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REVIEW ARTICLE

Japanese Guideline for Atopic Dermatitis 2014

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ABSTRACT

Given the importance of appropriate diagnosis and appropriate assessment of cutaneous symptoms in treatment of atopic dermatitis, the basics of treatment in this guideline are composed of (1) investigation and countermeasures of causes and exacerbating factors, (2) correction of skin dysfunctions (skin care), and (3) pharmacotherapy, as three mainstays. These are based on the disease concept that atopic dermatitis is a inflammatory cutaneous disease with eczema by atopic diathesis, multi-factorial in onset and aggravation, and accompanied by skin dysfunctions. These three points are equally important and should be appropriately combined in accordance with the symptoms of each patient. In treatment, it is important to transmit the etiological, pathological, physiological, or therapeutic information to the patient to build a favorable partnership with the patient or his/her family so that they may fully understand the treatment. This guideline discusses chiefly the basic therapy in relation to the treatment of this disease. The goal of treatment is to enable patients to lead an uninterrupted social life and to control their cutaneous symptoms so that their quality of life (QOL) may meet a satisfactory level.

The basics of treatment discussed in this guideline are based on the "Guidelines for the Treatment of Atopic Dermatitis 2008" prepared by the Health and Labour Sciences Research and the "Guidelines for the Management of Atopic Dermatitis 2012 (ADGL2012)" prepared by the Atopic Dermatitis Guidelines Advisory Committee, Japanese Society of Allergology in principle. The guidelines for the treatment of atopic dermatitis are summarized in the "Japanese Guideline for the Diagnosis and Treatment of Allergic Disease 2013" together with those for other allergic diseases.

KEY WORDS

atopic dermatitis, exacerbating factors, guideline, pharmacotherapy, skin care

1. Definition/Disease Concept, Pathophysiology/Etiology of Atopic Dermatitis

1.1. Definition and Disease Concept

The guidelines adopt the definition (concept)[1] of the Japanese Dermatological Association on atopic dermatitis that states "atopic dermatitis is a disease with repeated exacerbation and remission, chiefly characterized by eczema with itch, mostly exhibited by patients with atopic diathesis."

Note: Atopic diathesis. (i) Personal or family history of bronchial asthma, allergic rhinitis and conjunctivitis, and/or atopic dermatitis and/or (ii) predisposition to overproduction of immunoglobulin E (IgE) antibodies. Patients with eczematous lesions that develop during infancy or childhood and persist

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without complete recovery or repeatedly recur even in adulthood.

1.2. Pathophysiology

1.2.1. Inflammatory mechanism

Atopic dermatitis is a disease included in the eczema/dermatitis group. The dominant mechanisms of atopic dermatitis in lesional skin are governed by Th2 cell-related cytokines such as IL-4 and IL-13, and chemokines such as TARC (thymus and activation-regulated chemokine) and eotaxin.[2] Among such chemokines, the so-called Th2 chemokines such as TARC/CCL17 and MDC/CCL22 deserve special attention. These chemokines are chemotactic for Th2 cells expressing the chemokine receptor CCR4. Accordingly, Th2 cells are usually observed at an eczematous site.[3]

This is, however, a pathology in the acute stage, and Th1 cells producing IFN-γ and IL-12 are reportedly dominant in the chronic stage.[4] Langerhans cells and mast cells are involved in the inflammatory response by expressing a high affinity IgE receptor (FcεRI) that causes antigen presenting cells and mast cells to release histamine, cytokines, etc.

The Th2 cytokines IL-4 and IL-13 stimulate fibroblasts to produce periostin, protein causing keratinocytes to produce TSLP,[5] which induces TARC/CCL17 production by dendritic cells.[6] Serum TARC/CCL17 levels are useful as a short-term disease marker for atopic dermatitis and the test is covered by health insurance. Research on Th17 as a new effector cell for allergic reactions[7] and on Treg (regulatory T cell)[8] that controls overreaction is also in progress.

In an eczematous lesion of atopic dermatitis, antimicrobial peptides (defensins, cathelicidins, etc.) are inhibited from being expressed by keratinocytes.[9]

1.2.2. Skin dysfunctions

Expression of ceramide[10] and filaggrin[11] decreases in skin with atopic dermatitis, particularly in lesions, and is considered as a primary cause of barrier dysfunctions. It is also considered as a secondary phenomenon associated with inflammation and as a cause of atopic dermatitis. Atopic dermatitis is accompanied by an acute itch allegedly due to a lowered threshold of itch. Involvement of IL-31 has been reported as a cause of the above.[12]

It is often experienced that itch due to atopic dermatitis cannot be well controlled with antihistamines. Histamine, substance P, and their receptors have been shown to play an important role in itch at the peripheral level. Recently, the role of endogenous opioids such as beta-endorphin and their receptors in itching at the central level has received attention. It has been reported that morphine induces itch via GRP receptors.[13]

1.3. Etiology

Atopic dermatitis is caused by combination of genetic and environmental factors.

1.3.1. Genetic factors

Regarding genetic factors, some etiological candidate genes associated with atopic dermatitis have been reported. Major candidate genes reported to date include CTLA4, IL18, TLR9, CD14, CARD4, PHF11, TLR2, SCCE, MCC, IL4R, GM-CSF, TIM1, CARD15, GSTT1, SPINK5, eotaxin, TGFβ1, IL13, RANTES, IL4, and FcεRIβ. In a recent GWAS of Japanese samples, "2q12 (IL1RL1/IL18R1/IL18RAP)," "3p21.33 (GLB1)," "3q13.2 (CCDC80)," "6p21.3 (MHC region)," "7p22 (CARD11)," "10q21.2 (ZNF365)," "11p 15.4 (OR10A3/NLRP10)," and "20q13 (CYP24A1/PFDN4) " have been reported as candidate genes.[14]

1.3.2. Etiological and exacerbating factors

A wide variety of etiological and exacerbating factors has been proposed, with the importance level of each varying among individual patients. In addition, inflammation associated with this disease will be elucidated by both allergic and non-allergic mechanisms. Etiological and exacerbating factors vary among age groups. While the dominant factors in the first half of childhood include foods, sweating, physical irritation (including scratching), environmental factors, microbes/fungi, the dominant factors in the second half of childhood to adulthood include environmental factors, sweating, physical irritation (including scratching), microbes/fungi, contact allergens, stress, and foods (Fig. 1).

It is commonly experienced that sweating induces itch leading to the aggravation of atopic dermatitis symptoms. Clinically, psychological stress is well known to exacerbate atopic dermatitis symptoms. Although the mechanism is mostly unknown, an increase in sensory nerve fibers containing substance P and CGRP is observed at inflammatory skin sites of patients with this disease.[15]

2. Epidemiology of Atopic Dermatitis

2.1. Global Prevalence of Atopic Dermatitis and Its Changes

An epidemiological survey (Phase I) was conducted from 1994 to 1996 by the International Study of Asthma and Allergies in Childhood (ISAAC).[16] The global prevalence in 6-7 year olds ranged from 1.1% in Iran to 18.4% in Sweden and was 7.3% on average. The global prevalence in 13-14 year olds ranged from 0.8% in Albania to 17.7% in Nigeria and was 7.4% on average. The highest prevalence was seen mostly in industrial nations including Sweden, Finland, UK, Japan, Australia, and New Zealand. In the epidemiological survey (Phase II) conducted from 2001 to 2003 by the ISAAC, few nations showed a significant decrease in the prevalence in 6-7 year olds compared with their

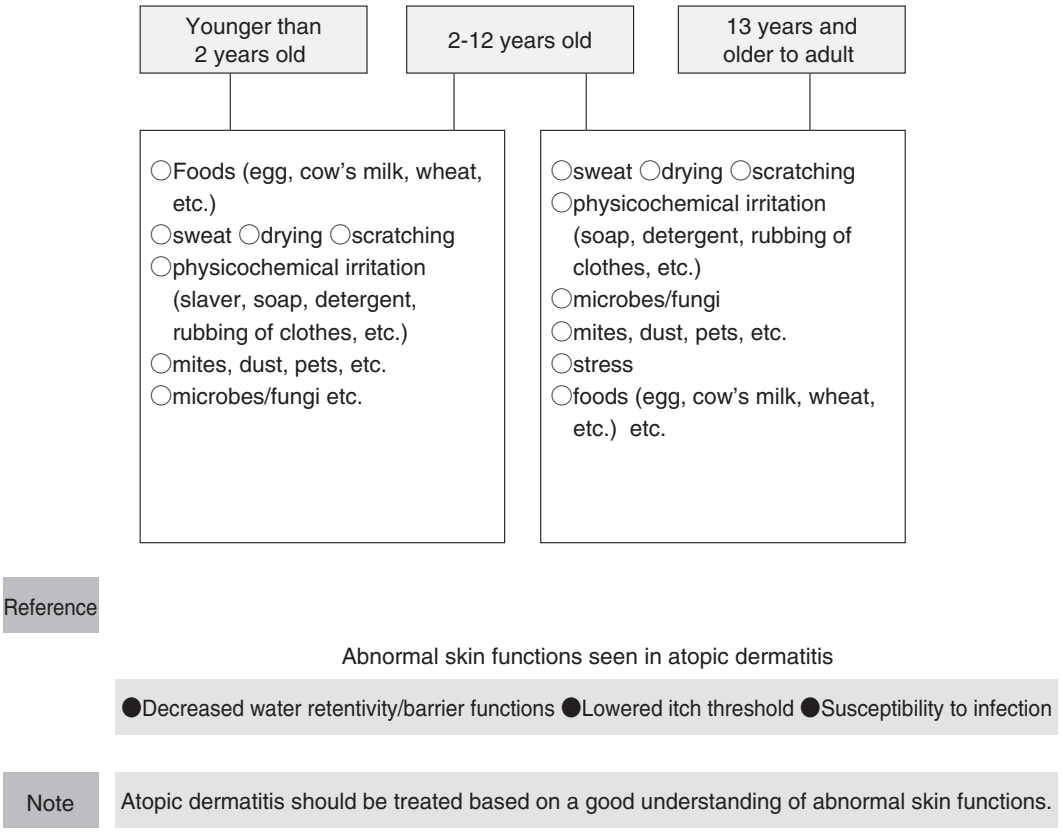

Fig. 1 Causes and exacerbating factors. Since causes and exacerbating factors vary among patients, care should be taken to identify them sufficiently for each patient before taking removal measures. Modified from Ministry of Health and Welfare, Japan. *[Guidelines for the Treatment of Atopic Dermatitis 2008]* (in Japanese).

prevalence reported in Phase I of the survey.[17] In terms of the age group of 13-14 year olds, some of the advanced nations with a high prevalence reported in Phase I (UK, New Zealand, etc.) showed a decrease in Phase II.

2.2. Epidemiological Survey in Japan

A nationwide prevalence survey was conducted in Japan from 2000 to 2008 using the medical examination data from public health centers, elementary schools, and universities. Figure 2 shows the prevalence by age groups. In addition, a prevalence survey on the adult atopic dermatitis was performed using the medical examination for 2,943 personnel of 2 universities[18] (Fig. 2). The data on occurrence and progression of infantile atopic dermatitis is provided by a report based on a follow-up study of infants of 4 months to 3 years old performed in the Health and Labour Sciences Research, from 2006 to 2008, in Yokohama City, Chiba City, and Fukuoka City. The report shows that 16.2% of ordinary infants, who received a medical examination at 4 months of age, developed atopic dermatitis. Atopic dermatitis remitted in 50% of the 4-month-old patients before the age of 18 months, indicating an extremely dynamic change in progression of atopic dermatitis in infancy.[19] This survey showed a cumulative incidence rate before 3 years of age of a little more than 30%, similar to reports from overseas (Fig. 3).

3. Diagnosis of Atopic Dermatitis

3.1. Diagnostics Criteria for Atopic Dermatitis

(1) Diagnostic criteria proposed by Hanifin and Rajka: The diagnostic criteria of Hanifin and Rajka are internationally most popular.

(2) Diagnostic criteria proposed by the Japanese Dermatological Association: The Japanese Dermatological Association developed diagnostic criteria in 1994, which was partly revised in 2008 (Table 1). Using these criteria, all diseases that meet the 3 requirements of itch, characteristic rashes and distribution, and chronic/recurrent progression, will be diagnosed as atopic dermatitis irrespective of the severity of symptoms.[1]

3.2. Laboratory Data Used as a Reference for Diagnosis

(1) Serum total IgE level: A high serum total IgE

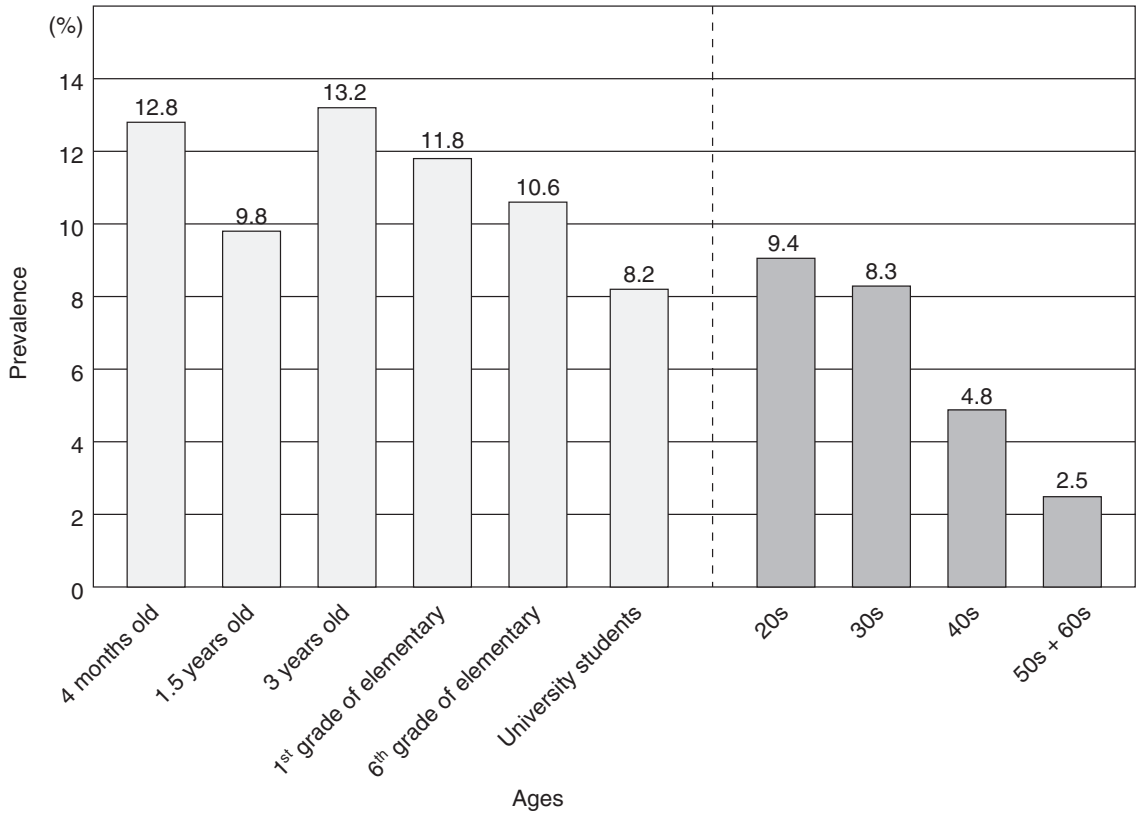

Fig. 2 Prevalence of atopic dermatitis by age groups in the fiscal year of 1996-2008. 4 months old from: Hokkaido, Kanto, Chubu, Kinki, Chugoku, Shikoku, and Kyushu (seven districts, *n* = 2744). Children with 1.5 years old, 3 years old , 1st grade of elementary, 6th grade of elementary from: Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku, Shikoku, and Kyushu (eight districts, *n* = 6424). University students from: University of Tokyo, Kinki University, Hiroshima University (*n* = 8317). Adult (20s to 60s) from: Personnel of University of Tokyo and Kinki University (*n* = 2943). Modified from Ministry of Health and Welfare, Japan. *[Guidelines for the Treatment of Atopic Dermatitis 2008]* (in Japanese).

level is observed in approximately 80% of patients with atopic dermatitis. It is also reportedly significantly correlated with the severity (the later discussed SCORing Atopic Dermatitis [SCORAD] severity index).

(2) Blood eosinophil count: Eosinophilia is seen in blood and the rash tissue of many but not all patients. Because it changes more rapidly than IgE, it serves as an index to assess changes of the disease condition.

(3) Specific IgE antibody titer: Patients with atopic dermatitis are apt to produce IgE antibodies in response to various allergens such as mites, foods, and pets and often show positive reactions to multiple allergens. Preventing exposure to the allergens that have been proven positive is expected to improve or prevent exacerbation of rashes.

(4) Serum TARC level: The serum level of TARC, a Th2 chemokine, has been shown to sensitively reflect the short-term condition of atopic dermatitis and is regarded as a useful auxiliary marker to assess the severity of atopic dermatitis.

(5) Others: Laboratory data reportedly used as a reference for disease conditions include lactate dehydrogenase (LDH). The soluble IL-2R level, which is high in skin lymphoma, is a useful assessment tool.

3.3. Severity Criteria for Atopic Dermatitis

(1) SCORAD: SCORAD is an international severity criterion that has been most popularly adopted in the English written literature at present. These criteria grade the rash areas, severity of rash elements such as erythema, edema/papule, exudation/crust, lichenification, scratch marks, xerosis cutis, and subjective symptoms such as itch, and insomnia, by weighting them at a ratio of approximately 2 : 6 : 2.

(2) Atopic dermatitis severity classification of the Japanese Dermatological Association: This severity criteria assesses severity based on the total scores of 3 rash elements (erythema/acute papule, moistening/crust, chronic papule/tubercle/lichenification) and rash areas of the body divided into the following 5 sections: head and neck, anterior body trunk, posterior body trunk, upper limbs, and lower limbs.[20]

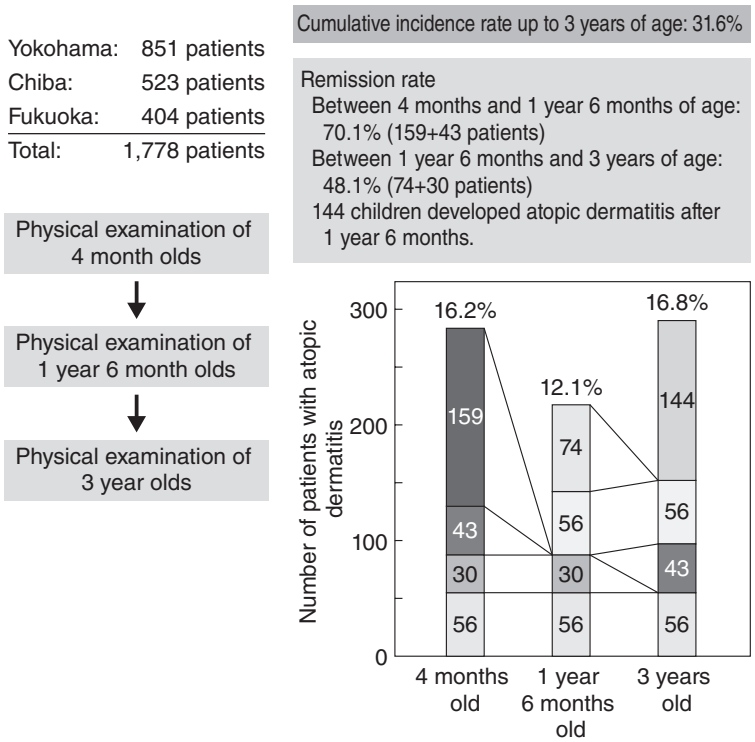

Fig. 3 Individual follow-up analysis of symptom onset/progression of atopic dermatitis in patients aged 4 months to 3 years (fiscal years surveyed: FY2006-FY2008).

(3) Severity indicators: Although the above-mentioned severity criteria are more objective than the conventional criteria, they are difficult to use in daily medical practice because of too many endpoints. Accordingly, the "Guidelines for the Treatment of Atopic Dermatitis 2008" of the Health and Labour Sciences Research proposes a simpler indicator of severity (Table 2). This indicator measures severity by assessing both the severity and the spread of the rash and defines mild rashes and rashes with severe inflammation based on photographic images (Fig. 4).

4. Clinical Symptoms of Atopic Dermatitis

Clinical symptoms: Clinical symptoms of atopic dermatitis are divided into 3 age groups: infancy (younger than 2 years old), childhood/school-age (2-12 years old), adolescence/adulthood (13 years and older).

4.1. Cutaneous Symptoms

The most important cutaneous symptoms for atopic dermatitis are rashes and itches.

4.1.1. Rash

There is a report on classification of rashes of atopic dermatitis from 3 perspectives: age groups, morphology and distribution, and sites.

(1) Rash morphology: Atopic dermatitis is a cutaneous disease that belongs to eczema/dermatitis. Patients with atopic dermatitis under long-term treatment with a topical steroid develop further diverse symptoms with such side effects as skin atrophy and telangiectasia. These symptoms will develop into further complicated cutaneous symptoms when an infectious disease occurs concurrently.

(2) Characteristics of rashes by age groups

a) Infancy (younger than 2 years old): A rash usually develops on the cheek, forehead, or the head, and causes flushing or papules. It will erode and exude by being scratched and the exudate will form a crust when it is dried.

b) Childhood/school-age (2-12 years old): The skin is apt to develop an atopic condition by gradually tending to be dried due to degradation of the sebum-secretion capacity. In addition, the atopic skin may be repeatedly scratched to develop prurigo nodularis, erosions, blood crusts, and so on. Rashes most typically observed in the childhood to the school-age group include a bend type.

c) Adolescence/adulthood (13 years and older): This age group is apt to suffer from seborrhea or acne due to the increase in sebum secretion with modified rashes. The rash extends from the neck to the upper chest region and the upper part of back and spreads like a clothes hanger. Together with the rashes on the face and the neck, it is distributed like

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) Eczematous dermatitis
      - Acute lesions: erythema, exudation, papules, vesiculopapules, scales, crusts
      - Chronic lesions: infiltrated erythema, lichenification, prurigo, scales, 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, nonspecific eczema.

Differential diagnosis (association may occur)

Contact dermatitis, seborrheic dermatitis, prurigo simplex, scabies, miliaria, ichthyosis, xerotic eczema, hand dermatitis (nonatopic), cutaneous lymphoma, psoriasis, immune deficiency diseases, collagen diseases (systemic lupus erythematosus, dermatomyositis), Netherton's 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

Adapted from reference 1.

a sculptural portrait (portrait type).

(3) Secondary cutaneous changes

a) White dermographism

b) Goosebumps skin

c) Pityriasis alba

d) Pigmentation: This includes postinflammatory pigmentation, frictional pigmentation, dirty neck, etc. and is clinically known for orbital darkening and punctate pigmentation in the lips.

e) Folds: Folds may be seen in from the inner angle to the outer downward of the palpebra inferior (Dennie-Morgan infraorbital fold), in the neck (anterior neck folds), and in the abdomen. A finding called palmar hyperlinearity indicates a large number of inborn palmer folds.

f) Hair loss: Hair loss is seen in the occipital region for infant patients, in the temporal region for school age or older patients, and in the eyebrow for adult patients. Eyebrow hair loss is seen mostly in the outer half (Hertoghe's sign).

Table 2 Severity index

There are several criteria proposed for severity assessment of atopic dermatitis at present that require proficiency in assessment. Accordingly, the following severity levels are defined as indices for treatment.

Mild: Only mild rashes are observed irrespective of the area.

Moderate: Rashes with severe inflammation are observed in less than 10% of the body surface area.

Severe: Rashes with severe inflammation are observed in ≥10% to <30% of the body surface area.

Most severe: Rashes with severe inflammation are observed in ≥30% of the body surface area.

Mild rash: Lesions are seen chiefly with mild erythema, dry skin, or desquamation.

Rashes 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).

g) Nail luster: Hard scratching causes pearl-like luster of nails (pearly nail).

h) Diffuse flushing of the facial surface: The face may acutely flush over the entire surface. It is likely caused by sustained inflammation and scratching.

4.1.2. Itch

Itch is caused by increase in skin temperature resulting from bathing, exercise, sleep, ointment application, etc., sweating due to irritation and body warmth (itch when sweating), and perspiration stimulation. It also occurs when woolen clothes contact the skin (wool intolerance).

(1) Control of itch: In early infancy, the negative impact of scratching can be weakened by covering the scratched site with bandages, clothing, etc., or by wearing gloves. It is not until adolescence that one understands that scratching will aggravate the cutaneous symptoms and comes to restrain oneself from scratching.

(2) Sleep disorders: Sleep disorders include difficulty in falling asleep and awakening during the night. The difficulty in falling asleep is caused by a strong sensitivity to itch due to body warmth while sleeping.

(3) Scratch addiction: While scratching during the nighttime is an unconscious reflex movement, scratching during the daytime involves a conscious element. It is reportedly a scratching phenomenon that is performed unintentionally but preferably (scratch addiction).[21]

4.2. Symptoms Other than Cutaneous Symptoms

4.2.1. Symptoms/findings incidental to rashes

Dermatopathic lymphadenopathy occurs when a cutaneous symptom with certain severity and spread may cause swelling of regional superficial lymph nodes. It is indolent and not indicative of infection.

4.2.2. Symptoms in other organs

(1) Cataract: Cortical cataract with an anterior subcapsular or posterior subcapsular opacity may progress to cover all layers. With a gender ratio of approximately 1:2, it occurs most frequently in individuals 15-24 years of age, with a severe form of rash on the facial surface in particular. The frequencies of complications with cataracts are reported to be 2.0% of all patients and 5.5% of severe patients.

(2) Retinal detachment: The retinal detachment accompanying atopic dermatitis is reported to occur with a hiatus caused by continuous external forces applied to the eyeball. It occurs predominantly between the ages of 16 to 25 and frequently among patients who strongly rub their eyelids or who pat their own faces. The frequencies of complications with retinal detachment are reported to be 0.5% of all patients and 2% of severe patients.

(3) Airway hyperresponsiveness: A study on airway hyperresponsiveness caused by histamine inhalation load in children with atopic dermatitis found that patients with atopic dermatitis not complicated with asthma showed significantly worse airway hyperresponsiveness compared with healthy controls.

(4) Mental symptoms: Atopic dermatitis may cause symptoms such as social withdrawal resulting from disappointment with existing therapies, discontent with responses of doctors, disappointment with the probability of cure, and so on. Severe atopic dermatitis cases may be accompanied by psychosomatic problems.

(5) Neurological symptoms: Paresthesia may occur in the distal extremities with aggravation of dermatitis symptoms and lesional atopic myelitis cervicalis may be observed in the cervical region in MRI.

(6) Intestinal tract symptoms: Severe cases may be accompanied by such symptoms as diarrhea and constipation.

5. Investigation of Causes and Exacerbating Factors for Atopic Dermatitis and Countermeasures

Given that causes and exacerbating factors may vary according to age, individual differences of patients, environment, and lifestyle, it is important to take countermeasures in consideration of the conditions of the individual patients.

5.1. Foods

Food allergens are investigated by performing detailed history taking, allergen tests and then by com-

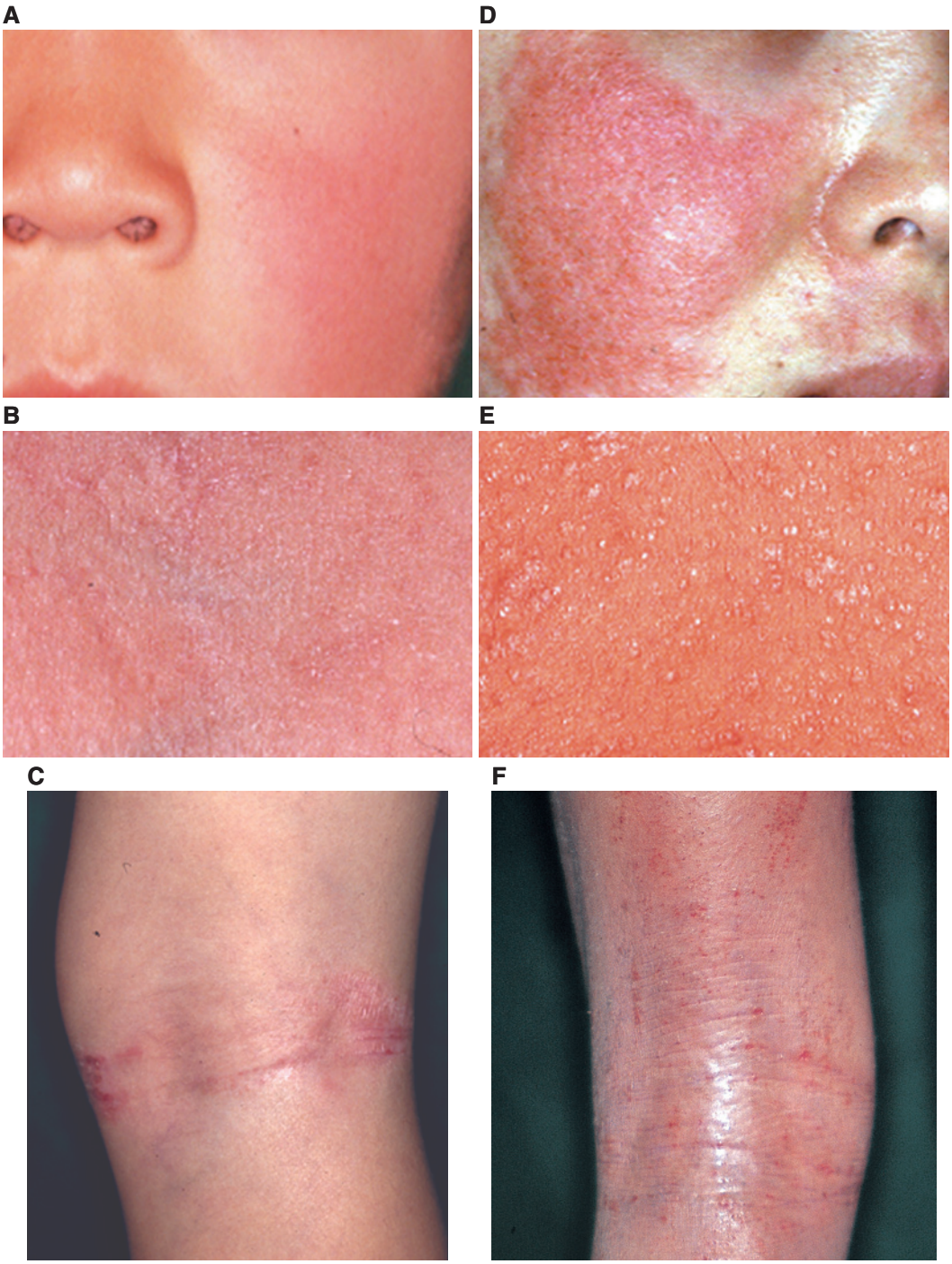

Fig. 4 Examples of mild rashes and rashes with severe inflammation of atopic dermatitis. Examples of mild rashes includes (**A**) Face: Mild desquamation, erythema, (**B**) Body trunk: mild desquamation, dry skin, (**C**) Lower limb: Mild desquamation, erythema, including partial mild lichenification. Examples of rashes with severe inflammation includes (**D**) Face: Apparent erythema, desquamation, apparent infiltration, (**E**) Body trunk: Apparent erythema and lichenification, (**F**) Lower limb: Apparent erythema, papule, scratch mark, lichenification.

bining elimination tests and provocation tests (not performed for cases accompanied by anaphylaxis) for suspicious allergens detected to remove the determined allergens. Countermeasures are taken by nutritional care introducing alternative foods introduced and providing guidance to the family without ran-

domly removing allergens.

5.2. Sweating
Sweating is an important cause and exacerbating factor for atopic dermatitis, hence washing away sweat by bathing and showering will lead to the improvement of symptoms. Bathing and showering are important not only for washing away the components of perspiration but also for washing away allergens, such as dust and pollens, and microbes on the skin surface.

5.3. Physical Irritation
Causes and exacerbating factors other than the above-mentioned perspiration include clothes, dry air, hairs, and cosmetics for adult patients. Cosmetics, shampoo, and soaps need to be selected appropriately, exchanging products that cause symptoms.

5.4. Environmental Factors
Allergens such as mites and house dust, pollen allergens in specific seasons, and organic solvents such as formaldehyde and toluene can become problematic. Being sensitized to mites in infancy is reportedly a marker for the development of asthma.[22] Periocular pathological changes are often observed during airborne pollen seasons.[23]

5.5. Microbes/Fungi
If no infectious symptoms are seen in the affected part, a topical steroid can be applied to encourage the improvement of the cutaneous symptom, even if the site is densely populated with Staphylococcus aureus (with bacterial counts of 1000 cfu/10 cm2 or more as detected by the stamp method).

(1) An antimicrobial therapy should be performed if any infectious symptoms are observed.

(2) Care should be taken against microbial substitution with methicillin-resistant *Staphylococcus aureus* (MRSA).

(3) The skin should be kept clean by frequent bathing or showering, etc.

(4) Disinfectants such as povidone-iodine solution should not be applied.

5.6. Contact Antigen
Contact dermatitis is divided into allergic contact dermatitis, which is developed by a sensitized patient, and primary irritant contact dermatitis, which can be developed by anyone depending on the antigen level.

5.7. Stress
Aggravation by mental stress is often experienced in daily medical practice. The high rate of aggravation of atopic dermatitis reported in areas affected by the Great Hanshin-Awaji Earthquake definitely proves the correlation between stress and atopic dermatitis.[24]

5.8. Scratching
Scratching will not only damage the cutaneous barrier functions by injuring the skin, but also worsen the symptoms by causing the release of various phlogogenic agents.

5.9. Perinatal Prevention
A randomized comparative study that assessed whether consumption of an elimination diet free of highly sensitized food antigens such as eggs and cow's milk by pregnant or lactating mothers can prevent newborns from developing sensitization to food allergens or atopic dermatitis revealed that elimination of eggs or cow's milk has no preventive effect.[25]

A case-series study in high-risk children was conducted to determine whether moisturizer application during the newborn period prevents the development of atopic dermatitis, in light of the importance of cutaneous barrier functions in atopic dermatitis. The results showed that the subject group, in which moisturizer was applied during the newborn period, had a low incidence rate of 15%.[26] However, the effect of moisturizer application during the newborn period needs to be demonstrated in a randomized comparative study in future.

5.10. Others
The pathology of atopic dermatitis is a chronic inflammation of the skin that is aggravated by the deterioration of compliance. It is necessary to educate patients repeatedly so they may understand the pathology and realize that a long-term antiinflammatory therapy is required.

6. Summary of the Basic Therapy of Atopic Dermatitis

6.1. Basics of Treatment
Because the treatment of atopic dermatitis requires appropriate diagnosis and evaluation of cutaneous symptoms, the basics of treatment under this guideline include 3 mainstays. These are investigation and countermeasures of causes and exacerbating factors; second, correction of skin dysfunctions (skin care); and third, pharmacotherapy. These are based on the concept that this disease is an inflammatory cutaneous disease that forms an eczematous lesion against a backdrop of atopic diathesis, with numerous factors involved in the occurrence and aggravation and aberrant function in the skin (Fig. 5). These 3 points are equally important and thus need to be appropriately combined in accordance with the symptoms of each patient.

(1) Investigation and countermeasures of causes and exacerbating factors: Because the importance of the individual factors depends on the individual patients, it is important to investigate fully the factors through diagnosis, and to take reasonable and appropriate countermeasures.

1. Diagnosis
   Appropriate diagnosis should be ensured by discriminating them from other diseases with similar symptoms, such as eczema and dermatitis, in accordance with the abovementioned concept.

2. Assessment of cutaneous symptoms
   In selecting a therapy, cutaneous symptoms need to be properly assessed.

3. Basics of treatment
   Based on the above assessment, investigation/countermeasures against causes and exacerbating factors, skin care, and pharmacotherapy should be implemented by being optimally combined for each patient. Sufficient information about the treatment should be transmitted to the patient to build a favorable partnership.

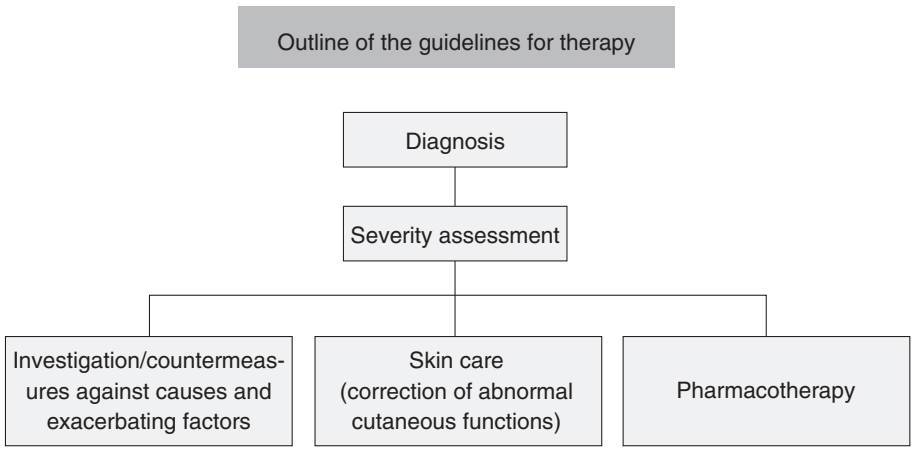

Fig. 5 Important points of these guidelines. Modified from Ministry of Health and Welfare, Japan. *[Guidelines for the Treatment of Atopic Dermatitis 2008]* (in Japanese).

(2) Skin care (correction of abnormal cutaneous functions): The skin barrier functions of patients with atopic dermatitis are deteriorated due to abnormality in function such as deteriorated water retentivity, lowered threshold of itch, and susceptibility to infection. Correcting those abnormalities (skin care) is extremely important in treatment, chiefly by good hygiene and moisture retention of the skin.

(3) Basics of pharmacotherapy: If countermeasures against the causes and exacerbating factors and the skin care have not resulted in improvement of dermatitis, pharmacotherapy will be needed.

a) Final objective: The final objective of treatment is to achieve a level with no or mild symptoms, if any, which should not interfere with daily life and require minimal pharmacotherapy.

b) Assessment of severity and activity level: Attempts have been made to assess the severity and activity level by using the IgE level, eosinophilic leukocyte count, LDH level, TARC level, and VAS itch score.

c) Remission-induction therapy: To maximize the therapeutic effect, in particular the pharmacotherapeutic effect, and to minimize the side effects, the patient should be follow up every 1 or 2 weeks to evaluate and verify the effects and change the therapeutic agents and method as needed. If no improvement is observed or if an abnormal change in symptoms is observed after approximately 1 month of remission-induction therapy, referral of the patient to a more specialized medical institution should be considered.

d) Remission maintenance therapy: If symptoms cannot be controlled or if symptoms frequently relapse after completion of remission induction, therapy should be changed to remission maintenance therapy. Remission maintenance therapy is mainly based on the external application of tacrolimus. If remission cannot be maintained after approximately 6 months, the patient should be referred to a specialized medical institution to define the condition as severe, most severe, or intractable, in consideration of prolonged use of topical tacrolimus.

e) Severe, most severe, or intractable conditions (cases where remission maintenance therapy is difficult to execute): If remission cannot be maintained, external application of a higher ranked steroid, oral administration of immunosuppressive agents (cyclosporine), oral administration of steroids, ultraviolet

light therapy, or psychosomatic medical therapy should be used.

Hospital treatment is effective for severe, most severe, and intractable cases. Education should be provided to such patients on environmental factors, lifestyle, dietary habits, personal hygiene management, and correction of psychological problems, during hospitalization.

Oral administration of steroids should not be executed in principle. However, if the patient develops extremely severe symptoms that cannot be controlled with external medication, such oral administration may be used for a short period of time.

f) Precautions during treatment: Given that the duration of illness is often prolonged, its association with growth in children and with lifestyle related diseases, vitamin D deficiency, and ophthalmologic problems in adults should be considered.

6.2. Precautions During Treatment

If an abnormal change is observed in symptoms during treatment or if no improvement is observed after treatment based on a basic therapy for approximately one month, referral to a more specialized medical institution should be considered. Hospital treatment is effective for patients with severe or most severe cases.

7. Skin Care Against Atopic Dermatitis

Skin care is highly important, as is shown by consideration of the fact that the skin tends to become more prone to drying due to aging, and given the adverse effects of settlement of Staphylococcus aureus on the skin on the aggravation of symptoms.

7.1. Dry Skin

The skin of patients with atopic dermatitis is generally in a dried condition, not only in the lesion but also in an apparently normal area, due to insensible water loss (transepidermal water loss; TWL). In such conditions, with facilitation of transcutaneous invasion of allergens and irritants, likely resulting in allergic reactions and irritability, patients may come to suffer from itch due to the lowered threshold of itch. Abnormality in the water barrier function and the water retention capability of the horny cell layer are considered as causing/exacerbating factors of atopic dermatitis. Accordingly, the incidence rate of atopic dermatitis could be decreased by moisturizer application during the newborn period.

7.2. Staphylococcus Aureus Flora

If the bacterial count is small (in the case of a bacterial count of 1000 cfu/10 cm2 or less by the stamp method), dry skin symptoms will be improved only by continuous use of a moisturizer. If the bacterial count is larger, it is important to take a skin care regimen with consideration of the bacterial flora on the skin surface.

7.3. Important Points in Skin Care

(1) Skin care against dry skin: Hydrophilic ointments and water absorptive ointment with high moisture retention include urea preparations, heparinoid preparations, water-soluble collagen preparations, sodium lactate preparations, and elastin hydrolysis preparations.

(2) Skin care against injured skin: An oleaginous ointment (ointment in a narrow sense) with skin protective action should be externally applied. Given that a moisturizer is known to exert a higher moisturizing effect when externally applied twice a day than when applied once a day, consideration should be given to the number of external applications.[27]

(3) Good hygiene of the skin and skin care: To ensure healthy skin, bathing and showering should be strictly observed with appropriate moisturizer or skin protectant applied externally as needed.

(4) Practical home skin care

a) Bathing: Although moisturizer application is recommended immediately after bathing, reports have shown that the moisturizing effect is not influenced by a time lapse after bathing. Therefore, physicians should instruct patients not to forget the external application of moisturizers.[28]

b) Shower: Sweating is considered as an exacerbating factor for atopic dermatitis. In the sweaty summer season, washing away sweat by showering improves rashes.[29]

c) Shampoo: Given that shampoo and soap residue may aggravate rashes, soap and shampoo should not be left in such regions as the hairline, the side of the nose, and jaws, etc.

8. Pharmacotherapies for Atopic Dermatitis

8.1. External Medicine

8.1.1. Topical therapy

Topical therapy refers to skin care chiefly with moisturizers, and to inflammation control chiefly with topical steroids and tacrolimus ointments (immunosuppressive ointment, topical calcineurin inhibitor).

Although basic therapy for controlling inflammation in the acute phase consists of topical steroids, the use of tacrolimus ointment or topical steroids intermittently in combination with a moisturizer is useful in the remission maintenance period. This therapy is referred to as proactive therapy (Fig. 6) as opposed to reactive therapy (Fig. 7), in which topical therapy is administered only when the rash worsens. Proactive therapy has been shown to not only control the relapse of cutaneous symptoms, but also to be cost-effective.[30] The use of a medical dressing or Tubifast (Allergy Health Care, Nara, Japan) with an externally applied medicine is effective for the prevention of scratching.

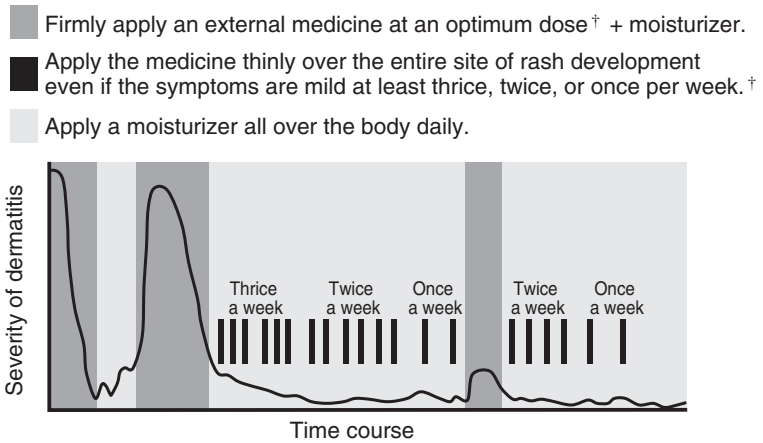

Fig. 6 Proactive therapy for atopic dermatitis.
† Topical steroid/topical tacrolimus.

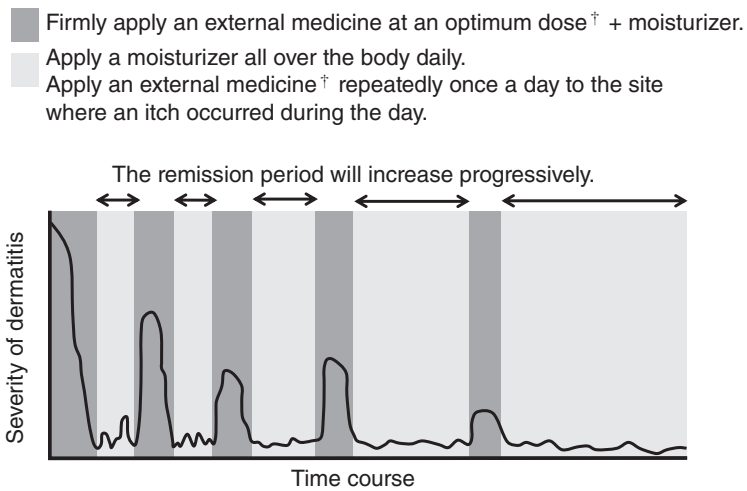

Fig. 7 Reactive therapy for atopic dermatitis.
† Topical steroid/topical tacrolimus.

8.1.2. Moisturizer

Although the use of an ointment-based drug product with high moisture retaining properties is recommended for the treatment of mild cases with the aim of moistening and protecting the skin, recovering and maintaining the barrier function, the drug product should be selected in consideration of the outdoor air temperature, humidity, and usability. For the treatment of weeping lesions in the acute phase, a surface dressing with a zinc ointment may be effective. Urea preparations should be used with caution, as they can stimulate an eroded surface or strongly inflammatory skin. A moisturizer can also cause contact dermatitis. The use of a moisturizer is useful to prevent relapse of atopic dermatitis; however, studies have shown that the continuous use of a moisturizer since the newborn period may reduce the incidence rate or delay the development of atopic dermatitis.[31,26]

8.1.3. Pharmacology/action mechanism of the steroid drug

Upon entering a cell, steroids bind receptors that form complexes with heat shock protein (HSP90), which is found in the cytoplasm, and migrate with the complex into the nucleus. There they activate steroid-responsive genes to exert their pharmacological actions that include antiinflammatory action in a narrow sense, antiallergic action, and immunosuppressive action.[32]

8.1.4. Administration method of topical steroids

(1) Selection of topical steroid: Topical steroids are classified into 5 ranks from weak to strongest. A steroid of an appropriate rank should be used in accordance with the severity of cutaneous symptom[33] (Fig. 8).

(2) Points to note in external application of steroid:

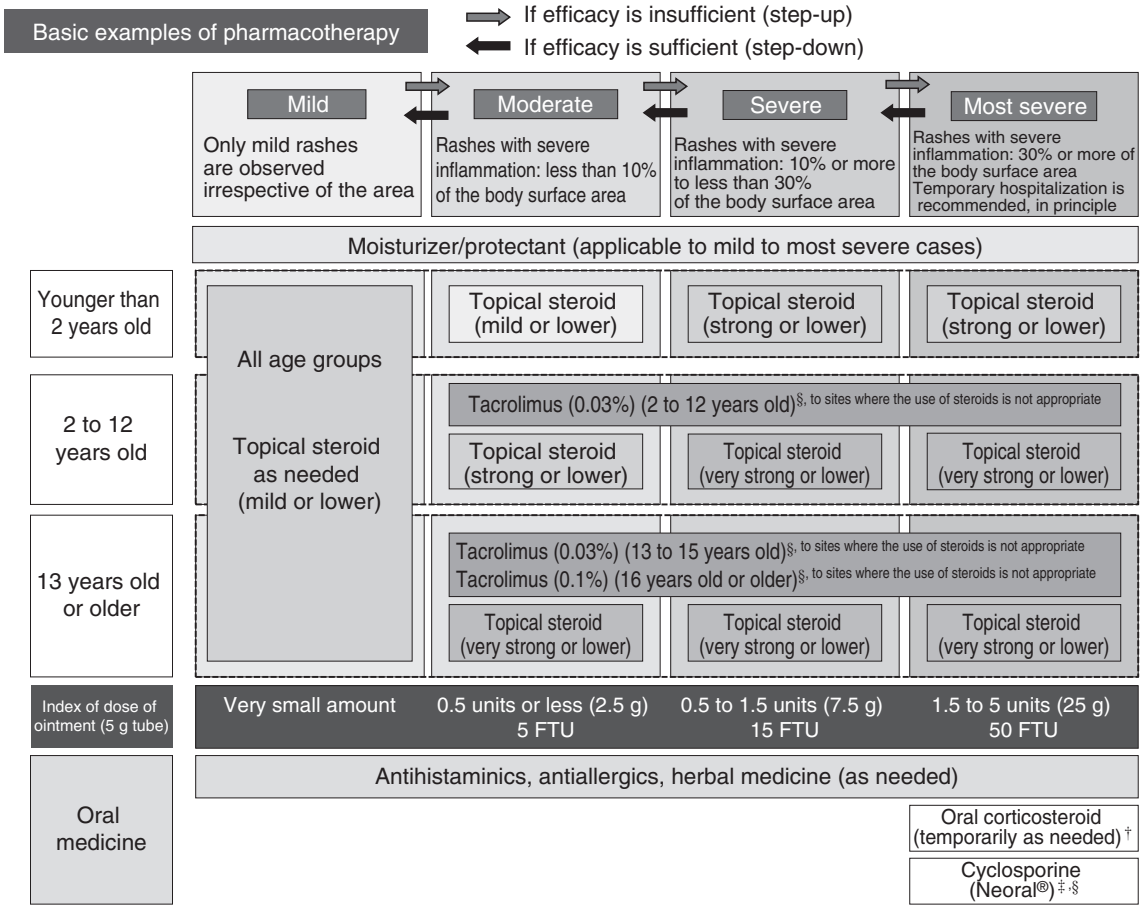

Fig. 8 Administration method of topical steroid against atopic dermatitis.

† This medicine should be applied to an inpatient in liaison with specialist doctors.

‡ Indicated for patients with most severe symptoms aged 16 years old or older. To be discontinued within 3 months.

§ This medicine should be applied in accordance with the package insert instructions.

A topical steroid to be applied to atopic dermatitis must be selected in accordance with the severity and the site of symptoms and the age of the patient.

a) Application to the facial surface and points to note: A topical steroid should be applied carefully to the facial surface, neck, etc., which have an active percutaneous absorption. When it is applied to such sites, the administration should be limited to the shortest period possible in consideration of progressive reduction, intermittent administration, and a change to tacrolimus ointment as soon as possible.

b) Topical steroids and side effects: Patients should be evaluated for severity of their condition approximately 1-2 weeks after the start of treatment with a topical steroid to identify any side effects and the need for stepping down or stepping up the dose. The absorption ratio of steroids varies significantly among skin sites. In children and the elderly with deteriorated cutaneous barrier functions and in summer when there is a higher sweat volume, the absorption ratio changes. Well-known side effects of steroid directly affecting the skin are shown in Table 3. If side effects are seen during treatment with topical steroids, the therapy should be shifted to a tacrolimus ointment while gradually stepping down the dose.

c) Monitoring of the dose of topical steroid: Monitoring should be performed twice daily (morning, evening, and after bathing). Improvement in symptoms should be evaluated with the goal of gradual progressive reduction to change the therapy to a topical nonsteroidal agent, while ensuring the absence of relapse after once a day to alternate-day administration. The finger-tip unit (FTU) will be used as an index of external dose.[34] One FTU is a quantity of ointment that will be pushed out of a tube of 5 mm in diameter onto the distal end on the pulp side of an adult's forefinger and is equivalent to approximately 0.5 g. One FTU can cover two palms of an adult (2% of the body surface area) (Fig. 9). The dose required to cover the whole body is 50 FTU or 25 g. A dose for children is also proposed.[35]

It has been reported that a topical steroid of the

Table 3 Side effects of topical steroid in the skin or affected part

1. Acne-like rash, including folliculitis and rosacea
2. Eyelid and perioral dermatitides
3. Epidermal-dermal atrophy, dermal vulnerability (most likely to occur on the geriatric or sunlight damaged skin, intertriginous zone, or facial surface)
4. Delay in wound healing
5. Gluteal granuloma
6. Purpura
7. Telangiectasia and erythema
8. Skin striae
9. Depigmentation
10. Hypertrichosis
11. Hidden or exacerbated dermatophyte infection
12. Secondary infection or exacerbation of existing infection
13. Contact dermatitis
    (i) May be caused by an ingredient of the preservative or other base material.
    (ii) May be caused by a corticosteroid molecule. In this case, the skin may cross-react with a corticosteroid molecule of similar structure.
14. Others

Adapted from Drake LA, *et al*. J Am Acad Dermatol 1996;35:615-9.

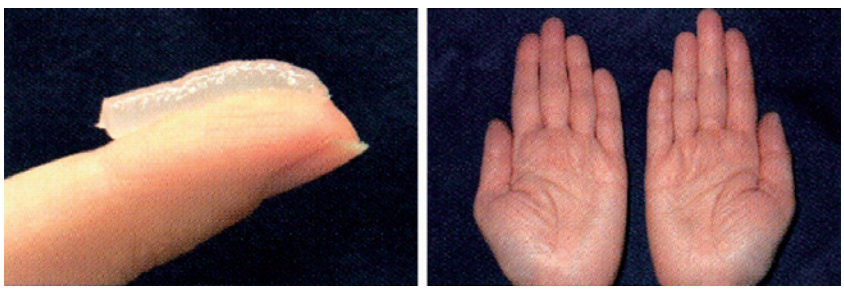

Fig. 9 Index of external dose of topical steroid: finger tip unit (FTU). 1 FTU is the quantity of ointment that will be pushed out of a tube of 5 mm in diameter onto the region from the DIP joint to the distal end on the pulp side of an adult's forefinger and is equivalent to approximately 0.5 g. 1 FTU can cover 2 palms of an adult. Modified from Ministry of Health and Welfare, Japan. *[Guidelines for the Treatment of Atopic Dermatitis 2008]* (in Japanese).

strong class or higher shows no difference in efficacy after 3 weeks or more between twice-a-day external application and once-a-day external application. It is recommended that a strong topical steroid be initially applied twice a day and then changed to once-a-day application after remission of an acute or intractable lesion is observed, for the purpose of enhancing the compliance of the patient, reducing side effects, and reducing medical expenses.[36]

d) Response to exacerbation due to discontinuation of long-term application of a topical steroid: Patient should be advised against discontinuing the use of the drug on his own judgment. In addition, sufficient explanation should be provided to the patient about the side effects likely to be caused by the topical steroid and that the side effects can be avoided by evaluating cutaneous symptoms and monitoring drug consumption.[37]

e) Measures against acute exacerbation: In the event of acute exacerbation of a cutaneous symptom due to a change of treatment on the patient's own judgment, etc., a topical steroid should be administered at a necessary and sufficient dose. If systemic aggravation is observed, the patient should be hospitalized for a short period and a steroid systemically administered as needed.

f) Precautions in external application of steroid in children: It should be emphasized in children as well that antiinflammatory therapy plays a central role in pharmacotherapy chiefly with a topical steroid. Administration methods for children are divided into the age groups of <2 years of age, 2-12 years of age, and

>13 years of age. Care should be taken so that insufficient administration for fear of side effects likely generated in the treatment of children may not result in prolonged symptoms.

(3) Selection of external medicine according to symptoms: In principle, in the treatment of atopic dermatitis, a moisturizer or skin care product should be applied to a mild eczematous lesion or dry skin on the facial surface without applying any topical steroids. It is reported that twice-a-day external application of a moisturizer (preparation containing heparinoid) significantly inhibits the relapse of inflammation of atopic dermatitis compared with the untreated group (no application group).

8.1.5. Topical immunosuppressant (tacrolimus ointment [Protopic®])

(1) Pharmaceutical form and mechanism of action of tacrolimus ointments: Tacrolimus ointments will be used when existing therapies are not effective enough or not indicated because of side effects. It should be used in consideration of precautions and after obtaining informed consent from the patients.

Tacrolimus ointments (trade name: protopic ointment) are available in 2 dose forms: ointment 0.1% applicable to patients 16 years of age or older and ointment 0.03% applicable for children aged 2-15 years. The action mechanism of tacrolimus is the inhibition of the function of T lymphocytes, which play a central role in the development of allergic inflammation, and improvement in the barrier function. Although tacrolimus ointments have a similar beneficial effect as that of strong steroids, their absorption from normal skin is lower than that of steroids because of their higher molecular weight. This property is considered an advantage because they are more absorptive and effective for the treatment of lesions with acute dermatitis associated with compromised cutaneous barrier function, whereas they become less absorptive and less likely to show side effects as dermatitis subsides.

(2) Instructions for the use of tacrolimus ointments: The tacrolimus ointment is usually applied externally once a day after bathing. Excessive exposure to ultraviolet light should be avoided when the ointment is applied externally. A 0.1% tacrolimus ointment for adults should be administered at a dose of 5 g or less. A 0.03% tacrolimus ointment for children aged 2 to 5 years (<20 kg in body weight) should be administered at a dose of ≤1 g; for children aged 6 to 12 years (20-50 kg in body weight), at a dose of 2-4 g; and for children 13 years or older (≥50 kg in body weight), at a dose of ≤5 g. The tacrolimus ointment should be administered at a maximum of twice per day. When applied twice per day, an interval of approximately 12 hours between applications is recommended. Occlusive dressing therapy should not be used because it may cause an increase in the blood level. Continuous external application of a tacrolimus ointment two to three times per week after remission induction can significantly inhibit the relapse of symptoms (proactive therapy).[38-40]

(3) Side effects of tacrolimus ointments: No severe systematic adverse events were observed in a study of post-marketing prolonged administration; therefore, tacrolimus ointments are considered safe. Precautions for the use of tacrolimus ointment include the possibility of skin effects such as a burning sensation at the start of external application and the potential aggravation of local infectious disease in the skin. Although the stimulatory effects of the ointment on the skin will most likely disappear after several days, a tacrolimus ointment can become intolerable because of the burning sensation. This problem can be managed by using a moisturizer before the application of the ointment or by using a tacrolimus ointment in combination with a topical steroid for a short period of time. Combinations with other external medicines should be avoided because of potential effects on the stability and absorptive properties of the tacrolimus ointment. Tacrolimus ointments should not be used on rashes associated with infectious diseases of the skin. Tacrolimus ointments cannot be applied to an eroded surface or the surface of an ulcer because of its stimulatory effects and absorption. A tacrolimus ointment cannot be applied to patients with ichthyosiform erythroderma (such as Netherton's syndrome), whose blood tacrolimus level can increase because of elevated percutaneous absorption and because it can cause side effects such as nephropathy. In addition, tacrolimus ointments cannot be applied for reasons of safety to patients with nephropathy, pregnant women, infants younger than 2 years of age (at this point in time), and patients receiving phototherapy. Regarding the risk of lymphoma and skin cancer, it has been reported that the external application of tacrolimus ointment will not lead to an increase in the incidence rate of these diseases.[41-44]

8.1.6. Topical non-steroidal antiinflammatory drugs

No data definitely shows that nonsteroidal antiinflammatory drugs (NSAIDs) are effective for eczematous lesions of atopic dermatitis. There is no description of NSAIDs in the guidelines for the treatment of atopic dermatitis of the United States or Europe.[45]

8.2. Oral Medicine

8.2.1. Antihistaminics/antiallergics

(1) Pharmacological actions/action mechanism

a) Antihistamines: The main pharmacological action of antihistamines is to antagonize histamine in the histamine H1 receptor in tissues to inhibit its action. In recent years, a new concept of inverse agonism has been advocated for the H1 receptor.[46] The inverse agonist (H1 receptor antagonist) combines

with the inactive receptor to shift the equilibrium of the receptor towards the inactive state in addition to acting as a competitive inhibitor of the agonist.

b) Antiallergics: Antiallergics are divided into mediator antireleasers, which are antiallergics in a narrow sense, thromboxane A2 inhibitors, leukotriene receptor antagonists, and cytokine inhibitors, as well as classic antihistamines.

(2) Administration method: Since differences in efficacy are found amongst individual patients in daily medical care, it is necessary to explore and replace drugs that are not effective after 2 weeks of administration with another drug appropriate for the individual patient.

a) Treatment of itch: Since itch is normally caused by irritation of the end of C nerve fiber located at the epidermal-dermal junction. The histamine H1 receptor is located at the C fiber, and antihistaminics and antiallergics with antihistaminic action are expected to inhibit itch.

b) Evidence of efficacy of antihistaminics: Hoare *et al*. reported that oral antihistaminics lack grounds for efficacy after their evidence-based analysis of randomized studies on the efficacy of treatments for atopic dermatitis extracted from various databases.[47] Recently, however, a large-scale clinical study was conducted with fexofenadine hydrochloride that showed its usefulness in a randomized, double-blind, parallel-group comparative study.[48]

(3) Side effects

a) Central nervous system effect: The drug generally generates side effects in the form of sleepiness, loss of concentration, or malaise, and it may cause excitement if administered in a large quantity. Precaution is necessary in use of antihistaminics in children, particularly against convulsion. A second-generation antihistaminics is characterized by reduced sleepiness and central nervous system effects because it has more difficulty in passing through the blood-brain barrier. In evaluating sedation, sleepiness should be differentiated from impaired performance (a condition with deteriorated operating efficiency).[49]

b) Anticholinergic action: The anticholinergic action may cause dry mouth, sense of mucosal dryness, urinary retention, and so on. This drug is contraindicated for patients with glaucoma or lower urinary tract obstructive disease (prostatomegaly, etc.).

c) Digestive symptoms: These include nausea, vomiting, diarrhea, and abdominal pain.

d) Teratogenicity: An antihistaminics generally passes through the placenta and through the blood-brain barrier of the fetus. Antihistaminics known to be safe to pregnant women are chlorpheniramine and clemastine, and these are first-line drugs for pregnant patients. Most antiallergics are relatively new and thus their safety for pregnant women is not well known. Accordingly, the aforementioned antihistaminics should be selected as needed.

e) Application to patients with hepatic dysfunction: Antiallergics are mostly metabolized in the liver and excreted into the urine. However, the frequency of the occurrence of drug induced hepatopathy due to antiallergics is low.

f) Application to patients with renal dysfunction: For drugs excreted through the kidney as the main excretion pathway (ketotifen fumarate, cetirizine hydrochloride, epinastine hydrochloride, oxatomide, bepotastine besilate, tranilast, etc.), decreased renal function may inhibit the excretion of the drug, resulting in a rise in blood levels of that drug. In that case, use of drugs that are decomposed chiefly in the liver (azelastine hydrochloride, ebastine, emedastine difumarate, etc.) or excreted into feces (fexofenadine hydrochloride) is recommended.

g) Drug interactions: A general drug interaction of an antihistaminics is caused by concomitant use with other central depressants. Concomitant use of the drug with alcohol, hypnotic, or psychotropic drugs and so on, may cause massive sedation, vertigo, malaise, weakness etc. Concomitant use with tricyclic antidepressants or anticholinergics may cause dry mouth, intestinal obstruction, aggravated glaucoma, memory disorder, etc.. Concomitant use with a monoamine oxidase (MAO) inhibitor may cause headache, arrhythmia, hypertension, etc. because of the strengthened action of catecholamine. Few antiallergics have similar interactions as are seen in antihistaminics.

8.2.2. Other oral medicines

(1) Oral steroid: Because the oral administration of a steroid has various severe side effects, long-term administration of the agent should be avoided. In general, prednisolone should be administered to an adult patient at a dose of 10-15 mg/day in combination with antihistaminics or antiallergics and discontinued within as few days as possible. The use of these drugs in children with atopic dermatitis is not recommended in consideration of the side effects.

(2) Immunosuppressant: Cyclosporine (Neoral®) was added to the list of treatments of atopic dermatitis in October 2008, in Japan. Cyclosporine is newly applicable to patients aged 16 years or older with resistance to existing therapies, subject to a washout within 3 months of administration, as required by the administration guidelines. The drug will be usually administered twice a day at a daily dose of 3-5 mg/kg/day. If a problematic side effect is reported or if a side effect does not improve by dose reduction, administration should be discontinued. The duration of administration should be minimized as much as possible. If the side effect does not improve after 8 weeks of treatment, the administration of this drug should be discontinued. Even if the drug shows efficacy, one treatment period should be limited to 12 weeks or less. If the drug will be re-administered, a washout

period of 2 weeks or longer is necessary. The patients need to be periodically inspected for several side effects, similar to cases of psoriasis vulgaris (e.g., renal function test, hypertension measurement, and blood cyclosporine level measurement [trough value]).[50]

9. Adjunctive Therapies Other than the Basic Therapy of Atopic Dermatitis

This section introduces adjunctive therapies other than the basic therapy with relatively firm evidence.

9.1. Ultraviolet Light Therapy

Ultraviolet light therapy has been shown to be useful in patients with severe, most severe, or intractable conditions who do not show significant improvement after the administration of topical moisturizers, the provision of appropriate patient education, remission induction therapy, and remission maintenance therapy based on a reliable diagnosis.[51] Narrow-band UVB (NB-UVB) therapy is used. UVA1 is also effective in the acute exacerbation phase. In addition to topical PUVA therapy, bath-PUVA therapy and oral PUVA therapy are also available. Further, a 308-nm Excimer laser is also available. Ultraviolet light therapy and photochemotherapy are associated with a risk of skin cancer as a side effect.[52] Therefore, they should not be applied to underage patients or patients receiving tacrolimus ointment therapy or oral CYA therapy.

9.2. Herbal Medicines

Those herbal medicines covered by the health insurance system and medicines with safety proven in controlled studies, such as Hochuekkito are used.

Jumihaidokuto, Shofusan, Saikoseikanto, and Hochuekkito are Chinese medicine prescriptions that contain a licorice that may cause pseudoaldosteronism or myopathy. Hochuekkito is reported to cause interstitial pneumonitis, hepatic dysfunction, and jaundice and thus requires due caution in use.[53]

9.3. n-3 Polyunsaturated Fatty Acid

This therapy should be applied when a rise in the n-6/n-3 ratio is observed in measurements of blood unsaturated fatty acid levels. Adoption of this therapy should be consideration when both poor intake of the n-3 polyunsaturated fatty acids and excessive intake of n-6 polyunsaturated fatty acids are confirmed with a rise in the n-6/n-3 ratio observed in a review of the menu of meals (food diary) conducted together with a nutritionist.

9.4. Psychosomatic Approach

Counseling will be given by the attending physician or, as appropriate, by a psychosomatic physician, psychiatrist, or psychotherapist. For general physicians not specialized in psychosomatic medicine, treatment by antianxiety agents, antidepressant, or hypnotic is recommended instead of a psychotropic agent for pharmacotherapy.

9.5. Alternative Therapy

Many reports are published on the efficacy of acupuncture and moxibustion in journals of Eastern medicine. Balneotherapy, aromatherapy, herb therapy are also reported to be effective. However, since many of them lack scientific verification and such therapies may cause aggravation of cases, they should be performed under the supervision of a physician. Probiotics are evaluated as having prophylactic effects when administered to the mother and child and reportedly expected to improve rashes with slight adjunctive therapeutic effects to children.

10. Points of Referral to a Specialist

In the treatment of atopic dermatitis, if the rash does not improve after approximately 1 month of treatment in accordance with the guidelines, as we discuss later, referral of the patient to a specialist or special institution should be considered. Caution should be exercised when complications are observed or when the patient is a child.

10.1. Complications and Countermeasures

(1) Allergic diseases: Allergic diseases such as asthma and allergic rhinitis/conjunctivitis are the most frequent complications.

(2) Cutaneous infectious diseases: The causative microorganisms for impetigo contagiosa are Staphylococcus aureus and Streptococcus hemolyticus. Lesions should be kept clean by regular showering and then covered with clean gauze so that it cannot be scratched. For expanding rashes, antimicrobials should be administered to the whole body. Kaposi varicelliform eruption indicates a condition with a wide area of the body being percutaneously infected with herpes simplex virus. For treatment, an antiherpesvirus agent will be systemically administered. In the case of a rash in the area surrounding the eye, consult an ophthalmologist in consideration of probable complication with herpes corneae.

(3) Ophthalmological diseases: Potential ophthalmological diseases include cataract, retinal detachment, blepharitis, keratoconjunctivitis, and keratoconus. It is important to treat rashes in the eye area and allergic keratoconjunctivitis appropriately since infancy or childhood in liaison with an ophthalmologist.

10.2. Other Precautions

1) Referral to a specialist: If the rash does not improve after 1 month of treatment in accordance with the "Guidelines for the Management of Atopic Dermatitis 2012 (ADGL 2012)," referral of the patient to a specialist (e.g., a specialist in cutaneous allergy, a

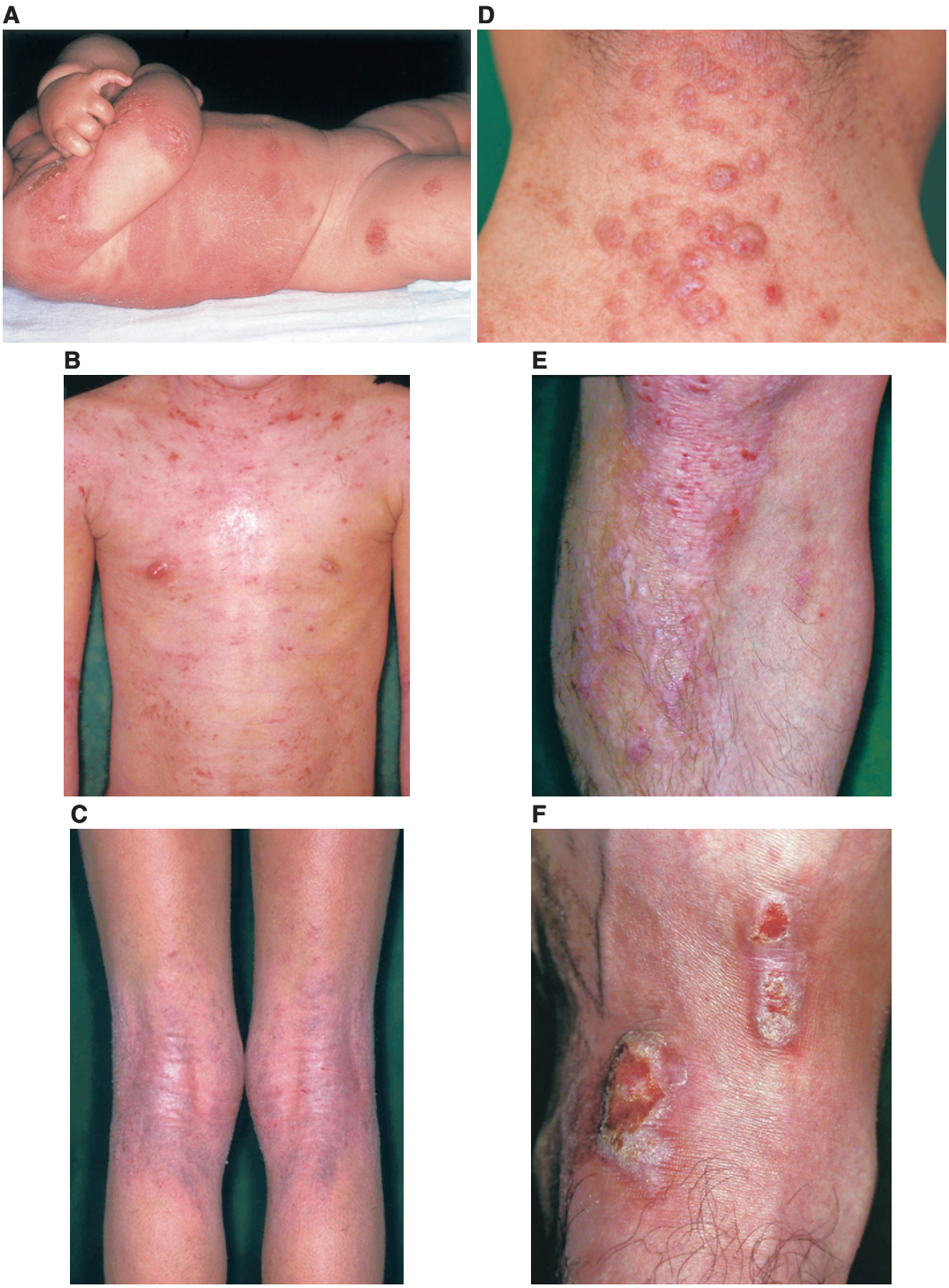

Fig. 10 Rashes likely to require referral to a specialis. (**A**) Body trunk and upper limb in an infant: marked erythema, desquamation, and scratch marks, (**B**) Body trunk in a child: marked erythema, scratch marks, and erosion, (**C**) Popliteal fossa in a child: erythema, scratch marks, and marked lichenification, (**D**) Head and neck in an adult: prurigo, (**E**) Lower leg in an adult: marked lichenification and scratch marks, (**F**) Lower limb in an adult: papule with marked scratch marks.

specialist in childhood allergy) or a specialized institution should be considered. Figure 10 shows specific examples of rashes requiring referral to a specialist.

2) Hospital treatment: In principle, hospital treatment should be considered for patients with the most severe cases in the severity index defined in the

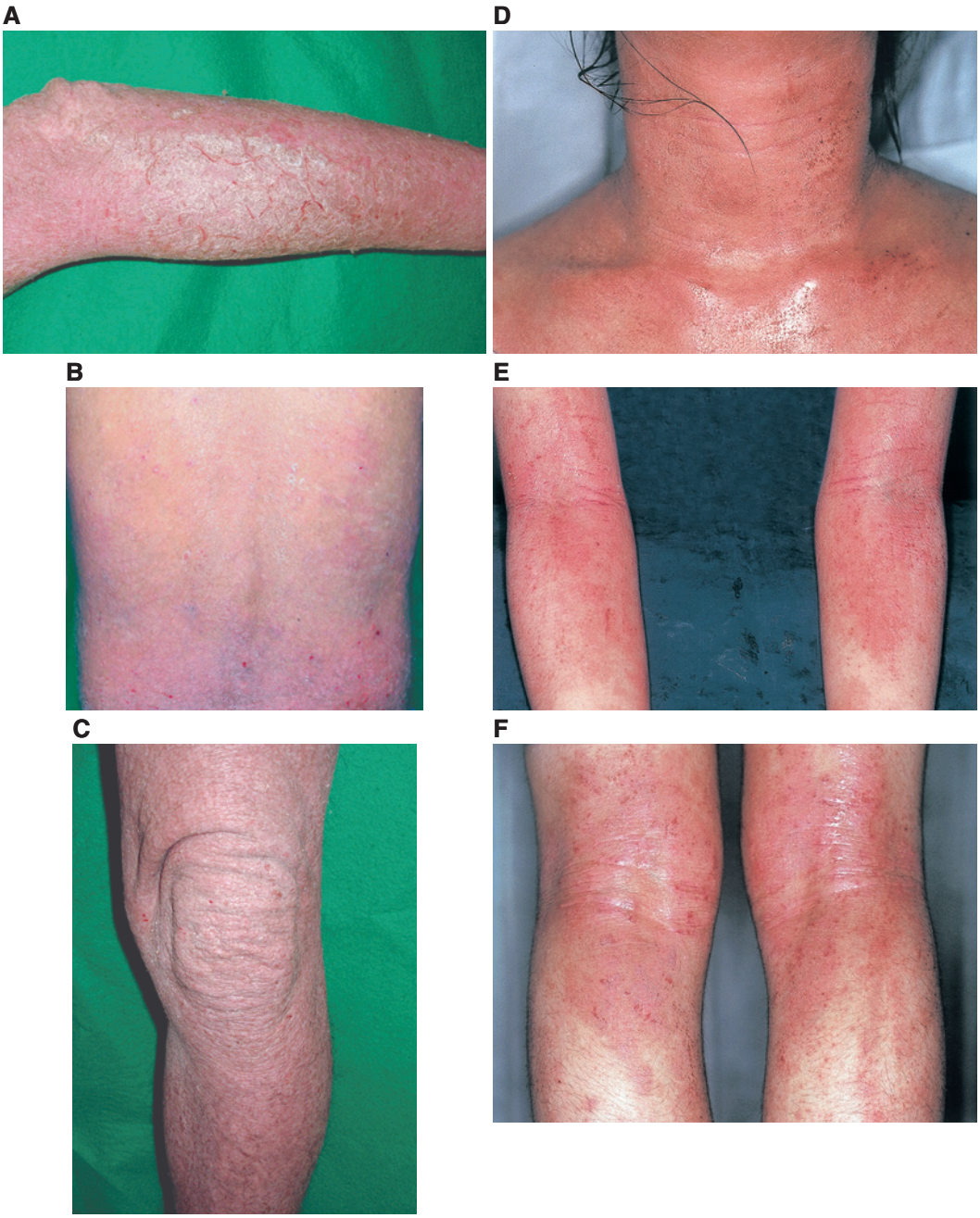

Fig. 11 Rashes likely to require hospitalization. (**A**) Upper limb: marked desquamation, erythema, and scratch mark, (**B**) Body trunk: marked desquamation, erythema, and scratch marks, and lichenification, (**C**) Lower limb: marked desquamation, erythema, scratch marks, and lichenification, (**D**) Neck and anterior chest: marked erythema, desquamation, erosion, and scratch marks, (**E**) Upper limb: marked erythema, desquamation, erosion, scratch marks, and lichenification, (**F**) Lower limb: marked erythema, desquamation, erosion, scratch marks, and lichenification.

ADGL 2012. Figure 11 shows specific examples of cases requiring hospitalization.

3) Precautions in children: The ADGL 2012 describe the oral administration of steroids for the most severe case as a measure "to be taken temporarily as needed." However, affected children, particularly those cases complicated by asthma, require a close liaison with a specialist (e.g. a specialist in cutaneous allergy, a specialist in childhood allergy), since discontinuation of the oral administration of steroids may aggravate the symptoms (Fig. 12).

4) Precautions for oral steroids: Oral steroids

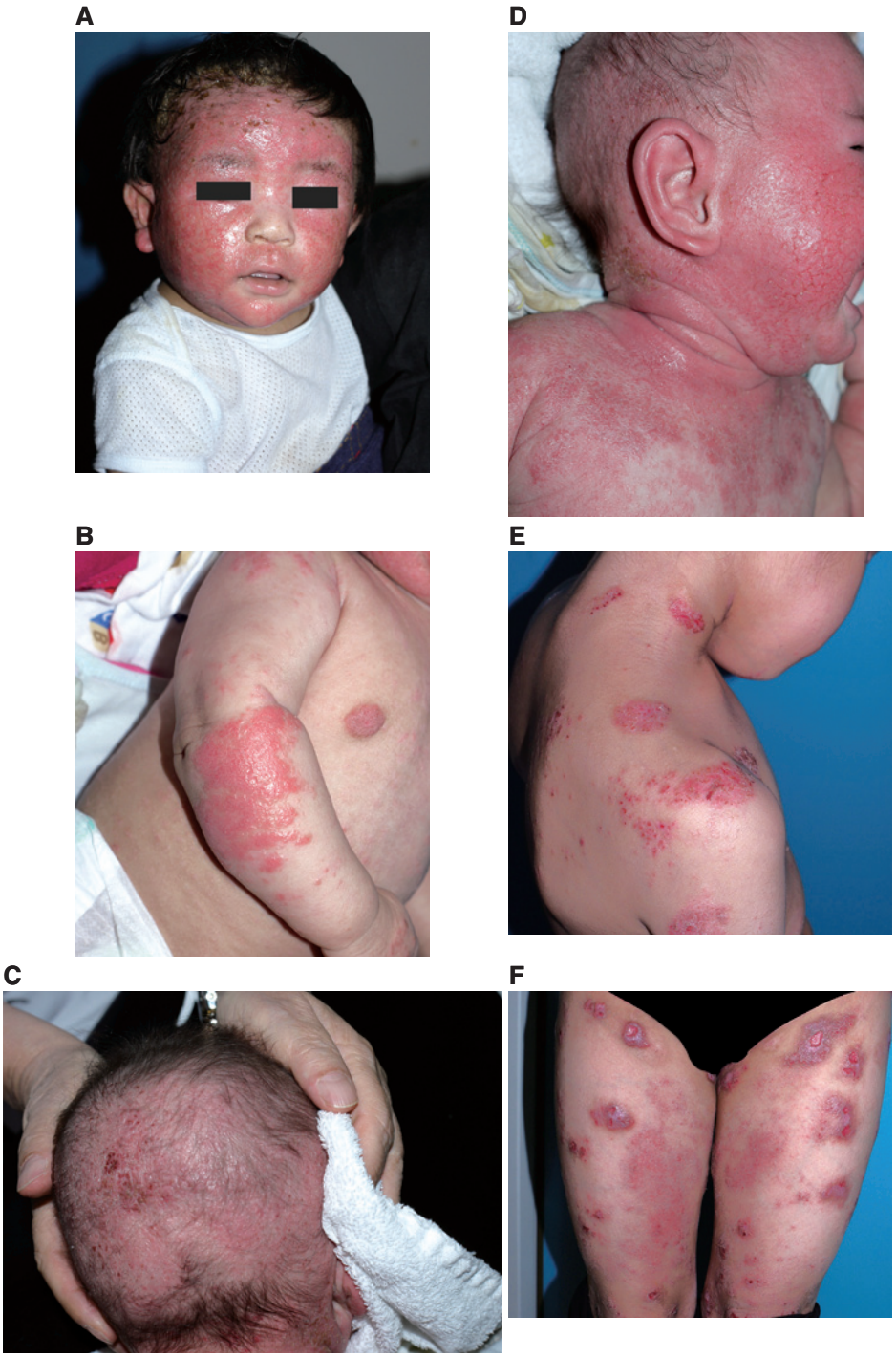

Fig. 12 Cutaneous symptoms of children requiring referral to a specialized medical institution. (**A**) Face of an infant (9 months old): Aggravation by steroid withdrawal. Extreme flush and erosion on the face, (**B**) Forearm of an infant (4 months old): Edematous and erosive flush, (**C**) Scalp of an infant (4 months old): Red papule and crust spreading over the head, (**D**) Cheek and ear of an infant (4 months old): Marked weeping flush and edema on the face and neck, (**E**) Neck and shoulder of a child (9 years old): Severely scratching multiple nummular eczema, (**F**) Femurs of a child (9 years old): Lichenification and pruritic tubercles due to poor compliance with application of steroid.

should not be used at all or should be used with consideration of the minimum dose and the duration of use.

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