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CLINICAL GUIDELINE

Clinical Practice Guidelines for the Management of Atopic Dermatitis 2016

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ABSTRACT

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

Key words: **atopic dermatitis, clinical practice guideline, diagnosis, evidence-based medicine, treatment.**

CHAPTER I

Introduction

Atopic dermatitis (AD) is frequently encountered in clinical practice. The Guidelines for the Management of Atopic Dermatitis of the Japanese Dermatological Association (JDA) were first prepared in 2000 and basically designed for dermatologists who treat patients in primary care to advanced specialty-required phases in the treatment of AD.[1] Thereafter, they were revised in 2003 and 2004.[2,3] In 2008 and 2009, the guidelines for the management of AD, in which diagnostic criteria for AD, severity classification and treatment guidelines were integrated, were prepared.[4,5] The present guidelines were prepared as a regular revision for all children to adults with all severities of AD, involving internationally published novel findings on AD. In this revision, in Chapter II, 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

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several important points requiring decision-making in clinical practice are presented.*[6]

More than 15 years have passed since the first guidelines were prepared in Japan. In clinical practice, we still encounter a large number of patients in whom the protracted symptoms of AD reduce their quality of life (QOL) or affect their social lives. This is a great loss not only for patients and their families, but also socioeconomically. It is one of our duties to improve this situation. Multiple factors are involved in the pathogenesis and triggering factors of AD and several factors must also be considered for treatment. They, thus, lead to confusion when determining therapeutic strategies. In addition, topical therapy may be influenced by the discretion of the patients or parents, and treatments with topical anti-inflammatory agents such as corticosteroids are more likely to be avoided.

In such a situation, descriptions regarding medical activities in the present guidelines reflect an aim and goal in the current† strategies to treat AD in Japan from the perspective of evidence-based medicine (EBM). They can be utilized as a material for evaluations of decision-making in clinical practice. Attending physicians must make a final decision in cooperation with patients so that their values and preferences are reflected. If the contents of medical activities based on an individual's circumstances differ from those stated in the present guidelines, they may not be checked, or the experience of healthcare professionals may not be denied. In contrast, even if the contents stated in the present guidelines are not performed, the responsibilities of physicians may not be pursued.

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

Definition

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

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.[4]

Pathogenesis

The pathogenesis of AD can be explained from the perspectives of the skin barrier, allergic inflammation and pruritus.[7]

Skin barrier

The stratum corneum plays a major role in skin barrier function. It is known that three factors comprising this layer are important for maintaining skin barrier function: (i) intercellular lipids, such as ceramide; (ii) the parenchyma of cornified cells consisting of the metabolites of keratin and filaggrin; and (iii) cornified cell envelope consisting of a protein comprising the membrane of cornified cells. Skin barrier function is reduced in patients with AD; therefore, skin irritability to non-specific stimuli is enhanced, frequently causing inflammation. Extrinsic factors, such as an excessive air conditioning-related dry environment, are considered to affect the skin barrier. A recent study reported that filaggrin gene (*FLG*) mutations were involved in the pathogenesis of AD.[8] Even when no *FLG* gene abnormalities were present, the expression of filaggrin was reduced under the T-helper (Th)2‡ cytokine (interleukin [IL]-4 and -13)-predominant environment in the skin tissues of most patients with AD.[9] Filaggrin aggregates keratin fibers, and, when decomposed, contributes to water retention/pH reductions in the cornified layer as a natural moisturizing factor. Therefore, the skin of patients with AD in whom filaggrin levels are decreased tends to be dry and alkaline.

Allergic inflammation

A reduction in skin barrier function leads to antigen (allergen) invasiveness in the skin. Non-self-antigens are eliminated by immune/allergic reactions. Allergens, such as mites and pollen, function as protein antigens, and induce Th2-type immune responses that are mediated by the proteases contained in them. Th2-type immune responses then induce the production of IgE. The Th2 chemokine produced in the epidermis, thymus and activation regulated chemokine (TARC, CCL17), is also generated under a Th2 environment.[10]

Pruritus

The effects of histamine H_1-receptor antagonists (antihistamines) on AD-related pruritus vary among patients, and differ from those on urticaria which respond to antihistamines. Therefore, the presence of a mediator other than histamine has been suggested. A recent study reported that IL-31, a cytokine produced by Th2 cells, induced pruritus.[11] Furthermore, pruritus-transmitting C fibers were found to be distributed in the epidermis and cornified layer of patients with AD, and may lead to hypersensitivity to pruritus.[12]

Course and prognosis

Although AD shows a chronic course, remission may be achieved when symptoms are continuously controlled by appropriate treatments. According to the published work, age-related remission was achieved in a specific proportion of patients with AD (CQ18: Evidence level: B). The remission rate

*Recommendation grades: 1, strong recommendation: the advantage of the recommended treatment is significant, and may exceed treatment-related stress; and 2, weak recommendation (suggestion): the advantage of the recommended treatment is inaccurate, or may antagonize treatment-related adverse reactions and stress (refer to Chapter II).

†In principle, data of clinical studies available by the end of December 2013 were used.

‡Th2: a subgroup of helper T cells that produces the cytokines involved in humoral immune responses, such as IL-4, IL-5 and IL-13. This group plays an important role in the pathogenesis of allergic inflammation.

was higher in patients with milder symptoms. The proportion of mild-status patients was higher, and the remission rate was higher in a survey performed to determine morbidity rates in health check-ups than in a survey involving patients who consulted hospitals.

Diagnosis

Diagnostic criteria

Based on the "Definition and Diagnostic Criteria for AD" (revised in 2008) prepared by the JDA in 1994, patients meeting three basic items are regarded as having AD regardless of the severity of symptoms: (i) pruritus; (ii) typical morphology and distribution of the eczema; and (iii) chronic or chronically relapsing course (usually coexistence of old and new lesions).[4,13] Eruption is symmetrically distributed, and frequently develops on the forehead, periorbital area, perioral area, lips, periauricular area, neck, joint areas of limbs, and trunk. Its distribution is characterized by age. During infancy, eruptions initially appear on the scalp and face, often expanding to the trunk and limbs. It appears in AD-specific sites during childhood, such as the neck, and the flexural surfaces of the arms and legs. During adolescence/adulthood, it becomes marked in the upper body, including the face. AD-suspected patients are regarded as having acute or chronic eczema, and diagnoses are made based on their age and courses. In a revision published in 2008, cutaneous lymphoma, psoriasis, immunodeficiency diseases (such as hyper-IgE syndrome and Wiskott–Aldrich syndrome), collagen disease (systemic lupus erythematosus and dermatomyositis), and Netherton syndrome were newly added as disorders to be ruled out (Table 1).[4,5] Therefore, it is essential to differentiate these disorders and be familiar with the complications of AD. Internationally, the diagnostic criteria prepared by Hanifin and Rajka in 1980 are widely used.[14]

Severity classification

Severity classification for the whole body. The classification of the severity of AD prepared by the Atopic Dermatitis Severity Classification–Reviewing Committee of the JDA is available for clinical studies because its statistical reliability and usefulness have been verified (Fig. 1) (maximum score, 60).[15] As a simple method reviewed by this committee, a method to divide the whole body into five sites – the head and neck region, anterior trunk, posterior trunk, upper limbs, and lower limbs – and calculate the sum of the global assessment scores of these sites is also presented (Fig. 2) (maximum score, 20).[16] In addition, as another simple method, the target of severity has also been proposed by the Research Group of the Ministry of Health, Labor and Welfare (Reference Table S1).[17] Internationally, the Severity Scoring of Atopic Dermatitis (SCORAD) (maximum score, 103)[18] established by the European Task Force on Atopic Dermatitis or the Eczema Area and Severity Index (EASI) (maximum score, 72)[19] in the USA is widely used.

Reference: Evaluation of pruritus— The visual analog scale (VAS) is useful for evaluating pruritus.[20,21] In this scale, 1 point is marked on a 10-cm axis in accordance with the degree of pruritus, and the distance (mm) from the left end to the marked point is evaluated as the pruritus scale score, regarding the left end "no itch" as 0 and the right end "the worst imaginable itch" as 100.

Reference: Evaluation of the QOL— The Skindex-16 and Dermatology Life Quality Index (DLQI) have been statistically analyzed.[22,23] Their Japanese versions were published, and have been applied to the treatment of various skin diseases including AD.[24,25]

Severity of eruptions. The primary treatment, application of topical corticosteroid, should be determined based on "the severity of each eruption" (Tables 2,3).[4,26,27] Briefly, potent topical therapy is selected to treat severe eruption even when its extent is narrow. However, it is not required for patients with mild eruption even when its area is extensive. Therefore, "the severity of each eruption" is the most important factor to consider when selecting topical therapy, and a severity assessment must be performed by physicians with dermatological skills in order to evaluate severity and predict the treatment response.

Examinations for diagnosis and severity assessment

Serum IgE level. Total serum IgE levels are high in approximately 80% of patients with AD. This parameter is useful for making diagnoses. In adults, a total serum IgE level of 200 IU/mL or greater is regarded as high (differs among examination organizations). In infants, the upper limit of its normal range is lower at a younger age.[28] The total serum IgE level reflects the long-term severity and activity of AD, but not its short-term changes. The IgE antibody may be produced in patients with AD in response to several allergens, such as mites, house dust, pollen, fungi and foods. Most patients show positive reactions on serum allergen-specific IgE antibodies and skin prick tests.

Peripheral blood eosinophil counts, serum lactate dehydrogenase (LDH) levels and TARC levels. The parameters of the short-term severity and activity of AD include peripheral blood eosinophil counts, serum LDH levels and TARC levels.[10] According to the published work, serum TARC levels were useful as a marker of the disease activity of AD. The published work analysis indicated that serum TARC levels more sensitively reflected the activity of AD than serum IgE levels, LDH levels and peripheral blood eosinophil counts in children and adults with this disease (CQ11: Evidence level: B).[29,30]

It may also be possible to review patient education and treatments by using serum TARC levels as a parameter. Serum TARC levels are higher in younger children. Therefore, its reference range differs among ages (adults, <450 mg/mL; children aged ≥2 years, <743 pg/mL; children aged 1 year, <998 pg/mL; and infants aged 6–11 months, <1367 pg/mL).

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

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

Diagnostic criteria for atopic dermatitis

1. Pruritus.
2. Typical morphology and distribution.

(1) Diagnostic criteria for eczematous dermatitis

- acute lesions: erythema, exudation, papules, vesiculopapules, scales and crusts
- chronic lesions: infiltrated erythema, lichenification, prurigo, scales and crusts.

(2) Distribution

- Symmetrical.
  Predilection sites: forehead, periorbital area, perioral area, lips, periauricular area, neck, joint areas of limbs, trunk.
- Age-related characteristics

Infantile phase: starts on the scalp and face, often spreads to the trunk and extremities
Childhood phase: neck, the flexural surfaces of the arms and legs
Adolescent and adult phase: tendency to be severe on the upper half of body (face, neck, anterior chest and back).

3 Chronic or chronically relapsing course (usually coexistence of old and new lesions)

- More than 2 months in infancy
- More than 6 months in childhood, adolescence and adulthood.

Definitive diagnosis of atopic dermatitis requires the presence of all three features without any consideration of severity.
Other cases should be evaluated on the basis of the age and clinical course with the tentative diagnosis of acute or chronic, non-specific eczema.

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

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

Clinical types (not applicable to the infantile phase):
Flexural surface type, extensor surface type, dry form in childhood, head/face/neck/upper chest/back type, prurigo type, erythroderma type, combinations of various types are common.

Table 1. (continued)

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

Cited from references[4,13] with modification.

Treatments

Goal of treatment

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

Treatment measures

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

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

Drug treatment

Topical anti-inflammatory drugs. Drugs that potently reduce AD-related inflammation and of which the efficacy and safety have been scientifically examined include topical corticosteroids and tacrolimus (a topical calcineurin inhibitor). Other topical preparations include non-steroidal anti-inflammatory drugs (NSAIDs). However, the anti-inflammatory actions of NSAIDs are extremely weak, and contact dermatitis is often induced. Patients for whom NSAIDs are indicated are limited. It is important to promptly and accurately reduce inflammation related to AD, and treatments are based on how topical corticosteroids and tacrolimus should be selected/combined for this purpose. Therefore, it is necessary to adequately evaluate the site of inflammation based on a visual inspection and palpation and apply these drugs to a sufficient extent.

Topical corticosteroids— Previous studies indicated that the efficacy of topical corticosteroids was significantly greater than that of a placebo regardless of age, excluding a few articles.

This severity classification can be adopted only for the cases that are definitely diagnosed as atopic dermatitis.

Three elements of eruption are evaluated in the most severely affected part of each of the five body regions (15 times in total).

The areas of eruption on the five body regions are also evaluated (5 times in total). Both scores are totalized (20 times in total).

For evaluation of severity of eruption on each region, the severest part is selected for each element.

Evaluation of the area of eruption should be done considering all three elements for all five body regions.

The highest possible score is 60 points.

	Head/neck	Anterior trunk	Posterior trunk	Upper limbs	Lower limbs	
Erythema/acute papules						
Exudation/crusts						
Chronic papules/nodules/ lichenification						
Area of eruption						

Total Score

Evaluation method

I. Evaluation criteria for three elements of eruption

0 = absent, 1 = mild, 2 = moderate, 3 = severe

*Explanation of three elements of eruption

Erythema: All the redness, flushing and edema are included, acute papules: Papules not affected by scratching.

Exudation/crusts: Erosion by scratching is included.

Chronic papules: Papules affected by scratching. Nodules/lichenification: Eruption in which chronic papules progressed further.

II. Evaluation criteria for area of eruption

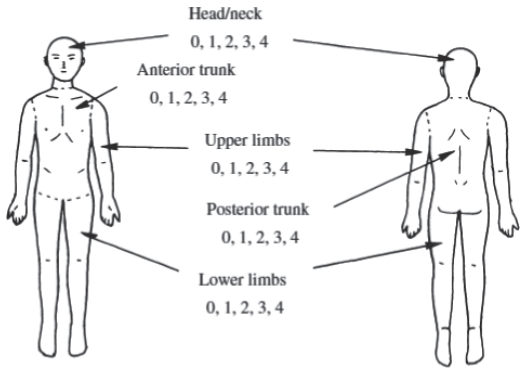
0 = no eruption, 1 ≤ 1/3, 2 = 1/3 ~ 2/3, 3 ≥ 2/3

(Cited from Ref. 15 with modification).

Figure 1. Severity classification of atopic dermatitis by the Japanese Dermatological Association.

Severity in each region (evaluated globally by considering both degrees and areas of eruption).

(Evaluation of area of eruption should be done considering all the eight elements; erythema, papules, erosion, crusts, excoriation, lichenification, pruriginous nodules, depilation)



Evaluation method

The entire body is divided into five regions as illustrated in the figure.

Severity is evaluated globally for each region (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe), and their total is calculated.

The highest possible score is 20 points.

(Cited from ref. 16 with modification)

Figure 2. Severity classification of atopic dermatitis by the Japanese Dermatological Association (simple method).

These drugs may reduce inflammation related to AD (CQ1: Recommendation grade 1, Evidence level: A). In some cases, a method to apply different topical corticosteroids on the left and right sides, or another method to apply a topical corticosteroid and topical preparation other than topical corticosteroids on the left and right sides, respectively, is useful for selecting appropriate topical preparations for individual patients.

1 Rank: A rank table of topical corticosteroids prepared by modifying Takeda's classification is shown in Table 3.[4,26,27] It is important to adequately select drugs at a rank that matches the severity of each eruption using this rank as an index and use them at the required volume for the required period.

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

3 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).[31,32] This may be adopted as a reference, considering the physical status of Japanese individuals and the tube size of topical corticosteroids available in Japan.

4 Frequency of application: As a rule, topical corticosteroids should be applied twice a day (morning and evening: after bathing) in cases of acute exacerbation. When inflammation is reduced, the number of applications should be decreased to once a day to induce remission. Further evidence needs to be accumulated in order to determine whether efficacy differs between twice-a-day and once-a-day applications. However, several randomized controlled studies and systematic reviews reported no significant difference in efficacy between twice-a-day and once-a-day applications.[33,34] It is generally recognized that even a once-a-day application exhibits potent effects. If the number of applications is low, the incidence of adverse reactions may be low, thereby improving adherence. Therefore, topical corticosteroids should be applied twice a day to control acutely exacerbated eruptions for an early recovery. When the condition subsides,

Table 2. Severity of eruption and topical corticosteroid application

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

Cited from reference [1].

Table 3. Rank of topical corticosteroids

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

As of September 2015. Cited from reference [1] with modification.
In the guidelines adopted in the USA, corticosteroids are classified into seven ranks (I, very high potency; II, high potency; III–IV, medium potency; V, lower-medium potency; VI, low potency; VII, lowest potency).[26] In Europe, they are classified into four ranks (very potent, potent, moderately, mild).[27] When referring to international clinical trial data, it must be considered that the rank classification of topical corticosteroids differs from that in Japan.

topical corticosteroids should be applied once a day to achieve remission (CQ2: Recommendation grade 1, Evidence level: B).

5 Discontinuation of application: When discontinuing topical corticosteroids after reductions in inflammatory symptoms have been achieved, the dose should be gradually decreased, or intermittent administration (including proactive therapy [described below]) should be performed while maintaining remission.

6 Infants/children: As a rule, topical corticosteroids one rank lower than those presented in Table 2 should be used when the severity of eruption is evaluated as severe or moderate. However, when their effects are not obtained, higher-rank topical corticosteroids may be used under strict management to promptly reduce the condition without protracting marked inflammation.

7 Face: In the area including face and neck where the drug absorption rate is high, the appearance of local adverse reactions to topical corticosteroids must be particularly considered. Therefore, long-term continuous use should be avoided. As a rule, medium-class or lower topical corticosteroids should be used. For patients with severe dermatitis, such as eruption with lichenification, drugs should be initially selected in accordance with the severity of eruption to promptly achieve remission, and then the dose should be gradually decreased, or continuous therapy must be switched to intermittent administration. Tacrolimus ointment is frequently indicated for the face, and its guidance-based administration should be positively considered.

8 Adverse reactions: With respect to systemic adverse reactions, previous studies reported that the application of potent topical corticosteroids induced adrenal hypofunction in some patients.[35,36] However, neither adrenal hypofunction nor a growth disorder was observed in patients treated with weak topical corticosteroids.[37,38] If these preparations are adequately used, the incidence of systemic adverse reactions is low, and safety is high. Skin atrophy, capillary dilatation, steroid acne, steroid flushing, hypertrichosis, atrophic striae and the deterioration of bacterial/fungal/viral skin infections may sometimes occur as local adverse reactions; however, most of them except for atrophic striae are relieved by discontinuation of topical corticosteroids or an appropriate treatment.

9 Combination therapy with antimicrobial drugs: Some topical corticosteroids contain antimicrobial drugs. The addition of antimicrobial drugs have not shown advantage to monotherapy with topical corticosteroids for relieving the symptoms of AD. Therefore, monotherapy with corticosteroids is appropriate for reducing the symptoms of AD. When infection concomitantly develops in the affected site, topical corticosteroids with antimicrobial drugs should not be applied; infection-specified treatments should be considered if necessary (CQ4: Evidence level: A).

10 Management of anxiety for topical corticosteroid therapy: The misunderstanding of topical corticosteroids (confusion with adverse reactions to oral corticosteroids, confusion regarding the exacerbation of AD with adverse reactions to topical corticosteroids) results in excessive fear/avoidance of topical corticosteroids, which reduces treatment adherence. Thus, there are often cases in which the expected therapeutic effects are not obtained. Furthermore, inappropriate use-related ineffectiveness sometimes leads to doubt about the usefulness of topical corticosteroids. In order to resolve these misunderstandings, it is necessary to explain how to use topical corticosteroids and guide patients over a sufficient consultation time.

Reference: Adverse reactions to topical corticosteroids in the eyes— Adverse reactions to topical corticosteroids for lesions around the eyes include cataracts and glaucoma (CQ3: Evidence level: B, cataract [the risk is not increased]; C, glaucoma [the risk is increased]). The exacerbation of facial eruption, habitual percussion and AD-related inflammation are considered to be risk factors for cataracts.[39–41] Therefore, eruption control is important for the prevention of cataracts. The risk of glaucoma may be low if weak, low-dose corticosteroids are

applied.[42] However, not a few patients have been reported to develop glaucoma following topical corticosteroid therapy; therefore, the volume and application period of topical corticosteroids (especially strong corticosteroids) must be carefully established when applying them around the eyes or to the palpebral skin, and switching to tacrolimus ointment should also be considered. If these ocular complications are suspected, patients should be referred to a department of ophthalmology at an appropriate time.

Reference— With respect to tachyphylaxis: In some cases, symptoms that have initially subsided may recur during treatments with topical corticosteroids. Previous studies indicated that this phenomenon was associated with rapid effect attenuation (tachyphylaxis) related to the long-term use of topical corticosteroids. The vasoconstrictive actions of corticosteroids have been investigated, and the influence of topical corticosteroids on histamine-related vasodilatation was examined. The findings obtained revealed a reduction in the vasoconstrictive actions of corticosteroids 14 days after initiating their application, and their effects were attenuated earlier in the presence of dermatitis.[43,44] These studies also performed experiments to inhibit the effects of histamine using corticosteroids. We cannot directly apply these findings to AD because mechanisms other than those involving histamine may be important. In a previous study involving patients with the chronic inflammatory disease, psoriasis, none of them showed detectable signs of tachyphylaxis during 12 weeks of treatment with topical corticosteroid.[45] If the expected effects are not obtained during treatments for dermatitis, it is also important to confirm whether the topical corticosteroid has been correctly applied.

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

The efficacy of this drug depends on drug absorption: the site of application and barrier function. It is recognized as a drug to be frequently indicated for the eruption on the face and neck. However, there are restrictions for its application that differ from topical corticosteroids: tacrolimus ointment cannot be applied to erosive or ulcerative surfaces, and its drug efficacy is limited. This drug must be administrated according to the "Guidance for the Application of Tacrolimus Ointment in Patients with Atopic Dermatitis".[46] It has to be prescribed by physicians, with high-level specialty, who understand the guidance contents; that is, items such as patients for whom this drug should be indicated, age, contraindications, relative contraindications and careful administration. Tacrolimus ointment is available at the following concentrations: 0.1% for adults and 0.03% for children. It cannot be selected for children aged 1 year or younger as its safety has not yet been established for this age group. Its application should also be avoided in pregnant or lactating women.

1 Volume: A volume of 0.1 g (corresponding to a volume squeezed by 1 cm from a 5-g tube commercially available in Japan) is appropriate for a 10-cm square. Based on the findings of a long-term observational study involving adults, the upper limit of the volume of a 0.1% ointment per session for adults was established as 5 g to avoid an increase in its blood concentration and maintain its safety. In accordance with the physical status, the maximum volume of a 0.03% ointment per use was established as 1 g for children aged 2–5 years (bodyweight, <20 kg), 2–4 g for those aged 6–12 years (bodyweight, 20–50 kg) and a maximum of 5 g for those aged 13 years or older (bodyweight, ≥50 kg). The target volume of this ointment per area measuring 10 cm × 10 cm is 0.1 g (1-cm volume pushed out from the 5-g tube commercially available in Japan).
2 Application method: Irritative symptoms, such as a transient burning sensation and hot flushes, often appear at the site of application. However, these symptoms appear at the start of treatment, and most symptoms disappear with improvements in eruption. This should be explained to patients before the start of treatment. This ointment is very effective for the face and neck, in which its percutaneous absorption is favorable. This ointment should be indicated when conventional therapy with topical corticosteroids is ineffective (e.g. sites in which local adverse reactions to topical corticosteroids are observed) or when physicians hesitate to administrate these drugs due to adverse reactions. The efficacy of this ointment (0.1% for adults) for the trunk and limbs may be similar to that of strong-class topical corticosteroids.[46] When treating the site of severe eruption, which requires potent drug efficacy, very-strong-class or stronger topical corticosteroids should initially be used to reduce eruption, as a rule. The regimen should then be switched to tacrolimus ointment. The volume of topical corticosteroids can be decreased in many cases by combining them with this ointment. If an improvement in eruption is achieved by this ointment, the interval of application should be prolonged at an appropriate time. This ointment should not be used in sites/eruption areas in which blood transfer of this drug may increase and enhance irritability, that is, mucosa/genital areas and erosive/ulcerative surfaces. Occlusive dressing technique and superposition methods should not be adopted because they may increase the blood transfer of this drug. When erosive/ulcerative surfaces are markedly affected, the application of this ointment should be started after the amelioration of the eruption using other topical drugs. Percutaneous absorption is increased in patients with ichthyosiform erythroderma including Netherton syndrome. The blood concentration of this drug may increase, inducing adverse reactions such as nephropathy. This ointment cannot be used in such cases.
3 Adverse reactions: A burning sensation, pruritus and erythema have been identified as local adverse events. These symptoms decrease or disappear with improvements in eruption in many cases. Furthermore, the appearance of infectious diseases of the skin, such as secondary skin

infections with bacteria and viral infections (e.g. herpes simplex, molluscum contagiosum and verruca), must be considered. Skin atrophy, which is observed with the long-term use of topical corticosteroids, has not been confirmed. Tacrolimus is detected in the blood following its topical application. Individual differences have been reported in blood levels of tacrolimus due to differences in percutaneous absorption (application of 0.1% tacrolimus: ≤1 ng/mL). Neither systemic adverse events nor toxicity related to blood transfer has been confirmed.

Risk of carcinogenesis — Evidence to show that the use of tacrolimus ointment does not increase the risk of skin cancer or lymphoma is increasing (CQ6: Evidence level: B). Although previous studies reported the development of lymphoma during treatments with tacrolimus ointment, these were retrospective in nature. Limitations have been associated with the accuracy of lymphoma diagnoses, and lesions evaluated as AD-related eruption before the use of this ointment may have been lymphoma.[47,48] In addition, a previous study indicated that severe AD increased the risk of lymphoma. Therefore, AD may increase the incidence of lymphoma. An interim report was published in Japan on the safety of applying tacrolimus ointment (for children) in children with AD over a long period,[49] in which the onset of malignant neoplasms was not identified as an adverse event during a maximum follow-up period (7 years). However, a large sample size and long-term follow up are needed for a carcinogenetic analysis. In the future, the relationship between the volume of tacrolimus ointment/application period and the development of malignant neoplasms must be analyzed through a long-term follow up.

Proactive therapy— Proactive therapy refers to a treatment method in which, after inducing remission by an acute-phase treatment for repeatedly relapsing eruption, topical corticosteroids or tacrolimus ointment is periodically applied to the skin (e.g. twice a week) in addition to skin care with moisturizers in order to maintain remission (CQ8: Recommendation grade 1, Evidence level: A). On the other hand, a method to control inflammation by using anti-inflammatory drugs for topical use again at the time of flare is termed reactive therapy.

In patients with AD, inflammatory cells were histologically shown to remain, even in skin that appeared to be normal after inflammation subsided, causing the recurrence of inflammation.[50] In such cases, the levels of markers that reflect the disease activity, such as TARC, would not decrease to the normal range. The recurrence of inflammation can be prevented in many cases in the period during which latent inflammation persists by continuing anti-inflammatory drugs for topical use, such as topical corticosteroids and tacrolimus ointment, or performing proactive therapy.[51] However, it is important to switch the continuous topical application of anti-inflammatory drugs to proactive therapy after sufficient improvements in dermatitis are achieved. It is necessary to establish the extent of application, timing of switching to intermittent application and timing of completion in accordance with individual patients. With respect to the appearance of adverse reactions, careful follow up is needed. Therefore, proactive therapy should be performed by physicians who are familiar with the assessment of skin symptoms in patients with AD or in cooperation with physicians who are familiar with the assessment of skin symptoms. Daily skin care with moisturizers should also be continued during proactive therapy.

Oral antihistamines. Pruritus is a symptom that reduces the QOL of AD patients, as is stated in the definition of this disease. Because pruritus-related scratching induces the aggravation of dermatitis, infectious diseases and ocular complications, its control is important. Histamine H_1-receptor antagonists (antihistamines) are widely used to treat AD-related pruritus (CQ7: Recommendation grade 1, Evidence level: B). However, their effects markedly differ among patients. Although many studies support this therapy in Japan,[52–57] there are many negative opinions in Europe and the USA.[58,59] In the treatment of AD, it is the most important to reduce dermatitis by using topical anti-inflammatory drugs, such as corticosteroids and tacrolimus. The p.o. administration of

Table 4. Antihistamines and anti-allergic drugs used for atopic dermatitis

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

As of January 2015. Cited from reference [60] with modification.

Table 5. Classification of antihistamines by sedative effect

Non-sedative
Fexofenadine hydrochloride (120 mg)
Epinastine hydrochloride (20 mg)
Levocetirizine (5 mg)
Loratadine (10 mg)
Ebastine (10 mg)
Cetirizine hydrochloride (10 mg)
Olopatadine hydrochloride (5 mg)
Bepotastine besilate (10 mg)
Less sedative
Azelastine hydrochloride (1 mg)
Mequitazine (3 mg)
Cetirizine hydrochloride (20 mg)
Sedative
d-Chlorpheniramine maleate (2 mg)
Oxatomide (30 mg)
Diphenhydramine tannate (30 mg)
Ketotifen fumarate (1 mg)
d-Chlorpheniramine maleate (5 mg/ i.v.)

Cited from references[62–64] with modification.

antihistamines is recommended as adjuvant therapy. Antihistamines have been classified into two types: (i) first-generation drugs, the anticholinergic and sedative actions of which are relatively strong; and (ii) second-generation drugs without anticholinergic actions (Table 4).[60] The use of non-sedative second-generation antihistamines is recommended for the following reasons: no differences have been reported in treatment responses, and the incidences of adverse reactions, such as sleepiness, malaise and impaired performance, are low (Table 5).[61–64] On the other hand, antihistamines are not effective for pruritus in all patients with AD. It currently remains unclear which type of patient or eruption should be treated with antihistamines. When administrating these drugs, it is important to consider whether eruption/pruritus control is possible with topical anti-inflammatory drugs and moisturizers alone. In addition, the effects of antihistamines on pruritus should be evaluated at an appropriate time.

Cyclosporin. The efficacy of cyclosporin for AD has been demonstrated in many countries in Europe and the USA.[65] It has been approved for use by patients with AD (CQ12: Recommendation grade 2, Evidence level: A). A high-quality clinical study was conducted in Japan,[66] and, in 2008, the use of cyclosporin was approved for patients with severe adult AD who do not respond to conventional treatments, showing eruption with marked inflammation involving 30% or more of the body surface area. This drug is also effective for patients with refractory erythema on the face or erythroderma. Because the severity of pruritus promptly decreases after its administration, cyclosporin is also useful for improving the QOL of patients with marked pruritus-related eruption or scratching. The initial dose of this drug is 3 mg/kg per day. It should be increased or decreased in accordance with symptoms, but in such a manner that it does not exceed 5 mg/kg per day. Its administration should be completed in 8–12 weeks. Factors such as nephropathy, hypertension and infection must be considered during therapy with cyclosporin. As the safety of its long-term administration has not yet been established, it is important to promptly switch cyclosporin therapy to conventional topical treatment after the amelioration of symptoms. Intermittent administration involving a 2-week or much longer period of discontinuation should be performed if long-term administration is necessary.

Cyclosporin is administrated p.o. after meals twice a day. However, a pharmacokinetic study involving patients with psoriasis showed that the blood concentration of this drug was higher when administrated before eating once a day.[67] Therefore, the therapeutic effects of once-a-day administration before meals may be more prominent than those of twice-a-day administration after meals.

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

Chinese herbal medicine. Previous clinical studies examined the usefulness of traditional Chinese herbal medicine for the treatment of AD. In most studies, the number of patients was approximately 20–30. Only two double-blind, randomized controlled studies examined the Chinese herbal medicine preparations which are possible to be prescribed by general dermatological clinics in Japan: *Shofu-san* or *Xiano-Feng-San*[68] and *Hochu-ekki-to* (CQ13: Recommendation grade 2, Evidence level: B).[69] The former was administrated to patients in whom treatments with topical anti-inflammatory drugs, such as corticosteroids, did not reduce eruption, while the latter was given to patients regarded as having a delicate constitution based on a questionnaire score (such as easy fatigability or lack of perseverance), in combination with conventional treatments with topical anti-inflammatory drugs, such as corticosteroids. The severity of eruption was significantly less in a *Shofu-san*-treated group than in a placebo group, while *Hochu-ekki-to* allowed doses of topical corticosteroids to be decreased. Furthermore, an international double-blind, randomized controlled study with Zemaphyte® (Phytopharm, Cambridge, UK) indicated its efficacy,[70,71] whereas another study group did not.[72] Traditional Chinese herbal medicine for AD must be carefully reviewed in the future by evaluating whether a uniform prescription of "*Kampo* preparation A for AD" or selecting a *Kampo* preparation based on the characteristics of eruption is adequate or not.

Considerations for pregnant/lactating women (such as drug therapy and the significance of dietary restrictions). During pregnancy, many pregnant women become anxious about the

influence of drugs that they take on their fetuses as well as the onset of childhood AD or food allergies.

Some patients discontinue drug therapy due to anxiety regarding its influence on fetuses, leading to the deterioration of symptoms. However, the required treatments should also be adequately performed during pregnancy/lactation.[73,74] Standard topical corticosteroid therapy (CQ22: Evidence level: B) shows low-level absorption in systemic circulation, and neither congenital anomalies nor the influence on fetal growth has been raised as an issue. However, we cannot rule out the possibility that birthweight may be decreased by the massive application of topical corticosteroids classified as potent/very-potent groups according to the classification used in Europe. Therefore, attention should be paid to the volume of ointment used and fetal growth. Furthermore, it is important to favorably control dermatitis before pregnancy in order to avoid this anxiety. If the application of corticosteroids to the breasts of lactating women is necessary, care must be taken to prevent infants from directly ingesting topical corticosteroids.

Regarding antihistamines among those for systemic administration, an epidemiological study did not show relationship between first-generation antihistamines, loratadine or cetirizine, and congenital anomalies.[73] Therefore, it may be appropriate to administrate these drugs, if necessary (CQ21: Evidence level: B). However, in clinical practice, management should be conducted based on the package inserts and latest information on safety. For lactating women requiring the administration of antihistamines, the use of non-sedative second-generation antihistamines is commonly recommended,[74] but caution is needed for individual drugs as mentioned above.

Topical therapy/skin care for abnormalities in skin barrier function

The water content of the stratum corneum is reduced in patients with AD, leading to dry skin and reduced skin barrier function.[7] Skin inflammation related to non-specific stimuli or pruritus may frequently occur in the presence of this physiological abnormality in the epidermis, and percutaneous sensitization or allergic inflammation may be induced through the invasion of various allergens. The use of moisturizers (moisturizing/protecting agents) for the dry skin reverses the reduction in the water content of the stratum corneum, thereby promoting skin barrier function recovery, preventing the recurrence of dermatitis/invasion of allergens, and inhibiting pruritus (CQ9: Recommendation grade 1, Evidence level: A).[75,76] Furthermore, the continuous application of moisturizers after the relief of dermatitis related to treatment with topical anti-inflammatory drugs is useful for maintaining remission.[77,78] Topical corticosteroids or tacrolimus should be used in sites in which the recurrence of dermatitis is observed during maintenance therapy in accordance with the grade of inflammation to reduce inflammation in the early phase and resume maintenance therapy. On the other hand, the development of contact dermatitis, as an adverse reaction to moisturizers, must be considered. It is important to differentiate contact dermatitis from the recurrence of AD.

Investigation of triggering factors and avoidance

If the above drug therapy is sufficiently performed based on a relationship of mutual trust established between patients and physicians, the objective of treatment can be achieved in many cases. However, daily/social life-related aggravating factors specific to individual patients exist in most cases. It is important to investigate such factors and establish strategies to avoid them.

Food. The involvement of food allergens has been suggested in patients with AD, especially in infants. However, an allergen-free diet is not useful for treating children and adults with AD in whom the involvement of food allergies is not clear, as previously reported.[79–81] A dietetic issue, a developmental/growth disorder related to an inappropriate elimination diet, has been raised as a limitation of an elimination diet in children. Elimination diet therapy should be performed under the guidance of physicians after determining, prior to its initiation, whether it should be indicated based on an evaluation of the involvement of food allergies (CQ15: Evidence level: B). Briefly, when improvements in skin symptoms are not achieved by topical therapy with topical corticosteroids at an appropriate intensity and volume, any possibility for food allergen that deteriorates eruption should be identified. When dermatitis control is insufficient, it is difficult to make an accurate diagnosis.

The association of food allergens should be evaluated based on the results of oral food challenges, which should be conducted after causative food elimination in addition to an inquiry regarding a detailed medical history and skin/blood tests. For example, it should not be evaluated based on clinical symptoms or specific IgE antibody titer-positive findings alone. Even when the involvement of food allergens is clarified, this disease is related to multiple factors, and food-allergen elimination is only an adjuvant treatment for drug therapy; it is important to note that a complete cure will not be achieved by this method alone.

The American Academy of Pediatrics previously recommended an allergen-free diet for pregnant women (2000). In 2006 and 2012, a systematic review of a randomized controlled study using an allergen-free diet for pregnant/lactating women was reported.[82] It was indicated that dietary restrictions by allergen elimination in pregnant/lactating women did not prevent the onset of AD in infants aged 18 months or younger.[81] In addition, there may be no sufficient weight gain during pregnancy in diet-restricted pregnant women, or the fetal nutritional status may be affected (e.g. an increase in the risk of immature babies). Thus, dietary restrictions (allergen elimination) in pregnant/lactating women may not be useful for preventing the onset of AD in infants (CQ16: Evidence level: A).

Environmental and contact antigens. Environmental allergens, such as mites, house dust, pollen and animal hair, may lead to the exacerbation of AD after infancy.[83] In order to determine whether these allergens aggravate eruption, a comprehensive evaluation is needed based on information, such as medical histories, environmental changes and changes in eruption (including elimination or tolerance tests, if possible), but not on

clinical symptoms or specific IgE antibody titers/prick test results alone (CQ14: Recommendation grade 2, Evidence level: B). Furthermore, strategies to eliminate environmental allergens consist of drug therapy and skin care (adjuvant therapy), as stated for food allergens. It is important to note that a complete cure cannot be achieved by this alone.

Contact allergies to topical drugs, cosmetics, perfumes, metals, shampoos and body soap may deteriorate eruption.[84,85] It is necessary to establish whether eruption subsides by avoiding contact with suspected substances, make a definitive diagnosis based on the results of patch tests and avoid contact with causative substances (refer to the Guidelines for the Management of Contact Dermatitis by the JDA).[86] As a residual of shampoo/rinse/soap or their excessive use may induce irritant dermatitis, it is important to guide patients on an appropriate washing method.

Even non-specific daily stimuli, such as contact with saliva (infants)/sweat/hair, friction with clothes and scratching, may deteriorate AD. Saliva and sweat should be washed out, or wiped off with a piece of wet, soft gauze. Stimuli related to clothes made of wool/stiff materials or contact with hair ends may also induce pruritus in skin with hypersensitivity. Therefore, it is necessary to select clothes without such stimuli, and cut hair and tie it up with hair rubbers. Furthermore, nails must be cut so that they cannot hurt the skin on scratching. If necessary, long sleeves/trousers and gloves should be worn while sleeping so that the skin is not directly scratched.

Sweat. Sweat plays important roles in the maintenance of skin homeostasis: the regulation of skin temperature, protection against infections and moisture retention.[87] Although sweat has been identified as an AD-triggering factor,[88] "sweating" must be differentiated from "sweat after sweating" with respect to its involvement in the pathogenesis of AD. There is no evidence to show that sweating deteriorates the symptoms of this disease or that guidance to avoid sweating reduces the severity of symptoms. Briefly, it is not necessary to avoid sweating. Sweating function is known to be affected in patients with AD, along with the sweat rate.[89–91] Therefore, the recovery of sweating function may also become a goal of treatment. On the other hand, sweat after sweating may induce pruritus.[92] Because taking a shower (with tap water) is effective for relieving symptoms in seasons with a high sweat rate (CQ10: Recommendation grade 1, Evidence level: B),[93–95] excess sweat after sweating should be washed away.

Psychosomatic aspects

Severe AD markedly influences the QOL of patients and their families, and also deteriorates in the presence of stress. A psychosomatic correlation has been reported; skin symptoms affect psychosocial aspects and psychosocial factors influence skin symptoms. A vicious circle has been shown to persist in many patients with protracted AD.[96] Therefore, a psychosomatic approach is necessary for providing medical services in many cases. The conditions of AD that require psychosomatic considerations have been classified into the following three groups:

- **A** Stress-related deterioration/protraction of AD: In this group, psychosocial stress plays an important role in the onset, recurrence, exacerbation and protraction of AD. Life events, daily psychosocial stress and emotional states, such as depression/anxiety, are associated with the exacerbation of symptoms.
- **B1** Maladjustment caused by AD: Mental stress or social function disturbances are secondary in this group due to chronic skin symptoms with marked pruritus, leading to sleep disorders, a disturbance in personal relationships, a depressive mood, anxiety, avoidance of social circumstances/social withdrawal, or a reduction in student/occupational performance.
- **B2** Maladjustment to the treatment/management of AD: In this group, compliance with self-treatment is reduced due to psychosocial factors, affecting appropriate treatment/management and influencing the treatment/course. Anxiety regarding drugs, distrust in medical practice or a sense of helplessness in symptom control has been reported in many patients.

These three groups are not independent and are often mutually associated. Even in such cases, mental aspect-focused treatments alone should not be performed, and conventional treatments must be reviewed after establishing a favorable physician–patient relationship through listening with receptive, consensual attitudes. Dermatological treatments should then be guided/conducted. If necessary, psychosomatic medical treatments should be designed in cooperation with specialists. Medical services for AD should be provided while evaluating the QOL of patients so that insufficient medical care does not result in the B1 or B2 group.

Complications

Bacterial/fungal/viral infections may concomitantly occur in patients with AD. The incidences of these infectious diseases increase with disturbances in skin barrier function related to the deterioration of eruption or reduction in skin immune activity. Furthermore, their conditions frequently become severe. Therefore, it is important to maintain skin in a favorable state. Bacterial infectious diseases include contagious impetigo, erysipelas and cellulitis. Viral infectious diseases include Kaposi varicelliform eruption and molluscum contagiosum. These complications cause symptoms, such as topical heat sensation and pain, and sometimes induce fever, general malaise and organ disorders. Ocular diseases, such as eyelid dermatitis, keratoconjunctivitis, keratoconus, cataracts and retinal detachment, frequently develop when skin symptoms in the face are severe. It is important to promote regular ophthalmological consultations, instruct patients not to rub/hit their eyes and control eruptions.

Other therapies

Ultraviolet (UV) therapy is considered for non-responders to treatments with topical anti-inflammatory drugs, antihistamines or moisturizers, as well as for patients with adverse reactions to conventional treatments.[4,97] As UV therapy for AD, the

efficacy of psoralen plus UV-A therapy (PUVA), UV-A1 (not approved in Japan), UV-B and UV-A + UV-B therapies has been reported.[98] Previous studies indicated the efficacy of narrowband UV-B and UV-A1 therapies.[99] In Japan, irradiation systems for narrowband UV-B therapy with a peak of 311 nm have been installed in an increasing number of hospitals and clinics. This therapy may be applied further in the future because of its safety and needlessness of post-treatment light shielding, which is required for PUVA therapy. A previous study indicated that a larger number of patients with AD responded to a lower radiation dose of narrowband UV-B than those with psoriasis.[100] A protocol of UV therapy should be established in the future for patients with AD. When administrating UV therapy, it is important to initially consider whether it should be indicated, and it should also be carefully performed by UV therapy-skilled physicians who sufficiently understand the action mechanism, radiation dose, acute skin disorders, deterioration of concomitant infectious diseases, various long-term adverse reactions, including skin cancer, and management methods.

Many studies have focused on probiotics since a study regarding their preventive effects on AD was published in the *Lancet* in 2001.[101] Thereafter, several studies reported that probiotics, including *Lactobacillus rhamnosus* GG, contributed to preventing the onset and deterioration of AD in infants/children. In Japan, a study indicated that the consumption of a *Lactobacillus* beverage (*Lactobacillus acidophilus* L-92) reduced the clinical symptoms of AD. However, according to a review in Taiwan, probiotics did not prevent infantile/childhood AD or inhibit its deterioration. There is currently no evidence to support probiotics being useful for relieving the symptoms of AD (CQ17: Evidence level: B).

Hospital care

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

In patients with chronically protracted severe dermatitis, there are problems regarding disease activity (enlargement of eruption related to inflammation with strong activity or scratching), patient adherence (insufficient understanding of the pathogenesis of AD or treatment methods, no goal of treatment in the absence of experience at the level of remission, experience-based misunderstanding of topical therapy and insufficient understanding of the significance of topical therapy or its methods) and aggravation factors (environmental/lifestyle-related factors and overworking) as background factors. In many cases, these problems are resolved through interactions. Hospital care may make it possible to thoroughly perform intensive topical therapy with isolation from the daily environment, establish a health-care professional–patient relationship of mutual trust, review triggering factors/application methods/skin care and overcome these problems in the early phase. Several hospitals reported that such therapeutic interventions improved long-term prognoses after patient discharge.[102,103]

Because continuous topical treatment is required after the discharge of severe patients for whom hospital care is indicated, it is essential to understand their conditions and treatment methods. Therefore, the goal of hospital care is to achieve the early remission of dermatitis by intensive topical therapy and improve adherence through educational guidance.

Education

In patients with AD, insufficient understanding of their condition or treatment and anxiety often lead to inappropriate treatments. To overcome these issues, various patient education programs have been internationally provided for patients with AD or their parents, and their usefulness has been reported. Previous studies indicated that several sessions of a multioccupational patient population education program involving physicians and nurses markedly improved the QOL of patients and severity of eruptions.[104–106] However, the effects of a single session (short duration) of education by nurses or educators on the QOL of patients and eruptions varied.[107–109] Briefly, patient education may be useful if its contents and methods are sufficiently reviewed (CQ19: Recommendation grade 1, Evidence level: B).

Adherence

In medical care for AD, a chronic disease, it is important for patients and their parents to understand their condition/the significance of treatments, positively participate in the selection of therapeutic strategies, accomplish treatments according to these strategies, and improve the will to continue treatments, that is, adherence to treatments. Treatment adherence-associated factors include patient-/disease-/treatment-/health-care professional-related and socioeconomic factors.[110,111] Patient-related factors include the pressure of business and belief in medical practice/drug therapy. As treatment-related factors, complex treatment methods, those with a high incidence of adverse reactions and expensive procedures lead to a reduction in adherence. It is important to explain the merits and demerits of treatment with topical corticosteroids in order to improve adherence. As factors related to health-care professionals, their relationships with patients, explanations of the disease and treatment methods, and continuous information provision/support contribute to improvements in adherence. It is important to explain the necessity of drug therapy/skin care to patients and motivate them. Socioeconomic factors include a family's cooperation and human support by babysitters. To improve adherence, health-care professionals should initially try to achieve factors that they can perform.[111–113]

Treatment procedures

Treatment procedures for AD are shown in Figure 3.[4,114] After making an accurate diagnosis and evaluating its severity, appropriate treatment methods should be combined in accordance with the state of eruption. In the initial consultation, it is

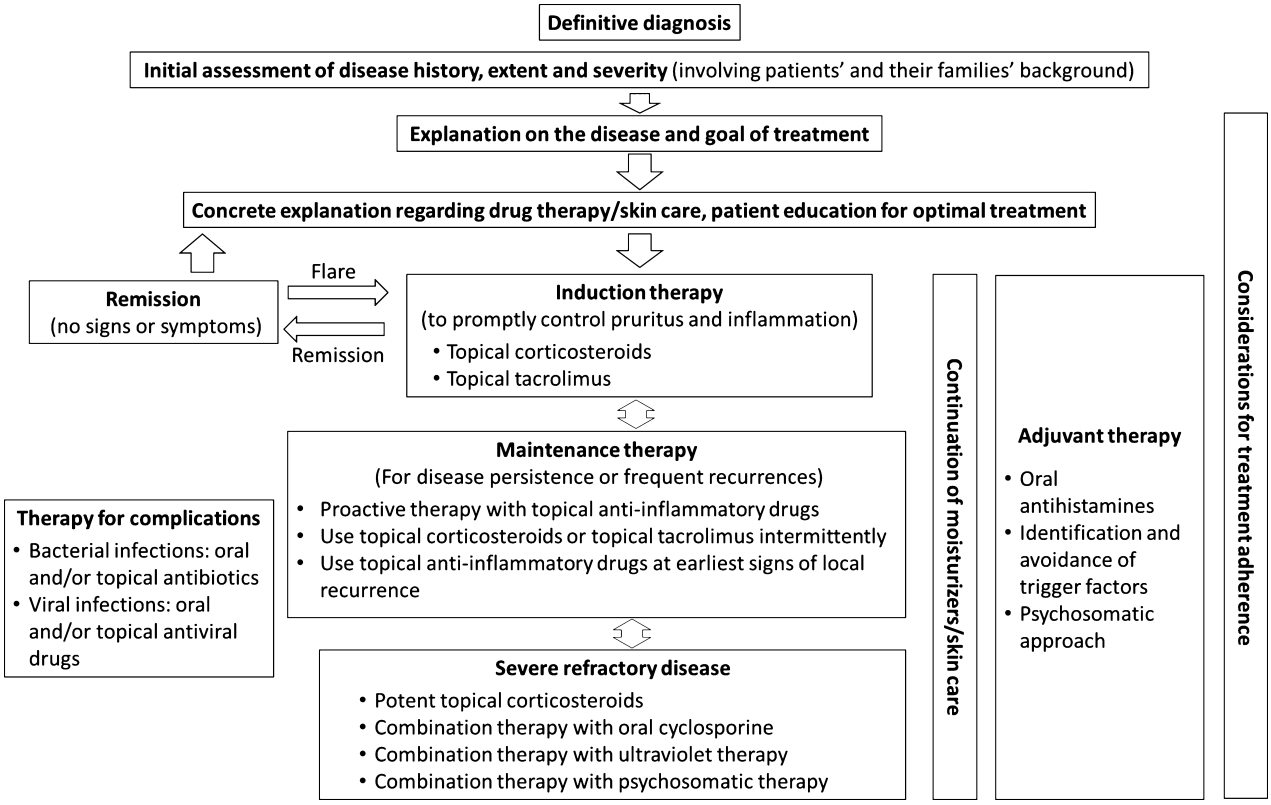


Figure 3. Algorithm for treatment of atopic dermatitis.

important to explain the condition of AD and treatment methods to patients and have a common understanding with them.

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CONFLICT OF INTEREST

Based on the Guidelines and Detailed Rules on Conflicts of Interest in Medical Research established by the JDA, members of the Committee for the Development of Clinical Practice Guidelines self-reported their situations in relation to conflicts of interest as follows. The costs to develop these guidelines have been supported by: grants for research from the JDA; Grant-in-Aid for Scientific Research from the Ministry of Health, Labor and Welfare (as a Research Project on Measures for Intractable Diseases [Research on Allergic Disease and Immunology]); and those from the Japan Agency for Medical Research and Development (as a Practical Research Project for Allergic Diseases and Immunology [Research on Allergic Diseases and Immunology]). Committee members have not received any remuneration for developing the guidelines or attending related meetings. There has been no intervention by the JDA that may influence the contents of the guidelines. Those who had conflicts of interest with companies, corporate bodies or profit organizations related to specific drugs, procedures or tests for the diagnosis or treatment of AD did not write the text of the relevant section or recommendations, or participate in the process of determining recommendation levels. Members of the Committee for the Development of Clinical Practice Guidelines and their relatives defined within the first degree of consanguinity self-reported whether or not they had received some remuneration that corresponds to one of the following categories from companies or other bodies involved with the diagnosis or treatment of AD. The target period was between 1 January 2012 and 31 December 2014: (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)

travelling costs or gifts. Corresponding companies and bodies: Norito Katoh: Maruho Co., Ltd, Kyowa Hakko Kirin Co., Ltd, Sanofi K.K.; Mitsubishi Tanabe: Pharma Corporation; Hidehisa Saeki: Mitsubishi Tanabe Pharma Corporation, Janssen Pharmaceutical K.K., Maruho Co., Ltd; Takeshi Nakahara: Maruho Co., Ltd; Akio Tanaka: Mitsubishi Tanabe Pharma Corporation, GlaxoSmithKline K.K.; Kenji Kabashima: Japan Tobacco Inc., Janssen Pharmaceutical K.K., Daiichi Sankyo Co., Ltd, Novartis Pharma K.K., Maruho Co., Ltd, Chugai Pharmaceutical Co., Ltd, Mitsubishi Tanabe Pharma Corporation; Hiroyuki Murota: Kyowa Hakko Kirin Co., Ltd; Yoko Kataoka: Janssen Pharmaceutical K.K.; Michiko Aihara: Kewpie Corporation; Takafumi Etoh: Maruho Co., Ltd, LEO Pharma K.K.

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CHAPTER II

EBM of AD

In Chapter II, to optimize the patient outcome by medical interventions, reports of clinical research are reviewed, balance between benefits and harm of medical interventions is evaluated, and recommendation grades and evidence levels are shown concerning 22 important points that require decisions in clinical settings (Clinical Questions; CQs) including matters that could not be presented in the text of the Guidelines in Chapter I. Recommendations, recommendation grades, and their explanations concerning CQs are shown.

Methods

MEDLINE, *Japana Centra Vevuo Medicina*, and Cochrane Library were searched for the relevant literature (including the literature in electronic media) published by the end of December 2013, in principle. CQs were established by selecting 22 topics in February 2014 after discussion at the committee in consideration also of the opinions obtained in January 2014 from the Japan Allergy Tomono Kai as representatives of patients.

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 system,[115] Minds handbook for clinical practice guideline development 2014,[116] and clinical guidelines for infusion therapy in advanced cancer patients 2013.[117]

The evidence level was an eventual judgment concerning the "quality of evidence" based on evidence concerning important outcomes reached as a consensus of the committee by comprehensive evaluation of the design and quality of research, whether or not the results were coherent/consistent, and whether or not the subjects, intervention, and outcome of the study were consistent with the assumed situations. The evidence levels range from A to C, of which A is for "The results are nearly established and are unlikely to be changed markedly by future studies," B is for "There are studies that support the results, but as they are insufficient, they may be changed markedly by future studies," and C is for "There is no high quality studies that support the results." (Table 6) The research design was used as a starting point for the determination of the evidence level and was distinguished as in Table 7.[117]

Table 6. Evidence level

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

Table 7. Designs of studies used as references for the determination of the evidence level

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

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

Table 8. Recommendation grade

1: Strong recommendation	The advantage of the recommended treatment is significant, and may exceed treatment-related burdens.
2: Weak recommendation (suggestion)	The advantage of the recommended treatment is inaccurate, or may antagonize treatment-related harms and burdens.

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

"Strong recommendation" means that, from the evidence obtained and clinical experience, the benefits obtained by the recommended treatment are judged to be large and to surpass the harm or burdens caused by the treatment (Table 8). 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

Table 9. Clinical significance of the recommendation grade and evidence level

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

of the benefits obtained by the recommended treatment is uncertain, or the benefits and harm or burdens that may result from the treatment are considered nearly equal (Table 8). In this event, the physician is required to hold careful counsel with the patient about whether or not the recommended treatment should be performed by taking the patient's values, preferences, and wishes into consideration. CQs that were difficult to give a recommendation grade were rated with the evidence level alone.

As explained above, in the present Guidelines, there are recommendations of the combinations shown in Table 9 based on the strength of recommendation and evidence level.[117]

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CQ1. ARE TOPICAL CORTICOSTEROIDS RECOMMENDED FOR THE TREATMENT OF AD?

Recommendation comments: Topical corticosteroids may be effective for AD. As such, they are recommended, with consideration given to adverse reactions.[118–126]

Recommendation grade: 1, Evidence level: A

Explanation: Regarding efficacy, several articles indicate that topical corticosteroids are significantly more effective than a placebo regardless of age, although a few articles disagree. As such, they may be effective for AD. Studies showing no significant differences in efficacy involved weak corticosteroids; adequately strong corticosteroids should be prescribed. Concerning local adverse reactions, topical application of betamethasone valerate, mometasone furoate, or prednicarbate for 6 weeks was demonstrated to induce skin thinning in comparison with a vehicle in healthy subjects. In patients with AD, however, daily application of mometasone or fluticasone for several weeks followed by twice weekly application of these agents for several months did not induce serious adverse reactions, and skin atrophy was rarely observed. It is thus considered that risk of skin thinning would be reduced by decreasing the frequency of application after improvement of the eruption.

Concerning the frequency of application, there was no significant difference in the remission rate between patients who had applied very strong class corticosteroids once a day and several times, but there was a difference between those who applied moderate class corticosteroids once a day and several times. Based on clinical experience, we recommend twice-a-day application for the acute phase, but once-a-day application may also be effective.

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CQ2. IS IT POSSIBLE TO REDUCE THE FREQUENCY OF TOPICAL CORTICOSTEROID APPLICATION PER DAY IN ACCORDANCE WITH THE GRADE OF SYMPTOMS?

Recommendation comments: Once-a-day application of topical corticosteroids may be effective to some degree. Furthermore, a decrease in the frequency of application may reduce adverse reactions to long-term steroid application, improving treatment adherence. Therefore, the frequency of application per day should be decreased with the improvement of symptoms.

Recommendation grade: 1, Evidence level: B

Explanation: In the package inserts of most topical corticosteroids, it is recommended that they should be applied once to several times a day, and that the frequency of application should be increased or decreased in accordance with symptoms. Based on clinical experience, twice-a-day application may reduce eruption earlier than once-a-day application. However, some randomized controlled trials (RCT) indicated that there were no differences in the efficacy or incidence of adverse reactions between the once-a-day and twice-a-day application of topical corticosteroids during a survey period of 2–4 weeks.[127–131] Although we cannot standardize/make conclusions based on these reports alone, once-a-day application may be effective to some degree. Concerning adverse reactions, we cannot conclude that there is no influence of the frequency of application. The influence of the frequency of application on the appearance of adverse reactions to long-term (4-weeks or more) administration remains unclear. The

incidence of adverse reactions to steroid application, such as skin atrophy, may be reduced by decreasing the frequency of application. In addition, a decrease in the frequency of application may contribute to an improvement in treatment adherence.[132,133] When acute flare is observed, or when dermatitis control is insufficient, a topical corticosteroid should be applied twice a day, and, after relieving symptoms, the frequency of application should be decreased to once a day.

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CQ3. DOES THE PERIOCULAR APPLICATION OF TOPICAL CORTICOSTEROIDS INCREASE THE RISK OF OCULAR COMPLICATIONS?

Recommendation comments: The periocular application of topical corticosteroids in patients with AD may increase the risk of glaucoma, but not the risk of cataracts.

(Cataracts) Evidence level B (the risk is not increased)

(Glaucoma) Evidence level C (the risk is increased)

Explanation: In patients with AD, incidences of ocular complications, such as cataracts, glaucoma, retinal detachment, and conjunctivitis, are high. As such, adverse reactions to steroid therapy, such as cataracts and glaucoma are important. Concerning cataracts, seven case series have been published. Risk factors include steroid avoidance-related deterioration of facial eruption, hitting face due to pruritus, and AD-associated inflammation.[134–136] These studies indicate that there is no relationship between the onset of cataracts and periocular application; periocular application of topical corticosteroids may not increase the risk of cataracts. Concerning glaucoma, there was 1 case series study. The use of weak corticosteroids at a low dose may be safe.[137] However, there is little evidence to rule out all risk. As some patients with glaucoma after topical steroid therapy have been reported, it may increase the risk of glaucoma.

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CQ4. IS IT USEFUL TO ADD ANTIMICROBIAL OR -FUNGAL DRUGS TO TOPICAL CORTICOSTEROIDS FOR THE TREATMENT OF AD?

Recommendation comments: The use of topical corticosteroids containing antimicrobial or -fungal drugs to relieve AD-related skin symptoms is not advantageous in comparison with the use of topical corticosteroids that do not contain these drugs, with respect to their therapeutic effects. As such, it may not be useful.

Evidence level: A

Explanation: We investigated literature comparing the therapeutic effects of topical corticosteroids containing antimicrobial or -fungal drugs with those of topical corticosteroids alone. Since 2008, there have been four international references: three clinical research reports[138–140] and one systematic review.[141] In the three clinical studies, the effects of adding tetracycline and mupirocin, as antimicrobial drugs, and miconazole, as an antifungal drug, to topical corticosteroids were examined. The addition of these drugs was not advantageous with respect to therapeutic effects.[138–140] Based on the results of a meta-analysis establishing an improvement in skin symptoms as an outcome, there was no advantage in adding antimicrobial drugs.[141] Thus, the addition of antimicrobial drugs to topical corticosteroids for relieving AD-related skin symptoms may not be useful in comparison with topical corticosteroids that do not contain such drugs.

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CQ5. IS TOPICAL TACROLIMUS RECOMMENDED FOR THE TREATMENT OF AD?

Recommendation comments: Topical tacrolimus is recommend for AD patients aged 2 years or older.

Recommendation grade: 1, Evidence level: A

Explanation: Tacrolimus inhibits T lymphocyte function through a mechanism differing from that of corticosteroids. Its efficacy and safety have been confirmed in clinical studies using a vehicle or topical corticosteroid as a control agent. In clinical studies establishing an improvement in symptoms of AD as a primary endpoint, 0.03 or 0.1% tacrolimus ointment was more advantageous than a base or weak topical steroid, and the efficacy of 0.1% tacrolimus ointment was similar to that of medium to strong topical corticosteroids.[142,143] The more potent efficacy of tacrolimus ointment was confirmed in children or adults with mild/moderate to severe AD. In particular, it was more marked in mild-status patients.[144,145] Tacrolimus ointment is indicated for AD patients aged 2 years or older. Concerning the concentration of tacrolimus, 0.03% ointment is selected for children (2–15 years), and 0.1% ointment for adults (16 years or older). After the short-term (approximately 3 week) application of tacrolimus ointment in children (2–15 years), there was no difference in the efficacy between 0.03 and 0.1% ointments.[143] For local adverse reactions, a burning sensation, pruritus, and erythema were confirmed.[146] These symptoms are reduced during continuous application, or promptly disappear after discontinuation in many cases. With respect to infectious diseases of the skin, secondary skin infection with bacterial and viral infection (herpes simplex, molluscum contagiosum, and viral warts) must be considered.[146] Skin atrophy, which has been reported as an adverse reaction due to the long-term use of topical corticosteroids, has not been confirmed in patients treated with tacrolimus ointment. Concerning tumor development, refer to CQ6. Based on these findings, we recommend tacrolimus ointment for the treatment of AD in patients aged 2 years or older, if it is adequately used.

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

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

Evidence level: B

Explanation: According to eight of nine original articles in Japan and other countries, there is no evidence that tacrolimus ointment increases the risk of skin cancer or lymphoma.[147–152] On the other hand, a retrospective cohort analysis showed that the incidence of T cell lymphoma in patients treated with tacrolimus ointment was higher than in non-tacrolimus-treated patients.[153] However, this survey method had a limitation regarding the accuracy of AD/lymphoma diagnosis. In addition, a study reported that severe AD increased the risk of lymphoma. Based on this, the FDA (US Food and Drug Administration) indicated that the above finding did not provide evidence that tacrolimus ointment increases the risk of T cell lymphoma (May 10, 2011). Briefly, currently, tacrolimus ointment may not be involved in the risk of skin cancer or lymphoma. However, in the future, the sample size should be increased, or meta-analysis based on long-term follow-up must be conducted to clarify the relationship between dose or administration period of this ointment and the development of malignant tumors. Therefore, it is important to comply with the limits of application dose.

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CQ7. DO YOU RECOMMEND ANTIHISTAMINES FOR THE TREATMENT OF AD?

Recommendation comments: Antihistamines may reduce pruritus related to AD. We recommend these drugs as adjuvant therapy for treatment with topical anti-inflammatory drugs and moisturizers.

Recommendation grade: 1, Evidence level: B

Explanation: In Japan, many study reports have discussed the effects of antihistamines on AD. In Europe and the United States, many reports have presented negative opinions.[154–159] Eleven reports in Japan and seven in Europe and the United States compared the efficacy of antihistamines with a placebo or antihistamine-free groups, or compared the advantage of an antihistamines with other antihistamines; on the other hand, four reports in Europe and the United States ruled out the efficacy of antihistamines. As the evidence level is not high, even in reports indicating effectiveness, combination therapy with antihistamines is not positively recommended in meta-analysis reports or guidelines in Europe and the United States. Examination, regarding the effects of antihistamines, has some limitations: (i) there are few placebo-controlled studies; (ii) topical preparations, such as corticosteroids and tacrolimus, are combined with antihistamines in most patients; and (iii) although there is an improvement in pruritus, skin finding-scoring systems, such as the SCORAD and EASI, are not used for evaluation. Furthermore, adverse reactions, such as sleepiness, and health expenditure must be considered. On the other hand, a study reported that the continuous oral administration of antihistamines relieved pruritus, reducing the rank of topical corticosteroids.[157] As the severity, age, and administration period differ between the reports in Japan and Europe/the United States, it is impossible to simply compare results. Therefore, Japanese guidelines recommend that antihistamines be orally administered as adjuvant therapy for treatment with topical anti-inflammatory drugs and moisturizers. When administering these drugs, non-sedative antihistamines should be used, as their therapeutic effects are similar to those of sedative antihistamines.[160]

On the other hand, antihistamines are not effective for pruritus in all patients with AD. The type of patient or eruption for which antihistamines are effective remains unclear. When administering antihistamines, it is necessary to consider whether or not eruption/pruritus control with topical anti-inflammatory drugs and moisturizer alone is possible and evaluate the efficacy of antihistamines for pruritus at appropriate points after the administration of these drugs.

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CQ8. IS PROACTIVE THERAPY USEFUL FOR MAINTAINING THE REMISSION OF AD-RELATED ECZEMA LESIONS CHARACTERIZED BY REPEATED RECURRENCE?

Recommendation comments: Proactive therapy is useful for maintaining the remission of eczema lesions characterized by repeated recurrence, and is relatively safe.

Recommendation grade: 1, Evidence level: A

Explanation: Proactive therapy is a treatment in which a topical corticosteroid or tacrolimus ointment is applied to the skin, where there is no inflammation after acute-phase treatment, twice a week, to prevent the recurrence of dermatitis. Recently, it has commonly been selected as a strategy for maintaining the remission of AD. Ten RCTs and 1 systematic review indicated that proactive therapy was useful for maintaining remission.[161–171] Proactive therapy with topical corticosteroids or tacrolimus ointment is useful for preventing the recurrence of eczema. Concerning its safety, many studies reported that there was no difference in the incidence of adverse events between a vehicle and topical corticosteroids/tacrolimus during a 16-week/1-year follow-up[161–170]; proactive therapy may be relatively safe. However, no study has examined the safety of proactive therapy, with a longer period of follow-up. With respect to the appearance of adverse reactions, careful observation is necessary. Furthermore, it must be considered that proactive therapy is not a treatment method for patients without a marked improvement in dermatitis. In addition, the extent of application required, timing of switching daily administration to intermittent application, and timing of completion should be determined in accordance with individual patients. Therefore, proactive therapy should be performed by physicians specializing in the assessment of AD-related skin symptoms or in cooperation with physicians specializing in the assessment of skin symptoms.

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CQ9. IS THE APPLICATION OF MOISTURIZERS RECOMMENDED FOR THE TREATMENT OF AD?

Recommendation comments: Moisturizers should be combined with topical steroids in patients with symptoms of dermatitis. Even in the absence of such symptoms, the continuous application of moisturizers is recommended.

Recommendation grade: 1, Evidence level: A

Explanation: Dry skin is one of the primary symptoms of AD. It is an etiological factor for disturbance of the barrier function of the epidermis. Many basic and clinical studies have shown that the application of moisturizers is effective in reducing dryness and improving skin barrier function.[172–181] In particular, the continuous application of moisturizers after treatment-related remission of dermatitis may prevent the recurrence of dermatitis, maintaining a pruritus-reduced state.[182,183] The use of moisturizers alone is not generally be effective for dermatitis, but combination therapy with topical corticosteroids may relieve dryness and pruritus, maintaining remission after the reduction of dermatitis.[184] Furthermore, the dose of a topical steroid may be decreased by combining it with a moisturizer.[185] However, adverse events must be considered, such as moisturizer-related contact dermatitis, which may occur.

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CQ10. IS SHOWERING USEFUL FOR REDUCING SYMPTOMS OF AD?

Recommendation comments: Showering is useful for reducing symptoms of AD.

Recommendation grade: 1, Evidence level: B

Explanation: In Japan, three school tap water showering intervention studies, involving children with AD, were conducted.[186–188] Showering significantly reduced symptoms of AD. Its effects may be more marked in seasons with an increase in sweat volume. There were no adverse events. Based on these results, tap water showering at school may be useful for reducing symptoms of childhood AD.

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CQ11. IS THE SERUM TARC LEVEL USEFUL AS A MARKER OF THE DISEASE ACTIVITY OF AD?

Recommendation comments: Measurement of the serum TARC level may be useful for evaluating the disease activity of AD in children and adults.

Evidence level: B

Explanation: In Japan and other countries, 33 original articles on the usefulness of the serum TARC level as a marker of the disease activity of AD have been published. In 31 of these, this marker was evaluated as useful.[189–192] Based on the results of analysis, the serum TARC level may more sensitively reflect the disease activity compared to the serum IgE level, LDH level, and peripheral blood eosinophil count in children and adults with AD. Furthermore, it may be possible to promote patient education and review treatment methods using the serum TARC level as a parameter. However, the serum TARC level is higher in younger children; therefore, age-related differences in the reference value must be considered.

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

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

Recommendation grade: 2, Evidence level: A

Explanation: The results of previous clinical studies in Japan and other countries demonstrate the efficacy of cyclosporin therapy for AD.[193–196] In a clinical study involving Japanese adults (aged 16 years or older) with severe AD, an initial dose was established as 3 mg/kg per day (if necessary, it was increased or decreased in accordance with symptoms so that it did not exceed 5 mg/kg per day), while reviewing the efficacy and adverse events. The authors concluded that treatment involving the discontinuation period is effective and safe when administration is completed in 8–12 weeks, or continued.[197,198] However, neither the efficacy nor safety of long-term administration has been established; therefore, cyclosporin should be used after explaining its efficacy and safety to patients. In addition to safety-related problems, the drug price is high. When selecting cyclosporin therapy for severe patients who do not respond to conventional treatment, it is important to promptly switch it to topical therapy, as standard, after symptom relief. In children, the efficacy was investigated, but the safety of long-term treatment was not sufficiently examined. In Japan, cyclosporin therapy for childhood AD has not been approved.

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CQ13. IS TRADITIONAL CHINESE HERBAL MEDICINE USEFUL FOR THE TREATMENT OF AD?

Recommendation comments: For patients with AD who do not respond to topical anti-inflammatory drugs, such as corticos-

teroids or tacrolimus, oral antihistamines, skin care, or strategies against triggering factors, combination therapy with traditional Chinese herbal medicines may be considered.

Recommendation grade: 2, Evidence level: B

Explanation: Most clinical studies examining the usefulness of traditional Chinese herbal medicine for AD were case series studies involving approximately 20 to 30 patients. There were seven double-blind RCTs.[199–206] Of these, concerning preparations that can be prescribed at general dermatological clinics in Japan, there were only two studies using Xiano-Feng-San[200] and Hochu-ekki-to.[201] The former involved patients in whom treatment with topical anti-inflammatory drugs, such as corticosteroids, did not reduce eruption, and the latter involved those with Kikyo (easy fatigability or lack of perseverance) based on the results of a questionnaire survey. Both studies were conducted, while simultaneously performing conventional treatment with topical anti-inflammatory drugs, such as corticosteroids. The former showed a significant improvement in eruption in the prescription-treated group in comparison with the placebo group. The latter indicated that the doses of topical corticosteroids could be decreased. An international, double-blind, RCT using Zemaphyte reported its efficacy,[202,203] whereas another study group reported against it.[204] The usefulness of a standardized prescription, such as Preparation A for AD, remains controversial, as traditional Chinese herbal therapy is prescribed according to patient's "*Sho*" (constitution/condition). With respect to the usefulness of traditional Chinese herbal medicine for the treatment of AD, many issues, including the usefulness of selecting prescriptions based on the properties of eruption and adequacy of evidence assessment using simple methods, such as a questionnaire, must be examined. In the future, the results of multicenter, double-blind, RCTs, of which the accuracy is high, should be accumulated for careful examination. Furthermore, the adverse events related to Kampo preparations must be considered, such as pseudohyperaldosteronism related to licorice-containing preparations, which may occur.

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

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

Recommendation grade: 2, Evidence level: B

Explanation: In many patients with AD, IgE antibodies against mites are detected by blood test, or skin test with mite antigens showing a positive reaction. We have sometimes encountered patients in whom symptoms subsided with environmental arrangements to reduce exposure to mite allergens, e.g. in an environment such as a bedroom. In RCTs involving mite antigen avoidance using a bed cover that does not allow mite allergens to pass, the relief of AD-related eruption was achieved in addition to a decrease in the level of mite antigens in bedclothes.[207–211] On the other hand, according to some studies, such a strategy against mite antigens decreased the antigen level, but there were no effects on eruption.[212,213] This is consistent with the finding that 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. The characteristics of patients in whom mite antigen avoidance leads to an improvement in AD-related eruption are unclear. Evaluation should not thus be performed based on clinical symptoms or hematological data alone.

When eruption deteriorates or reduces with environmental changes, such as visits to a dusty place and travelling, in the presence of strong sensitization with mite allergen on blood or skin prick tests, mite avoidance strategies, such as ventilation, frequent bedroom/living room cleaning (every 3 days or more), bedclothes cleaning with a vacuum cleaner (for 20 to 30 seconds per m^2, once a week), sun drying, and sheet washing,[214] should be conducted to review whether or not eruption reduces.

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CQ15. IS AN ALLERGEN-FREE DIET USEFUL FOR THE TREATMENT OF AD?

Recommendation comments: An allergen-free diet is not useful for the treatment of AD in children and adults in whom it is unclear whether or not a food allergy is involved. However, a diet eliminating an allergen, as an etiological factor, may be effective in patients with AD in whom food allergy may be strongly involved in the exacerbation of eruption, but topical anti-inflammatory therapy with topical corticosteroids, which is standard, must be initially performed.

Evidence level: B

Explanation: We evaluated nine RCTs of food allergen-free diet therapy in patients with AD. In a study involving infants in whom sensitization with a specific food allergen (egg) was confirmed, the specific therapeutic effects of an elimination diet were obtained.[215] However, there was no difference in the improvement rating of eruption between elimination and non-elimination groups in non-selective AD patients in whom no food allergen was examined.[216,217] Furthermore, the dropout rates were high in many RCTs. As randomization methods were unclear, the evidence level was regarded as B.

In RCTs regarding the therapeutic effects of an allergen-free diet, the number of dropout cases is high due to the influence on daily diet, and it is difficult to conduct a double-blind method for a specific period. Therefore, it may be difficult to perform a study of which the evidence level is high. As a limitation of an elimination diet in children, there is a nutritional issue of developmental/growth disorder related to an inadequate elimination diet. Before the start of elimination diet therapy, it must be considered whether or not treatment should be indicated, involving the assessment of food allergy involvement, and, then, this therapy should be performed under physicians' guidance. Briefly, food allergens that cause the deterioration of eruption should be identified after topical therapy with an adequate intensity and volume of topical corticosteroids. When the anti-inflammatory effects of topical therapy are insufficient, it is difficult to make an accurate diagnosis. For the diagnosis of food allergy, an oral tolerance test should be conducted after eliminating the causative food, and a diagnosis should be made based on the results, but not based on the specific IgE antibody titer (positive findings) alone.

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CQ16. ARE DIETARY RESTRICTIONS DURING PREGNANCY/LACTATION USEFUL FOR PREVENTING THE ONSET OF AD IN INFANTS?

Recommendation comments: Dietary restrictions during pregnancy/lactation are not useful for preventing the onset of AD in infants.[218–222]

Evidence level: A

Explanation: Previously, the American Academy of Pediatrics (AAP) recommended an allergen-free diet for pregnant women (2000). However, subsequently, a Cochrane systematic review of the results of five RCTs (total: 952 patients) (Kramer MS *et al.,* 2006, 2012) was published, concluding that dietary restrictions by allergen elimination for pregnant women are not effective in preventing the onset of AD from birth until 18 months of age. Furthermore, the preventive effects of dietary restrictions during pregnancy on the onset of AD at 18 months of age or later, that is, their effects on long-term prognosis, remain unclear. On the other hand, pregnant women on dietary restrictions may not show sufficient weight gain during pregnancy, or such restrictions may deteriorate the fetal nutritional state, leading to an increase in the risk of premature babies.

Concerning the influence of dietary restrictions during lactation on the onset of AD in infants, a Cochrane systematic review was published: based on the results of a RCT (26 patients), it was concluded that dietary restrictions during lactation are not effective in preventing the onset of AD before 18 months of age. It was also shown that dietary restrictions during lactation did not decrease the proportion of children with positive reactions on prick tests for milk, eggs, and peanuts in 1-, 2-, and 7-year-old children (n = 497, 473, and 354, respectively). Based on these reports, the AAP switched the policy to a new one that allergen elimination is not recommended for pregnant/lactating women, in 2008.

However, a small-scale crossover study involving 17 patients, indicated that dietary restrictions for lactating mothers of infants with AD reduced eruption, although the effects were not significant. To verify this, a large-scale, high-quality study should be conducted in the future.

Based on these findings, we conclude that dietary restrictions (allergen elimination) during pregnancy or lactation are not useful for preventing the onset of AD in infants.

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CQ17. ARE PROBIOTICS USEFUL FOR REDUCING SYMPTOMS OF INFANTILE AD?

Recommendation comments: Specific probiotics may be effective in preventing the onset of infantile AD or reducing symptoms, but, currently, there is no evidence to recommend probiotics for infants with AD.[223–226]

Evidence level: B

Explanation: Since Kalliomaki and Isolauri *et al.* published a study in the *Lancet* in 2001, many investigators have investigated the preventive effects of probiotics on AD. Several studies report that probiotics, including *Lactobacillus rhamnosus* GG, contribute to the prevention of the onset/deterioration of AD in infants. In Japan, a study indicated that the consumption of lactic acid bacteria beverages (*L. acidophilus* L-92) reduced clinical symptoms of AD. However, according to a review in Taiwan, probiotics were not effective in preventing infantile AD or inhibiting deterioration.

Concerning the timing of probiotic administration, the symptom-relieving effects of administration to pregnant women and infants are more marked than those after birth. In the future, the influence of the type of probiotics or combination therapy on an improvement in symptoms of AD should be examined. In addition, this depends on race or diet; therefore, a large-scale clinical study, involving the efficacy of probiotics and identification of effective bacteria, should be conducted in Japan.

This issue is difficult to review through meta-analysis, because various protocols are not uniform. Therefore, currently, there is no evidence to recommend probiotics for patients with symptoms of AD.

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CQ18. DOES AD REDUCE WITH AGE?

Recommendation comments: AD may reduce with age in a specific proportion of patients. However, the remission rate depends on the grade of symptoms.[227–230]

Evidence level: B

Explanation: In Japan and other countries, there were 18 original articles regarding age-related remission of AD. All articles indicated that AD reduced with age in a specific proportion of patients. The remission rate was higher in patients with mild symptoms (surveys on health checkups rather than in hospitals). A representative health-checkup-based cohort survey in Japan showed that healing was achieved at 1 year and 6 months of age in approximately 70% of 4-month-old infants with AD, and that it was achieved at 3 years of age in approximately 50% of 1-year-and-6-month-old children. According to another survey, approximately 50% of children diagnosed with AD at 7 years of age showed healing at 12 years of age. In a survey regarding the prevalence on health checkups, the proportion of mild-status patients was higher than in a survey involving patients who consulted a hospital, and the remission rate was higher.

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CQ19. IS EDUCATION FOR PATIENTS WITH AD USEFUL?

Recommendation comments: Education for patients with AD or the caregivers of children with this disease is useful from the perspective of improvements in the severity of eruption and quality of life (QOL). However, patient education methods vary, and there are differences in efficacy among the methods.[231–235]

Recommendation grade: 1, Evidence level: B

Explanation: There are often cases of AD in which treatment is not adequately performed due to insufficient understanding of the condition/treatment or anxiety. To overcome these problems, various types of patient education for patients with AD have been performed in Japan and other countries, and their usefulness was reported. Some RCTs indicated that several sessions of a patient population education program by various health care professionals, including physicians and nurses, markedly improved the patients' QOL and severity of eruption.[231–233] However, a single session (short duration) of education by nurses and educators did not improve them.[234,235] These results suggest that a specific patient education program is useful for improving the severity of eruption and QOL. However, the contents of education programs differed among the RCTs. If the contents and methods of a program are sufficiently reviewed, patient education may be useful.

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CQ20. IS THE ORAL ADMINISTRATION OF ANTIMICROBIAL DRUGS USEFUL FOR THE TREATMENT OF AD WITHOUT SIGNS OF INFECTION?

Recommendation comments: The oral administration of antimicrobial drugs is not effective for AD without signs of infection. We cannot recommend it.[236,237]

Evidence level: B

Explanation: In a systematic review of the therapeutic effects of *Staphylococcus aureus* suppression on AD, RCTs were investigated. Although neither the period nor quality was sufficient, no study indicated the efficacy of the oral administration of antimicrobial drugs for AD without clinical signs of infection.

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CQ21. IS THE ORAL ADMINISTRATION OF ANTIHISTAMINES DURING PREGNANCY/ LACTATION SAFE?

Recommendation comments: Pregnancy and lactation periods are important for mothers and children. Drugs must be carefully administered. However, drugs of which the safety was demonstrated may be administered if they are therapeutically advantageous. With respect to individual drugs, their risks in comparison with the incidence of deformity (2–3%), as a background factor, should be presented with reference to package inserts and the latest information on safety, and informed consent must be obtained.[238,239]

Evidence level: B

Explanation: Internationally, nine case-controlled or prospective cohort studies regarding teratogenicity or spontaneous abortion, including three meta-analyses, have been published. As the subjects were pregnant women, there was no interventional study. Smedts *et al.* indicated the association between antihistamines and congenital heart disease, although the other studies reported that there was no influence on fetal disorder. Smedts *et al.* conducted a case-controlled study involving children who were brought to a heart disease-specialized hospital; therefore, the results may reflect a recall bias. As the influence of antihistamines was ruled out based on the results of other prospective cohort surveys involving a population consisting of a large number of patients, they may be safe with respect to teratogenicity. In Europe and the United States, antihistamines have often been orally administered to control hyperemesis gravidarum; concerning first-generation antihistamines, the risk of teratogenicity was ruled out based on the results of a meta-analysis involving a large number of patients. With respect to second-generation antihistamines, the teratogenicity of loratadine and cetirizine was ruled out in a large number of patients.

After the second pregnancy trimester, the influence of placenta-mediated drugs on fetuses must be considered. Of the above studies, four examined premature birth and low-birth-weight infants, ruling out their association with maternal therapy with antihistamines. However, a case report on convulsion and irritability in a newborn born from a mother who had taken a massive-dose, first-generation antihistaminic drug before delivery was published; caution is needed.

During lactation, the influence of breast milk drug transfer on infants must be considered. A study reported that first-generation antihistamines passed through the blood-brain barrier of infants, inducing somnolence and irritability. If administration to lactating women is necessary, second-generation antihistamines should be selected.

Pregnancy and lactation periods are important for mothers and children. Drugs must be carefully administered. However, drugs of which the safety was demonstrated may be administered if they are therapeutically advantageous. When women become pregnant during treatment with antihistamines, physi-

cians should instruct them not to feel anxious. To females who may become pregnant and pregnant women, risks in comparison with the incidence of deformity (2–3%), as a background factor, should be presented before obtaining informed consent.

With respect to individual drugs, it is important to review whether or not they should be administered based on package inserts and the latest information on safety.

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CQ22. IS TOPICAL STEROID THERAPY DURING PREGNANCY/LACTATION SAFE?

Recommendation comments: Topical corticosteroids are safe during pregnancy/lactation. They may be used without considering the influence on fetuses if standard application methods are adopted. However, we cannot rule out the possibility that the massive-dose application of potent/very potent topical corticosteroids (European classification) may reduce birth weight. Therefore, if the massive-dose application of potent/very potent topical corticosteroids is necessary during pregnancy, the dose and fetal growth must be considered.[240–243]

Evidence level: B

Explanation: Case-controlled or prospective cohort studies regarding teratogenicity, low-birth-weight infants, premature birth, fetal death, delivery abnormalities, and low Apgar scores have been published. As the subjects were pregnant women, there was no interventional study. There were 10 original articles and one systematic review.

With respect to the teratogenicity of corticosteroids, seven studies investigated the risk of cleft lip and palate, and two examined congenital anomalies. Of the seven studies, four were cohort studies, and four were case-controlled studies (one was duplicated). One of these indicated the risk of cleft lip and palate. This was a case-controlled study involving patients who consulted specialists on cleft lip and palate. There may have been a recall bias. The other six studies reported that topical corticosteroids did not increase the risks of cleft lip and palate or other congenital anomalies. Considering that standard topical steroid therapy shows low-level systemic absorption, there may be no teratogenicity of topical corticosteroids.

There was no influence on premature birth, fetal death, delivery abnormalities, low Apgar scores, or low-birth-weight infants. However, a study indicated that a massive-dose application of potent/very potent topical corticosteroids (European classification) led to a reduction in birth weight. In such cases, the dose and fetal growth must be considered. To avoid such a situation, dermatitis control before pregnancy is important.

During lactation, topical corticosteroids may be safe, considering that systemic absorption is low. However, there was a case report on infantile iatrogenic hypertension induced by steroid application for eczema on mother's nipple during lactation. Physicians should instruct lactating women to avoid steroid application to the breasts immediately before lactation and clean them before lactation.

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SUPPORTING INFORMATION

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

Table S1 Measures of severity

