Methodic elaboration for practical lesson in

Dermatovenerology

for students of Medicine Faculty nr.2

Topic N7

Allergic dermatitis. Erythema multiforme

The word “eczema” comes from Greek for “boiling” a reference to the tiny vesicles (bubbles) that are often seen in the early acute stages of the disorder, but less often in its later chronic stages.

Dermatitis means inflammation of the skin and eczema is one of several possible types of skin inflammation. Those, dermatitis and eczema means the same things.

Classification:

I. Exogenous eczema:
- Irritant contact dermatitis (eczema)
- Allergic contact dermatitis (eczema)
- Systemic allergic dermatitis (eczema)

II. Endogenous eczema:
- Atopic dermatitis (eczema)

III. Mixt eczema:
- Nummular dermatitis
- Dyshidrotic eczema (pompholyx)
- Infective eczema
- Seborrheic eczema

Clinical appearance

I. Acute eczema is recognized by:
- weeping and crusting;
- blistering – usually with vesicles, sometimes with large blisters;
- redness, papules, and swelling – usually with ill-defined border;
- scaling

II. Subacute eczema manifested by:
- itching;
- crusting;
- scaling

III. Chronic eczema may show all of the above changes but in general is:
- less vesicular and exudative;
- more scaly, pigmented and thickened;
- more likely to show lichenification – a dry leathery thickened state, with increased skin margins, secondary to repeated scratching or rubbing;
- more likely to fissure.

Complications

Heavy bacterial colonization is common in all types of eczema.

All severe forms of eczema have a huge effect on the quality of life.

Eczema can interfere with works, sporting activities etc.

Investigations

Each pattern of eczema needs a different line of inquiry.

Exogenous eczema:

- in vivo tests – patch test

Endogenous eczema:

- in vivo test – prick test
- in vitro – RAST test

Treatment:

I. Topical treatment

Acute weeping eczema:

- rest and liquid applications;
- 10-min soaks in a cool 0.65% aluminum acetate solution twice daily, followed by a smear of a corticosteroid cream or lotion and the application of a non-stick dressing or cotton gloves;
- calamine lotion;
- wet wrap dressings.

Subacute eczema:

- steroid lotions or creams are the mainstay of treatment

Chronic eczema:

- this responds best to steroids in an ointment base;
- the strength of the steroid is important:
  - nothing stronger than 0.5% or 1% hydrocortisone ointment should be used on the face or in infancy;
  - in adults mildly potent steroid should be prescribed not more than 200g/week;
  - moderately potent steroid up to 50g/week
  - potent one not more than 30g/week for long periods
  - very potent topical steroids shouldn't be used for long terms

II. Systemic therapy:

1. *Corticosteroids:*
   - short courses of systemic steroids may be justified in extremely acute and severe eczema, particularly when the cause is known and already eliminated;
   - prolonged systemic steroid treatment should be avoided in chronic cases, particularly in atopic eczema.
2. *Antihistamines:*
   - H1-antihistamines are useful in treatment of conditions with histamine-driven pruritus;

- evidence supports the use of H1-antihistamines in treatment of atopic dermatitis;
- use of H1-antihistamines is contraindicated in patients who have narrow-angle glaucoma or who are also taken monoamine oxidase inhibitors.

3. Antibiotics:

- may be needed in widespread bacterial infection.

Irritant contact dermatitis

This accounts for more than 80% of all cases of contact dermatitis.

Etiology and pathogenesis

The main pathological features of irritant contact dermatitis are:

- no inflammatory reaction takes place;
- the intensity of the reaction is proportional to the dose of chemicals applied;
- is directly related to chemical concentration, duration of exposure, and general skin integrity.

Strong irritants elicit an acute reaction after brief contact and the diagnosis is usually obvious.

Prolonged exposure, sometimes over years, is needed for weak irritants to cause dermatitis, usually for the hands and forearms.

There is a wide range of susceptibility: those with very dry or fair skin are especially vulnerable.

Clinical manifestations

At the sight of contact with an irritant substance initially occurs:

- erythema
- vesicle or bulla
- erosion with oozing
- crust
- scale

All too often therefore irritant eczema, probably reversible in early stages, becomes chronic.

Differential diagnosis

It's often hard to differentiate irritant from allergic contact dermatitis as well as atopic eczema of the hands – atopic patients are especially prone to development irritant contact eczema.

Treatment:

- avoidance of the irritants responsible for the condition
- if avoidance isn't possible than reduction of exposure by the use of protective gloves and clothing

- washing facilities at work should be good – dirty hands shouldn't be cleaned with harsh solvents
- use of barrier creams, emollients
- administration of moderately potent topical steroids
- prevention is better than cure.

Allergic contact dermatitis

As the primary interface with the environment, the skin is placed in the precarious position of routine exposure and assault from exogenous chemicals and physical agents. Most of these exposure result in no clinically apparent disease.

However, in some circumstances, a panoply of immunologic events results in sensitization and subsequent elicitation of allergic contact dermatitis ACD.

The classic interpretation of the skin as a simple barrier to penetration by exogenous agents underestimates the immunologic capacity of the integument.

Nowadays is known that the complex of T-cell mediated events is specifically and sensitively targeted to one or more chemical entities.

Etiology and pathogenesis

ACD represents a delayed type IV hypersensitivity reaction to the over 3700 exogenous chemicals that have been described to provoke this reaction. Because this represents a true allergy with immunologic sequelae, only small quantities of a given chemicals are necessary to elicit overt allergic reactions.

To mount an immune reaction to an allergen the individual:

- must be genetically susceptible;
- have sufficient contact with a sensitizing chemical;
- than have repeated contact with the substance later.

Thus ACD is a systemic disease defined by hapten-specific T-cell-mediated skin inflammation and characterized three phases:

- sensitization
- elicitation
- resolution.

In the sensitization phase, low-molecular-weight hydrophilic hapten chemicals penetrate the skin and form hapten-protein complexes with epidermal carrier proteins, which produce a complete allergen. That allergen is loaded into MHC I and MHC II class molecules, which are present on the surface of Langerhans cells (LC). After that LC migrate into a regional

lymph node and present the allergen to naïve T cells. If hapten modifies extracellular proteins, these will be taken up by cutaneous APC's (antigen presenting cells) and loaded into MHC II molecules. Those will present the allergen to a CD4+ T cells in regional lymph node, which will leed to a clonal expansion of T cells. The primed T-cells begin to express skin-homing receptors (CLA) as well as receptors for various chemoattractants that promote then attachment to dermal microvascular endothelial cells and ultimately their entry into the tissue.

Homing CD4+ T cells arrived into the skin produce, cytokines (IFN-γ, IL-2), recruit macrophages which produce TNF-α. All this cascade of mediators will cause the inflammation, local edema and erythema in elicitation phase.

If hapten has a lipophilic structure than it easily crosses the cell membrane, modifying cytoplasmatic proteins. Such proteins are loaded into MHC I molecules, and is presented to a CD8+ T-cell by a keratinocyte. Effector CD8+ T-cells target hapten-related keratinocytes and provoke their cytolysis in elicitation phase.

Clinical approach

1. *History taking* starts with obtaining a comprehensive multi-year history from the patient regarding the present illness. Information regarding:
    - the patient's demographic characteristics (age, gender, race, ethnicity, religion, social aspects, job title, job description, regular and occasional chemical exposures and sources, location of employment, time at current job, previous occupations);
    - family medical history (genetic factors, predisposition);
    - personal medical history (drug allergies, concomitant diseases, surgeries);
    - dermatitis specific history (onset, location, temporal associations: waxing, treatment)
2. *Clinical symptoms:*
    - ACD may clinically present acutely after allergen exposure and initial sensitization or after elicitation in a previously sensitized individual;
    - the acute phase is characterized by the development of erythematous, indurated scaly plaques with severe cases demonstrating vesiculation and bullae in exposed areas;
    - repeated or continuous exposure of sensitized individual to allergens results in chronic disease, which is usually marked by

lichenified erythematous plaques with variable hyperkeratosis, scale and fissuring;

- hand, feet, eyelids and lips, which commonly come in contact with environment, are likely sites for ACD.

Laboratory findings

In vivo patch test:

- the gold standard method for the diagnosis of ACD remains the patch test;
- the T.R.U.E (Thin-layer Rapid Use Epicutaneous) test has 2 panel trays
- those, investigators who intend to fully evaluate their patients must prepare allergen tray with worldwide standardized commercially available allergens and add patients – specific test material for completeness;
- the identification of true-positive reactions with clinical relevance is the primary goal of the patch test and is based achieved with a high pre-test probability;
- assigning clinical relevance to a true – positive patch test result requires correlation between the involved areas of skin and the patient's environmental exposures and notation of significant improvement on avoidance of allergen or recurrence with its reintroduction;
- true-negative results are an equally important component of the patch test, because their provide some assurance that a chemical in question is not causing the dermatitis;
- patch testing remains the only reliable bioassay to ascertain sensitization to exogenous chemicals.

In vitro tests for allergic contact dermatitis:

- **lymphocyte transformation test** (measures the proliferation of T cells to an allergen in vitro – from which one concludes a previous *in vivo* reaction due to a sensitization);
- **macrophage migration inhibition test** (an *in vitro* method of testing for cellular immune response in which macrophages are placed in a capillary tube containing a specific antigen-allergen)

Differential diagnosis

Differential Diagnosis of the Eczematous Dermatoses

DIFFERENTIAL DIAGNOSIS	GEOGRAPHIC-MORPHOLOGIC DISTRIBUTION	DIAGNOSTIC CLUES
Allergic contact dermatitis	Eczematous, scaly edematous plaques with vesiculation	Primary lesions in distribution of contactant; pruritus
Asteotic dermatitis	Crackled parchment-like patches, absent edema and vesiculation	Lower legs
Atopic dermatitis	Eczematous, honey-crusted, scaled plaques; chronic lesions may be lichenified	Flexural areas in children and neck predominance
Autosensitization reaction	Eczematous, poorly defined patches of vesiculation	History of chronic dermatitis or infection with new widespread, less-defined patches
Dyshidrotic eczema	Deep-seated papulovesicles on palmar-plantar surfaces and volar edges	Palm and sole typically dorsal involvement
Irritant contact dermatitis	Sharply demarcated macular erythema, hyperkeratosis, absence of vesiculation	Burning exceeds itching
Mycosis fungoides (patch to plaque stage)	Poorly demarcated, atrophic, scaly pink patches and plaques	Torso predominance
Nummular dermatitis	Coin-shaped, well demarcated plaques with scale and vesiculation; variably exudative	Legs, dorsal hands, extensor surfaces
Psoriasis	Sharply demarcated papulosquamous plaques with no vesiculation	Scalp, retro-auricular area, elbows, knees, genitalia, nails; predominance in areas of trauma (Koebnerization); pustules may be acutely present, particularly on palms and soles; concomitant arthritis
Seborrheic dermatitis	Papulosquamous greasy, scaly plaques	Hair-bearing regions, glabella, and nasolabial folds
Stasis dermatitis	Papulosquamous plaques with dyschromia	Shins and medial surfaces, lower legs, concomitant varicosities

From Rietschel RL: Clues to an accurate diagnosis of contact dermatitis. *Dermatol Ther* **17**:224, 2004.

Systemic manifestations and generalized dermatitis

Systemic contact dermatitis is relatively uncommon and poorly understood aspect of ACD that highlights the potential for long-lasting immunologic memory in previously sensitized areas of skin.

This phenomenon occurs primarily in individuals who are initially sensitized topically to an allergen and then subsequently exposed systemically, which results in a wide array of outcomes, from a recall reaction (dermatitis at

the site of original sensitization) to extensive, bizarre-appearing dermatitis and erythroderma.

Treatment

The fundamental management of patients with ACD relies on both treatment of symptoms and avoidance of additional encounters with allergic contacts.

Atopic dermatitis (atopic eczema)

Atopy is a state in which an exuberant production of IgE occurs as a response to common environmental allergens.

Atopic subjects may, or may not, develop one or more of the atopic disease such as asthma, hay fever, eczema and food allergies, and the prevalence of atopy is steadily rising.

Inheritance

A strong genetic component is obvious, although affected children can be born to clinically normal parents. The concordance rates of atopic eczema in monozygotic and dizygotic twins are 86% and 21%, respectively. Probably the inheritance of atopic eczema requires genes that predispose to the state of atopy itself, and others that determine whether its asthma, eczema or hay fever that occurs. Candidate genes are 11q13, 3q21, 14q, 16p and 17p. Environmental factors too are important.

Presentation and course

75% of cases of atopic eczema begin before the age of 6 months, and 80-90% before the age of 5 years. Some 60-70% of children with atopic eczema will clear by their early teens, although subsequent relapses are possible. General dryness of the skin may persist throughout life.

The distribution and character of the lesions vary with age:

- **in infancy** atopic eczema tends to be vesicular and weeping; it often starts on the face with a non-specific distribution, elsewhere, commonly sparing the napkin area;
- **in childhood**, the eczema becomes leathery, dry and excoriated, affecting mainly the elbow and knee flexures, wrists and ankles;
- **in adults,** the distribution is as in childhood with a marked tendency towards lichenification and amore widespread but low-grade involvement of the trunk, face and hands.

The cardinal feature of atopic eczema is itching and scratching. Affected children may sleep poorly, be hyperactive. The condition remits spontaneously before the age of 10 years in at least 2/3 of affected children, although it may come back at time of stress.

Diagnostic criteria (Hanifin and Rajka)

Major criteria

1. Pruritus
2. Typical morphology and distribution:
   -flexural lichenification or linearity in adults;
   - facial and extensor involvement in infants and children.
3. Chronic or chronically – relapsing dermatitis
4. Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis).

Minor criteria:

1. Xerosis;
2. Ichtyosis, palmar hiperlinearity or keratosis pilaris;
3. Immediate (type I) – skin test reactivity;
4. Raised serum IgE;
5. Early age of onset;
6. Tendency towards cutaneous infection (especially S.aureus and herpes simplex);
7. Tendency toward non-specific hand or foot dermatitis;
8. Nipple eczema;
9. Cheilitis;
10. Recurrent conjunctivitis;
11. Dennie-Morgan infraorbital fold;
12. Keratoconus;
13. Anterior subcapsular cataracts;
14. Orbital darkening;
15. Facial pallor or facial erythema;
16. Pityriasis alba;
17. Anterior neck folds;
18. Itch when sweating;
19. Intolerance to wool and lipid solvents;
20. Perifollicular accentuation;
21. Food intolerance;
22. Course influenced by environmental or emotional factors;
23. White dermographism or delayed blanch.

Complications:

- Bacterial infections;
- Viral infections:
  - most dangerously with widespread herpes simplex (eczema herpeticum);
  - molluscum contagiosum;
  - warts.

Treatment

Management of atopic dermatitis is complex and should include the following: explanation, reassurance and encouragement; the avoidance of exacerbating factors such as irritants, extremes of temperature and contact with soaps and detergents; the judicious use of topical steroids and other applications as for other types of chronic eczema.

Tacrolimus is a macrolides immunosuppressant produced by a streptomycete. Trials of Tacrolimus in ointment form have shown that it can be a quick and highly successful topical treatment for moderate to sever atopic eczema.

The regular use of bland emollients; sedative antihistamines: trimeprezone or hydroxizine.

Acute flares are often induced by staphylococcal infection, so a course of systemic antibiotics like erythromycin may be useful.

Those with active herpes simplex infection should be avoided to cut the risk of developing eczema herpeticum.

In stubborn cases UVB, UVA-1 (340-400nm) or even PUVA therapy may be useful.

Cyclosporine: severe and unresponsive cases may be helped by short courses under specialist supervision.

Erythema multiforme

Erythema multiforme is an acute, self-limited, usually mild, and often relapsing mucocutaneous syndrome. The disease is usually related to an acute infection most often a recurrent herpes simplex virus (HSV) infection. EM is defined only by its clinical characteristics: target-shaped plaques predominant on the face and extremities.

Epidemiology

Erythema multiforme occurs in patients of all ages, but mostly in adolescents and young adults.

There is a slight male predominance (male-female ratio – 3:2). Erythema multiforme is recurrent in at least 30 percent of patients. There is no indication that the incidence may vary with ethnicity or geographic location.

Etiology

Most cases of erythema multiforme are related to infections. Herpes virus is definitely the most common cause, principally in recurrent cases. Proof of causality of herpes is firmly established from: clinical experience, epidemiology, detection of HSV DNA in the lesions of erythema multiforme, prevention of erythema multiforme by suppression of HSV recurrences.

M.pneumoniae is the second major cause of erythema multiforme and may even be the major cause in pediatric cases. In cases related to *M.pneumoniae* the clinical presentation is often less typical and more severe than in cases associated with HSV. The relationship to M.pneumoniae is often difficult to establish: clinical and radiological signs of atypical pneumonia can be mild; PCR testing of throat swats is the most sensitive technique. M.pneumoniae related erythema multiforme can recur.

Pathogenesis

Complete infective HSV has never been isolated from lesions of herpes-associated erythema multiforme. The studies demonstrate that keratinocytes didn't contain complete viral DNA but only fragments, always including the viral polymerase (Pol) gene. HSV Pol DNA is located in basal keratinocytes and in lower spinous cell layers. The viral Pol protein is synthesized in epidermal cells. HSV-specific T cells, including cytotoxic cells, are recruited, and the virus-specific response is followed by a non-specific inflammatory amplification by autoreactive T cells. These cells and the cytokines they produce induce the delayed hypersensitivity- like appearance of the pathology of erythema multiforme lesions. It has been shown that HSV DNA is transported to the epidermis by cells that engulf the virus and fragment the DNA. These cells are Monocytes, macrophages and especially CD34+ Langherhans cells. When reaching the epidermis the cells transmit the viral Pol gene to keratinocytes. The genes may persist for a few months, but the synthesis and expansion of the Pol protein will last only a few days. These may explain the transient character of clinical lesions. Incomplete fragmentation of viral DNA, increased number of circulating CD34+ cells and /or increased immune response to Pol protein may explain why only a small proportion of people with recurrent herpes develop erythema multiforme.

Clinical findings

History

Prodromal symptoms are absent in most of the cases. If present, they are usually mild, suggesting an upper respiratory tract infection (cough, rhinitis, low-grade fever). The events of the preceding 3 weeks should be reviewed for clinical evidence of any precipitating agent, with a special focus on recurrent herpes.

Cutaneous manifestations

The skin rash arises abruptly. In most patients all lesions appear within 3 days, but in some, several crops follow each other during one episode of erythema multiforme. Most of the lesions occur in a symmetric, acral distribution on the extensor surfaces of the extremities (hands and feet, elbows and knees), face and neck, and appear less frequently on thighs,

buttocks and trunk. Lesions first appear acrally and then spread in a centripetal manner. Mechanical factor (Kobner phenomenon) and actinic factors (predilection of sun-exposed sites) appear to influence the distribution of the lesions.

The typical lesion is a highly regular, circular, wheal-like erythematous papule or plaque that persists for 1 week or longer. It measures from a few millimeters to approximately 3cm and may expand slightly over to 24 or 48 hours. Although the periphery remains erythematous and edematous, the center becomes violaceous and dark; inflammatory activity may regress or relapse in the center, which gives rise to concentric rings of color. Often, center turns purpuric and/or necrotic or transforms into a tense vesicles or bulla. The result is classic target or iris lesion. According to the proposed classification, typical target lesion consists of at least three concentric components: 1) a dusky central disk or blister; 2) more peripherally, an infiltrated pale ring; 3) an erythematous halo.

In most cases, erythema multiforme affects under 1 percent of the body surface area.

Mucous membrane lesions

Mucosal lesions are present in up to 70 percent of patients, most often limited to the oral cavity. Predilection sites for mucosal lesions are lips, non-attached gingivae, ventral side of the tongue. On the mucosa proper there are erosions with fibrinous deposits and occasionally intact vesicles and bullae can be seen. The process may rarely extend to the throat, larynx and even the trachea and bronchi. Eye involvement begins with pain and bilateral conjunctivitis in which vesicles and erosions can occur. The nasal, urethral and anal mucosa can also be involved.

Laboratory findings

Histopathologic analysis:

- lymphocyte accumulation at the epidermal-dermal interface, with exocytosis into the epidermis;
- lymphocytes attached to the scattered necrotic keratinocytes:
- spongiosis;
- vacuolar degeneration of the basal cell layer;
- focal junctional and sub-epidermal cleft formation.
- the papillary dermis may be edematous but principally contains the monocyte infiltrate.

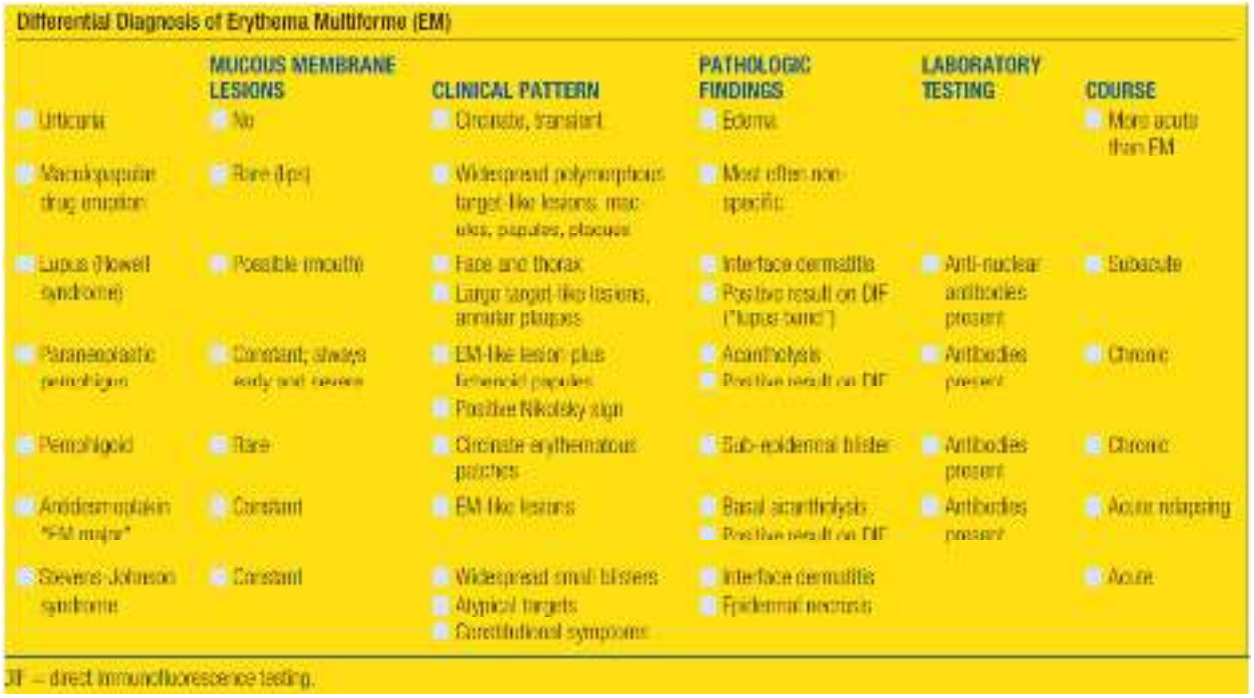
There are no specific laboratory tests for erythema multiforme.

Most investigations are directed towards identifying the cause.

Course

Erythema multiforme runs a mild course in most of cases, and each individual attack subsides within 1 to 4 weeks.

Differential diagnosis



Differential Diagnosis of Erythema Multiforme (EM)

	MUCOUS MEMBRANE LESIONS	CLINICAL PATTERN	PATHOLOGIC FINDINGS	LABORATORY TESTING	COURSE
Urticaria	No	Circinate, transient	Edema		More acute than EM
Maculopapular drug eruption	Rare (5%)	Widespread polymorphous target-like lesions: macules, papules, plaques	Most often non-specific		
Lupus (Rowell syndrome)	Possible mouths	Face and thorax Large target-like lesions, annular plaques	Interface dermatitis Positive result on DIF ("lupus band")	Anti-nuclear antibodies present	Subacute
Paraneoplastic pemphigus	Constant; always early and severe	EM-like lesion plus [illegible] papules Positive Nikolsky sign	Acantholysis [illegible] on DIF	Antibodies present	Chronic
Pemphigoid	Rare	Circinate erythematous patches	Sub-epidermal blister	Antibodies present	Chronic
Antidesmoglein "EM major"	Constant	EM-like lesions	Basal acantholysis [illegible] on DIF	Antibodies present	Acute relapsing
Stevens-Johnson syndrome	Constant	Widespread small blisters Atypical targets Constitutional symptoms	Interface dermatitis Epidermal necrosis		Acute

DIF – direct immunofluorescence testing.

Treatment

The aims of treatment are to reduce the duration of fever, eruption and hospitalization.

The best treatment for erythema multiforme is to identify and remove its cause. In mild case, only symptomatic treatment is needed and this includes the use of antihistamines.

The use of systemic corticosteroids seems to shorten the duration of fever and eruption but may increase the length of hospitalization because of complications.

Symptomatic *M.pneumoniae* infection should be treated with antibiotics (macrolides in children, macrolides or quinolones in adults).

Liquid antacids, topical steroids, and local anesthetics relive symptoms of painful mouth erosions.

The Stevens-Johnson syndrome is a severe variant of erythema multiforme associated with fever and mucous membrane lesions. The oral mucosa, lips and bulbar conjunctivae are most commonly affected, but the nares, penis, vagina, pharynx, larynx and trachea-bronchial tree may also been involved. Sever lesions may lead to asphyxia or blindness. Cornel ulcers, anterior uveitis and panophtalmitis can also occur. Genital ulcers can cause urinary retention, phimosis or vaginal stricture after they heal.

The Stevens-Johnson syndrome may demand immediate consultation between dermatologist and specialists in other fields such as ophthalmology, urology and infectious diseases, depending on the particular case. This is

because the affected mucosa can scar and affected skin can slough. The use of systemic steroids is debatable but many believe that a short course of prednisolone 80mg/day in divided doses in an adult helps. However doses should be stopped rapidly because prolonged treatment has been linked with a high complication rate. The prevention of secondary infection, maintenance of patient airway, good nutrition and proper fluid and electrolyte balance are important.

Epidermal necrolysis (toxic epidermal necrolysis)

Toxic epidermal necrolysis (TEN) is acute life-threatening mucocutaneous reaction characterized by extensive necrosis and detachment of the epidermis.

Epidemiology

Epidermal necrolysis is rare. The overall incidence is estimated at 0.4 to 1.2 cases per million person-years. Patients infected with human deficiency virus and to a lesser degree patients with collagen vascular diseases and cancer are at increased risk. The overall mortality associated with TEN is more than 30 percent. Increasing age, significant co-morbidities, and greater extent of skin involvement correlate with poor prognosis.

A prognosis score (SCORTEN) has been constructed for TEN and its usefulness has been confirmed by several teams.

Etiology

The pathophysiology of TEN is still unclear; however, is now established that drugs are most important etiologic factors. More than 100 different drugs have been reported as possible causes. The importance of one medication can be established in approximately 70 percent of cases.

Medications and the Risk of Epidermal Necrolysis

High Risk	Lower Risk	Doubtful Risk	No Evidence of Risk
Allopurinol	Acetic acid NSAIDs (e.g., diclofenac)	Paracetamol (acetaminophen)	Aspirin
Sulfamethoxazole	Aminopenicillins	Pyrazolone analgesics	Sulfonylurea
Sulfadiazine	Cephalosporins	Corticosteroids	Thiazide diuretics
Sulfapyridine	Quinolones	Other NSAIDs (except aspirin)	Furosemide
Sulfadoxine	Cyclins	Sertraline	Aldactone
Sulfasalazine	Macrolides		Calcium channel blockers
Carbamazepine			β Blockers
Lamotrigine			Angiotensin-converting enzyme inhibitors
Phenobarbital			Angiotensin II receptor antagonists
Phenytoin			Statins
Phenylbutazone			Hormones
Nevirapine			Vitamins
Oxicam NSAIDs			
Thiacetazone			

NSAIDs = nonsteroidal anti-inflammatory drugs.

Pathogenesis

The immunologic pattern of early lesions suggests a cell-mediated cytotoxic reaction against keratinocytes leading to massive apoptosis. Immunopathologic studies have demonstrated the presence of CD8+ T killer

lymphocytes in the epidermis and dermis in bullous adverse reactions during the initial phase of TEN, whereas monocytes are present more during the late phase. These CD8+ T cell are able to kill through perforin and granzyme B but not trough Fas or Trail.

Clinical findings

History

TEN clinically begins within 8 weeks (usually 4 to 30 days) after the onset of drug exposure. Only in very rare cases with prior reaction it appears more rapidly, within a few hours. Non-specific symptoms such as fever, headache, rhinitis and myalgias may precede the mucocutaneous lesions by 1 to 3 days. Whatever the initial symptoms are, their rapid progression, the addition of new signs, sever pain, and constitutional symptoms should alert one to the onset of a severe disease.

Cutaneous lesions

The eruption is initially symmetrically distributed on the face, the upper trunk, and the proximal extremities. The rash can rapidly extend to the rest of the body within a few days or even within a few hours.

The initially skin are characterized by erythematous, dusky red, purpuric macules, irregularly shaped, which progressively coalesce. Confluence of necrotic lesions leads to extensive and diffuse erythema. Nicolsky sign or dislodgment of the epidermis by the lateral pressure is positive in the erythematous zones.

Patients are classified into one of three groups according to the total area in which the epidermis is detached:

- Stevens-Johnson syndrome (SJS) less than 10 percent of body surface area (BSA);
- SJS/TEN overlap between 10 to 30 percent of BSA;
- TEN more than 30 percent of BSA.

It is helpful to remember that surface of one hand represents a little less than 1 percent of a BSA.

Mucous membrane involvement

Mucous membrane involvement (on at least two sites) is observed in approximately 90 percent of cases and can precede or follow the skin eruption. It begins with erythema followed by painful erosions of the buccal, ocular and genital mucosa. The oral cavity and lips are almost invariably affected and future painful hemorrhagic erosions coated by grayish coated pseudomembranes and crusts of the lips. Conjunctival lesions are mainly manifested by hyperemia, erosions, chemosis, photophobia and lacrimation. The may be shedding of eyelashes.

Extra-cutaneous symptoms

TEN is associated by high fever, pain and weakness. Visceral involvement is also possible, particularly with pulmonary and digestive complications.

Histopathology

Skin biopsy for routine histologic and immunofluorescence studies must be performed in any case of TEN, even if the diagnosis is clinically obvious, because of the high probability of the future legal actions and because it is the only way to exclude most differential diagnosis.

Complications

During the acute phase, the most common complication of TEN is sepsis.

Multisystem organ failure and pulmonary complications are observed in more than 30 percent of cases. Late ophthalmic complications are seen in 20 to 75 percent of patients with TEN.

Treatment

Symptomatic treatment

Patients should be transferred to intensive care units or burn centers.

Supportive care consists of maintaining hemodynamic equilibrium and preventing life-threatening complications. The aims are basically the same as for extensive burns.

Specific treatment

- Corticosteroids
- Intravenous immunoglobulin
- Cyclosporin A
- Plasmapheresis or hemodialysis
- Anti-tumor necrosis factor agents.