groups in terms of efficacy.[161]

Topical side effects of difamilast include hyperpigmentation, folliculitis, pruritus, impetigo, acne, and contact dermatitis.[159] Difamilast can be absorbed percutaneously owing to its low molecular weight of approximately 446;[159] however, systemic adverse events such as gastrointestinal disorders or headaches, commonly observed following treatment with oral PDE inhibitors, were not observed in the above-mentioned phase III trial and long-term administration trial in Japan.[433] The recommended dose of application is approximately 1 g/0.1 m^2 of the eruption. Application on eroded surfaces, occlusive dressing, and pasting a cloth containing zinc oxide ointment should be avoided as these measures increase percutaneous absorption.[162] Furthermore, animal experiments have shown that difamilast can cross the placenta. The safety margin of difamilast was wide in animal experiments; nevertheless, women of

childbearing age must be advised to use appropriate contraception during and for a certain period after the administration of this drug owing to the lack of human data, and it should not be used it in pregnant women or women who may be pregnant.[162]

Thus, when used properly, difamilast ointment is recommended for the purpose of improving symptoms of AD in patients aged ≥3 months.

2.11 | CQ11: Is proactive therapy effective in maintaining remission of repeatedly relapsed eczema lesions in AD?

Recommendation

Proactive therapy is an effective treatment to maintain remission of eczema lesions and is a relatively safe treatment.

Recommendation grade 1, Evidence level A

Comments: Proactive therapy is a treatment in which 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 AD remission. Thirteen RCTs[403–407,434–441] and one systematic review[167] indicated that proactive therapy was useful for maintaining remission. Proactive therapy with TCS or tacrolimus ointment is useful for preventing the recurrence of eczema (Evidence level A). Concerning its safety, many studies have reported the lack of difference in the incidence of adverse events between a vehicle and TCS or tacrolimus during a 20-week/1-year follow-up; proactive therapy may be relatively safe. However, no study has examined the safety of proactive therapy, with a longer follow-up period. With respect to the appearance of adverse reactions, careful observation is necessary. A clinical study targeting pediatric patients with AD compared the efficacy of proactive therapy twice a week with the that of lowering the rank of TCS as the maintenance therapy after treatment with betamethasone valerate. No statistically significant difference was observed; however, the relapse rate of eruption was lower in the proactive therapy group.[408]

Furthermore, 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 for each patient. 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.

2.12 | CQ12: Is the oral administration of cyclosporin recommended for the treatment of refractory AD?

Recommendation

For patients with AD in whom control is difficult, despite the application of TCS or 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.[169,442–444] In a clinical study involving Japanese adults (aged ≥16 years) with severe AD, an initial dose was established as 3 mg/kg/day (if necessary, it was increased or decreased in accordance with symptoms so that it did not exceed 5 mg/kg/day) while reviewing the efficacy and adverse events. Treatment involving the discontinuation period is effective and safe when the administration is completed in 8–12 weeks, or continued.[170,445] 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 cost of the drug pr is high. When selecting cyclosporin therapy for patients with severe AD 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 topical 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.[446] In children, the efficacy was investigated, but the safety of long-term treatment was not sufficiently examined. Cyclosporin therapy for childhood AD has not been approved in Japan.

2.13 | CQ13: Is the oral administration of baricitinib recommended for the treatment of refractory AD?

Recommendation

The oral administration of baricitinib is recommended to patients with moderate-to-severe AD in whom it is difficult to induce and maintain remission by topical therapy.

Recommendation grade 1, Evidence level A

Comments: Both monotherapy with baricitinib[174] and combination therapy with TCS[162,163] significantly reduced eruptions at 16 weeks after initiation in comparison with a placebo in clinical studies involving patients with moderate-to-severe AD with intolerance to topical therapy or insufficient effects. Moreover, generally sustained efficacy was observed even at 68 weeks after initiation in a group of patients who responded to baricitinib.[177] Although it is impossible to directly compare the results as the same patients were not included, combination therapy with TCS is more effective than monotherapy; therefore, topical therapy should also be performed as basic AD treatment during baricitinib administration. However, adverse events are similar to those related to monotherapy; no marked changes in the safety were noted even when TCS are concomitantly used. A merge analysis of clinical studies[178,179] reported that baricitinib administration reduced the risk of infection in comparison with the placebo group, and that the risk of conjunctivitis was comparable. Main serious infectious diseases included Kaposi's varicelliform eruption, cellulitis, and pneumonia. The incidence of herpes simplex virus infection in the 4-mg group was higher than that in the 2-mg and placebo groups.

Thus, baricitinib is useful for inducing and maintaining remission in patients with moderate-to-severe AD in whom it is difficult to induce and maintain remission by topical therapy. TCS should also be combined. For administration, herpes simplex virus infection, including Kaposi's varicelliform eruption, must be particularly considered.

2.14 | CQ14: Is the oral administration of upadacitinib recommended for the treatment of refractory AD?

Recommendation

The oral administration of upadacitinib is recommended to patients with moderate-to-severe AD in whom it is difficult to induce and maintain remission by topical therapy.

Recommendation grade 1, Evidence level A

Comments: Both monotherapy with upadacitinib[182] and combination therapy with TCS[183] significantly reduced eruptions in comparison to placebo in clinical studies involving patients with moderate-to-severe AD with intolerance to topical therapy or insufficient effects. Combination therapy with TCS is more effective than monotherapy; therefore, topical therapy should also be performed as basic AD treatment during upadacitinib administration. However, the adverse events are similar to those related to monotherapy; no marked changes in the safety were noted even when TCS are concomitantly used. The safety profile of patients with AD receiving upadacitinib 15 mg or 30 mg was similar to that of patients with rheumatoid arthritis. Main serious infectious diseases included pneumonia, sepsis, fungal infections, and tuberculosis. The frequency of oral herpes, acne, and the increase in the blood creatine phosphokinase levels was higher in the upadacitinib 30 mg group than those the upadacitinib 15 mg and placebo groups. An open-label, non-blinded, long-term trial that did not restrict the use of topical drugs was conducted in Japan to determine the long-term efficacy and safety of upadacitinib.[184] After 112 weeks of treatment, it has shown favorable efficacy with a safety profile similar to that of short-term studies, demonstrating sustained long-term efficacy in adults and adolescents with moderate-to-severe AD.

Thus, upadacitinib is useful for inducing and maintaining remission in patients with moderate-to-severe AD in whom it is difficult to induce and maintain remission by topical therapy. TCS should also be combined. For administration, oral herpes, acne, and the increase in the blood creatine phosphokinase levels, must be particularly considered.

2.15 | CQ15: Is the oral administration of abrocitinib recommended for the treatment of refractory AD?

Recommendation

The oral administration of abrocitinib is recommended to patients with moderate-to-severe AD in whom it is difficult to induce and maintain remission by topical therapy.

Recommendation grade 1, Evidence level A

Comments: Both monotherapy with abrocitinib[187] and combination therapy with TCS[188,189] significantly reduced eruptions in comparison with a placebo in clinical studies involving patients with moderate-to-severe AD with intolerance to topical therapy or insufficient effects. Combination therapy with TCS is more effective than monotherapy; therefore, topical therapy should also be performed as basic AD treatment during abrocitinib administration. However, adverse events are similar to those related to monotherapy; no marked changes in the safety were noted even when TCS were concomitantly used. In the safety profiles of patients receiving abrocitinib 100 mg or 200 mg, the main serious infectious diseases included opportunistic infections such as sepsis, pneumonia, fungal infections, and tuberculosis. The frequency of nausea, oral herpes, acne, and thrombocytopenia was higher in the abrocitinib 200 mg group than those in the abrocitinib 100 mg and placebo groups. An open-label, non-blinded, long-term trial that did not restrict the use of topical drugs was conducted in Japan to determine the long-term efficacy and safety of abrocitinib.[190] After 48 weeks of treatment, it has shown favorable efficacy with a safety profile similar to short-term studies, demonstrating sustained long-term efficacy in adults with moderate-to-severe AD.

Thus, abrocitinib is useful for inducing and maintaining remission in patients with moderate-to-severe AD in whom it is difficult to induce and maintain remission by topical therapy. TCS should also be combined with this drug. For administration, oral herpes, acne, and thrombocytopenia must be particularly considered.

2.16 | CQ16: Is the subcutaneous injection of dupilumab recommended for the treatment of refractory AD?

Recommendation

The subcutaneous injection of dupilumab is recommended to patients with moderate-to-severe AD in whom it is difficult to induce and maintain remission by topical therapy.

Recommendation grade 1, Evidence level A

Comments: In adult patients with AD, monotherapy with dupilumab significantly reduces eruptions in comparison with a placebo.[37,39,447] Frequent adverse events in the dupilumab group include injection site reactions and conjunctivitis.[37,447] When the administration interval is prolonged by the 16th week, the effects decrease and the frequency of anti-drug (anti-dupilumab) antibody detection slightly increases.[200] Considering maintenance of remission, administration at 2-week intervals should be continued without prolonging the administration interval after inducing remission. Combination therapy with TCS also significantly reduces eruptions in comparison with a placebo.[201] Although it is impossible to directly compare the results as the same patients were not included, combination therapy with TCS is more effective than monotherapy[201]; therefore, topical therapy should also be performed as basic AD treatment during dupilumab administration.

However, the adverse events are similar to those related to monotherapy; no marked changes were observed in safety even when topical steroids were concomitantly used. Furthermore, dupilumab is effective in patients who do not respond to orally administered cyclosporin.[203] The 5-year results of long-term, non-blinded studies with no restrictions on topical drugs were published,[202,205,448] and primary adverse events were similar to those in previous studies; the effects gradually increased. Therefore, it is effective to administer dupilumab in the maintenance phase. Moreover, the anti-drug antibody level was slightly higher in the discontinuation group, but there may be no marked differences in the blood drug concentration or efficacy related to the presence of anti-drug antibody.[202] However, in this study, a dose of 300 mg/QW was adopted; it is unclear whether the results at 300 mg/Q2W, which was approved in Japan, are comparable. A meta-analysis of infectious diseases in clinical studies of dupilumab for AD,[449] merge analysis,[450] and sub-analysis involving a Japanese population[447] demonstrated that the risks of skin infection and Kaposi's varicelliform eruption decreased in comparison with a placebo, and that the risks of all types of herpes virus infection and systemic infectious diseases were similar to those related to a placebo. Furthermore, the incidence of skin infection was lower in the topical steroid-combined group than in the dupilumab monotherapy group.[450] There were increases in the incidences of injection site reactions and conjunctivitis in comparison with a placebo, and the severity of these events was mild to moderate. Based on these studies, treatment with dupilumab may increase the incidences of injection site reactions and conjunctivitis, but not the risk of infection. Indeed, the incidence of skin infections may decrease through dermatitis controlled by dupilumab.

The administration of dupilumab, when used concomitantly with TCS, significantly improved eruption and pruritus compared to placebo in pediatric patients aged ≥6 months in Japan. The increased adverse event in the dupilumab group was conjunctivitis.[451]

Thus, dupilumab is useful for inducing remission in patients with moderate-to-severe AD aged ≥6 months in whom it is difficult to induce remission by topical therapy. TCS should also be combined. In addition, this drug can be used to maintain remission because of its long-term effects and safety. For administration, continuous administration at adequate administration intervals should be selected rather than prolongation of the administration interval or discontinuation or resumption of administration. When administering this drug, injection site reactions and conjunctivitis must be considered.

2.17 | CQ17: Is the subcutaneous injection of nemolizumab recommended for the treatment of refractory pruritus due to AD?

Recommendation

The subcutaneous injection of nemolizumab is recommended for the treatment of moderate-to-severe pruritus due to AD where it is difficult to induce and maintain remission with topical therapy and oral antihistamines.

Recommendation grade 1, Evidence level A

Comments: Nemolizumab significantly improved pruritus compared to a placebo from an early stage[104,221–223] and sustained its efficacy[104,221,222] with 1 year of continuous administration in combination with TCS or tacrolimus ointment in clinical trials targeting patients with moderate-to-severe AD who exhibited inadequate response or intolerance to topical therapy and oral antihistamines. The efficacy of nemolizumab in the management of skin eruption was gradual in onset.[104,221–223] However, its efficacy became progressively higher over time following 1 year of continuous administration.[104,221,222] Furthermore, the QOL, including sleep and work productivity, exhibited improvement early on,[104,221,224,225] and these effects were maintained with the continued administration of nemplozimab for 1 year.[104,221,222,224] Nempolizumab is used primarily to treat pruritus; thus, it is necessary to continue topical treatment (the use of topical anti-inflammatory drugs and moisturizers) for AD during the administration of nemolizumab.[227] The main adverse events observed during 1 year after the administration of nemolizumab were rhinitis and exacerbation of AD.[221] Cases reported as exacerbations of AD in clinical trials include skin eruptions that differ from the typical features of AD.[226] Therefore, the exacerbation of AD itself must be differentiated from other skin eruptions when observing the exacerbation of skin eruptions. Appropriate management measures (such as the application of topical anti-inflammatory drugs) must be commenced in accordance with the pathophysiology. Clinical laboratory tests may reveal a transient increase in the serum TARC levels that do not correlate with the clinical symptoms of AD.[226] Consequently, the serum TARC levels cannot be used as a short-term disease marker for AD for a certain period after the initiation of nemolizumab.

Thus, nemolizumab is useful for inducing and maintaining remission in AD patients with moderate-to-severe pruritus in whom it is difficult to induce and maintain remission by topical therapy and oral antihistamines. Topical therapy should also be combined. During administration, particular attention should be paid to the exacerbation of skin eruptions, including AD.

2.18 | CQ18: Is the subcutaneous injection of tralokinumab recommended for the treatment of refractory AD?

Recommendation

The subcutaneous injection of tralokinumab is recommended to patients with moderate-to-severe AD in whom it is difficult to induce and maintain remission by topical therapy.

Recommendation grade 1, Evidence level A

Comments: Tralokinumab is an antibody drug targeting IL-13 that neutralizes the activity of IL-13 by inhibiting the interaction between IL-13 and its receptor, IL-13Rα1. Both monotherapy with tralokinumab[230] and combination therapy with TCS[231] significantly reduced

eruptions, pruritus, sleep disturbances, and QOL compared to placebo in clinical studies involving patients with moderate-to-severe AD with intolerance to TCS or insufficient effects. Although it is impossible to directly compare the results as the same patients were not included, combination therapy with TCS is more effective than monotherapy; therefore, the use of topical anti-inflammatory drugs should be continued as basic AD treatment during tralokinumab administration. Tralokinumab demonstrated high tolerability lasting up to 1 year in clinical trials. Furthermore, no significant differences were observed between the tralokinumab and placebo groups in terms of frequency of the incidence of adverse events, including serious adverse events.[230–232] An integrated analysis of five clinical trials demonstrated that the risk of skin infections, Kaposi's varicelliform eruption, and severe infections was decreased following the administration of tralokinumab compared to placebo.[233] The frequency of the incidence of conjunctivitis and injection site reactions, which were mild-to-moderate in severity, was increased compared to placebo. These findings indicate that treatment with tralokinumab increases the risk of injection site reactions and conjunctivitis; however, it does not increase the risk of infections. Rather, the incidence of skin infections may decrease owing to the control of AD by tralokinumab.

Thus, tralokinumab is useful for inducing remission in patients with moderate-to-severe AD in whom it is difficult to induce remission by topical therapy. In addition, this drug can be used to maintain remission because of its long-term effects and safety. TCS should also be combined with tralokinumab. When administering this drug, injection site reactions and conjunctivitis must be considered.

2.19 | CQ19: Are 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; therefore, their use is proposed as an "add-on" therapy to topical anti-inflammatory treatment for AD. Non-sedative, second-generation antihistamines should be selected.

Recommendation grade 2, Evidence level B

Comments: Antihistamines are used for the treatment of itching in AD in clinical practice in Japan and abroad. A meta-analysis to assess the therapeutic effects of antihistamines alone concluded no high-quality RCT has been conducted yet.[239] A meta-analysis examining the therapeutic effects of administering TCS in addition to antihistamines has demonstrated a synergistic effect on AD-associated pruritus.[236] In addition, 32 RCTs investigated the efficacy of a combination of antihistamines and topical anti-inflammatory drugs such as steroids and tacrolimus.[237,452–458] Of these, 24 involved adults and eight involved children or adolescents. The effects of this combination on pruritus and safety were examined as primary endpoints, and the interval until the initial flare was also investigated in some RCTs. As secondary endpoints, the reduction of dermal symptoms, dose reduction or drug efficacy-rank reduction of topical steroids and decreases in the serum soluble IL-2 receptor and TARC levels were evaluated. The treatment period ranged from 3 days to 18 months, and 15 antihistamines were used. According to a report from a meta-analysis, the duration and dose of intervention, drug type, combined topical drugs, and evaluation items varied among RCTs, and pooled analysis was impossible. Therefore, three drugs, namely, cetirizine, fexofenadine, and loratadine, were analyzed.[237] As to the final results, no evidence regarding the effectiveness of antihistamines as an "add-on" therapy to topical anti-inflammatory treatment was found. Therefore, the role of antihistamines has not been sufficiently established in guidelines in Europe or the United States. However, studies of non-sedative, second-generation antihistamines in Japan suggested that these drugs reduced pruritus[452–458] and that their combination with topical proactive therapy prolonged the interval until the initial flare.[455,456] Non-sedative, second-generation antihistamines can be safely used for a long period[238] and relieve symptoms of allergic rhinitis or conjunctivitis, urticaria, and dermatographia; therefore, they should be used as an "add-on" therapy to topical anti-inflammatory treatment. However, the long-term use of first-generation antihistamines in children influences the quality of sleep; therefore, it is not recommended.

There is ample variability in the mechanisms that are involved in the itching observed in AD, and the effects of antihistamines on inhibiting itching vary depending on the disease severity and clinical conditions. Therefore, it is recommended to determine whether "add-on" therapy with antihistamines is required on an individual patient basis and to evaluate the effects on itching after the start of therapy.

2.20 | CQ20: Is Chinese medicine effective for the treatment of AD?

Recommendation

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

Recommendation grade 2, Evidence level B

Comments: Most clinical studies examining the usefulness of traditional Chinese herbal medicine for AD were case series involving approximately 20–30 patients. The results of nine double-blind RCTs[242–246,459–462] and one evaluator-blind RCT[463] were reported. Of these, concerning preparations that can be prescribed at general dermatological clinics in Japan, only two studies used Xiao-Feng-San[242] and Hochu-ekki-to.[243] The former involved patients in whom treatment with topical anti-inflammatory drugs, such as TCS, did not reduce eruption, and the latter involved those with Kikyo (easy fatigability or lack of perseverance) based on a questionnaire survey. Both studies simultaneously provided conventional treatment with topical anti-inflammatory drugs, such as TCS. The former reported a significant improvement in eruption in the prescription-treated group in comparison with the placebo group. The latter indicated that the doses of TCS could be decreased.

The basis of Chinese herbal medicine is "zuisho therapy," in which the best suitable treatment is selected based on the 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," whereas eruption is considered a local "pattern;" thus, treatment is provided as a combination of root treatment (to improve the patient's constitution) and symptomatic treatment (to improve symptoms). In this respect, a stereotypical prescription for AD, such as Formulation A, is not useful. 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 of the efficacy of Chinese herbal medicine.

In Japan, formulations of which the effects were investigated in RCTs, or case series studies include Oren-gedokuto, Unseiin, Byakko-ka-ninzinto, Shosaikoto, and Jumihaidokuto.[464] Several studies have suggested their usefulness, but the evidence level is low. Furthermore, pseudohyperaldosteronism related to licorice-containing formulations, as well as Hochuekkito-related interstitial pneumonia, liver dysfunction, and jaundice, has been reported. Adverse events related to traditional Chinese herbal medicines must be considered.

2.21 | CQ21: Are TCS safe during pregnancy and breastfeeding?

Recommendation

The use of TCS according to standard methods during pregnancy or breastfeeding is safe. They may be used without worrying about their influence on fetuses or infants. However, the use of high-dose and high-rank TCS for extended periods may cause low weight at birth.

Evidence level B

Comments: A systematic review in 2015 (involving 1 601 515 participants from 14 observational studies) demonstrated that the use of TCS during pregnancy was not associated with the mode of delivery, congenital malformations (including cleft lip/palate and hypospadias), low birthweight, preterm birth, fetal death, abnormal delivery, or a low Apgar score.[249] Even in the stratified analysis (light to moderate use, heavy to heaviest use), no changes were observed in the risk of cleft lip/palate, preterm delivery, or low Apgar score. An analysis of the Danish birth registry conducted in 2021 revealed no association between the use of TCS during pregnancy and an increase in the risk of low birthweight or small for gestational age infants.[465]

However, an increase in the cumulative use of high-rank TCS can cause a tendency towards low birthweight.[249,252] Although the latest reports suggest no increased risk of low birthweight,[465] it is advisable to avoid excessive or long-term use of high-rank TCS, considering the potential impact on the mother.[253] In contrast, the use of low- or moderate-rank TCS may have a protective effect against fetal death.[249,253]

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

2.22 | CQ22: Are antihistamines safe during pregnancy and breastfeeding?

Recommendation

No association between the use of oral antihistamines during pregnancy and an increased risk of congenital anomalies, miscarriage, or other fetal risks has been observed in previous studies. However, since the evidence is not sufficient, the administration of oral antihistamines may be commenced after receiving informed consent by explaining the risk in comparison with the incidence of malformations as a background (2%–3%) if the therapeutic advantage of administration is great. Certain drugs have been reported to be safe; thus, it is advisable to select these drugs in such cases. The volume of a drug secreted into the breast milk is quite small; thus, their administration during breastfeeding is considered safe. However, first-generation antihistamines can cause irritability and drowsiness in infants owing to their sedative effect. Thus, it is advisable to administer second-generation antihistamines.

Evidence level B

Comments: A meta-analysis (case–control study or prospective cohort study) consisting of more than 200 000 participants who received first-generation antihistamines revealed that the incidence of in congenital malformations did not increase.[466] A recent meta-analysis involving second-generation antihistamines also reported similar results.[467]

Concerning respective antihistamines, the influence of loratadine was examined in many patients. Regarding hypospadias, its lack of association with loratadine was confirmed by a meta-analysis involving 2694 boys exposed to loratadine and 450 413 control boys.[468] Based on this, loratadine was recommended as a second-generation antihistamine to be selected for pregnant women in the guidelines for the management of urticaria.[469] A study reported that desloratadine, an active metabolite of loratadine, is also not associated with a significant increase in the risk of adverse outcomes in fetuses in comparison with loratadine.[470] Concerning cetirizine, the risk of congenital malformations was excluded based on results of several studies,[471] and a prospective cohort study also demonstrated that it has no risk of adverse events in fetuses.[472] 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. Concerning terfenadine (manufacturing was discontinued because of QT prolongation as a side effect), its lack of teratogenicity was confirmed, and also no differences were found in the incidence of congenital malformations or teratogenicity between its active metabolite, fexofenadine, and cetirizine.[473] However, in a case–control study, the National Birth Defects Prevention Study, in the United States, 340 logistic analyses

regarding congenital anomalies and antihistamines involving 44 029 study participants (32 200 patients and 11 829 controls) between 1997 and 2011 revealed 20 significant associations. These associations were not significant through strict statistical adjustment, but some significant associations remained on slightly loose adjustment; neural tube defect, left ventricular hypoplasia, and tetralogy of Fallot were associated with exposure to antihistamines in the first trimester. However, the influence of confounding factors cannot be excluded, and evidence is insufficient. Therefore, future examinations are necessary.[474] On the other hand, a study reported that administration of antihistamines duringearly pregnancy reduced the risk of developing pre-eclampsia.[475]

In a telephone survey of first-generation antihistamines administered during breastfeeding, irritability or somnolentia was observed in a small group of infants; however, none exhibited symptoms sufficiently severe to warrant a visit to a medical facility.[476] In a study examining drug passage into the breastmilk after a single dose of loratadine, four times the recommended dose, the assumed maximum dose transferred to the infant was 1.1% of the mother's general daily dose considering the infant's degree of sucking.[477] A similar pharmacokinetic study was conducted for fexofenadine and suggested that the assumed maximum dose transferred to the infant was 0.45% of the mother's general daily dose.[478] The results of both studies suggested that second-generation antihistamines transferred into the breastmilk were unlikely to have any effects on infants.

Thus, the administration of antihistamines during pregnancy and breastfeeding is considered safe, but the evidence is not complete. If it is therapeutically necessary (i.e., when severe pruritus interferes with the mother's QOL and inhibits the performance of daily activities), drugs that are reported to be safe, such as loratadine, desloratadine, cetirizine, fexofenadine, may be administered. Careful consideration of the contents of package inserts and the latest information on safety profiles is necessary.

2.23 | CQ23: Is UV irradiation therapy recommended for the treatment of refractory AD?

Recommendation

Ultra-violet irradiation therapy may be performed in patients in whom the relief of AD is not achieved by topical therapy, skin care, or strategies to avoid exacerbating factors, or in patients with moderate-to-severe AD with adverse reactions to other treatments.

Recommendation grade 2, Evidence level B

Comments: UV light has inhibitory effects on immune-related cells of the skin; thus, improvement of eruption in AD can be expected.[479,480] As therapy for AD, many studies have reported the usefulness of UVA1 at a wavelength of 340–400 nm and narrow-band UVB with a peak wavelength of 311 nm. In Japan, narrow-band UVB is more routinely used. Some investigators noted that UVA1 is more effective in acute exacerbation and that narrow-band UVB is more effective in the chronic phase. However, neither selection criteria nor irradiation protocol has been established.[256,257,481] Long-term psoralen UVA therapy increases the risk of developing skin cancers,[482] whereas narrow-band UVB therapy does not significantly increase the risk.[483–485] However, with respect to narrow-band UVB therapy, information on the safety of long-term treatment in children is limited. Furthermore, this therapy should be avoided in patients receiving combination therapy with immunosuppressive drugs, those with a history of skin cancer, or a high-risk factor for skin cancer, and those with photosensitivity. Thus, UV therapy must be performed by skilled physicians.

2.24 | CQ24: Are topical moisturizers recommended for the treatment of AD?

Recommendation

The use of topical moisturizing agents is recommended for treatment of dermatitis in combination with TCS 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. A topical moisturizer restores the reduction of water content in the stratum corneum and reduces symptoms and itching caused by skin dryness.[260–262,486–491] Any direct effects on dermatitis cannot be expected; however, moisturizers improve skin dryness and itching when used in conjunction with TCS with anti-inflammatory activity and are effective in maintaining remission of dermatitis after symptoms were resolved.[262,492] Continuous use of moisturizers even after achieving remission of dermatitis is effective to prevent relapses of dermatitis and maintain mitigated itching.[262,266,493–495] The moisturizing efficacy of twice-daily topical applications (morning and evening) is higher than that of once-daily applications.[263] The amount of application plays an important role in determining the moisturizing efficacy; the finger-tip unit is used as a guide for the amount of application (refer to Chapter I). However, it should be noted that adverse events such as contact dermatitis might occur following the use of moisturizers.

2.25 | CQ25: Is the application of moisturizers in neonates recommended for the prevention of AD onset?

Recommendation

Currently, the application of moisturizers in neonates for the prevention of AD onset is not unconditionally recommended.

Recommendation grade 2, Evidence level B

Comments: Skin barrier dysfunction is closely involved in AD onset.[496] Therefore, improving the skin barrier function may prevent AD onset. Moisturizers potentiate the water-retaining function of the skin, thereby improving the skin barrier function. Furthermore, they are evaluated as safe.[497] Two RCTs regarding the preventive effects of neonatal moisturizer application on AD onset were reported

in 2014. Simpson et al.[308] and Horimukai et al.[309] conducted RCTs and reported that the application of moisturizers from infancy significantly aids in the prevention of the onset of AD. Several RCTs conducted subsequently have reported evidence supporting the preventive effect of the application of moisturizer on the onset of AD; however, several RCTs have reported contrasting results.[498–503] Conflicting evidence regarding the preventive effect of the application of moisturizers from infancy on the onset of AD has been presented. Notably, this effect was not conclusively demonstrated, even in a recent meta-analysis.[504]

Table S10 summarizes the main points of these RCTs. As shown in the Table, study design factors such as participants, sample size, content of the moisturizer, or even the climate of the region, the results may vary in the RCTs. Further systematic reviews should be conducted in the future to accumulate further data.

Currently, neonatal moisturizer application for the prevention of AD is not unconditionally recommended.

2.26 | CQ26: Is showering useful for reducing AD symptoms?

Recommendation

Showering is useful for reducing AD symptoms.

Recommendation grade 1, Evidence level B

Comments: A study reported that many patients select showering rather than soaking in the bath regardless of the presence of eczema.[505] Furthermore, there is an expert opinion that showering inhibits sweat-induced pruritus.[506] In Japan, three school tap water showering intervention studies involving children with AD were conducted.[507–509] Showering significantly reduced AD symptoms. Its effects may be more marked in seasons that induce increased sweat volume. In addition, a significant decrease was found in the number of *S. aureus* colonies on the skin 4 weeks after the start of the showering intervention.[509] No adverse events were recorded. A meta-analysis analyzed the relationship between the frequency of bathing/showering and the improvement in the severity of AD.[510] A quantitative meta-analysis revealed that the severity of AD in patients receiving bath/shower therapy decreased at one or more time points compared with that at baseline. A qualitative meta-analysis revealed that bathing/showering frequency of ≥7 times per week resulted in significant improvement in IGA, extent of skin lesions, and pruritus. However, no statistically significant difference was observed between the bathing/showering ≥7 times per week and <7 times per week groups in terms of effectiveness. Furthermore, no association between daily showering/bathing and exacerbation of severity was observed. Larger and more rigorously designed RCTs must be conducted in the future to determine the optimal frequency of bathing/showering. Based on the above-mentioned studies, including the absence of reports of adverse events, showering may aid in reducing AD symptoms.

2.27 | CQ27: Are soap and detergents effective for the management of AD?

Recommendation

Soap and detergents may be useful for the 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 skin symptoms. Therefore, keeping the skin clean using detergents is important to maintain the physiological functions of the skin. Despite the lack of high-quality evidence supporting the efficacy of soap and/or detergent in the treatment of AD, a case series study evaluating the use of general soap conducted in patients who did not use soap, but rather prolonged bathing reported an improvement of symptoms without evidence of exacerbation.[271,272] In another study, soap washing on the unilateral upper and lower limbs and hot water washing on the contralateral upper and lower limbs were continued for 4 weeks in the autumn and winter in children with AD in whom AD control was favorable, and no difference was found in the eruption score between the soap and hot water sides.[511]

As the major component of soap and/or detergent is surfactants, excessive use of these products may exacerbate skin dryness by dissolving lipids on the skin surface or intercellular lipids present in the stratum corneum. Transient pH elevation after soap use causes a temporary decrease in barrier functions.[512,513] Moreover, additives in detergents, such as pigments and perfumes, are believed to cause skin irritation. Based on these results and the above studies, soap or cleanser may be useful for keeping the skin clean. However, when using them, the status of AD-related eruption control, age-, site-, or season-based skin condition, type of soap or cleanser, and washing methods must be considered.

Thus, the use of soap should be limited and thoroughly rinsed using hot water (approximately, 38°C–40°C). If patients exhibit marked dry skin or exhibit specific skin areas with severe dryness, or have severe irritation caused by soaps and/or detergents, or if the climate is seasonally dry, cleansing products with markedly low degreasing power should be selected. For oily skin or seborrheic areas, areas in which ointment is applied daily and areas presenting recurrent skin infections, the active use of soaps and/or detergents can be considered to circumvent exacerbating factors. No evidence currently available supports the superiority of product types (soap [solid] or detergent [liquid using synthetic surfactant]). Selecting appropriate detergents is important, for example, detergents with basic chemical properties to ensure 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 avoidance of detergents that lead skin dryness after cleansing. It is also important that the detergent produces sufficient foam, so as not to damage the skin,

and allows the removal of dirt from the skin in the least irritating way. Patients should be cautious of residual detergents on the skin.

2.28 | CQ28: Is the allergen elimination diet effective for the treatment of AD during infancy?

Recommendation

Unless the 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[277] of nine RCTs was reported in the Cochrane Collaboration 2008.[514–522] Overall, the quality of those RCTs was poor; thus, their evidence level was 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 ineffective for AD.

2.29 | CQ29: Are dietary restrictions during pregnancy and breastfeeding effective for preventing AD development 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 AD onset. The 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 (AAP) recommended avoiding 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.[304,523,524] Thus, the recommendation was waived in 2008, and the AAP decided not to recommend dietary restrictions 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.[278] In the same review, dietary restriction during pregnancy was likely to impair fetal growth. Several studies noted no preventive effects of dietary restriction for the mother during pregnancy or breastfeeding on the onset of AD.[525,526] Based on the above, dietary restriction during pregnancy is not useful in preventing AD; thus, it is not recommended.

Dietary restriction in breastfeeding mothers was also not useful in preventing AD development in their children similarly to during pregnancy in the above-mentioned Cochrane systematic review.[278] A measure was taken for indoor mites, whereby allergen elimination occurred concomitantly with dietary restriction during breastfeeding; as a result, the rate of AD development decreased in some cases. However, the efficacy of dietary restriction alone has not been elucidated.[527] A study reported that dietary restriction for the mother during breastfeeding within 3 months after birth did not prevent the onset of allergy at age 10 years.[528] For all these reasons, dietary restriction during breastfeeding is not useful in preventing AD development; thus, it is not recommended. The excessive intake of a specific food during pregnancy may promote the onset of food allergy because a frequent intake of peanuts during pregnancy was reported to be associated with sensitization to peanuts in infants.[529,530] In 2019, the AAP commented that dietary restriction for the mother during pregnancy or breastfeeding is not recommended, as announced in 2008.[531]

With respect to the maternal diet during pregnancy, the incidence of AD in children was high when free sugar or resistant starch intakes were high;[532,533] however, no report of the incidence of AD being suppressed by restricting these substances has been published.

No sufficient evidence actively recommends dietary restriction during pregnancy and breastfeeding to prevent AD development in children; thus, dietary restriction is not useful.

2.30 | CQ30: Should environmental mite antigens be eliminated for the treatment of AD?

Recommendation

Strategies to decrease the mite antigen level in a living environment may be considered for patients in whom the results of an interview 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 tests, or skin tests are positive for mite antigens. 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), whereas 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 through, the relief of AD-related eruption was achieved in addition to a decrease in the level of mite antigens in bedclothes.[534–538] In contrast, according to some studies, such a strategy against mite antigens decreased the antigen level, but there were no effects on eruption.[539,540] A clinical study involving long-term follow-up should be conducted by unifying the subject background and strategies against mite antigens.[541]

The characteristics of patients in whom mite antigen avoidance leads to an improvement in AD-related eruption are unclear. Thus, evaluation should not be performed based on clinical symptoms or hematological data alone.

When eruptions deteriorate or reduce with environmental changes, such as visits to a dusty place or traveling, in the presence of strong sensitization with mite allergen on blood or skin prick tests, mite avoidance strategies such as ventilation, frequent bedroom or living room cleaning (every 3 days or more), bedclothes cleaning with a vacuum cleaner (for 20–30 s/m^2, once a week), sun drying, and sheet washing[542] should be conducted to review whether or not eruption reduces.

2.31 | CQ31: Are instructions to avoid keeping pets or to avoid contact with animals effective to prevent AD development or improve symptoms?

Recommendation

It is not useful to instruct pregnant women and children to avoid contact with pets and animals for the prevention of AD. For patients sensitized to pets and animals in whom contact-related exacerbation is expected, guidance to avoid contact is useful.

Evidence level B

Comments: (From the viewpoint of AD prevention) A meta-analysis regarding the relationship between pet parenting and contact with animals during pregnancy, infancy, and childhood and the risk of AD revealed that a history of pet parenting or contact with animals in pregnant women or children reduced the risk of AD or did not influence it.[543–545] From the viewpoint of AD prevention, it is not always useful to instruct pregnant women and children to avoid contact with pets or animals.

(From the viewpoint of symptom reduction) When sensitization to animal antigens is established, contact with pets or animals may exacerbate symptoms. Not a few patients are sensitized to cat antigens regardless of a history of pet parenting. The result of the specific IgE test for cat antigens discloses that contact with cats is an exacerbation factor in some cases.[546] For patients sensitized to pets or animals in whom contact-related exacerbation is expected, guidance to avoid contact for the prevention of symptom exacerbation is useful. However, pets may support the mental state of humans, and it is necessary to review guidance in accordance with each patient's relationship with pets.

2.32 | CQ32: Are antibacterial topical drugs recommended to improve AD symptoms?

Recommendation

The use of topical antimicrobial drugs for reducing the skin symptoms of AD is not recommended.

Evidence level A

Comments: According to a systematic review to evaluate the therapeutic effects of intervention with topical antimicrobial drugs on AD, no sufficient evidence confirmed their efficacy regardless of the presence of infection.[547] The tested antimicrobial drugs included erythromycin, povidone-iodine, farnesol, and hyperforin. A study compared the therapeutic effects of antimicrobial drug-containing TCS (combination drugs) with those of TCS alone (monotherapy) and found that the effects of these combination drugs in a short period were slightly more potent (however, the quality of evidence is not favorable), whereas there was no improvement in the QOL.[547] Antimicrobial drugs contained in the tested combination drugs were flucloxacillin, mupirocin, fusidate, neomycin, tetracycline, gentamicin, didecyldimethylammonium chloride, and triclosan.[547] In addition, the clinical efficacy of a topical steroid containing an antimicrobial drug (neomycin) and an antifungal drug (nystatin) was not superior to that of a topical steroid free from these drugs.[547]

In AD patients with skin infection, the use of topical antimicrobial drugs may be a treatment option.[548,549] However, the demerits of topical antimicrobial drug application must be considered. As antimicrobial drugs, chlorhexidine and fradiomycin, may serve as sensitizing antigens for patients with AD.[550,551] Furthermore, the long-term use of antimicrobial drugs may induce resistant bacteria.[548] The local application of fusidic acid can lead to the emergence of fusidic acid-resistant *S. aureus* strains. A study conducted in Denmark revealed that 41% of *S. aureus* isolates obtained from patients with AD showed resistance to fusidic acid. Furthermore, the positivity rate for the resistant strains was 94% among the strains isolated from patients who had received topical treatment with fusidic acid within the past 3 months.[552]

Thus, the use of topical antimicrobial drugs for reducing AD symptoms, excluding their short-term use for skin infection control, is not recommended.

2.33 | CQ33: Is povidone-iodine solution effective for the treatment of AD?

Recommendation

No medical evidence actively recommends the use of povidone-iodine solution. It may be considered an adjuvant therapy for cases that are difficult to treat using first-line TCS because of infection; however, povidone-iodine should not be used without careful consideration of safety concerns.

Evidence level C

Comments: *S. aureus* is more frequently isolated on skin lesions in patients with AD than in the healthy population and is considered a well-known exacerbation factor of AD.[553] Therefore, eradication of *S. aureus* using disinfectants (e.g., povidone-iodine solution and hypochlorous acid) has been applied for the treatment of AD.

In Japan, povidone-iodine solution is often used as a disinfectant, and a study reported the potential efficacy of some disinfectants for AD.[554] However, no RCTs using a control group have been conducted; thus, its efficacy is limited to empirical evidence. A study reported that the effects of povidone-iodine solution on the eradication of *S. aureus* were similar to those of soap.[555] Side effects may include

the progression of dermatitis caused by irritation on the eroded surface, allergic contact dermatitis, anaphylaxis, and effects on thyroid function.[556,557]

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 is not recommended for general use. Povidone-iodine solution may be considered an adjuvant therapy for cases that are difficult to treat with first-line TCS and topical moisturizers and whose concomitant skin infections will lead to additional difficulty in controlling eczema.

2.34 | CQ34: Is bleach bath therapy recommended for the treatment of AD?

Recommendation

Bleach bath therapy is not currently recommended.

Evidence level B

Comments: *S. aureus* is more frequently isolated from skin lesions in patients with AD than in the healthy population. A reduction in the variety of the skin bacterial flora with an increase in the number of *S. aureus* may be one of the exacerbation factors for AD.[291,296,558]

In Europe and United States, hypochlorous acid has been used as a disinfectant. Recent studies have reported the efficacy of bleach bath therapy, (i.e., taking a bath containing 0.005% hypochlorous acid twice a week) as a treatment method to control the proliferation of *S. aureus* and maintain the variety of the skin bacterial flora.[291,295,559–561]

In 2014, the American Academy of Dermatology announced that bleach bath therapy should be recommended as a treatment option for patients with moderate-to-severe AD and possible presence of infection.[146] In 2018, the European Task Force on Atopic Dermatitis suggested that taking a bath containing a disinfectant, such as hypochlorous acid, is effective for AD.[207]

Conversely, several studies have reported that bleach bath therapy did not have better effects on skin barrier functions than in the control group.[562,563]

Furthermore, no product is available for human use in Japan, and the environment for implementing bleach bath therapy is not well-established. Thus, bleach bath therapy is not recommended in Japan at present.

2.35 | CQ35: Are baby bathing products effective for eczema during infancy?

Recommendation

There is no evidence that the use of baby bathing products improves eruptions. There is also no evidence of moisturizing effects. Thus, its use for the improvement of eczema is not recommended.

Evidence level C

Comments: Products available for baby bathing in Japan contain ingredients such as saturated fatty acids, fatty alcohols, animal-derived waxes, plant-derived fats and oils, and animal-derived fats and oils. These ingredients are expected to have moisturizing and anti-inflammatory effects. In addition to these agents, cleansing agents such as surfactants, fragrances, preservatives, are also included. However, the composition varies depending on the product. Among 25 articles retrieved using the search term "baby bathing product" in the Japan Medical Abstracts database, none reported moisturizing effects or improvement in eczema.[564–569] In contrast, a study reported that switching from washing the face with baby bathing products to washing it with foamy soap reduced the frequency of eruptions in neonates.[570]

A systematic review conducted overseas revealed that several baby bathing products (Dead Sea salt, hard water, commercially available infant cleansing agents (different from products in Japan), oatmeal, rice, and natural oils) were effective as adjunctive therapy for AD.[571] However, few high-quality studies have analyzed this effect. A large-scale RCT that followed up children with AD aged 1–12 years for 1 year revealed no difference in the primary evaluation parameter, the POEM score, the amount of TCS use, or QOL.[572]

Thus, there is no evidence supporting the notion that the use of baby bathing products is effective in treating eczema during infancy. However, it cannot be denied that preservatives such as parabens or surfactants may cause contact dermatitis.[573–576] Thus, the use of these products for the purpose of improving eczema during infancy is not recommended.

2.36 | CQ36: Is sunscreen recommended for the prevention of exacerbation of AD?

Recommendation

As excessive sunlight exposure is an exacerbating factor of eruption in AD, using sunscreen products that do not contain a UV-absorbing agent should be considered when spending extended time outdoors and when the exposure to UV light is prolonged.

Recommendation grade 2, Evidence level C

Comments: UV light has inhibitory effects on immune-related cells of the skin; thus, improvement of AD eruptions can be expected.[479,480] Indeed, UV light therapy is occasionally performed under a doctor's guidance to improve eruptions and itching in AD.

Conversely, high temperatures on the skin surface and sweating due to the action of infrared radiation, a part of sunlight, may exacerbate erythema or itching of the eczematous lesion,[577] and UV light may reduce skin barrier functions.[578,579] Therefore, excessive exposure to sunlight may be an exacerbating factor for AD.[580]

As AD is not known to be photosensitive, strict protection from sunlight is unnecessary. However, some clinical studies have reported the preventive effects of sunscreen on the exacerbation of AD.[581–583] Therefore, precautions are recommended, for example, wearing a hat and walking in shadows as much as possible when the patient goes out between May and August under intense UV light in Japan, especially between 10 am and 2pm when the amount of UV light is at its maximum. Sunscreen is recommended in the case of prolonged exposure to UV light.[479]

Recommended sunscreens are those that are easy to apply, have a certain degree of protection from UV light (sun protection factor and protection grade of UVA are the indexes), do not have chemical UV-absorbing agents (non-chemical), and contain a UV-scattering agent.[479] However, sunscreens should not be used on weeping and moist lesions or scarred lesions caused by scratching. If possible, a sample of the product should be tested in a small area on the posterior ear or on the arm for several days to confirm that there are no contraindicating issues.

2.37 | CQ37: Can probiotics or prebiotics improve AD symptoms?

Recommendation

Specific probiotics or prebiotics cannot be recommended to all patients with AD to reduce their symptoms at present.

Evidence level A

Comments: Makrgeorgous et al.[337] reported a systematic review and meta-analysis involving 39 RCTs regarding probiotics-related reduction of AD symptoms in the Cochrane Collaboration. Of these RCTs, 14 involved infants aged ≤18 months. In these RCTs, *Lactobacillus* or *Bifidobacterium* alone or a combination of several probiotics was administered, or a combination of probiotics and prebiotics was administered. A meta-analysis revealed that the administration of probiotics resulted in no significant improvement in pruritus, sleep disturbances, and QOL. However, a slight improvement in the severity score of SCORAD was observed but is unclear whether it is meaningful for patients. Five meta-analyses published subsequently reported significant improvement in SCORAD.[333,584–587] RCTs targeting adults[588,589] and RCTs administering multiple probiotics[590–592] reported improvement in SCORAD. In contrast, RCTs targeting children reported mixed results, with some exhibiting efficacy[590–596] and others exhibiting no such effect.[597–599]

No systematic review or meta-analysis has evaluated the reduction of AD symptoms related to the administration of prebiotics alone. However, Boženský et al.[340] conducted an RCT to assess the effects of monotherapy with prebiotics on infantile AD symptoms and noted no significant prebiotics-related reduction of symptoms. On the contrary, Shibata et al.[339] reported that prebiotics administration with ketose was effective in reducing infantile AD symptoms. A consensus regarding the reduction of AD symptoms related to the administration of prebiotics alone has not been reached.

Chang et al.[336] reported a systematic review and meta-analysis regarding the reduction of AD symptoms related to synbiotics in which probiotics are combined with prebiotics. A meta-analysis of six RCTs involving children and adults demonstrated that synbiotics significantly reduced AD symptoms. However, a subgroup meta-analysis of three RCTs involving infants aged <1 year suggested no significant synbiotics administration-related reduction of AD symptoms. An RCT involving infants aged <1 year published in 2022 revealed that the administration of multi-strain synbiotics and vitamin D resulted in improvement in SCORAD.[591]

The emerging consensus from numerous references is that there are both highly effective and less effective probiotics. The combinations of various *Bifidobacteria* and *Lactobacilli* strains tend to be effective; however, their effectiveness in infants is generally low. The duration of administration and evaluation times vary; however, evaluations were often conducted at 4, 8, and 12 weeks. Thus, while it is clear that some probiotics and their combinations have therapeutic effects on AD, specific probiotics or prebiotics cannot be recommended to all patients with AD. Further research is necessary to determine the differences in efficacy based on strains and patient ages.

2.38 | CQ38: Are probiotics or prebiotics effective to prevent AD development?

Recommendation

The administration of probiotics or prebiotics for the prevention of AD onset is not recommended.

Evidence level B

Comments: The preventive effects of probiotics, prebiotics, and a combination of these (synbiotics) on AD onset were examined in ≥20 RCTs. The timing of administration (to mother during pregnancy or breastfeeding and to children between the neonatal period and infancy), bacterial species (*Lactobacillus*, *Bifidobacterium*, a mixture of them), and type of oligosaccharides varied among studies.

Several systematic reviews of RCTs have been published.[334,335,600–607] Most systematic reviews concluded that the administration of probiotics to the mother during pregnancy and infant after birth prevented AD during childhood.[600–604] In contrast, some studies have noted no effect of administration to the infant after birth alone or the administration of only *Lactobacillus*.[334,604,605] Furthermore, even some RCTs demonstrating the preventive effects on AD onset during infancy have reported the disappearance of such effects during long-term follow-up.[608–610]

Regarding the administration of prebiotics alone, several RCTs have noted its preventive effects, but a systematic review concluded that they have no preventive effects.[335]

Although probiotics are expected to be effective in preventing AD onset, further studies are needed to determine the methods, such as the subject, timing, and bacterial species. Currently, it is too early to recommend probiotics or prebiotics for the prevention of AD in pregnant women or infants in clinical practice.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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