Improving People's Lives Through Innovations in Personalized Health Care

# Allergic Skin Disorders and HAE

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# Disclosures

- Dr. Martin has no relevant financial relationships to disclose.

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# Objectives

- At the end of this presentation, the participant will have reviewed the recognition and treatment of allergic skin disorders, to include:

1. Urticaria and Angioedema
2. Hereditary Angioedema
3. Atopic Dermatitis
4. Allergic Contact Dermatitis

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# Urticaria and Angioedema

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# Urticaria/Angioedema

- Urticaria
  - Pruritic, erythematous, cutaneous elevations that blanch with pressure, indicating the presence of dilated blood vessels and edema
- Angioedema
  - Similar pathologic alterations in deep dermis and subcutaneous tissue; swelling is predominant manifestation, little or no pruritis; may be painful or burning

# Angioedema

- Unlike other forms of edema
  - Not characteristically in dependent areas
  - asymmetrically distributed
  - transient
- Often seen with urticaria

# Urticaria

- Acute vs chronic
  - Urticaria that exceeds 6 weeks is arbitrarily designated chronic
- Dermagraphism
  - Ability to write on skin:  2-5% of population
  - Only small fraction warrant chronic treatment with antihistamines

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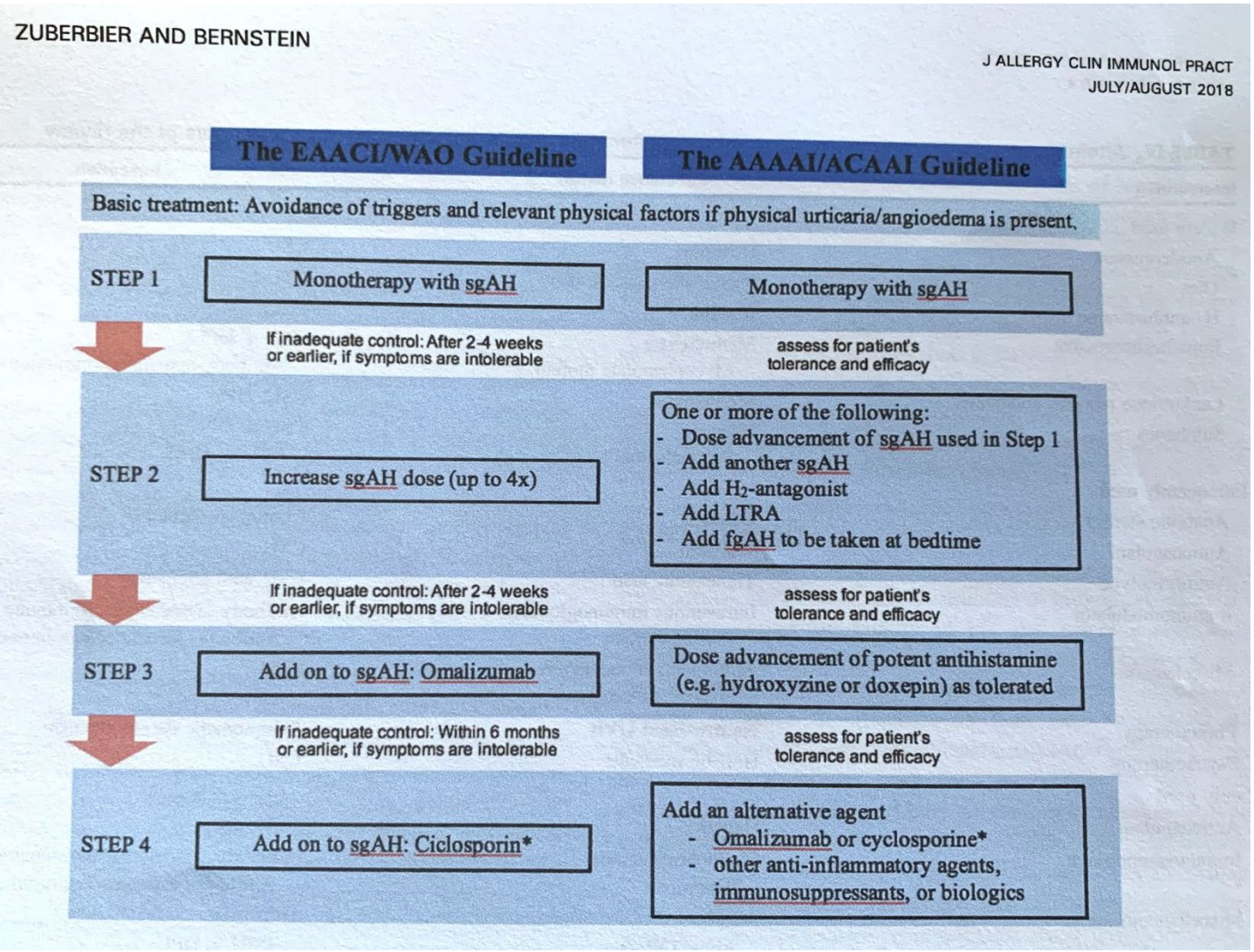
JULY/AUGUST 2018



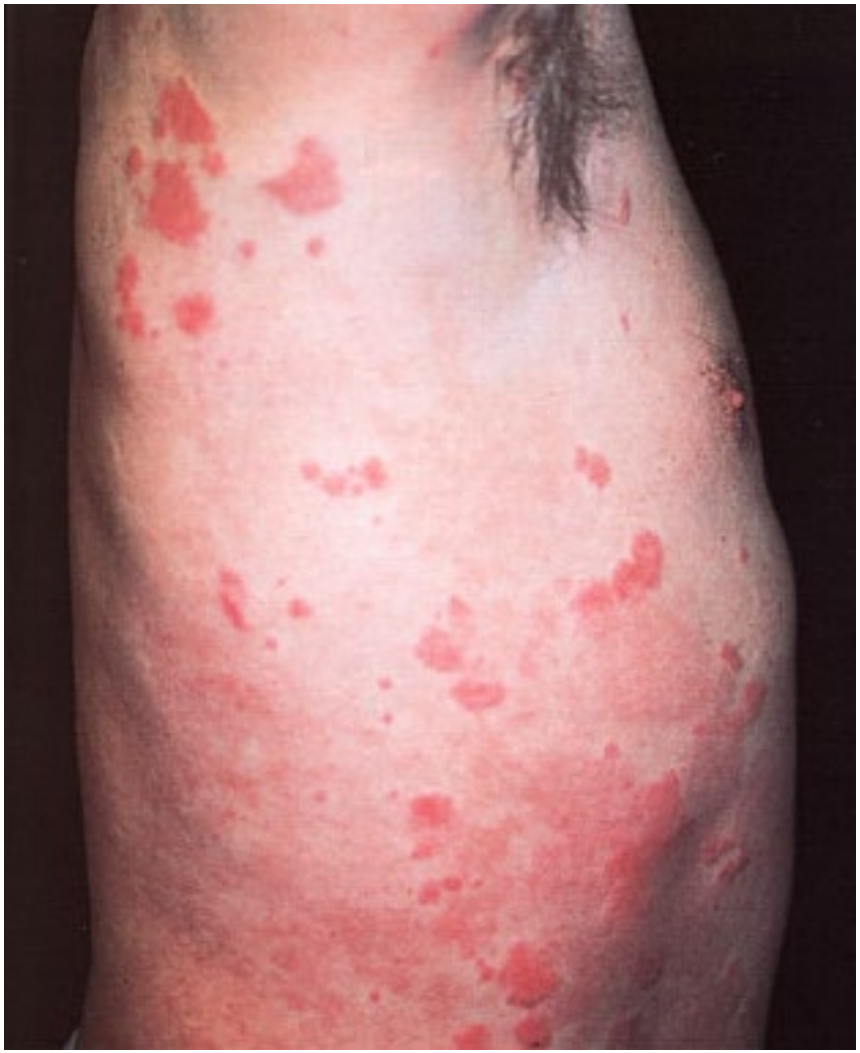
# Urticaria Guidelines

- Relatively new Urticaria Guidelines have been published
  - **First line treatment** of Chronic Spontaneous Urticaria is 2nd Generation antihistamines
  - **Second line treatment** is to increase antihistamine dose
    - Often to 2 to 4 times recommended dose
    - US:
      - May add another 2nd gen antihistamine
      - May add H2-antagonist
      - May add LTRA
      - May add 1st gen antihistamine at bedtime
  - **Third line**, there is disagreement between US and European/WAO guidelines
    - US: dose advancement of potent (1st gen) antihistamines
    - European: Add on omalizumab
  - **Fourth line**
    - US: omalizumab or cyclosporine
    - European: Add on cyclosporine
- **Not present: corticosteroids**

# CASE 1: MJ

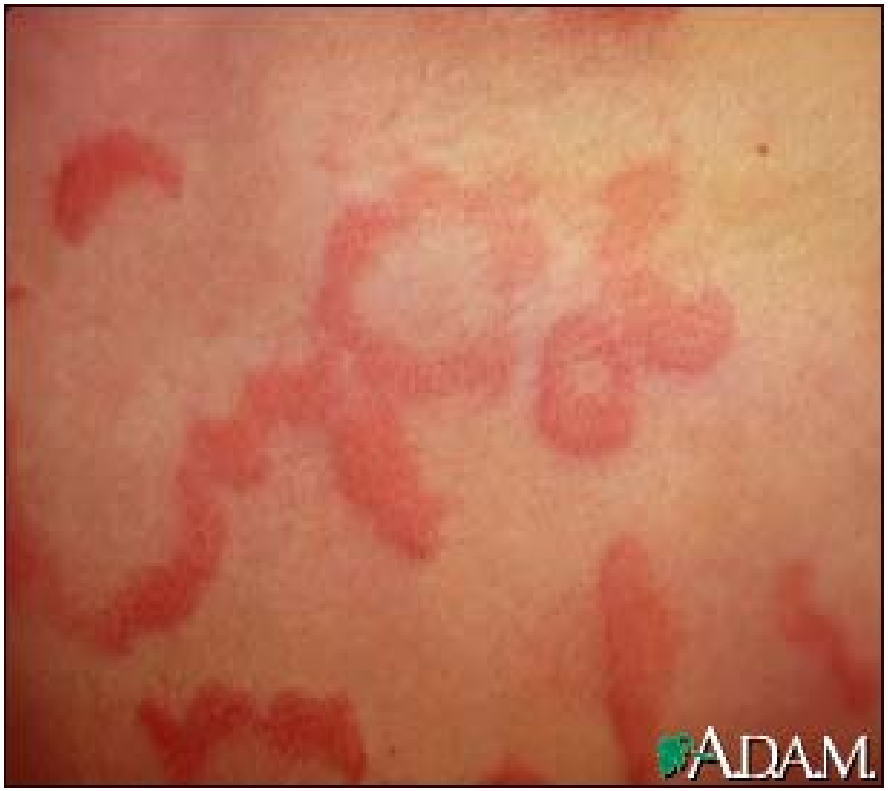
- 42 y/o w/m with CC: “whelps” x 2 months
  - Itching
  - 1st episode: No lifestyle changes
  - Doctors didn’t help
    - Benadryl, Claritin, Tavist w/o relief
    - Lab work, x-rays normal
- PE: 0.5-5 cm urticarial lesions

# Urticaria



# Urticaria

- Papules and plaques:
  - pruritic
  - erythematous
  - edematous
  - blanchable
  - 1mm to several cm in diameter
  - last < 24 hours

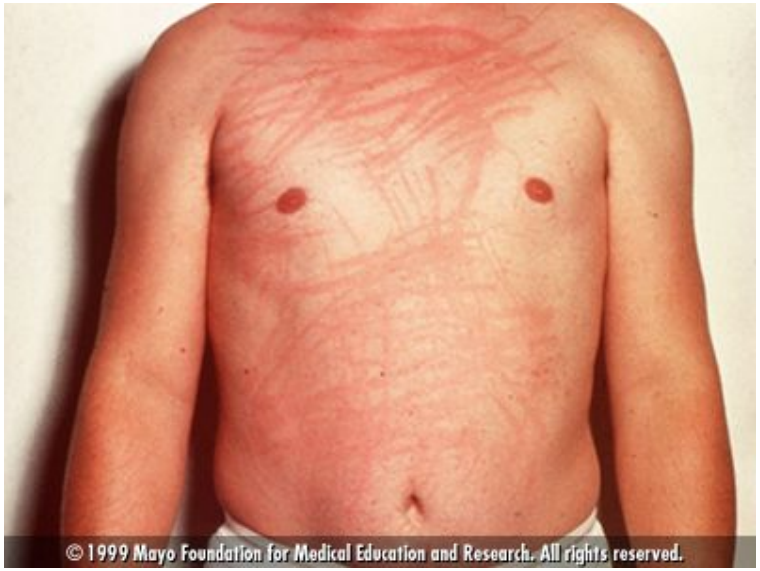


# Urticaria Evaluation
## History

- Duration - < or > 6 weeks
- Triggers – identifiable cause more likely in acute but < 5% in chronic
  - ingestants, contactants, physical stimuli, infections
- Lesional hx
  - duration, purpura, pain
  - refer to Dermatology if suspected vasculitis for Bx
- **PMH/ROS suggestive of systemic disease**

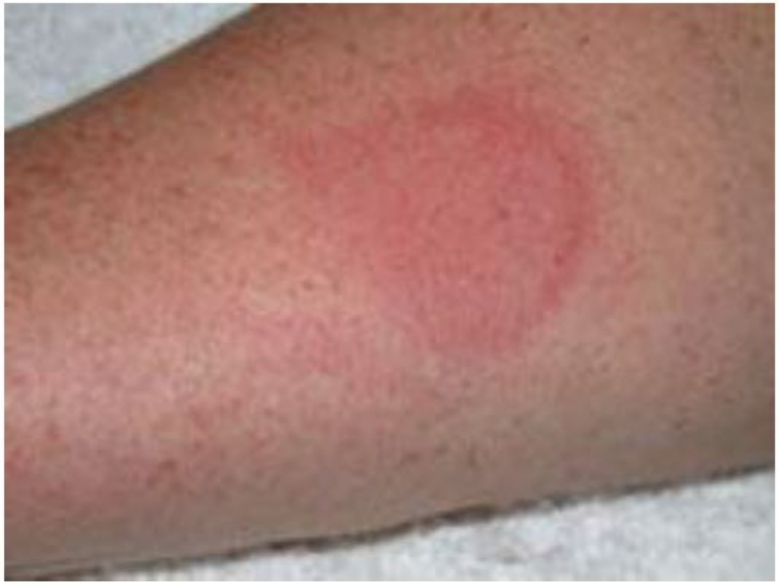
# Physical Urticaria

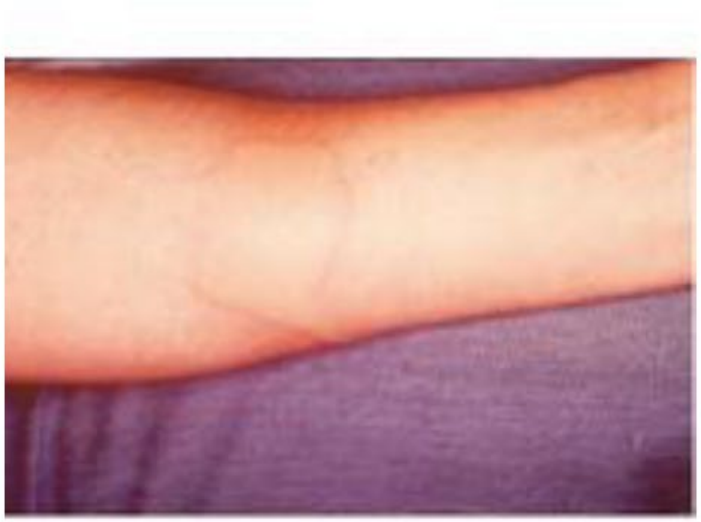
- Dermatographism
- Cholinergic
- Cold
- Delayed pressure urticaria/angioedema
- Solar
- Vibratory
- Aquagenic




# Ice cube test

- Cold Urticaria

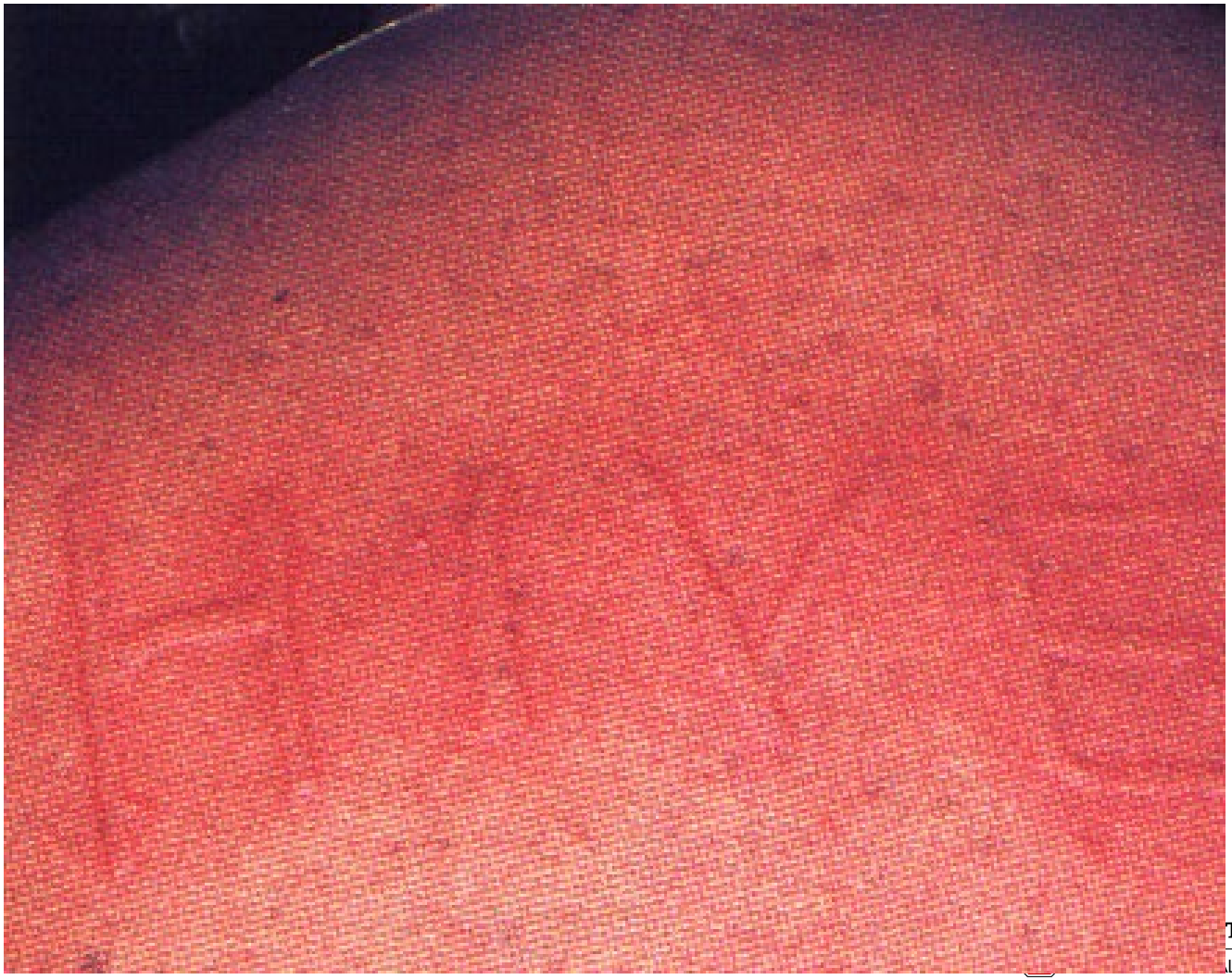




Similar images have been on the board in the past.

# What's this?

Again, similar images have been on past board exams

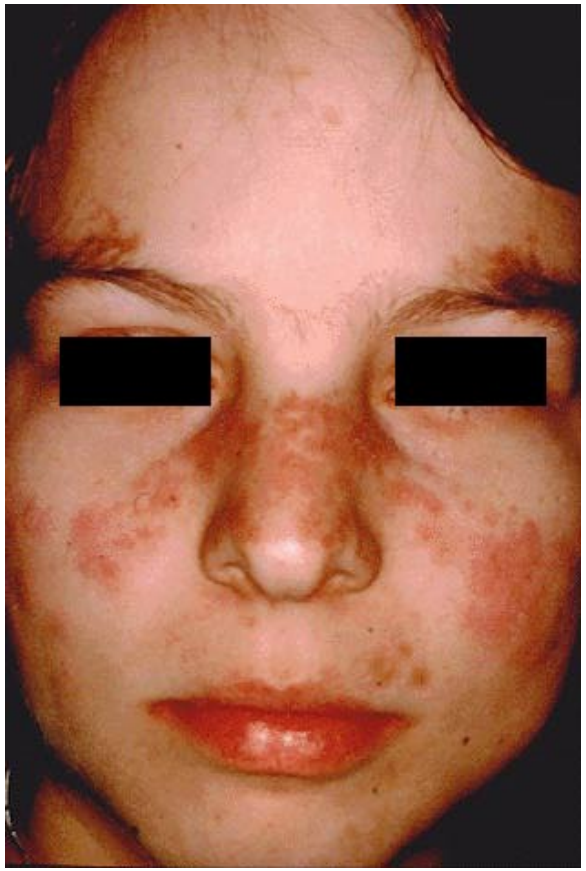


# Urticaria Evaluation
# Labs

- Skin tests
  - Seldom indicated
  - Of questionable value
    - can't get the patient off antihistamines
    - many patients have dermatographism
  - Most urticaria is **not** triggered by food or aeroallergens
- Labs as indicated by Hx/PE (look for underlying cause – Not routine)
  - TSH, CBC, LFT's, ESR, ANA, C4
- Skin Biopsy as indicated by History

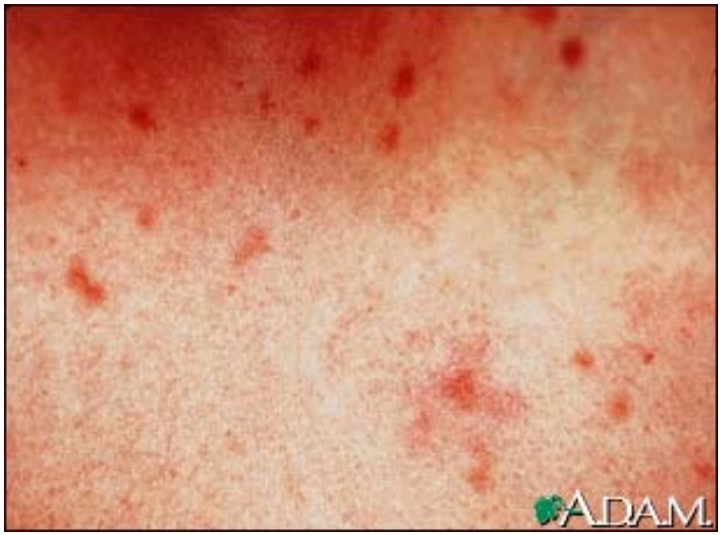
# Urticaria Differential Diagnosis
# Other pruritic skin conditions

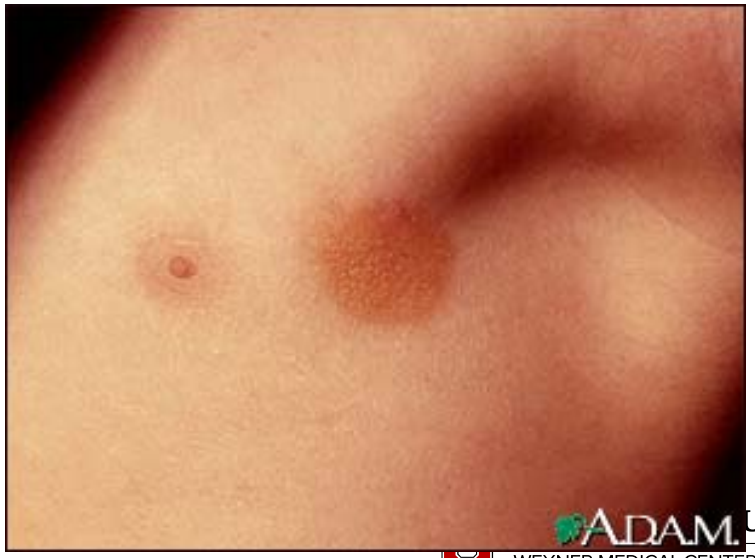
- Urticarial vasculitis
- Viral exanthema
- Contact dermatitis
- Parasites
- Liver disease
- SLE
- Malignancy

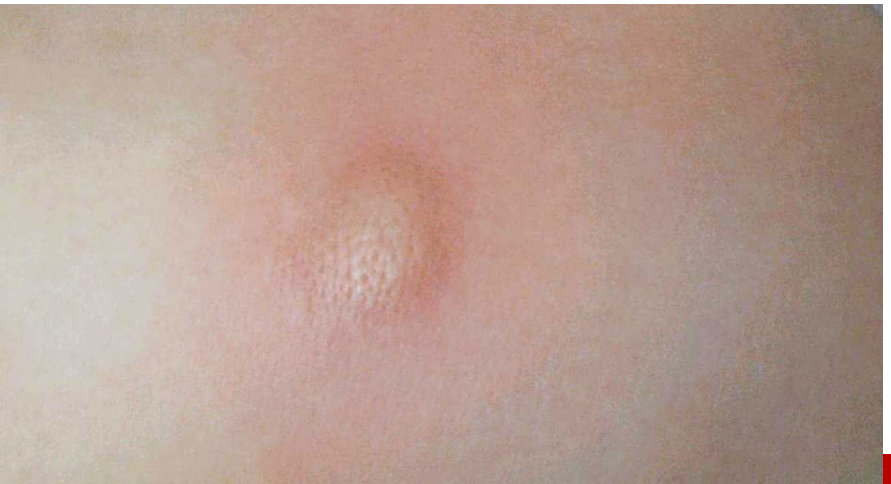


# Urticaria Pigmentosa

- Persistent pigmented macular lesions
- Darier's sign
- Adult cases more likely to progress to systemic disease



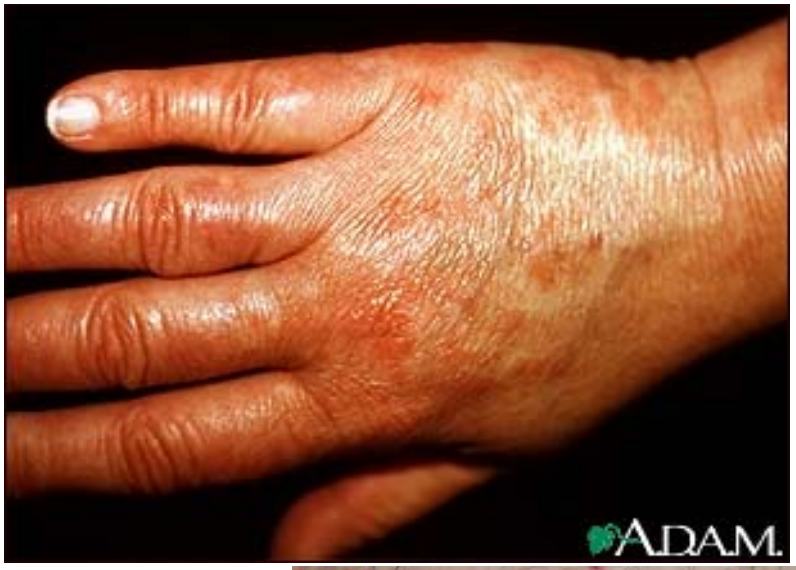



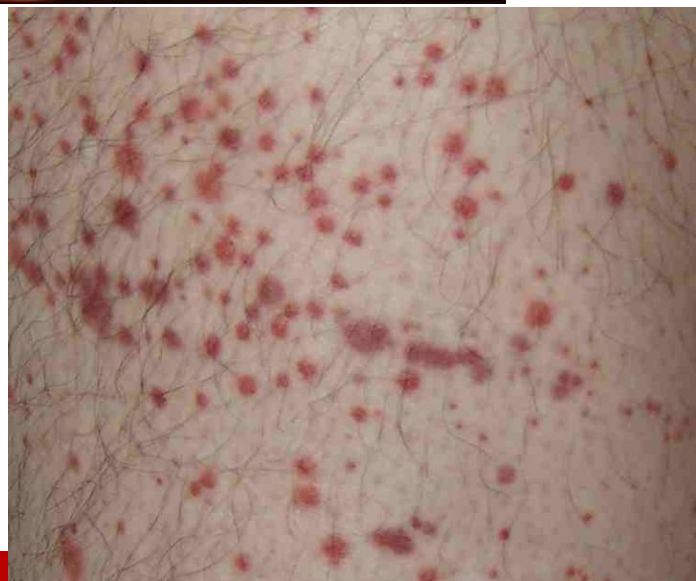
# Mastocytosis

- Excessive Mast cells
- Four classifications
  - indolent
  - with hematologic abnormalities
  - aggressive
  - mast cell leukemia
- Multiple organ involvement
  - BM, GI, liver, skin, long bones

# Urticarial Vasculitis

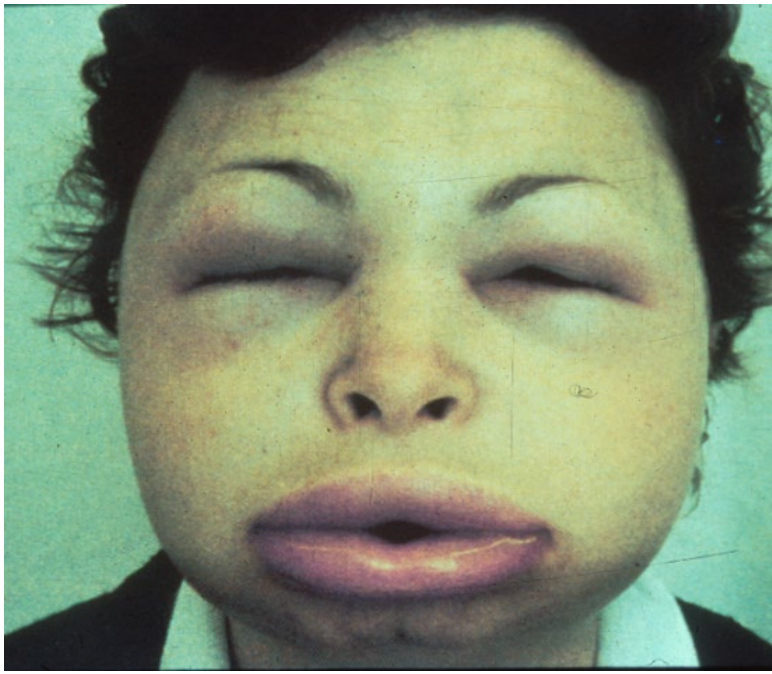
- Necrotizing vasculitis
  - endothelial cell edema
  - perivascular PMN infiltrate
  - fibrinoid deposits in venules
  - leukocytoclasis - nuclear debris
- Last > 24 hours
- Painful and leave purpura/bruising with resolution



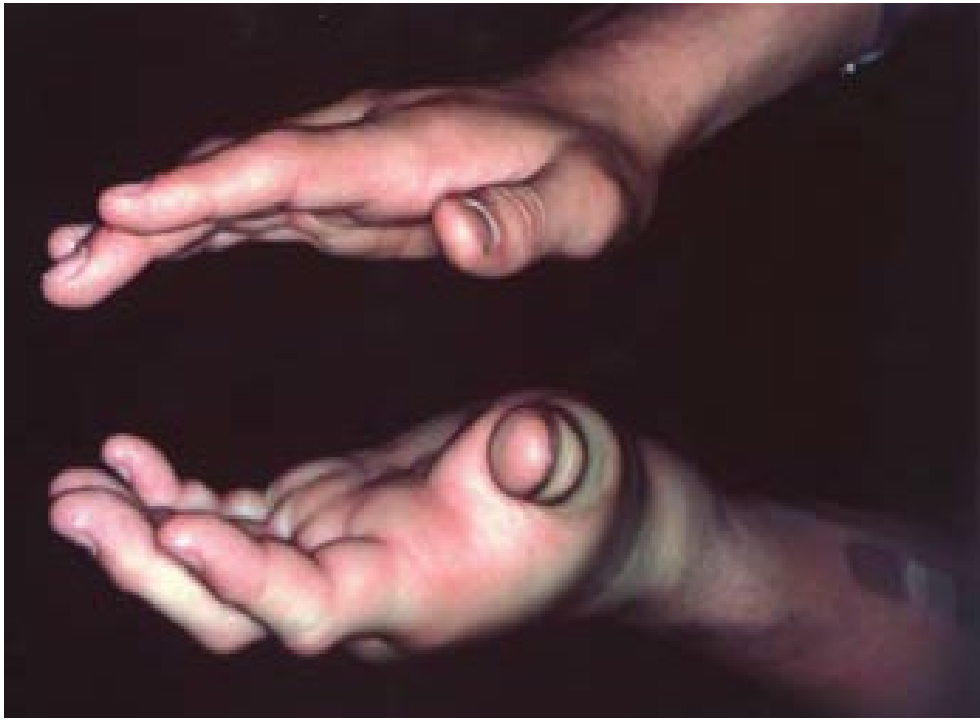
# Angioedema

- 10-20% of the population
- 94% of cases are drug induced
  - ACEI
  - NSAIDS
  - Others
- Hereditary
- Autoimmune acquired
    - very rare, < 50 case reports



# Angioedema

- Non-pitting edema
- Occurs deeper than urticaria
- Overlying skin is usually normal
- Usually burns and is not pruritic



# ACEI Induced Angioedema

- 1-2 cases per 1000 persons
- >70% symptomatic within first week of therapy
- Likely precipitated by increased bradykinin
  - Angiotensin II inhibits bradykinin
    - ACEI blocks conversion of angiotensin I → II
  - Vasodilatation, increased vascular permeability
- Can lead to life-threatening upper airway obstruction
  - 22% require intubation with11% mortality
- Rare in Angiotensin II receptor blockers

# Hereditary Angioedema

- Rare (1/150,000)
- Autosomal dominant
- Onset in adolescence
- Angioedema is
  - painless and non-pruritic
  - lasts 3-5 days
  - unrespsonsive to Epi, antihistamines, pred.
  - triggered by mild trauma

# Hereditary Angioedema

- C1 Inhibitor (C1-INH) deficiency
  - Type I (85%)
    - Quantitative deficiency (5-30% normal)
  - Type II (15%)
    - Qualitative deficiency
    - Quantity is normal or elevated
    - Functional activity is markedly reduced
  - Type III
    - Unknown cause
    - C1q, C1-INH, C4 normal with suggestive history
    - C4, C1-INH normal during attack

# Hereditary Angioedema

- C4 and C2 markedly low
  - both between and during attacks
  - **C4 is screening test**
- Autosomal dominant inheritance
- Symptoms related to subcutaneous and/or submucosal edema
- C1 normal
  - Low C1 consider acquired form
    - Lymphoma
    - Low C4, C2 and C3

# Acquired Angioedema

- Very rare
- Present in adults
- CLL, NHL, cryoglobulinemia, Waldenstrom macroglobulinemia,myeloma
- Decreased C4 like in HAE
- Decreased C1q which distinguishes HAE from AAE

# HAE vs AAE

| DZ | C1 INH Quant | C1 INH Activity | C1q | C4 |
|---|---|---|---|---|
| HAE I | Low | Low | NL | Low |
| HAE II | NL | Low | NL | Low |
| AAE I | Low | Low | Low | Low |
| AAE II | Low/NL | Low | Low | Low |

# HAE Treatments

- **Prophylaxis**
  - Cinryze:  IV; C1-esterase inhibitor
  - Haegarda:  SC; C1-esterace inhibitor
  - Takhzyro:  SC; plasma Kallikrein inhibitor (monoclonal antibody)
- **Acute**
  - Berinert:  IV; C1-inhibitor concentrate.  Approved for self-administration
  - Ruconest:  IV; Plasma free recombinant C1-inhibitor concentrate.  Approved for self administration
  - Firazyr:  SC; B2 bradykinin receptor antagonist.  Approved for self-administration
  - Kalbitor:  SC; kallikrein inhibitor.  Must be administered by healthcare professional

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# Atopic Dermatitis

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# Atopic Dermatitis

Atopic Dermatitis is a characteristic cutaneous inflammatory condition that typically occurs in individuals with a personal or family history of atopy.

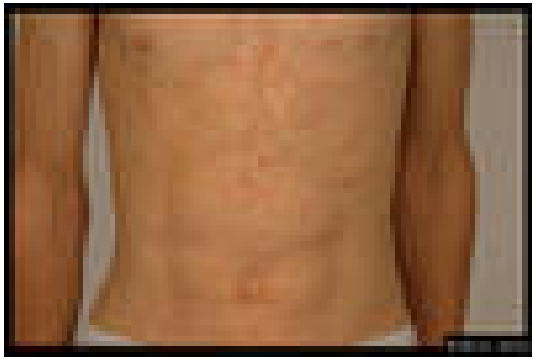
Atopic Dermatitis (AD) is a chronic, relapsing, inflammatory skin manifestation of the *Atopic Triad.*

Incidence of AD is increasing in all industrialized nations.

# Clinical features

Acute atopic dermatitis

- No primary lesion
- Intensely pruritic
- Erythematous papules associated with excoriations,vesiculations, and serous exudate

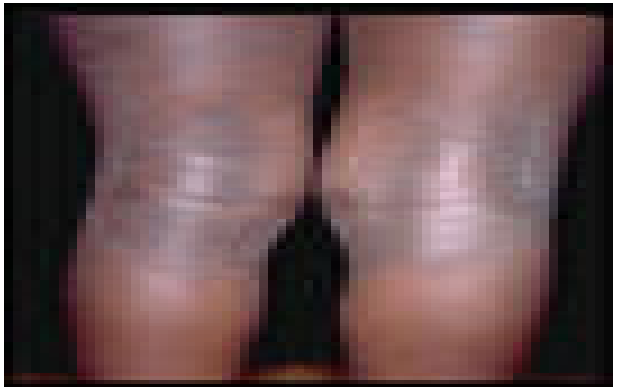


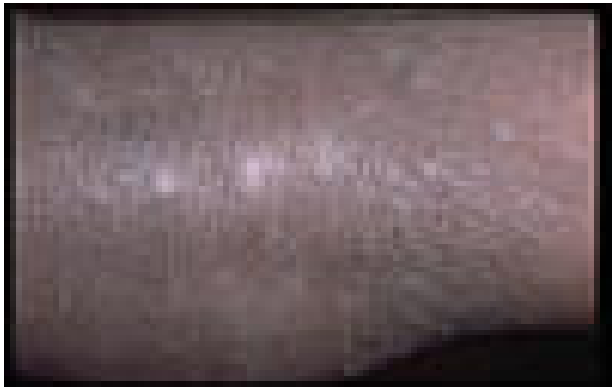
# Clinical features

**Chronic atopic dermatitis**

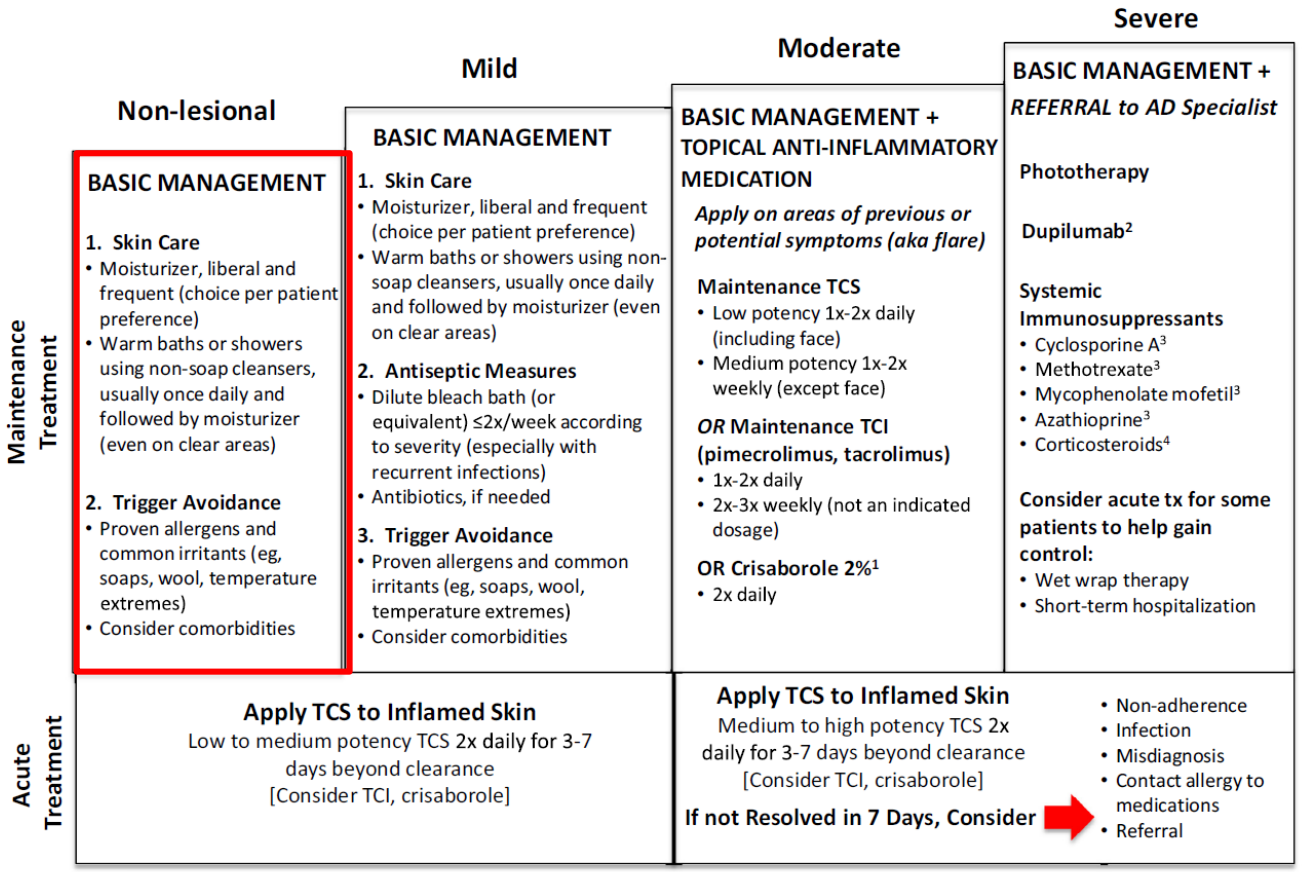
***Lichenification***

- Extensor surfaces during infancy
- Flexural surfaces during childhood and adult years





# 2018 Atopic Dermatitis Yardstick




Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, Silverberg J, Farrar JR. Atopic Dermatitis Yardstick: Practical recommendations for an evolving therapeutic landscape. Ann Ann Allergy Asthma Immunol. 2018 Jan; 120(1):10-22

# Diagnostic Features of AD Clinical

**Essential**

- Atopy
  - Personal Hx / FHx of Eczema, hay fever, asthma.
- Pruritus
- Eczema
  - Acute
  - Subacute
  - Chronic

# Genetics of AD

- Atopy is the result of a complex interaction of multiple genes, and does not fit a simple autosomal dominant model

- 81% of the offspring of two parents with AD will develop AD, 60% when one parent has AD and the other has respiratory allergies, 56% when one parent is atopic.

# Attributes of AD

## I. *Atopy*

- Polygenic immunologic aberrations
- Th1 / Th2 imbalance (transitory)
- Increased IgE antibody production
- Eosinophilia
- Hyper-releasable basophils (& mast cells)
- Increased E-selectin, VCAM-1, and ICAM levels

# Attributes of AD

## II. *Pruritus*

- Probably the “primary” symptom of AD
- Mildest mechanical stimulation of atopic skin is perceived as “itch”
- *Alloknesis* - once itching has started, the likelihood of the surrounding skin to itch increases
- Questionably induced by histamine

  (Antihistamines minimally effective)

# Triggers of Itch for AD

- Irritants
  - Wool
  - Soaps / detergents
  - Disinfectants
  - “Occupational”
  - Tobacco smoke
- Xerosis (Dry skin)
- Microbial agents
  - *S. aureus*
  - Viral infection
  - ? Dermatophytes
- Heat / Sweating
- Contactants including dust mites
- Psychological
- Foods (IgE-induced) & those having vasodilatory properties
- Aeroallergens
- Hormones
- Climate

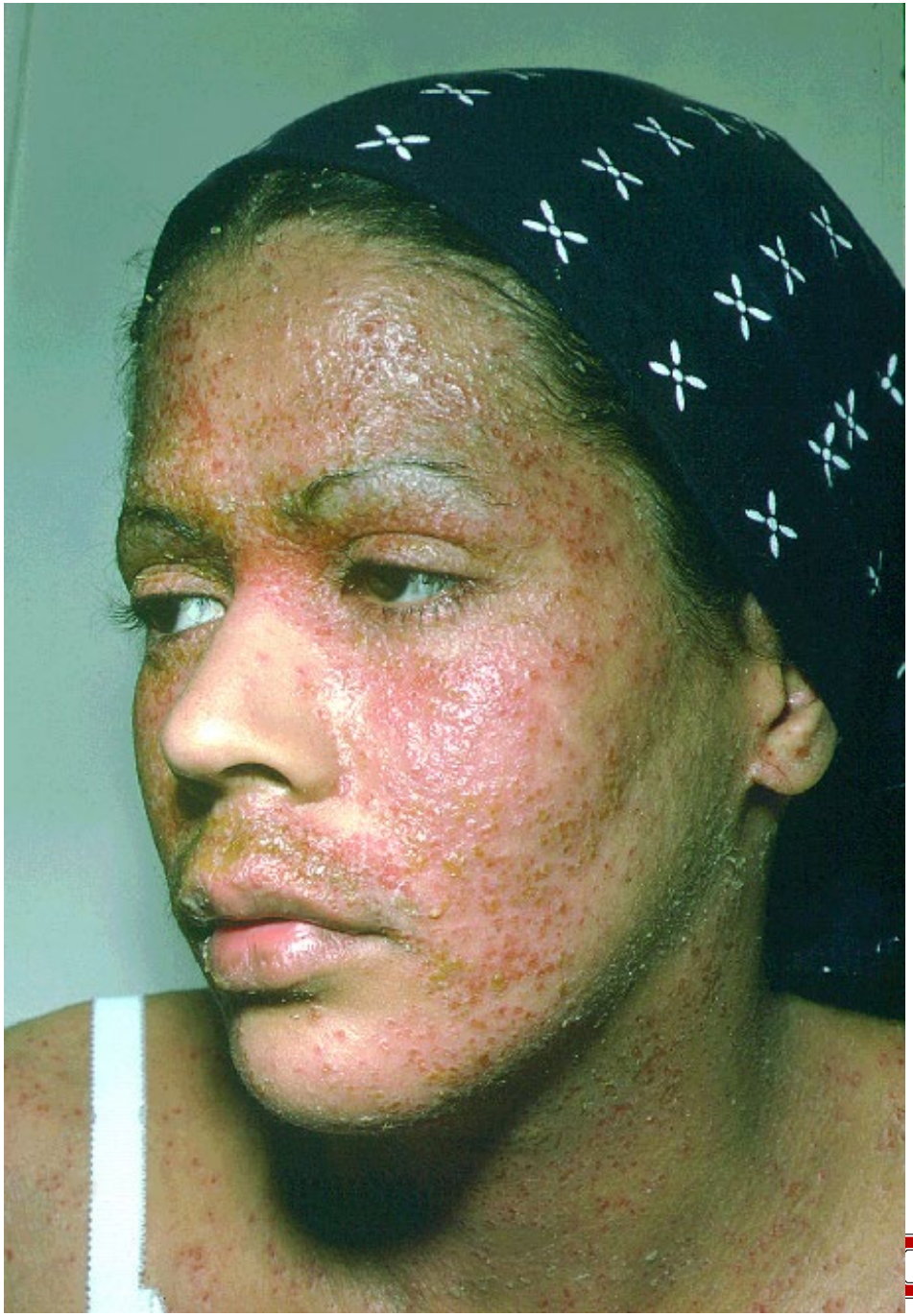
# Attributes of AD

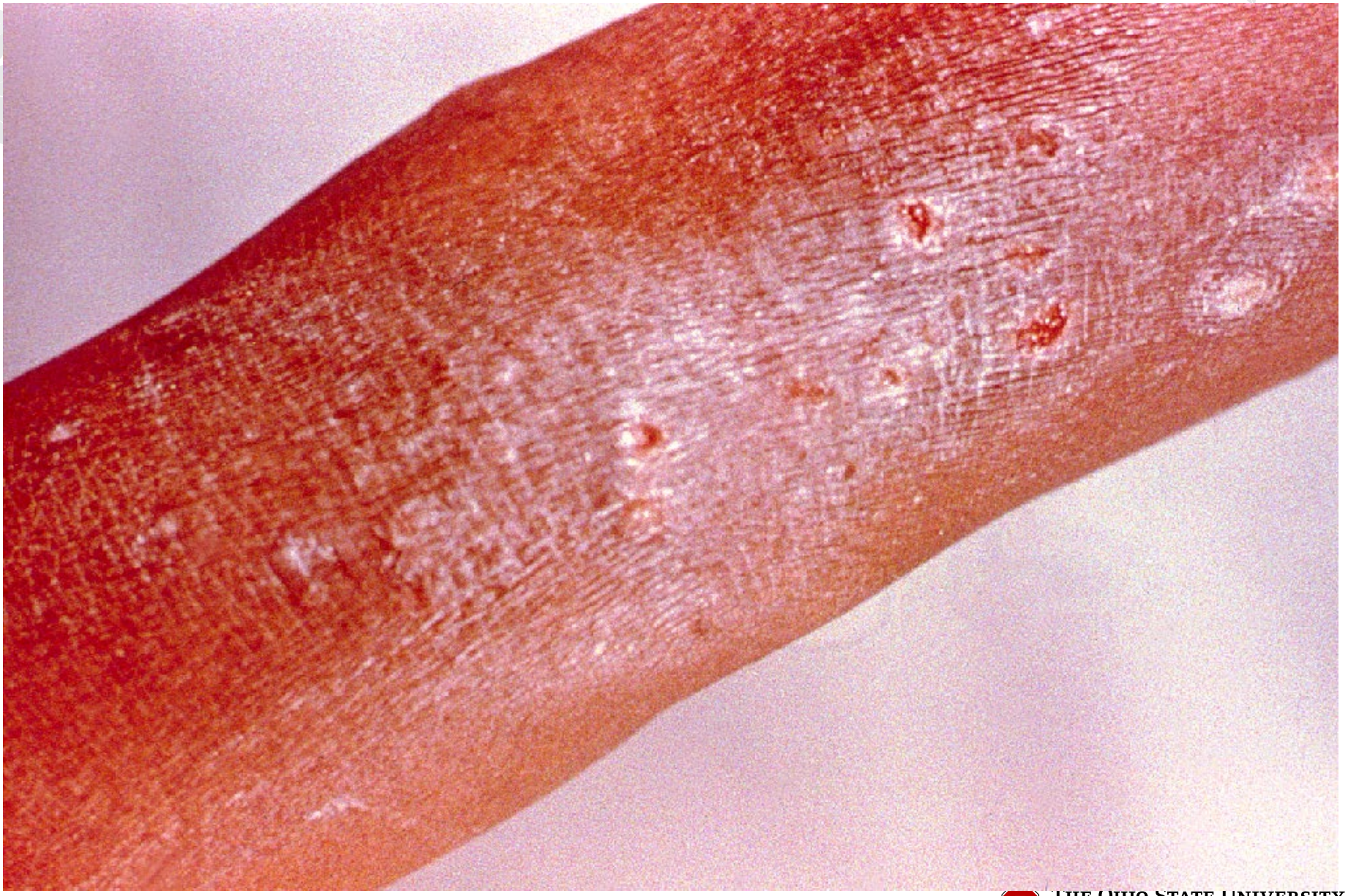
## III. *"Eczema"*

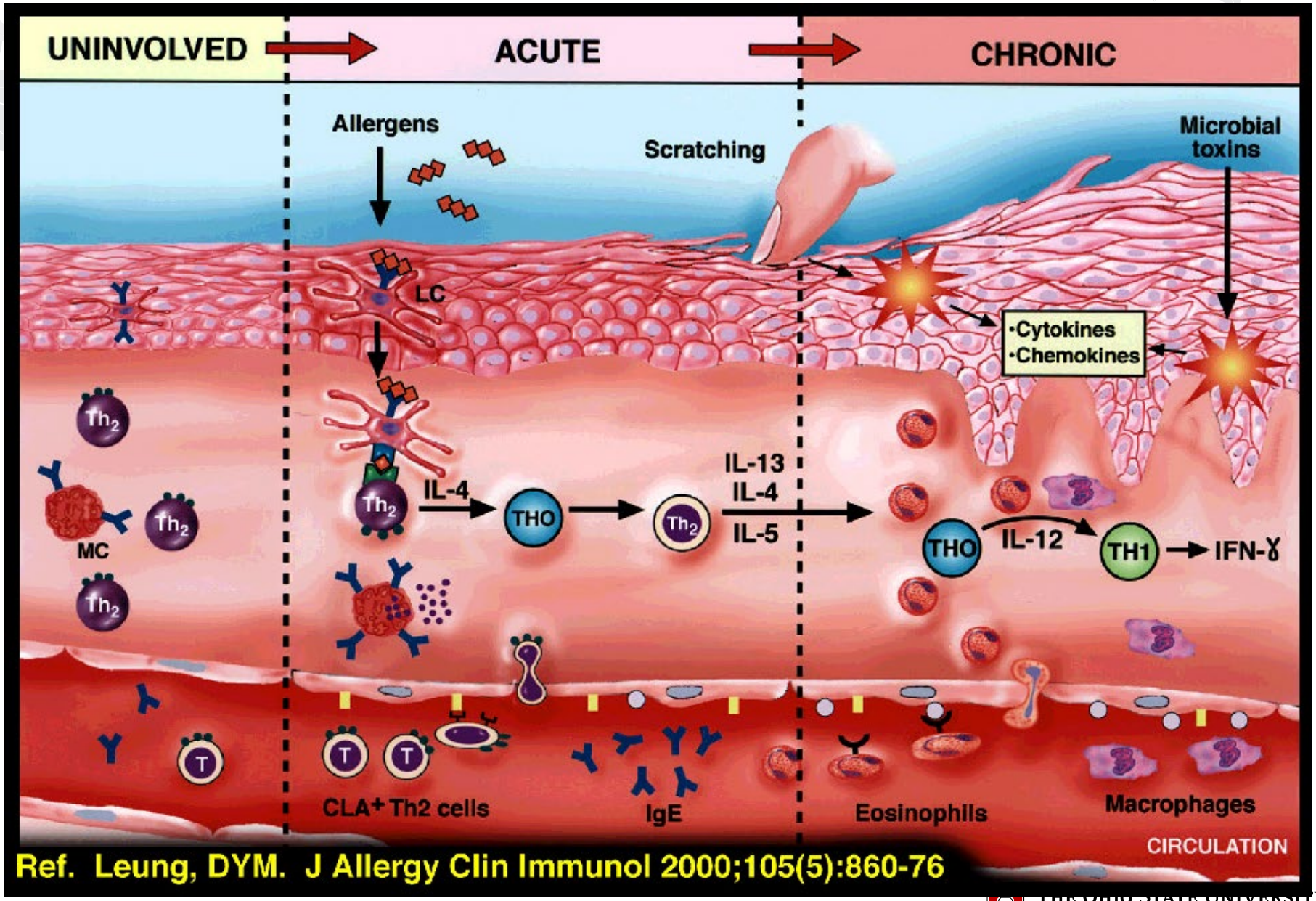
- An "isomorphic" response to trauma (i.e. scratching and/or rubbing) with the distribution restricted to those areas
- Must be differentiated from all the "other" eczemas
- "Polymorphic" can appear as acute, sub-acute, and/or chronic
- "Excoriated"
- Chronic, or chronically relapsing

# Differential Diagnosis of Adult Eczematous Eruptions

- Allergic Contact Dermatitis
- Irritant Contact Dermatitis
- Seborrheic Dermatitis
- Cutaneous T-cell Lymphoma
- Psoriasiform eruptions
- Pityriasis rubra pilaris
- Scabies
- Glucogonoma Syndrome
- Pellagra





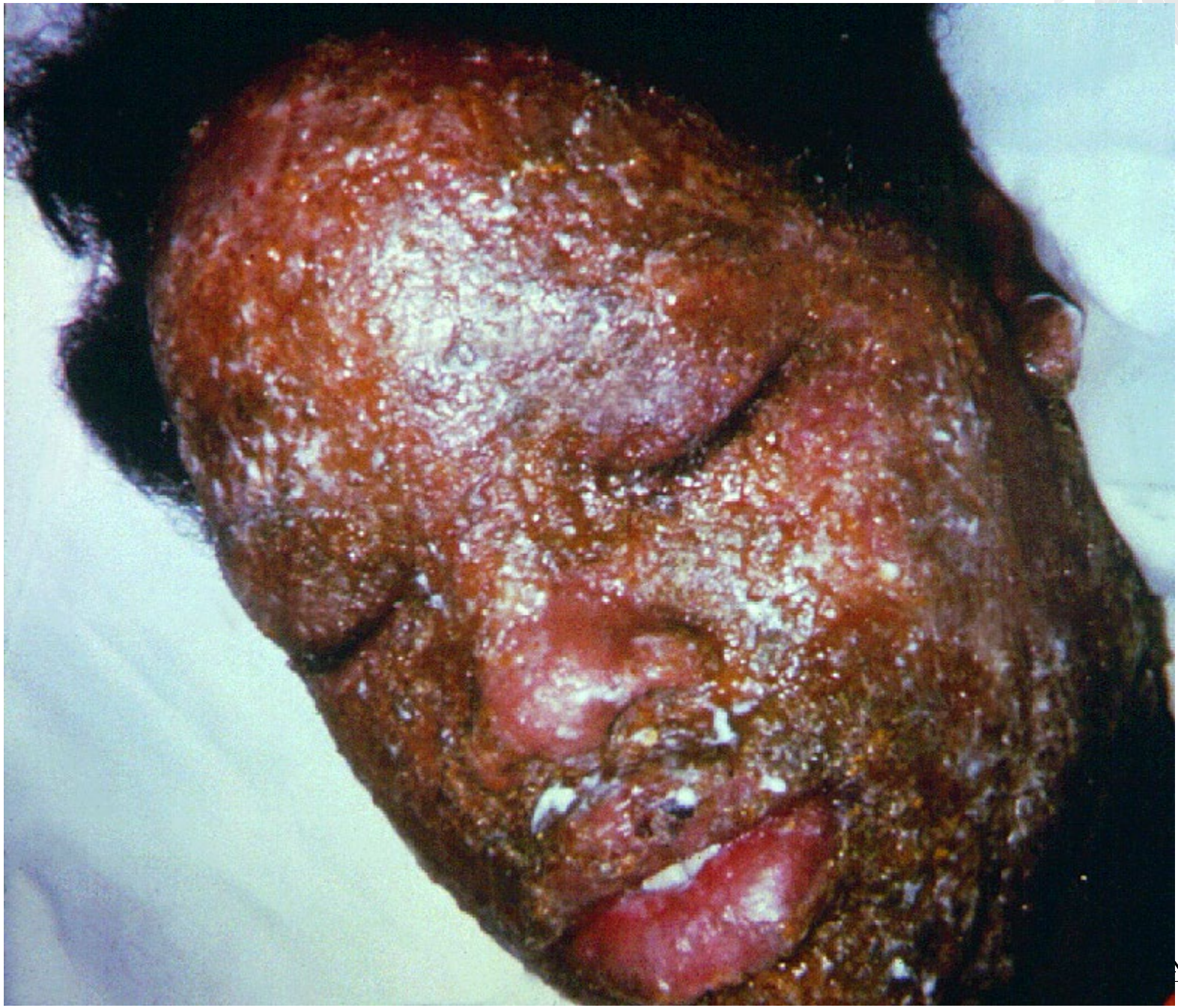

UNINVOLVED
ACUTE
CHRONIC
Allergens
Scratching
Microbial toxins
LC
•Cytokines
•Chemokines
Th2
MC
IL-4
THO
IL-13
IL-4
IL-5
IL-12
TH1
IFN-γ
T
CLA+ Th2 cells
IgE
Eosinophils
Macrophages
CIRCULATION
Ref. Leung, DYM. J Allergy Clin Immunol 2000;105(5):860-76

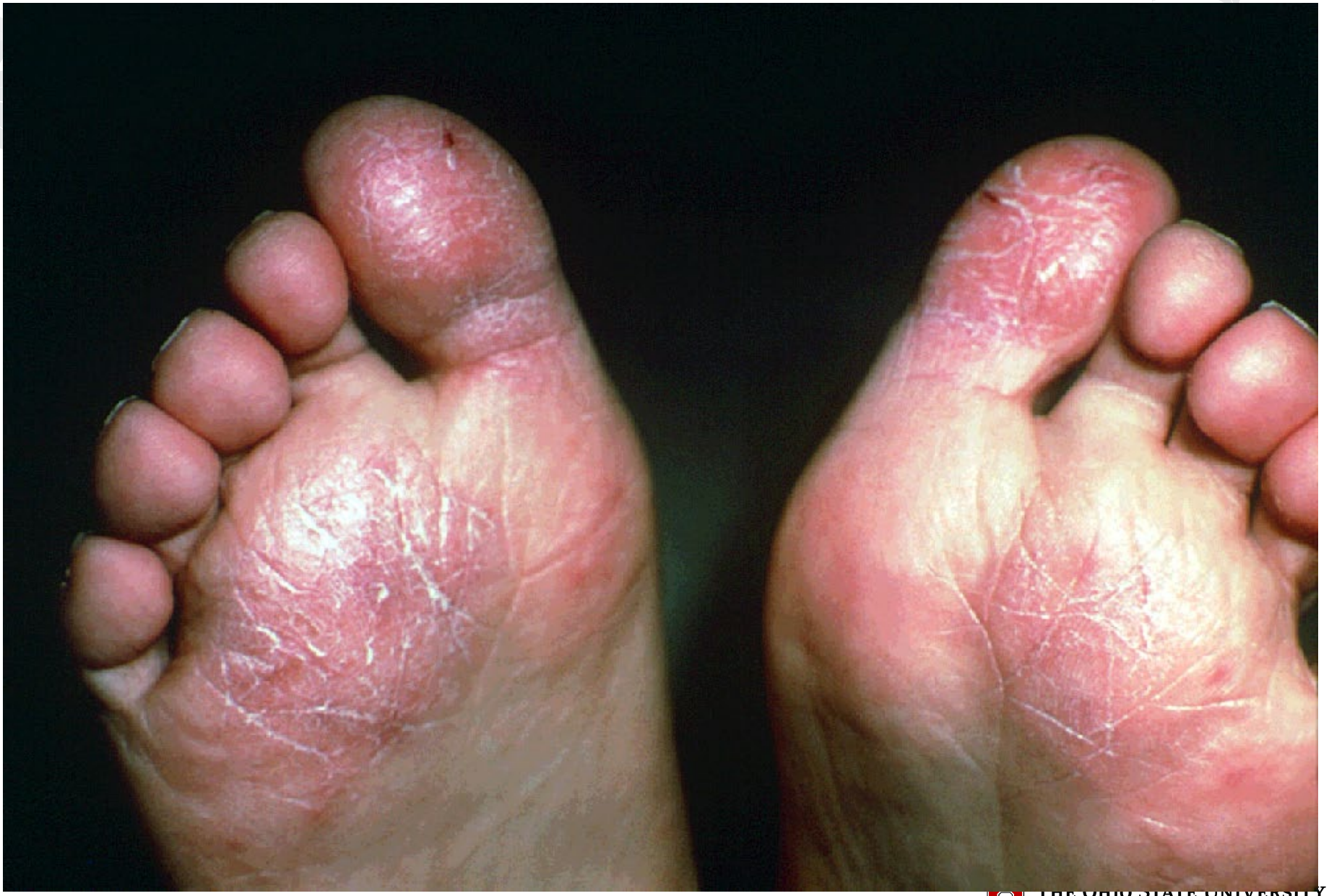
# Diagnosis of AD

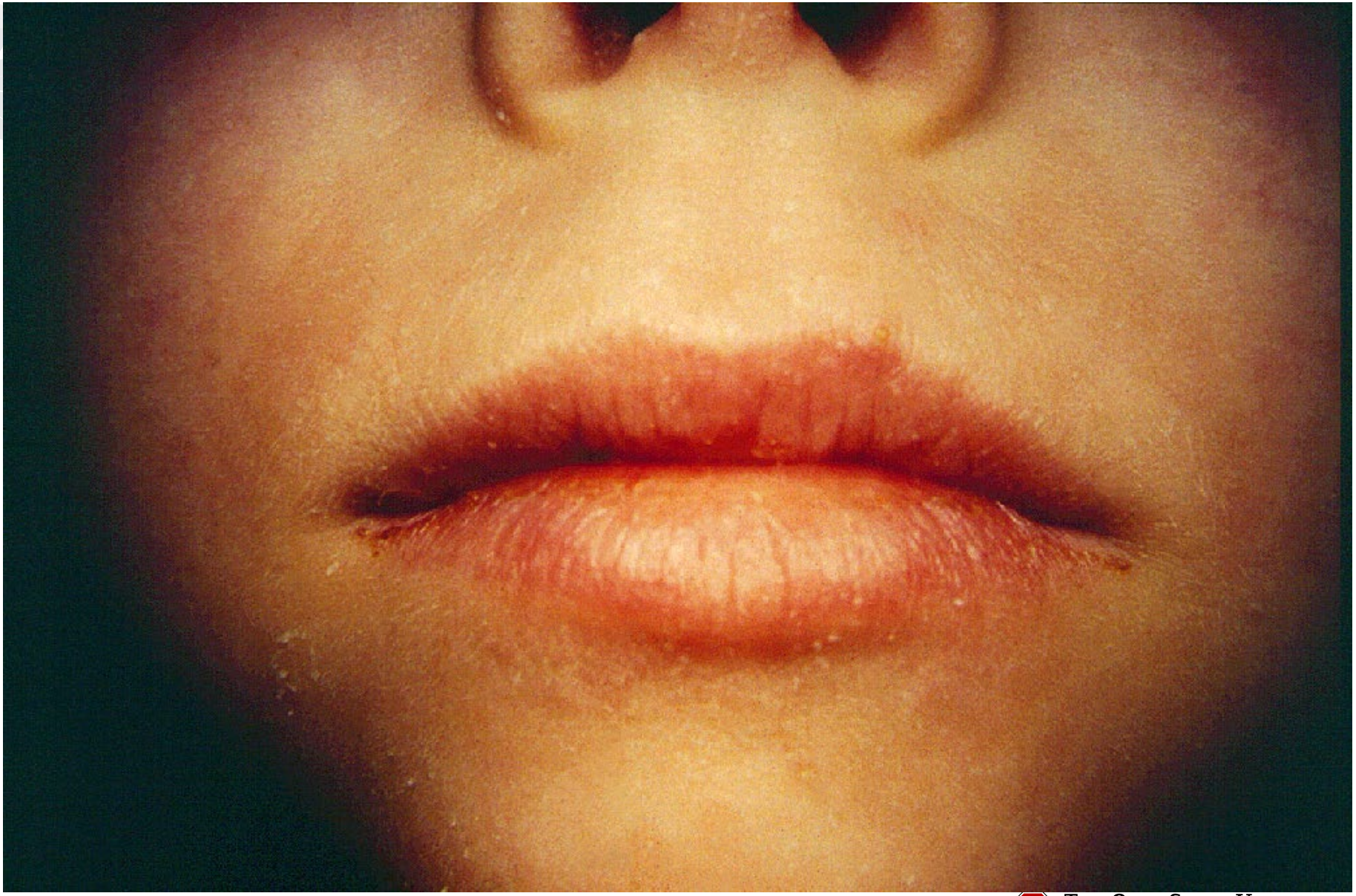
- History and physical examination
- Laboratory - (*never* routine)
  - Serum IgE level
  - Serum test for allergen-specific IgE (CAP-RAST)
  - Skin Biopsy
  - Skin culture (bacterial, viral, fungal)
  - Patch test (corticosteroids, aeroallergens)
- Prick skin test - (*never* routine)

# Complications of AD

- Secondary Infection
  - a) bacterial
    - impetiginization
    - “super-antigenicity”
  - b) viral
    - localized – verruca, molluscum, herpes
    - systemic – Kaposi’s herpetiform eruption
  - c) mycotic
    - Dermatophyte
    - Candidal







# Natural History of AD

- 60% of patients develop AD by 1 year of age
- 85% of patients develop AD by age 5
- Earlier onset often indicates a more severe course
- Many cases resolve by age 2, improvement by puberty is common
- 80% of occupational skin disease occur in atopics
- It is rare to see AD after age 50
- 50% - 60% of patients develop respiratory “allergies”

# Managing AD (Preventative)

- Carefully eliminate all the triggers of itch
  - a) environmental, occupational, and temperature control
  - b) bathing - NO SOAP ON ECZEMA
  - c) lubrication

- Prevent “scratching” or rubbing
  - a) apply cold compresses to itchy skin

# Managing AD (Therapeutic)

- Topical anti-inflammatory agents
  - a) corticosteroids (ointments > creams)
    - more potent - when “acute”
    - least potent needed for “chronic”
  - b) Tacrolimus 0.1% ointment
  - c) Ultra Violet Light
  - d) Tar preparations

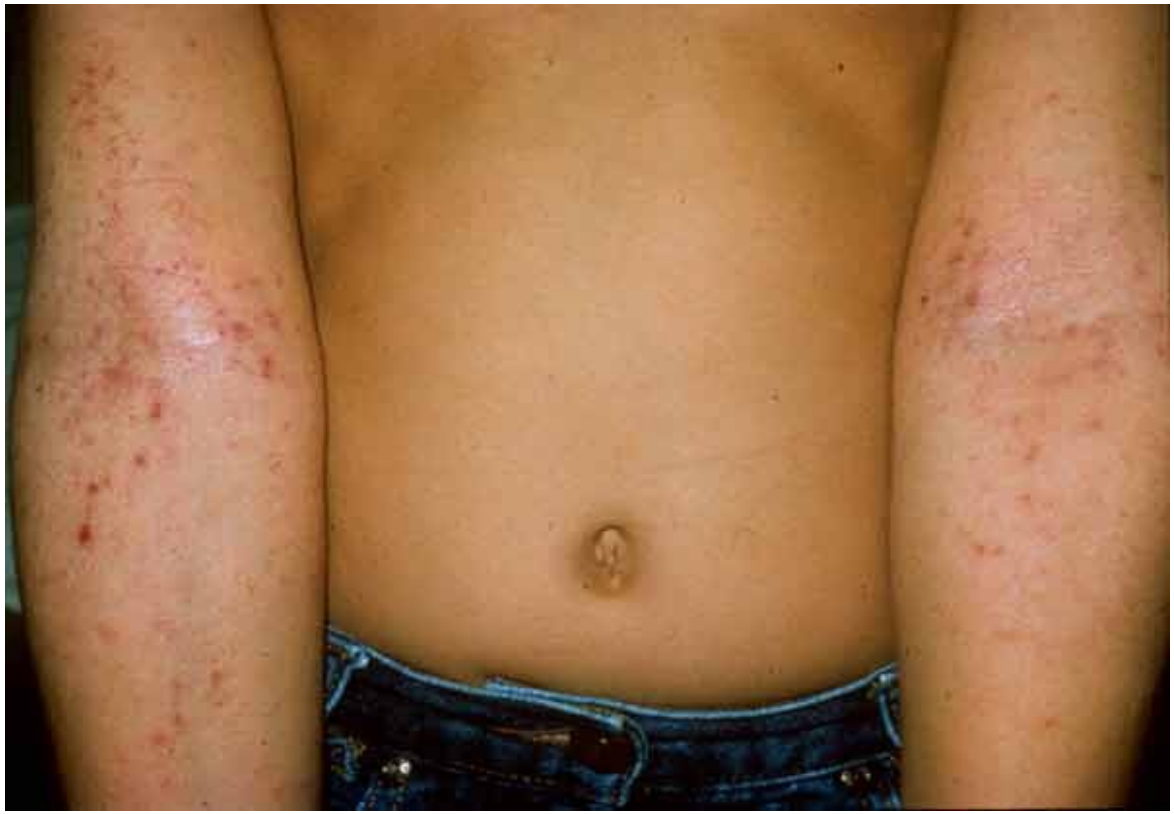
# Managing AD (Therapeutic)

- **Systemic**
  - **a) antibiotics**
  - **b) anti-inflammatory drugs**
    - **I. Prednisone**
    - **II. Cyclosporine A**
  - **c) antihistamines (?)**

# “Take-home” Message

**Atopic dermatitis has a profound impact on the social, personal, emotional and financial perspectives of afflicted families.**

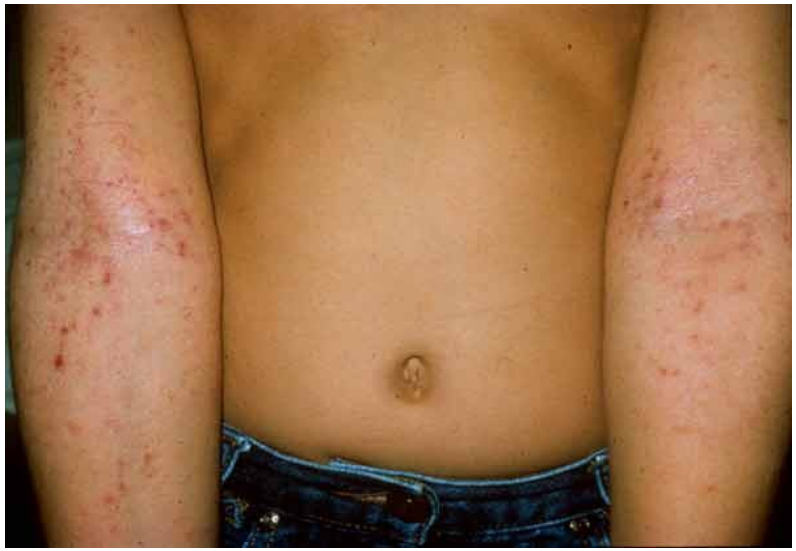
21 year old with itchy rash.
Worse in winter and summer.
Worried about food allergies.
Presented for diagnosis and therapy.



# Your patient with the this rash should be treated with?

- A. topical antibiotics
- B. topical corticosteroids
- C. oral steroids
- D. dapsone
- E. famciclovir

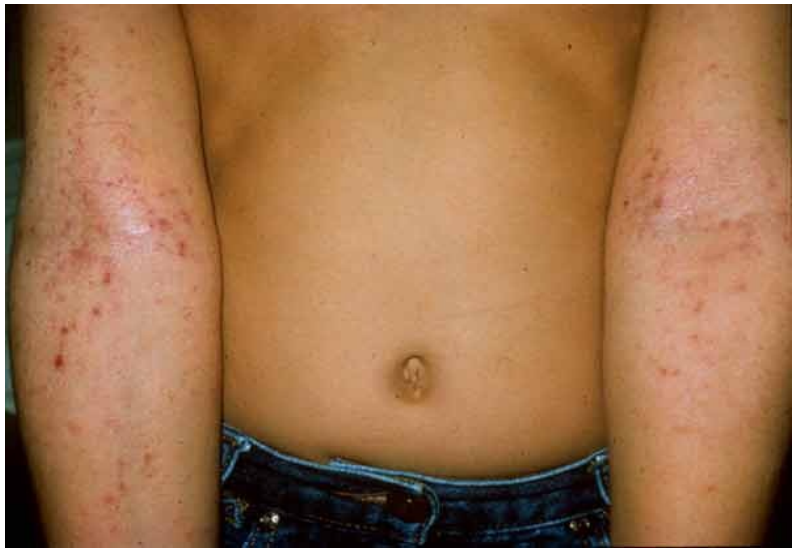
- Ans:

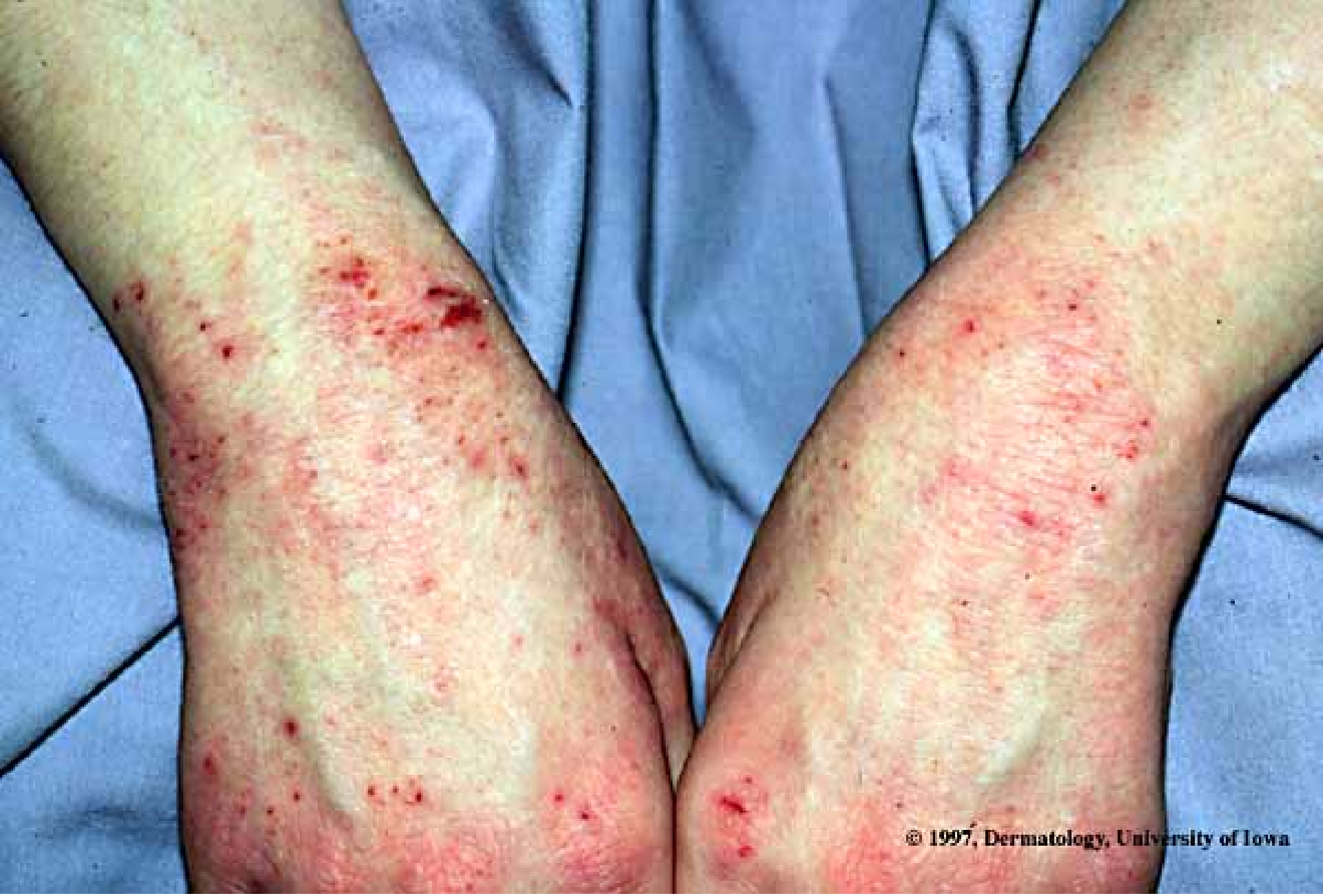


# Your patient with the this rash should be treated with?

- A. topical antibiotics
- B. topical corticosteroids
- C. oral steroids
- D. dapsone
- E. famciclovir

- Ans: B

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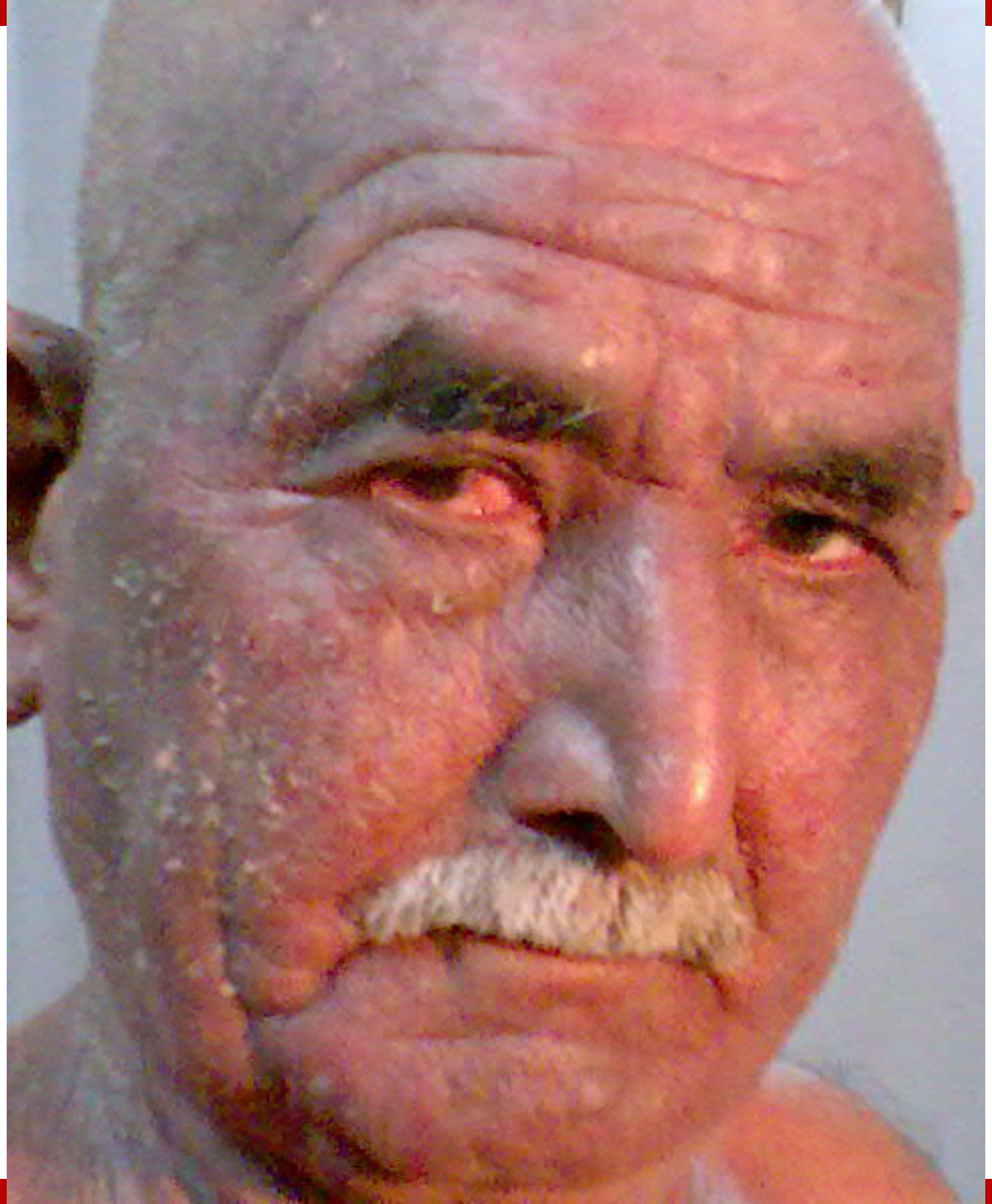


# Atopic Dermatitis

- Adults - flexure areas, hands
- Eyes- think atopic kearatoconjunctivitis
- Exacerbations – think Staph or Herpes simplex
- Anergy: decreased TH-1 cell and decreased interferon predispose to skin infections
- increase IgE, $IL_4$ , $IL_5$, GM-CSF, $IL_{13}$, (lymphocytes T helper type 2 phenotype)
- Filaggrin gene defect is very important
- Rx - lubricants, topical steroids, pimecrolimus and tacrolimus and phospodiesterase 4 inhibitor

# IMPORTANT INFORMATION ABOUT TOPICAL CORTICOSTEROID THERAPY

- Potency- ointments> creams> lotions
- Limit use of high potency on face, breasts and genitals
- Skin side effects
  - Atrophy
  - Telangiectasia
  - Striae
  - Perioral dermatitis

# TOPICAL IMMUNE MODULATORS

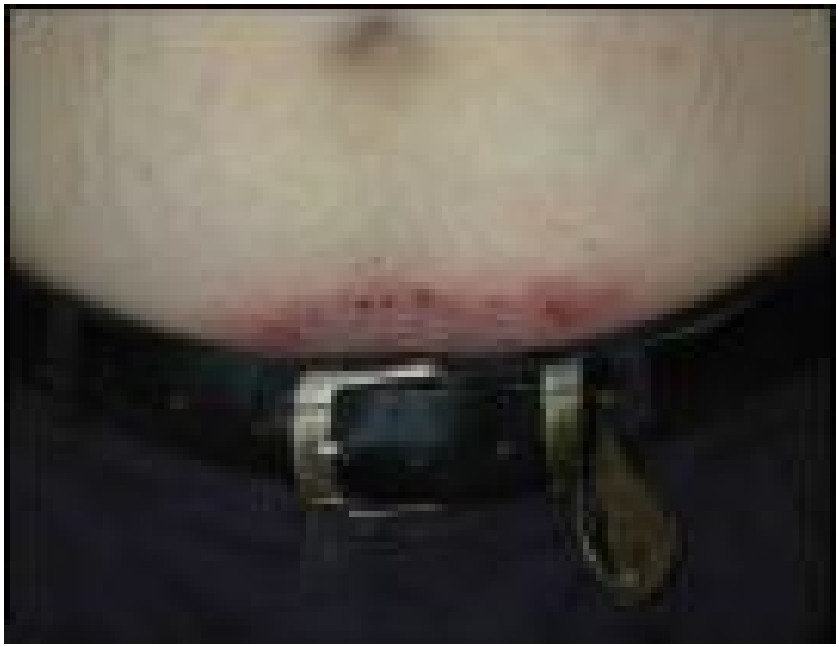
- Tacrolimus (Protopic) ointment
- Pimecrolimus (Elidel) cream

- Derived from fungal polypeptides and Inhibit T-lymphocyte activation
- Potent immunosuppressive if given systemically
- Slow acting anti-inflammatory
- Great substitute for potent steroids on face
- Questionable risk of lymphoma with chronic use

# TOPICAL IMMUNE MODULATORS (Tacrolimus (Protopic) ointment Pimecrolimus (Elidel) cream)

- Effective in childhood and adult AD
- No skin atrophy / steroid side effects
- Stinging and burning at initiation of therapy
- Slight increase in skin infections ?
- ? Risk of neoplasms?
- Long-term safety seems safe

20 year old male with isolated itchy rash below.  WHAT IS THIS?



# The preferred test to exclude the diagnosis is?

- A. Patch testing
- B. Delayed hypersensitivity intradermal skin testing
- C. IgE mediated skin tests
- D. No testing is effective

- Answer:

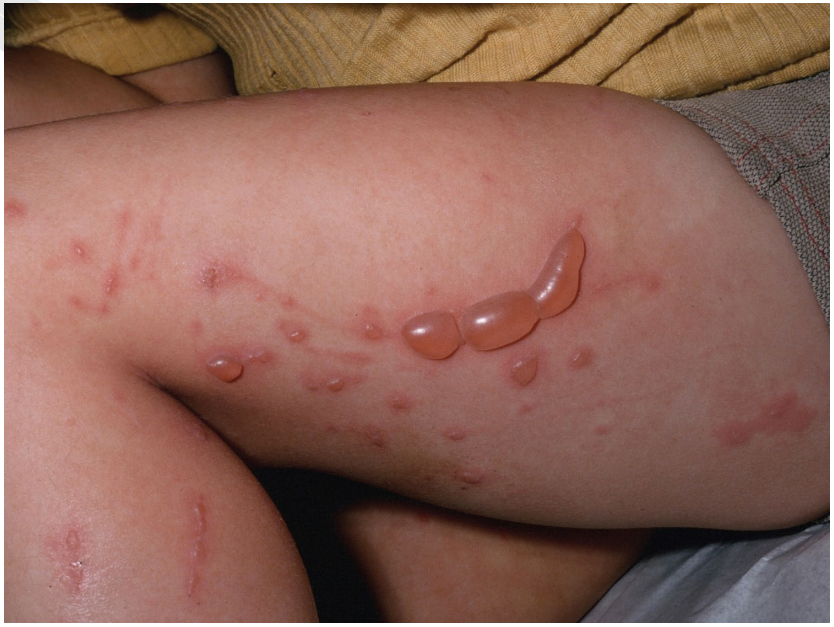
# The preferred test to exclude the diagnosis is?

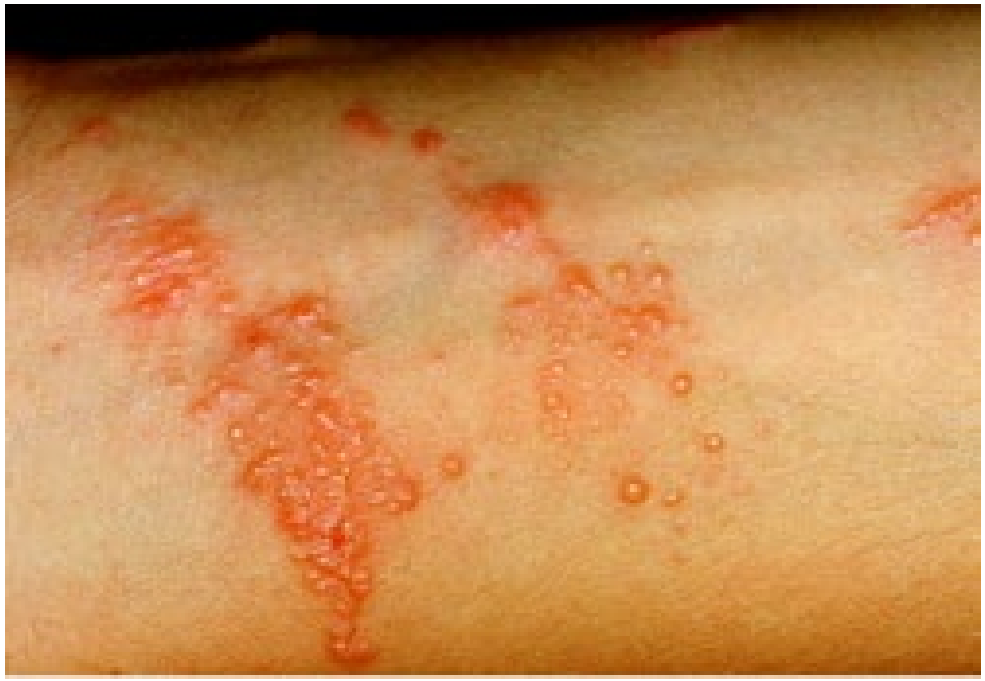
- A. Patch testing
- B. Delayed hypersensitivity intradermal skin testing
- C. IgE mediated skin tests
- D. No testing is effective

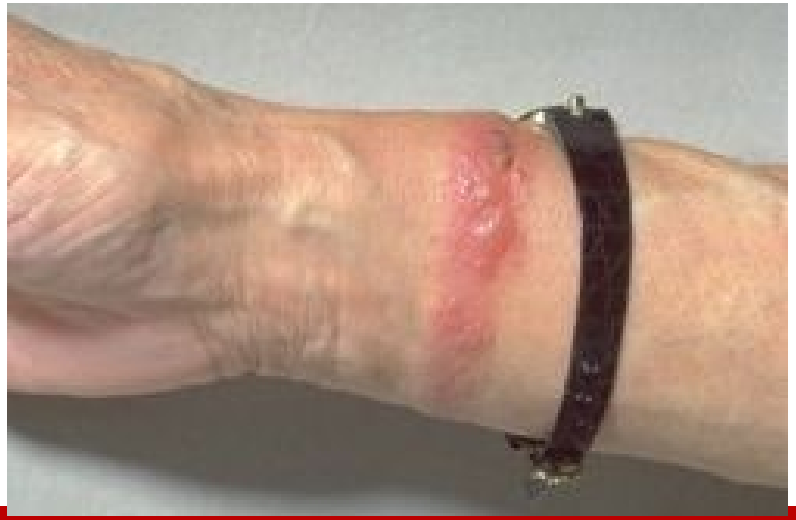
- Answer: A

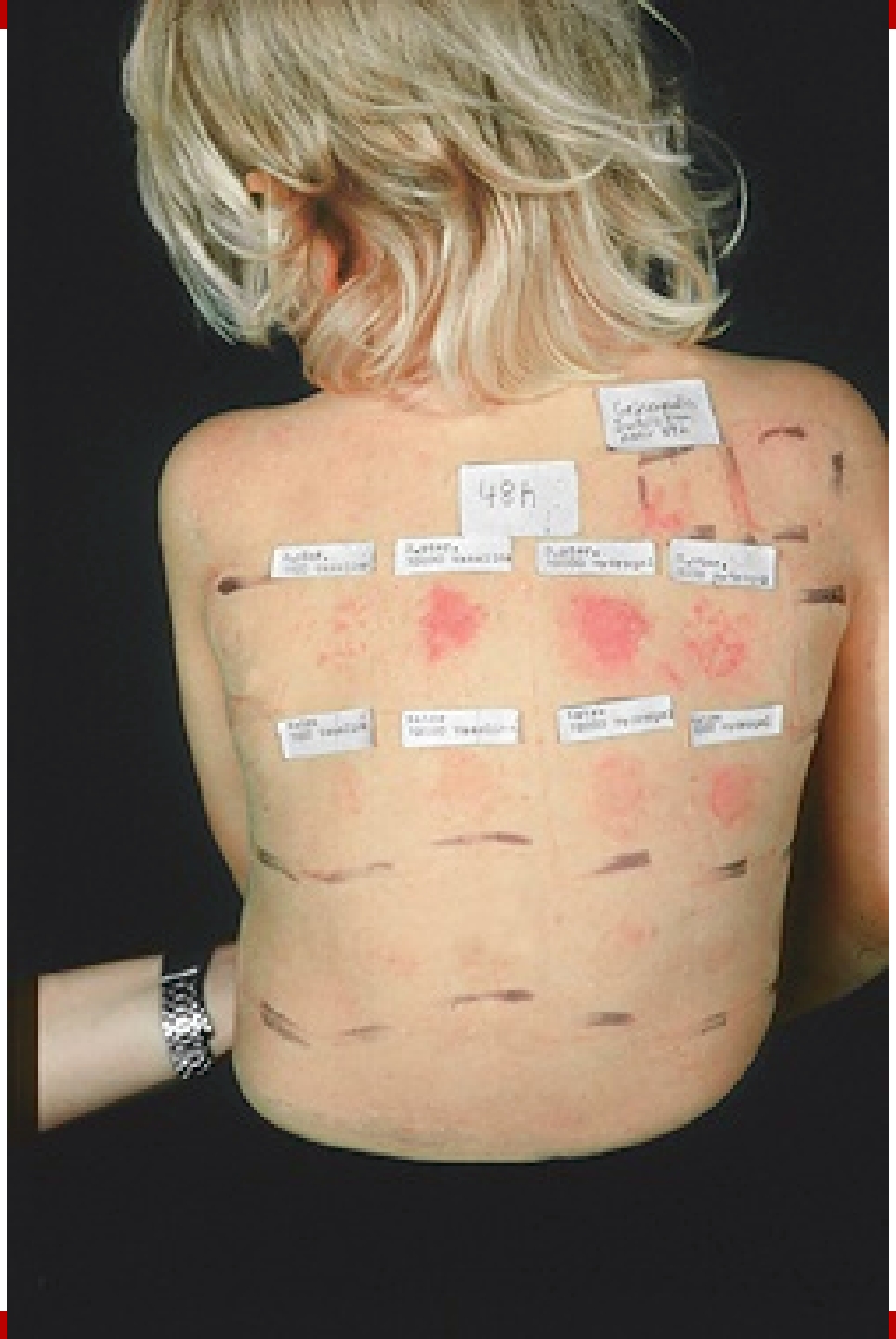
# Allergic Contact Dermatitis

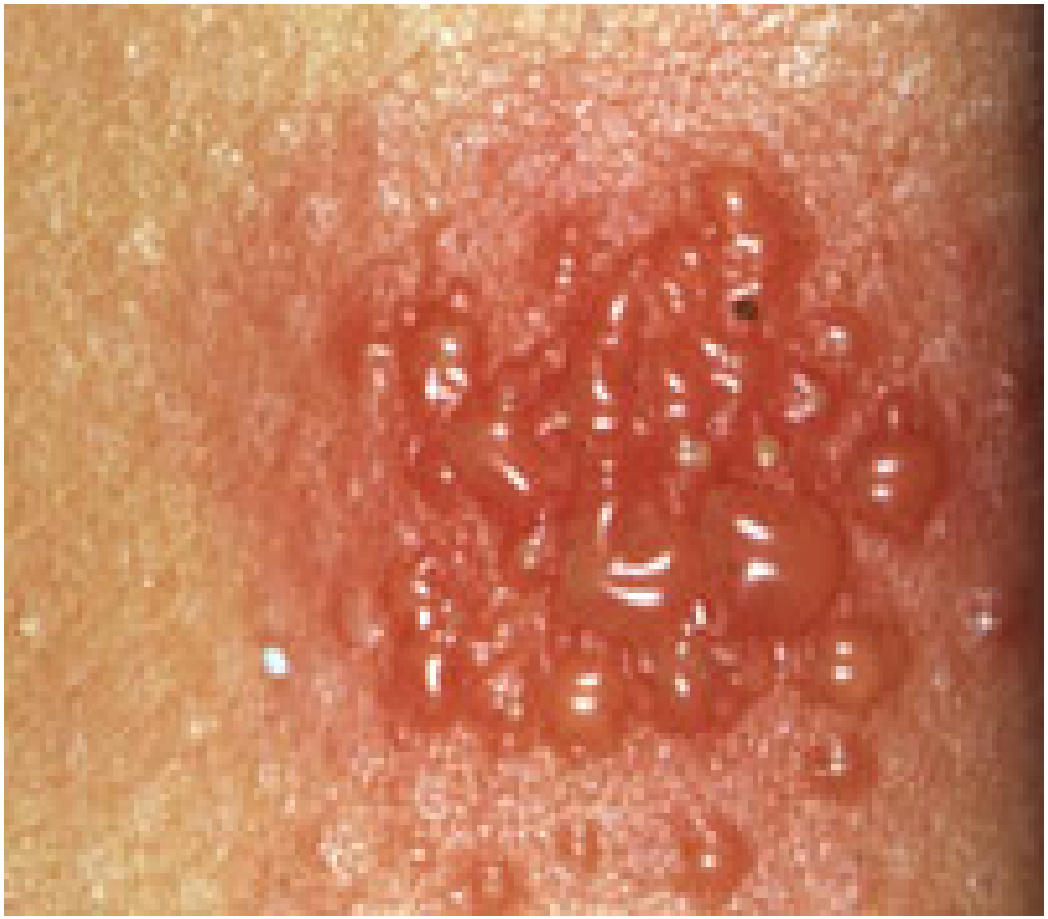
- Type 4 cell mediated reaction with T-helper-type 1- lymphocytes
- delayed 48 hours
- Rhus is the best example
- patch test for diagnosis
- nickel, rubber additives (latex), thimerosal (eye gtt), benzocaine, neomycin, topical doxepin
- Rx - avoidance, topical steroids, or 2 weeks of oral steroids





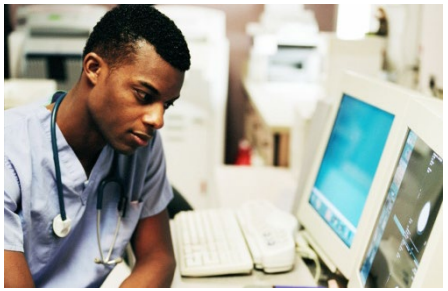






# GOOD LUCK ON THE EXAMS



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