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Pruritus:
Scratching the surface

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ITCH

- defined as an ***"unpleasant sensation of the skin leading to the desire to scratch"***

-- *Samuel Hafenreffer* (1660)

- The definition offered by the German physician Samuel Hafenreffer in 1660 has yet to be improved upon.

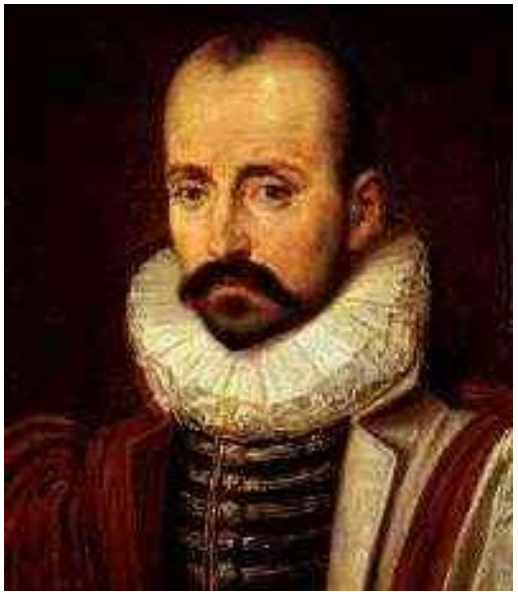
- However, it turns out that itch is, indeed, inseparable from the desire to scratch.

Savin JA. How should we define itching? J Am Acad Dermatol. 1998;39(2 Pt 1):268-9.

Pruritus

- *"Scratching is one of nature's sweetest gratifications, and the one nearest to hand…."*

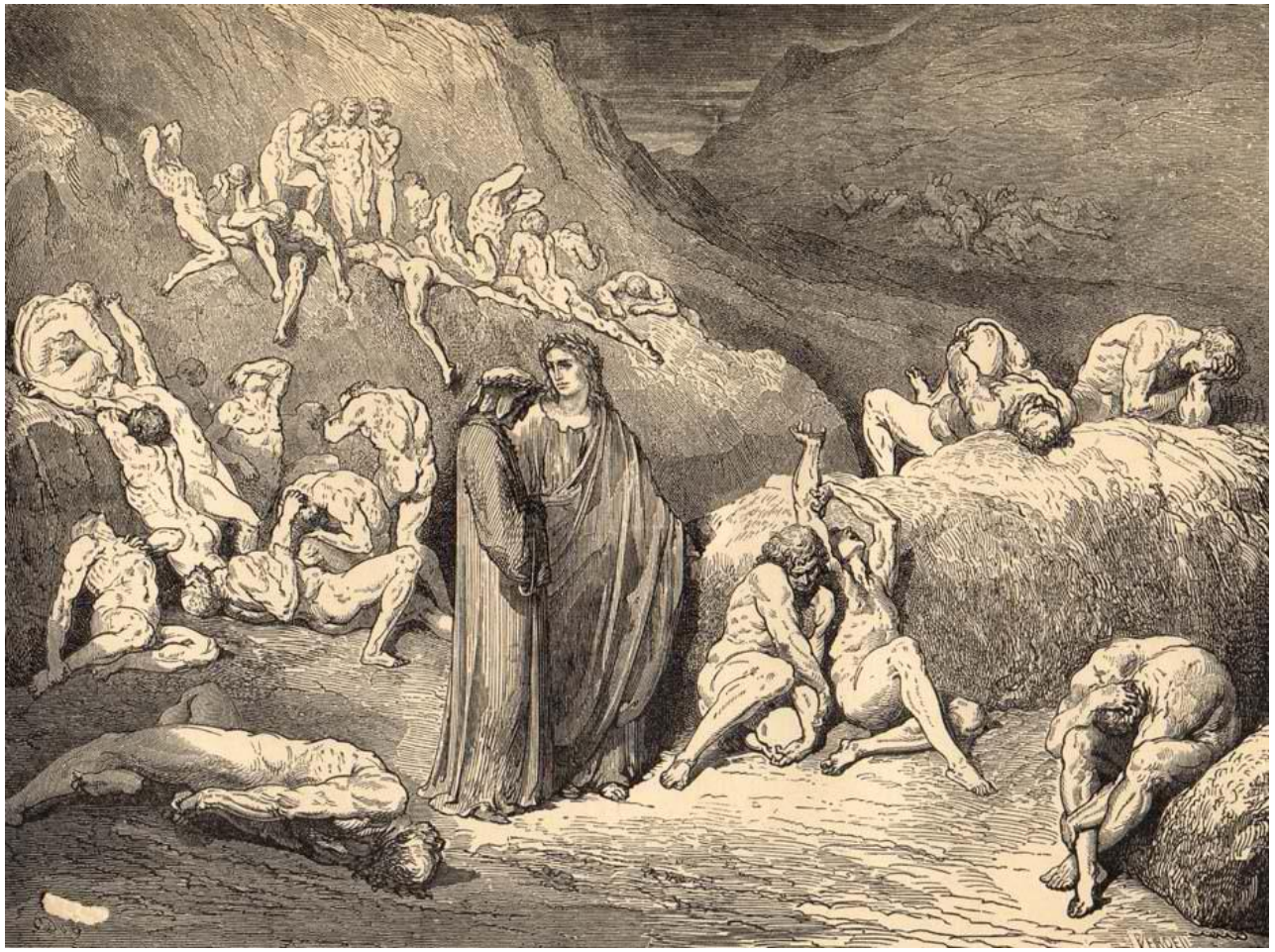
  -- *Michel de Montaigne* (1553)



"…..But repentance follows too annoyingly close at its heels."

The Essays of Montaigne

Itch has been ranked, by scientific and artistic observers alike, among the most distressing physical sensations one can experience:



In Dante's Inferno, falsifiers were punished by ***"the burning rage / of fierce itching that nothing could relieve"***

Pruritus and body defence

- Pruritus fulfils an essential part of the innate defence mechanism of the body.
- Next to pain, itch may serve as an alarm system to remove possibly damaging or harming substances from the skin.
- Itch, and the accompanying scratch reflex, evolved in order to protect us from such dangers as malaria, yellow fever, and dengue, transmitted by mosquitoes, typhus-bearing lice, plague-bearing fleas
- However, chronic itch lost this function.

Chronic Pruritus

- Chronic pruritus is a common and distressing symptom, that is associated with a variety of skin conditions and systemic diseases

- It usually has a dramatic impact on the quality of life of the affected individuals

Chronic Pruritus

- Despite being the major symptom associated with skin disease, our understanding of the pathogenesis of most types of itch is limited, and current therapies are often inadequate.
- Management of chronic itch usually poses a therapeutic dilemma
- Understanding of the basic principles is important for development of target-specific treatment of patients with chronic pruritus

Classification of itch

- Based on pathophysiologic criteria
- Based on symptom-associated criteria

Pathophysiological classification of pruritus

(i) pruritoceptive (originating in the skin)

(ii) neuropathic (caused by damage of the itch-transmitting afferents of the peripheral nerves or the spinal cord, e.g. in brachioradial pruritus, postherpetic pruritus or notalgia paraesthetica

(iii) neurogenic (central mediators generate itch without neuronal damage)

(iv) psychogenic (somatoform).

Twycross R, et al. Itch: scratching more than the surface. QJM 2003; 96: 7-26

Clinical classification of pruritus

- The International Forum for the Study of Itch (IFSI) distinguished three clinical groups of patients:

(i) pruritus on primarily inflamed skin (pruritus originated on skin disease)

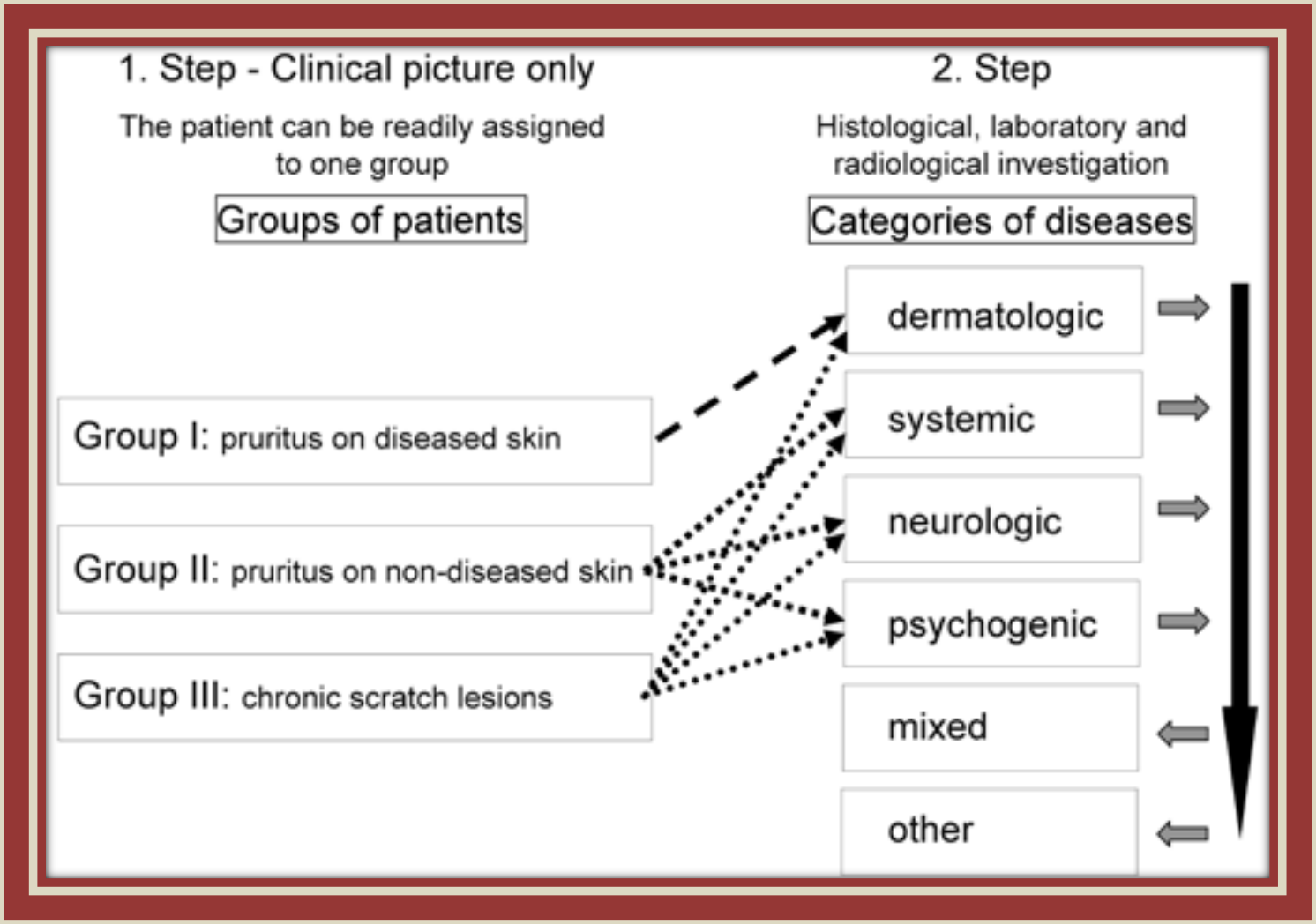
(ii) pruritus on primary non-diseased, non-inflamed skin (pruritus on normal skin)

(iii) pruritus with chronic nonspecific secondary scratch lesions.

Clinical classification of pruritus

- To properly treat a patient with pruritus, it is mandatory to determine the underlying cause.
- As this can be difficult, pruritus is first classified by the clinical picture and then as a second step categorized in the respective diseases

Clinical classification of chronic pruritus



The International Forum for the Study of Itch (IFSI)

Ständer S, et al. Acta Derm Venereol 2007;87:291–4

Category I: Dermatological origin of chronic pruritus

DERMATOLOGICAL DISEASES	EXAMPLES OF DIAGNOSES
Inflammatory dermatoses	Atopic dermatitis, urticaria, contact dermatitis, psoriasis, drug reactions,"invisible dermatoses"
Infectious dermatoses	Mycotic, bacterial and viral infections, folliculitis, scabies, pediculosis, arthropod reactions, insect bites
Autoimmune dermatoses	Bullous dermatoses, especially dermatitis herpetiformis, bullous pemphigoid, dermatomyositis
Genodermatoses	Darier's disease, Hailey-Hailey disease, ichthyoses, Sjögren-Larsson syndrome, EB pruriginosa
Dermatoses of pregnancy	Polymorphic eruption of pregnancy, pemphigoid gestationis, prurigo gestationis
Neoplasms	Cutaneous T-cell-lymphoma (especially erythrodermic variants), cutaneous B-cell lymphoma, leukaemic infiltrates of the skin

Category II: Systemic origin of chronic pruritus

SYSTEMIC DISEASES	EXAMPLES OF DIAGNOSES
Endocrine and metabolic diseases	Chronic renal failure, liver diseases hyperthyroidism, malabsorption, perimenopausal pruritus
Infectious diseases	HIV-infection, helminthosis, parasitosis
Haematological and lymphoproliferative diseases	Iron deficiency, polycythaemia vera, Hodgkin's disease, Non-Hodgkin's lymphoma, plasmocytoma
Visceral neoplasms	Solid tumours of the cervix, prostate, or colon, carcinoid syndrome
Pregnancy	Pruritus gravidarum
Drug-induced pruritus (selection)	Opioids, ACE-inhibitors, amiodarone, hydrochlorothiazid, estrogens, simvastatin, hydroxyethyl starch, allopurinol

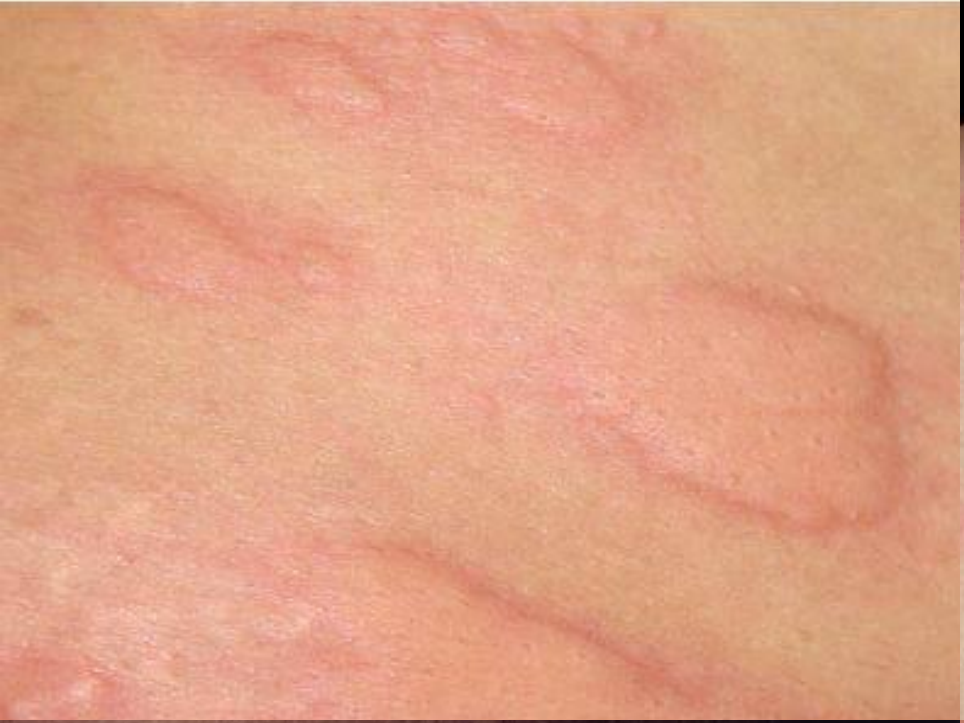
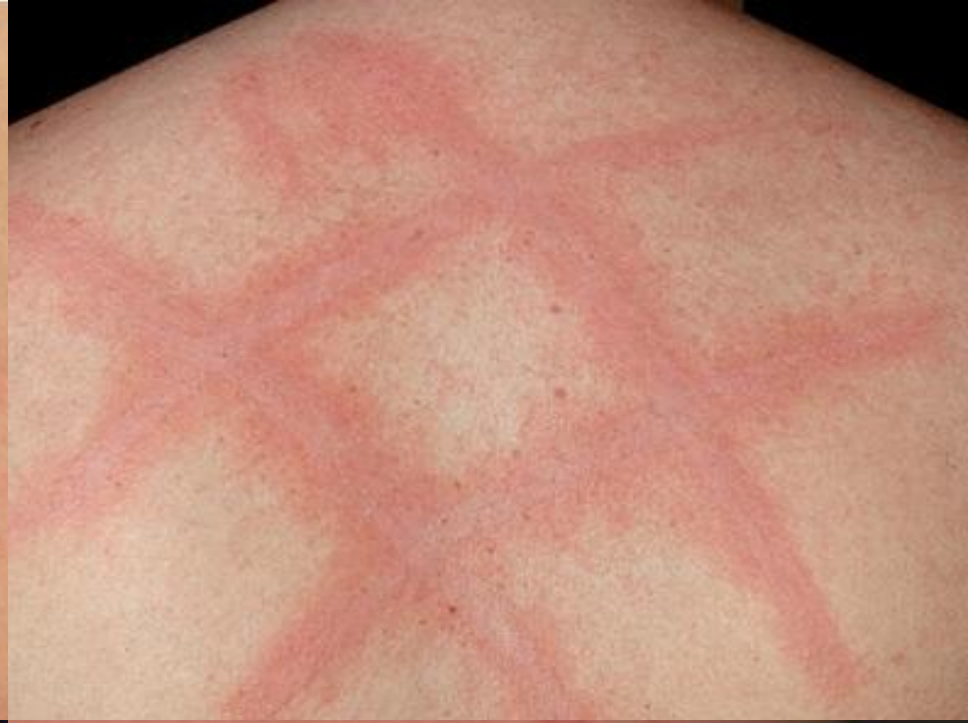
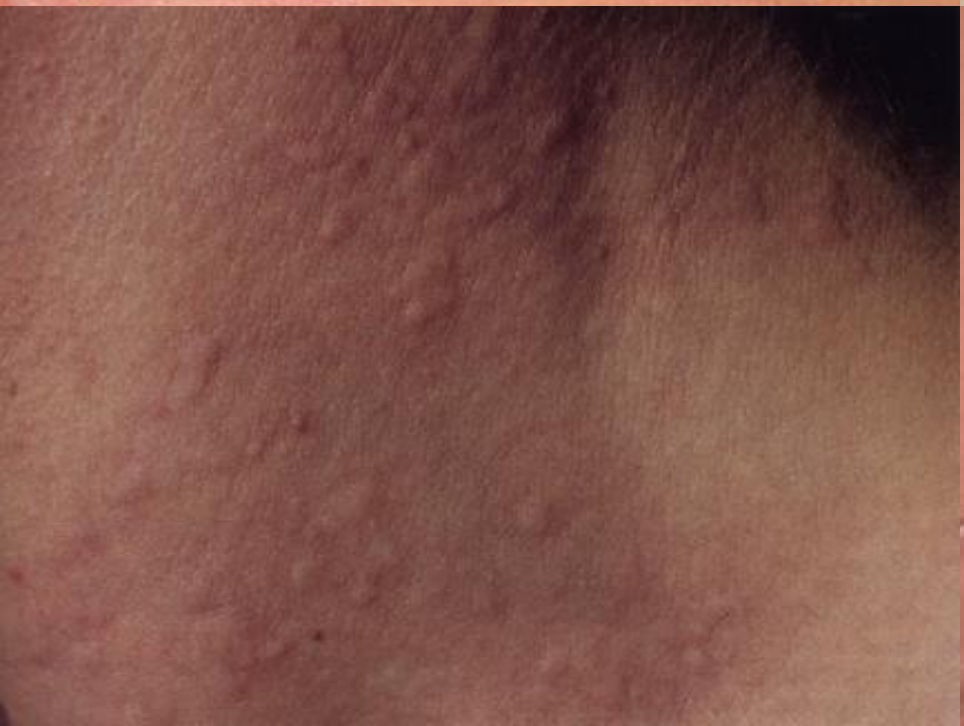
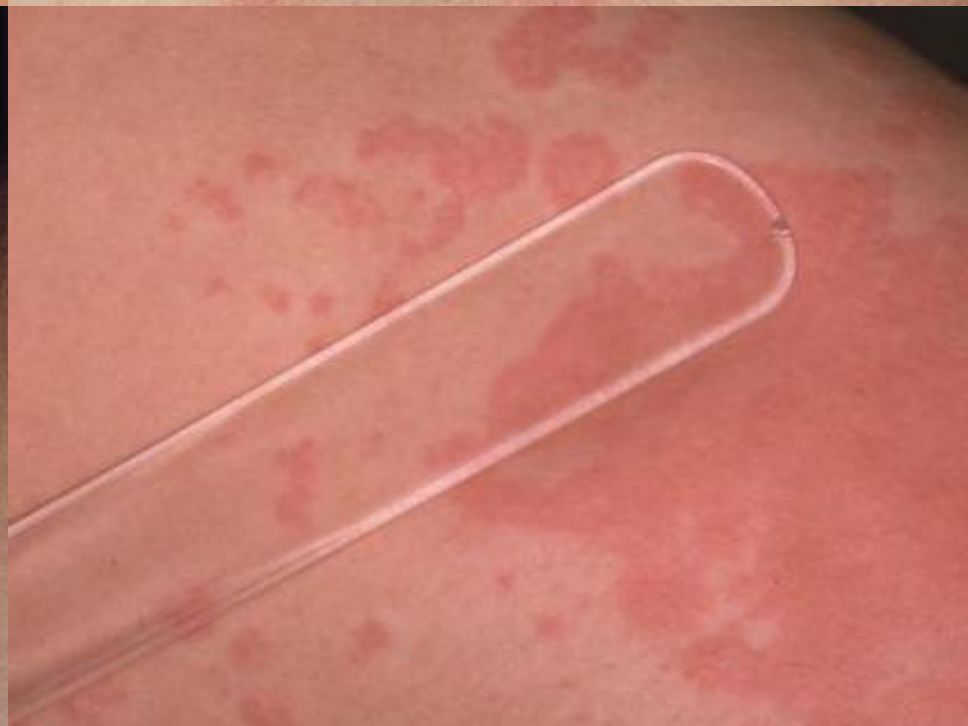
Identifying the cause…

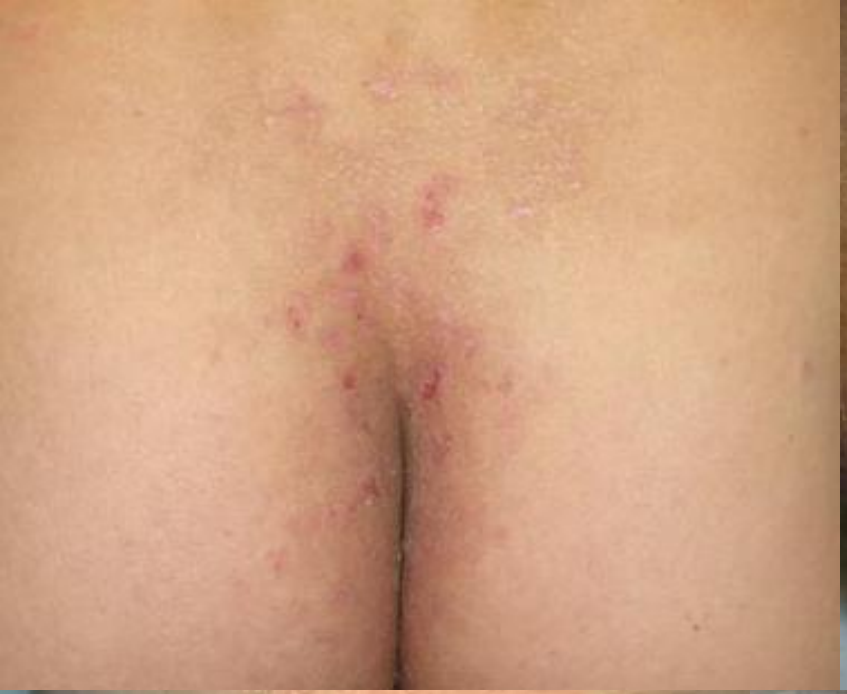
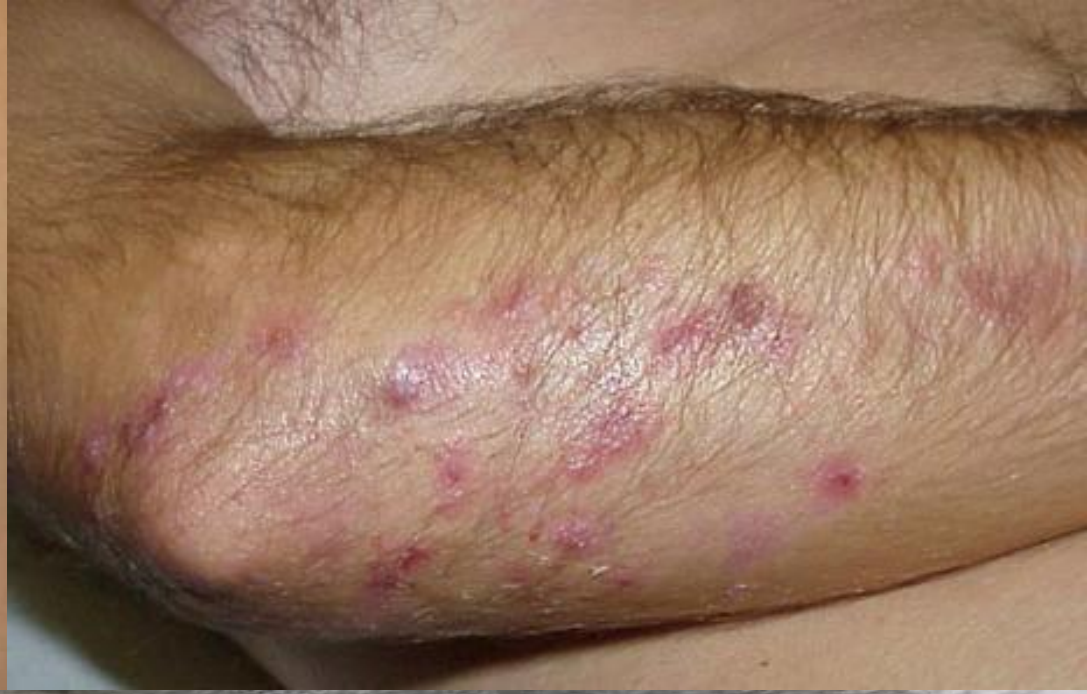
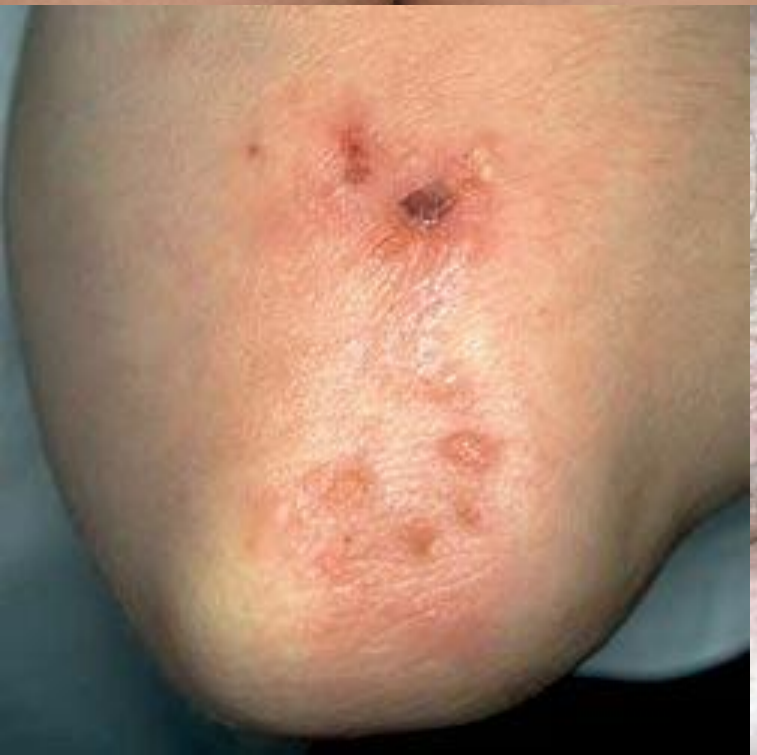
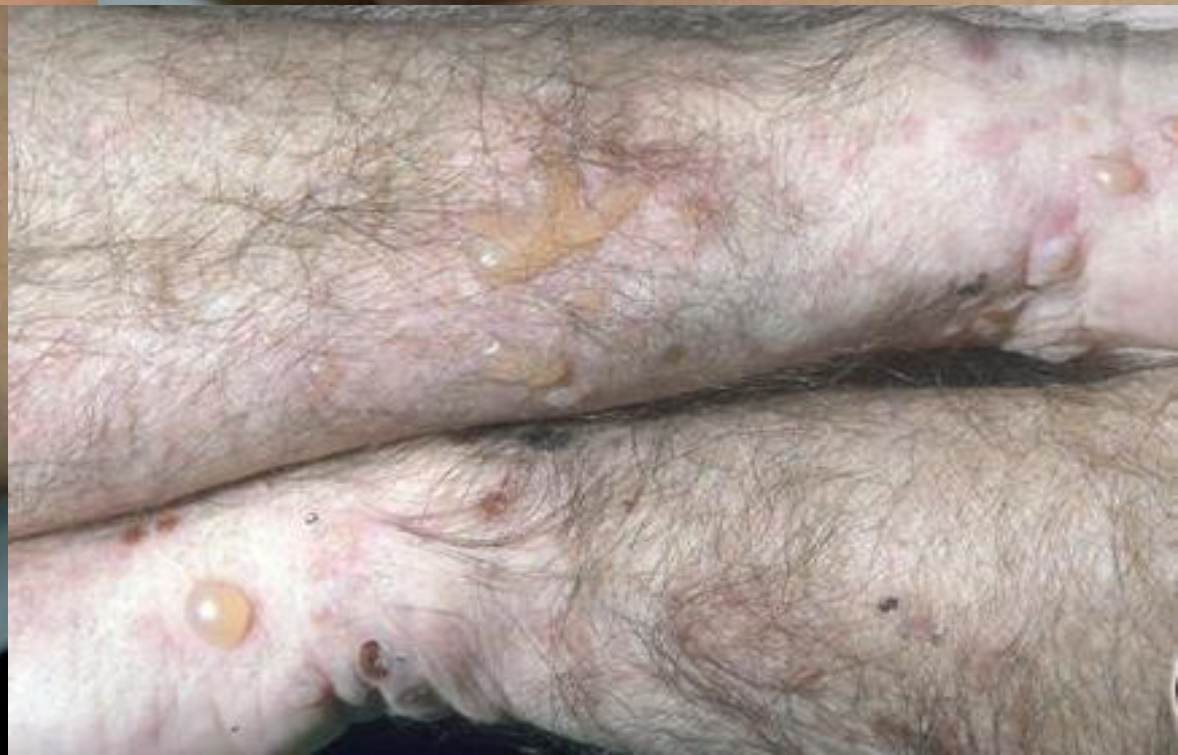
- Identifying the cause of a chronic itch is a challenge.
- A detailed history and full skin examination should be performed
- If necessary, further histological, laboratory and radiological investigations should be performed

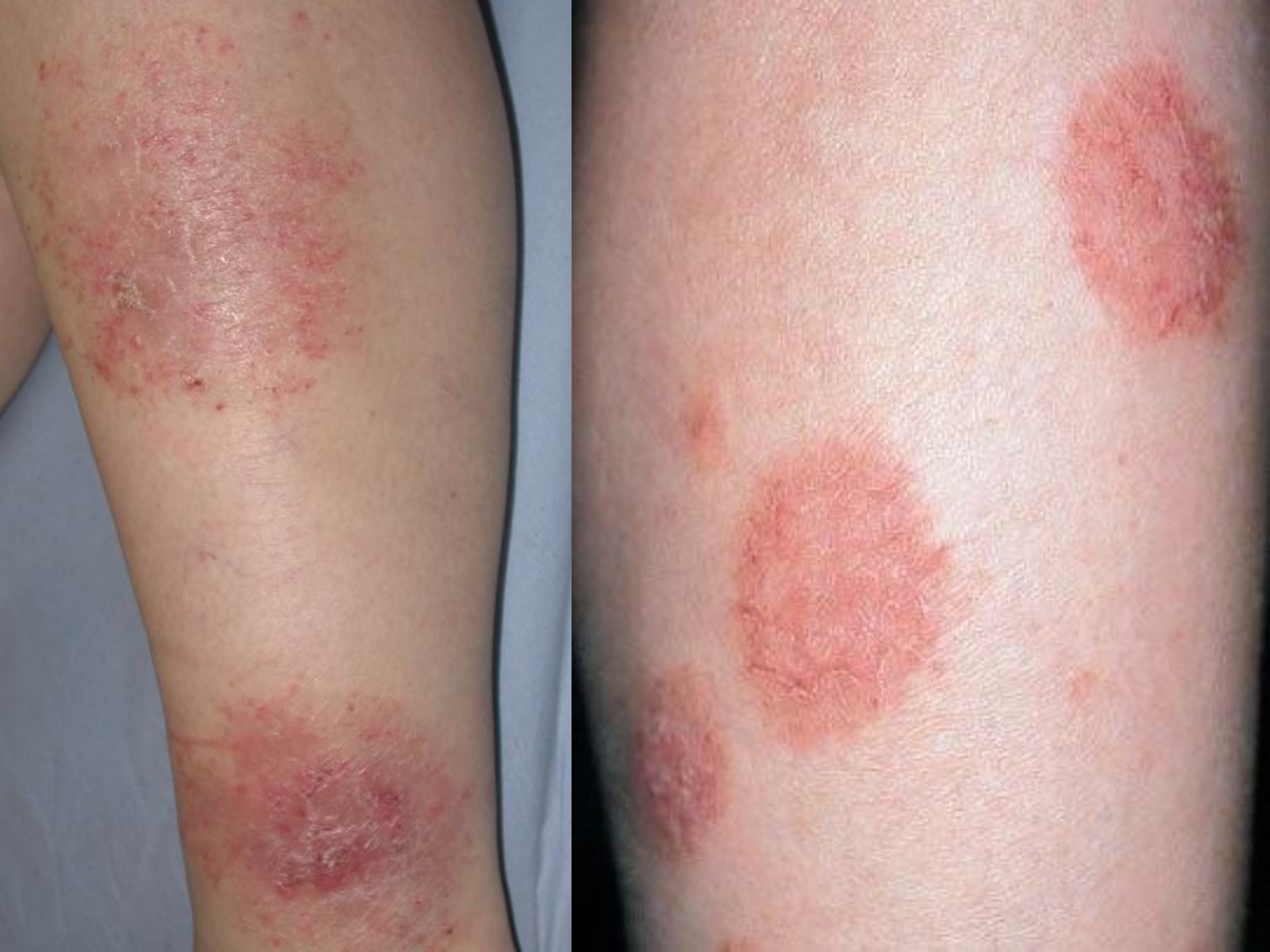
Clinical History in patients with chronic pruritus

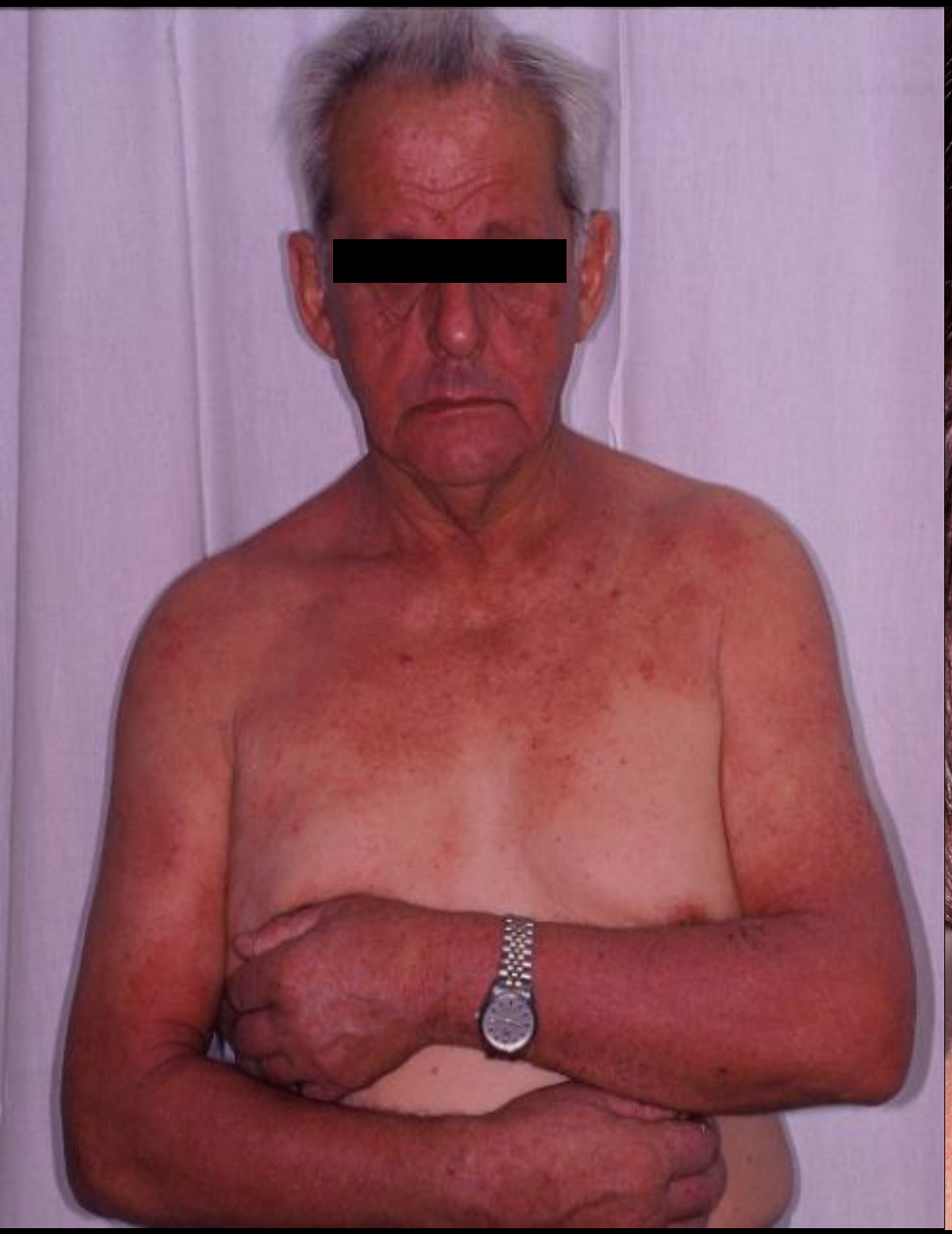
Characteristics of pruritus Alloknesis	Onset and course of pruritus, timing, location, severity
Presence of skin lesions	Type , location, severity, clinical course, scratching ‘‘artifacts’’
Known dermatological diseases	Eczema, Urticaria, Psoriasis
Known systemic diseases	Hepatic, Renal, Thyroid
Allergies	
Environmental factors	Irritants or allergens (domestic, work, hobbies) Infections, infestations, etc.
Exacerbating factors	Heat, Physical or chemical irritation, Exercise, Food
Drug exposure	
Psychoemotional factors	Stress, Depression, Anxiety

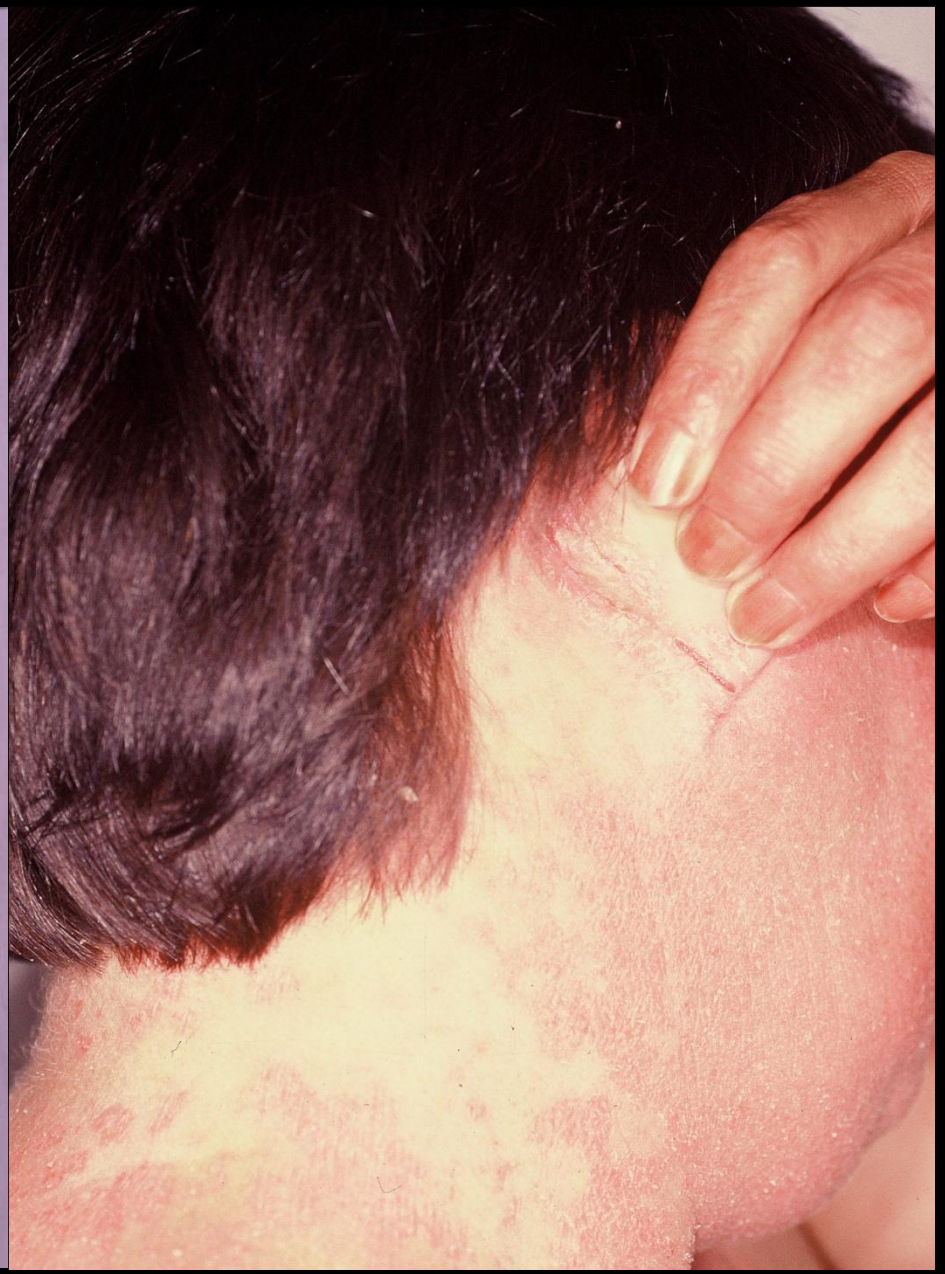
Complete skin and general examination
Specific lesions (erythema, hives, papules, vesicles)
Typical distribution (flexures, photodistribution, contactant)
Secundary scratching lesions (excoriations, liquenification, prurigo)
Xerosis
Dermographism
Manifestations of systemic diseases: Jaundice, Pallor, Hepatomegaly, splenomegaly, lymphadenopathy, weight loss

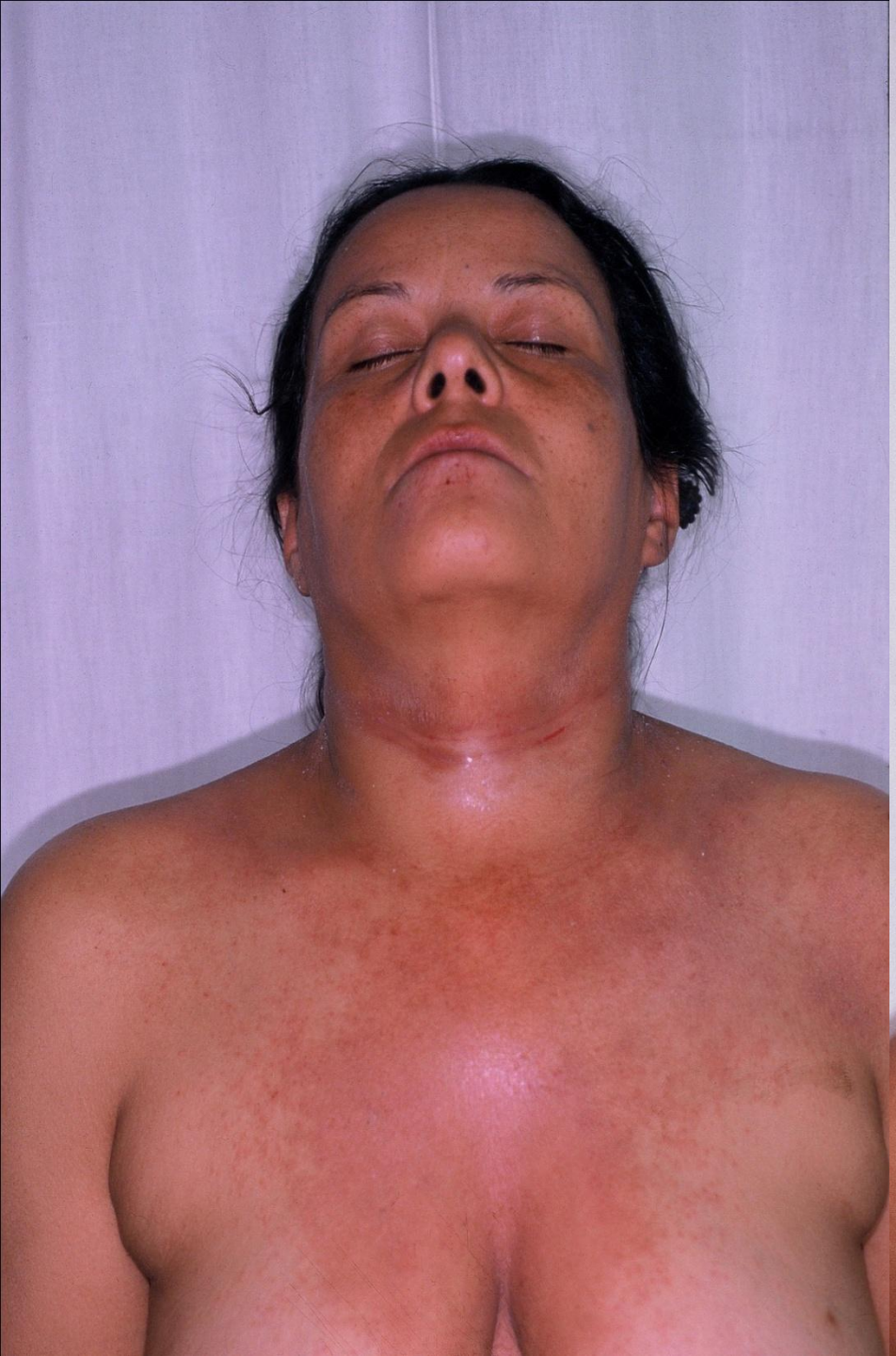
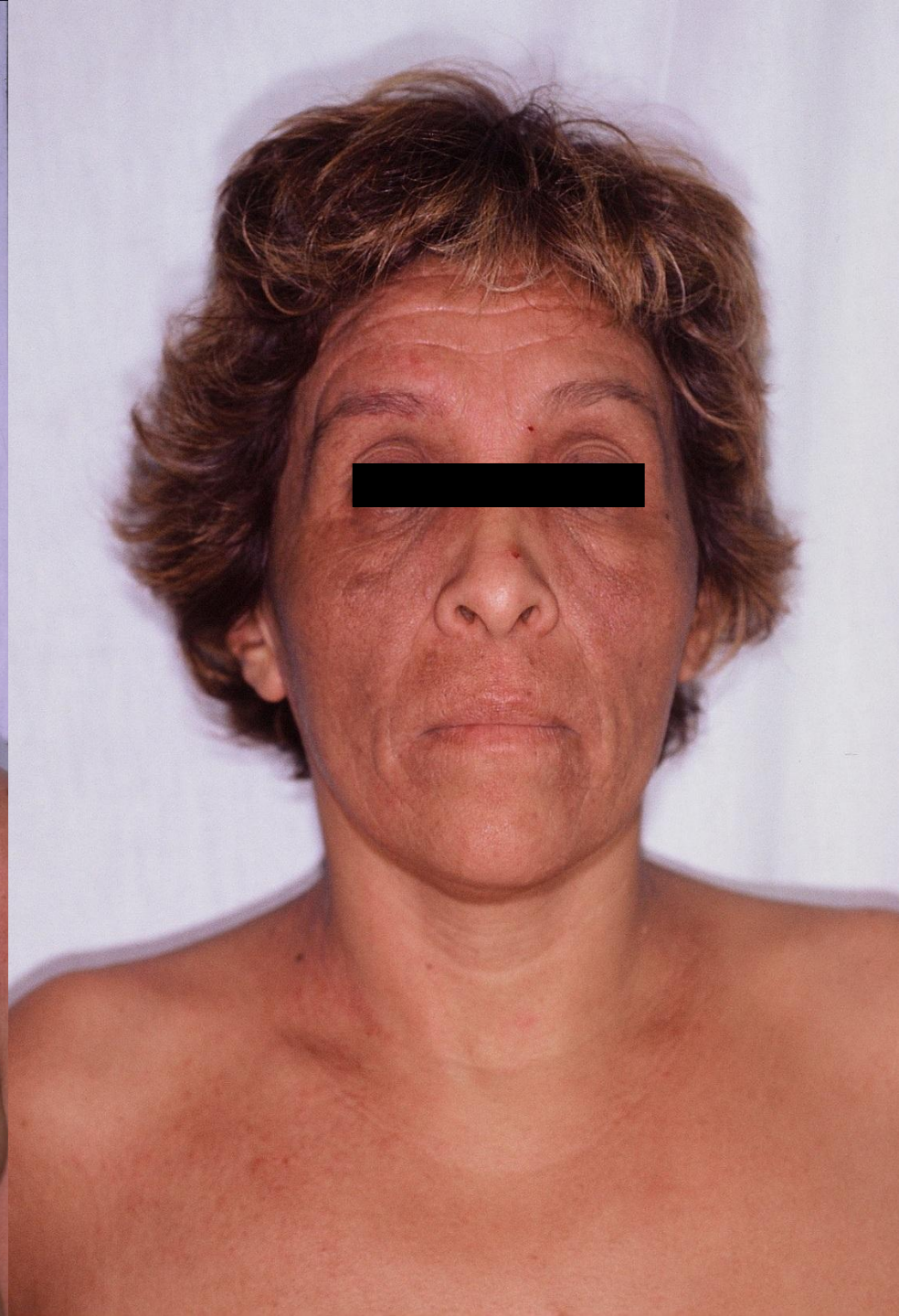





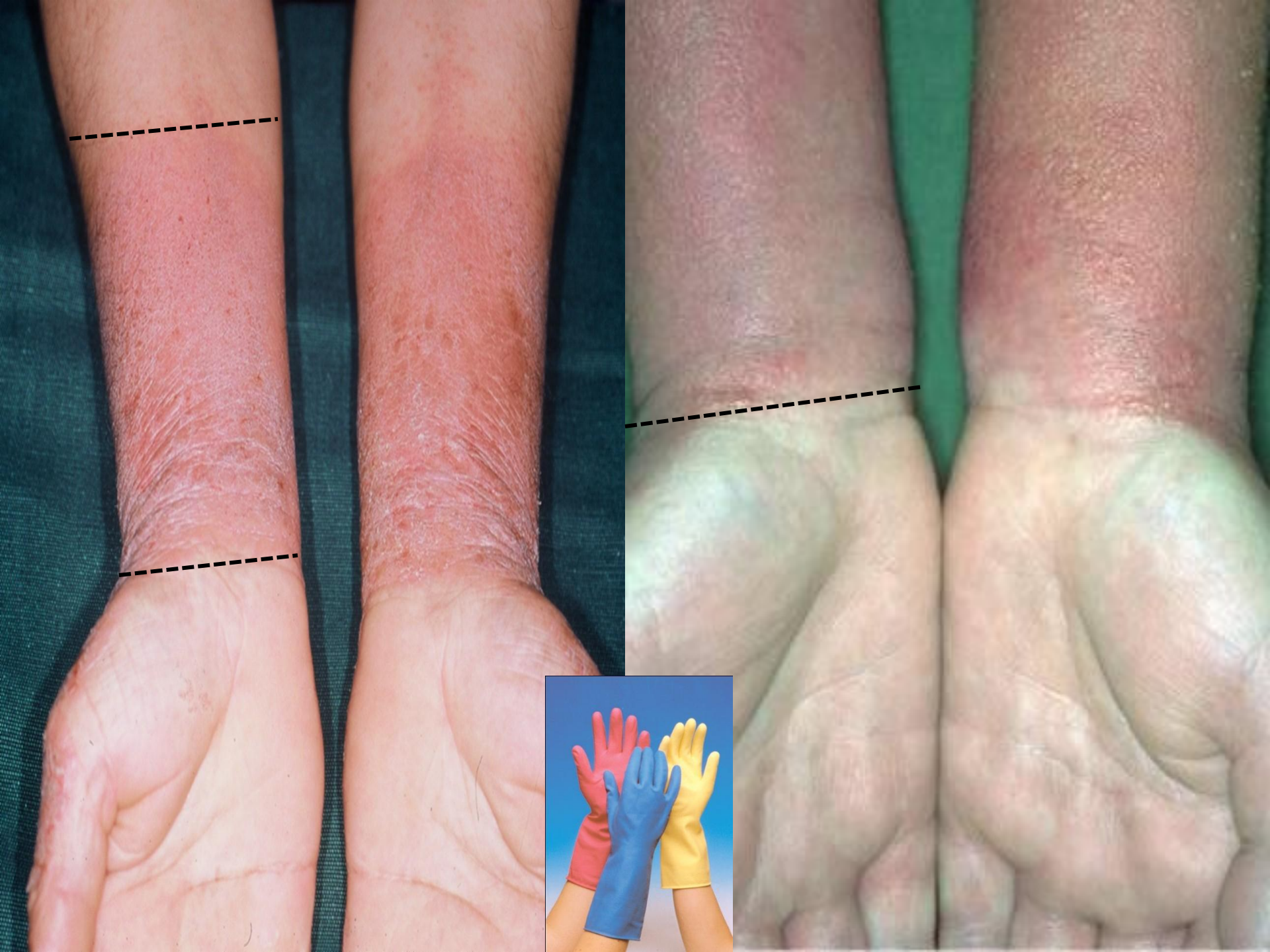





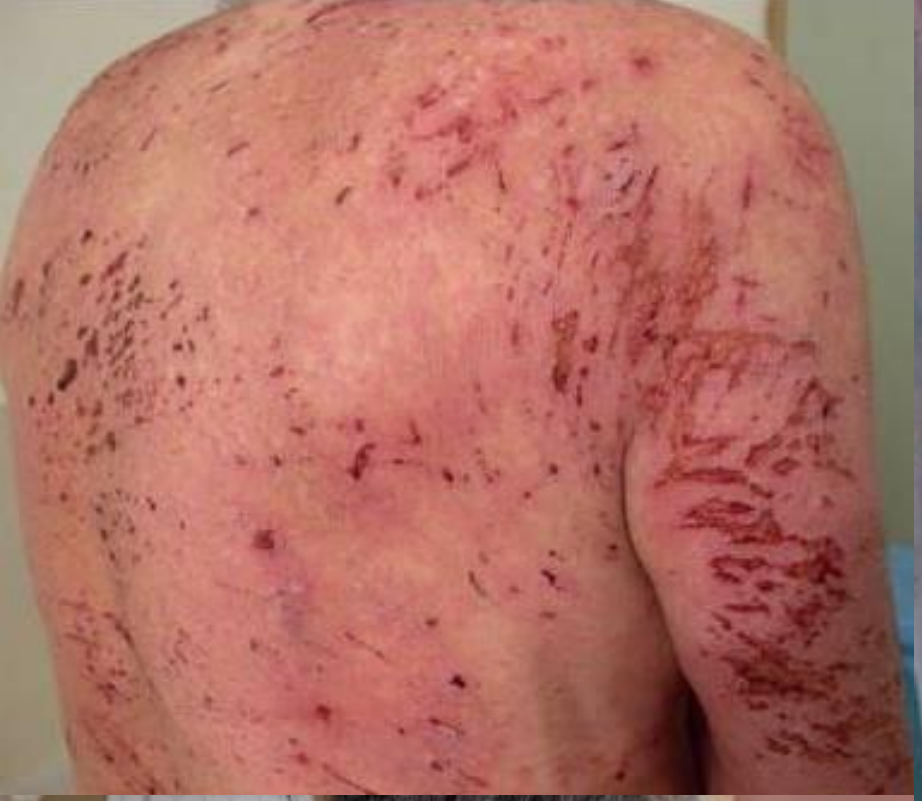


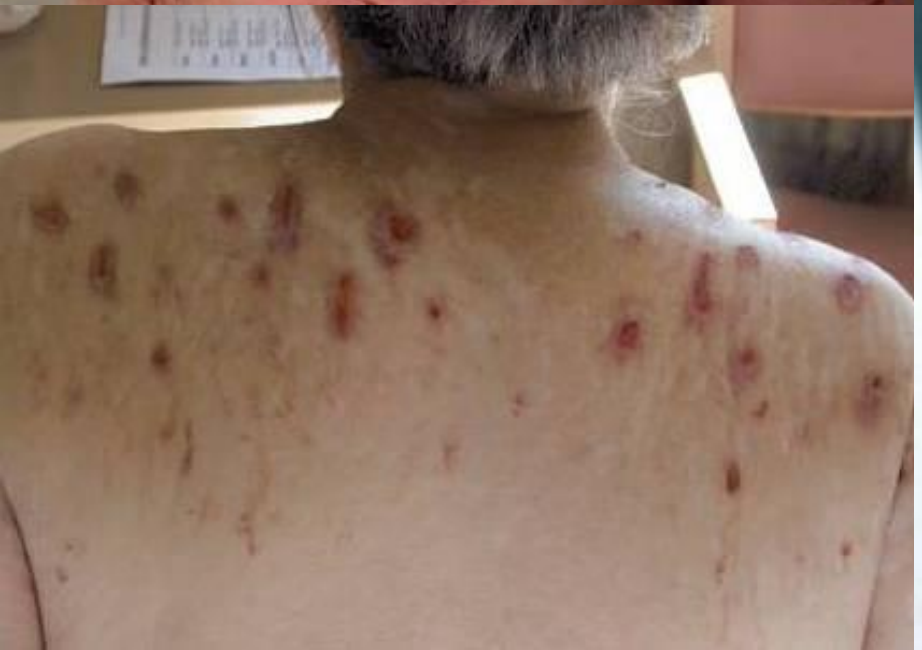


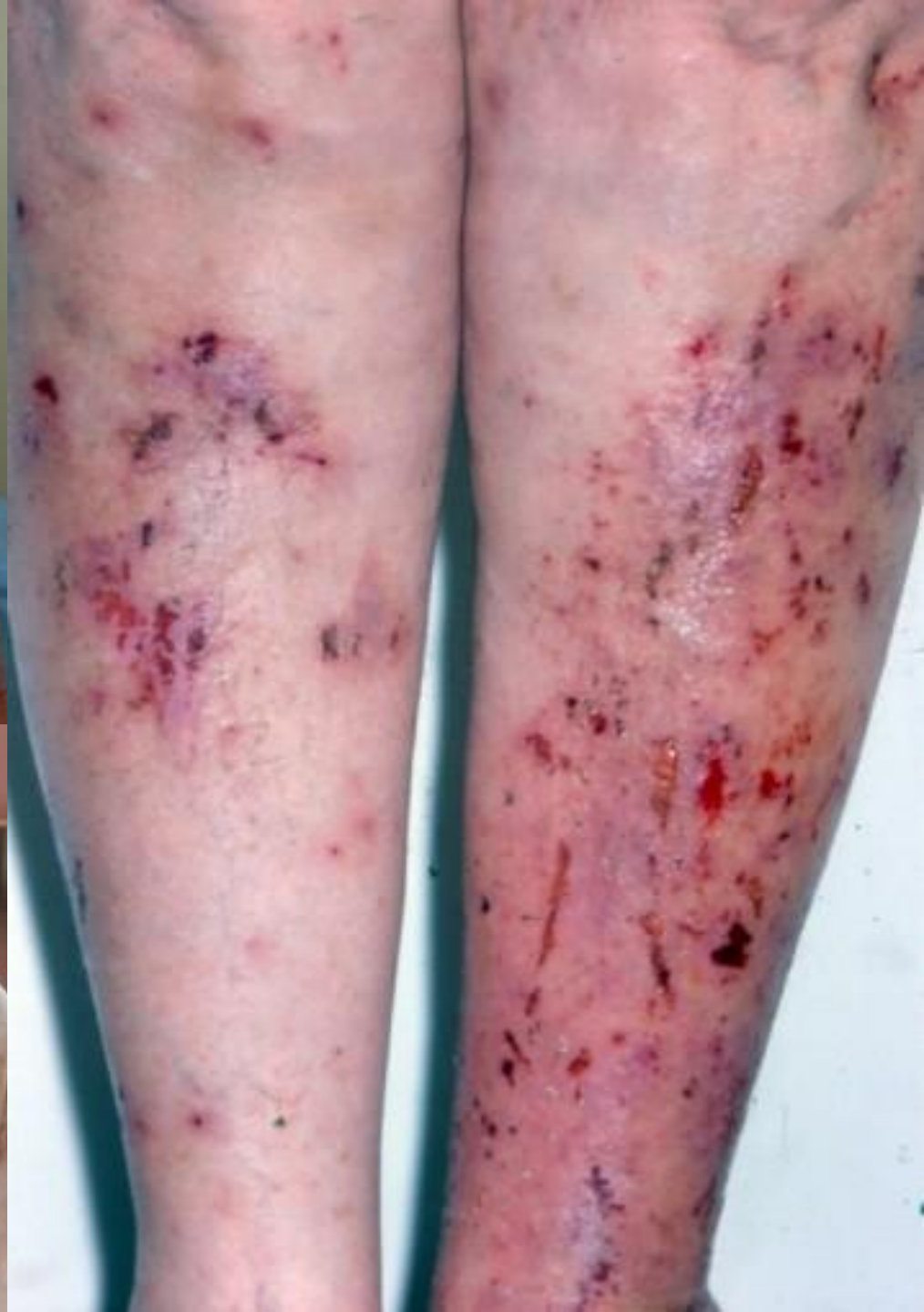










Diagnostic workup I

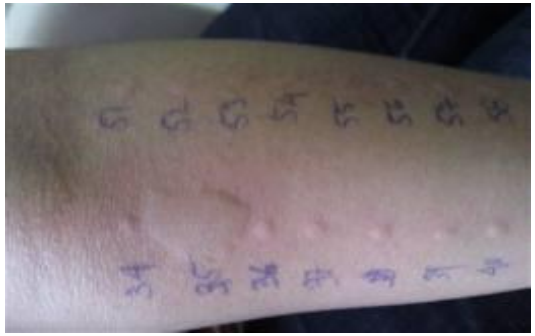
Complete red and white blood cell counts
Sedimentation rate
C-reactive protein
Creatinine
Glucose levels
Liver function tests (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, LDH, γGT, total bilirubin),
Thyroid function tests (thyroid-stimulating hormone, free T4).
Iron, ferritin, transferrin
Immunoglobulin E
Stool for ova and parasites

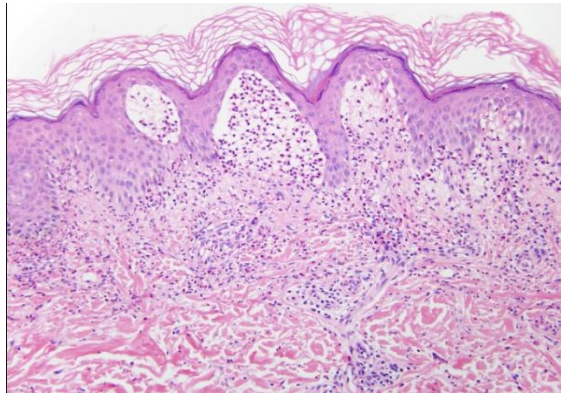
Diagnostic workup I

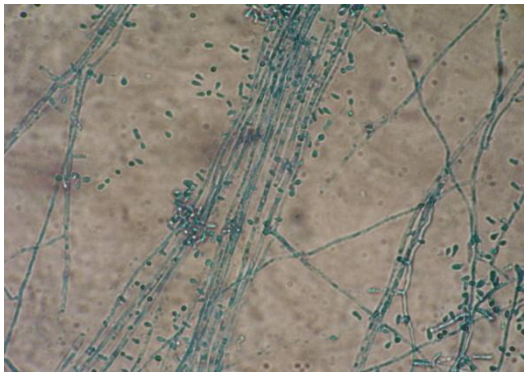
Hepatitis serology
Autoantibodies (antigliadin, antitransglutaminase, ANA
Stool occult blood examination
RPR test for syphilis
HIV antibody test
Iron, ferritin, transferrin
Immunoglobulin E
Stool for ova and parasites
Chest radiograph
Ultrasound, computed tomography, magnetic resonance imaging
Malignancy work-up (regular monitoring)

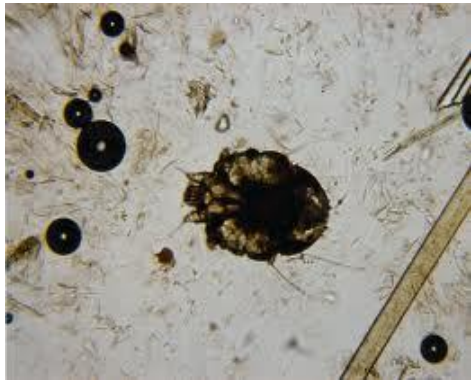
Diagnostic workup III

- Allergy testing
- Histologic examination of affected skin & immunofluorescence
- Microbiology laboratory tests (mycological& bacteriological)
- Skin scrapings for mites









Clinical Management

- In most conditions, pruritus is best resolved by treatment of the underlying condition; however, this treatment may not always be possible or sufficient
- chronic pruritus is a complex, multifactorial phenomenon, therefore an integrative management plan should be adopted

Clinical Management

- The current guidelines for the treatment of pruritus recommend a step-by-step treatment procedure, tailored to the severity of symptoms, accompanying diseases, patient´s age, co-medications, and the severity of lesions due to scratching

Elimination of triggering factors

- External triggers can intensify pruritus
  - physical factors such as overheated rooms, insulating clothing, or being in a warm bed.
  - Irritants (physical or chemical) rough fabrics or wool clothing
  - Frequent washing, use of harsh soap
- Internal triggers
  - hot spices, alcohol, hot beverages
- Emotional stress

Topical antipruritic therapies

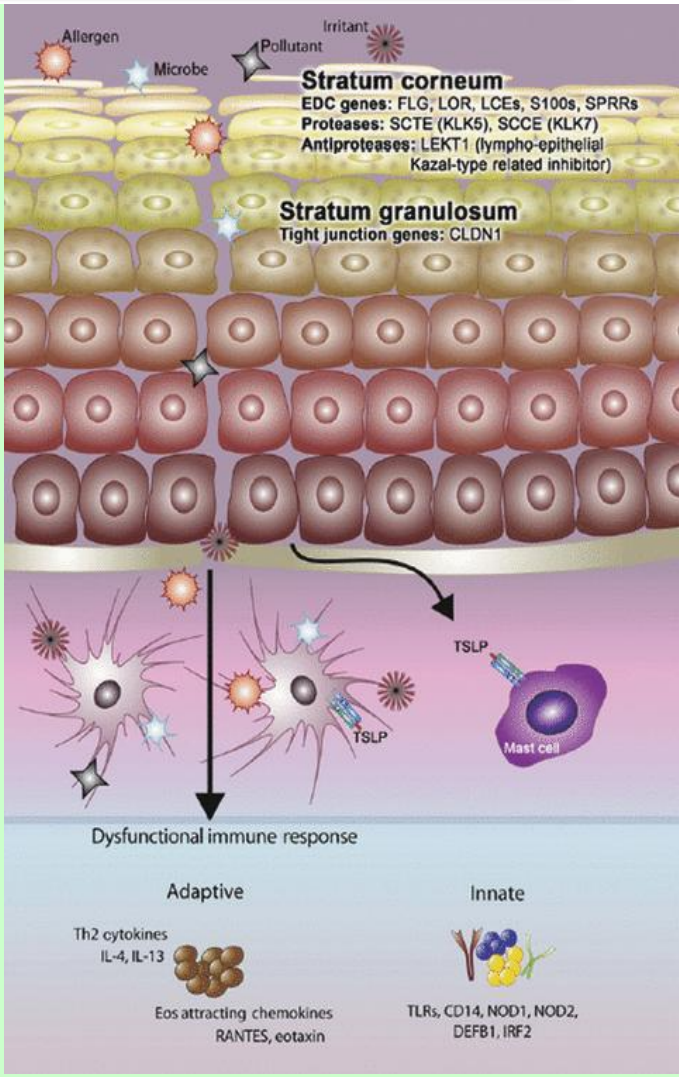
- Moisturizers are aimed at replenishing the damaged stratum corneum:
  - Rehydrating or “plumping” the corneocytes
  - Restoring the structure of the lipid bilayer of the SC
  - Occlusive properties of the lipid components provides a ‘shielding’ effect and prevents water loss
- Moisturizers contribute to maintain the integrity of the epidermal barrier
- Protects against dehydration, irritants, allergens, and infectious pathogens, all of which may precipitate itch.

Moisturizers

- Moisturizer formulations contain a combination of:
- **Humectants:** attract and hold water in the skin e. g., glycerol, lactate, urea
- **Occlusives:** prevent evaporation, e. g., petrolatum, mineral oil
- **Emollients:** provide partial hydration and occlusion, e. g., sterols, lanolin, glycol and glyceryl stearates.
- In general, moisturizers should be applied one to three times daily to xerotic skin and especially within minutes of bathing for optimal effects

Moisturizers and Barrier function

- In atopic dermatitis and contact dermatitis, disturbance of the skin barrier is a primary event
- Diminished BF enhance the ability of an irritant or an allergen to penetrate the SC
- Barrier disruption *per se* produces
  - a cytokine response (IL-1α and IL-1β, TNF- α and GM-CSF)
  - increase in dendritics' cells density
  - T cell activation
- Thus, barrier disruption not only increases the penetration of xenobiotics, but may also prime the inflammatory response



➢ Epidermal contribution in the initiation and maintenance of inflammatory skin diseases

Atopic Eczema and Barrier dysfunction

- One of the hallmark features of AE is an impaired skin barrier:
- increased TEWL
- low hydratation of the stratum corneum
- shift of the pH,
- Structural and physiologic abnormalities in epidermal lipids (anomalous lipid synthesis and metabolism)
- Increased protease activity
- Structural abnormalities in peptides and proteins (filaggrin, hornerin)

Maintz L, Novak N Getting more and more complex: the pathophysiology of atopic eczema. Eur J Dermatol. 2007;17(4):267-83

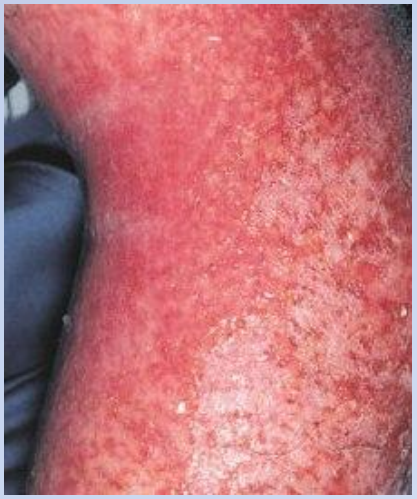
Corneotherapy for skin diseases

- New topical products (moisturizers/emollients & barrier creams) classified as medical devices
- These formulations contain various combinations of lipids, such as ceramides, triglycerides, free fatty acids, cholesterol, phospholipids,, squalene, and phytosterol, as well as antiinflammatory agents, such as glycyrrhetinic acid, N-palmitoylthanolamine,and antioxidants
- These agents are thought to incorporate directly into the structural framework of the stratum corneum, where they serve as building block materials for the SC repair
- Safe and effective in treating atopic pediatric and adult patients

Lübbe J: Evidence-based corneotherapy. Dermatology 2000;200:285–289
Tabata N, et al: Evaluation of corneotherapy. Dermatology 2000;200:308–313.

Baths and compresses

- In acute itchy dermatitis moist compresses are useful to reduce pruritus, and enhance drying
- Burrow's solution, aluminum sulfate, calcium acetate, physiological saline, silver nitrate or plain tap water
- applied for 20 – 30 min many times a day



- Colloidal oatmeal baths may help to dry and soothe acute, oozing lesions.
- Oatmeal has antiinflammatory and antipruritic activity

Baths and compresses

- Colloidal oatmeal is a natural product that has an excellent safety record and a long history of use in health care
- **Antioxidant and anti-irritant properties**
- **Emollient, humectant and occlusive effect**
- **Enhancement of the skin barrier**
- Induce the formation of a protective moisturizing barrier over skin by the proteins and polysaccharides
- **Anti-inflammatory and antipruritic properties**
  - Inhibition of histamine
  - Inhibition of the release of proinflammatory cytokines
  - Inhibition of the activity of nuclear factor kB

Cerio R. et al. J Drugs Dermatol. 2010 Sep;9(9):1116-20
Sur R, et al. Arch Dermatol Res. 2008;300(10):569-574

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Avenanthramides

- The avenanthramides are responsible for many of the oatmeal therapeutic effects
- Avenanthramides significantly reduced:
  - compound 48/80-induced, histamine-mediated itch
  - oxazolone-induced contact hypersensitivity
  - VIP-induced neurogenic inflammation
  - phospholipase A2-dependent mobilization of arachidonic acid from phospholipids
- **In 2003 the FDA approves colloidal oatmeal as one of the few natural products recognized as a safe over-the-counter (OTC) skin protectant** (Final Monograph. Federal Register. 2003;68:33362-33375)

Vie K. et al. Skin Pharmacol Appl Skin Physiol. 2002;15(2):120-124
Guo W et al. Free Radio Biol Med. 2008;44(3);415-429

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Topical corticosteroids & ACD

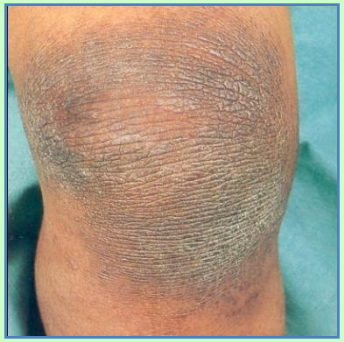
- Topical corticosteroids are the first-line treatment for localized forms of eczematous dermatitis (Strengh of recomendattion A)
- They provide rapid relief and are used for short periods to settle dermatitis flare ups (Strengh of recomendattion A)
- Corticosteroids have broad immunomodulatory effects inhibiting the afferent and efferent pathways of Allergic reactions
  - reduces the number of LCs, activated T cells, and mast cells in the skin
  - produce depletion of CD1 and HLA-DR molecules on LCs
  - inhibit antigen-specific activation and proliferation of lymphocytes
  - inhibit T-cell effector functions
  - inhibit release of IL-2 and IFN-γ by T lymphocytes
  - inhibit the production of IL-1 and TNF-α
  - inhibit keratinocyte apoptosis mediated by FAS triggering

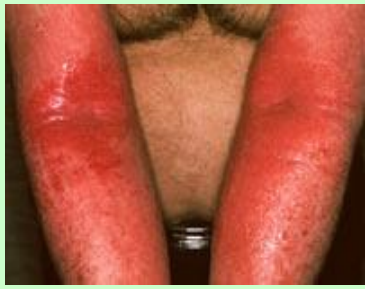
Topical corticosteroids

- Topical corticosteroids are thought to activate glucocorticoid receptors that inhibit cytokine activation, thereby decreasing local inflammation and indirectly controlling pruritus.
- It must be emphasized that topical corticosteroids are of limited to no benefit in patients with noninflammatory itch.

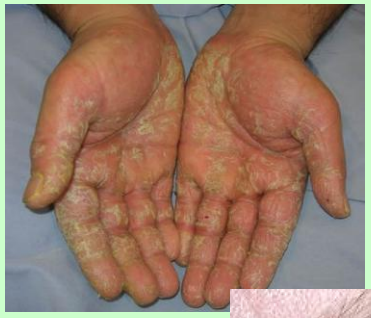
Topical corticosteroids

- Choice regarding the strength and vehicle of a TC depends on the anatomic area of application, severity of the condition, evolutive stage, extent of involvement and age of the patient

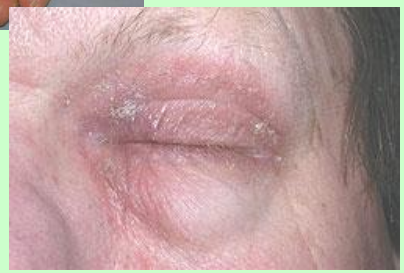




- ointment for dry scaling lesions
- emollient and occlusive effects, enhance Tc potency by increasing skin permeability
- lotion or cream for weeping areas of dermatitis

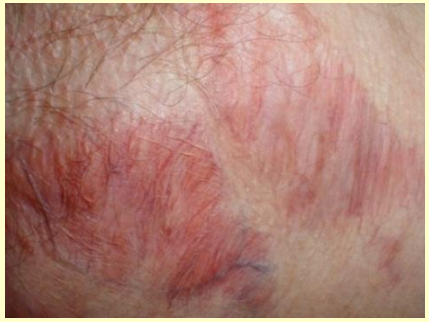


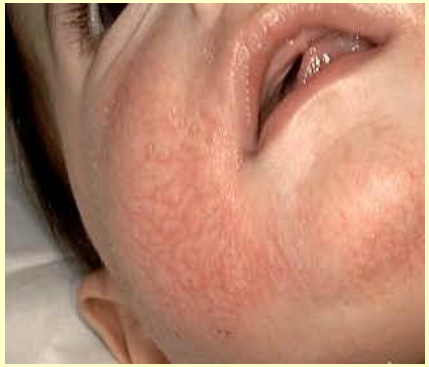
- High potency for areas with thick SC such as palms and soles (clobetasol propionate or betamethasone dipropionate)
- Low (or medium) potency for areas with thin SC such as eyelid and intertriginous areas (Hydrocortisone and desonide)



Topical corticosteroids

- Application should be restricted to once or twice daily, according to the pharmacokinetics of the corticosteroid
- An emollient should be applied in between times
- Use no more than 50 g/week of potent CT in an adult and no more than 15 g/week in a child
- Unless specifically indicated, short-term treatment is preferred
- When limited to two to three weeks, use of TC is usually safe.
- Prolonged treatment, high potency agents, occlusion, use on large areas or areas of thin skin can lead to adverse local or systemic effects

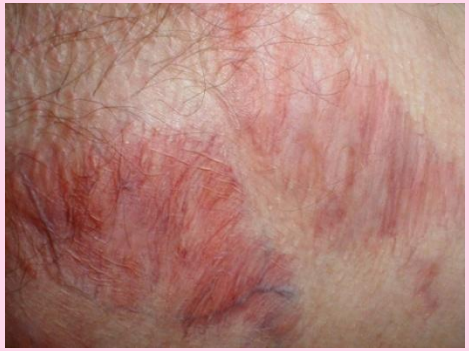


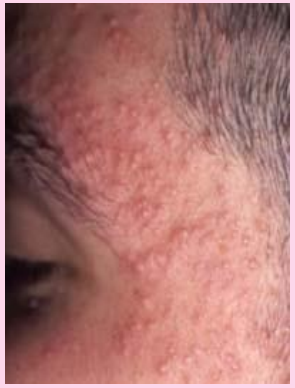


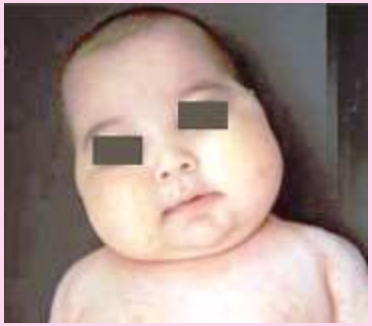
Topical corticosteroids

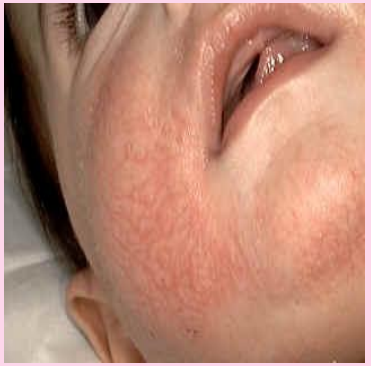
- Unless specifically indicated, short-term treatment is preferred
- When limited to two to three weeks, use of TC is usually safe.

- Prolonged treatment, however, can lead to adverse effects (skin atrophy and telangiectasia, striae distensae, steroid-induced acne, rosacea, and folliculitis)
- Significant systemic absorption of topical corticosteroids can occur with high-potency agents especially if used over large areas of skin and/or under occlusion.
- Adverse events may also be seen after use of inappropriately potent preparations to given body sites









Combination strategies

- Topical corticosteroids may produce depletion of intercellular lipids and decrease in barrier function
- Adjunctive barrier repair-moisturizers improve the skin barrier function and may lead to a reduction of steroid therapy
- Studies have shown a decrease in the need for topical corticosteroids while maintaining efficacy in treatment of eczematous dermatitis
- Emollients may serve as steroid-sparing agents and may even improve the clinical efficacy of topical corticosteroids, including their effects on pruritus (synergistic phenomenon)
- **Working co-ordinately at dermal (topical corticosteroid) and epidermal (corneotherapy agent) levels is the optimal topical management of eczematous dermatitis**

Sheu et al.; Br. J. Dermatol., 1997; 136: 884-890

Potency Class Corticosteroid Available Formulations

I (ultra high)
Clobetasol propionate 0.05%
Halobetasol proprionate 0.05%
Fluocinonide 0.1%
Diflorasone diacetate 0.05%

II (high)
Betamethasone dipropionate 0.05%
Desoximetasone 0.25%
Amcinonide 0.1%
Desoximetasone 0.05-0.25% Gel,
Diflorasone diacetate 0.05%
Fluocinonide 0.05%

III (medium)
Betamethasone dipropionate 0.05%
Betamethasone valerate 0.1%
Amcinonide 0.1%
Fluticasone propionate 0.005%
Triamcinolone diacetate 0.5%
Mometasone furoate 0.1%

IV (medium)
Hydrocortisone valerate 0.2%
Triamcinolone acetonide 0.1%

V (medium)
Betamethasone valerate 0.1%
Fluticasone propionate 0.05
Hydrocortisone butyrate 0.1%
Hydrocortisone valerate 0.2%
Triamcinolone acetonide 0.025-0.1%

VI (low)
Alclometasone dipropionate 0.05%
Desonide 0.05%
Fluocinolone acetonide 0.01%

VII (very low)
Hydrocortisone 0.5-2.5%

Topical Immunomodulators

- Topical immunomodulators such as tacrolimus or pimecrolimus are prescribed when they offer safety advantages over TC
- They are preferred in the face, neck, genital area and skin folds
- Constitute a valid alternative in patients with allergy to steroids
- Allow therapeutic strategies combined with TC

Topical Doxepin

- Topical doxepin, a tricyclic antidepressant and potent H1 and H2 antagonist, has been shown to significantly reduce pruritus in patients with AD, lichen simplex chronicus, contact dermatitis and nummular dermatitis
- However, topical doxepin may induce contact dermatitis

Other topical agents

- Substances such as urea, menthol, camphor and polidocanol to these creams leads to an immediate short-term interruption of the itch.