Allergic skin diseases

Atopic dermatitis

- Atopic dermatitis (AD) is a chronic, highly pruritic, eczematous skin disease that follows patients from early childhood into puberty and sometimes adulthood

- Also reffered to as eczematous dermatitits, the disease often has a remitting/flaring course, which may be exacerbated by social, enviromental and biological triggers

Atopic dermatitis

The rash in AD is characterized by itchy papules (occasionally vesicles in infants) which become excoriated and lichenified, and typically have a flexural distribution

Atopic dermatitis: prevelence

- approximately 15% in the USA and Europe
- this represents a profound increase in recent years (from as low as 3% in 1960)

Children 10 – 15%

Adult 1 – 3 %

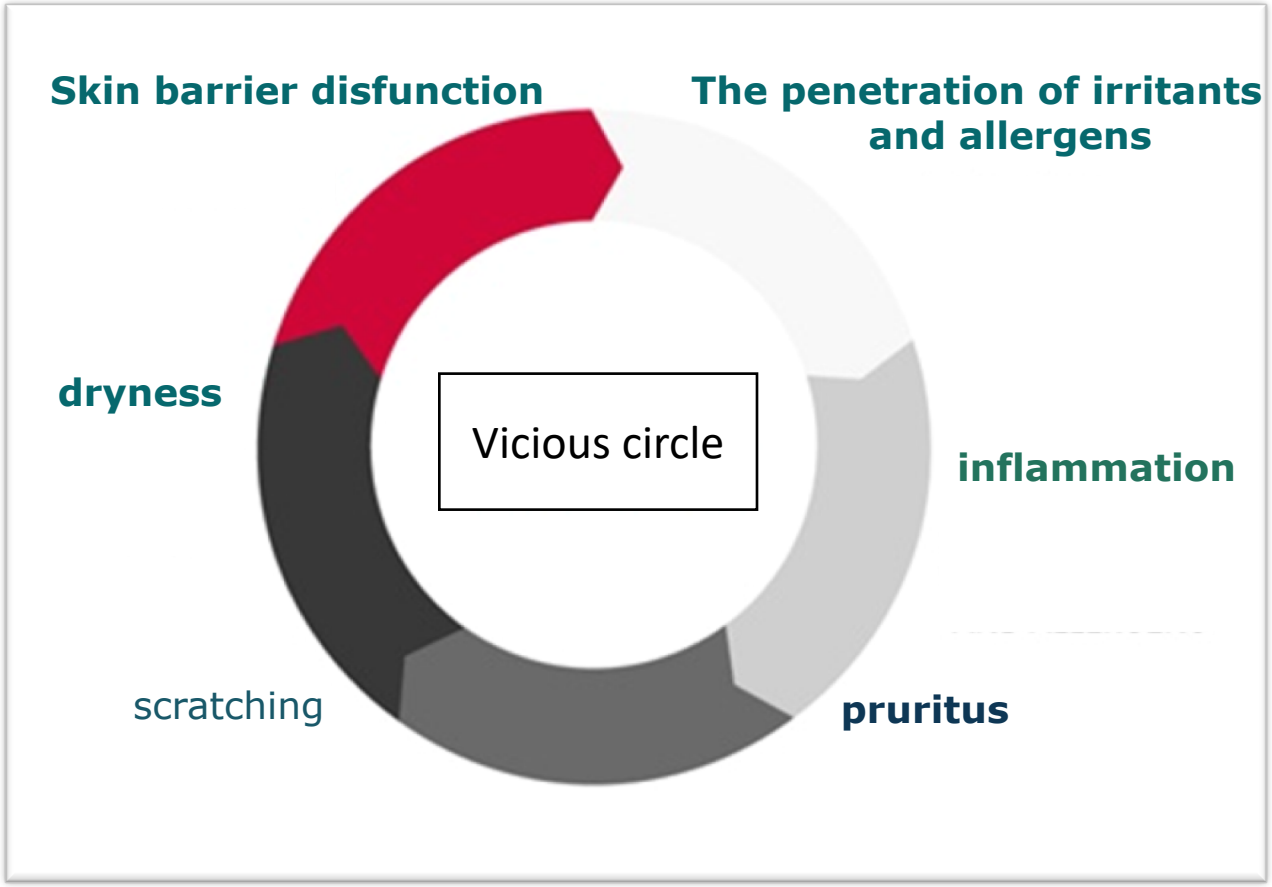
Atopic dermatitis: epidemiology

- 60 % of patients develop AD by 1 year of age
- 85 % of patients develop AD by age 5
- 10 % develop AD between 6 and 20 years of age
- Rarely AD has an adult onset
- Earlier onset often indicates a more severe course

Atopic dermatitis: epidemiology

- Many cases resolve by age 2, improvement by puberty is common
- 50-60 % of patients develop respiratory allergies or asthma
- 80 % of occupational skin disease occur in atopics
- It is rare to see AD after age 50
- **GENDER:** slightly more common in males than females

Atopic dermatitis



Atopic dermatitis: aetiology

THE INHERITANCE

- **The inheritance pattern has not been ascertained. However, in one series, 60 % of adults with AD had children with AD.**
- **The prevalence in children was higher (81 %) when both parents had AD.**

Atopic dermatitis: aetiology

ELICITING FACTORS

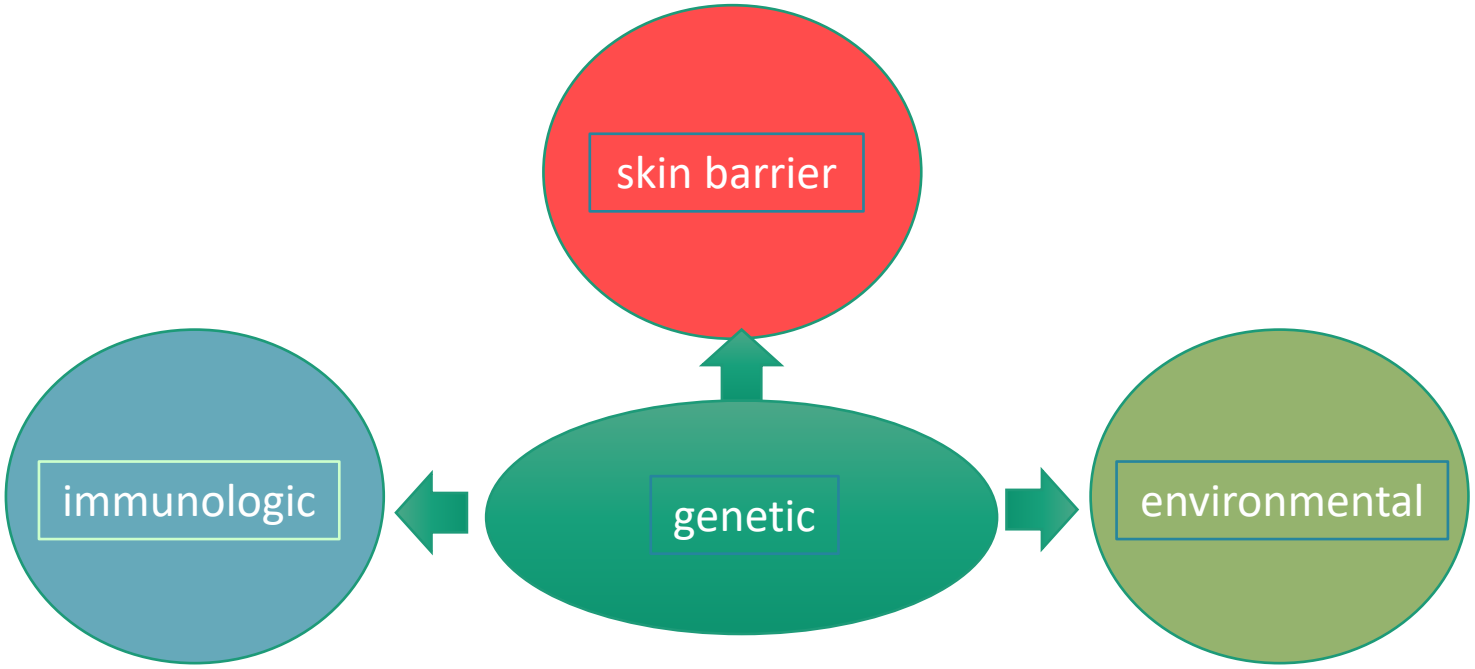
- **Inhalants: Specific aeroallergens, especially dust mites and pollens, have been shown to cause exacerbations of AD**
- **Microbial Agents: Exotoxins of *Staphylococcus aureus* may act as superantigens and stimulate activation of T cells and macrophages**
- **Autoallergens: IgE antibodies directed at human proteins**
- **Foods: Subset of infants and children have flares of AD with eggs, milk, soybeans, fish and wheat**

Atopic dermatitis: aetiology

EXACERBATING FACTORS

- **Skin barrier disruption: increase transepidermal water loss (TEWL)**
- **Infections: *S. aureus* present in severe cases; rarely fungus (dermatophytosis, candidiasis)**
- **Season: AD improves in summer, flares in winter**
- **Clothing: wool is important trigger; wool clothing or blankets (also wool clothing of parents)**
- **Emotional stress**

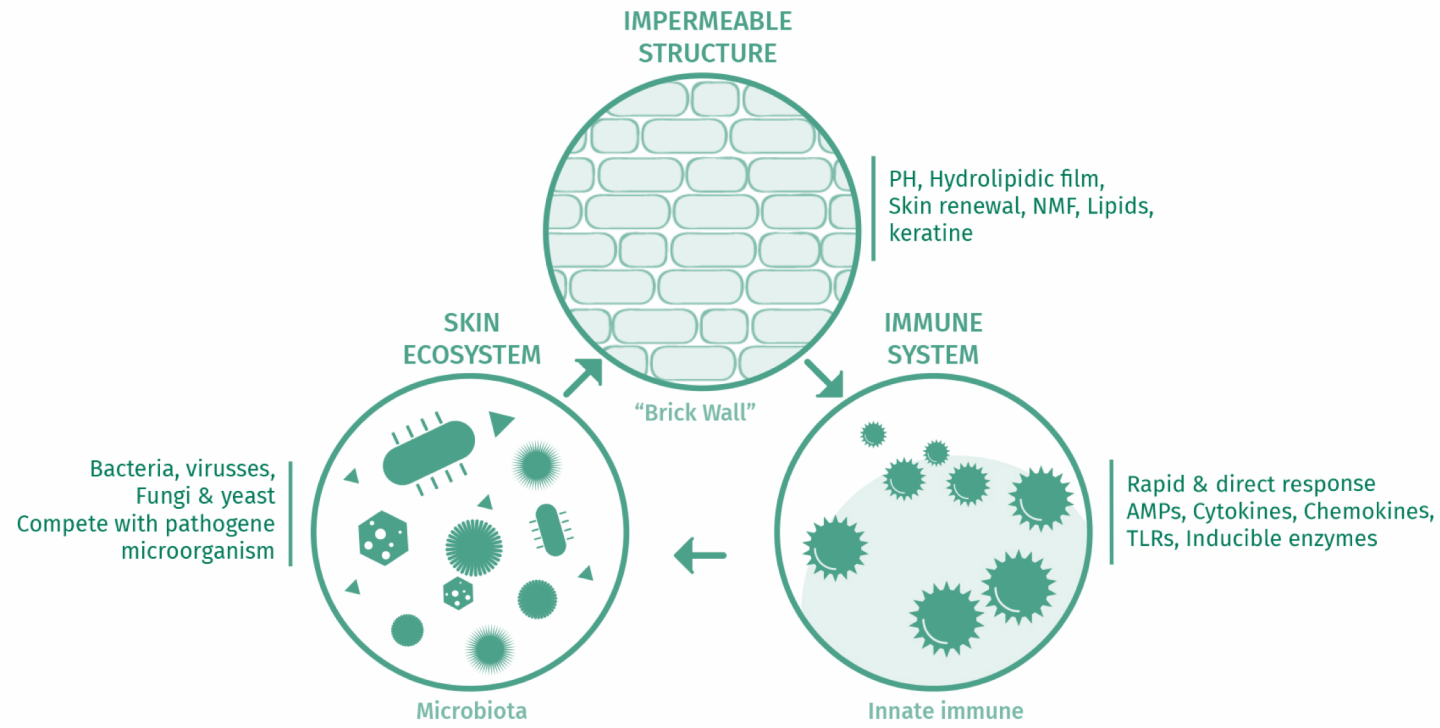
Atopic dermatitis: pathogenesis



Atopic dermatitis: pathogenesis genetics

- **higher risk was associated with maternal rather than paternal atopy**
- **„loss-of-function” mutations in the gene encoding filaggrin**

Atopic dermatitis: pathogenesis



Atopic dermatitis: pathogenesis
SKIN BARRIER DYSFUNCTION

- **Xerosis is hallmark of AD, which affects lesional and nonlesional skin areas increasing TEWL.**
- **Several mechanisms have been postulated:**

1) **abnormal construction of the "corneal cell envelope" (corneocytes and ECM)**
2) **decrease in skin *ceramides***
3) **alternations of the stratum corneum *pH* -** physiological 5,4-5,9; changing the pH from 7.5 to 5.5 reduces the activity of proteases by 50%
4) **overexpression of the chymotryptic enzyme *(chymase)***
5) **abnormal synthesis of structural proteins of the epidermis: filaggrin, NMF**

Atopic dermatitis: epidermal barrier

FILLAGRIN

- Fillagrins are filament-associated proteins which bind to keratin fibers in epithelial cells
- Persons with mutations in the gene coding for filaggrin are strongly predisposed to a severe form of dry skin, eczema and / or ichthyosis vulgaris
- almost 50 % of all severe cases of eczema may have at least one mutated filaggrin gene

Atopic dermatitis: epidermal barier

MICROBIOTA AND SKIN MICROBIOM

- **SKIN MICROBIOME** = the sum of all GENES of skin microorganisms
- **SKIN MICROBIOTA** = all skin microorganisms; is an invisible ecosystem of various microorganisms that support the skin's protective barrier

Atopic dermatitis: epidermal barier
MICROBIOTA AND SKIN MICROBIOM

- **PARTICIPATES IN THE SYNTHESIS OF NATURAL MOISTURIZERS**

  maintaining the proper hydro-lipid balance of the skin

- **SUPPORTS THE BARRIER FUNCTIONS OF THE SKIN**

  improves the integrity of the epidermal barrier

Atopic dermatitis: pathogenesis

Immunological

1) **ELEVATED IgE in majority of case type 1 hypersensetivity reaction**
2) **INCREASE NUMBER OF Th2 ???**

- **The hygiene hypothesis**
- **Low birth weight**
- **Maternal smoking**
- **Early infection with respiratory syncytial virus (RSV)**
- **Vaccination against *Bordetella pertussis***
- **Early allergen contacts**

Atopic dermatitis: diagnostic criteria

Hanifin and Rajka diagnostic criteria for AD

- pruritus
- typical location
- characteristic morphology of skin lesions
- coexistence with atopic diseases patient or his family

  (asthma, hay fever and eczema)

Major Criteria *(need three or more of the following):*

Pruritus
Typical morphology and distribution
- Facial and extensor involvement in infants and children
- Flexural lichenification or linearity in adults

Chronic or chronically relapsing dermatitis
Personal or family history of atopy (allergic rhinitis, asthma, atopic dermatitis)

Minor Criteria *(need three or more of the following):*

Anterior neck folds
Anterior subcapsular cataracts
Cheilitis
Course influenced by environmental or emotional factors
Dennie-Morgan infraorbital fold
Early age of onset
Facial pallor or facial erythema
Food intolerance
Keratoconus
Ichthyosis, palmar hyperlinearity, or keratosis pilaris
Immediate skin test reactivity
Intolerance to wool and lipid solvents
Itch when sweating
Nipple eczema
Orbital darkening
Perifollicular accentuation
Pityriasis alba
Raised serum IgE
Recurrent conjunctivitis
Tendency toward cutaneous infections (especially S. aureus and herpes simplex) or impaired-cell immunity
Tendency toward nonspecific hand or foot dermatitis
White dermatographism or delayed blanch
Xerosis

AD: associated clinical features
XEROSIS

- **cardinal feature of AD**
- **xerosis seen in 80-98% of AD patients**

AD: associated clinical features
KERATOSIS PILARIS

- **excessive keratinization leading to horny plugs within hair follicle orifices**
- **Seen primarily on the lateral aspects of the upper arms and thighs and the cheeks in children**
- **A small rim of erythema surrounds**

  the involved hair follicles

AD: associated clinical features

ICHTHYOSIS VULGARIS

- **Up to 50% of AD patients have this autosomal dominant disorder**
- **Characterized by excessive scaling**

PITYRIASIS ALBA

- **Infants and children with AD may have patches of hypopigmentation with fine scale, most commonly on the face**

AD: associated clinical features

CHEILITIS

- **dry, crusty, „chapped" lips or fissuring of the commisures (angular cheilitis) is more common in infants and children with AD than in adults**

Dennie-Morgan lines

- **Symmetric, prominent fold (single or double) beneath the margin of the lower eyelid**

PRURIGO NODULARIS

AD: associated clinical features

- Course influenced by enviromental or emotional factors
- Early age of onset
- Food intolerance
- Immidiate skin test reactivity
- Intolerance to wool and lipid solvents
- Itch when sweating
- Raised serum IgE

AD: other clinical features

- Lymphadenitis dermatogenes
- Dry, brittle hair
- Skin overly sensitive to stimulation

AD: clinical features

The distribution of the eruption varies with age

AD: infantile phase

- most frequently start on the face especially cheeks, but may occur anywhere; often the napkin area spared
- the lesions consist of erythema and discrete or confluent oedematous papules
- secondary infection and lymphadenopathy are common

AD: childhood phase

- **papular lesions, lichenified plaques, erosions, crusts, especially on the antecubital and popliteal, the neck: „atopic dirty neck" and face; may be generalized**
- **Eczema in this group often affects the extensor (outer) aspects of joints, particularly the wrists, elbows, ankles and knees; it may also affect the genitals**

AD: adult phase

- **There is a similar distribution, mostly flexural but also face and neck, with lichenification and excoriations**
- **May be generalized**

AD: rating scales

SCORAD *Scoring Atopic Dermatitis Index*

EASI *Eczema Area and Severity Index*

DLQI *Dermatology Life Quality Index*

VAS *Visual Analogue Scale*

AD: complications

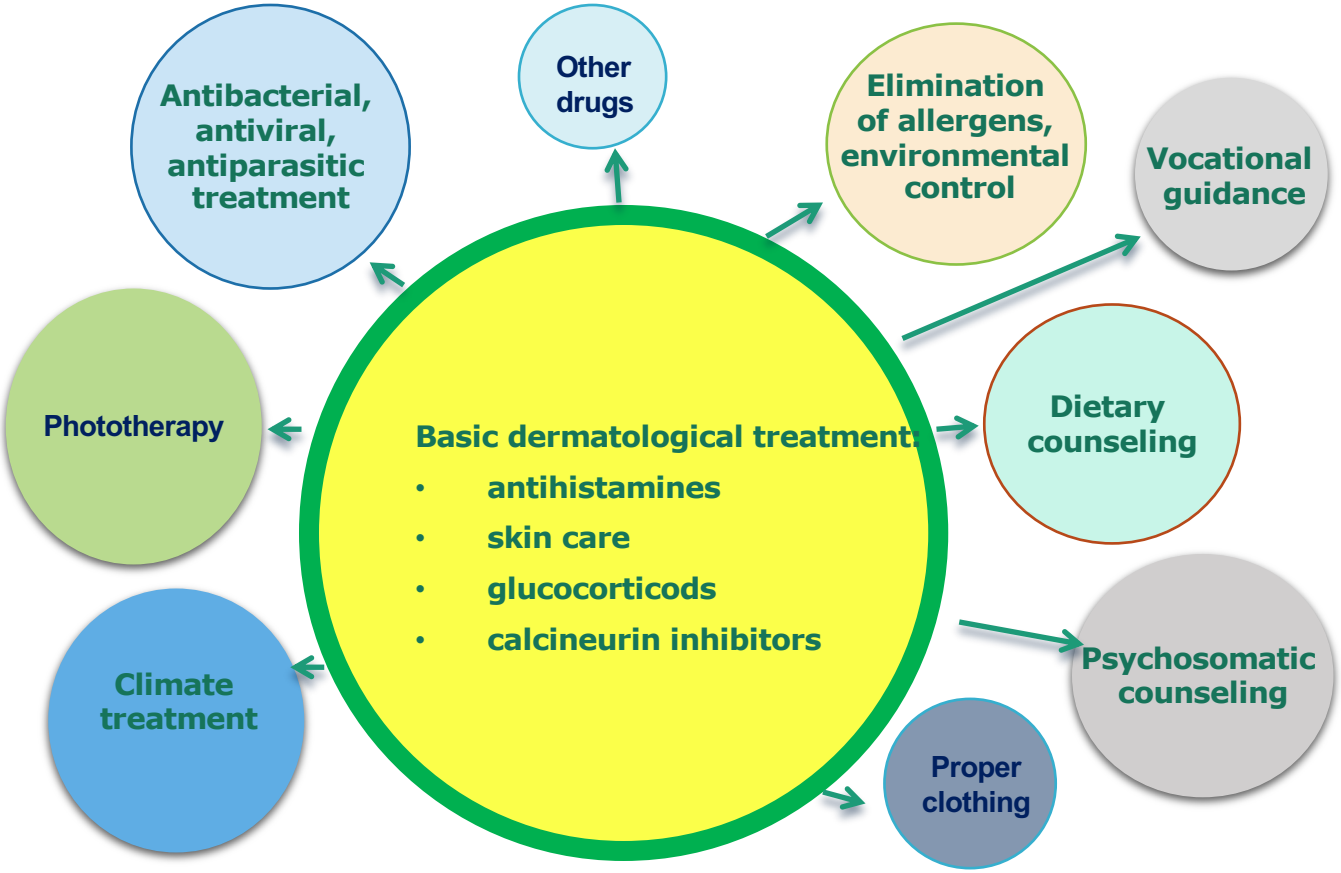
Secondary infection with *S. aureus*	
Herpes simplex virus (*eczema herpeticum)*	
Rarely	• Keratoconus • Cataracts • Keratoconjunctivitis with secondary herpetic infection and corneal ulcers

AD: differential diagnosis

- Psoriasis
- Rosea Gibert
- Mastocytosis
- Pityriasis versicolor
- Dermatophytosis
- Mycosis fungoides
- Nummular eczema
- Seborrheic dermatitis
- Irritant contact dermatitis

AD: TREATMENT

AD: integrated treatment model



AD: treatment

PRIMARY PREVENTION

- **Allergen avoidance during pregnancy, infancy or both**
- **Breastfeeding (which is though to have immunomodulatory effects), but there are suggestion of a higher risk of AD with a longer duration of breastfeeding**

AD: treatment

PRIMARY PREVENTION

- **Prevent „scratching” or rubbing**
- **Carefully eliminate all the triggers of itch**
  - **Enviromental, occupational and temperature control**
  - **Bathing (soapless cleansers)**
  - **Lubrication**

AD: treatment

SUPPORTIVE CARE

1) **After the onset of AD, a reduction of trigger factors:**

- **Irritants**
- **Wool clothing**
- **Winter chapping**
- **Excessive heat**
- **Sweating**
- **Airborne allergens**
- **Food allergens**
- **Skin infections: S. aureus, viral, dermatophytes**
- **Soaps**
- **Detergents**
- **Habitual scratching**
- **Stress**
- **Occupational**
- **Tobacco smoke**
- **Psychological**
- **hormones**

AD

CLOTHES

- **cotton** - avoiding irritation, e.g. by wool, synthetics
- **avoiding excess clothing** - hyperhidrosis and itching
- **reduction of exposure to irritants and injuries** - covering the skin with airy clothing

PROFESSION

- Choosing a profession

AD

BATH

The 5-minute rule

- T 27-30^{o}C (in infants 35-37^{o}C)
- remove from the skin allergens, irritants and epidermal cells
- increase the penetration of external drugs
- have a relaxing effect
- antibacterial agents should be avoided

Emollients:

- after bathing, tapping the skin dry followed by application to wet skin of a drug and/or emollient to reduce TEWL

Darsov et al. JAEDV 2010; 24: 317

AD: treatment

MANAGEMENT OF ACUTE AD

- **Wet dressing and topical glucocorticosteroids, topical antibiotics**
- **Hydroxyzine 10-100mg orally against pruritus**
- **Oral antibiotics to eliminate *S.aureus* and treat MRSA according to sensitivity as shown by culture**

AD: treatment

TOPICAL

Emolients

Topical steroids

Topical calcineurin inhibitors (TCIs)

AD: treatment

TOPICAL

Emollients

- 17th century Latin emollire - to soften
- Neutral moisturizing and greasing substances that restore the skin's natural protective barrier function, they:
  - form a lipid coat on the skin
  - protect the skin against water loss - they lower TEWL
  - increase skin elasticity
  - reduce the feeling of itching
  - prevent complications after GCS
  - strengthen the action of GCS

Hanifin J et al. J Am Acad Dermatol 2014; 3: 391.

AD: treatment

TOPICAL

Emollient regime

- every day, even during periods of remission
- application 2-3 times a day
- maximum effect after approx. 30-60 minutes, lasts for approx. 4-6 hour
- recommended amount of emollient: children 250 g/week, adults 500 g/week
- under a moist dressing - increases effectiveness, prolongs their action, cooling effect, reduces itching and increases the absorption of topical drugs

AD: treatment

TOPICAL

Emollients

CLASSES OF EMOLLIENTS	SUBSTANCES	ACTION
I GENERATION	paraffin, vaseline, hypoallergenic lanolin, fatty acids, hydrophilic polymers, fatty alcohols, vegetable oils	occlusion
II GENERATION	humectants: hyaluronic acid, glycerol, sorbitol, urea (3-10%), propylene glycol, lactic acid, dexpanthenol, ceramides, collagen, NMF components	hydration
III GENERATION	natural oils containing polyunsaturated fatty acids omega 3, 6, 9; ceramides, cholesterol, pyrrolidic acid	strengthening the skin barier, differentiation of epidermal cells, TEWL reduction

Raone R., et al. Austin J Allergy 2015,

AD: treatment

TOPICAL

Modern emollients / emollients **PLUS**

- with agonists for peroxisome proliferator receptors (PPAR), e.g. highly unsaturated fatty acids enriched with active substances:
  - reconstructing the epidermal barrier
  - anti-inflammatory saponins, niacinamide, flavonoids
    - inhibition of cytokines: TSLP, IL-2, IL-4, IL-12, IL-17, IL-18, IFN-γ, IL-1β, TNF-α and chemokines: MCP3/CCL7, MDC/CCL22, MIP-3α/CCL20

AD: treatment

TOPICAL

Modern emollients / emollients **PLUS**

- antipruritic ingredients that increase innate antimicrobial immunity:

- by activating TLR2, TLR4, TLR5, by stimulating the synthesis of natural epidermal antibacterial peptides beta-2-defensin (hBD-2), cathelicidin LL-37, psoriazine

- lowering the pH of the emollient increases the production of antimicrobial peptides and accelerates the repair of the epidermal barier
- oligosaccharides f.ex. from the root of the Japanese lily of the valley inhibiting the formation of biofilm

Aberg KM i wsp. Co-regulation and interdependence of the mammali- an epidermal permeability and antimicrobial barriers. J Invest Dermatol. 2008

AD: treatment

TOPICAL

Emollients

- common skin care products can damage the epidermal barrier while some emollients+ improve the epidermal barrier function
- emollients with a balanced composition of three physiological lipids:

ceramides

cholesterol

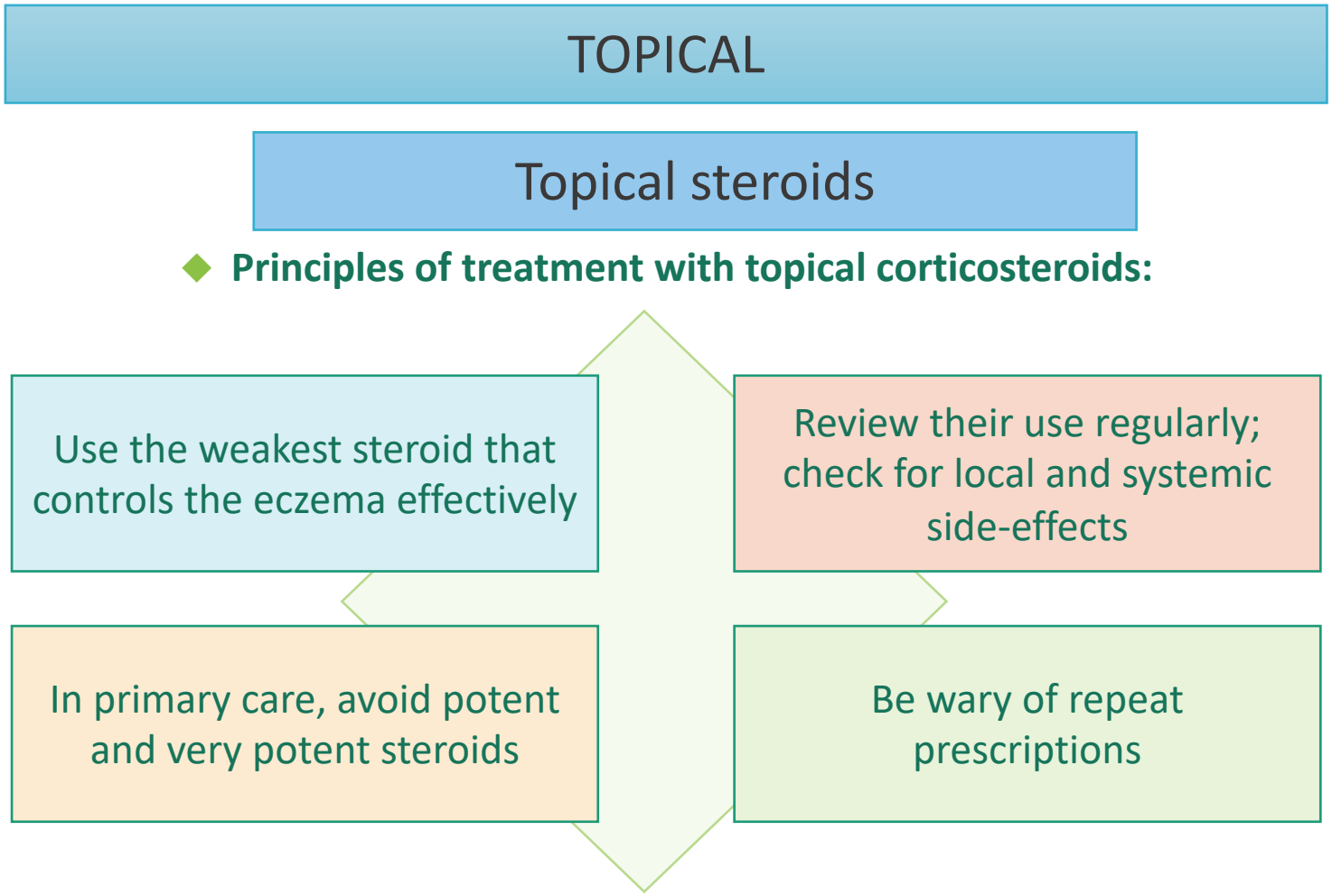
fatty acids

3:1:1

and NMF ingredients: urea, glucose, hydrophilic aminoacids

- optimally accelerate the reconstruction of the epidermal barrier

AD: treatment



AD: treatment – topical GKS

Clinical effects:

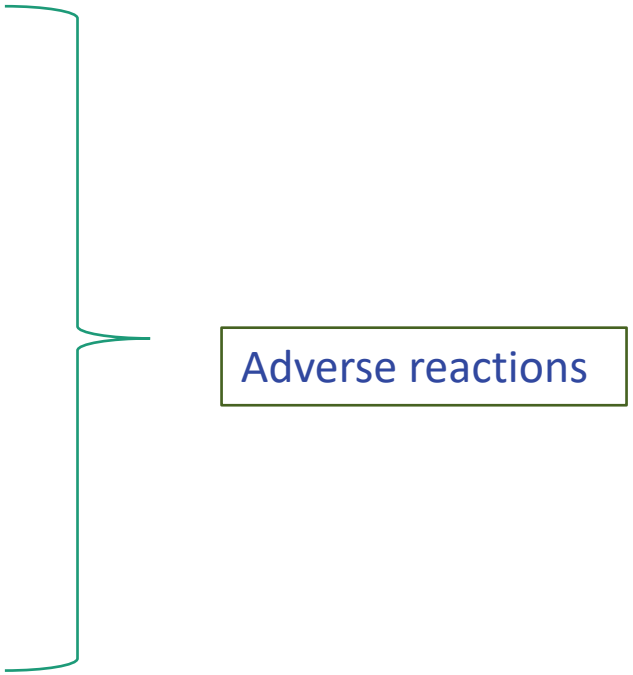
1) **Immune cells:**
   - **Immunosupression**
   - **Anti-inflammatory**
   - **Antiallergic**
   - **Pain relief (secondary)**
2) **Vessels:**
   - **Decrease permeability**

Desired therapeutic effects

AD: treatment – topical GKS

Clinical effects:

3) **Skin:**
   - **skin thinning**
   - **echymoses**
4) **Eyes:**
   - **cataract**
   - **glaucoma**



AD: treatment – topical GKS

Clinical effects:

5) **Metabolism:**
   - **Weight gain/obesity**
   - **Fluid retention/oedema**
   - **Cushingoid appearance**
   - **Impaired glucose metabolism**
6) **Muscle:**
   - **myopathia**

Adverse reactions

AD: treatment – topical GKS

Clinical effects:

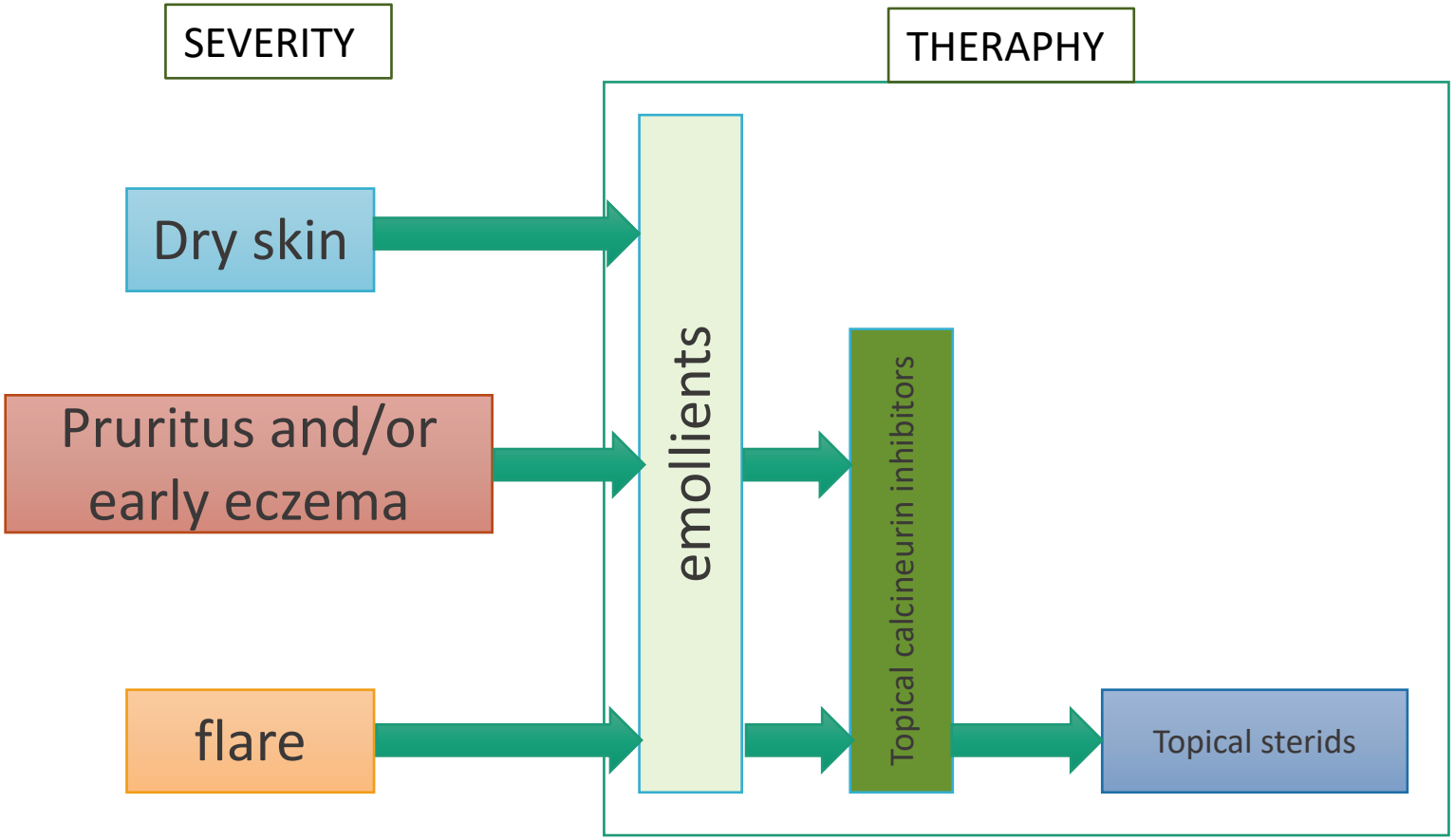
7) **Bone:**
   - **osteoporosis**
   - **osteonecrosis**
8) **CNS:**
   - **Neuropsychiatric**
9) **Infections**
10) **Cardiovascular**

Adverse reactions

AD: treatment – topical calcineurin inhibitors (TCIs)

- **Tacrolimus (0,03%, 0,1% ointment) and pimecrolimus (1% cream) are gradually replacing glucocorticosteroids in most patients**
- **Potently suppress itching and inflammation and do not lead to skin atrophy**
- **Not effective enough to suppress acute flares but work very well in minor flares and subacute atopic dermatitis**

AD: strategy for topical treatment



AD: treatment

SYSTEMIC

ANTIHISTAMINES

SYSTEMIC GLUCOCORTICOSTEROIDS

ANTIMICROBIALS

PSYCHOLOGICAL APPROACHES

AD: systemic treatment

SYSTEMIC
GLUCOCORTICOSTEROIDS

- **SHOULD BE AVOIDED EXCEPT in rare instances in adults for only short courses**
- **For severe disease, prednisone, 60-80mg daily for 2 days, then halving the dose each 2 days for the next 6 days**
- **Patients tend to become dependent on oral glucocorticosteroid**

AD: systemic treatment

ANTIMICROBIALS

- **Are important for AD patients with coutaneous infections**
- **ANTISTAPHYLOCOCCAL THERAPHY (e.g.cephalosporins) can improve superinfected AD and may provide some benefit to non-infected skin**
- **KETOCONAZOLE has been useful for head- or neckbased AD, presumably to reduce *Malassezia* colonization**

AD: treatment

PHOTOTHERAPY

- **Improve AD, but some patients cannot tolerate the heat generated by the equipment**
- **UVA, UVB, UVB 311nm (narrowband), combined UVA and UVB and PUVA have all been effective in AD**
- **Some patients benefit from natural sunlight**

AD: treatment

PHOTOTHERAPY

- PUVA 320-400nm
- UVA1 340-400nm
- SUP 300 i 325nm (selective phototherapy)
- UVB TL-01 311nm *(narrow band, NB-UVB)*
- UVB 290-320nm
- combined UVA and UVB

AD: treatment

PHOTOTHERAPY

- **Sweat exacerbates skin lesions in >75%**
- **UV radiations:**
  - Langerhans cell suppression
  - Eosinophil superession
  - Stimulation of Ts lymphocytes
- **Complications:**
  - Neoplastic transformation
- **Contraindications:**
  - Cataract
  - Some pigmented skin lesions

AD: advanced therapies

- **For the unusually difficult-to-manage AD patient**

CYCLOSPORINE

METHOTREXATE

AZATHIOPRINE

BIOLOGICS

AD: advanced therapies

AD: advanced therapies

CYCLOSPORINE

- **Oral cyclosporine at a dose of 2,5-5 mg/kg per day**

METHOTREXATE

- **Mtx 2,5-25 mg per week**
- **depending upon patient: age, weight, renal function**

AD: advanced therapies

AZATHIOPRINE

- **Dosage 2-3,5 mg/kg/day if normal, 0,5-1 mg/kg/day if low**

- **Side effects including:**
  - **myelo-suppression**
  - **hepatotoxicity**
  - **gastrointestinal disturbances**
  - **increased susceotibility for infections**
  - **possible development of skin cancer**

AD: advanced therapies

BIOLOGICS

- **DUPILUMAB**

– against IL-4 and IL-13

– 600mg s.c. in two 300mg injections and then 300mg s.c. every 2 weeks

- **UPADACITINIB**

– selective JAK1 inhibitor

– 15mg or 30mg orally/day

AD: advanced therapies

BIOLOGICS

- **TRALOKINUMAB**

– Il-13 inhibitor

– 600mg s.c. - 4 injections a 150mg and then 300mg s.c. every 2 weeks

- **ABRICITINIB**

– selective JAK1 inhibitor

– 200mg orally/day

– after 65 years of age 100mg/day

AD: advanced therapies

BIOLOGICS

- **BARICITINIB**
  - JAK1 and JAK2 inhibitor
  - 4mg/day and maintenance dose 2mg/day
- **RUXOLITINIB**
  - topical JAK1 and JAK2 inhibitor
  - 1.5% cream twice a day on the surface of the skin not exceeding 20%
  - max 60g/week or 100g/2 weeks

AD: advanced therapies

BIOLOGICS

- **CRISABOROLE 2%**

– topical phosphodiesterase 4 inhibitor (PDE-4)

– the drug is used for about 3 months

- **Anti-IgE**

- omalizumab, which is approved for asthma and utricaria, has been tried with variable results in AD

AD: conclusions

The effectiveness of treatment depends on:

- systematic care and treatment
- age of the patient
- dominant character of skin lesions
- exacerbation of skin dryness
- coexistence of secondary superinfections
- severity of itching
- food hypersensitivity and intolerance
- the influence of airborne and contact allergens
- the influence of the professional environment
- psychosomatic factors
- coexistence of other atopic diseases
- prevoius treatment

URTICARIA

Urticaria

- Urticaria (hives) is a vascular reaction of the skin characterized by wheals surrounded by a red halo or flare (area of erythema)
- Cardinal symptom is **PRURITUS** (itch)
- Urticaria is caused by swelling of the upper dermis

Urticaria: epidemiology

- 15-20% of the population experience urticaria at some point in their lives
- Affected females > males
- Peak age of onset in adults – between 20 and 40 years
- Associated with angioedema in about 40% of cases

Angioedema

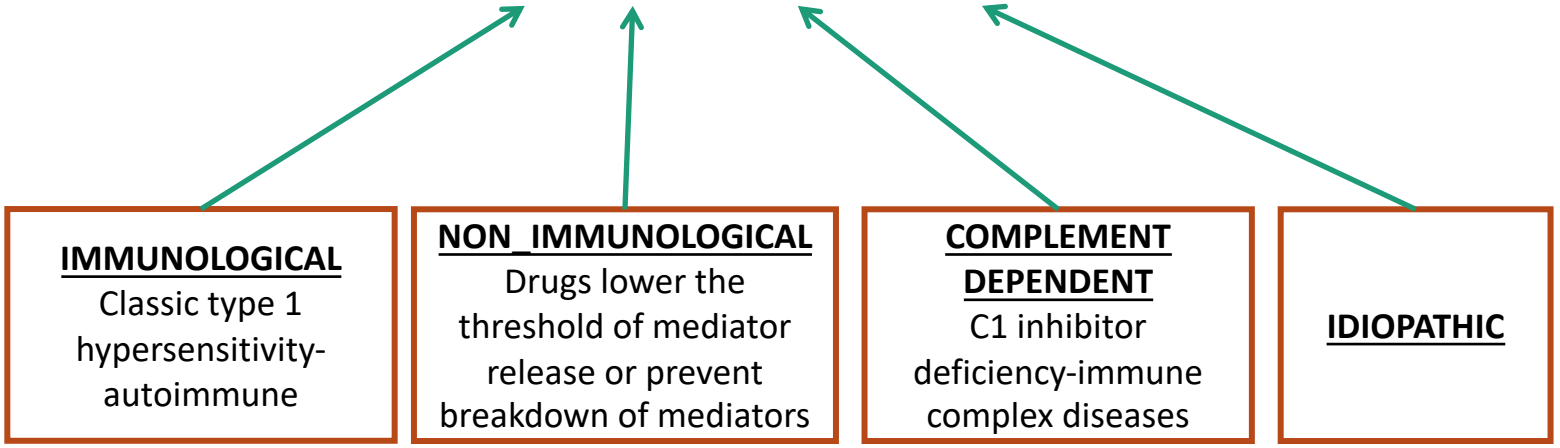
- Angioedema can be caused by the same pathogenic mechanisms as urticaria, but the pathology is in the deep dermis and subcutaneous tissue and swelling is the major manifestation
- Angioedema commonly affects the face or a portion of an extremity

Angioedema

- Involvement of the lips, cheeks, and periorbital areas is common, but angioedema also may affect the tongue, pharynx, larynx and bowels
- May be painful or burning, but not pruritic
- May last several days

Angioedema: pathogenesis

- Release of vasoactive mediators from mast cells and basophils (especially histamine): increased capillary permeability, erythema, itch



Urticaria: pathophysiology

- The mast cell is the major effector cell in urticaria
- Immunologic urticaria: antigen binds to IgE on the mast cell surface causing degranulation, which results in release of histamine

25-30% of chronic urticaria patients have autoantibodies that bind to IgE Rc or IgE

Urticaria: pathophysiology

- Non-Immunologic Urticaria: not dependent on the binding of IgE receptors:
- Direct mast cell releasing agents (f.ex. Codeine, radiocontrast media)
- For example aspirin (NSAIDs, dietary pseudoallergens, salicylates, azo dyes, food preservatives) may induce histamine release through a pharmacologic mechanism where its effect on arachidonic acid metabolism causes a release of histamine from mast cells
- Physical stimulation may induce histamine release through direct mast cell degranulation
- ACE I – inhibition of kinin breakdown by ACE

Urticaria: pathophysiology

- Complement dependent (C1 inhibitor deficiency)
  - 2% cases of angioedema
  - Recurrent angioedema without wheals
  - Abdominal pain – often severe
  - Laryngeal oedema
  - Does not respond well to normal treatments for angioedema
  - Trauma (pressure) precipitates attack in 30%
  - Autosomal dominant

Urticaria: pathophysiology

- Complement dependent (C1 inhibitor deficiency)
  - Type 1: 85% cases; low level of normal C1 inhibitor
  - Type 2: non-functioning C1 inhibitor but normal level
  - Low C4 levels, normal C3

Urticaria: clinical findings

- Lesions typically appear over the course of minutes, enlarge and then disappear within hours, individual wheals rarely last >12hrs

- **LESIONS:** surrounding erythema will blanch with pressure

- LOCATION:
  - any part of skin may be affected
  - Mucous membranes of lips, mouth, tongue, glottis, pharynx, larynx, eyelids, genitalia, trunk, hands, feet
  - May be localized or generalized

Urticaria: clinical findings

❖SYMPTOMS:

- Intense itching
- Burning
- Sense of heat

Urticaria: clinical classification

① ORDINARY URTICARIA

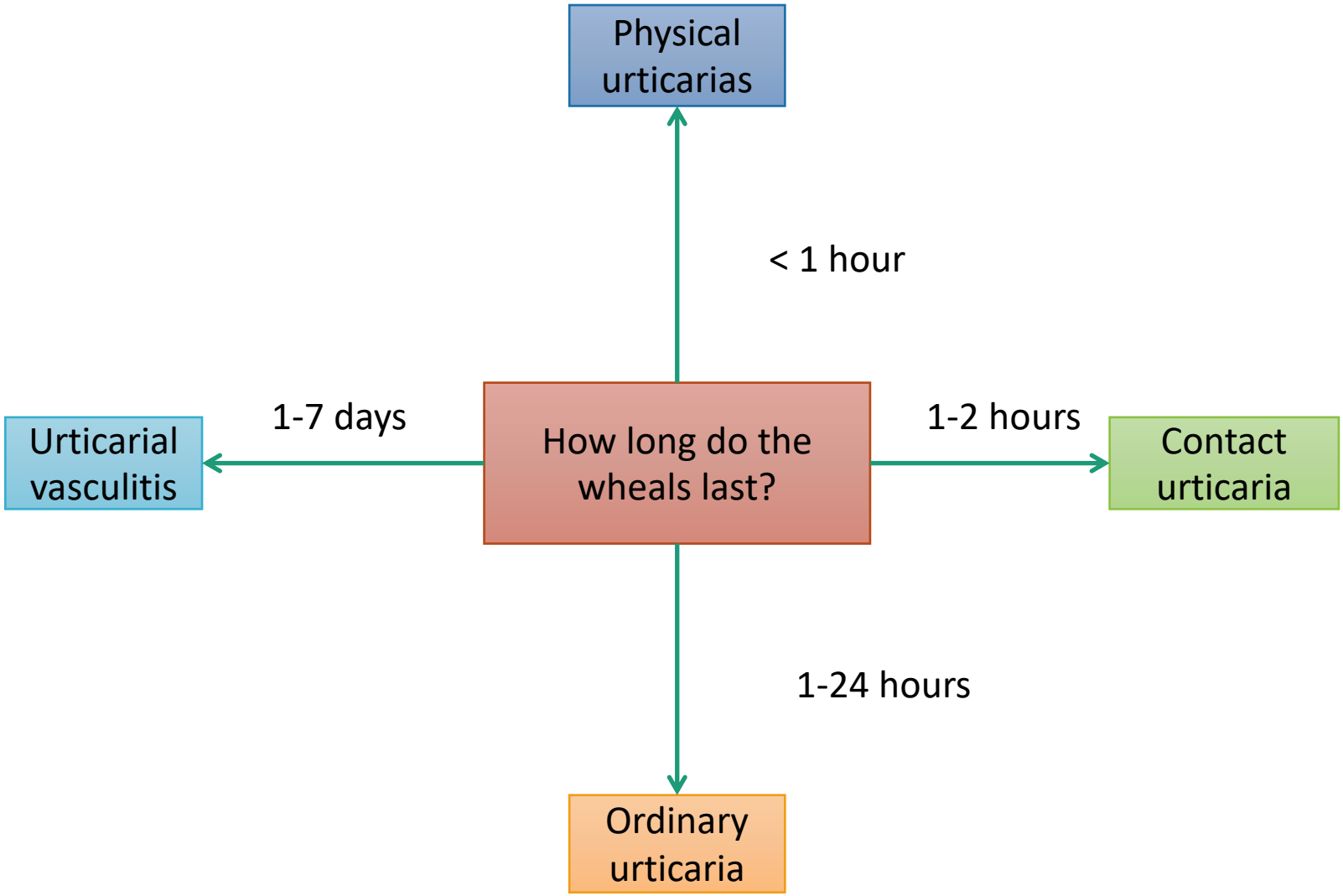
② PHYSICAL URTICARIA

③ ANGIO-OEDEMA (without weals)

④ CONTACT URTICARIA (induced by biological or chemical skin contact)

⑤ URTICARIAL VASCULITIS (defined by vasculitis on skin biopsy)

⑥ AUTOIMMUNE URTICARIA


Physical urticarias
< 1 hour
Urticarial vasculitis
1-7 days
How long do the wheals last?
1-2 hours
Contact urticaria
1-24 hours
Ordinary urticaria

Urticaria: clinical classification

① ORDINARY URTICARIA

a) **Acute** = new onset urticaria < 6 weeks of continous activity

b) **Chronic** = recurrent urticaria (most days) > 6 weeks

c) Episodic - intermittent

1a) Etiology of ACUTE urticaria

- Idiopathic in 50% of cases
- Infection: upper respiratory, Streptococcal infections, EBV, hepatitis B, paresites (round worm, tape worm, hook worm, hydatid disease, filariasis)
- Food reactions: shellfish, nuts, fruit, eggs, strawberry, mashroom, food preservatives, artificial colours
- Drug reactions: usually occurs within 36 hrs of drug administration; salicylates, bromides, iodides, NSAIDs, opiates, radiocontrast etc

1a) Etiology of ACUTE urticaria

- i.v. administration: blood products, contrast agents
- Insect bites: nettles, wasps, bugs, caterpillars
- Plants: nettles
- Psychogenic: emotional stress, over-exertion
- Systemic disease: rheumatoid arthritis, systemic lupus erythematous
- Immunization vaccines e.g.: MMR, tetanus toxoid

1b) CHRONIC URTICARIA

- 1% of acute cases
- 50% of them, no specific cause could be identified – chronic idiopathic urticaria
- 30% settle in the first year
- 85% resolve by 5 years

1b) CHRONIC URTICARIA: etiology

- Physical urticarias (35%): many patients with chronic urticaria have physical factors that contribute to their urticaria
  - These factors include pressure, cold, heat, water (aquagenic), sunlight (solar), vibration and exercise
  - Cholinergic urticaria is triggered by heat and emotions
  - Chronic autoimmune (25%): possibly a third or more of patients with chronic urticaria

1b) CHRONIC URTICARIA: etiology

- Other: infections, medications

- 5% vasculitic

- 60% “ordinary”:
  - Pseudoallergic 2-3%
  - Infection related 2-3%
  - Idiopathic 30%

2) PHYSICAL URTICARIA

reproducibly induced by the same physical stimulus

❖COMMON:

- **DERMOGRAPHISM** (reaction when skin is scratched)
- **CHOLINERGIC URTICARIA** (on exercise, overheating, hot water or stress)
- **DELAYED PRESSURE URTICARIA** (reaction to standing for long period, bra-straps, elastic bands on undergarments, belts; check for cryoglobulins, cold agglutinins, cryofibrinogen)

2) PHYSICAL URTICARIA

❖LESS COMMON:

- **COLD URTICARIA** (reaction to cold, such as ice, cold air or water – worse with sudden change in temperature)

2) PHYSICAL URTICARIA

❖RARE

- **SOLAR URTICARIA** - reaction to direct sunlight (rare, though more common in those with fair skin)
- **LOCALIZED HEAT URTICARIA** (reaction to hot food or objects)
- **AQUAGENIC URTICARIA** (reaction to water)
- **VIBRATORY ANGIOEDEMA** (reaction to vibration)
- **ADRENERGIC** (reaction to adrenaline / noradrenaline)

Urticaria: investigation/diagnosis

- ACUTE URTICARIA
  - None needed unless suggested by history
  - IgE, specific RAST tests, prick tests
- ANGIOEDEMA
  - C4 (highly sensitive, but not specific)
  - If low then check quantitative and functional C1 inhibitor assays

Urticaria: investigation/diagnosis

- CHRONIC URTICARIA
  - ESR, CRP, blood morhology, urine, ANA
  - Thyroid function and thyroid autoantibodies screen
  - 14% patients have thyroid autoantibodies – patients may respond to low dose thyroxine
  - Chest X-ray
  - Abdomen usg, mammography
  - Autologous serum prick test
  - Skin biopsy if urticarial vasculitis suspected

Urticaria: investigation/diagnosis

- complement activating IgG_1 and IgG_3 autoantibodies with histamine releasing functional activity against the high affinity IgE receptor FcεR1 or less commonly against IgE itself

Urticaria: investigation/diagnosis

❖ DERMOGRAPHISM

- firm stroking of uninvolved skin causes almost immediate linear red wheal and itch. A variable pressure dermographometer which can be calibrated is commercially available

❖ DELAYED PRESSER URTICARIA

- firm application of tip of a 3mm diameter rod to uninvolved skin for 2 min; positive result – persistent firm red papule developing in 3-5 hours

Urticaria: investigation/diagnosis

❖CHOLINERGIC URTICARIA

- exercise challenge eg treadmill or jogging in place usually elicits a positive response; Heat challenge e.g., hot bath to evoke the rash

❖COLD CONTACT URTICARIA

- place icepack on uninvolved skin for 15 min, remove and inspect site for cold–evoked wheal 5 min after removal

Urticaria: investigation/diagnosis

❖SOLAR URTICARIA

- expose skin to direct sunlight, slide projector lamp; a local pruritic wheal and flare reaction denotes a positive result

❖HEAT CONTACT URTICARIA

- place warm beaker base (45^{o} C) on clinically uninvolved skin for 5 min; a local pruritic wheal and flare reaction denotes a positive result

Urticaria: investigation/diagnosis

❖AQUAGENIC URTICARIA

- expose face, neck, upper trunk skin to tepid water (eg squeezing a sponge); elicits a transitory pruritic erythematous maculopapular eruption

❖VIBRATORY URTICARIA

- vibrate forearm with a laboratory vortex or rub a towel vigorously across the back (assuming no dermatographism)

Urticaria: differential diagnosis

- Psoriasis
- Rosea Gibert
- Erythema multiforme
- Mastocytosis
- Rheumatoid arthritis
- Vasculitis
- Polymorphic light eruption
- Reactive erythema f.ex. insect bites
- Maculopapular exanthems (viral, drug rashes)

Urticaria: treatment of ACUTE urticaria

- May not need treatment if obvious cause avoided and settling spontaneously
- If severe with angioedema may need to consider s.c. adrenaline, oral steroid
- Most cases just require non-sedating H1 blockers

Urticaria: treatment of CHRONIC urticaria
FIRST LINE

- NON-SEDATING H1 ANTIHISTAMINES and if necessary increasing dosage up to fourfold (off-label dosage)
- "first generation" H1 antihistamines do have a role particularly in patients with sleep disturbance due to urticaria
- H2 ANTAGONIST + H1 BLOCKER

Zuberbieret al., EAACI/GA$_2$LEN/EDF guideline:management of urticaria.Allergy 2006;61:321-331

Urticaria: treatment of CHRONIC urticaria SECOND LINE TREATMENT

- Doxepin (tricyclic antidepressant) 10-50mg or 25-75mg daily
- Leukotriene antagonists: montelukast 10mg at night (especially in aspirin sensitive urticaria and autoimmune urticaria)
- Corticosteroids (non controlled trials in CU)
- Dapsone (starting dose 75mg/daily, can be increased upto 150mg/day; in delayed pressure urticaria)
- Sulfasalazine (starting dose 1g BD, increasing by 500mg daily at intervals of 2 weeks to maximum regular dose of 4g daily)
- Narrow band UVB

Urticaria: treatment of CHRONIC urticaria THIRD LINE TREATMENT (immunotherapies)

- **Steroids – short** tapering course
- **Cyclosporin**: 3-6mg/kg/day, usually given for 2-3 months; about 80% experience remission

Grattan ae al., BJD 2000;143:365-72; Vena et al., JAAD 2006;5:705-09;Inalozet al., J Dermatol.2008;35:276-82

- **Methotrexate**: 10-15mg per week for 3-6 months; there are no RCT's of Mtx in CU; there are several anecdotal reports describing successful outcomes in deciding the therapy

Weiner, Ann IntMed.1989;110:848; Gachet al. BJD 2001;145:340-43; Perez et al.Abs WCD 2007

Urticaria: treatment of CHRONIC urticaria THIRD LINE TREATMENT (immunotherapies)

- **Intravenous immunoglobulin:** 0,4g/kg for 5 days in autoimmune urticaria; the exact mechanism of action is unknown, presence of anti-idiotypic antibodies, in the IVIG preparation has been suggested

- **Plasmapheresis:** found to be beneficial in a small series of patients with autoimmune urticaria by eliminating the functional autoantibodies from system

Urticaria: treatment of CHRONIC urticaria THIRD LINE TREATMENT (immunotherapies)

- Mycophenolate mofetil
- Tacrolimus
- **Omalizumab:** is a recombinant humanised mAb that selectively binds to, and lowers serum IgE and as a consequence lowers the population density of IgE receptors expressed on mast cells and basophils

Urticaria: treatment of CHRONIC urticaria

❖NON-DRUGS METHODS:

- ❖ Explanation and information
- ❖ Cooling lotions eg. 1% menthol in aqueous cream
- ❖ Avoidance of aggravating factors
- ❖ Minimise stress, overheating, alcohol
- ❖ Diet: if indicated by history only
- ❖ In non-responsive to drugs low pseudoallergen diet (eg. Azo/salicylate free)

Urticaria: conclusions

- Most cases of urticaria/angioedema are not due to allergy those that are, usually being obvious
- Always consider duration of wheals as a clue
- Any investigation should be guided by history

ECZEMA

ECZEMA: dermatological definition

- An **ACUTE**, **SUBACUTE** but usually **CHRONIC** pruritic inflammation of the epidermis and the dermis, often occurring in association with a personal family history of hay fever, asthma, allergic rhinitis or atopic dermatitis.

ACUTE eczema: clinical features

- Well demarcated plaques of **erythema and** o**edema** on which are superimposed and closely spaced small vesicles filled with clear fluid with punctate erosions and crusting

- Distribution may be isolated and localized or general

SUBACUTE eczema: clinical features

- ✧Plaques of mild ERYTHEMA with small dry scales and or superficial DESQUAMATION, swelling, sometimes associated with small red, pointed or round papules

- ✧NO lichenification

- ✧Distribution may be isolated and localized or general

CHRONIC eczema: clinical features

- Plaques of **LICHENIFICATION** with deepening of the skin lines with satellite, small, firm flat or round top PAPULES, EXCORIATIONS and PIGMENTATIONS or mild erythema

- Distribution – isolated and localized or generalized

CLASSIFICATION of eczema

We can also divide eczema into:

ENDOGENOUS

Atopic or IgE

Seborrheic

Discoid or nummular

Pompholyx

Venous

Asteatotic

Juvenile plantar

Erythoderma

EXOGENOUS

Allergic

Toxic irritant contact

Photosensitive

Atopic / IgE eczema

- 60% have onset in the first year of life
- Influenced by genetics and environmental factors
- More common in males than females
- Ethnicity may be a factor – less common in Asians; more common in Westerners and higher socioeconomic families
- Rare to have adult onset
- 2/3 of patients have family history of asthma, hay fever or allergic rhinitis

Alergic contact eczema

- Delayed, cell mediated hypersensitivity
- Strong sensitizer results in reaction soon after exposure
- Weak sensitizer my take months or years to develop reaction
- Age does not influence capacity for sensitization but more common in adults
- Black skin is less susceptible
- Important cause of disability in industry
- Non seasonal

Alergic contact eczema

Characteristics:

- ✧ usually clears quite rapidly on withdrawal of offending agent
- ✧ may appear as erythematous papules, vesicles or bullous

Distinctive characteristics:

- ✧ Initial lesions usually limited to contact area
- ✧ not bilateral
- ✧ lesions with sharp borders or angles are pathognomonic

Causes of alergic contact eczema

- Metals - nickel, platinum (10% of women)
- Detergents
- Plants and fibers
- Chemicals and dyes
- Polyethylene glycol and polysorbate 60
- Topical antibiotics and medications
- Animal keratin

Alergic contact eczema: treatment

- Remove causative agent
- Systemic antihistamines
- Topical steroids oral steroid taper
- Antibiotics for secondary infection

Irritant / toxic eczema

OCCURRING IN NON ALLERGIC SKIN

Characteristics:

- Accounts for 75% of exogenous eczema
- Age, race and sex are insignificant
- Results from repeated exposure to toxic or subtoxic agents
- Severity of skin symptoms vary with the individual and the type of irritant and the length of contact
- Symptoms: itching, stinging and burning
- Usually associated with chronic disturbance of the barrier function of the skin

Irritant / toxic eczema

Common causes:

- ✧ Repeated exposure to alkaline detergents
- ✧ Repeated exposure to organic solvents
- ✧ Corrosive agents
- ✧ Industrial chemicals
- ✧ Chronic self perpetuating habits that irritate the skin

Irritant / toxic eczema: treatment

- Remove the cause
- Application of emollients
- Use of soap substitutes
- Barrier creams
- **Biopsy/testing** - usually NOT necessary

SUBACUTE irritant / toxic eczema

Lip licking

- ✧ often seen in children who have atopic eczema
- ✧ variant of irritant eczema

CHRONIC irritant / toxic eczema

- Note: papulosquamous dermatosis with hyperkeratosis, maceration, fissuring and erosions
- Eruptions tend to be sore rather than itching

Pompholyx

from Greek word meaning blister

Characteristics:

- ✧ Intense itching and burning proceed lesions
- ✧ Blisters and vesicles on hands / feet
- ✧ Becomes highly exudative
- ✧ Dries up in about 2 weeks leaving painful fissuring
- ✧ Usually no cause but can be associated with fungal infection of the feet

Pompholyx: treatment

- Avoidance of soap
- Emollients
- Potent or very potent topical steroids
- Antibiotics for infection
- Systemic steroids
- Biopsy/testing – usually NOT necessary

Nummular eczema

Characteristics:

- **usually -** personal or family history of allergy, especially asthma, hay fever and childhood eczema
- Coin-shaped papulovesicular patches that develop in to scaling and crusting lesions; lesions may be as large as 4-5cm in diameter with distinct margins, initial eruptions on arms and legs
- intense itching
- tends to be chronic

Nummular eczema

- Most severe during winter
- may be aggravated by systematic administration of iodine or bromine
- secondary bacterial infections are common

TREATMENT:

- skin hydration, topical corticosteroids, intralesional injection, UVB treatment, treat secondary infection

Asteatotic Eczema (xerotic eczema, “winter itch”)

Characteristics:

- ✧ Seen mainly in elderly
- ✧ Worse in the winter
- ✧ Precipitated by excessive washing

Treatment:

- ✧ Avoid excessive washing and use of soap
- ✧ Emollients
- ✧ increase humidity in the environment
- ✧ Topical steroids for a short periods of time

Eczema: diagnostics

1. Medical history (anamnesis)
2. Physical examination
3. Biopsy + histopathological examination
4. Patch tests

Patch tests

- At the first appointment: tiny quantities of 25 to 150 materials in individual square plastic or round aluminium chambers are applied to the upper back
- They are kept in place with special hypoallergenic adhesive tape
- The patches stay in place undisturbed for 48 hours

Patch tests

- At the second appointment, usually two days later, the patches will be removed
- The back is marked with an indelible black felt tip pen or other suitable marker to identify the test sites
- These marks must still be visible at the third appointment, usually two days later (4 days after application)

Eczema: treatment

1. Education (chronicity, prevention and trigger)
2. Use of astringents and emollients/moisturizers
3. **Low to mid potency steroid creams**
4. **High potency steroid creams**
5. **Immunomodulators – tacrolims oinment, pimecrolimus** cream
6. **P.o. therapy: anti-histamines,** antiprurutics, steroids, cyclosporine, methotrexate
7. **PUVA therapy** (phototherapy)