Atopic dermatitis

- strongly pruritic chronic or chronically relapsing non-infectious dermatitis with variable morphology and clinical course, usually starting during early childhood

- often associated with positive personal or family history of allergic rhinitis, conjunctivitis and bronchial asthma.
- genetic predisposition
- In about 80% associated with ↑ IgE levels

Atopic dermatitis - epidemiology

Incidence in population: 0,5 - 5%

(higher incidence – scandinavian countries)

infants	**20-30%**
children under 2 y	**15-20%**
children under 14 y	**15%**
adults	**2-10%**

Atopic dermatitis usually starts early in life

Infancy[1]

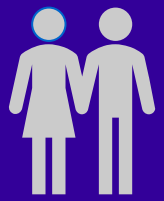
Onset usually between 3 and 6 months, 60% in the first year of life

Early onset form

Childhood[2,3]

85% of childhood onset occurs before 5 years of age

70% of childhood AD does not persist by 8 years of age



Adolescence[3-5]

Risk factors for persistence: later onset, gender (female), severity, atopic comorbidities, family history of atopy

Sometimes AD occurs in adulthood

Late onset form

AD=atopic dermatitis

1. Eichenfeld LF, et al. J Am Acad Dermatol 2014;70(2):338-51; 2. Silverberg NB, Durán-McKinster C. Dermatol Clin 2017;35:351-63; 3. Kim JP, et al. J Am Acad Derm 2016;75:681-87 e11; 4. Wen HJ, et al. Br J Dermatol 2009;161(5):1166-72; 5. Mortz CG, et al. Allergy 2015;70(7):836-45

Atopic dermatitis

two forms, same clinical picture

extrinsic 80% — **elevated IgE**

sensitization to airborne and/or food allergens (sIgE)

- association with allergic rhinoconjunctivitis and/or allergic asthma

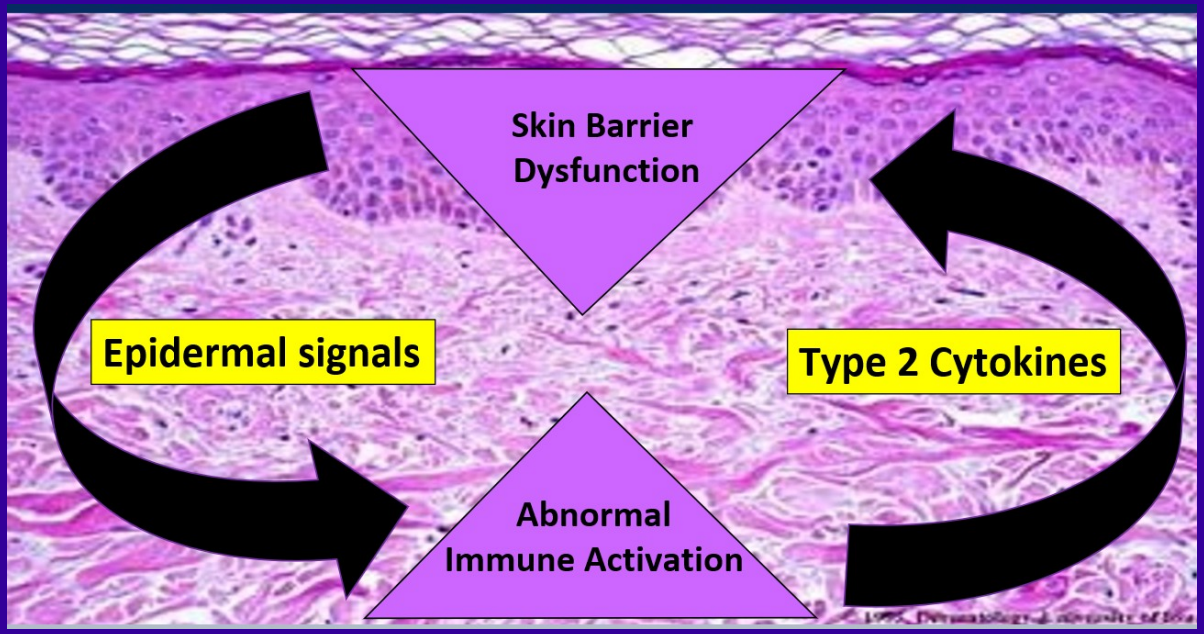
intrinsic 20% — **normal levels of IgE**

skin barrier disturbace

Etiopathogenesis of AD:

genetic predisposition

1) skin barrier dysfunction
2) abnormal immune activation



environmental triggers:

1) irritant substances, allergens
2) stress
3) many others ….

I. skin barrier dysfunction

Genetically conditioned:

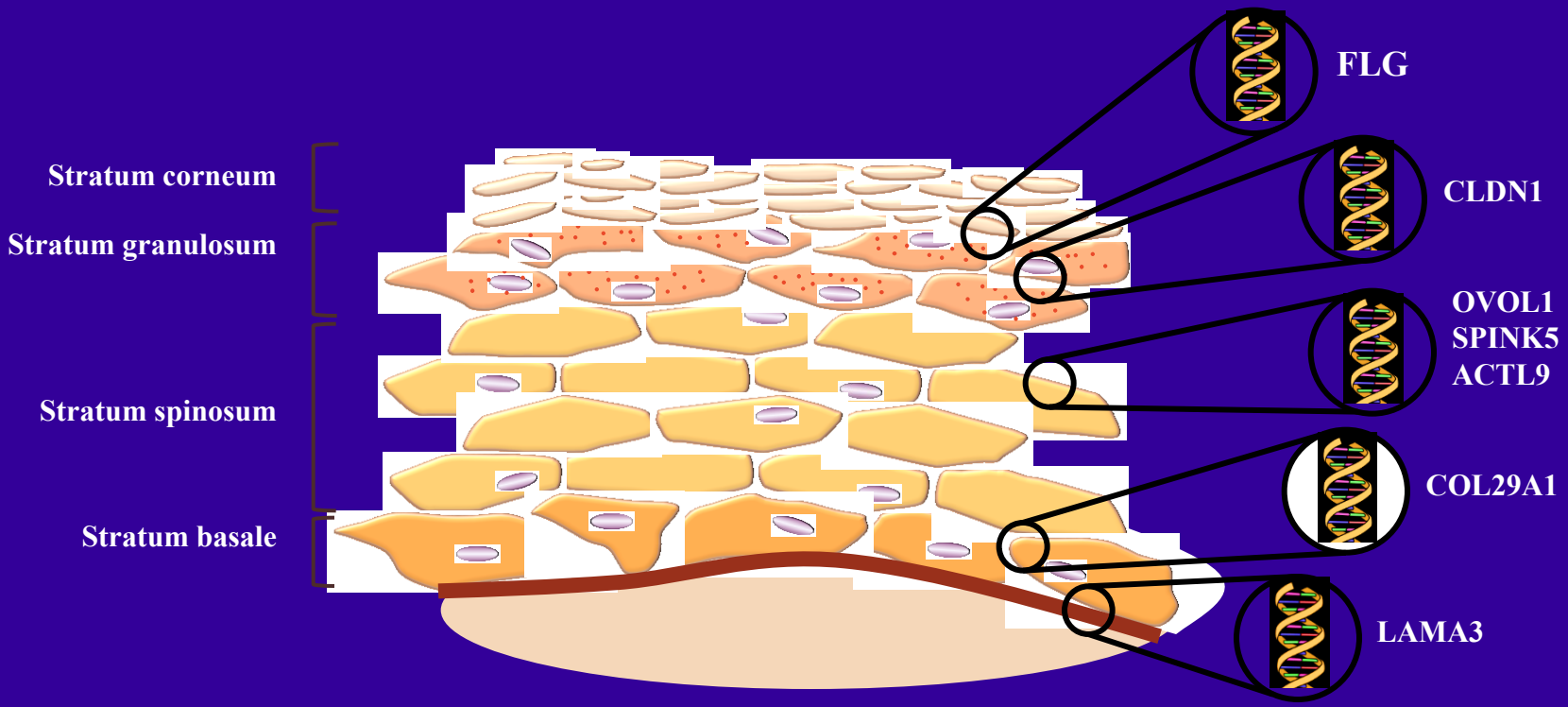
Filaggrin: null mutation of FLG R501X and 2282del4 alleles lead to increased permeability of skin barrier and they are

associated with AD (in about 50% cases), as well as with ichtyosis vulgaris

Claudin - 1, corneodesmosin, loricrin, involucrin

Increased activity of serin proteases

Mutation of key genes for structural epidermal proteins

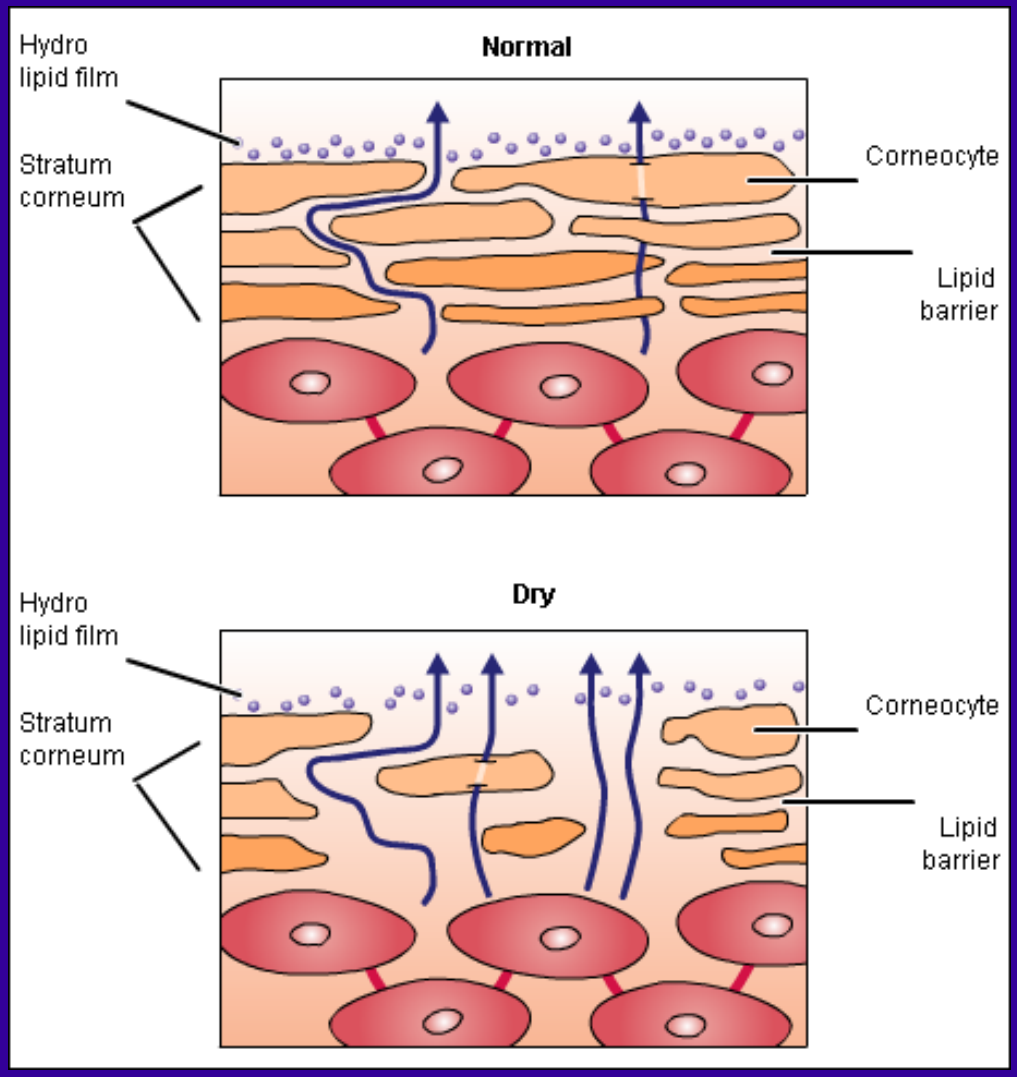


1. Hoffjan S & Stemmler S. *Arch Dermatol Res* 2015;307(8):659-70; 2. Esaki H et al. *J Allergy Clin Immunol* 2015;135(1):153-63; 3. Stemmler S et al. *BMC Dermatol* 2014;14:17; 4. Söderhäll C et al. *PLoS Biol* 2007;5(9):e242; 5. Yang T et al. *Genes Dev* 2004;18(19):2354-8; Lee B et al. *Dev Cell* 2014;29(1):47-58

skin barrier disturbance

- defective synthesis of ceramides

(in lamellar bodies in granular layer of epidermis)



decreased ability to bind water in the skin

AD and skin barrier

Defective structure and function of skin barrier

↓

insufficient hydration (TEWL ↑)

↓

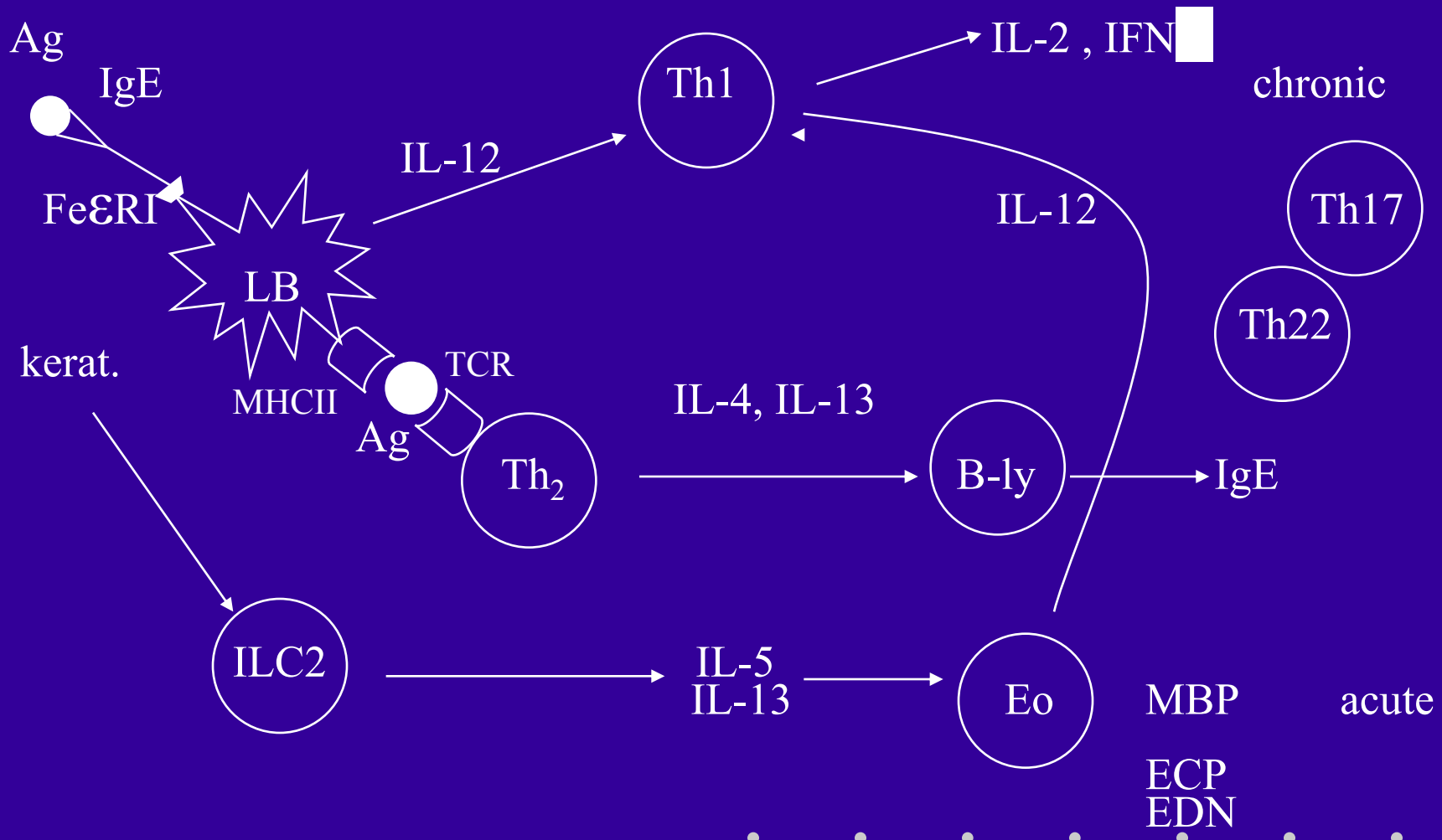
dryness - xerosis

↓

increased irritability of the skin

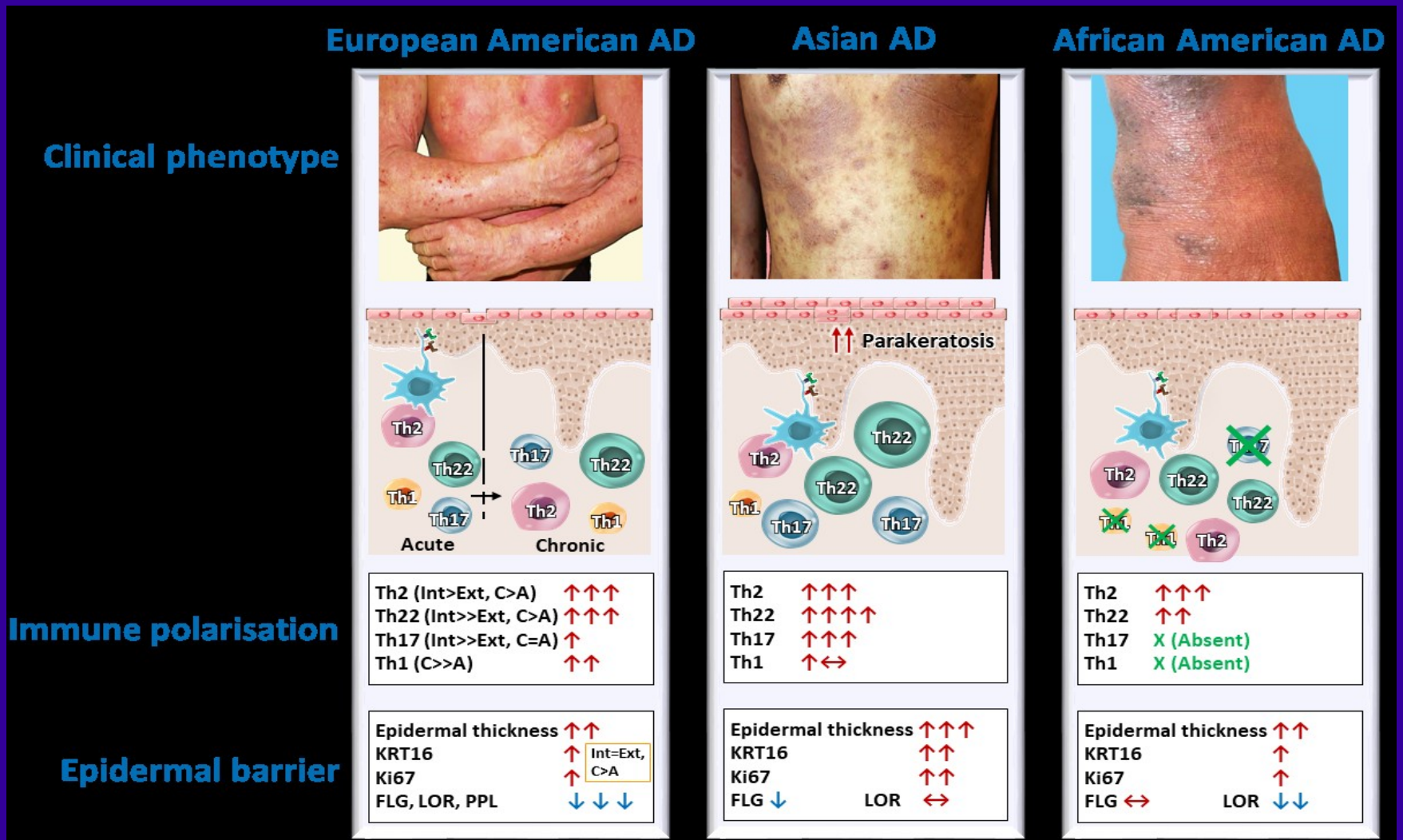
possibility of contact sensitization

II. Immune dysregulation



Phenotypes of AD

according to the activiation of Th cell populations



III. Staphyloccus aureus and AD

- colonization of AD lesions in 74 - 96% atopic patients, 30 - 56% even on „healthy“ skin

Mechanisms:

- Defective skin barrier with „naked“ laminin and fibronectin enables SA binding the skin

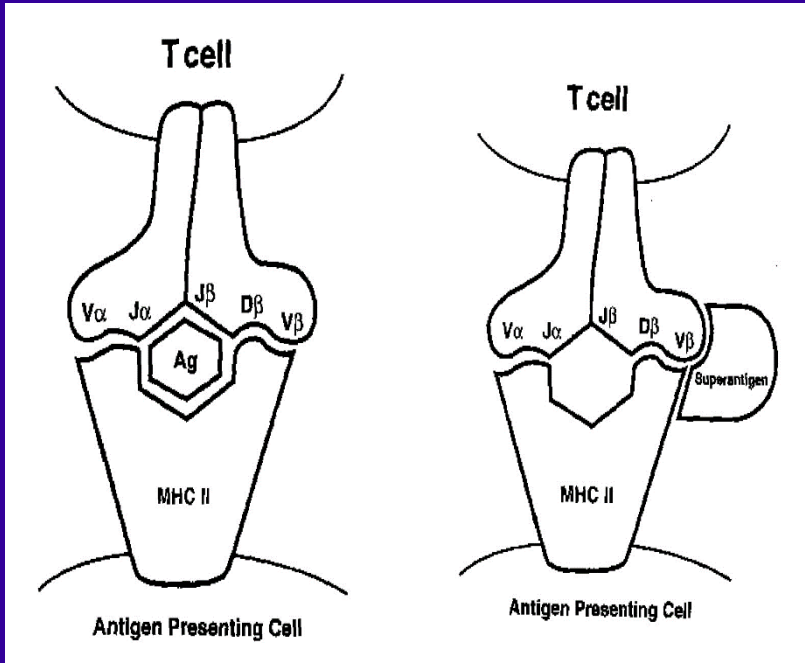
- Decreased defensive mechanisms: defective signallization via TLR 2

[redacted] defensine a kathelicidine

[redacted]roduction of IFN [redacted]

Staphyloccus aureus and AD

1) Toxic effect: staphylococcal exfoliatine
2) Stimulation of sIgE production (sIgE → stimulation of basophils → histamine)
3) superantigens: SEA- SEE a TSST-1



- without previous processing by LC
- able to bridge V chain of TC Receptor,
- not necessary exact conformity of all 5 subunits of the receptor

  1000x stimulation
- non-specific but huge stimulation of Tly

  (1 SA even 20% of circulating lymph.)

Triggering and mainaining factors of AD

Allergy (house dust mites, pollen, pets, molds, foods – milk, eggs, wheat, soya, nutts, fish)

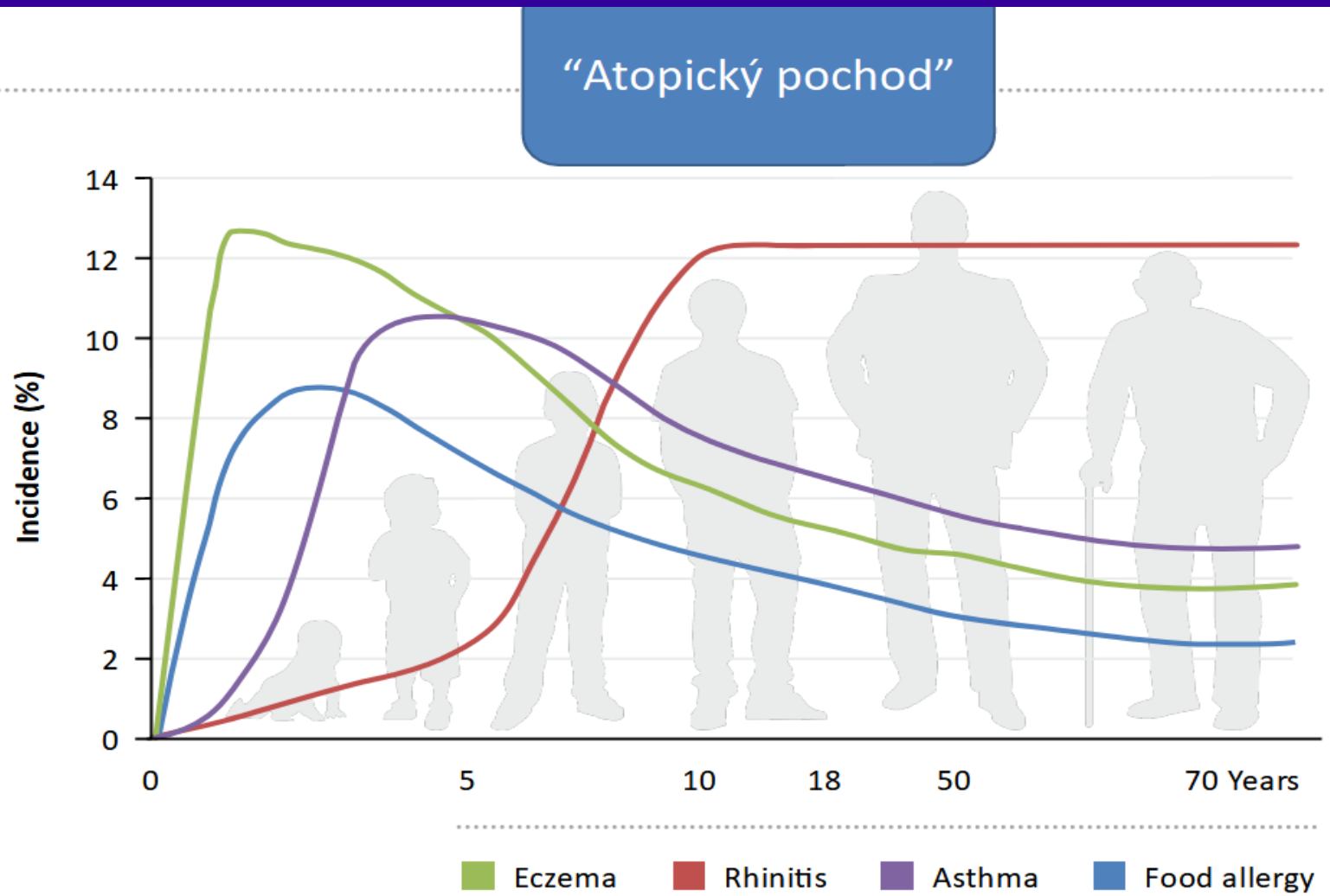
Microbes – Staphylococcus aureus

Irritant substances (water,detergents etc.)

- climatic (temperature, wind, low humidity ..)

Psychological stress

Atopic march



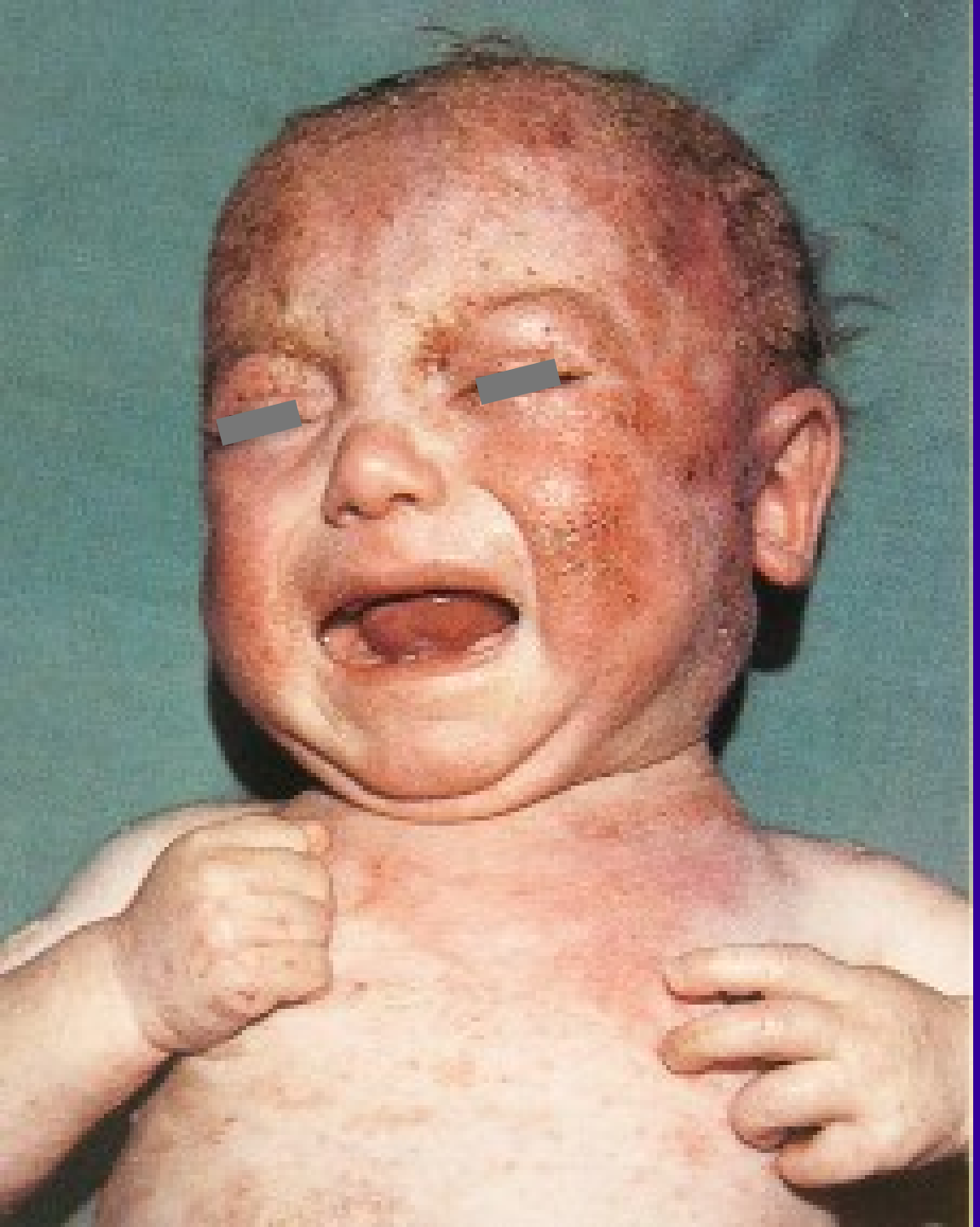
Clinical picture of AD

AD in infants

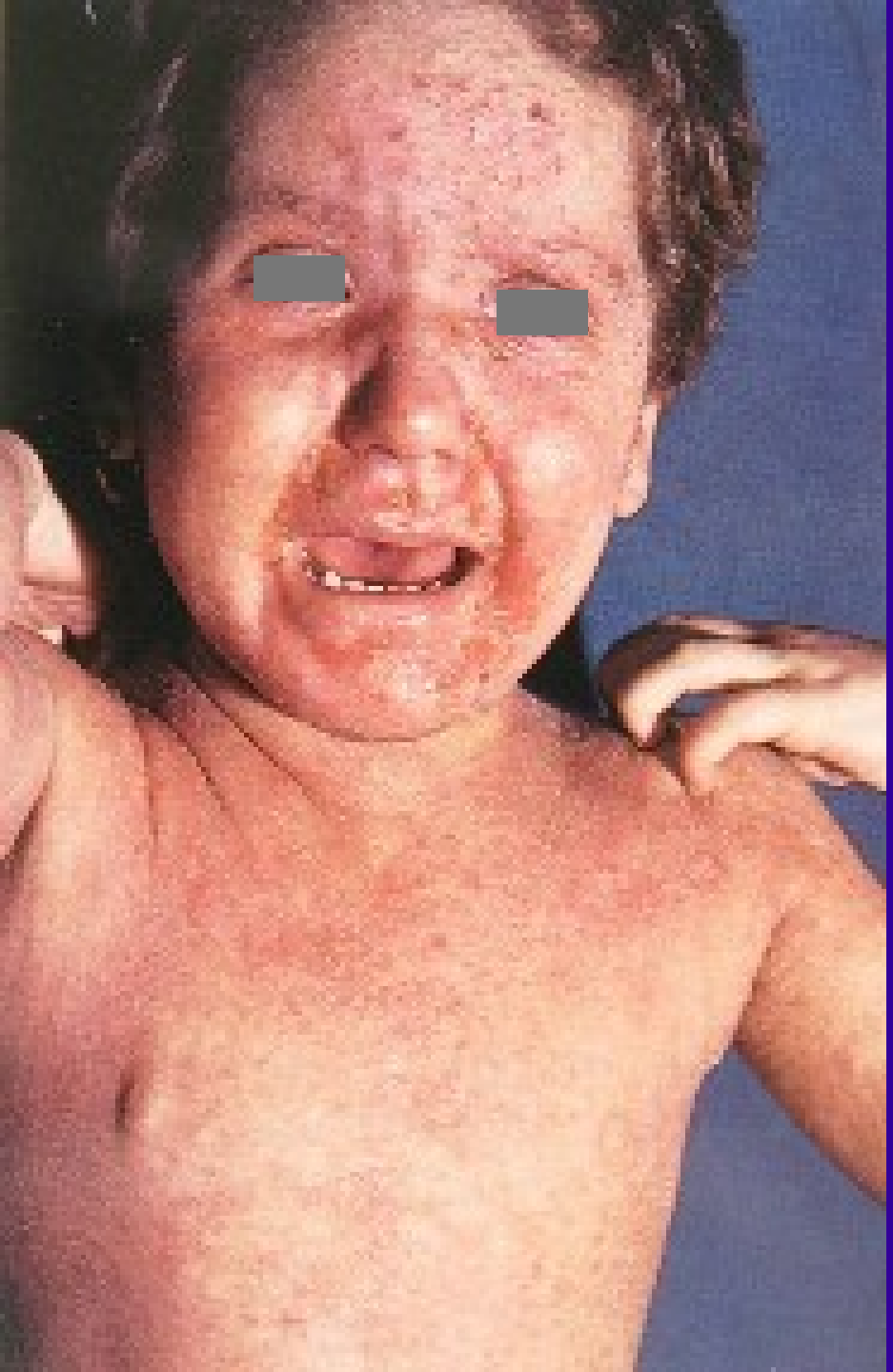
Exudative form – acute eczema (oozing, crusting)

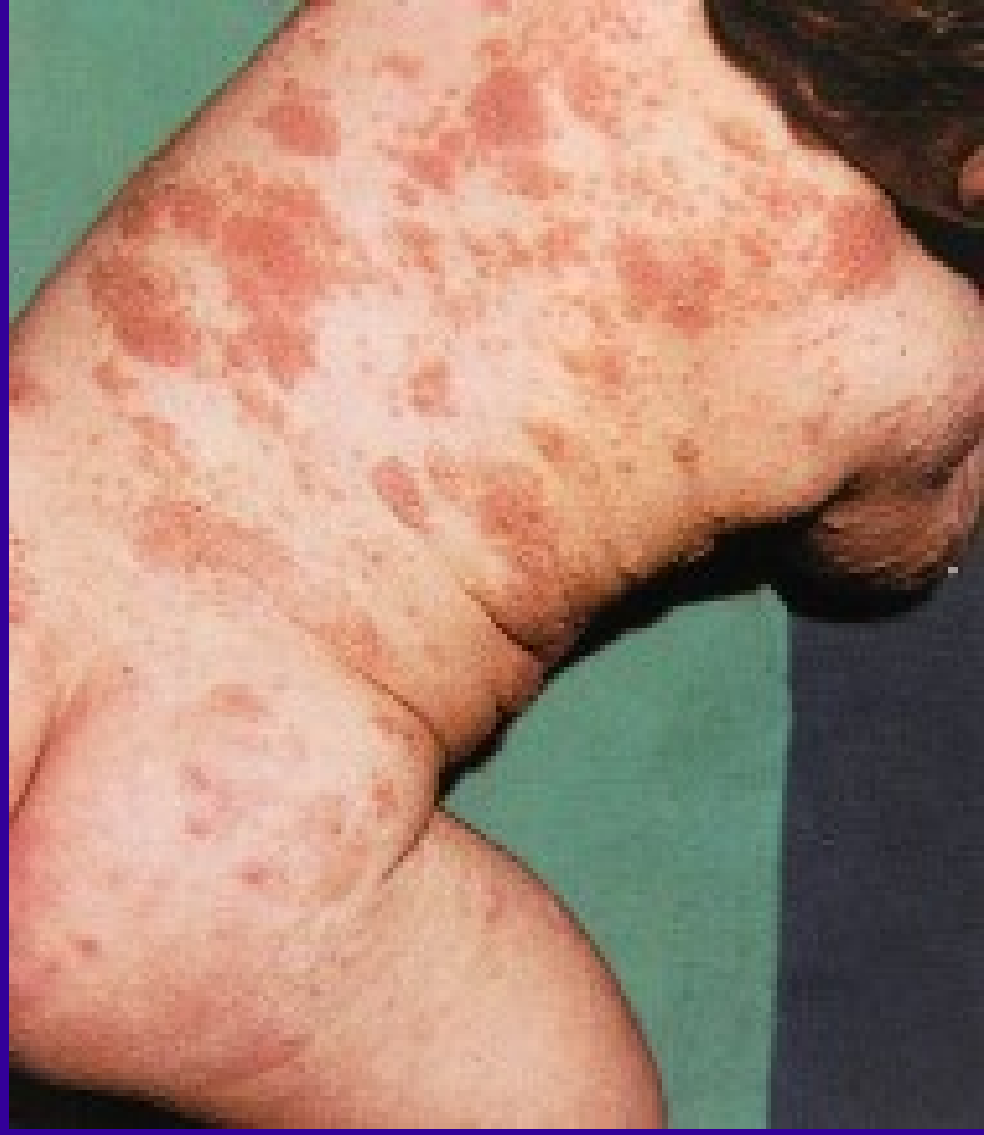
- **Localization** - periorally
  - periorbitally

- **Possibility of spreading - erythroderma**



Atopic dermatitis – Infant AD





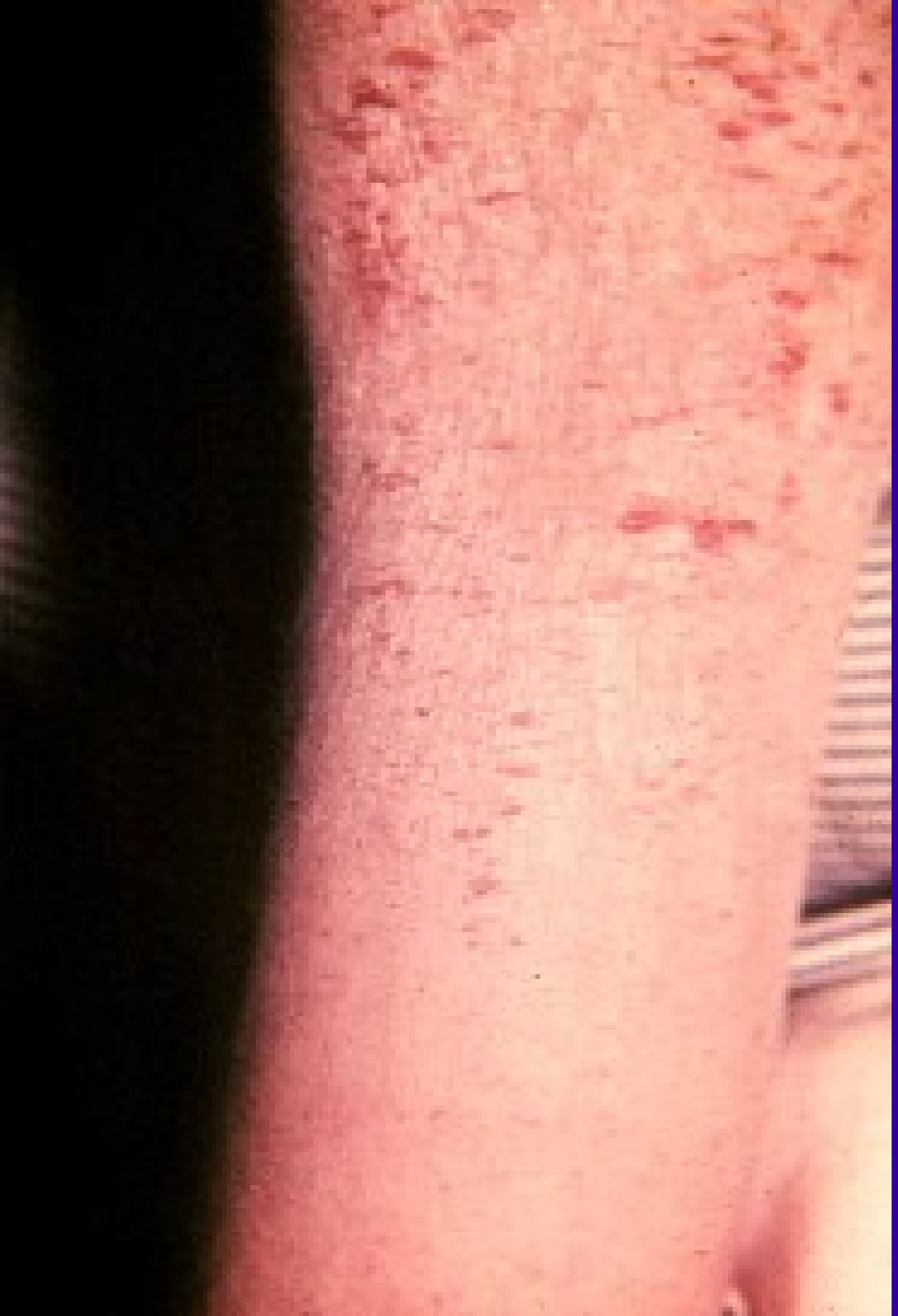
Infant AD

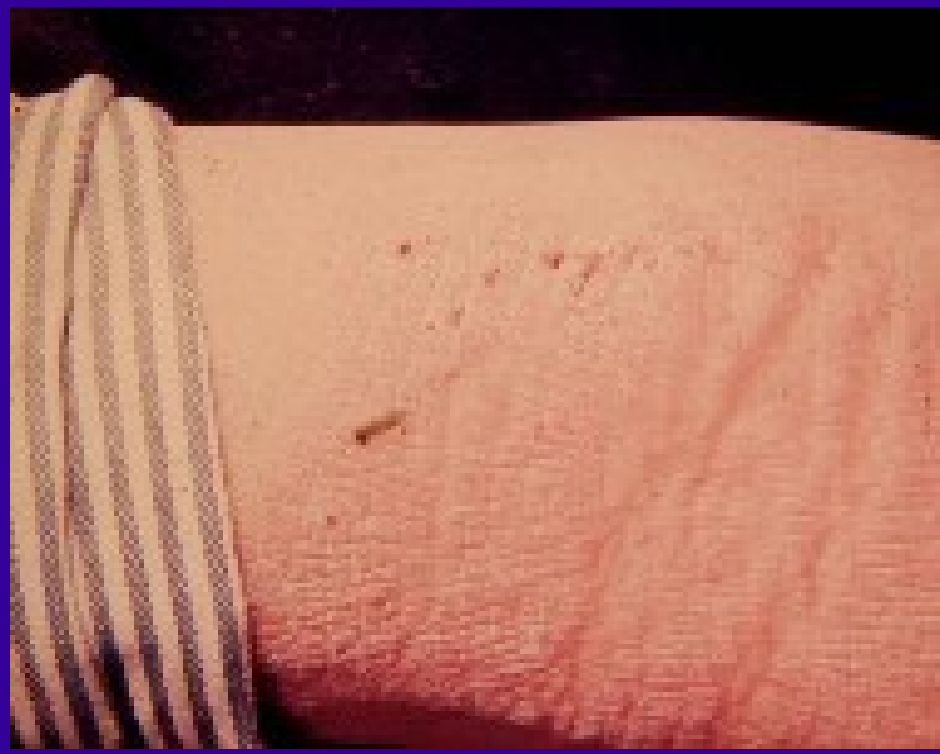
Clinical picture of AD

AD in children and adolescents

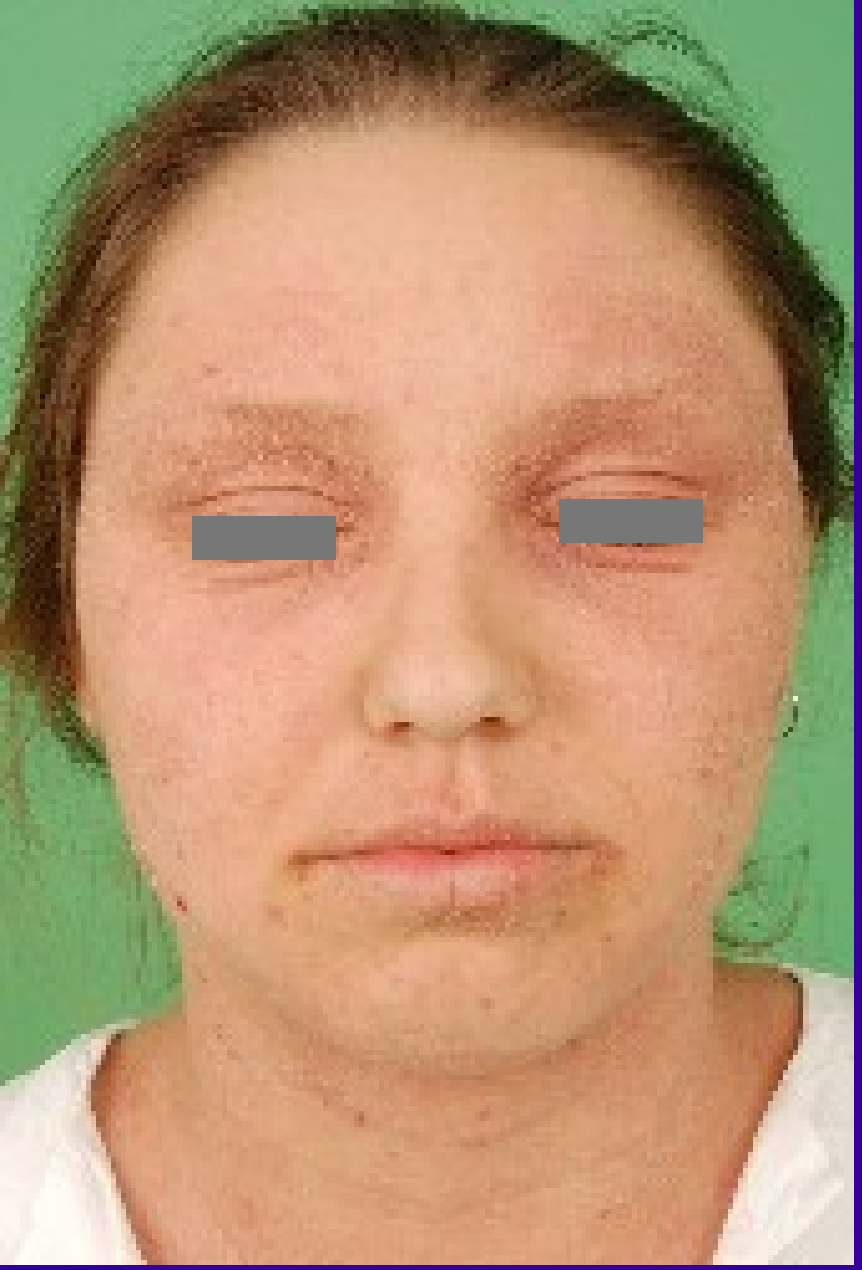
Decrease of exudation - lichenification

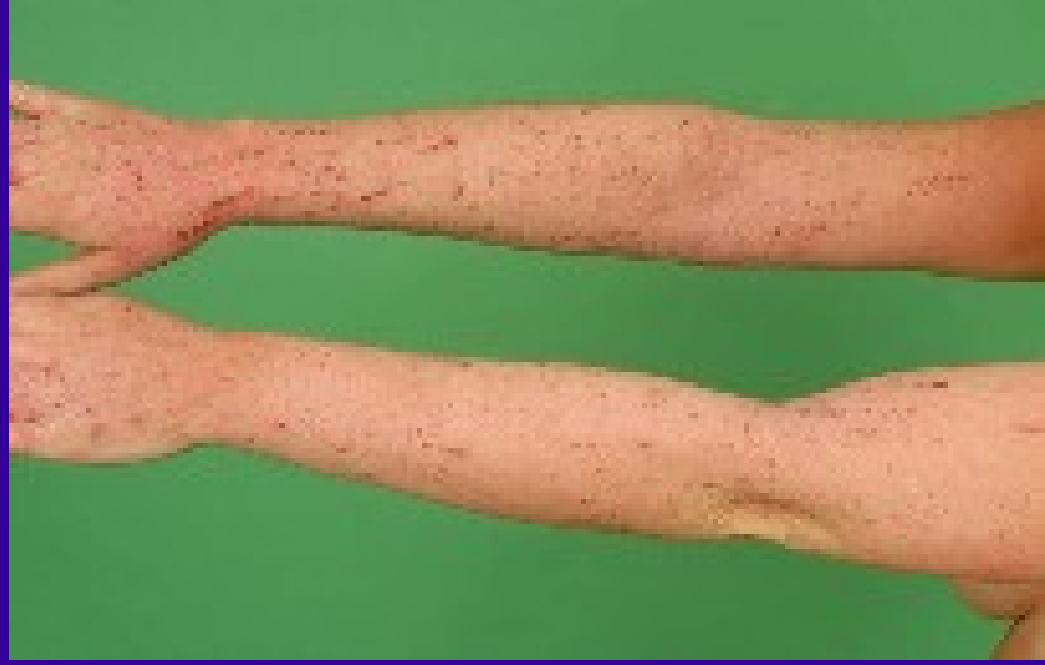
- most often – flexural eczema
  - facial eczema
- less often - erythroderma

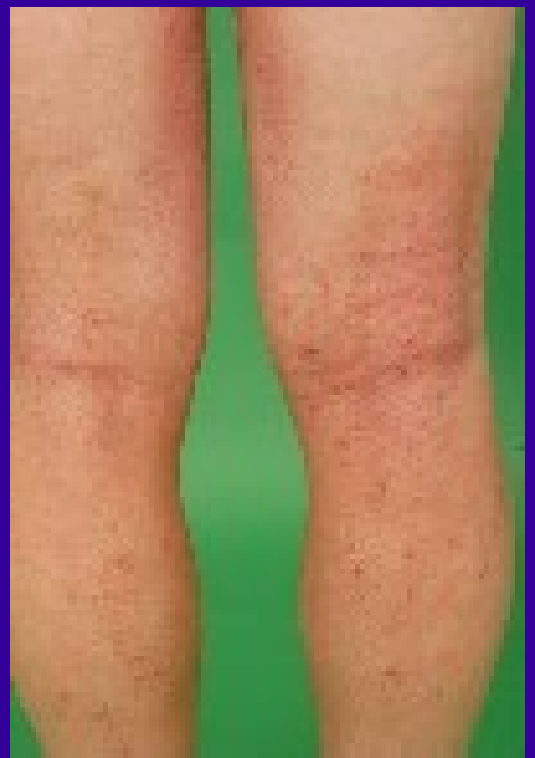


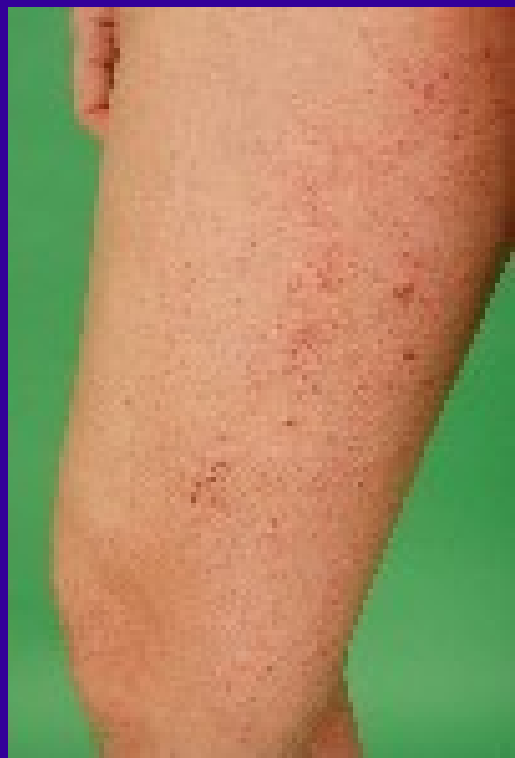


Atopic dermatitis – flexural eczema









Atopic dermatitis – erytrodermic form

Clinical picture of AD

AD in adults

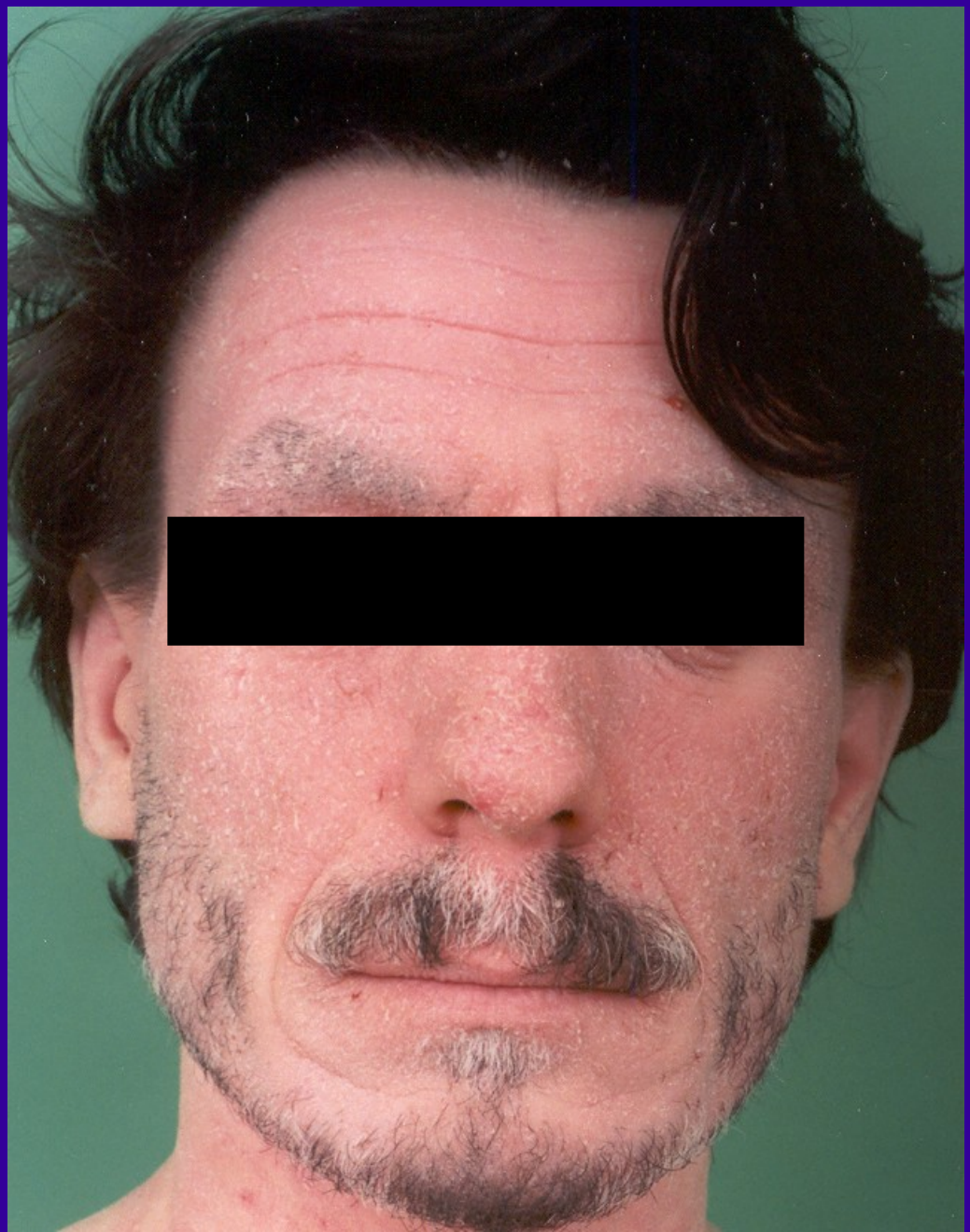
(about 15% of cases appear after puberty)

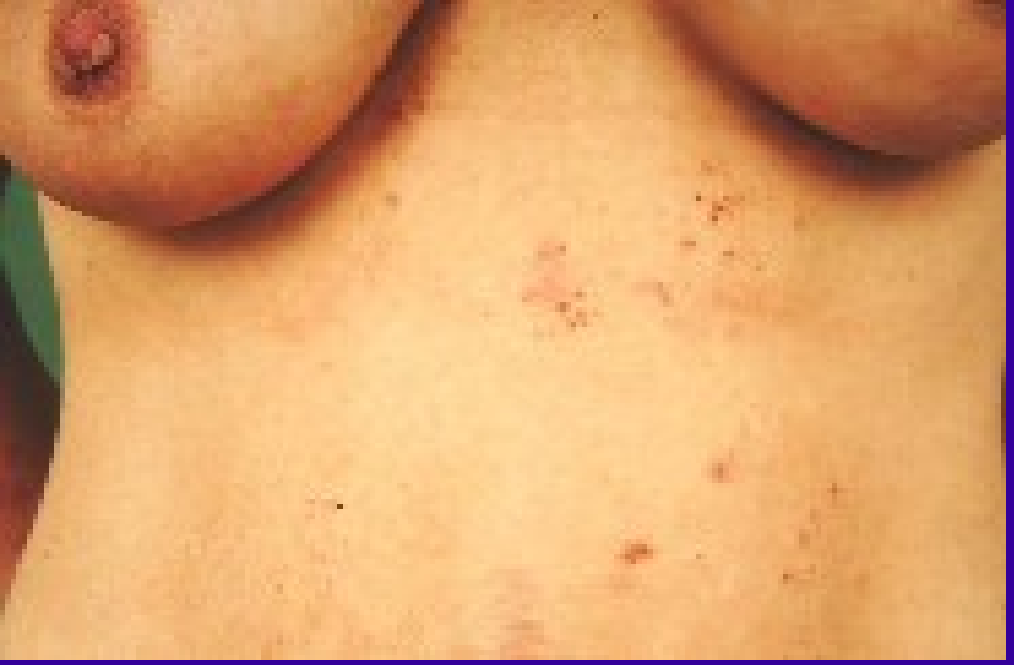
- **head& neck**
- **flexural**
- **prurigininous**
- **neurodermitic**
- **erythrodermic**

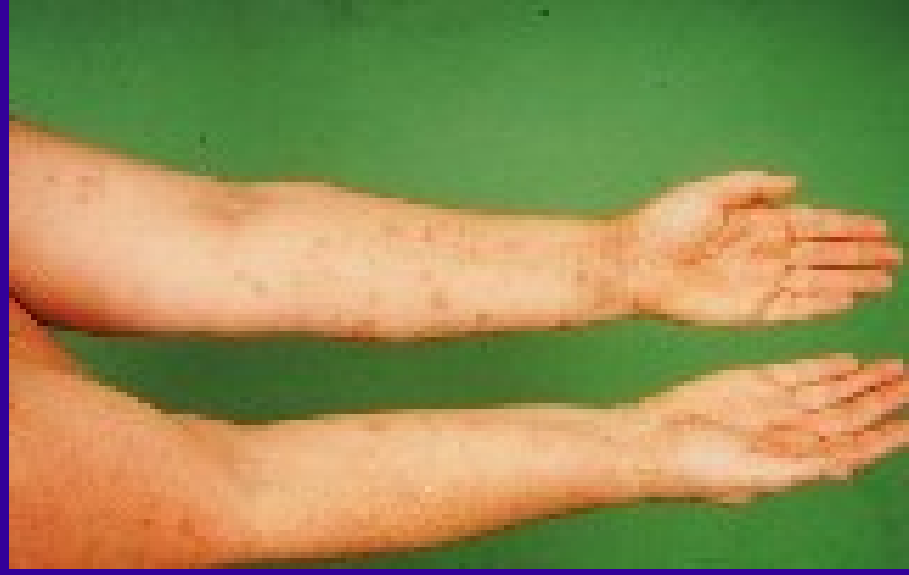
chronic course

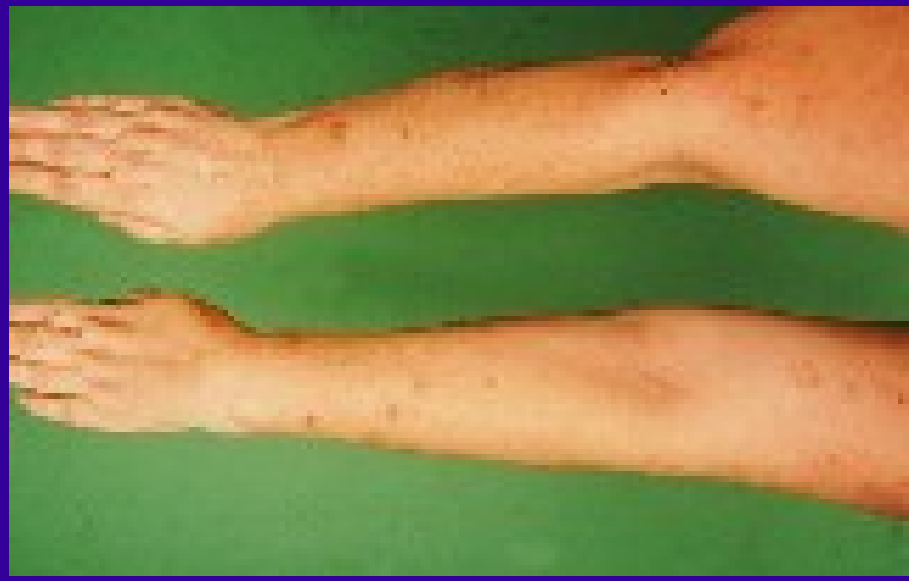
acute flares

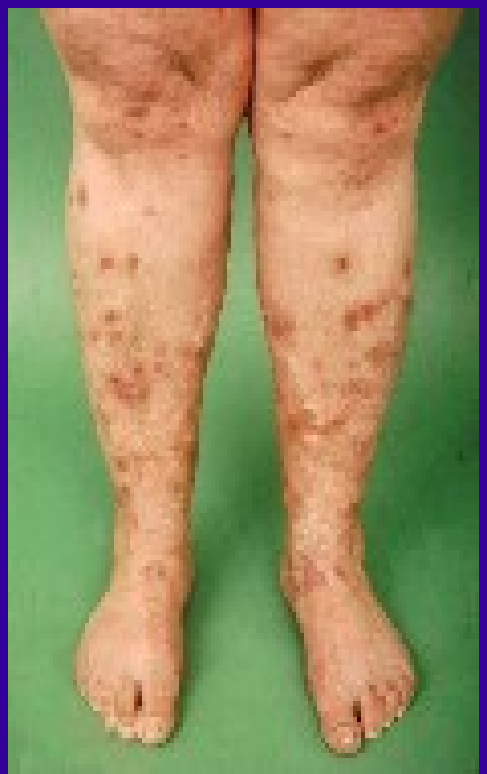
possible



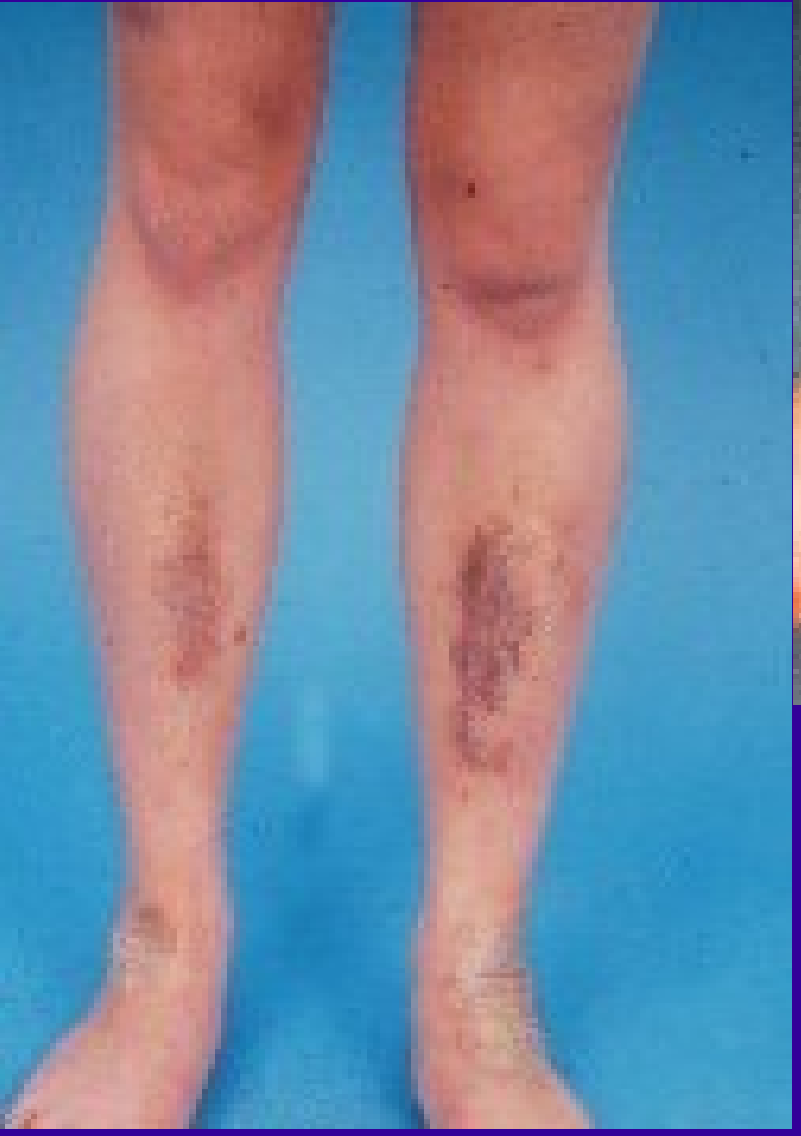


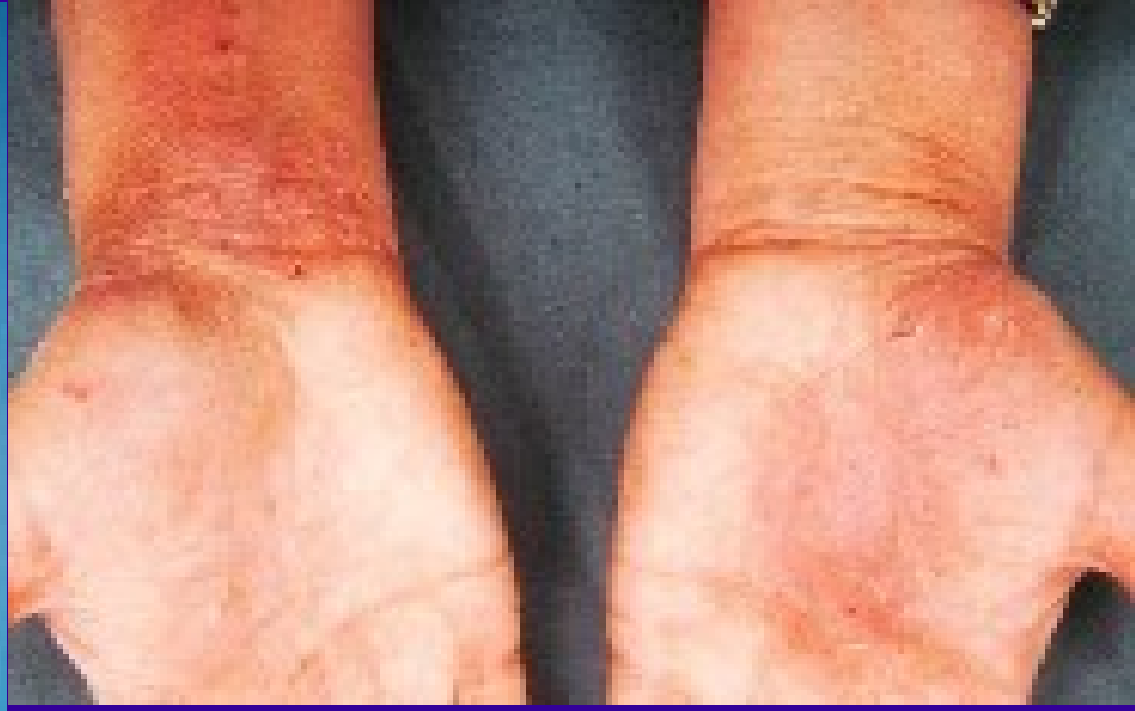


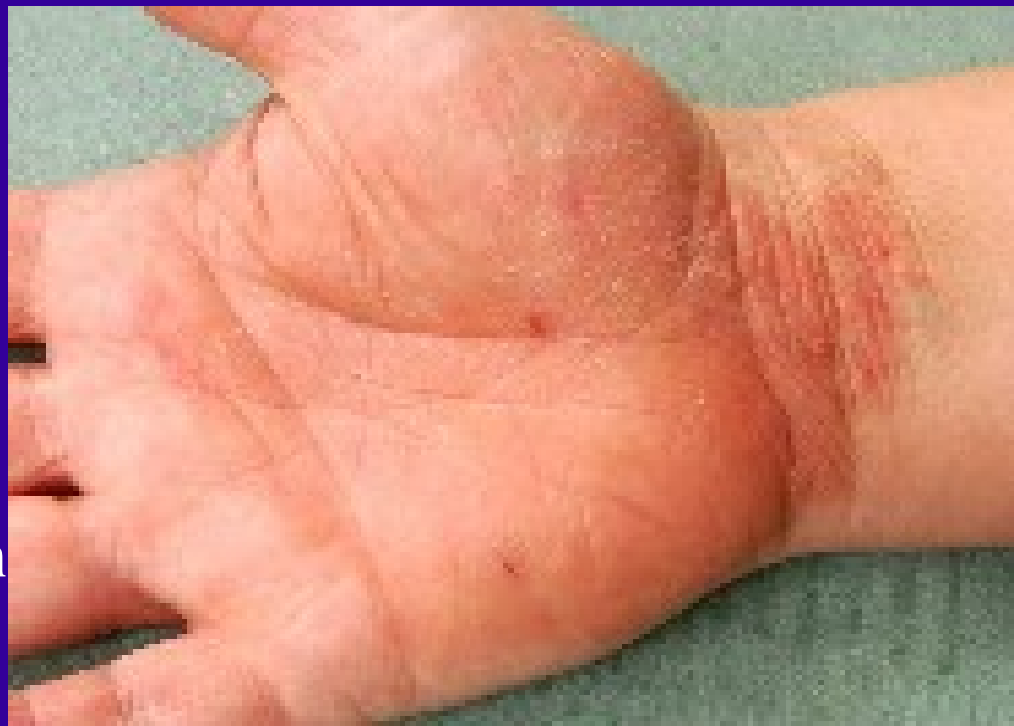




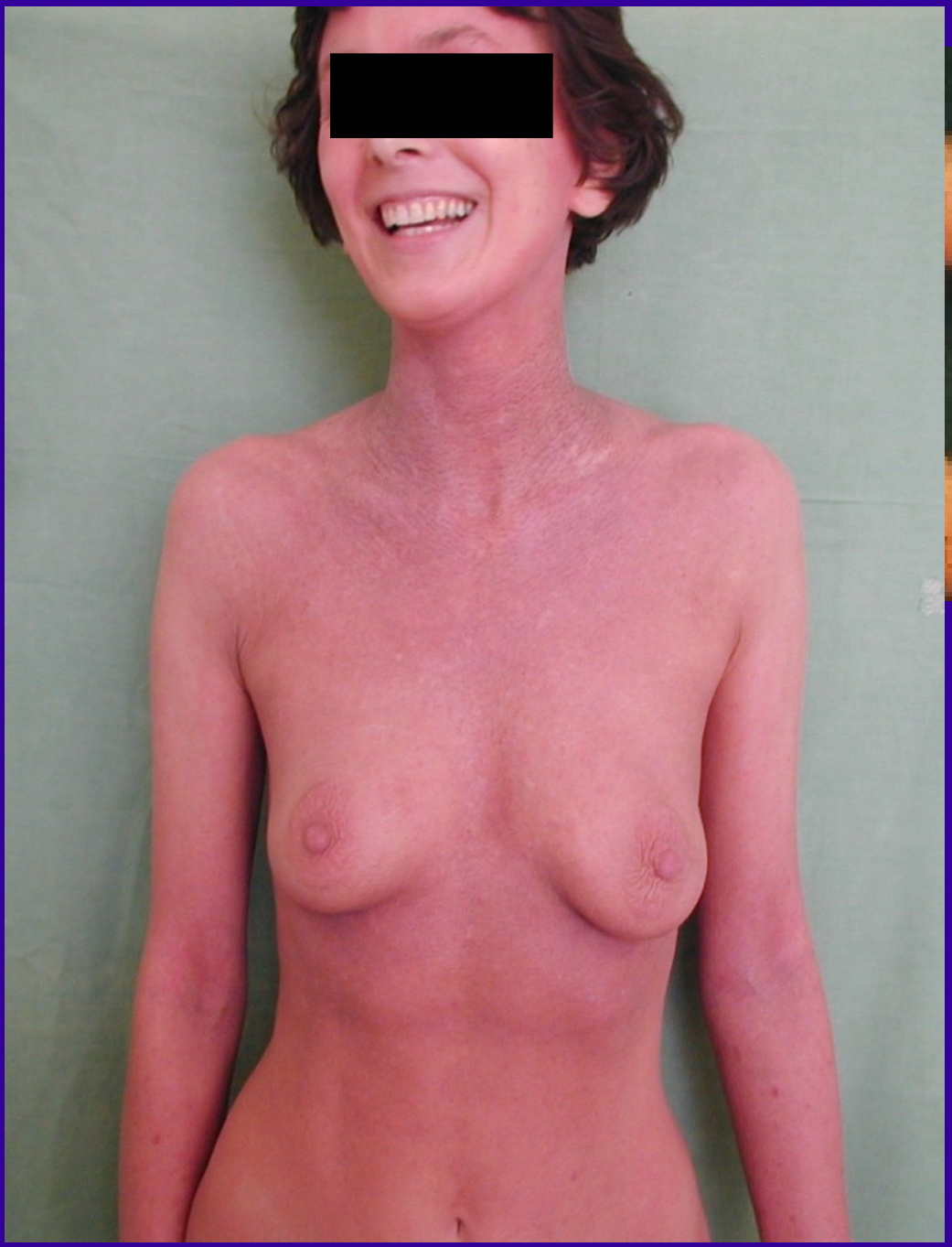
Adult AD – pruriginous form

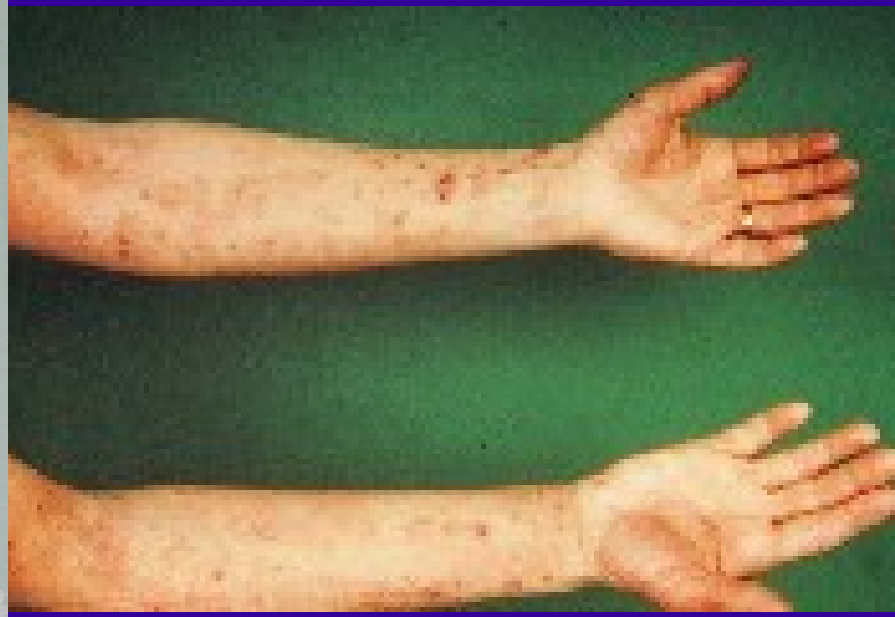






Adult AD – neurodermitic form



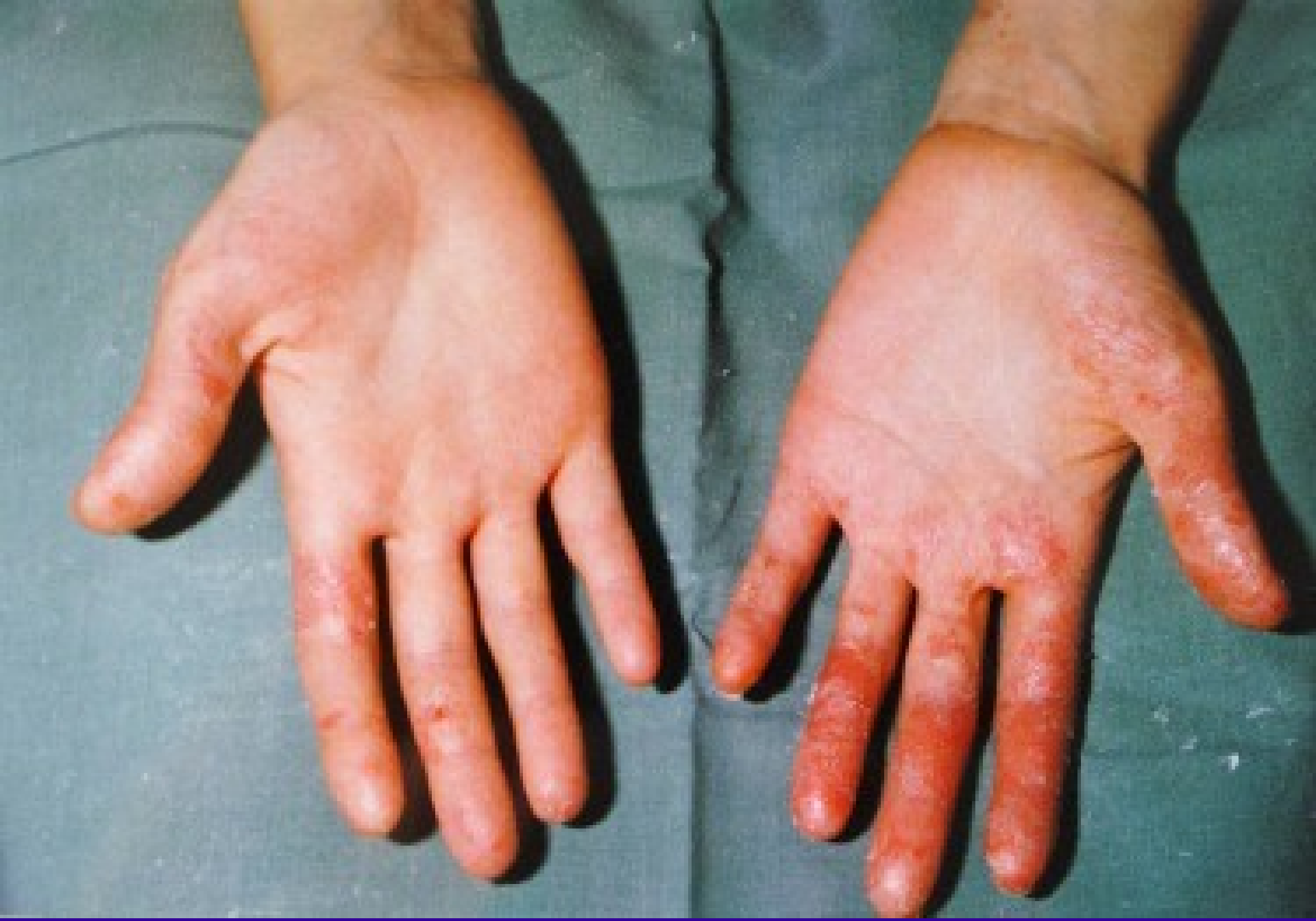


Adult AD – erythrodermic form

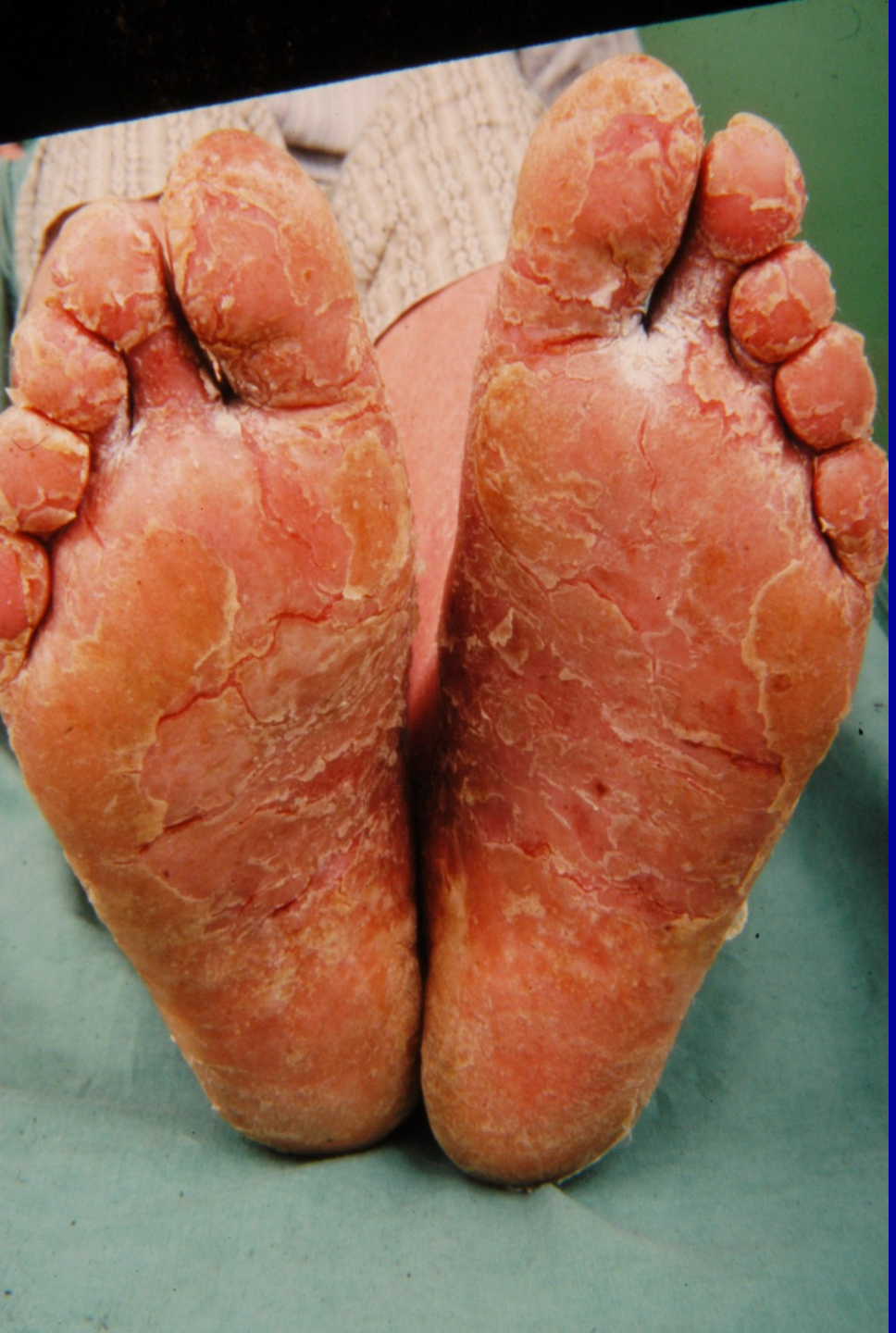
AD in adults

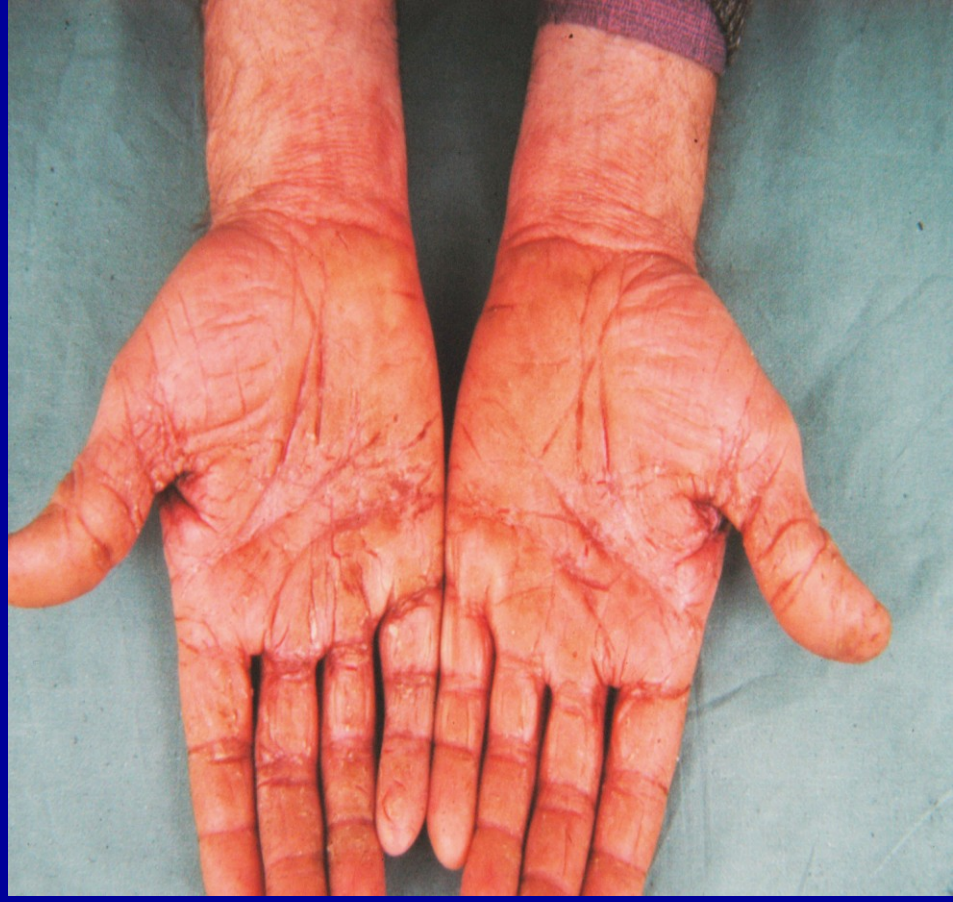
- **atypical forms** - nummular, dyshidrotic, hyperkeratotic forms

- **minimal forms** - cheilitis sicca, stomatitis angularis, pulpitis sicca, intertrigo retroauricularis, aj.

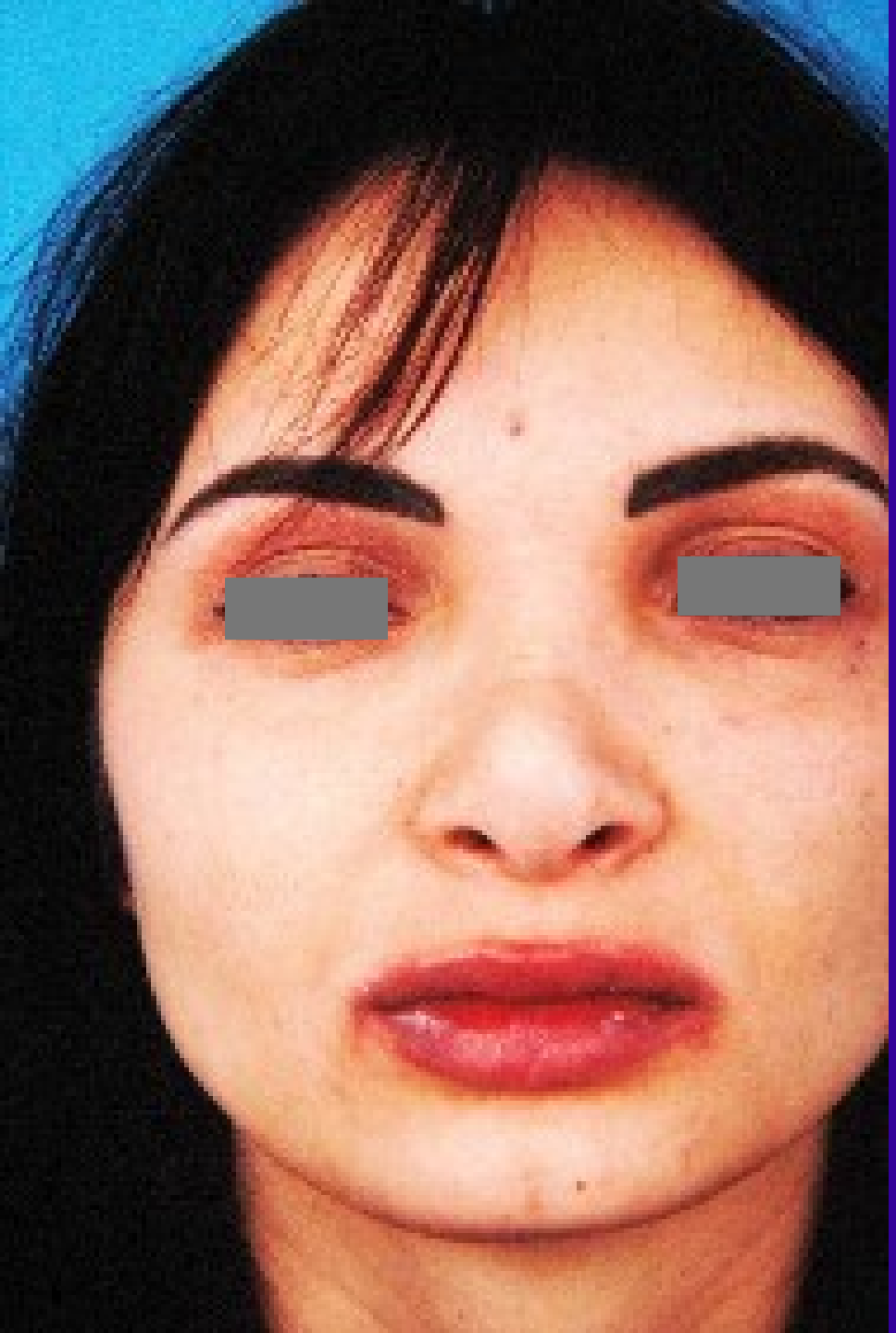


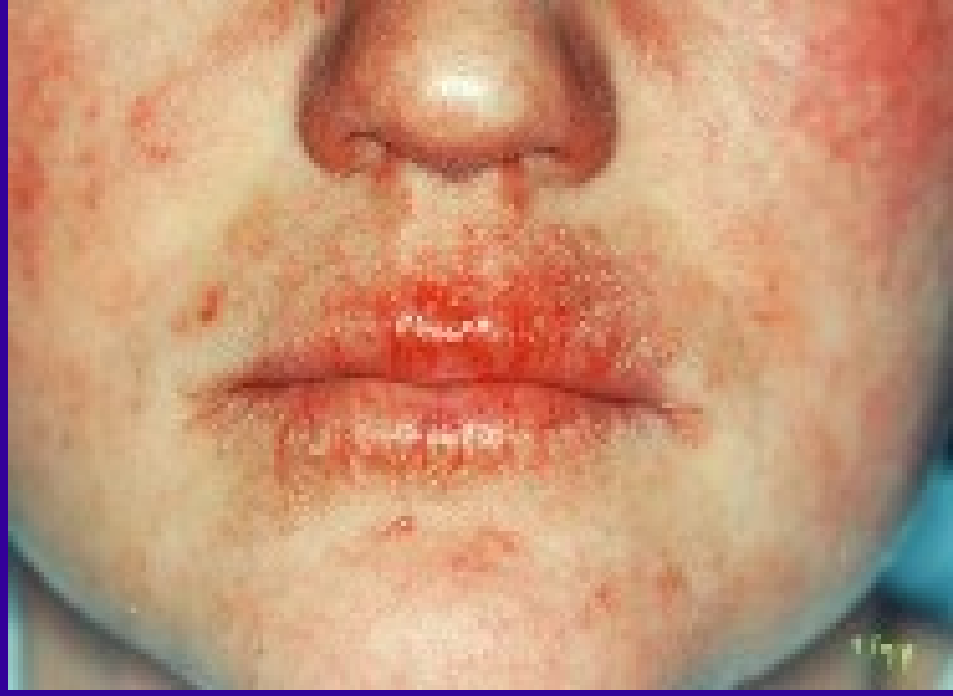
Adult AD - dyshidrotic form



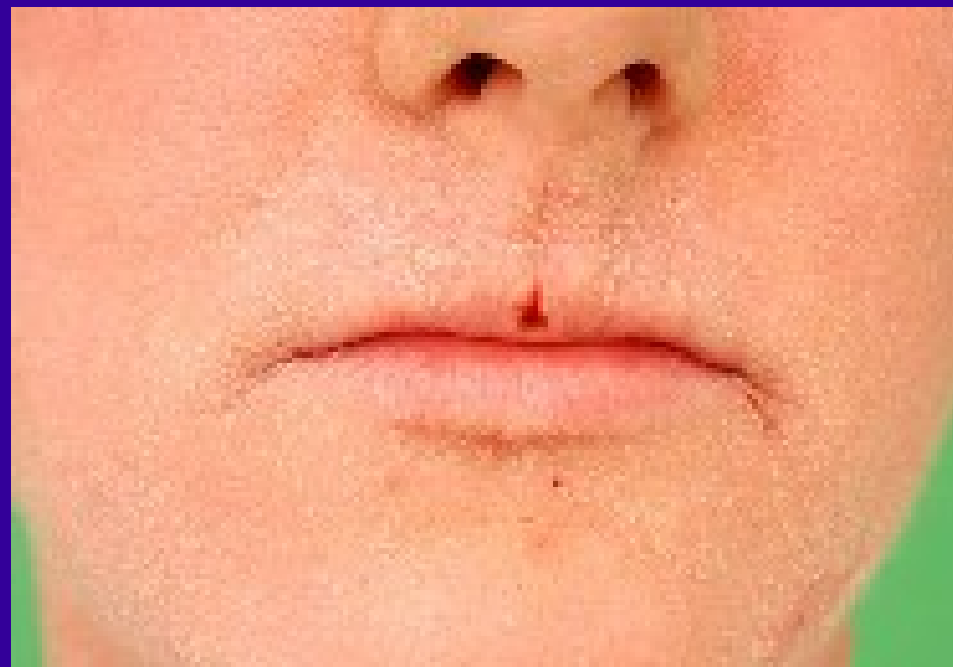


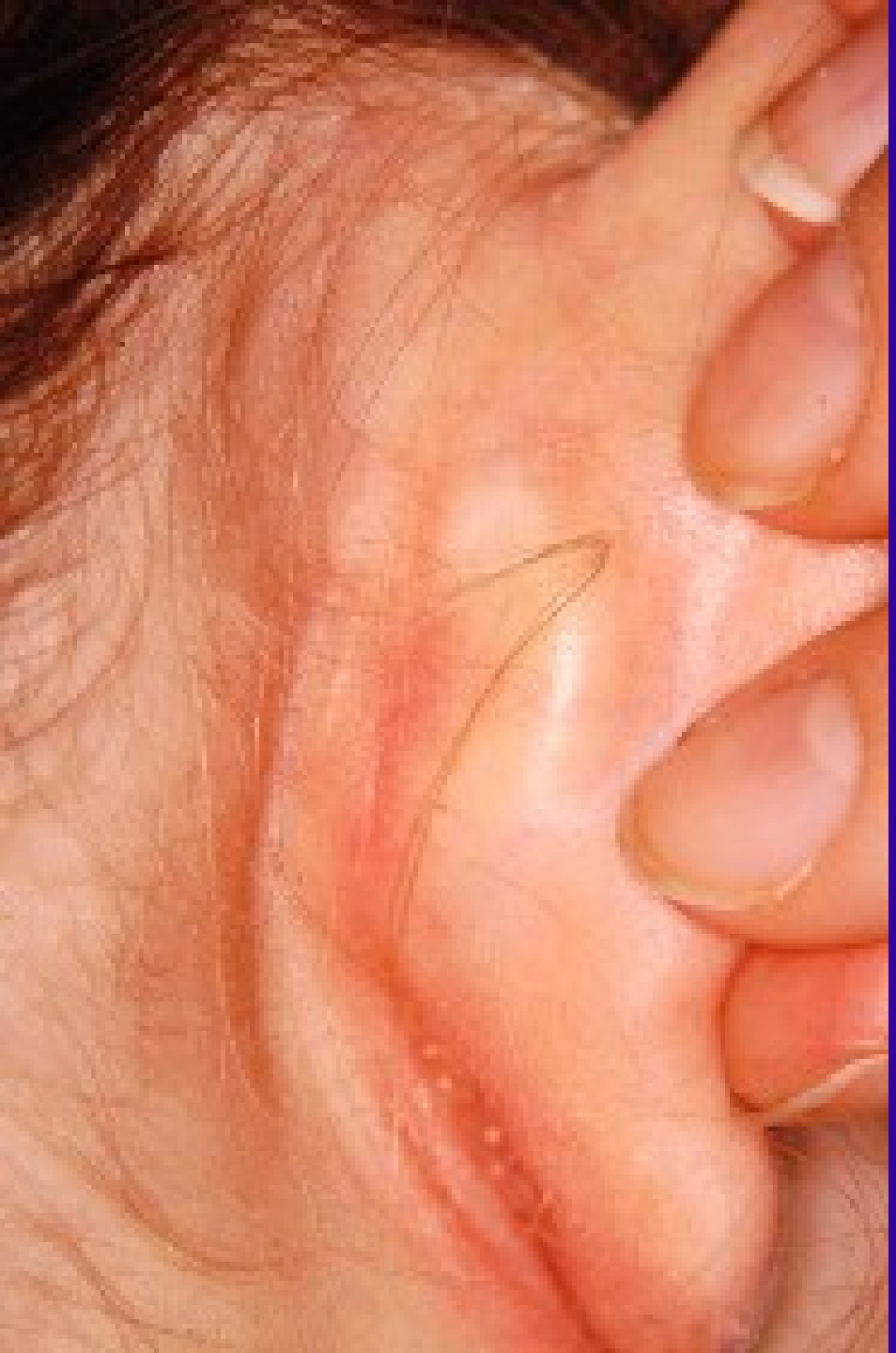
Eczema atopicum hyperkeratoticum

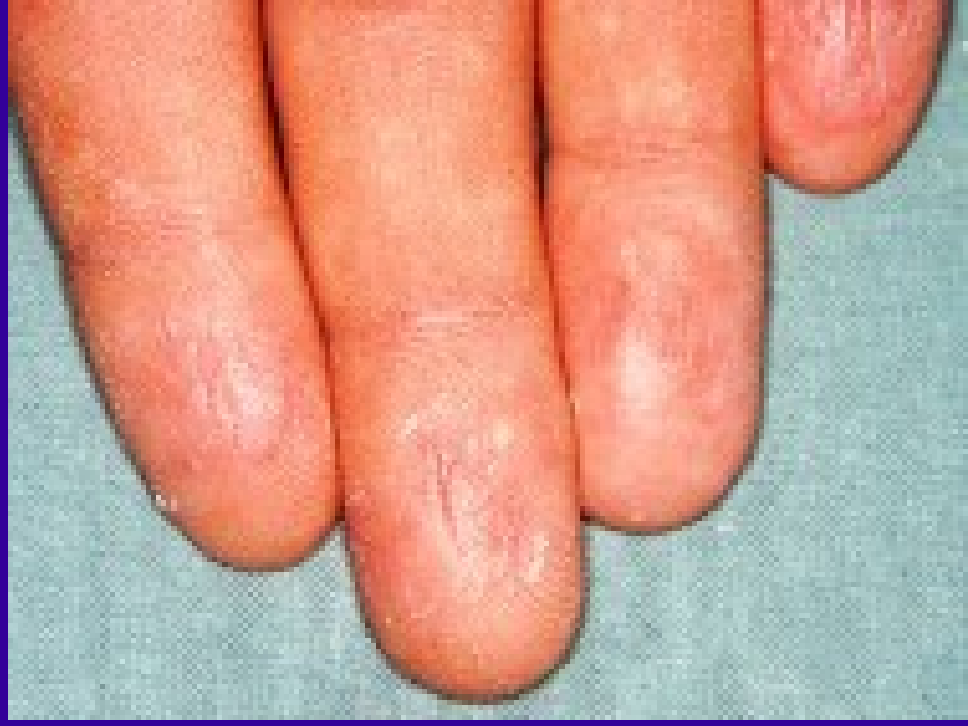




AD eyelid dermatitis, lip dermatitis







AD retroauricular dermatitis

Diagnosis according to Hanifin and Rajka (1980)

Atopic dermatitis diagnosis =
≥3 basic features + **≥3 minor** features

Requires the presence of **at least 3 basic features**:

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

Requires the presence of **at least 3 minor features**:

- Xerosis
- Ichthyosis/palmar hyperlinearity/ keratosis pilaris
- Immediate (type 1) skin test reactivity
- Elevated serum IgE
- Early age of onset
- Tendency towards cutaneous infections (especially *Staphylococcus aureus* or herpes simplex)
- Nonspecific hand or foot dermatitis
- Nipple eczema
- Cheilitis
- Recurrent conjunctivitis
- Dennie–Morgan infraorbital fold
- Keratoconus
- Anterior subcapsular cataracts
- Orbital darkening
- Facial pallor/erythema
- Pityriasis alba
- Anterior neck folds
- Itch when sweating
- Intolerance to wool and lipid solvents
- Perifollicular accentuation
- Food intolerance
- Course from environmental/emotional factors
- White dermographism/delayed blanching

IgE=immunoglobulin E

Hanifin JM, Rajka G. Acta Derm Venereol 1980;92 Suppl:44-7

Differential diagnoses to consider in adult patients with suspected severe AD

Condition	Clinical features
Contact dermatitis	Atypical or localized distribution
Severe, suberythrodermic psoriasis	Less pruritus and lack of eczematous change such as oozing/crusting
Severe seborrheic dermatitis	Lack of pruritus with greasy scale in scalp
Scabies infestation	Inguinal, axillary, and genital papules
Widespread tinea corporis	Annular papulosquamous lesions without eczematous change
Cutaneous T-cell lymphoma	Lack of classic eczematous skin changes such as oozing and crusting

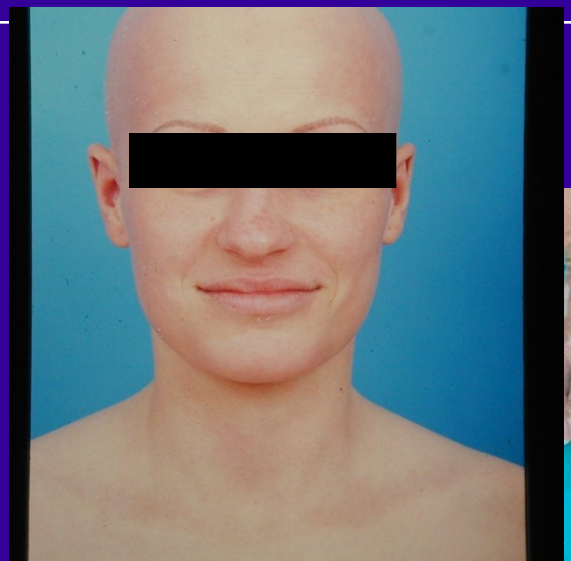
AD=atopic dermatitis
Simpson EL et al. *J Am Acad Dermatol* 2017;77(4):623-33

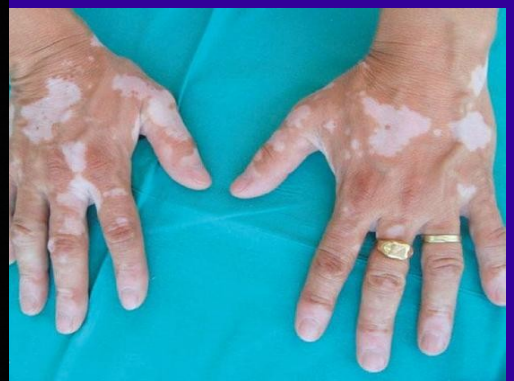
Complications of AD

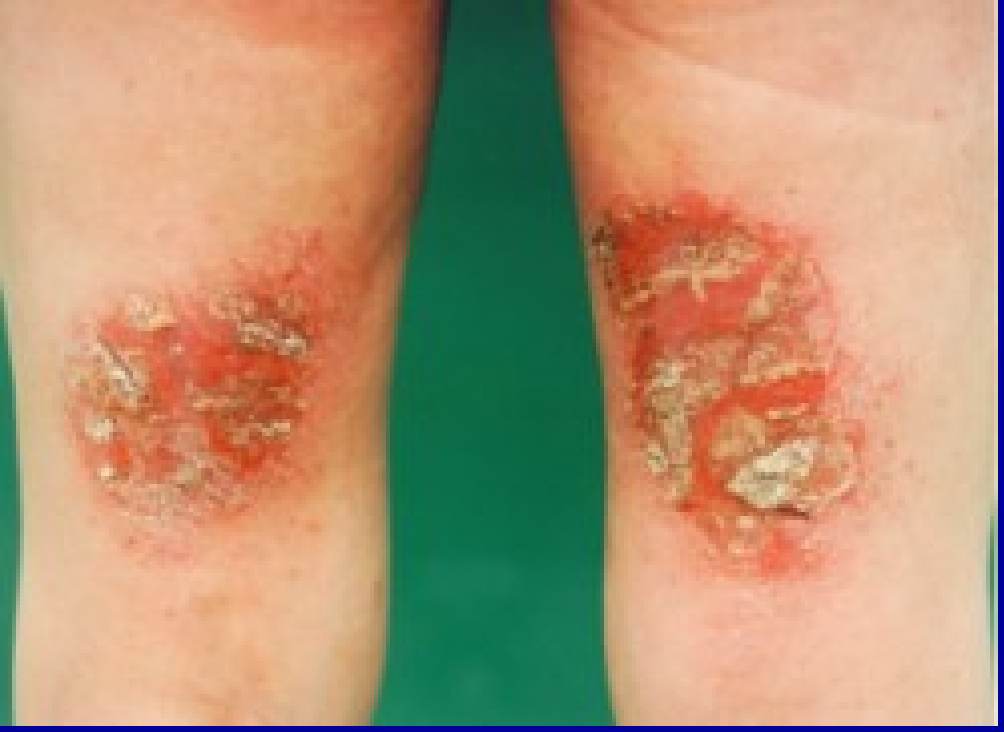
bacterial - impetiginization (St. aureus)
viral – herpetication-HSV, warts, mollusca
fungal (Tr. rubrum, Pityrosporum ovale)
contact sensitization (nickel, fragrances, KS…)

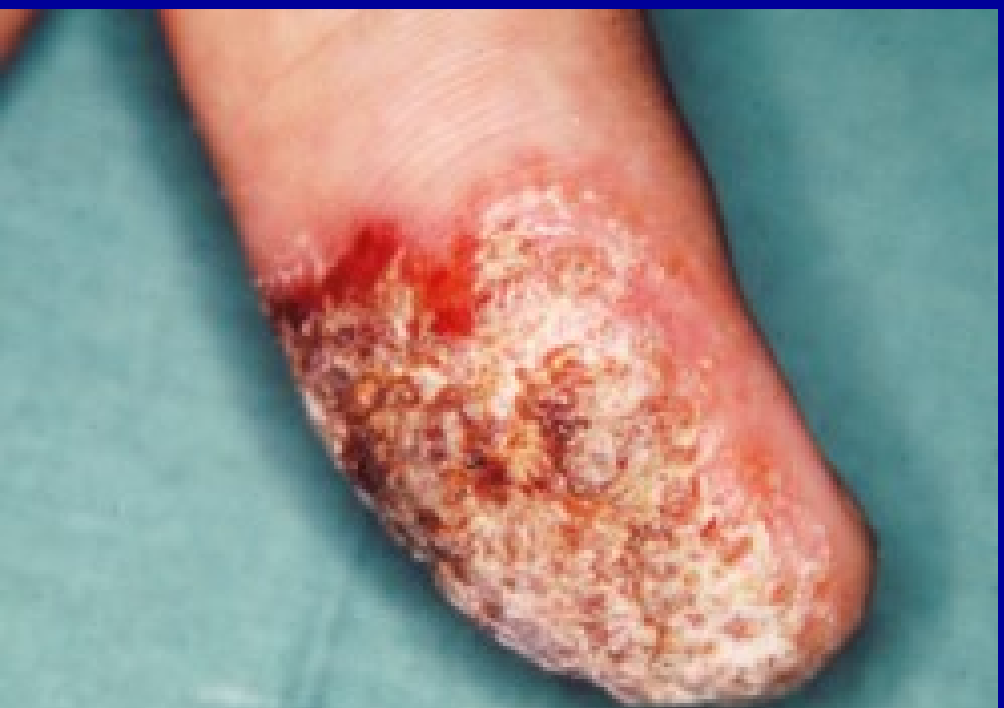
association:

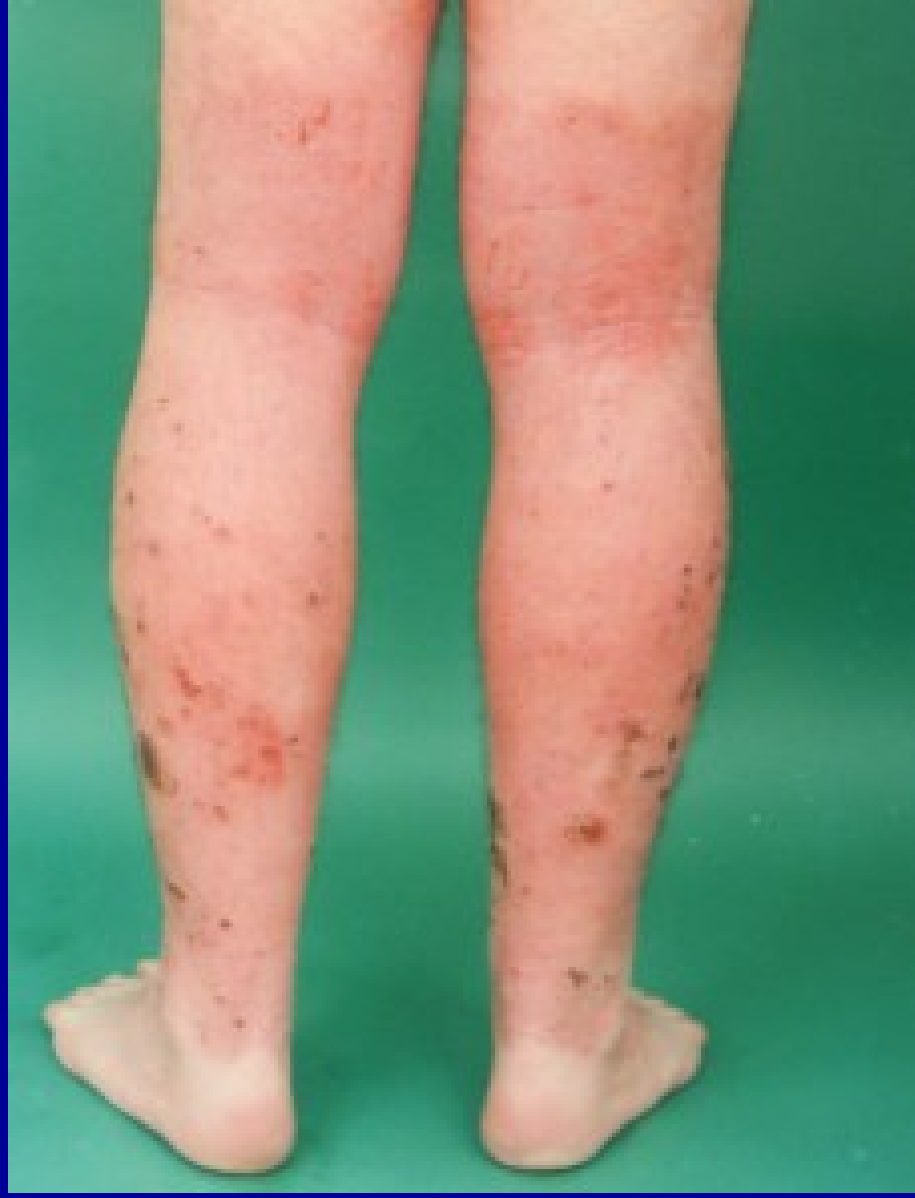
- **alopecia areata**
- **ichtyosis vulgaris**
- **vitiligo**



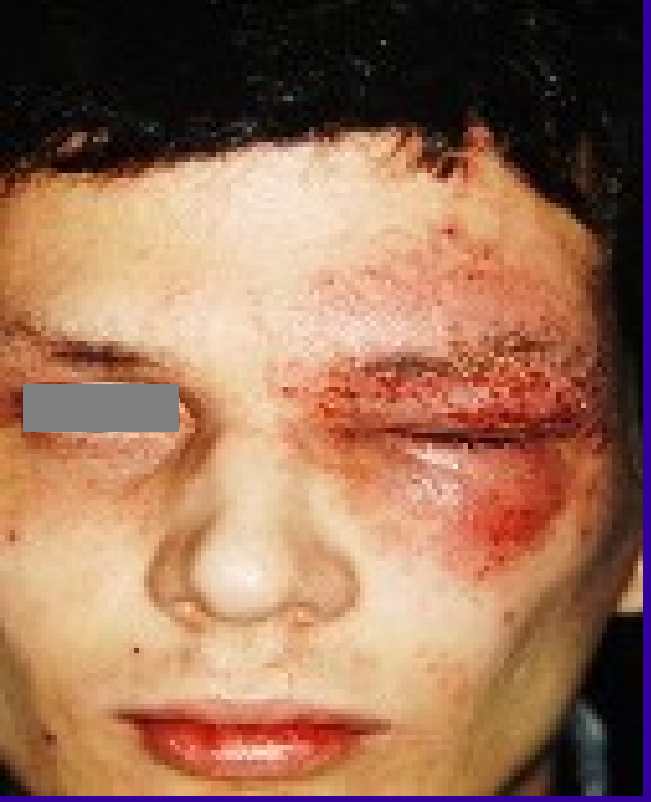
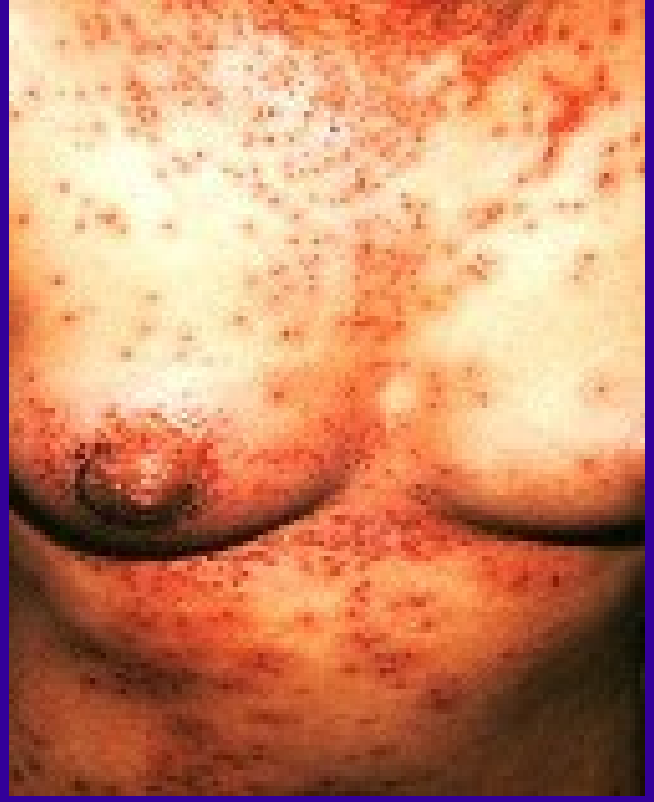
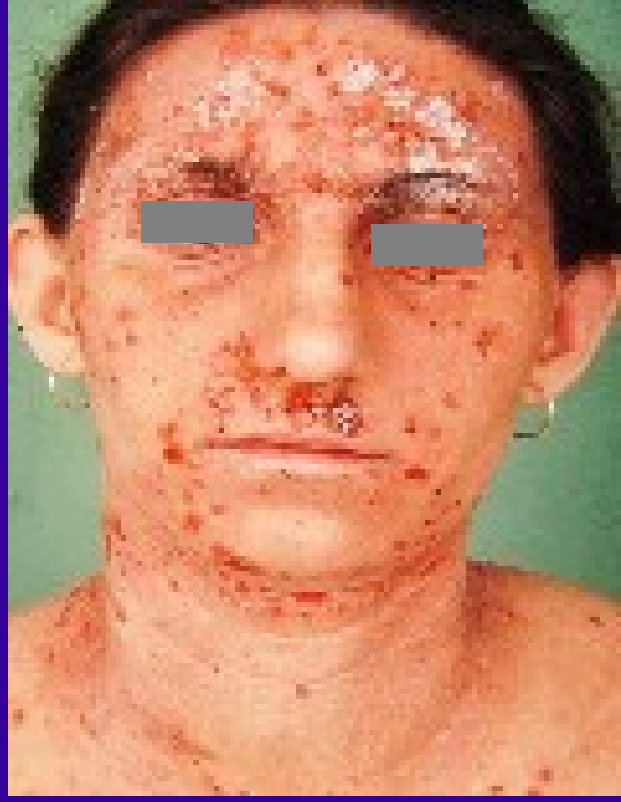
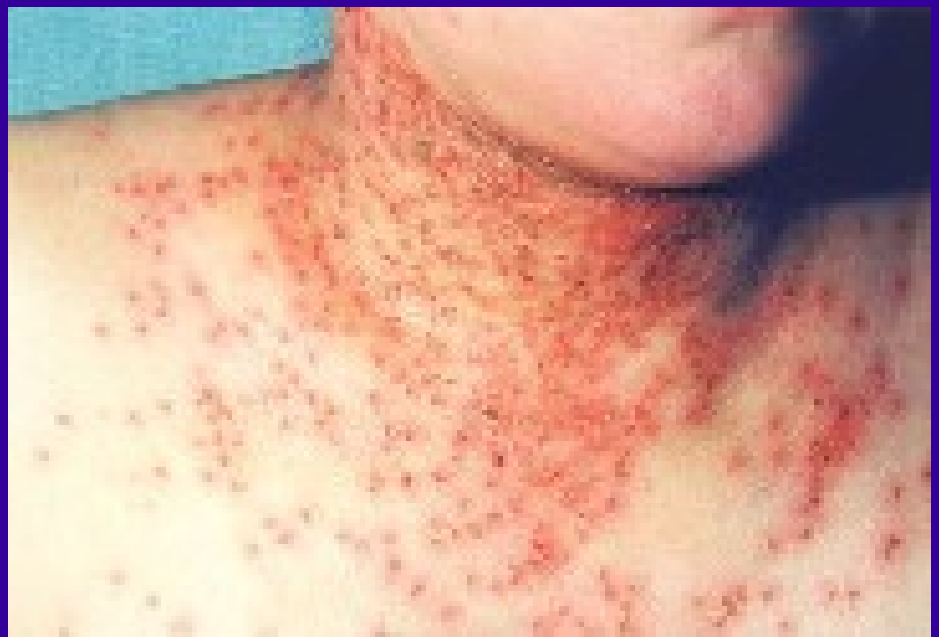




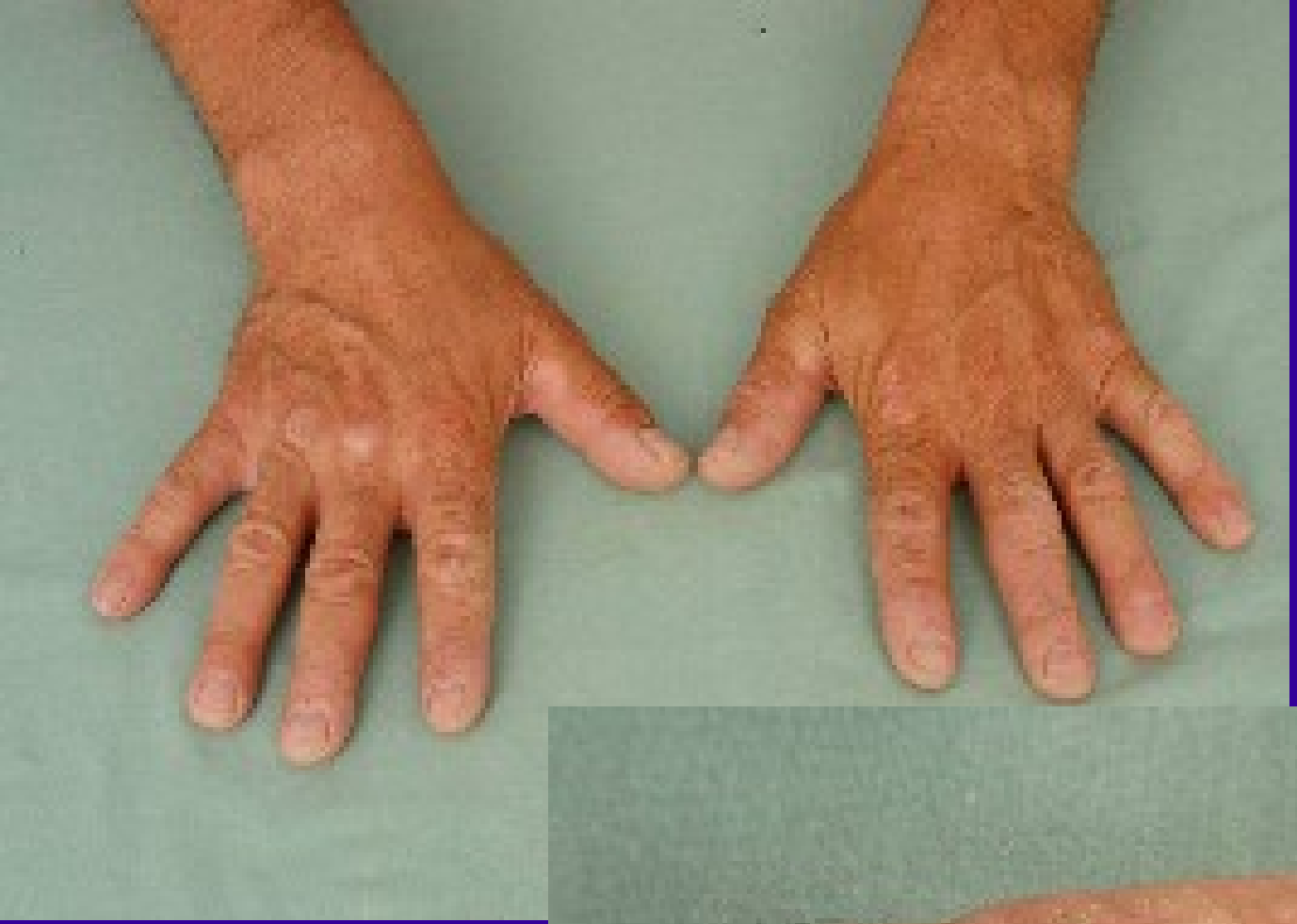


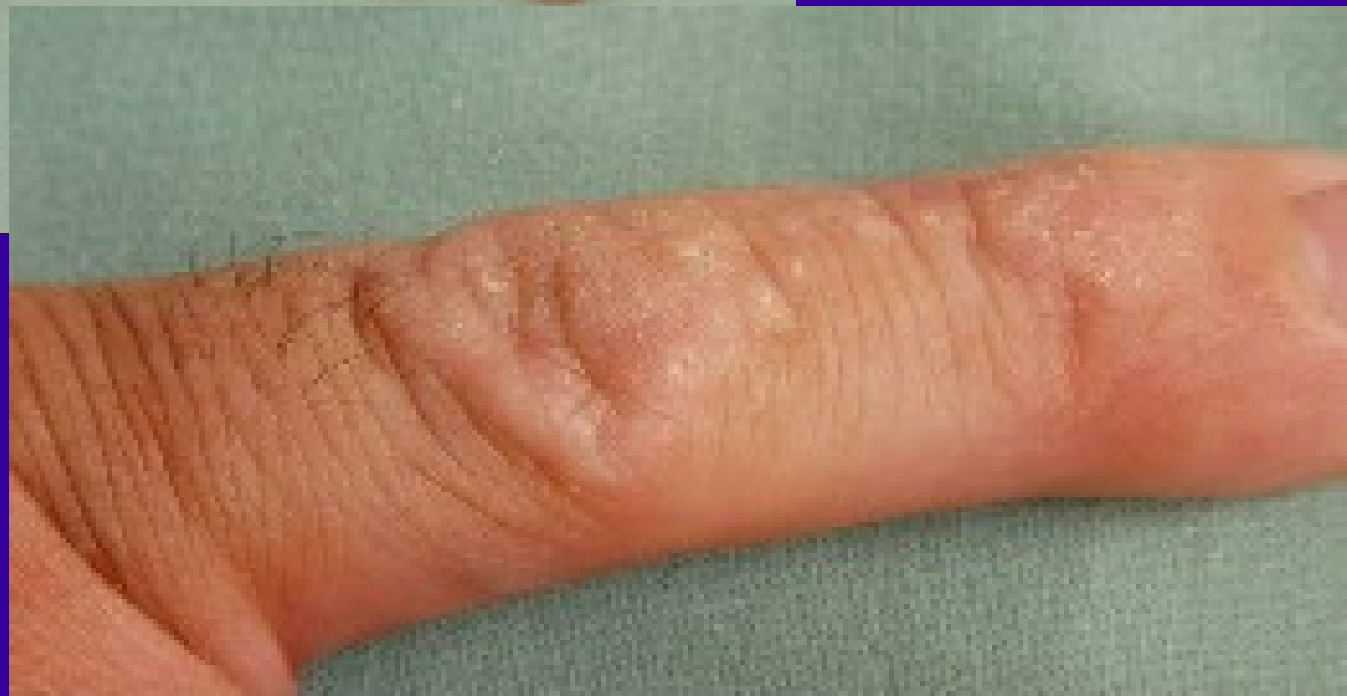


Eczema atopicum impetiginisatum

Eczema atopicum herpeticatum





Eczema atopicum – verrucae vulgares – warts

Treatment of AD

mild form of AD (30-40% of patients):

education of pacient (or parents)

identification of triggering factor
and their elimination

emmolients and baths

topical corticosteroids

pimecrolimus

antihistamines during flares

Benefits vs. risks of topical corticosteroids in atopic dermatitis

BENEFIT

Large body of evidence on efficacy[1]:

- Decreases acute and chronic signs of AD
- Decrease in pruritus

RISK

Adverse events:

- Skin atrophy
- Telangiectasias (spider veins)
- Ecchymosis (bruising)
- Stretch marks
- Hypertrichosis (excessive hair growth)
- Rosacea-like dermatitis
- Systemic effects (adrenal suppression)

AD=atopic dermatitis

1. Eichenfield LF, et al. J Am Acad Dermatol 2014;71(1):116-32; 2. Wollenberg A, et al. J Eur Acad Dermatol Venereol 2018;32:657-82

Treatment of AD

- mid-severe form of AD (40-50% of patients):

  treatment similar as in mild form

  \+ tacrolimus

  or

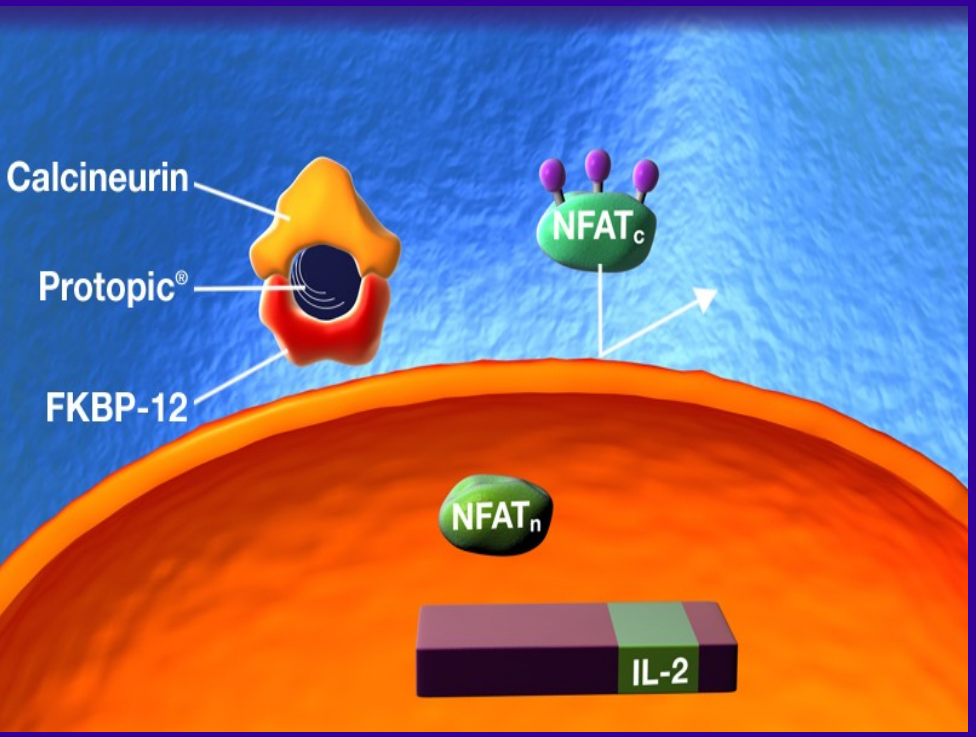
  hospitalization – lab. and clinical tests (triggers)

  traditional topical treatment /tar/

  or

  phototherapy (UVB 311nm, UVA-1)

Tacrolimus (PROTOPIC oinment)



- Topical Immunomodulator
- Blocks calcineurin
- antiinflammatory
- antipruritic
- Long - term treatment
- No skin atrophy

Benefits vs. risks of topical calcineurin inhibitors in atopic dermatitis

BENEFIT

Demonstrated efficacy in short-term trials and up to 12 months:

- Decreases in physician's global evaluation scores
- Decrease in percentage BSA involved
- Decrease in patient-reported signs and symptoms of AD
- No risk of skin atrophy

RISK

Adverse events:

- Transient burning sensation at site of application
- Their onset of action is slower than in TCS
- Generalized cases of viral infections (eczema herpeticum and molluscatum)
- Black box warning of rare case of malignancy (skin cancer and lymphoma – not proven later)

AD=atopic dermatitis; BSA=body surface area

1. Eichenfield LF, et al. J Am Acad Dermatol 2014;71(1):116-32; 2. Wollenberg A, et al. J Eur Acad Dermatol Venereol 2018;32:657-82

Treatment of AD

- severe form of AD (5-10% patients)

  phototherapy (PUVA, UVA-1)

  systemic corticosteroids (short courses)

  imunosupressives: cyclosporine A, MMF, AZT,MTX

  new therapies: i.v. Ig

  JAK, PDE ihibitors

  biologicals (dupilumab....)

European treatment recommendations for adults with atopic dermatitis

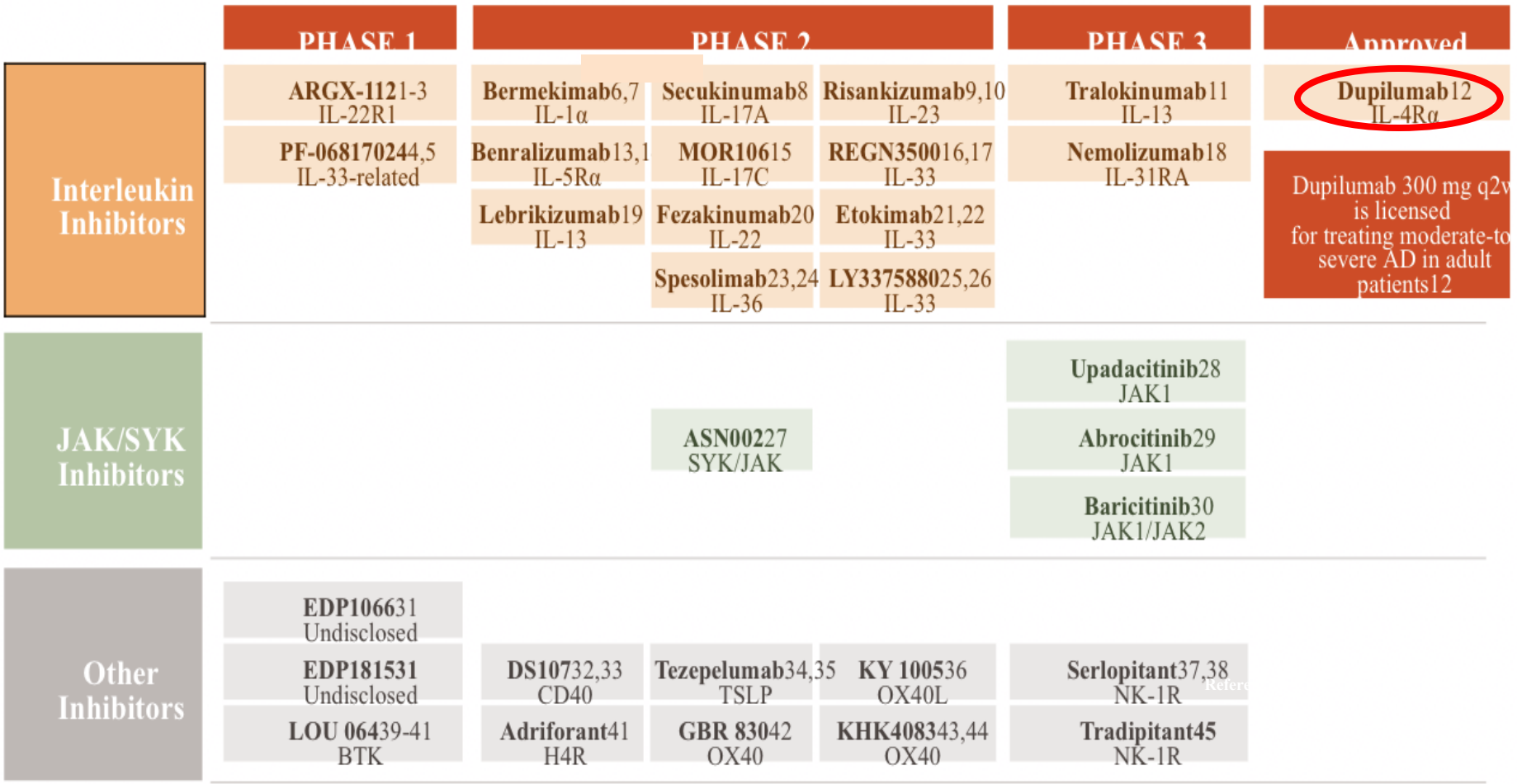
Severe SCORAD >50 or persistent AD	Hospitalization, PUVA,[a] systemic immunosuppression: cyclosporine A,[b] short course of oral corticosteroids,[b] dupilumab,[a,b] MTX,[c] AZA,[c] MMF[c]; alitretinoin[a,c]
Moderate SCORAD 25–50 or recurrent AD	Proactive therapy with topical tacrolimus[b] or TCS (class II or class III[c]), wet wrap therapy, UV therapy (UVB 311 nm,[d] medium-dose UVA1), psychosomatic counselling, climate therapy
Mild SCORAD <25 or transient AD	Reactive therapy with TCS (class II[b]) or TCI,[b,e] antiseptics including silver[b,e] and silver-coated textiles[a,e]
Baseline Basic therapy	Education, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests)

[a]Licensed indication; [b]Off-label use; [c]Narrow-band UVB; [d]Treatments with particular restrictions on use

AD=atopic dermatitis; AZA=azathioprine; MMF=mycophenolate mofetil; MTX=methotrexate; PUVA=psoralen and ultraviolet A; SCORAD=SCORing Atopic Dermatits; TCI=topical calcineurin inhibitor; TCS=topical corticosteroids; UV=ultraviolet

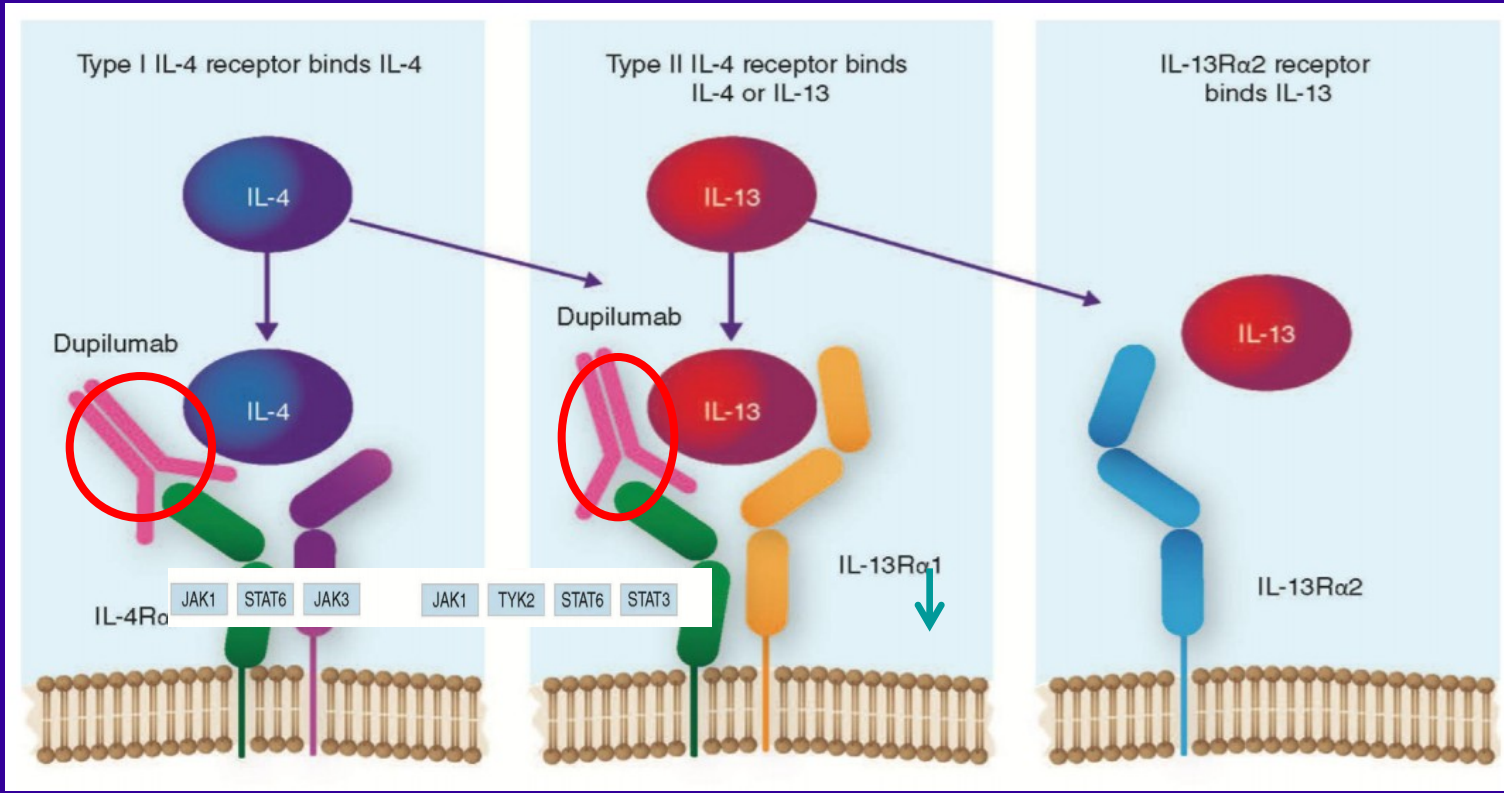
Wollenberg A, et al. J Eur Acad Dermatol Venereol 2018;32:657-82.

New treatments of AD

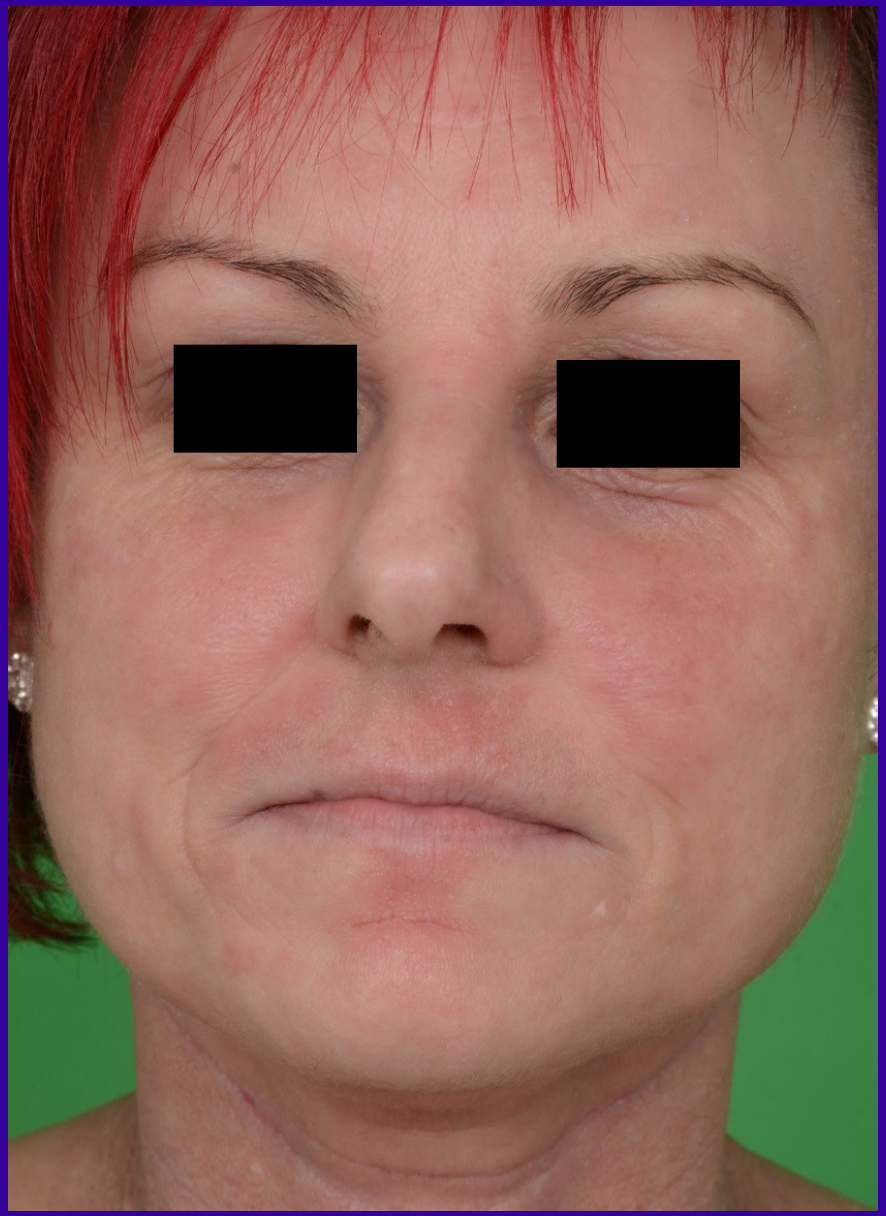


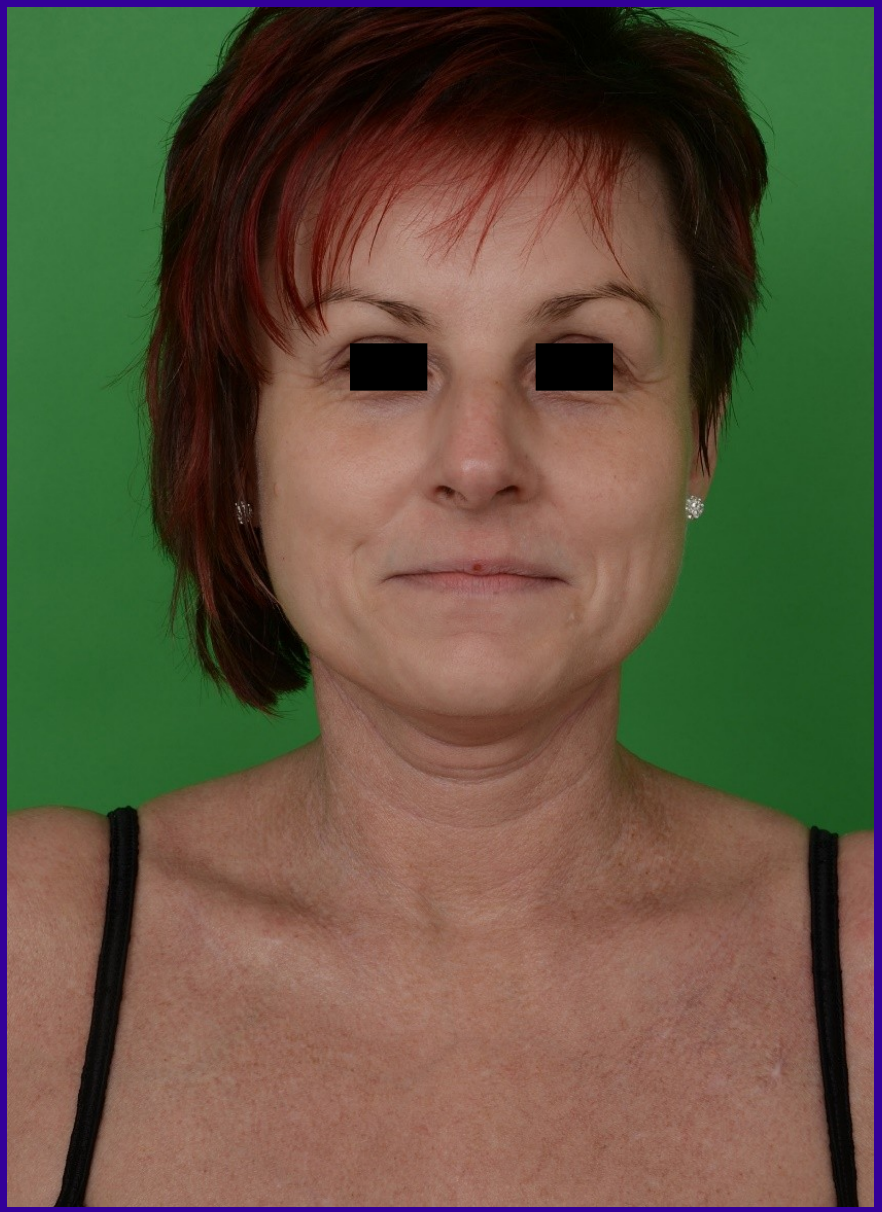
Dupilumab
- mechanism of action

human IgG4 class monoclonal antibody that specifically binds to the α subunit of the IL-4 and 13 receptors, thereby blocking the activation of protein kinases JAK 1 or 3 or TYK2

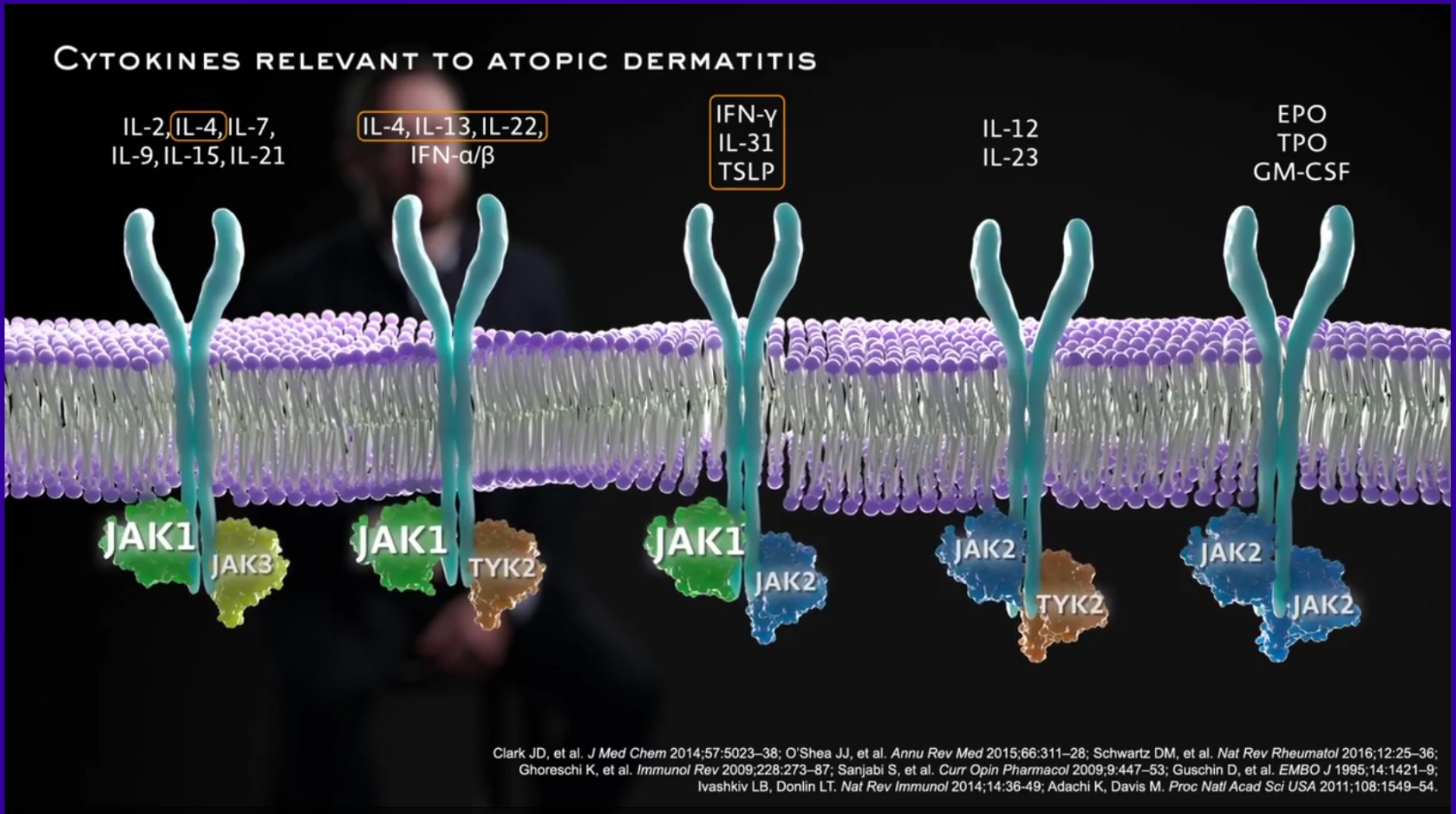


Effect of dupilumab treatment





JAK pathway in AD



Clark JD, et al. *J Med Chem* 2014;57:5023–38; O'Shea JJ, et al. *Annu Rev Med* 2015;66:311–28; Schwartz DM, et al. *Nat Rev Rheumatol* 2016;12:25–36; Ghoreschi K, et al. *Immunol Rev* 2009;228:273–87; Sanjabi S, et al. *Curr Opin Pharmacol* 2009;9:447–53; Guschin D, et al. *EMBO J* 1995;14:1421–9; Ivashkiv LB, Donlin LT. *Nat Rev Immunol* 2014;14:36-49; Adachi K, Davis M. *Proc Natl Acad Sci USA* 2011;108:1549–54.

Oral JAK Inhibitor Development in Atopic Dermatitis

DRUG	TARGET	PHASE 3 STUDIES COMPLETED	PHASE 3 STUDIES ONGOING
Baricitinib (Lilly)	JAK 1/2	• Monotherapy Ex-US (BREEZE AD1) • Monotherapy Ex-US (BREEZE AD2) • Monotherapy- US (BREEZE AD5) • Combo with TCS (BREEZE AD7)	Pediatric studies Cyclosporine failures Long-term extension
Abrocitinib (Pfizer)	JAK 1	• Monotherapy Global (MONO-1) • Monotherapy Global (MONO-2)	Abro vs Dupi (COMPARE) MOA study Combo with TCS Long-term extension
Upadacitinib (Abbvie)	JAK 1	None, but +P2 monotherapy	Monotherapy X 2 Combo with TCS Lon-term extension Upa vs. Dupi
Gusacitinib (Asana)	Pan JAK + SYK	None, but +P2b	None

JAK Inhibitors: Adverse Events of Interest

- Major adverse cardiac events (MACE)[13,5]
- Venous thromboembolism (VTE)[14]
- Malignancy[14]
- Acne/folliculitis[4]
- Laboratory abnormalities[5,15,16]
  - Anemia, neutropenia, lymphopenia
  - Elevated creatine phosphokinase (CPK)
  - Increased serum lipid levels

These adverse events appear to be a class effect of JAK inhibitors[4,5,13-16]; however, long-term safety data on these are limited,[17] and current studies in AD show low incidence of serious AEs[18-20]