

Atopic Dermatitis in Infants and Young Children

Jean-Christoph Caubet¹ and Anna Nowak-Węgrzyn²

¹Division of Allergy, Department of Pediatrics, University Hospitals of Geneva, Geneva, Switzerland

²Department of Pediatrics, Division of Allergy/Immunology, Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

OVERALL BOTTOM LINE

- Atopic dermatitis (AD) is a common, chronic, relapsing, inflammatory skin disorder and may be the initial step of the so-called atopic march.
- Pathogenesis is complex and not fully understood, but recent investigations have highlighted two cornerstone features of AD: defective epidermal barrier and cutaneous inflammation involving both IgE- and T-cell-mediated responses.
- Diagnosis of AD is based on clinical features.
- A complete allergy investigation is required in patients with moderate to severe AD or a history of exacerbation after food ingestion. The younger the age of onset and the more severe the rash, the more likely foods are to trigger AD in children.
- Although there is no cure for AD, the goals of treatment are to reduce symptoms, prevent exacerbations, minimize side effects, and provide adequate psychological support.

Section 1: Background

Definition of disease

- AD is a familial, common, inflammatory skin disorder characterized by chronically relapsing course and intensely pruritic eczematous flares. The term “eczema” alone generally refers to AD and these terms are often used interchangeably.

Disease classification

- Although clinically indistinguishable, AD has been categorized into an immunoglobulin E (IgE) associated form (true AD, formerly called extrinsic AD) and a non-IgE-associated form (“non-atopic” dermatitis, formerly called intrinsic AD). However, this classification is controversial as the absence of sensitization to common food allergens and aeroallergens may be only a transient factor.

Incidence/prevalence

- AD affects an estimated 18 million people in the United States.
- The estimated lifetime prevalence in children ranges from 10–30%.
- Wide variations in prevalence have been observed between countries, suggesting that environmental factors determine AD expression.

Mount Sinai Expert Guides: Allergy and Clinical Immunology, First Edition. Edited by Hugh A. Sampson.

© 2015 John Wiley & Sons, Ltd. Published 2015 by John Wiley & Sons, Ltd.

Companion website: www.mountsinaexpertguides.com

Economic impact

- The economic impact of AD is important and will likely increase in proportion to increasing disease prevalence. The current estimates range widely, from \$364 million to \$3.8 billion dollars per year.

Etiology

- The exact etiologic factors leading to AD are not well defined.
- Genetically predisposed patients with AD have an epidermal barrier dysfunction, linked to decreased or impaired function of essential barrier proteins (i.e. filaggrin and ceramide).
- Common triggers in AD include food proteins, aeroallergens, stress, climate, irritants, and microbes.

Pathology/pathogenesis

- AD is mainly characterized by a defective epidermal barrier and cutaneous inflammation.
- Genetically predisposed patients with AD have an epidermal barrier dysfunction; contributing factors include decreased ceramide levels and loss of function of crucial protein (e.g. filaggrin). This can result in enhanced transepidermal water loss and facilitated penetration of environmental allergens, promoting allergic skin inflammation.
- The complex underlying immune response of AD involves both IgE-mediated and T-cell-mediated delayed immune responses. Acute skin lesions of AD are characterized by cells containing Th2 cytokines (i.e. IL-4, IL-5, IL-13 and IL-22), whereas Th1 cells expressing γ -interferon (IFN- γ) are most commonly found in more chronic lesions.
- Although elevated serum total IgE levels can be found in 80–85% of patients with AD, the clinical relevance of associated sensitizations has been difficult to ascertain.
- Foods can cause exacerbation in a subset of patients (i.e. approximately one-third of young children with a moderate or severe AD). Similarly, exacerbation of AD can occur with exposure to aeroallergens such as house dust mites, animal danders, and pollens.
- Most patients with AD have an inadequate innate immune response to epicutaneous microbes, in part responsible for increased susceptibility to infections (bacteria, yeast, viruses) and colonization with *Staphylococcus aureus*. These microbes contribute, at least partially, to the skin inflammation and can potentially lead to exacerbations of the disease.

Predictive/risk factors

Risk factor	Odds ratio
Genetic factors (filaggrin mutation)	3.73–7.1
Breastfeeding	Controversial
Tobacco	1.97
Familial history of atopy	2–6

Section 2: Prevention

BOTTOM LINE/CLINICAL PEARL

- For infants at high risk of atopy, exclusive breastfeeding for at least 4 months and/or feeding with extensively hydrolyzed formula decreases cumulative incidence of AD in the first 2 years of life. There is no prevention strategy proven to protect beyond the first few years of life.

Screening

Not applicable for this topic. Studies on screening for filaggrin mutations are ongoing.

Primary prevention

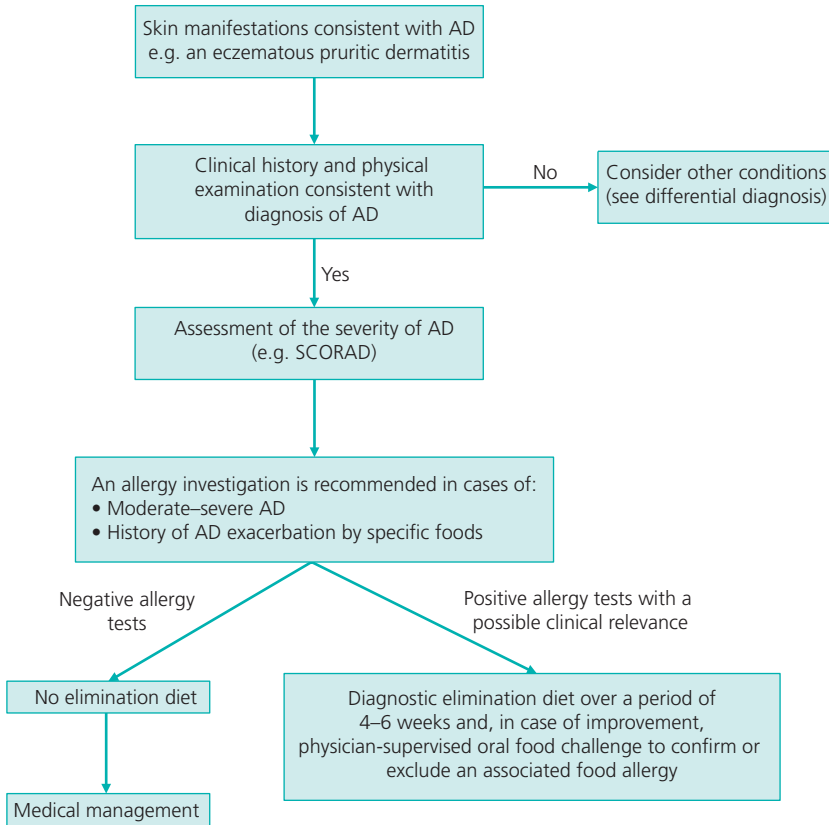
- Exclusive breastfeeding for at least 4 months and/or feeding with extensively hydrolyzed formula decreases cumulative incidence of AD in the first 2 years of life.
- Although several studies support a preventative effect of treating with probiotics during pregnancy or early infancy to delay the onset of AD, controversy persists and more studies are needed to confirm these data.

Secondary prevention

- Optimal skin care remains the cornerstone of the management of AD.
- Avoidance of common irritants and specific allergen triggers (foods and/or aeroallergens) in selected patients constitute a large part of secondary prevention of AD.
- Other important measures include control of household temperature and humidity; use of mild soaps for bathing (neutral pH and minimal defatting capabilities); bathing in warm water once a day for 15–20 minutes, pat dry and immediate application of emollients; nails trimming to decrease abrasion to skin; use of clothing made of cotton instead of synthetic fibers and wool.

Section 3: Diagnosis (Algorithm 1.1)

Algorithm 1.1 Diagnosis of atopic dermatitis



BOTTOM LINE/CLINICAL PEARLS

- The diagnosis of AD is based on a constellation of clinical features.
- Recurrent pruritus is the only symptom of AD.
- Physical examination reveals xerosis and typical eczematous lesions with different morphologic aspects and locations depending on the age of the patient. Eczematous rashes tend to be generalized and affect the face and extensor surfaces of the limbs in infants and toddlers, while in older children and adults rashes localize to the peri-orbital area, flexor surfaces of the joints, and about the wrists and ankles.
- Allergic investigations are usually not indicated for patients with mild AD.
- In patients with moderate–severe atopic dermatitis or with a positive history of exacerbation after exposure to a specific allergen, an allergy investigation including skin tests, specific IgE measurement, and/or an oral provocation test are indicated.

Differential diagnosis

Differential diagnosis	Features
Scabies	Papules, finger web involvement, positive scraping for scabies mite
Allergic contact dermatitis	Positive exposure history, rash in area of exposure, absence of family history
Seborrheic dermatitis	Greasy, scaly lesions, absence of family history
Zinc and biotin deficiency	Eczematous lesions localized in peri-oral area and rectum (oral, anal)
Psoriasis	Localized patches on extensor surfaces, scalp, buttocks, pitted nails
Ichthyosis	Usually non-pruritic, not the typical distribution pattern seen in AD, no inflammatory lesions (except in Netherton's syndrome)
Netherton's syndrome (severe, autosomal recessive form of ichthyosis associated with mutations in the <i>SPINK5</i> gene)	Chronic skin inflammation, universal pruritus, severe dehydration and stunted growth, hair shaft defect (trichorrhexis invaginata), also known as "bamboo hair"
Immunodeficiency: severe combined immunodeficiency syndrome, hyper-IgE syndrome, Wiskott–Aldrich syndrome	Severe eczema, positive history of multiple infections, growth failure

Typical presentation

- Atopic dermatitis occurs in the first year of life in 60% of cases, and by the age of 5 years in nearly 85% of cases. Patients typically present with pruritus and chronically relapsing/remitting eczematous lesions having a typical morphology and distribution related to the age of the patient.

Clinical diagnosis**History**

- The diagnosis of AD is based on a constellation of clinical features, pruritus being the cardinal symptom of this disorder.

- One of the major clinical features of AD is its chronicity, characterized by an intermittent course with flares and remission.
- A careful allergy history is of major importance to identify potential allergen triggers (e.g. aeroallergens and foods), particularly in patients with moderate–severe AD. Identification of common irritants is also an important part of the history.
- The clinician should evaluate the impact on quality of life, particularly sleeping and psychologic aspects.

Physical examination

- Characteristic skin findings in AD include primarily xerosis and eczematous lesions with different morphologic aspects and locations depending on the age of the patient.
- Acute and subacute eczematous skin lesions are typically found in infants and young children, with intensely pruritic, erythematous, papulo-vesicular lesions, excoriation, and serous exudate. The lesions are typically localized on the scalp, face (cheeks and chin), and extensor surfaces of the extremities. In older children, lesions are more commonly found in the flexor surfaces (antecubital and popliteal fossa), neck, wrists, and ankles.
- Lichenification is rarely seen in infancy but is characteristic of childhood AD.
- Of note, peri-orbital hyperpigmentation and Dennie–Morgan folds (prominent folds of skin under the lower eyelid) are common peri-ocular findings in patients with AD.

Useful clinical decision rules and calculators

- The UK diagnostic criteria are the most extensively validated for AD and are based on the classic diagnostic criteria of Hanifin and Rajka.
- The patient must have an itchy skin condition in the last 12 months plus three or more of the following criteria:
 - Onset below age 2 (not used in children under 4 years);
 - History of flexural involvement;
 - History of a generally dry skin;
 - Personal history of other atopic disease (in children aged under 4 years, history of atopic disease in a first degree relative may be included); and
 - Visible flexural dermatitis as per photographic protocol.

Disease severity classification

- There are many tools to evaluate the severity of AD, although they have been used mainly in clinical research trials. The most well known:
 - *Severity Scoring of Atopic Dermatitis (SCORAD)*: uses the “rule of 9’s” to assess disease extent and evaluates five clinical characteristics to determine disease severity; and
 - *Eczema Area and Severity Index (EASI)*: assesses extent of diseases at four body sites and measures four clinical signs on a scale of 0–3.

Laboratory diagnosis

List of diagnostic tests

- Skin prick tests and/or specific IgE to common food allergens should be restricted to patients with moderate–severe AD or to patients having a positive history of exacerbation after specific food ingestion.
- The most common food allergens in childhood AD are hen’s egg, cow’s milk, peanut, soybean, wheat, tree nuts, fish, and shellfish. Hen’s egg, cow’s milk, and peanut account for about 80% of food allergy diagnosed by food challenge in children with AD.

8 Part 1: Allergy

- Skin prick tests and/or specific IgE to aeroallergens (i.e. pollens, animal danders, and dust mites) should be performed according to the history and the age of the patient.
- Atopy patch testing is an additional tool in selected cases in which skin prick tests or specific IgE fail to identify a suspected food. It is not recommended as a routine diagnostic test in AD.
- Oral food challenges are considered the gold standard to diagnose an associated food allergy.
- Scraping to exclude tinea corporis is occasionally helpful.
- A swab of infected skin may help with the isolation of a specific organism and antibiotic sensitivity assessment.
- Skin biopsy is usually not required to confirm the diagnosis of AD but in rare difficult cases it can be useful to exclude other causes.

Lists of imaging techniques

Not applicable for this topic.

Potential pitfalls/common errors made regarding diagnosis of disease

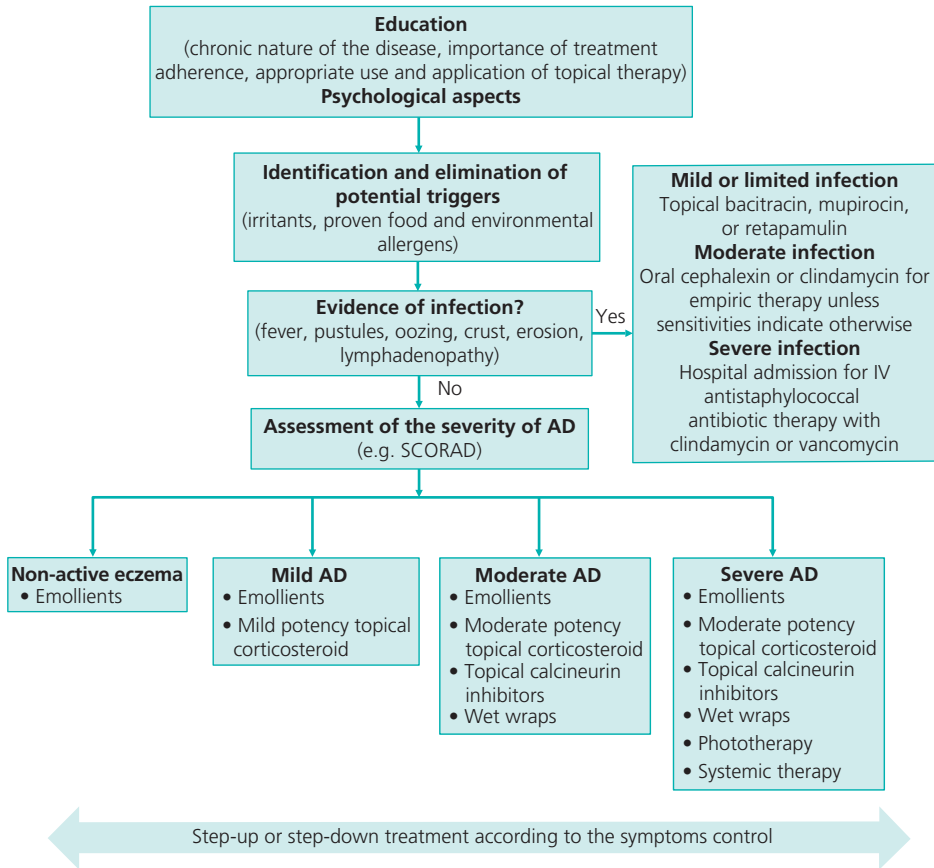
- Positive skin prick tests or specific IgE to food(s) should only lead to a restrictive elimination diet in selected patients with moderate–severe AD or a positive history of exacerbation after food ingestion. Elimination diets based on positive skin prick tests or food-specific IgE levels should be of limited duration unless there is clear evidence of clinical food allergy.
- Scabies should always be excluded in patients with severe pruritus.
- In patients with severe AD, poor growth, and/or frequent or severe infection, an immunodeficiency should be suspected.

Section 4: Treatment (Algorithm 1.2)

Treatment rationale

- The first line therapy is based on restoring skin hydration (e.g. hydrating baths and emollient creams) and reducing inflammation (e.g. topical corticosteroids and/or calcineurin inhibitors).
- Rarely, patients need systemic treatments with oral corticosteroids or immunosuppressive agents. These treatments should be re-evaluated and adapted regularly in order to minimize potential side effects.
- Antibacterial or antiviral drugs are indicated only in patients with clinical signs of active infection, particularly resulting from *Staphylococcus aureus* and herpes simplex virus infection. In addition, the role of allergens, irritants, physical environment, and emotional stressors need to be considered, as controlling these factors is of major importance in optimizing management.
- Food elimination diets should be restricted to selected patients with a positive allergy investigation and the potential benefits (decreased AD severity and improved quality of life) and potential disadvantages (decreased quality of life because of food avoidance and risk of anaphylactic reactions to a food) need to be discussed with the patient and his/her family.
- A 4–6 week trial of food elimination may be followed by food reintroduction (oral food challenge) under physician supervision to document reappearance of eczematous lesions. In a subset of children with persistent AD and no prior history of acute allergic reactions upon food ingestion, following food elimination, classic acute allergic symptoms may be observed following food reintroduction including hives or even anaphylaxis.
- Oral non-sedating antihistamines have a minor effect on the control of pruritus associated with AD. The first generation, sedating antihistamines (e.g. hydroxyzine) can be helpful when used at bedtime to facilitate falling asleep.

Algorithm 1.2 Management of atopic dermatitis



- Patients should understand that therapy is not curative but that avoidance of exacerbating factors together with proper daily skin care can result in control of symptoms and improve the long-term outcome. The clinician should take into account the impact of AD on quality of life and correctly manage the associated stress that can be responsible for acute exacerbations.

When to hospitalize

- Hospitalization is rarely required for patients with AD.
- Patients with severe AD who do not improve with correct outpatient therapy might require hospitalization.
- Patients with cellulitis or severe secondary infection (e.g. eczema herpeticum caused by primary infection with herpes simplex virus) may need intravenous antibiotics and sedation.
- Hospitalization is sometimes necessary to clear the patient's skin before skin testing and/or oral food challenge.

Managing the hospitalized patient

- Appropriate antimicrobial agent therapy.
- Intensive skin care may include soaking bath or wet wraps.
- Oral food challenges to the suspected food can be carried out during hospitalization.

- Hospitalization is beneficial in selected patients by removing the patient from environmental triggers (irritants, allergens) and by intensifying treatment.
- Adequate educational information should be provided to the patient and their family in order to improve adherence with the treatment regimen.
- Psychological issues are also more easily addressed during a hospitalization.

Table of treatment

Treatment	Comment
Identification and elimination of triggering factors	Avoidance of common irritants (e.g. soaps, toiletries, wool, and chemicals) are recommended as well as a correct control of temperature and humidity that may trigger the itch–scratch cycle Elimination diets should only be recommended in selected patients based on a positive allergy investigation
Emollients	An effective moisturizer constitutes the cornerstone of the treatment of AD as it helps to restore and preserve the skin barrier (e.g. CeraVe®, Vanicream®, Vaseline®)
Topical corticosteroids	Used primarily to control acute exacerbation of AD Seven classes ranked according to their potency. The choice and the duration will be based on the severity of the lesions and should be re-evaluated regularly. In general, the least potent steroid that is effective should be used
Topical calcineurin inhibitors	Currently indicated as second line treatment for intermittent use in children aged 2 years and older with moderate–severe AD (tacrolimus ointment 0.03%) and mild–moderate AD (pimecrolimus cream 1%). Of note, tacrolimus ointment 1% is indicated for patients 16 years and older
Systemic corticosteroids	Rarely indicated, but a short course of oral prednisone can be used in severe acute exacerbation of AD
Antistaphylococcal antibiotics	In patients with extensive skin infection, a course of systemic antibiotics is indicated: cephalosporin (e.g. cephalexin twice daily for 14–21 days) or penicillinase-resistant penicillins are usually beneficial Topical mupirocin is useful for the treatment of localized impetigo lesions
Antiviral therapy	In patients with disseminated herpes simplex virus infection, acyclovir is indicated, orally for less severe infection and intravenously for widely disseminated disease (30 mg/kg/day)
<ul style="list-style-type: none"> • Cyclosporine • Mycophenolate mofetil • Azathioprine • IFN-γ 	These drugs have multiple potential severe side effects and should be used only in selected patients with persistent severe AD
Psychological	Psychological evaluation or counseling should be considered in patients with AD due to the main impact on their quality of life and as stress is a potential trigger
Phototherapy	UV therapy can be a useful treatment for recalcitrant AD. The most effective phototherapy option that is available in the United States is narrow band UVB
Wet dressing	This tool can be used in combination with topical corticoids

Prevention/management of complications

- Patients should be carefully instructed in the used of topical corticosteroids (i.e. avoidance of face, genital, and intertriginous areas). Although the systemic effects of topical corticosteroids

are minor, corticophobia is one of the main limiting factors in the treatment of patients with AD. The clinician should provide full explanations to achieve good adherence.

- Although there was a Food and Drug Administration (FDA) Black Box warning in 2005, it seems that the benefits of using calcineurin inhibitors in the appropriately selected patient population outweighs the theoretical risk of increased malignancy.
- Use of systemic immunosuppressive drugs may be associated with several, potentially severe, side effects and these drugs should be restricted to patients with severe and uncontrolled AD unresponsive to standard treatment.

CLINICAL PEARLS

- Clinicians should use a systematic approach that includes skin hydration, topical anti-inflammatory medications, antipruritic therapy, and antibacterial measures.
- Elimination of exacerbating factors, including allergens, is a cornerstone of AD management.
- The clinician should recognize that AD has a significant effect on the patient's and family's quality of life.

Section 5: Special populations

Not applicable for this topic.

Section 6: Prognosis

BOTTOM LINE/CLINICAL PEARLS

- AD typically manifests in early childhood, with onset before 5 years of age in approximately 90% of patients.
- Although it was initially reported that more than 80% of children outgrow their AD by adolescence, more recent studies present less optimistic outcomes with AD persisting into adulthood, even if the relapses are often less common and mild.
- Adults with a history of childhood AD are at an increased risk for occupational hand dermatoses.
- AD is usually considered as the first step of the so-called atopic march and it is estimated that 30–60% of patients with AD will develop allergic rhinitis or asthma.

Natural history of untreated disease

Not applicable for this topic.

Prognosis for treated patients

Not applicable for this topic.

Follow-up tests and monitoring

- The patients and/or parents should be instructed on the specific aspects of the disease (i.e. mainly its chronicity and exacerbating factors) and on appropriate treatment options to control the symptoms. A treatment plan for skin care should be provided and re-evaluated regularly during follow-up visits.
- As the diagnosis is only based on clinical criteria, it is important to reassess if the diagnosis is correct, particularly in patients with uncontrolled symptoms despite an optimal treatment.

Section 7: Reading list

- Boguniewicz M, Leung DYM. Atopic dermatitis. In Adkinson NF, Busse WW, Bochner BS, et al. (eds) Middleton's Allergy: Principles and Practice, 8th edn. Saunders; 2013, 540–58
- Brennkmeijer EE, Schram ME, Leeflang MM, Bos JD, Spuls PI. Diagnostic criteria for atopic dermatitis: a systematic review. *Br J Dermatol* 2008;158:754–65
- Caubet JC, Eigenmann PA. Allergic triggers in atopic dermatitis. *Immunol Allergy Clin North Am* 2010;30:289–307
- Hanifin JM, Cooper KD, Ho VC, Kang S, Krafchik BR, Margolis DJ, et al. Guidelines of care for atopic dermatitis, developed in accordance with the American Academy of Dermatology (AAD)/American Academy of Dermatology Association. Administrative Regulations for Evidence-Based Clinical Practice Guidelines. *J Am Acad Dermatol* 2004;50:391–404
- Leung DY, Bieber T. Atopic dermatitis. *Lancet* 2003;361:151–60
- Mancini AJ, Kaulback K, Chamlin SL. The socioeconomic impact of atopic dermatitis in the United States: a systematic review. *Pediatr Dermatol* 2008;25:1–6
- Schneider L, Tilles S, Lio P, Boguniewicz M, Beck L, LeBovidge J, et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol* 2013;131:295–9, e1–27

Suggested websites

A website to evaluate the SCORAD: <http://adserver.sante.univ-nantes.fr/Scorad.html>

Section 8: Guidelines

National society guidelines

Guideline title	Guideline source	Date
Atopic dermatitis: A practice parameter update 2012	J Allergy Clin Immunol	2013 (http://www.ncbi.nlm.nih.gov/pubmed/23374261)
Guidelines for the diagnosis and management of food allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report	J. Allergy Clin Immunol	2010 (http://www.ncbi.nlm.nih.gov/pubmed/21134568)

International society guidelines

Guideline title	Guideline source	Date
Eczematous reactions to food in atopic eczema: position paper of the EAACI and GA2LEN	European Academy of Allergy and Clinical Immunology (EAACI)	2007 (http://www.ncbi.nlm.nih.gov/pubmed/17573718)
Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergy and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report	European Academy of Allergy and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Group	2006 (http://www.ncbi.nlm.nih.gov/pubmed/16867052)

Section 9: Evidence

Type of evidence	Title, comment	Date
Prospective study	Prevalence of IgE-mediated food allergy among children with atopic dermatitis Comment: This study demonstrates that approximately one-third of children with refractory, moderate–severe AD have IgE-mediated clinical reactivity to food proteins	1998 (http://www.ncbi.nlm.nih.gov/pubmed/9481027)
Prospective study	Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis Comment: This work establishes a key role for impaired skin barrier function in the development of atopic disease	2006 (http://www.nature.com/ng/journal/v38/n4/abs/ng1767.html)
Prospective study	Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy Comment: Filaggrin mutations represent a significant risk factor for IgE-mediated peanut allergy, indicating a role for epithelial barrier dysfunction in the pathogenesis of this disease	2011 (http://www.ncbi.nlm.nih.gov/pubmed/21377035)

Section 10: Images



Figure 1.1 A child with multiple food allergies and severe persistent atopic dermatitis (AD) with acute exacerbation due to *Staphylococcus aureus* superinfection. Note the diffuse erythroderma and open sores. See color plate 1.1.



Figure 1.2 AD chronic lesions of skin hypertrophy, lichenification, hyperpigmentation, and xerosis. See color plate 1.2.

Additional material for this chapter can be found online at:
www.mountsinaiexpertguides.com
This includes a case study, multiple choice questions, advice for patients, and ICD codes

