# The Atopic Child

ATOPIC DERMATITIS IN CHILDREN AND FOOD ALLERGY

MARTINE DOCX MD

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24/01/2015

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# Summary

- 1. Atopic Dermatitis
  - 1.1. Introduction
  - 1.2. Diagnosis
  - 1.3. Pathogenesis
  - 1.4. Treatment

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# Introduction

- Chronic or chronically relapsing disease
- 15-20 % of all children
- In 60% onset < 1 year
- In 85% onset < 5 years
- Impact on the quality of life of the patient and the patient's family
- Pediatricians and primary care physicians treat □ 30 %
- High public cost □ economic problem

# The Atopic March

- Bergmann (1998, Clin Exp Allergy)

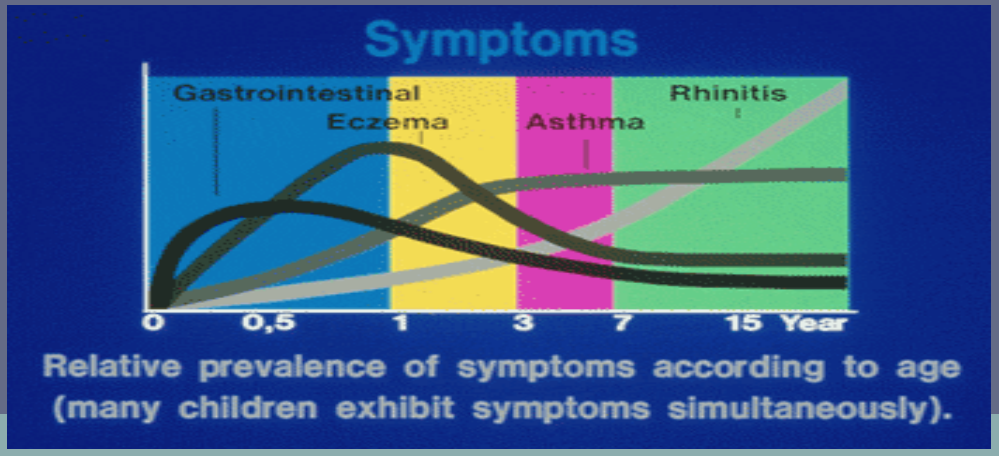
  Prospective birth cohort study, N= 1314, 5 y

  If AD at 3 mo and one parent/sibling atopic >50% chance of asthma at age 5-6

- Castro-Rodriquez (1999, AJRCCM)

  Longitudinal, retrospective study, N= 986

  If AD and parental asthma; >75% chance of asthma during school years.



Relative prevalence of symptoms according to age (many children exhibit symptoms simultaneously).

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# The Hanifin and Rajka criteria for the diagnosis of atopic dermatitis 1980

( Hanifin JM, Rajka G.: Diagnostic features of atopic dermatitis. Acta Dermato-Venereologica. 1980: Suppl 92: 44-7.)

## Major Criteria

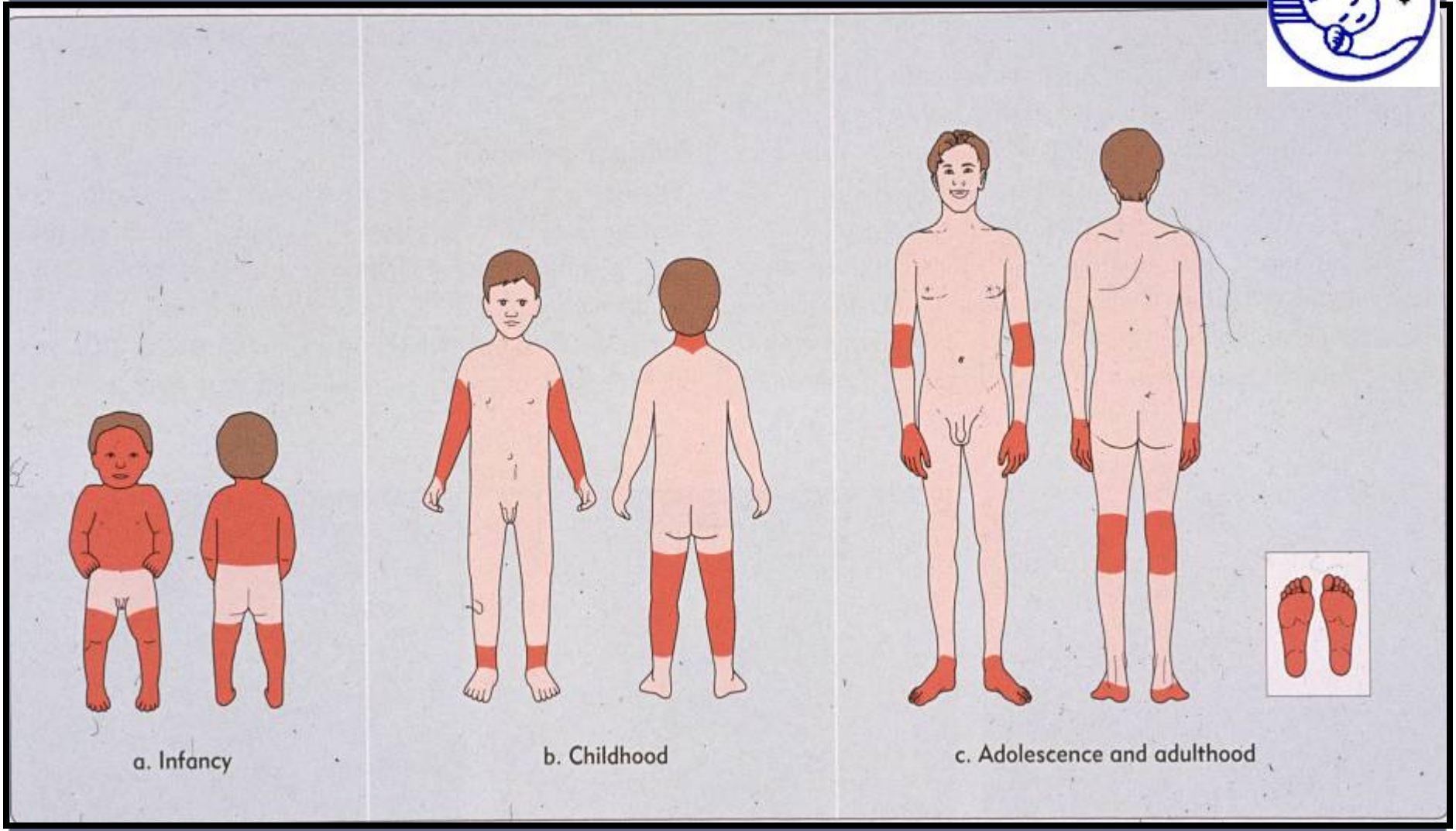
### Must have 3 or > basic features

- Pruritus
- Typical morphology and distribution
  - -Flexural lichenification or linearity in adults
  - -Facial and extensor involvement in infants and children
- Chronic or chronically relapsind dermatitis
- Personal or family history of atopy ( asthma, allergic rhinitis, atopic dermatitis)

## Minor Criteria

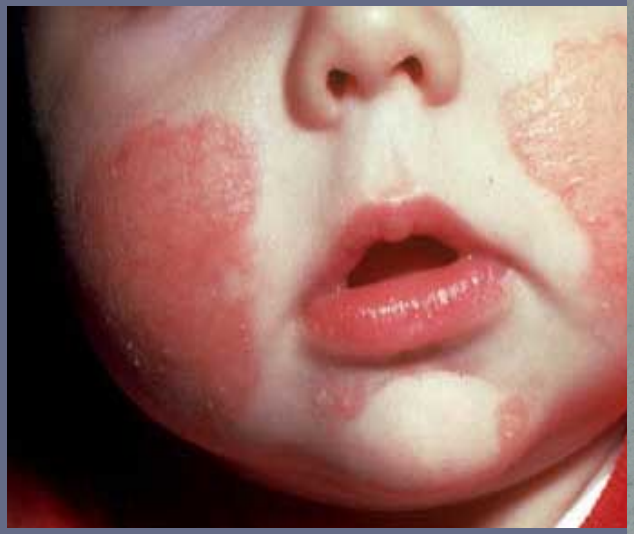
### + 3 or more minor features

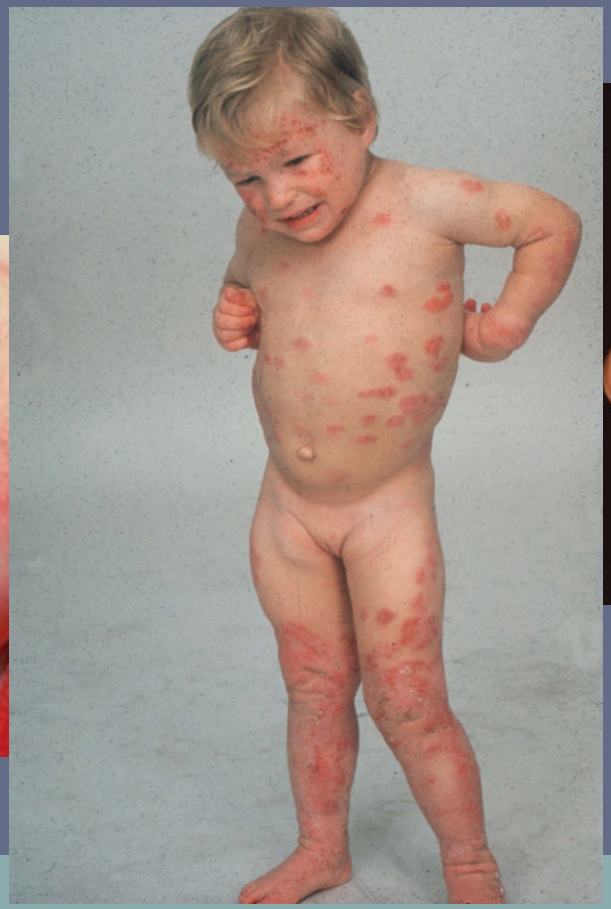
- Xerosis
- Ichthyosis/ palmar hyperlinearity/ keratosis pilaris
- Immediate ( type I) skin test reactivity
- Elevated serum Ig E
- Early age of onset
- Nipple eczema
- Cheilitis
- Tendency towards cutaneous infections/impaired cell-mediated immunity
- Tendency towards non-specific hand or foot dermatitis
- Recurrent conjunctivitis
- Keratoconus
- Dennie-Morgan infraorbital fold
- Orbital darkening
- Anterior subcapsular cataracts
- Facial pallor/ facial erythema
- Pityarisis Alba
- Anterior neck folds
- Itch when sweating
- Intolerance to wool and lipid solvents
- Food Intolerance
- Course influenced by environmental / emotional factors
- White dermographism/ delayed blanch
- Perifollicular accentuation

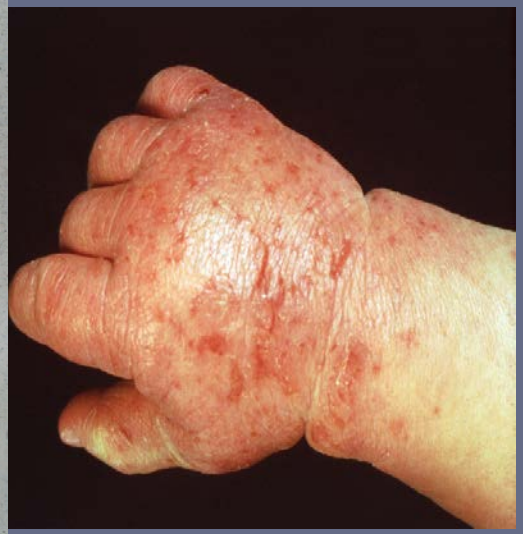

a. Infancy
b. Childhood
c. Adolescence and adulthood

# Distribution

- In infants, the *face* is often affected first, then the hands and feet; dry red patches may appear all over the body.

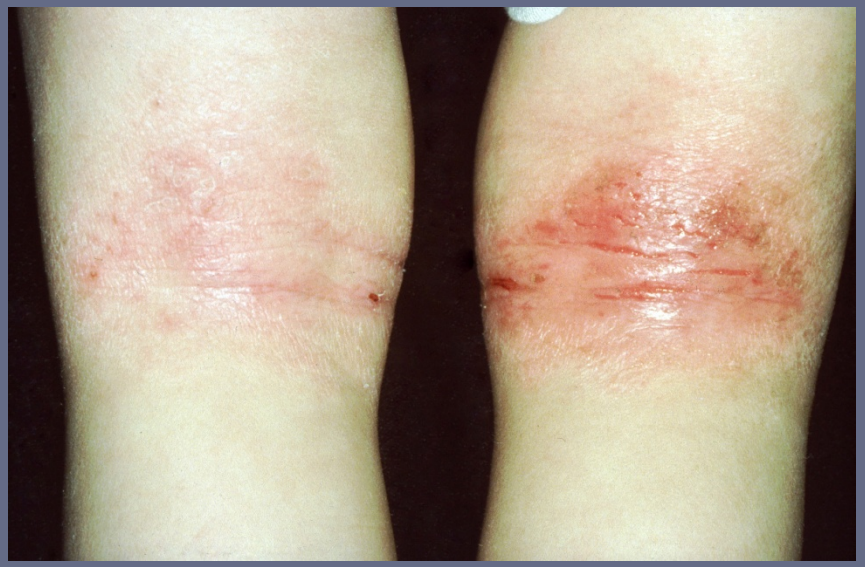


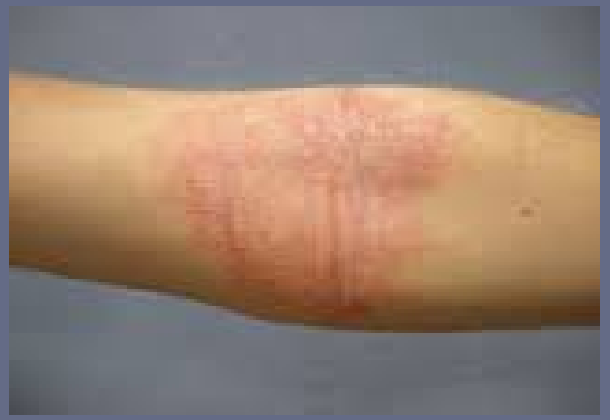




# Distribution

- In older children, the **skin folds** are most often affected, especially the elbow creases and behind the knees.

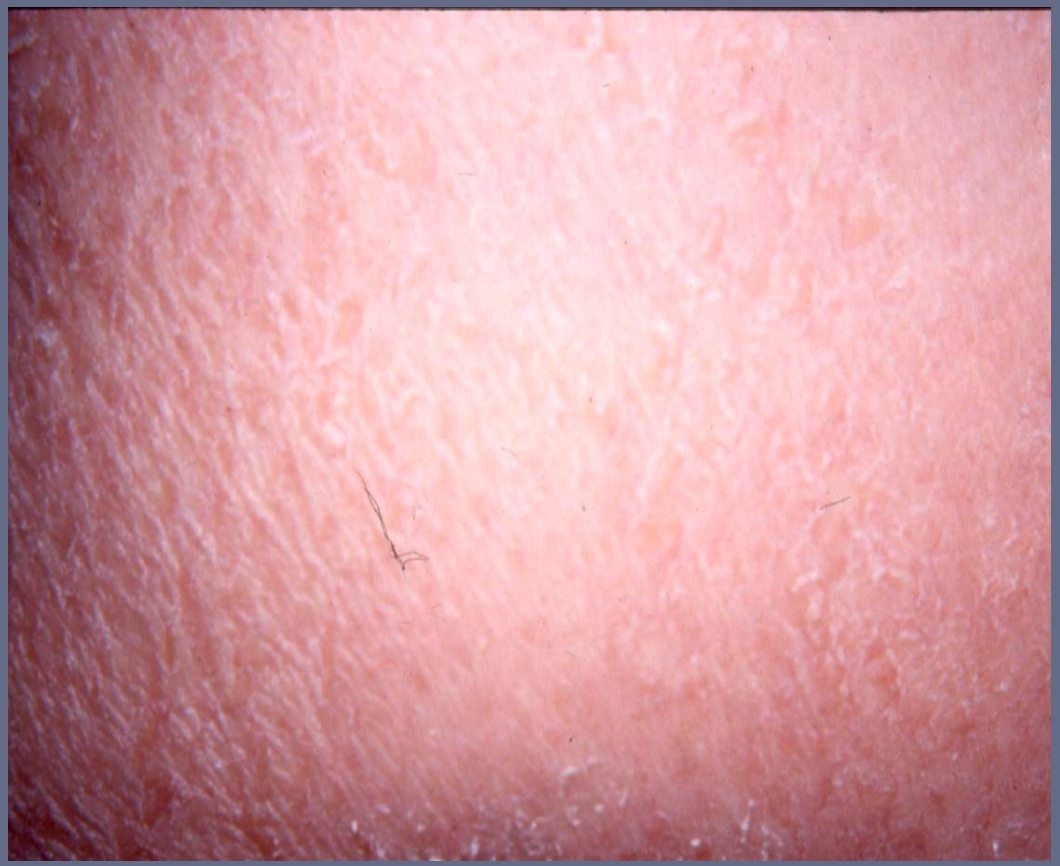




# Distribution

- In adults, the *face* and *hands* are more likely to be involved.


# Xerosis (dry skin)



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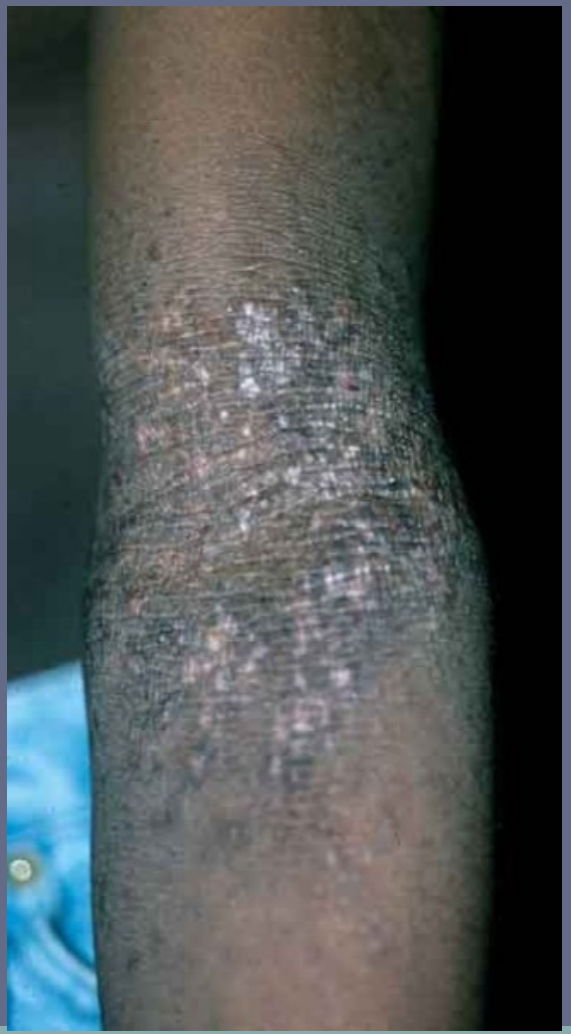
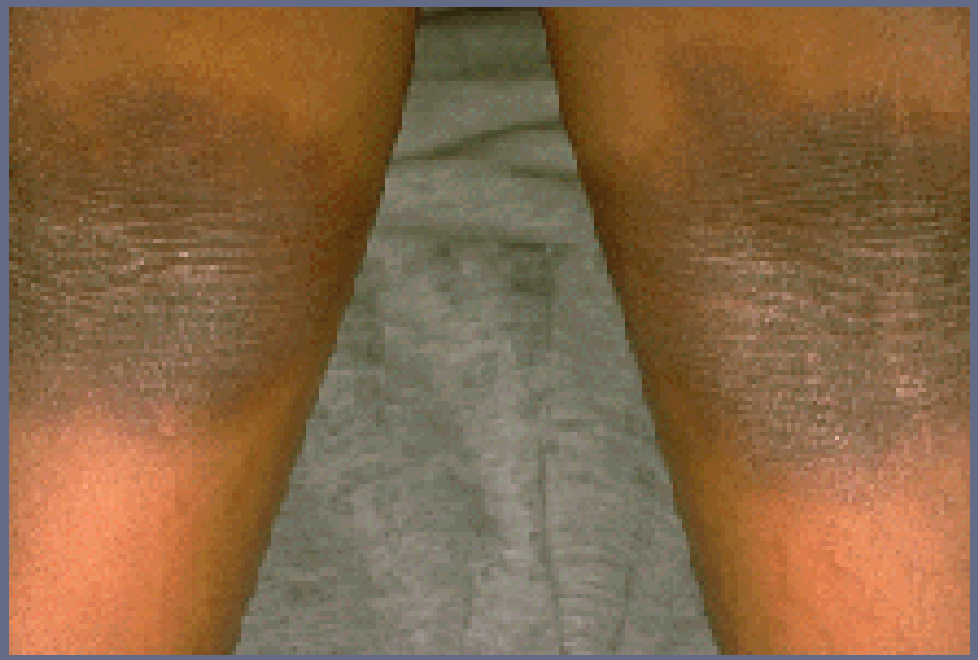
# Lichenification





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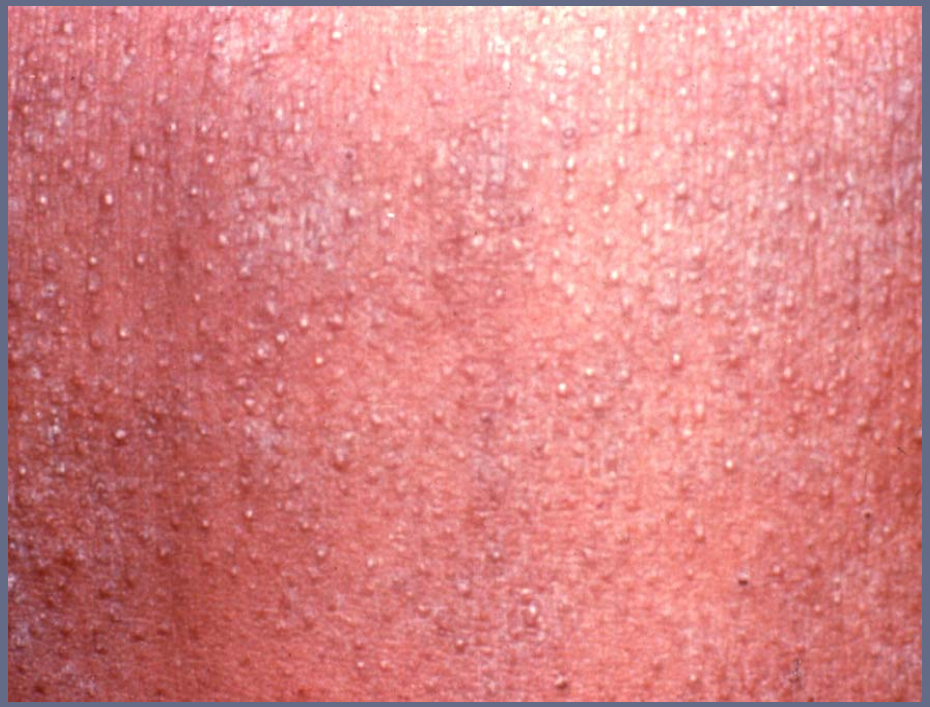
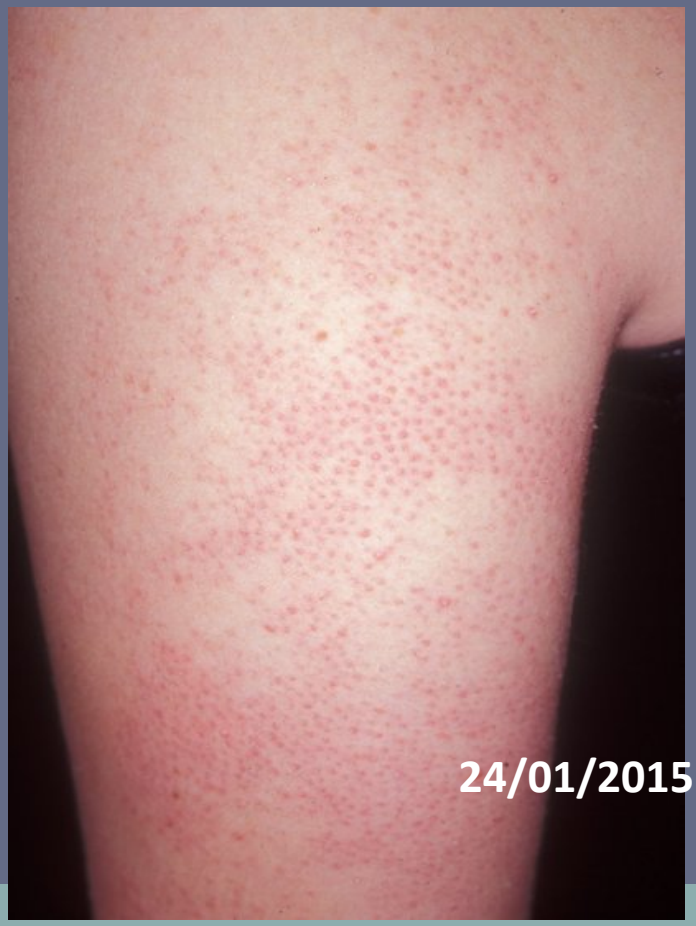
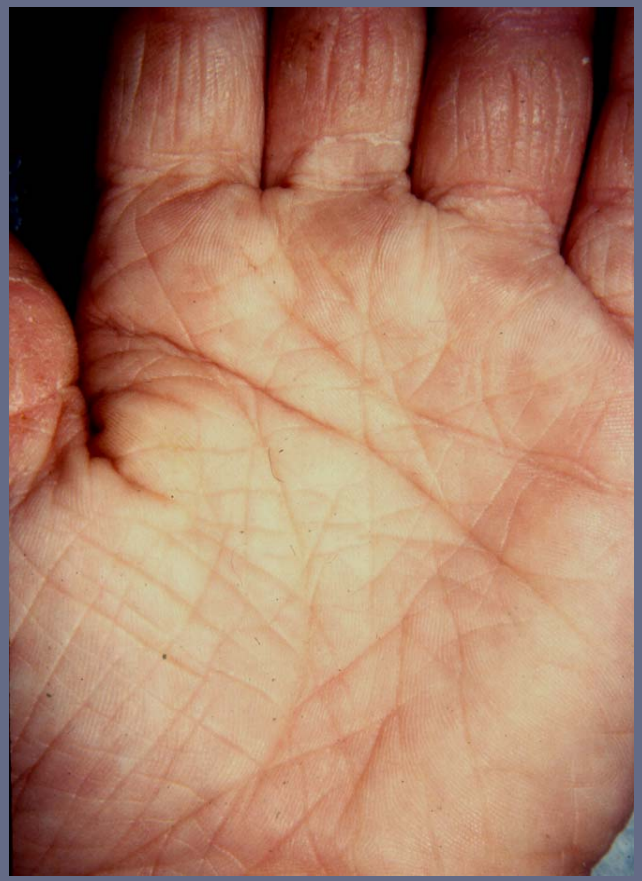
# Keratosis pilaris





# Palmar hyperlinearity



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# Pathogenesis

- 1. Defective Epidermal Barrier
- 2. Dysregulation of various types of immune responses
- 3. Genetic polymorphisms
- 4. Environmental Factors

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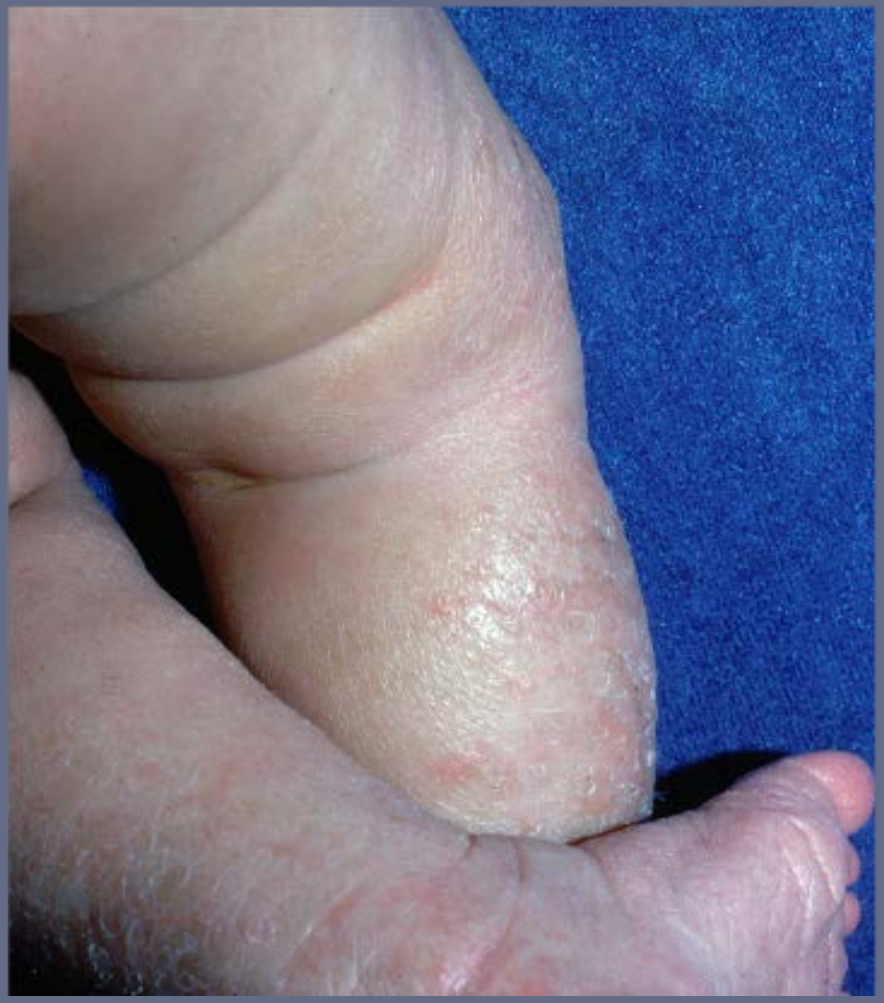
# Skin barrier dysfunction



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Child with atopic dermatitis

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# Pathogenesis

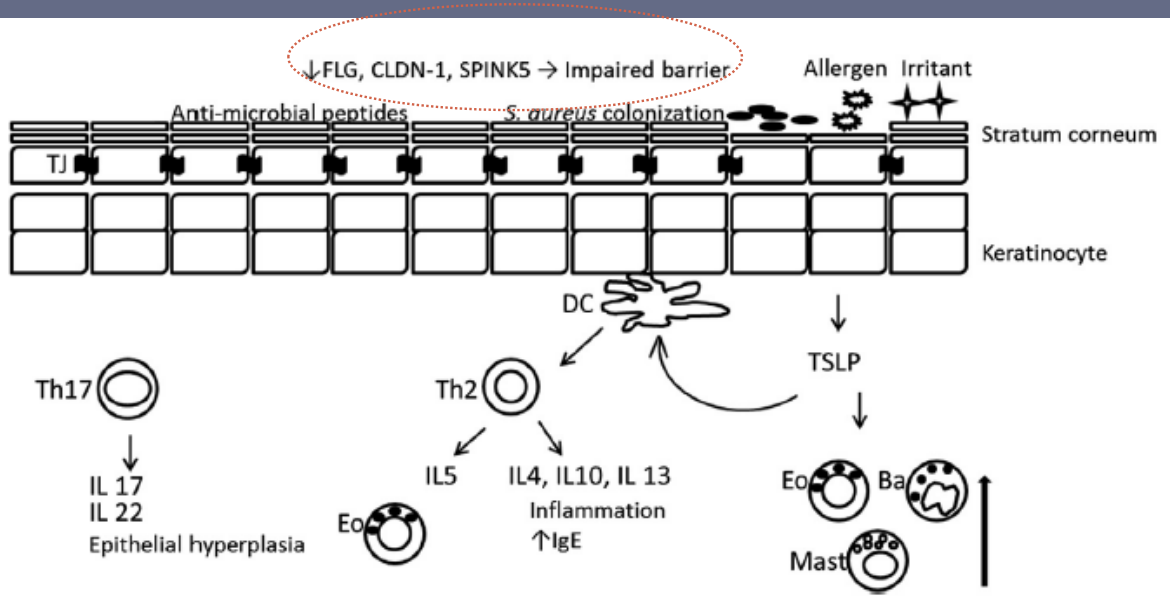


**Figure 1.** Defective epidermal barrier in the pathogenesis of atopic dermatitis. A decrease in FLG, CLDN-1, SPINK5, and other injuries lead to increased permeation of allergen and increased transepidermal water loss. Decreased antimicrobial peptides, such as β-defensins and cathelicidins, result in bacterial colonization. Activated DCs by TSLP from keratinocytes and by antigens stimulate proliferation of Th2 cells. Th2 cells secrete inflammatory cytokines that worsen the severity of atopic dermatitis. Ba, basophil; CLDN-1, claudin-1; DC, dendritic cell; Eo, eosinophil; FLG, filaggrin; IL, interleukin; Mast, mast cell; SPINK5: Kazal type 5 serine protease inhibitor; Th17, T-helper cell type 17; Th2, T-helper cell type 2; TJ, tight junction; TSLP, thymic stromal lymphopoietin.

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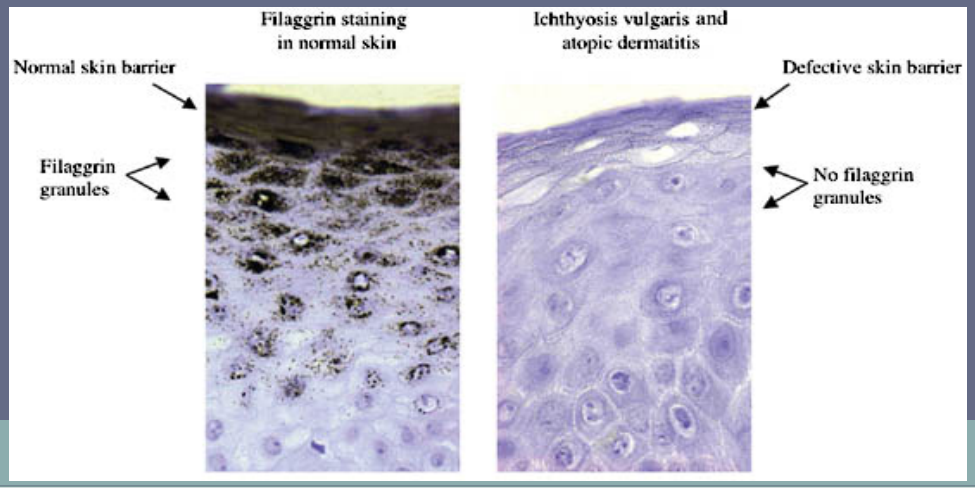
# Filaggrin

- **Filaggrins** are filament-associated proteins which bind to keratin fibers in epithelial cells
- Individuals with truncation mutations in the gene coding for filaggrin are strongly predisposed to a severe form of dry skin, ichthyosis vulgaris, and/or eczema
- It has been shown that almost 50% of all severe cases of eczema may have at least one mutated filaggrin gene.

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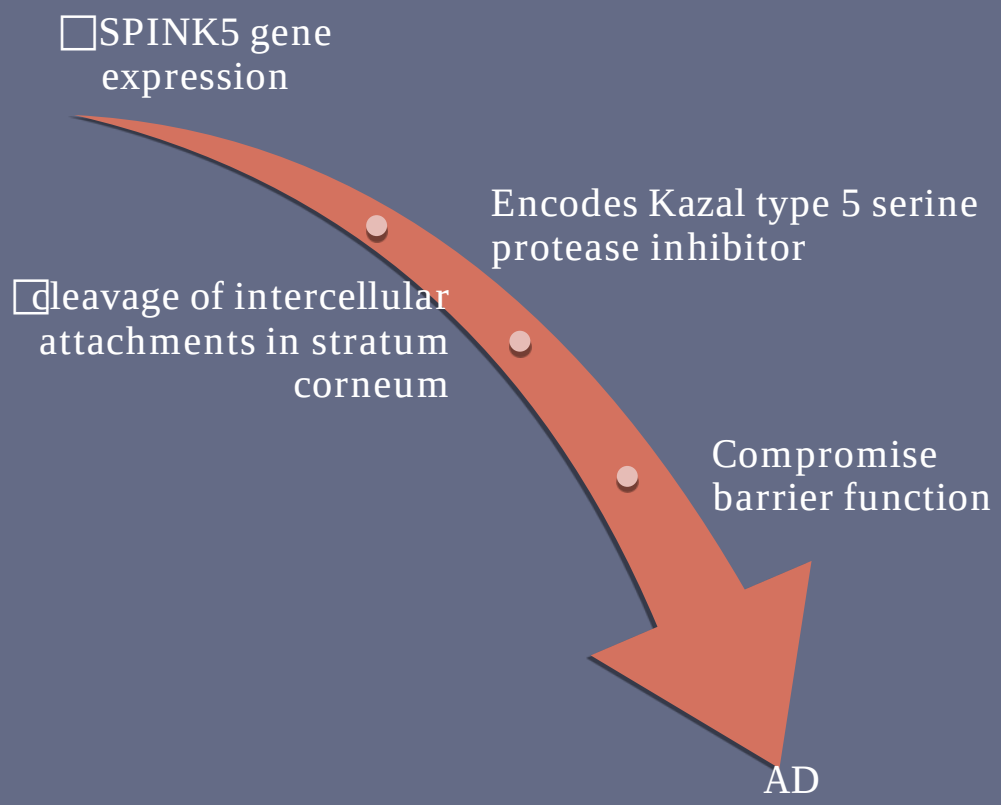
# Defective Epidermal Barrier

Mutations in the FLG gene, specially R501X and 2282del4

Natural moistering factors ( ceramides)

Transepidermal water loss and evaporation

# Defective Epidermal Barrier

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# Defective Epidermal Barrier

De Benedetto et al. expression of epidermal claudin-1
( transmembrane protein component of tight junctions)

Impairment in tight junctions

Skin Barrier Dysfunction

# Dysregulation of Cutaneous Immune Response

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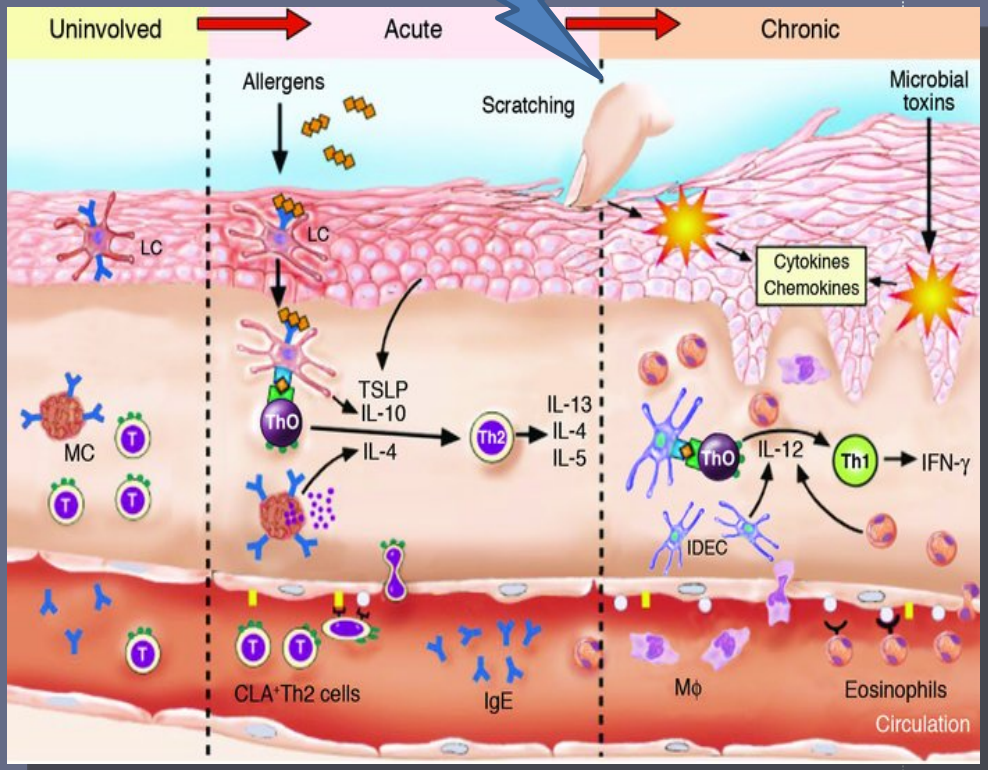


- Immunologic pathways in AD. Th2 cells circulating in the peripheral blood of AD express the skin homing receptor, CLA, and recipatients result in elevated serum IgE and eosinophils. These T cells rculate through unaffected AD skin where they can engage allergen-triggered $IgE^+$ LCs and mast cells (MCs) that contribute to Th2 cell development. Skin injury by environmental allergens, scratching, or microbial toxins activates keratinocytes to release proinflammatory cytokines and chemokines that induce the expression of adhesion molecules on vascular endothelium and facilitate the extravasation of inflammatory cells into the skin. Keratinocyte-derived thymic stromal lymphopoietin (TSLP) and DC-derived IL-10 also enhance Th2 cell differentiation. AD inflammation is associated with increased Th2 cells in acute skin lesions, but chronic AD results in the infiltration of inflammatory IDECs, macrophages (Mφ), and eosinophils. IL-12 production by these various cell types results in the switch to a Th1-type cytokine milieu associated with increased IFN-γ expression.

Figure modified with permission from The Journal of Allergy and Clinical Immunology (35).

# Genetic Polymorphism

- Genome screens have been performed to identify susceptibility loci for AD. One screen in families of German and Scandinavian children found a linkage for AD on chromosome 3q21 This region encodes the costimulatory molecules CD80 and CD86 and therefore may modulate T cell responses.
- A second screen reported linkage of AD to loci on chromosomes 1q21, 17q25, and 20p. Interestingly, these same regions are known to contain psoriasis susceptibility genes, which suggests common candidate genes involved in the control of skin inflammation. Although AD and psoriasis are distinct skin diseases, both conditions involve dry, scaly skin and disrupted epidermal differentiation.

Cookson, WO, Moffatt, MF. The genetics of atopic dermatitis. *Curr. Opin. Allergy Clin. Immunol.* 2002. **2:**383-387.

# Environmental Factors and Triggers

## Heat/sweating

Foods
( IgE-induced)

Irritants

-wool
-soaps/detergents
"Occupational"
Tobacco ....

## Aeroallergens

Hormones

Contactants

-nickel , dust ....

## Psychological(stress)

Climate

Microbial agents

-Staphylococcus aureus
-Viral infections
-Dermatophytes

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# Comorbidities

- Allergic comorbidities asthma ....
- Reduced risk of acute lymphoblastic leukemia, meningioma and gliomas
- ADHD ( Schmitt et al. 2009) correlation study healtcare database of 600000 individuals Germany)
- Impaired sleep and increased healthcare utilization ( Yaghamaie et al. 90000 children between the ages of 0-17 years) Link between eczema and depression, anxiety and autism)

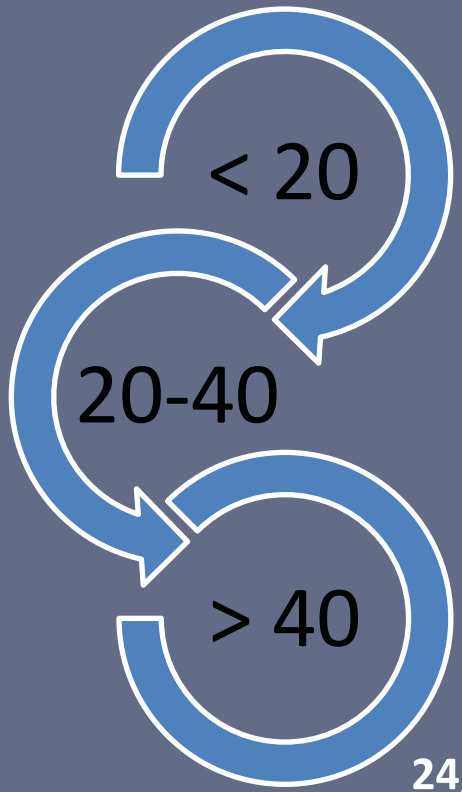
# Treatment ( SCORAD score)

# SCORAD score

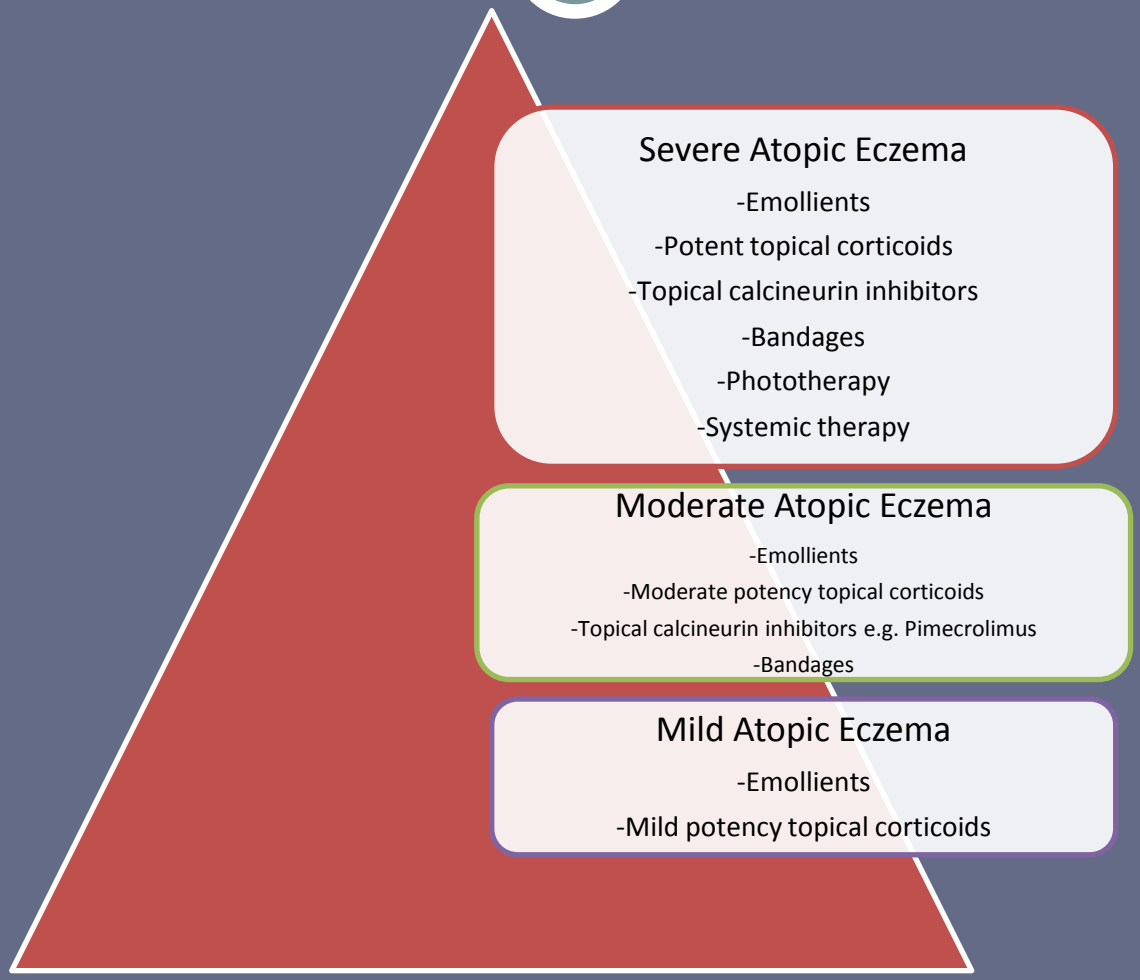
**3 major components**

- Percentage of affected surface area
- Intensity of eczema at lesions on a scale of 0 to 3
- Functional impact evaluated y a visual scale (0-10)

**A/5 + 7B/2 + C**



# Treatment

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# Treatment: Mild Atopic Eczema

## Moisturizers

- Immediately after bath
- Multiple times/daily ( 3x)
- Use creams
- Avoid lotions



## Weak topical cortisteroids

- Non-fluorinated ointments or creams (Hydrocortisone acetate 0.5,1.0 or 2.5%)


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# Treatment Moderate Atopic Eczema

**Emollients**

**Moderate Topical Corticoids**



**Topical calcineurin Topical Bandages**


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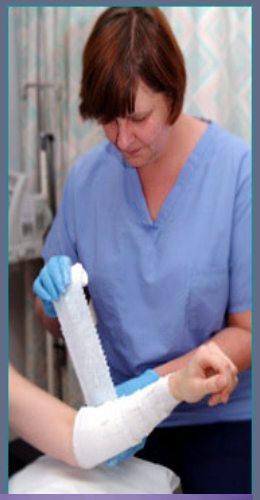
# Treatment Severe Atopic Eczema

Emollients
Potent topical corticoids
Topical calcineurin inhibitors

Phototherapy
Systemic therapy
Bandages



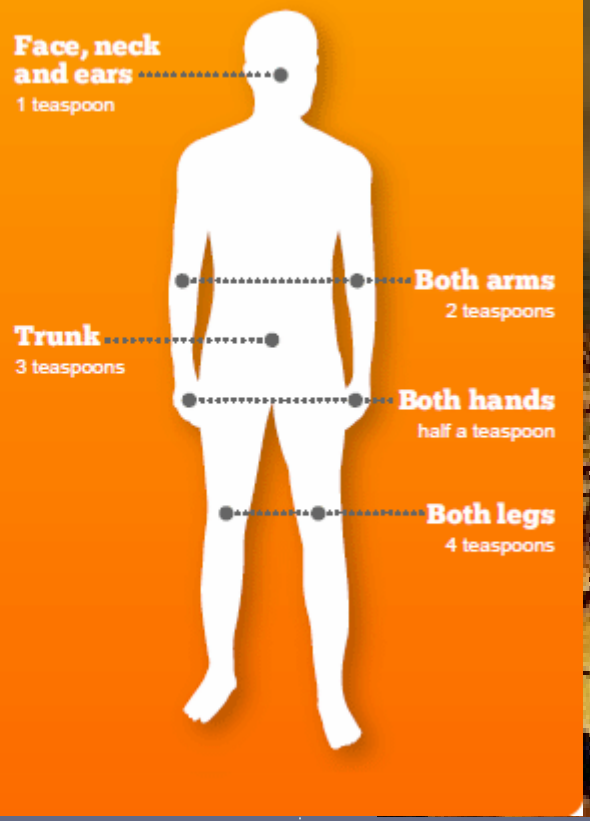


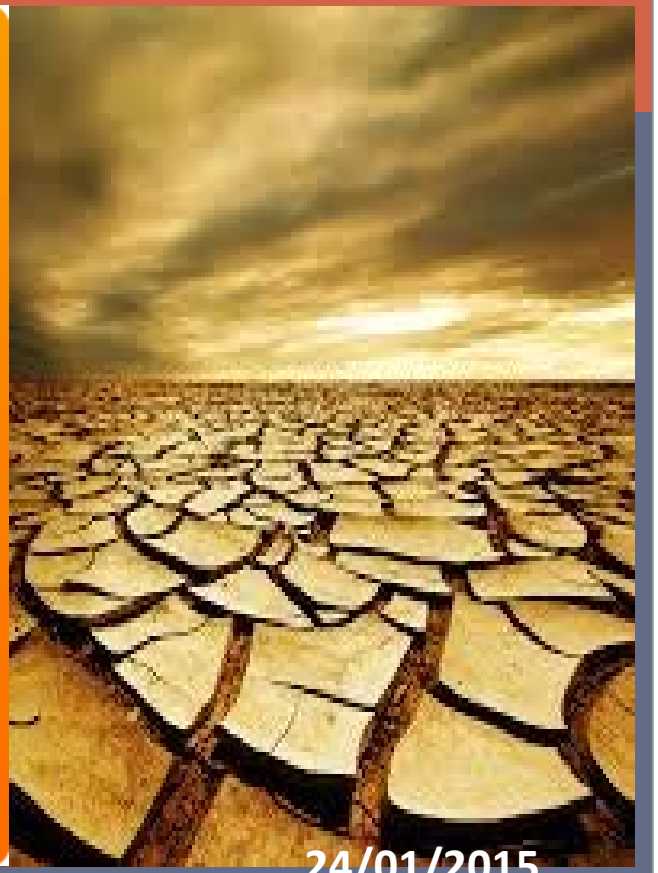



# Emollients

## How do I apply it?

- Gently smooth your emollient:
  - In the direction of hair growth
  - Like you would stroke a cat
- Avoid rubbing (this can make your skin even more itchy)
- Use the right amount of emollient for each part of your body (use the diagram opposite as a guide)
- Check you have used enough emollient:
  - If it completely disappears you have not applied enough
  - If your skin looks shiny, you've got it just right (but don't worry it normally absorbs in about 10 minutes so you won't be shiny all day!)
  - If it's still visible you may not have smoothed it in enough or you may have used too much



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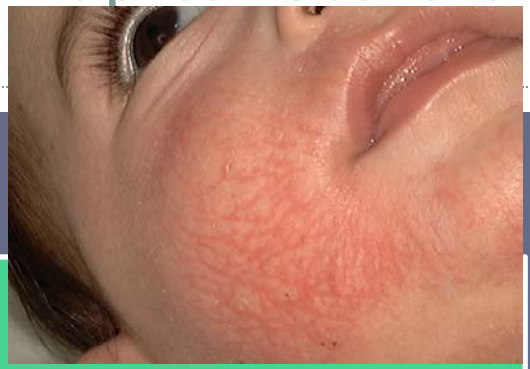
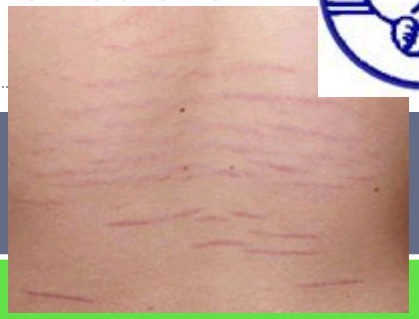
# Side Effects of Topical Steroid Medication

Skin Atrophy

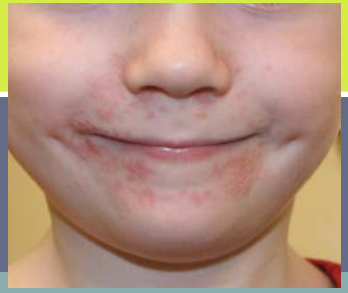


Telangiectasia



Striae

Perioral Dermatitis



Glaucoma

Cataract

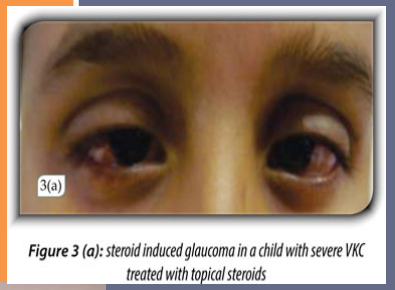



*Figure 3 (a): steroid induced glaucoma in a child with severe VKC treated with topical steroids*

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# Oral Corticosteroids

## Used short-term

- Increase in appetite
- Weight gain
- Insomnia
- Fluid retention
- Mood changes

## Used long-term

- Osteoporosis
- Hypertension
- Diabetes
- Weight gain
- Increased vulnerability to infection
- Cataracts and glaucoma
- Thinning of the skin
- Easy bruising
- Muscle weakness

# Calcineurin inhibitors

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## Advantages

- No skin atrophy
- For adults and children > 2 years
- Improvement within 1-3 weeks
- Long-term intermittent use

## Limitations

- Off-label for children <2 years
- Burning,stinging, itching (minimal and often transient, less side effects applicate cold)
- Black box warning

  2006 theoretical risk of malignancy such as lymphoma and skin malignancies

# Systemic Immunosuppressive Therapy

- 1. Corticosteroids : effective in controlling symptoms of a severe flare – side effects – rebound
- 2. Cyclosporine A : rapid onset of action – dose: 2.5-5 mg/kg/day – 50% rapid relapse
- 3. Methotrexate : major advantage used for many years in chronic cases ( psoriasis children: 0.2-0.7 mg/kg/week) Slow onset of action
- 4. Azathioprine : severe AD ; normal TPMT levels : 2.5 mg/kg/day and reduced TPMT activity: 1 mg/kg/day
- 5. Mycophenolate : severe AD – children ????

# Biologics

- 1. Interferon- □
- 2. Anti-CD20 ( Rituximab®)
- 3. Anti-IL-5
- 4. Anti-IgE
- 5. Anti-IL-4 Receptor
- 6. IVIG : severe, treatment refractory AD

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# Others

- 1. Dietary Factors
- 2. Probiotics
- 3. □. - Linolenic Acid
- 4. 25-OH-vitamin D
- 5. Psychosomatic Approaches
- 6. Therapeutic Patient Education and Eczema Schools

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# Pruritus

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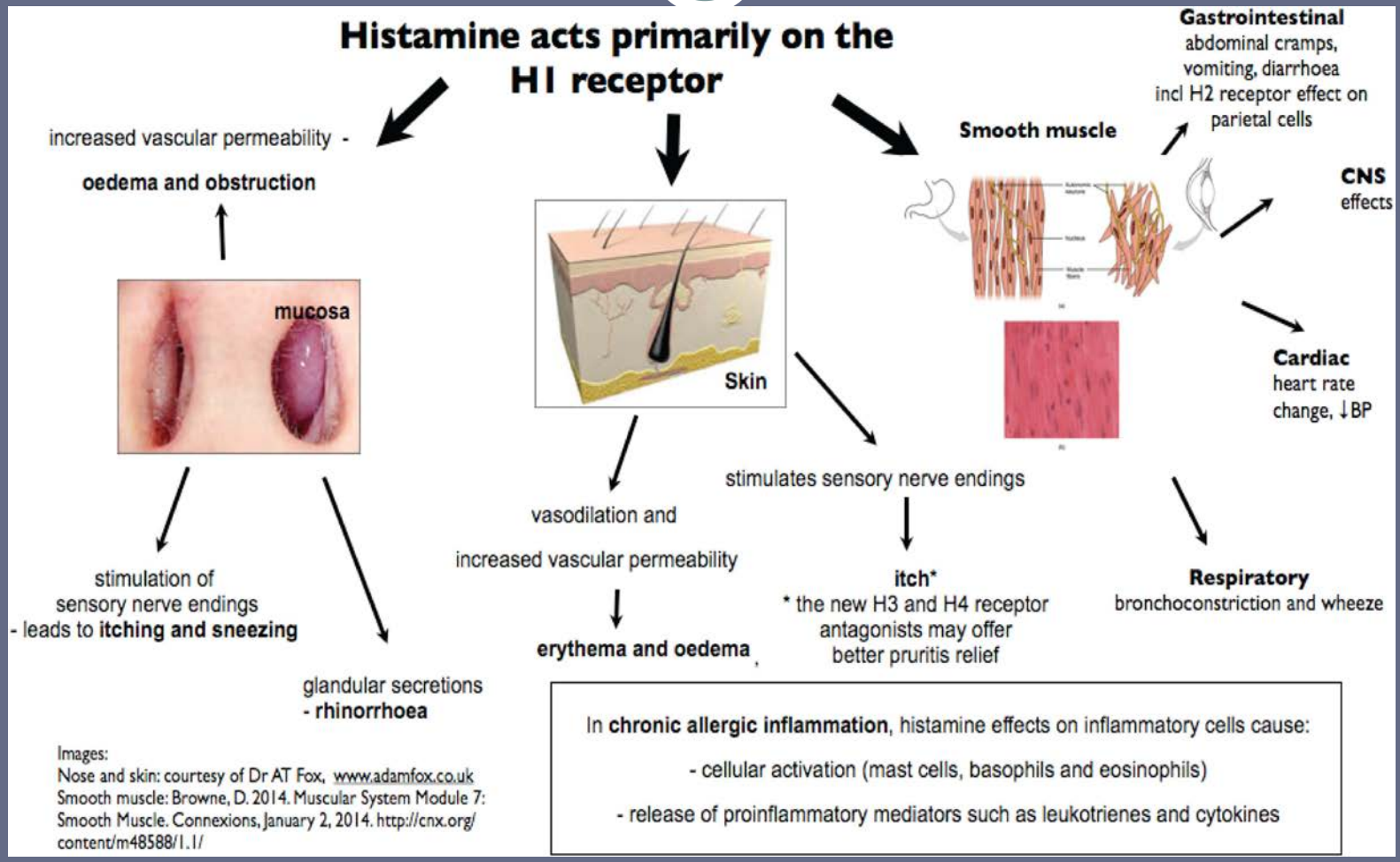
# Antihistaminica



# Dosage of Antihistamines

Table 1 Summary of the more commonly used H(1)-antihistamines licensed for use in children

| | | | | | |
|---|---|---|---|---|---|
| First-generation H(1)-antihistamines | The most common adverse effect of the first-generation H(1)-antihistamines is central nervous system depression, with effects varying from slight drowsiness to deep sleep. Paradoxical stimulation may occasionally occur, especially at high doses. These sedative effects, when they occur, may diminish after a few days of treatment.<br>Other first-generation H(1)-antihistamine side effects include headache, psychomotor impairment and anti-muscarinic effects, such as dry mouth, thickened respiratory-tract secretions, blurred vision, urinary difficulty or retention, constipation and increased gastro-oesophageal reflux.<br>Other rare side effects of first-generation H(1)-antihistamines include hypotension, palpitation, arrhythmias, extrapyramidal effects, dizziness, confusion, depression, sleep disturbances, tremour, convulsions, hypersensitivity reactions (including bronchospasm, angio-oedema, anaphylaxis, rashes, and photosensitivity reactions), blood disorders and liver dysfunction. | | | | |
| | **Proprietary forms** | **Availability** | **Licensed indication** | **Licensing age** | **Children's dose[1] (oral doses)** |
| Chlorphenamine (Chlorpheniramine) | Non-proprietary<br>Piriton<br>Allerief | P<br>GSL | Symptomatic relief of allergy such as hay fever, urticaria, food allergy, drug reactions, relief of itch associated with chickenpox | Liquid<br>1–18 years<br>Tabs<br>6–18 years | 1 month–2 years 1 mg twice daily<br>2–6 years 1 mg every 4–6 h, max. 6 mg daily<br>6–12 years 2 mg every 4–6 h, max. 12 mg daily<br>12–18 years 4 mg every 4–6 h, max. 24 mg daily |
| Hydroxyzine | Atarax<br>Ucerax | POM | Pruritus | 1–18 years | 6 months–6 years initially 5–15 mg at night, increased if necessary to 50 mg daily in 3–4 divided doses<br>6–12 years initially 15–25 mg at night, increased if necessary to 50–100 mg daily in 3–4 divided doses<br>12–18 years initially 25 mg at night, increased if necessary to 100 mg in 3–4 divided doses |
| Ketotifen | Zaditen<br>eye drops—Zaditen | POM<br>POM | Symptomatic relief of allergy, such as allergic rhinitis (AR)<br>eye drops—seasonal allergic conjunctivitis | 3–18 years<br>3–18 years | 3–18 years 1 mg twice daily<br>3–18 years apply twice daily |
| Promethazine hydrochloride | Non-proprietary<br>Phenergan | POM | Symptomatic relief of allergy, such as hay fever, insomnia associated with urticaria and pruritus | 2–18 years | 2–5 years 5 mg twice daily or 5–15 mg at night<br>5–10 years 5–10 mg twice daily or 10–25 mg at night<br>10–18 years 10–20 mg 2–3 times daily or 25 mg at night increased to 25 mg twice daily if necessary |
| Second-generation H(1)-antihistamines | Generally, the second-generation H(1)-antihistamines have little or no side effect of drowsiness or antimuscarinic effect. | | | | |
| Cetirizine | Non-proprietary<br>Piriteze<br>Benadryl for children | GSL<br>P<br>POM | Hay fever, chronic idiopathic urticaria, atopic eczema | 2–18 years | 1–2 years 250 µg/kg twice daily<br>2–6 years 2.5 mg twice daily<br>6–12 years 5 mg twice daily<br>12–18 years 10 mg once daily |
| Loratadine | Non-proprietary<br>Loratadine<br>Allereze, Clarityn | GSL<br>P<br>POM | Symptomatic relief of allergy, such as hay fever, chronic idiopathic urticaria | 2–18 years | 2–12 years<br>under 30 kg 5 mg once daily<br>over 30 kg 10 mg once daily<br>12–18 years 10 mg once daily |
| Fexofenadine | Non-proprietary<br>Telfast | POM | Symptomatic relief of seasonal AR<br>symptomatic relief of chronic idiopathic urticaria | 6–18 years | 6–12 years 30 mg twice daily<br>12–18 years 120 mg once daily<br>12–18 years 180 mg once daily |

Continued

# Dosage of Antihistamines

Table 1 Continued

| | Proprietary forms | Availability | Licensed indication | Licensing age | Children's dose[1] (oral doses) |
|---|---|---|---|---|---|
| Levocetirizine | Xyzal | POM | Symptomatic relief of allergy, such as hay fever, urticaria | Liquid<br>2–18 years<br>Tablets<br>6–18 years | 2–6 years 1.25 mg twice daily<br>6–18 years 5 mg once daily |
| Desloratadine | Desloratadine (non-proprietary).<br>Neoclarityn | POM | Hay-fever, chronic idiopathic urticaria | 1–18 years | 1–6 years 1.25 mg once daily<br>6–12 years 2.5 mg once daily<br>12–18 years 5 mg once daily |
| Olopatadine | Opatanol | POM | Seasonal allergic conjunctivitis | 3–18 years | Child 3–18 years apply twice daily; max. duration of treatment 4 months |
| Acrivastine | Non-proprietary<br>Acrivastine.<br>Benadryl allergy relief | GSL<br>P<br>POM | Hay fever, chronic idiopathic urticaria | 12–18 years | 8 mg three times a day |
| Azelastine | Optilast<br>Rhinolast<br>Dymista—with fluticasone | POM<br>POM<br>POM | Allergic conjunctivitis, seasonal allergic conjunctivitis<br>Perennial conjunctivitisSeasonal and perennial AR<br>Moderate to severe seasonal and perennial AR, if monotherapy with antihistamine or corticosteroid is inadequate | 4–18 years<br>5–18 years<br>12–18 years | Child 4–18 years apply twice daily, increased if necessary to 4 times daily<br>Child 12–18 years apply twice daily, increased if necessary to 4 times daily; max. duration of treatment 6 weeks<br>1 spray into each nostril twice daily<br>Child 12–18 years 1 spray into each nostril twice daily |

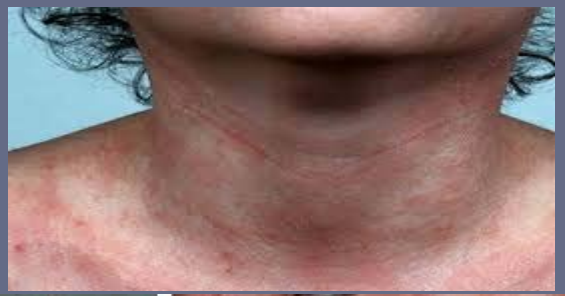
Availability based on UK licensing includes whether on prescription (POM), or over the counter medicines: including pharmacist only (P) and general sales list medicines (GSL), which varies depending on license, pack size and brands. The licensed age range also varies from brand to brand. The usual dosing for various age ranges is described at the time of publication. The Table comprises information from summary of product characteristics for each H(1)-antihistamine and other source references.[10 48 49]

24/01/2015

# Complications of AD

COMPLICATIONS

- Cutaneous Infections: reduced immunity + reduced barrier function of the skin
- Atopic cataract
- Growth retardation ( 10 %)



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Clinical reviews in allergy and immunology

Series editors: Donald Y. M. Leung, MD, PhD, and Dennis K. Ledford, MD

# Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment

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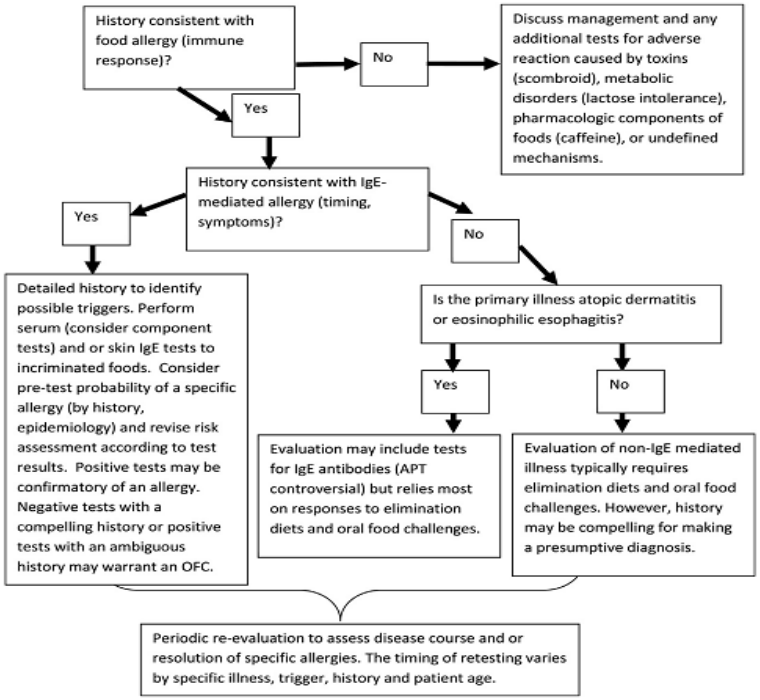


**FIG 1.** General approach to diagnosis of adverse reactions to foods. See text and Tables 1 and E1 for details.

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**TABLE I.** Pearls and pitfalls regarding diagnosis of food allergy[1,2,94,100,102-112]

| Pearl/observation | Additional details | Clinical application |
|---|---|---|
| A positive skin test or serum food-specific IgE test result indicates sensitization but not necessarily clinical allergy. | Screening with indiscriminate panels of tests is poorly informative.<br>Screening tests with common allergens that have not been ingested and tolerated but pose increased risk can be considered (eg, tree nuts for a child who reacted to peanut but has not ingested nuts). | History and epidemiologic considerations should guide test selection.<br>• Tolerated foods generally need not be tested.<br>• Differential diagnosis should include alternative allergen triggers (environmental aeroallergens) and nonallergic diseases (eg, intolerance). |
| Dose, manner of preparation, and ancillary (eliciting) factors might alter reaction outcomes. | • Alcohol, NSAIDs, and exercise are among eliciting factors that might facilitate a reaction.<br>• Heating might alter allergenicity (eg, bakery products with egg/milk might be tolerated when whole forms are not and cooked fruits might be tolerated when raw fruits are not).<br>• A low dose might be tolerated while larger amounts are not. | • History should focus on amounts triggering a reaction and ancillary factors.<br>• History should explore the types of foods tolerated or not tolerated. |
| IgE binding to homologous proteins among food groups and between foods and pollens might have variable clinical relevance. | Rates of clinical cross-reactivity:<br>Allergy to: / Related food / Approximate clinical reaction rate<br>Peanut / Most legumes / 5%<br>A tree nut / Other tree nut / 35%<br>Higher for: walnut-pecan, almond-hazel, cashew-pistachio<br>A fish / Other fish / 50%<br>Shellfish / Another shellfish / 75%<br>Grain / Another grain / 20%<br>Milk / Goat/sheep milk / >90%<br>Mare milk / 5%<br>Beef / 10% | • Care should be taken in not "overtesting."<br>• For some categories, food avoidance of entire group might be prudent, especially to avoid cross-contact in preparation, but individualization might be possible. |
| Tests for serum food-specific IgE might not provide comparable results among manufacturers. | In the United States, there are 3 major test manufacturers. | Care must be taken in evaluating test results over time when different manufacturers are used. |
| Component testing might differentiate clinical reactivity (IgE binding to "potent" stable allergens) from less clinically relevant sensitization (binding to labile proteins). | Food / Labile / Stable<br>Peanut / Ara h 8 / Ara h 1, Ara h 2, Ara h 3, Ara h 6<br>Hazelnut / Cor a 1, Cor a 2 / Cor a 9, Cor a 11, Cor a 14<br>Soy / Gly m 3, Gly m 4 / Gly m 5, Gly m 6 | Concentration of IgE binding to components also relates to outcomes, but similar to standard tests, correlations have not been established and vary by, for example, center and patient selection.<br>Caution: severe reactions can occur despite lack of noted binding to measured allergen (see text). |
| Serum/skin test results might be negative despite clinical reactivity. | • This could be due to reagent lacking relevant protein.<br>• This could be because the reaction is not IgE mediated. | • Do not discount a convincing history because of a negative test result.<br>• Consider testing with fresh food (prick-prick test); these can be stored frozen.<br>• Be cognizant of non–IgE-mediated allergic reactions. |
| Increasingly high serum food-specific IgE levels or increasingly larger skin test wheal size indicate higher chances of clinical allergy. | • Correlation of tests with outcomes vary by center, age, and disease (equivalent results are generally more predictive of allergy in a younger patient).<br>• Results are not highly correlated with severity. | • Test results should not be viewed solely as positive/negative.<br>• Results can be followed over time to monitor allergy persistence/resolution.<br>• Specific correlative values might not be applicable over all patient groups. |

*(Continued)*

**TABLE I.** *(Continued)*

| Pearl/observation | Additional details | | | | Clinical application |
|---|---|---|---|---|---|
| At specific high levels of IgE or large skin tests, clinical reactivity is highly likely; however, studies are limited, and variations in "diagnostic cutoff" values are reported. | Food | Mean age, 5 y; 50% react* | Mean age, 5 y; ~95% react | Age <2 y; ~95% react | • OFCs can be deferred, particularly if there is a clinical history.<br>• When evaluating individual studies, predictive values might not apply to populations with different demographic and referral patterns. |
| | Egg | 2 | 7 | 2 | |
| | Milk | 2 | 15 | 5 | |
| | Peanut | 2/5 | 14 | | |

Revised from Sicherer and Sampson.[1]

*NSAIDs*, Nonsteroidal anti-inflammatory drugs.

*Values are $kU_A/L$, the dual notation for peanut indictes with/without a clinical history.

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# Key Points

- The increased prevalence of AD has translated into more euros spent for the care and treatment of patients suffering from the disease.
- New links between AD and both allergic and nonallergic comorbidities
- Mutations in the FLG gene has placed an emphasis on barrier dysfunction in the development of AD
- Preventive, rather than curative management of AD is an important strategy to prevent flares
- The core treatment for moderate-severe AD are still topical corticosteroids and topical calcineurin inhibitors.

**24/01/2015**