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Invited Review Article

Japanese guidelines for atopic dermatitis 2020☆

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ABSTRACT

Atopic dermatitis (AD) is a disease characterized by relapsing eczema with pruritus as a primary lesion, which is frequently encountered in clinical practice. Skin barrier dysfunction leads to enhanced skin irritability to non-specific stimuli and epicutaneous sensitization. In the lesion site, a further inflammation-related reduction in skin barrier function, enhanced irritability and scratching-related stimuli deteriorate eczema, leading to vicious cycle of inflammation. 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.

1. Introduction

Atopic dermatitis (AD) is frequently encountered in clinical practice. 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[2]. They can be utilized as a material for evaluations of decision-making in clinical practice. Attending physicians must make a

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[2] Generally, the manuscripts published by the end of December, 2015 were reffered.

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final decision in cooperation with patients so that their values and preferences are reflected.

1.1. Disclaimer

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

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

2. Definition, pathogenesis, epidemiology, diagnosis, severity

2.1. Definition of atopic dermatitis: concept of disease

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

AD is an eczematous skin disease characterized by symmetrical distribution, and the skin areas typically affected vary depending on age.[1,2] AD may develop during infancy or early childhood and may lead to remission during childhood; however, AD may become chronic in some cases with repeated relapses without remission, and present with characteristic eczematous lesions that persist until adulthood.

(i) personal or family history (asthma, allergic rhinitis and/or conjunctivitis, and AD); and/or (ii) predisposition to overproduction of immunoglobulin (Ig)E antibodies. The presence of allergy is not always necessary for the definition of AD. This differs from allergic rhinitis for which the presence of allergy is mandatory for diagnosis.[3] Urticaria is not considered when investigating family and medical history. Total serum IgE levels and allergen-specific IgE antibody levels are considered as disease markers that tend to produce IgE antibodies. As total IgE level increases in response to disease activity, it is often low in patients with mild AD. In mild AD, the allergen-specific IgE antibody level can be a marker of disease.

2.2. Pathophysiology

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

2.2.1. Skin hypersensitivity - abnormalities of the horny cell layer

The stratum corneum forms a barrier contributing to the prevention of leakage of body fluids, retention of internal water within the cell layers, and contributes to biological defense (Fig. 1, 2). If the barrier function of the horny cell layer is dysfunctional, skin irritability to non-specific stimuli is enhanced, and allergen sensitization and inflammation are likely to occur.[4] Intercellular lipids of the stratum corneum are mainly composed of ceramide, cholesterol, and free fatty acids, and in the case of AD, the function of the intercellular lipids of the stratum corneum deteriorates due to an abnormal decrease of ceramide content, and the moisture retention capacity is impaired.[5,6] The horny cell layer consisting of keratin and filaggrin is structurally robust. Filaggrin loss-of-function mutation and filaggrin deficiency associated with inflammation have been observed in AD.[7,8]

2.2.2. Mechanisms involved in inflammation (Fig. 2)

A decline in skin barrier function may allow allergens to easily penetrate the skin. Allergens, which are foreign (non-self) molecules, are eliminated by immunization and allergic reactions. Allegens, such as the dust mite allergen, as well as protein

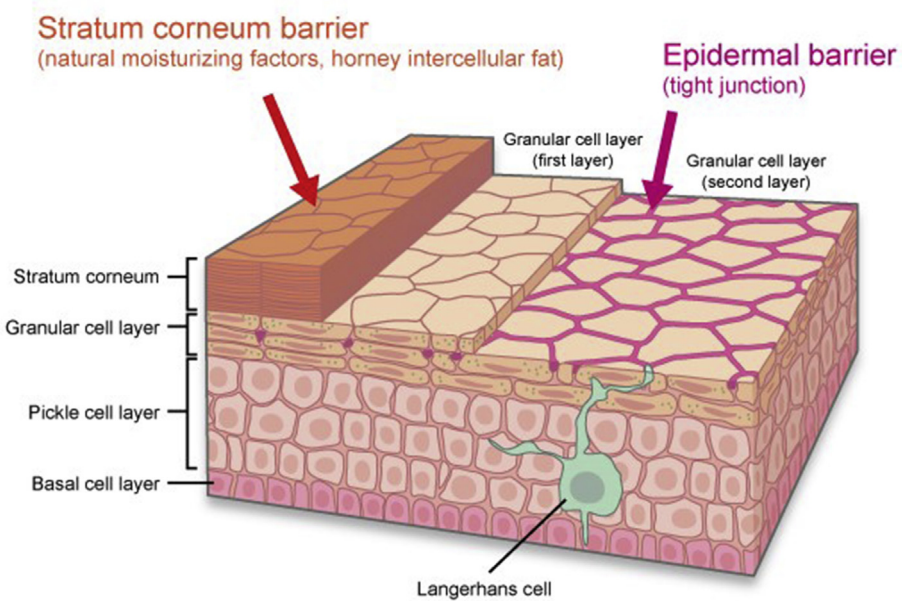

Fig. 1. Stratum corneum barrier and epidermal barrier.

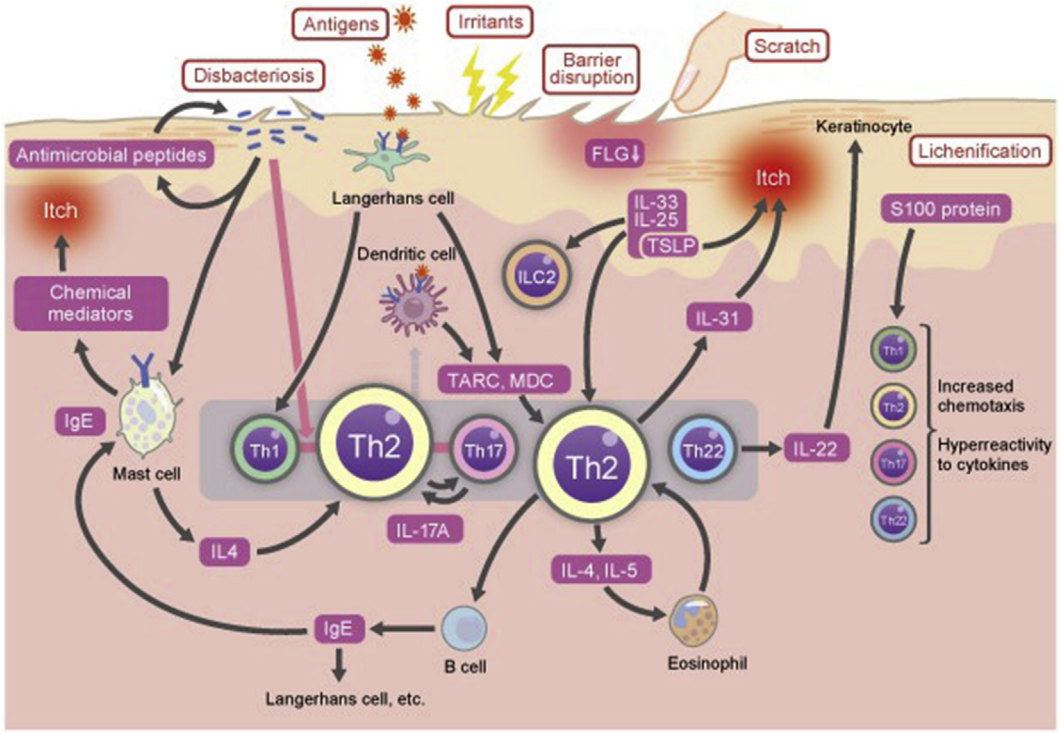

Fig. 2. Pathogenesis of atopic dermatitis. FLG, filaggrin; IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cells; MDC, macrophage-derived chemokine; TARC, thymus and activation-regulated chemokine; Th, T helper; TSLP, thymic stromal lymphopoietin.

allergens, induce type 2 immune reactions through protease activity. Helper T cells can be divided into Th1 and Th2 cells. Th1 cells have been demonstrated to be involved in cell-mediated immunity, while Th2 cells are mainly associated with allergic reactions. Interleukin (IL)-33, IL-25, and thymic stromal lymphopoietin (TSLP) produced by epidermal keratinocyte are associated with Th2 cell migration to the lesion. Serum thymus and activation-regulated chemokine (TARC) levels are also used as a marker of short-term progression.[9] The type 2 immune response leads to allergen-specific induction of IgE antibodies. Langerhans cells and mast cells express the high affinity IgE receptor (FcεRI) and release cytokines and chemical transmitters (e.g. histamine) via binding of allergen-specific IgE to induce inflammation. Th22 cells produce IL-22 after migrating to the skin; likely, via regulation by activated cutaneous dendritic cells, which induces epidermal acanthosis.[10] S100 protein produced by epidermal damage further activates lymphocytes.[11]

2.2.3. Pruritus

AD skin lesions release various substances (pruritogens), including cytokines and chemokines (e.g. IL-31, IL-4, and TSLP), and chemical mediators that induce pruritus. These substances act on nerves and thereby induce itching, which ultimately leads to scratching behavior. Scratching results in the further worsening of dermatitis. Skin hypersensibility can be observed in chronic inflammatory conditions such as AD. Hypersensibility may be partially caused by the extension of the cutaneous sensory nerve fibers to immediately below the horny cell layer of the skin surface due to dryness or inflammation.[12] An abnormal hypersensitivity reaction in which algesia or heat pain stimulation induces itching has also been reported for AD.[13] Besides dermatitis, visual and auditory stimulation suggestive of itching, such as the skin scratching sound, induces itching and becomes prominent in AD.[14] Imbalances between the sympathetic nerve system and the parasympathetic nerve system, emotional and psychogenic factors, and disturbances in life rhythm are associated with onset and worsening of itch.[15,16]

2.3. Genetic factors

Some genes have been described as candidate genes associated with AD: *CTLA4*, *IL18*, *TLR9*, *CD14*, *CARD4*, *PHF11*, *TLR2*, *SCCE*, *MCC*, *IL4R*, *GM-CSF*, *TIM1*, *CARD15*, *GSTT1*, *SPINK5*, *SCYA11*, *TGFβ1*, *IL-13*, *RANTES*, *IL4*, *and FCER1B*.[2] In addition, 2q12 (*IL1RL1/IL18R1/IL18RAP*), 3q21.33 (*GLB1*), 3q13.2 (*CCDC80*), 6p21.3 (MHC region), 7p22 (*CARD11*), 10q21.2 (*ZNF365*), 11q15.4 (*OR10A3/NLRP10*), 20q13 (*CYP24A1/PFDN4*) have been reported to be an AD-related region based on genome-wide linkage analysis from Japanese samples.[17]

2.4. Factors involved in onset and exacerbation

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

2.5. Diagnostic criteria

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

chronic or chronically relapsing course (Table 1).[1] AD-suspected patients are regarded as having acute or chronic eczema, and diagnoses are made based on their age and courses. It is essential to differentiate the disorders which should be ruled out in diagnosis of AD and be familiar with the complications of AD. Internationally, the diagnostic criteria prepared by Hanifin and Rajka in 1980[18] and by U. K. Working Party[19] are widely used.

2.6. Characteristics of eruption

2.6.1. Infancy (younger than 2 years of age)

Eruptions usually initially develop on the cheek, forehead, or head appearing as skin dryness followed by papules during early infancy. With a slight delay after the occurrence of facial symptoms, exudative erythema develops in intertriginous zones such as the neck, axilla, cubital fossa, and the popliteal fossa, moreover, erythema and papules also develop on the trunk and extremities.

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

Definition

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

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

Diagnostic criteria for atopic dermatitis

1. Pruritus
2. Typical morphology and distribution
   (1) Diagnostic criteria for eczematous dermatitis
   - acute lesions: erythema, exudation, papules, vesiculopapules, scales and crusts
   - chronic lesions: infiltrated erythema, lichenification, prurigo, scales and crusts

   (2) Distribution
   - Symmetrical
     Predilection sites: forehead, periorbital area, perioral area, lips, periauricular area, neck, joint areas of limbs, trunk
   - Age-related characteristics
     Infantile phase: starts on the scalp and face, often spreads to the trunk and extremities
     Childhood phase: neck, the flexural surfaces of the arms and legs
     Adolescent and adult phase: tendency to be severe on the upper half of body (face, neck, anterior chest and back)
3. Chronic or chronically relapsing course (usually coexistence of old and new lesions)
   - More than 2 months in infancy
   - More than 6 months in childhood, adolescence and adulthood

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

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

Differential diagnosis (association may occur)

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

Diagnostic aids

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

Clinical types (not applicable to the infantile phase)

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

Significant complications

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

Cited from reference.[1]

2.6.2. Childhood/school-age (2–12 years old)

From early childhood to school age, eruptions on the face decrease, instead, eruption is typically observed on the neck, axilla, cubital fossa, popliteal fossa, inguinal area, wrist, and ankle. In severe cases, eruptions extend to the face and limbs, while repeated scratching leads to repeated erosions and blood crusts. Lichen papule and prurigo may develop on the limbs. Dry skin- or goose bump-like follicular papules may be observed on the trunk and extremities.

2.6.3. Adolescence/adulthood (13 years and older)

After puberty, eruptions are more likely to develop on the upper body including the face, neck, chest, and back. In addition, face and neck involvement and a prurigo on the trunk and extremities may be observed. In severe cases, eruptions extend all over the body resulting in erythroderma.

2.6.4. Characteristics of eruption

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

Eruptions immediately after acute onset, present with erythema and papules. Some may have vesicles and erosion. Repeated scratching results in thickened skin caused by mechanical irritation forming lichenified lesions and prurigo nodularis.

2.7. Severity assessment

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

2.7.1. Overall assessment of severity

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

Severity classification methods with verified statistical reliability and validity include the Atopic Dermatitis Severity

Table 2
Severity index.

Mild: Only mild eruption are observed irrespective of the area.
Moderate: Eruption with severe inflammation are observed in less than 10% of the body surface area.
Severe: Eruption with severe inflammation are observed in ≥10% to <30% of the body surface area.
Most severe: Eruption with severe inflammation are observed in ≥30% of the body surface area.

Mild eruption: Lesions are seen chiefly with mild erythema, dry skin, or desquamation. Eruption with severe inflammation: Lesion with erythema, papule, erosion, infiltration, lichenification, etc. Modified from Ministry of Health and Welfare, Japan. *[Guidelines for the Treatment of Atopic Dermatitis 2008]* (in Japanese).

Classification[20,21] developed by the JDA, the Severity Scoring of Atopic Dermatitis (SCORAD) index,[22] and the Eczema Area and Severity Index (EASI).[23] The SCORAD index and the EASI are used internationally. The SCORAD index has been reported in many English-language papers and has been frequently used in clinical research and trials. The maximum score of the SCORAD Index is 103, and its score can be calculated using a dedicated website (http://adserver.sante.univ-nantes.fr/Scorad.html). The EASI is recommended by the Harmonising Outcome Measures for Eczema (HOME), an international multi-professional group dedicated to standardizing AD clinical research outcomes (http://www.homeforeczema.org/index.aspx). The EASI score chart can be downloaded from the dedicated website (http://www.homeforeczema.org/resources.aspx), and assessment training is available online. Either of the above methods can be selected, however, it is recommended that the simple "Severity index" be used for routine clinical practice and the international EASI or SCORAD index for clinical research or trials.

2.7.2. Assessment of eruption severity

Selection of topical steroids, a key treatment, depends on "the severity of individual eruption".[1] That is, a sufficiently potent topical therapy is selected for severe eruption even though the affected area is limited, while a potent topical therapy is not necessary for a milder eruption even if effects are more extensive. The severity of the eruption is categorized into 2 to 3 levels according to the above-mentioned assessment methods.

2.7.3. Assessment of pruritus

Itching is the most important feature of AD. As it is difficult to assess itching objectively, the visual analogue scale (VAS) and the numeric rating scale (NRS) are often used to obtain a patient's subjective assessment.[24] In VAS, patients are instructed to mark one point on a 100-mm long horizontal line in accordance with the degree of pruritus, and the distance (mm) from the left end to the marked point is evaluated as the pruritus scale score, regarding the left end "no itch" as 0 and the right end "the worst imaginable itch" as 100.

For the NRS, patients are instructed to rate verbally their itch using an 11-point scale from 0 ("no itching") to 10 ("the worst imaginable itch"). Subjective itch and insomnia due to itching can be assessed using the SCORAD index, and neither VAS nor NRS are suitable indexes. A good correlation of these methods with itching has been reported.[24]

2.7.4. Assessment by patients

The Patient Oriented Eczema Measure (POEM) is a severity scale, which was specifically designed to measure severity by the patient and/or patient's caregiver using a questionnaire (For adults: https://www.nottingham.ac.uk/research/groups/cebd/documents/methodological-resources/poem-for-self-completion.pdf, For children: https://www.nottingham.ac.uk/research/groups/cebd/documents/methodological-resources/poem-for-proxy-completion.pdf).[25,26] It is useful in sharing treatment goals between the physician and patient as has been shown to correlate with assessment by physicians. A self-administered patient-oriented SCORAD index (PO-SCORAD) has also been reported.[27]

2.7.5. Assessment of quality of life

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

For adult patients, the Skindex-16 and DLQI can be used as QOL assessment questionnaires for cutaneous diseases including AD[28–30]; their Japanese versions are currently available.

A Japanese version of the Children's Dermatology Life Quality Index (CDLQI) is available for children.[31] For younger children, a caregiver, often the mother is the main provider of treatment in many cases. As the burden borne by the caregiver is substantial, questionnaires evaluating "Quality of life in Primary Caregivers of children with Atopic Dermatitis" (QPCAD) (19 items)[32] and its abbreviated version QP9 (9 items)[15] have been specifically developed to evaluate the QOL of primary caregivers. The Japanese Culturally Modified Version of the CADIS (JCMV-CADIS),[16] a modified and translated version of the Childhood Atopic Dermatitis Impact Scale,[33] in which the caregiver responds to questions regarding the QOL of both the affected children and the caregiver, adapted to Japanese patients, is also useful.

2.8. Useful biomarkers for diagnosis and severity assessment (Supplementary Table 1)

2.8.1. Serum IgE levels

A high serum total IgE level is observed in patients with allergic diseases, however, a clear cut-off cannot be established because its distribution greatly overlaps with that of healthy individuals. In patients with AD, a total serum IgE level of 500 IU/mL or higher is commonly observed.[34] Serum total IgE level may represent allergic diathesis rather than short-term disease activity in AD. However, it can be an indicator of long-term response in severe cases as the high serum total IgE level decreases after several months of follow-up.

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

2.8.2. Peripheral eosinophil count

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

2.8.3. Serum lactate dehydrogenase level

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

2.8.4. Serum thymus and activation regulated chemokine level

Thymus and activation regulated chemokine (TARC: CCL17) is a ligand of the chemokine receptor CCR4 and induces Th2 cell migration.[35] Serum TARC in patients with AD increases consistently with severity, and testing for TARC levels is covered by the national insurance as it reflects disease progression more strongly than either serum IgE levels, LDH levels, or peripheral eosinophil counts.[35,36] Moreover, patient education and treatment can be reviewed using serum TARC levels as an index.[37] However, test values should be carefully interpreted because TARC levels are

generally higher in younger children, especially in children under 2 years of age.[38]

3. Treatment approaches

3.1. 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.

3.2. 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 viscous cycle of inflammation. Therefore, controlling inflammation by drug therapy will also reduce AD-exacerbating factors.

3.3. Drug treatment

3.3.1. Topical anti-inflammatory drugs

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

Hydrocortisone was the first TCS developed in 1952 and has been used as topical drug therapy for AD for over 60 years. Efficacy and safety of TCS have been examined in many clinical studies.[39] TCS are often used as a first-line anti-inflammatory topical agent for both children and adults.

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

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

(1) Topical corticosteroids (TCS)

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

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

a) Use of TCS

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

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

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

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

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

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

Selection of vehicles. Vehicles, such as ointment, cream, lotion and tape preparations, need to be selected based on lesion characteristics/sites. Ointment should be basically selected in order to

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 2016. 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).[40] In Europe, they are classified into four ranks (very potent, potent, moderately, mild).[41] When referring to international clinical trial data, it must be considered that the rank classification of topical corticosteroids differs from that in Japan.

Table 4
Severity of eruption and topical corticosteroid (TCS) application.

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

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

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

Way of application. i) 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)[42] (Supplementary Table 2). This may be adopted as a reference, considering the physical status of Japanese individuals and the tube size of topical corticosteroids available in Japan. On the other hand, the appropriate volume would change according to some factors including skin constion and vehicle of topicas agent.

ii) Frequency of application: As a rule, TCS should be applied twice a day (morning and evening: after bathing) in cases of acute exacerbation. When inflammation is reduced, the frequency of applications should be decreased to once a day to induce remission. Further evidence needs to be accumulated in order to determine whether efficacy differs between twice-a-day and once-a-day applications. However, several randomized controlled studies and systematic reviews reported no significant difference in efficacy between twice-a-day and once-a-day applications.[43] It is generally recognized that even a once-a-day application exhibits potent effects. If the number of applications is low, the incidence of adverse reactions may be low, thereby improving adherence. Therefore, topical corticosteroids should be applied twice a day to control acutely exacerbated eruptions for an early recovery. When the condition subsides, topical corticosteroids should be applied once a day to achieve remission.

b) Consideration for the use of TCS

Regions of application. The absorption rate of topical steroids by skin region is 13.0 on the cheek, 6.0 on the neck and 42 on the scrotum, with the extensor surface of forearm defined as having a rate of 1.0.[44] Such skin regions having a high drug absorption rate require attentive monitoring for the development of local side effects due to TCS treatment, and prolonged use should be avoided. For the face, medium class or lower raked TCS are generally used, while drugs consistent with the severity rank are used for severe dermatitis to introduce prompt remission, and then, drugs are gradually tapered or administered intermittently. Moreover, an effort to transition from TCS to tacrolimus ointments is made.

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

If TCS are suddenly discontinued in adult patients after prolonged use on the face or genitals, erythema, flushing, edema, papules, and pustules may appear and worsen.[45] In such cases, the patient should be referred to a dermatologist.

c) Side effects of TCS

Systemic side effects. While adrenal function suppression has been reported in some cases after the use of strong TCS,[46,47] adrenal function suppression and growth disorders have not been observed with the use of weak rank TCS.[48,49] If these drugs are used appropriately, less systemic side effects and higher safety can be expected.

Local side effects. Skin atrophy, capillary dilatation, steroidal acne, steroid flushing, trichopsis, and progression of microbes/fungi and viral skin infection can occur in some cases, however, they can also be resolved with drug discontinuation or appropriate treatment. Skin atrophy has been reported after the long-term use of the very strong class of TCS, when compared to similar use in healthy subjects. There are no reports of serious side effects after prolonged use of TCS, thus, most side effects are transient and can be resolved with reduced frequency of topical application, with the exception of lineae atrophicae of the skin. Rosacea-like dermatitis is a TCS-induced side effect presenting erythema, capillary dilatation, follicular papules, and pustules, and is mainly observed on the face of adult patients after prolonged use of TCS. If the TCS is stopped abruptly, erythema and edema may worsen.[45] If these symptoms are observed, the patient should promptly be referred to a dermatologist.

(2) 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.

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”.[50] Tacrolimus ointment is available at the following concentrations: 0.1% for adults and 0.03% for children. It cannot be selected for children aged 1 year or younger as its safety has not yet been established for this age group. Its application should also be avoided in lactating women.

a) Volume

A volume of 0.1 g (corresponding to a volume squeezed by 1 cm from a 5-g tube commercially available in Japan) is appropriate for a 10-cm square. Based on the findings of a long-term observational

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

b) Way of application

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

The efficacy of this ointment (0.1% for adults) for the trunk and limbs may be similar to that of strong-class topical corticosteroids.[50] When treating the site of severe eruption, which requires potent drug efficacy, very-strong-class or stronger TCS should initially be used to reduce eruption, as a rule. The regimen should then be switched to tacrolimus ointment. The volume of TCS can be decreased in many cases by combining them with this ointment. If an improvement in eruption is achieved by this ointment, the interval of application should be prolonged at an appropriate time.

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

c) Adverse reactions

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

(3) Proactive therapy

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

In AD, histological evidence of inflammatory cells is still present despite the normal appearing skin following the resolution of inflammation; inflammation can easily relapse due to external or internal factors.[51] In such cases, markers indicating disease progression, such as TARC, do not decrease to normal levels in many cases. During this latent inflammation stage, proactive treatment with anti-inflammatory topical drugs including TCS or topical tacrolimus may prevent relapse of inflammation.[52] However, it is important to transition from successive application of anti-inflammatory topical drugs to proactive treatment based on laboratory data indicative of disease progression, such as TARC levels, after the dermatitis has fully improved and there is no evidence of itching or erythema, and in absence of any slight elevation of skin on palpation. Moreover, dose, application range, and the time to complete the treatment of topical drugs should be determined individually for each patient. Development of side effects should be also carefully monitored. Proactive treatment should be performed in collaboration with a physician experienced in the evaluation of cutaneous symptoms of AD or in the evaluation of cutaneous symptoms in general. During proactive treatment, continuation of daily skin care with moisturizing topical drugs is recommended.

3.3.2. Antihistamines

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

Antihistamines include sedative antihistamines (first-generation) with relatively strong anticholinergic and sedative effects and non-sedative antihistamines (second-generation) causing less drowsiness and impaired performance (impaired concentration, judgment, and reduced operating efficiency without subjective sleepiness) and anticholinergic activity with less fatigue. Based on the extent these central effects, of histamine H1 receptor occupancy in the brain, antihistamines have been divided into 3 groups: sedative, 50% or more occupancy; mildly sedative, 50–20%, and non-sedative, 20% or less; the H1 receptor occupancy of almost second-generation antihistamines has been demonstrated to be 30% or less[53] (Supplementary Table 3). As there is no difference in treatment efficacy between sedative and non-sedative anti-histamines, it is recommended that a non-sedative antihistamine be selected.[54]

According to the package insert of the antihistamine ketotifen, this agent is contraindicated in patients with epilepsy or a history of epilepsy, and careful administration of clemastine, hydroxyzine, cetirizine, and levocetirizine is indicated for patients with convulsive disorders. Convulsions are reported as a serious side effect of chlorpheniramine, cyproheptadine, and loratadine treatment. Thus, special attention is needed when administrating these agents to children.

3.3.3. Cyclosporin

The efficacy of cyclosporin for AD has been demonstrated in many countries in Europe and the USA.[55] It has been approved for

use by patients with AD. 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.[56]

The initial dose of this drug is 3 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.

3.3.4. 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, longterm AD control with oral corticosteroids is not recommended. If necessary, administration should be completed in a short period.

3.3.5. Considerations regarding pregnant or breastfeeding mothers

Dietary restrictions (elimination of food allergens) for pregnant or breastfeeding mothers to prevent the onset of AD cannot be recommended. There is the possibility that AD may be exacerbated and transferred to the infant after ingestion of food allergens such as eggs through breast milk, however, these infants should be carefully diagnosed based on the results of food elimination and food challenge tests (via breast milk).[57]

Administration of antihistamines during pregnancy which is considered safe can be administered if it is deemed therapeutically beneficial. Most antihistamines that have been demonstrated not to increase the risk of congenital anomalies based on epidemiological observational studies and meta-analyses belong to first-generation agents. Among the second-generation antihistamines, loratadine and cetirizine have been reported not to be associated with congenital anomalies in epidemiology studies.[58–60] However, it is important to use these agents according to the information on package inserts and the latest reports on safety.

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

During both pregnancy and breastfeeding, topical steroids are considered safe, so they can be used without any concern about effects on the fetus of infant. Although long-term use of high doses of higher ranked topical steroids (300 g or more) may result in lower birth weight, complications are unlikely to occur with normal use.[58]

Standard TCS therapy shows low-level absorption in systemic circulation, and neither congenital anomalies nor the influence on fetal growth has been raised as an issue. However, we cannot rule out the possibility that birthweight may be decreased by the massive application of TCS classified as potent/very-potent[3] groups according to the classification used in Europe (especially 300 g or more). Therefore, attention should be paid to the volume of TCS used and fetal growth. Furthermore, it is important to favorably control dermatitis before pregnancy in order to avoid this anxiety. If the application of TCS to the breasts of lactating women is necessary, care must be taken to prevent infants from directly ingesting TCS.

3.4. Skin care

3.4.1. Topical moisturizers

In AD, the skin barrier functions and moisturizing factors are impaired. The use of moisturizer products improve moisture content in the stratum corneum and leads to the prevention of allergen invasion and relapse of dermatitis, as well as suppression of itching by recovering and maintaining skin barrier functions.[61,62] Moreover, skin care with moisturizers immediately after birth and thereafter, decreases the risk of onset of AD.[63,64]

An essential aim of skin care for dry skin is topical administration of hydrophilic ointments (oil in water: O/W) with a high moisture-retaining property or water-absorbing ointments (water in oil: W/O) to supplement the reduction of the moisture-retaining properties on the skin surface.

It is especially recommended to apply moisturizers immediately after bathing. Topical moisturizers should be applied all over the body including sites that appear to be normal. Continuous use of moisturizer products even after achieving remission of dermatitis with topical anti-inflammatory drugs is also useful to maintain the remission.[65]

3.4.2. Bathing, showering and washing

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

(1) Temperature

The temperature of hot water in bathing/showering should be set at about 38–40 °C because the itching response is induced at a skin temperature of 42 °C or higher, while 36–40 °C is the optimum temperature for recovery of skin barrier functions.[66–68] Water is diffused and evaporated from the skin surface immediately after bathing resulting in dry skin, thus, the skin should not be left without the application of a moisturizing agent for an extended time after bathing.

(2) Soap and/or detergent

Although there is no high quality evidence demonstrating the efficacy of using soap or detergent for AD, symptoms have been shown to improve without experiencing exacerbation in patients who did not use soap with prolonged bathing in a case series study of commonly used soap preparations.[69] As the major component of soap and/or detergent is surfactants, excessive abuse of these products may exacerbate skin dryness. Moreover, additives contained in detergent, such as pigment and perfume, are believed to irritate the skin. Based on the above, the use of soap and/or detergent may be useful to keep the skin clean, however, skin conditions that vary according to age, site, and season, type and usage of soap or detergent should be considered.

[3] In Europe, TCS are classified into four ranks (very potent, potent, moderately, mild).[41]

The use of soap should be limited to a minimum in patients with severe cases, during dry seasons, and in those sensitive to strong irritation by soap or detergents. In contrast, soap and detergents should be used aggressively in patients with oily skin or for seborrheic skin, in sites where ointment is applied every day, and in sites exhibiting recurrent skin infections to avoid exacerbating factors. Removal of residues on the skin should be removed using a minimal degree of mechanical irritation, and adequate rinsing of the skin in necessary to remove residual detergent is also important.

3.5. Search for exacerbating factors and measures

3.5.1. Non-specific irritation

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

In addition, the residues from shampoo, conditioner, and soap or excessive use of these agents may induce irritant dermatitis, thus, providing instructions on appropriate cleansing methods is important.

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

3.5.2. Contact allergy

Contact allergy to topical drugs, cosmetics, perfume, metal, shampoo, hair conditioners, and disinfectants may case progression of eczema.[70] When expected treatment efficacy for AD cannot be achieved, when the distribution of eczema is not typical, and when AD onset or progression has occurred recently in an adult patient, complications due to contact allergy should be suspected. In such cases, observe whether the eczema can be resolved by avoiding contact with a potential causal agent, and confirm the diagnosis by a patch test.

3.5.3. Food allergens

Food allergens may be present in patients with AD pathology, especially during infancy. However, a systematic review has reported that there is only weak evidence of the efficacy of an allergen elimination diet in treating AD in children and adults without any clear involvement of food allergy.[71] The allergen elimination diet presents nutritional issues associated with potential growth and development impairment when undertaken during childhood; thus, allergen elimination therapy should be provided under the close surveillance of physicians. Except for cases in which progression of AD due to a certain food is confirmed, the elimination of a specific food because it is likely to become an allergen is not recommended. In order to eliminate a specific food from the diet, an allergen elimination test should be conducted after adequate anti-inflammatory therapy for AD. If no improvement is achieved in cutaneous symptoms even after anti-inflammatory therapy with appropriate intensity and sufficient doses of TCS, food allergens causing progression of eczema should be identified. If AD is poorly controlled because of inadequate topical therapy, making a definitive diagnosis will be difficult.

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

The American Academy of Pediatrics recommends the allergen elimination diet for pregnant women in 2000. However, a systematic review of randomized comparative studies of allergen elimination diets in pregnant or breastfeeding mothers conducted between 2006 and 2012[72] reported that dietary restrictions with the aim of eliminating allergens these women did not show any efficacy in preventing the onset of AD in neonates or in infants up to 18 months of age. Furthermore, dietary restrictions may have a role in limiting adequate weight gain during pregnancy and may worsen nutritional status among children leading an increased risk of immature births. Based on the above, dietary restrictions (allergen elimination) in pregnant or breastfeeding mothers may not be useful to prevent the onset of AD in children.

3.5.4. Inhaled allergens

AD after infancy may experience progression due to the presence of environmental allergens such as mites, house dust, pollen, and pet hair.[73] Whether these allergens are to be considered exacerbating factors for eruption should be carefully evaluated by comprehensively considering medical history, environmental changes, and changes in eruption features, and should include results of elimination tests and challenge tests, if possible, rather be based on judgment of clinical symptoms alone, or by specific IgE antibody titer, or skin prick test results. Similar to handling of food allergens, eliminating environmental allergens is an adjuvant therapy to pharmacotherapy and skin care; thus, it should be noted that complete remission cannot be expected by eliminating these allergens alone.

3.5.5. Useful specific IgE antibodies to inhaled allergens

Mites and pollen (from cedar, cypress, white birch, *Alnus japonica*, *Anthoxanthum odoratum*, cocksfoot, and ragweed), animals (from pets including dogs, cats, other mammals, birds, and hamsters), and fungi (from aspergillus and malassezia).

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

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

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

3.5.6. Sweating

Disturbances in perspiration as well as excess sweat remaining on the skin surface exposed to high-temperatures and humidity may worsen symptoms of AD. Malassezia-derived allergens found in sweat residues on the skin surface that have not evaporated may lead to worsening of symptoms.[74] High-temperatures and humidity on the skin surface occludes sweat pores and induces perspiration. To protect the skin surface from having excessive sweat, and undergarment made of breathable and low hygroscopic fabric should be worn to avoid high-temperatures and humidity, and appropriate measures such as showering, rinsing using running water, wiping

with wet towels, and changing wet clothes after sweating should be adopted.

Among patients with AD, some sweat normally, while others produce moderate amounts (scanty sweat).[75] Inspection and palpation are helpful in determining whether a patient's sweating is normal. Significant dryness of the skin, flushing, and heat sensations are important findings indicating poor perspiration.

3.5.7. Bacteria and fungi

It is known that *S. aureus* is often detected in the lesion of patients with AD, and *S. aureus* may be an exacerbating factor of AD. The role of bacteria in AD is largely unknown, however, bacterial flora analysis of the skin has recently revealed its involvement in clinical conditions. On the skin of children with AD, it has been reported that the diversity of the bacterial flora of the skin decreases in the exacerbation phase, and the proportion of *S. aureus* increases.[76] The results of studies in animal models have shown that abnormal bacterial flora including the presence of *S. aureus* may induce AD-like dermatitis, and maintenance of normal bacterial flora with antibiotic treatment can inhibit the occurrence of dermatitis.[77]

There have been no reports suggesting that administration of oral antibiotics is effective for AD in the absence of infection, thus, administration of oral antibiotics is not recommended.[78]

The potential involvement of fungi on the pathology and worsening of AD has been suggested based on the results of measuring specific IgE antibodies levels to candida or malassezia and skin prick test results in patients with AD.[79] However, a clear correlation with the clinical conditions is still unknown. While there are some reports showing that oral antifungal drugs are effective for AD,[80] topical antifungal drugs have been shown to be effective for eruptions on the head and neck,[81] there have been no large-scale studies to date, thus, careful use is recommended.

3.6. Psychosomatic involvement

It is well known empirically that AD can be worsened by stress. AD is known to be associated with concomitant developmental disorders such as attention deficit hyperactivity disorder; however, such diagnosis is not helpful for treatment. When AD is poorly controlled, psychological burden or secondary cognitive abnormalities can occur, however, these patients should not be perceived as “special” by clinicians, and comprehensive treatment should be provided to all patients with specific attention to psychosomatic interaction.

3.6.1. Verification of drug therapy and patient adherence

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

3.6.2. Understanding of stressor effects as exacerbating factors

Adolescents often experience progression of skin conditions due to tension before school exams and lack of sleep. They also often experience progression of skin exacerbation by fever or high temperature. Such stressors are unavoidable factors; however, these may be surmounted by stress management and behavior modification, including changes in lifestyle habits, and relaxation training.

3.6.3. Habitual scratching behavior

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

3.6.4. Patient education

Psychosomatic interventions with verified efficacy in RCTs have reported results limited to behavioral science approaches, such as behavioral therapy and cognitive behavioral therapy,[82] while the efficacy of psychoanalysis and counseling with attentive listening have not been demonstrated. Implementing a comprehensive approach to patient education using behavioral science techniques such as appropriate drug therapy, supportive stress-reduction training, including relaxation training and cognitive behavioral therapy, behavioral therapy to stop habitual scratching, coaching to improve therapy adherence, and motivational interviewing[83] are important.

3.7. Ultraviolet irradiation therapy

Ultraviolet (UV) therapy is considered for non-responders to treatments with topical anti-inflammatory drugs, antihistamines or moisturizers, as well as for patients with adverse reactions to conventional treatments.[1] Narrow-band ultraviolet B (NB-UVB) irradiation therapy has been demonstrated to be effective in the treatment of AD.[84] When administrating UV therapy, it is important to initially consider whether it should be indicated, and it should also be carefully performed by UV therapy-skilled physicians who sufficiently understand the action mechanism, radiation dose, acute skin disorders, deterioration of concomitant infectious diseases, various long-term adverse reactions, including skin cancer, and management methods. Ultraviolet irradiation therapy can be used for children with psoriasis beginning at 10 years of age and older, but is not recommended for children younger than 10 years of age.[85]

3.8. Hospital care

It is difficult to induce remission in some severe patients in whom the area of eruption is extensive with topical anti-inflammatory agents. 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, patient adherence and aggravation factors as background factors. 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.[86] In addition, it is often the case that patients can

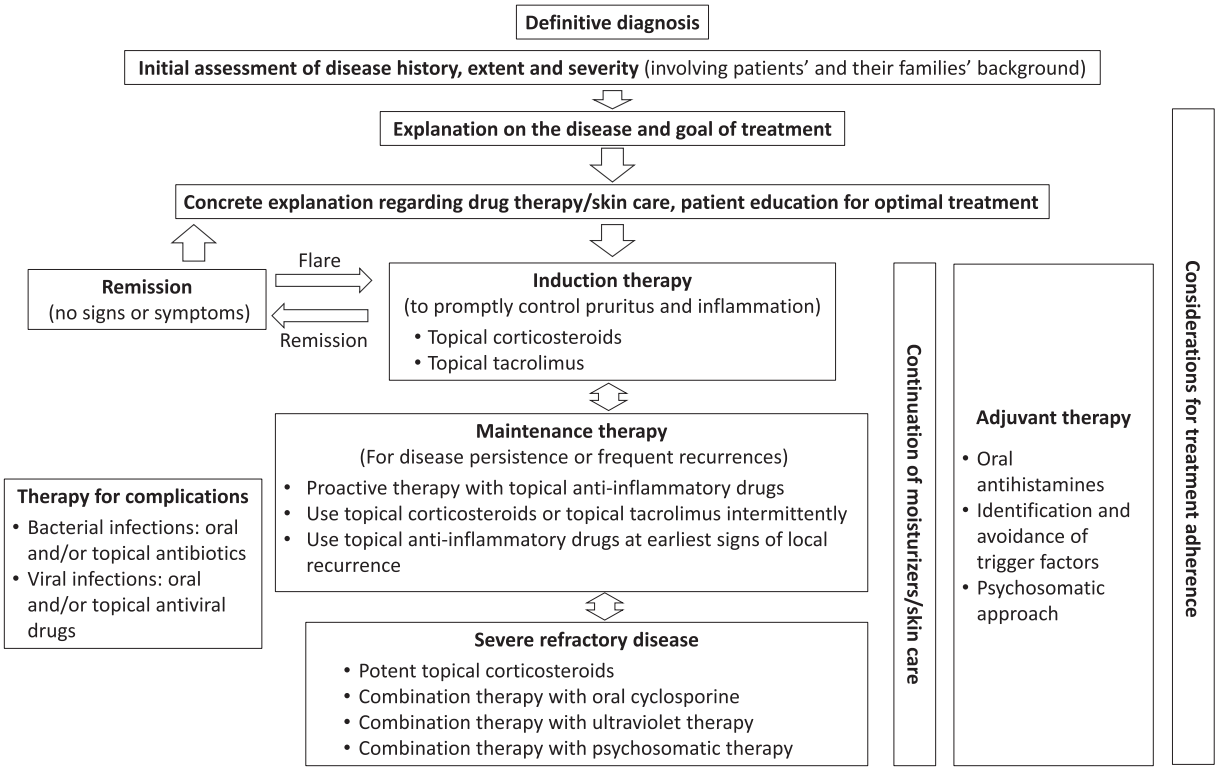

Fig. 3. Algorithm for the management of atopic dermatitis.

not continue appropriately the drug treatment, resulting in unexpected effects. For such patients with moderate to severe AD, hospital care would be considered as required. Because continuous topical treatment is required after the discharge of severe patients for whom hospital care is indicated, it is essential to understand their conditions and treatment methods. Therefore, the goal of hospital care is to achieve the early remission of dermatitis by intensive topical therapy and improve adherence through educational guidance.

3.9. Patient education

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

Different approaches have been successful in many studies regarding children, specifically, education by a multidisciplinary medical team, group work by a specialized nurse, educational hospital-stay for a short period of time, and education using online videos.[83,87–90] Other than above, websites and leaflets for young patients have been developed and have been used as educational tools for patients with AD in Japan.[91] In clinical practice, these tools should be selected as effective and feasible educational methods taking into consideration the individual patient's characteristics and medical care system provided at the treating facility. Confirmation on the use of topical drugs is important and appropriate instructions should be provided before changing treatment, not only during the treatment introduction phase, but also when the expected efficacy of the therapy cannot be obtained.

3.10. Referral to a specialist

When no improvement of eczema is observed even after implementing treatment in accordance with the present clinical practice guidelines for a period of about 1 month, referral to a specialist or to a specialized facility should be considered.[2] When prominent erythema, scars from scratching, erosion, lichenification, or prurigo is observed, or a wide range of erythema like erythroderma is observed, referral to specialist should be considered. In addition, when infection to bacteria or virus is concomitantly observed, or a detailed examination of the exacerbating factors including food allergies and contact allergy is necessary, referral to specialist should also be considered.

3.11. Treatment procedures

Treatment procedures for AD are shown in Figure 3. After making an accurate diagnosis and evaluating its severity, appropriate treatment methods should be combined in accordance with the state of eruption. In the initial consultation, it is important to explain the condition of AD and treatment methods to patients and have a common understanding with them.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2020.02.006.

Conflict of interest

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

reference to the opinions of the representatives of the JDA and JSA (public comment).

Members of the Committee for this 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 April 2015 and 31 March 2017: (i) directors' or advisors' fees; (ii) shares of profit; (iii) royalties; (iv) lecture fees; (v) manuscript fees; (vi) research costs; (vii) scholarship donations; (viii) chairs donated by companies or other bodies; and (ix) Relevant company/organization: traveling costs or gifts. Corresponding companies and bodies:

NK: Mitsubishi Tanabe Pharma (iv, vii), Maruho (iv, vii), Novartis Pharma (vi), Kyowa Hakko Kirin.(iv, vi), Torii Pharmaceutical (iv), Taiho Pharma (iv, vii), Sanofi (vi), Mochida Healthcare (vi), **YO:** Maruho (iv), **HS:** Mitsubishi Tanabe Pharma (iv, vii), Maruho (iv, vii), Tokiwa Pharmaceutical (vii), Torii Pharmaceutical (vii), Eisai (vii), Taiho Pharma (iv), Kyowa Hakko Kirin (iv), Kyorin Pharmaceutical (iv), Sanofi (iv), **TF**: Maruho (iv), **HM:** Maruho (iv), Mitsubishi Tanabe Pharma (iv), Taiho Pharma (iv), Sanofi (iv), **TN:** Maruho (viii), **NS:** Torii Pharmaceutical (iv), **IK:** Maruho (iv), **MH:** Mitsubishi Tanabe Pharma (iv, vii), Maruho (iv, vii), Novartis Pharma (iv, vi), Taiho Pharma (iv), Bathclin (vi), Sanofi (vi), **AT:** Sanofi (iv), Novartis Pharma (vi), Bathclin (vi), Sanofi (vi).The rest of the authors have no conflict of interest.

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