Viral disorders of skin. Differential diagnosis with the viral exanthema of child age. Bullous disorders.

* If you have some questions about lecture you may call to your lecturer

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*Plan of the lecture

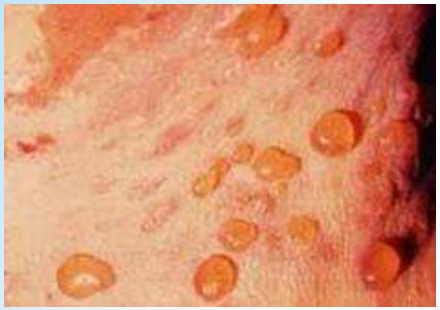
*1.Etiology, pathogenesis and transmission of viral and bullous disorders.

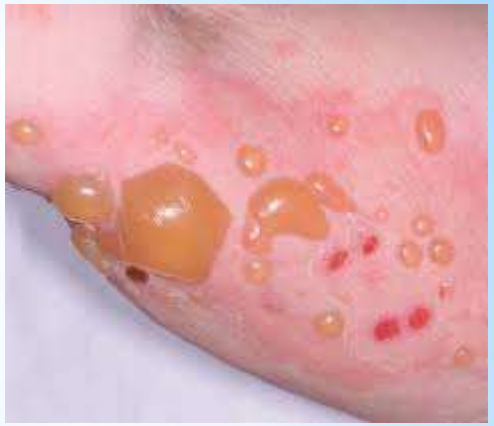
*2. Classification and features of clinical manifestations of viral and bullous disorders.

*3. Diagnostic of viral and bullous disorders.

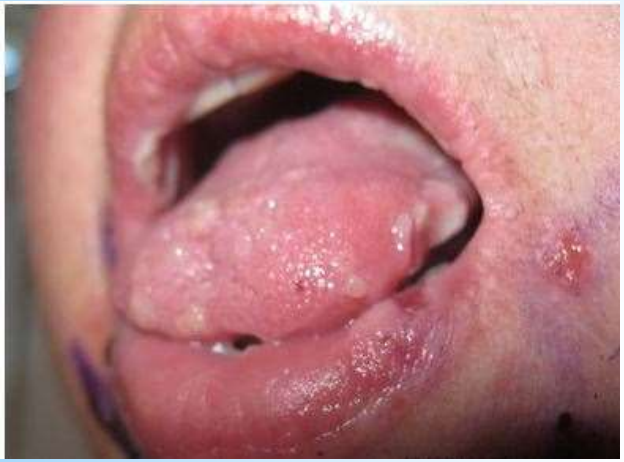
*4. Principles of general and local treatment of viral and bullous disorders.

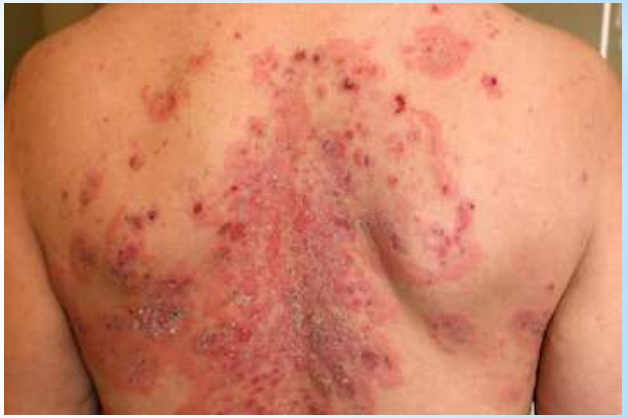
*5. Methods of primary and secondary prevention of viral and bullous disorders.





Bullous disorders





*Bullous dermarosis Classification:

*1. Pemphigus Vera(acantholytic):

- Pemphigus vulgaris
- Pemphigus vegetans
- Pemphigus foliaceus
- Pemphigus seborheal

*2. Nonacantholytic pemphigus of oral mucosa

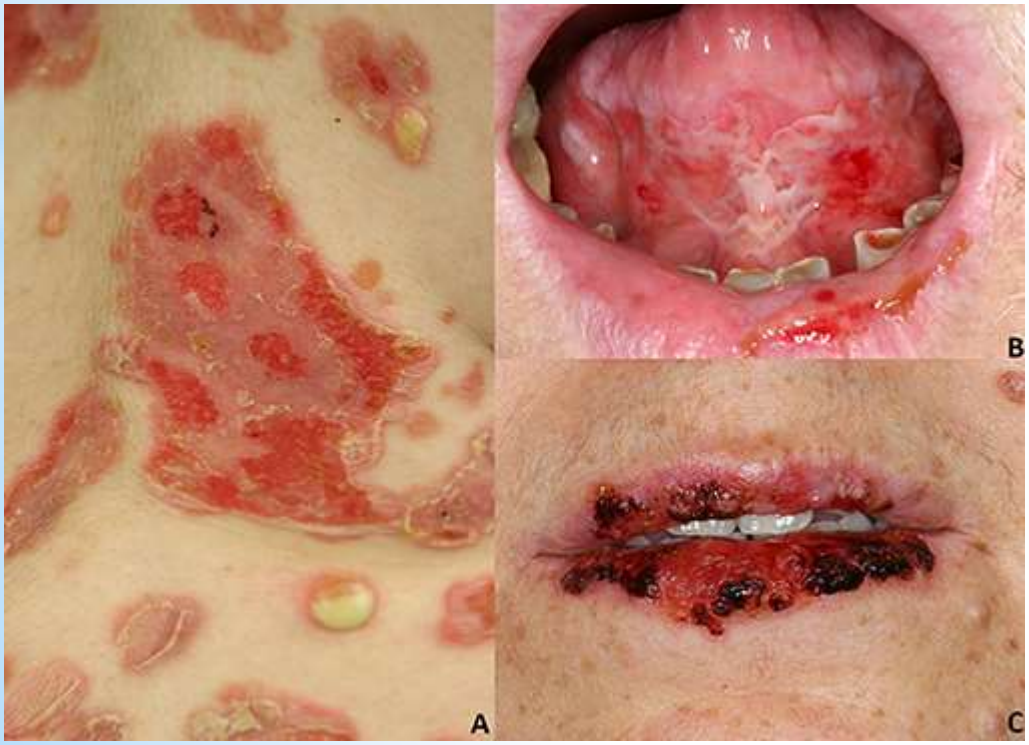
* 3. Pemphogoids:
- Bullous pemphogoid
- Cicatricial pemphogoid
- Pemphogoid gestationis

* 4. Dermatitis herpetiformis
- Duhring disease
- Sneddon-Wilkinson

* 5. Genetic bullous dermatosis
- Hialey-Hialey disease
- Group of bullous epidermolysis

Pemphigus Vera is autoimmune disease which declares itself as elaboration on uninflamed skin and mucous coats of bulla being developmental as a result of acantholysis and generalized for whole skin integument without appropriate treatment

Pemphigus can occur at any age, but it's most often seen in people who are middle-aged or older. It tends to be a long-lasting (chronic) condition, and some types can be life-threatening without treatment. Treatment with medication usually controls it.



*Pathogenesis

* The pathogenesis underlying all forms of pemphigus involves the development of autoantibodies to the desmosomal proteins, which can be found in many areas of the body, but which play a major role in the epidermal layers of the integumentary system.
* Pemphigus vulgaris (PV), pemphigus foliaceus (PF) are caused primarily by antibodies to desmoglein 1 (Dsg 1) in PF, desmoglein 3 (Dsg 3) in mucosal dominant PV, or both in mucocutaneous PV. Dsg 1 and 3 are found in varying amounts in the epidermis of the skin and mucosa.

Pathogenesis

* Dsg 1 is found in higher amounts in the upper layers of the epidermis, especially on the skin, while Dsg 3 is found in the lower layers of the epidermis with higher concentrations in the mucosa and skin.2,6 It is this variability in distribution which explains the 3 distinct clinical diseases.
* The disease usually occurs in patients with certain HLA genotypes who generate B-cells responsible for the specific autoantibodies. The activation of these B-cells requires a complex interaction with CD4+ T helper 2 (Th2) cells and it is this Th2 cell over-activation that leads to the autoantibody production that is necessary for PV and PF

*Pathogenesis

* Th2 cells are known for secreting multiple interleukins (IL), of which IL-4 plays a major role in pemphigus and the humoral immune response.2 IL-4 promotes antibody production by primed B cells and an isotype switching from IgG1 to IgG4 antibodies which have been shown to be important in the active form of PF and PV.
* Interaction of autoimmune antibodies with DSG1 and DSG3 leads to acantholysis (breaking of between keratinocytes) resulting in formation of clefts filled up with subcutaneous water inside the epidermis end mucous coats and appearance of bulls.

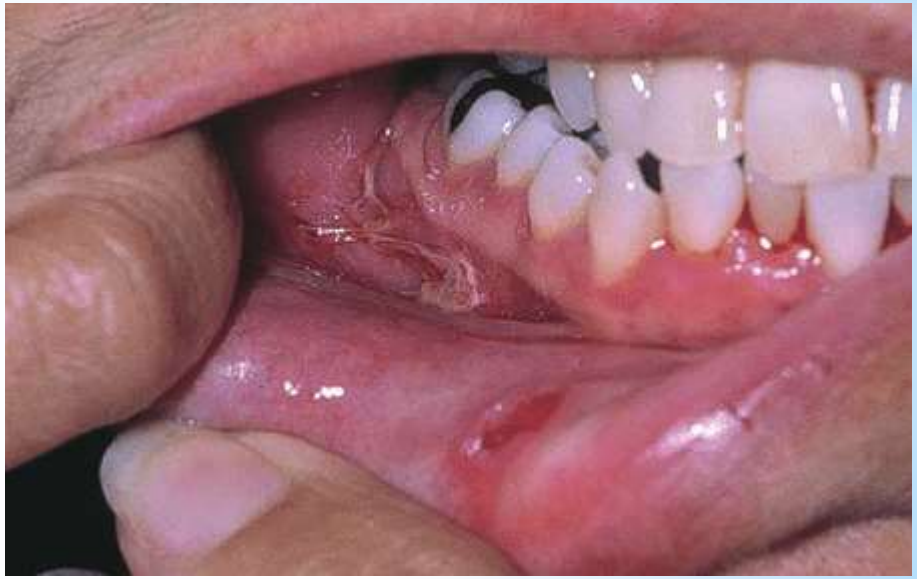
Clinical findings

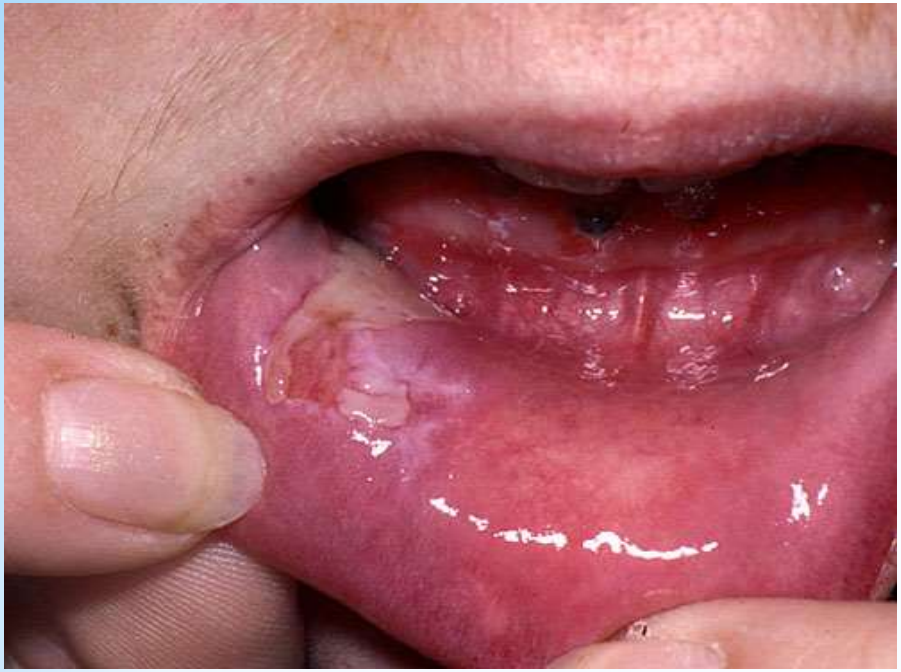
Pemphigus vulgaris occurs often in compares with other type. The blisters usually develop in the mouth first, before affecting the skin a few weeks or months later.

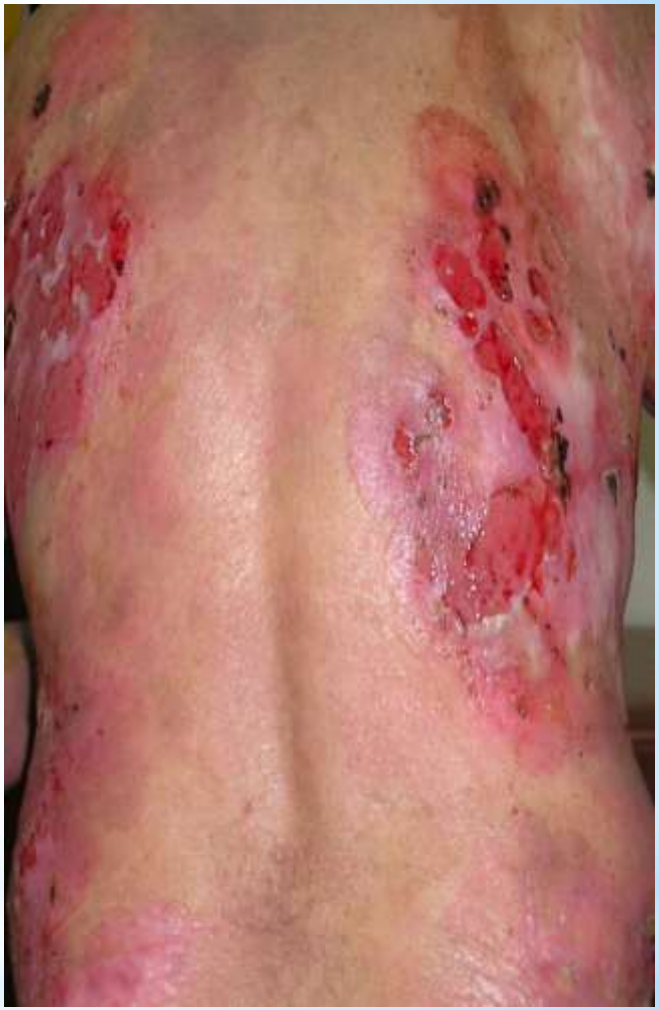
- The blisters typically are painful but don't itch. Blisters in the mouth often turn into painful sores, which can make eating, drinking and brushing teeth very difficult. The voice can become hoarse if the blisters spread to the voice box (larynx).
- Sores on the skin can join together to form large areas of painful, raw-looking skin, before crusting over and forming scabs. They don't usually leave any scars, although affected skin can occasionally become permanently discoloured.

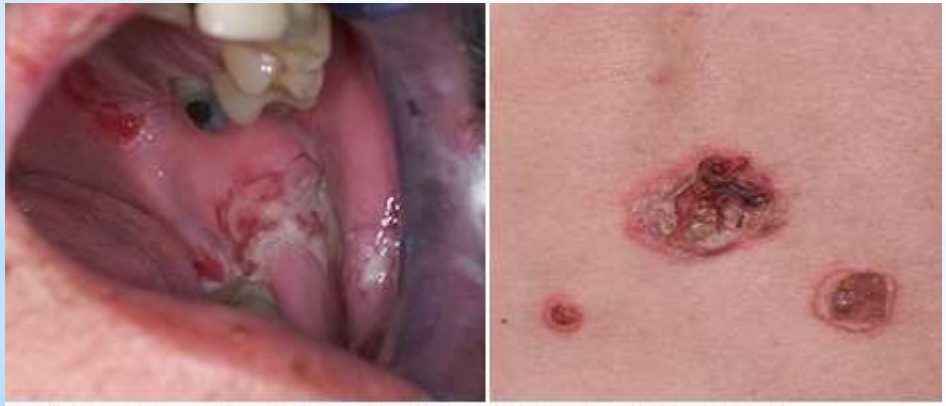
- As well as getting blisters in the mouth, they can also develop in other areas of the digestive system's soft tissue lining, including the nose, throat, anus, genitals and vagina. The thin membrane that covers the front of the eye and inside of the eyelids (conjunctiva) can also be affected.

- There may be times when the blisters are severe (flare-ups), followed by periods when they heal and fade (remission). It's impossible to predict when this might happen and how severe the flare-ups will be.









* **Pemphigus foliaceus** is part of the pemphigus group of autoimmune diseases.
* Lesions commonly begin on the trunk, but may also originate as localized lesions on the face or scalp. The patient may be unaware of the blisters because they rupture very easily. In these cases, there may only be a history of superficial sores or areas of crusting. Pain and/or a burning sensation localized to the areas of the lesions may be noted. Unlike pemphigus vulgaris (PV), there is typically no history of oral or other mucosal lesions. The lesions may become widespread.

Symptoms of PF include:

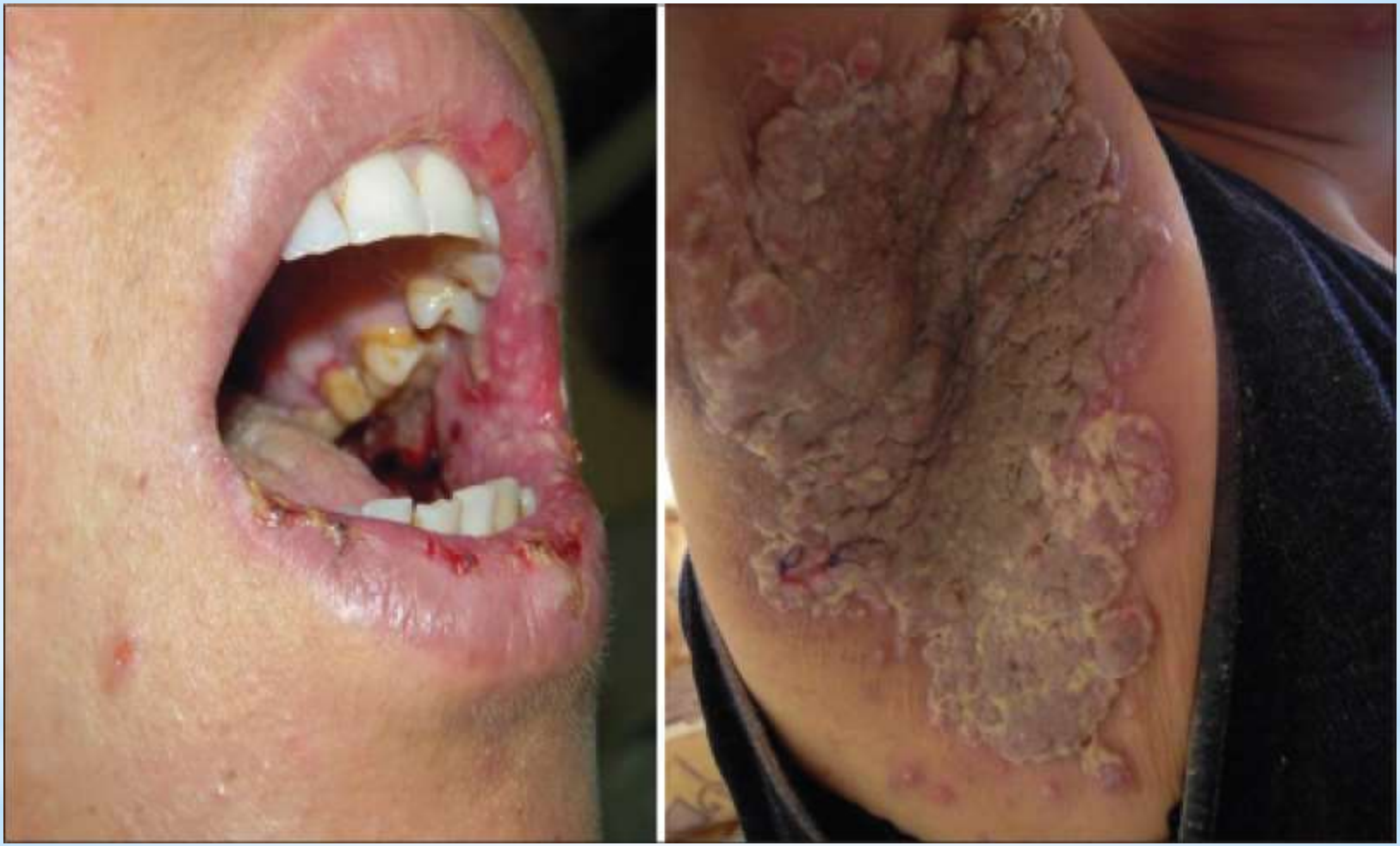
* Small fluid-filled skin blisters that typically begin on the face, scalp, or trunk.
* Ruptured blisters that cause sores, pockets, or scars in the skin.
* Scaly, inflamed, painful patches on the skin. These patches occur after blisters burst. Some people may only notice symptoms after the blisters burst.
* Burning, pain, and itching at the site of the blisters.
* Chronic skin infections due to ruptured and irritated blisters.

*Signs of a skin infection include:

* pus at a skin wound
* intense pain at the site of a blister
* red streaks out of a wound or blister
* fever
* exhaustion
* nausea

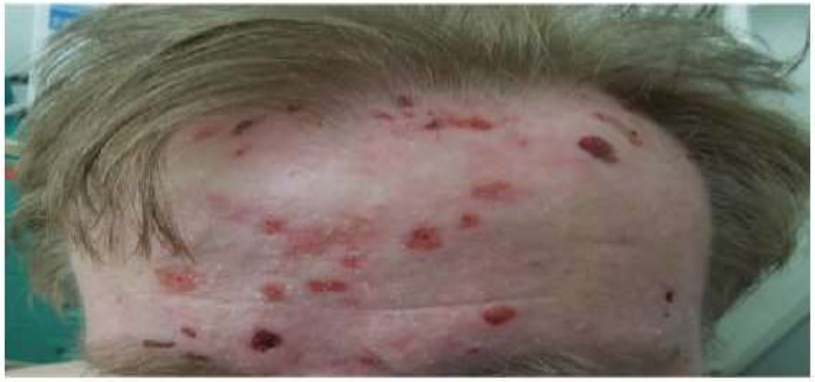
*Pemphigus vegetans

* is a rare verrucous variant of pemphigus vulgaris, affecting intertriginous areas.
* Two variants of pemphigus vegetans have been recognized.772 In the Neumann type the initial lesions are vesicular and erosive, resembling pemphigus vulgaris, but the lesions progressively evolve into vegetating plaques. The less common Hallopeau type commences with pustular lesions and has a relatively benign course with few, if any, relapses
* Oral lesions are almost invariably present in pemphigus vegetans
* On the bottom we may see vegetation



Seborrheic pemphigoid (SP)

* is a peculiar variant of BP which clinically resembles pemphigus erythematosus (known also as seborrheic pemphigus), since it is characterized by ruptured bullae and erosions covered with crusts involving the seborrheic areas (face, hair part of the head, cervix, dorsum)
* Spots and soft surface bulla with thin tegmentum which are fast-transformed into scaly crusts
* After crusts being removed the wet eroded surface is open



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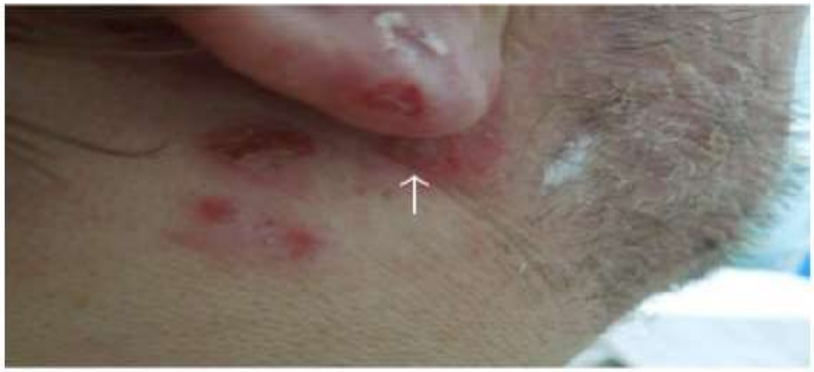

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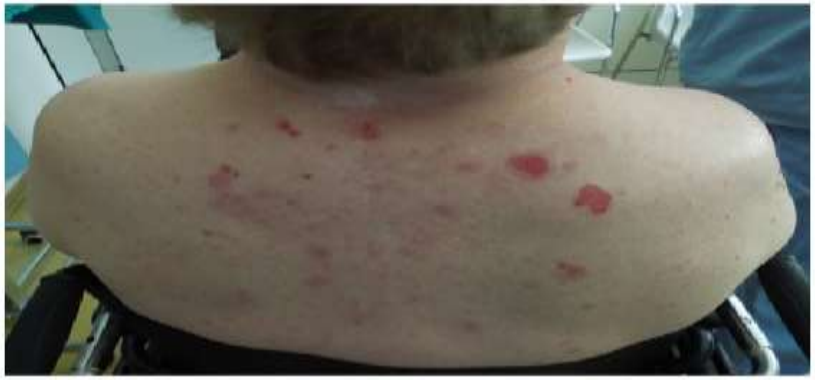

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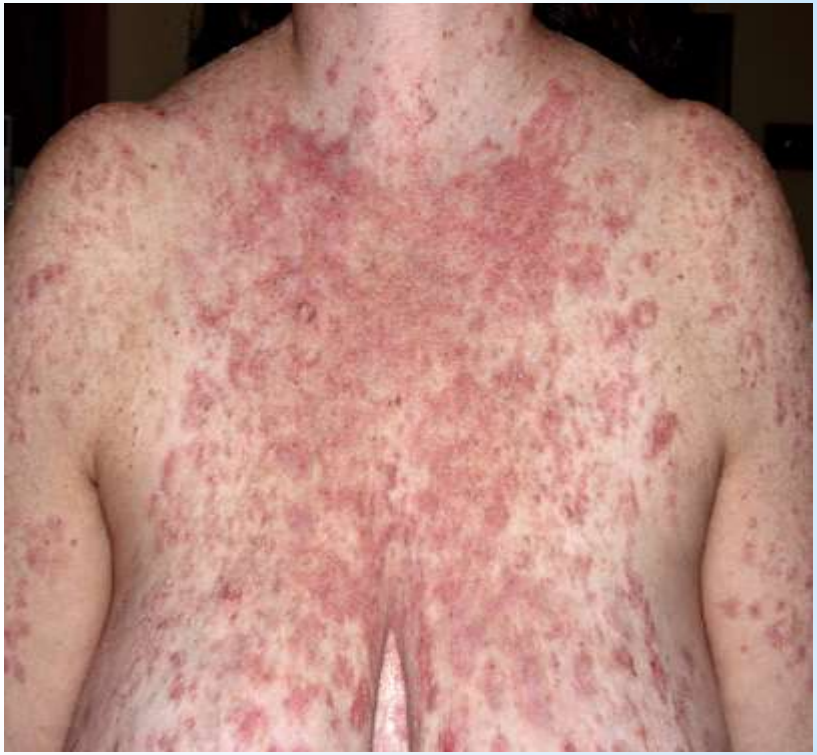


*Diagnostic

- Typical clinical presentation – visual examination of skin lesions

* Nikolsky's sign is a clinical dermatological sign, named after Pyotr Nikolsky (1858–1940), a Russian physician who trained and worked in the Russian Empire. Nikolsky sign is a skin finding in which the top layers of the skin slip away from the lower layers when rubbed.
* Asboe-Hansen sign. Pushing the bulla leads to increasing of its square
* Lesion biopsy — a sample of the blistered skin is removed and examined under the microscope. Additionally, the layer of skin in which cell-to-cell separation occurs can be determined.
*

* Direct immunofluorescence – the skin sample is treated to detect desmoglein antibodies in the skin. The presence of these antibodies indicates pemphigus.
* Indirect Immunofluorescence or antibody titer test. This measures desmoglein autoantibodies in the blood serum. It may be used to obtain a more complete understanding of the course of the disease.
* ELISA A serum assay for desmoglein antibodies, known as ELISA, is also available. Although in many cases there is a correlation between ELISA and disease activity it is not so in every case.

* Nikolsky sign
* Nikolsky sign is a skin finding in which the top layers of the skin slip away from the lower layers when rubbed.

* Considerations
* Your health care provider may use a pencil eraser or finger to test for Nikolsky sign. The skin is pulled to the side with a shearing pressure on the surface, or by rotating the eraser back and forth.

* If the test result is positive, the very thin top layer of skin will shear off, leaving skin pink and moist, and usually very tender.

* A positive result is usually a sign of a blistering skin condition. People with a positive sign have loose skin that slips free from the underlying layers when rubbed.
* Lesion biopsy — a sample of the blistered skin is removed and examined under the microscope. Additionally, the layer of skin in which cell-to-cell separation occurs can be determined.

*Treatment

* Eliminating triggers for the infection - some people experience an outbreak during times of stress, so reducing stress may help keep symptoms at bay. Eliminating medications that cause PF may also eliminate the blisters.
* **Hospitalization** - a severe outbreak of P may require hospitalization to reduce the risk of infection or treat an infection that has begun to spread.

* **Corticosteroids.** For people with mild disease, corticosteroid cream may be enough to control it. For others, the mainstay of treatment is an oral corticosteroid, such as prednisone pills.Using corticosteroids for a long time or in high doses may cause serious side effects, including diabetes, bone loss, an increased risk of infection, stomach ulcers and a redistribution of body fat, leading to a round face (moon face).
* **Steroid-sparing immunosuppressant drugs.** Medications such as azathioprine (Imuran, Azasan), mycophenolate (Cellcept) and cyclophosphamide help keep your immune system from attacking healthy tissue. They may have serious side effects, including increased risk of infection.
* **Other medications.** If first-line drugs aren't helping you, your doctor may suggest another drug, such as dapsone, intravenous immunoglobulin or rituximab (Rituxan).

- If the mouth and nose are the only involvement, treatment should be limited to topical steroids, intralesional steroid injections, or occasional short bursts of oral corticosteroids.

- If only the gums are involved, topical therapy applied with flexible dental trays (similar to the disposable molds used to deliver fluoride treatments to the teeth).

*Lifestyle and home remedies

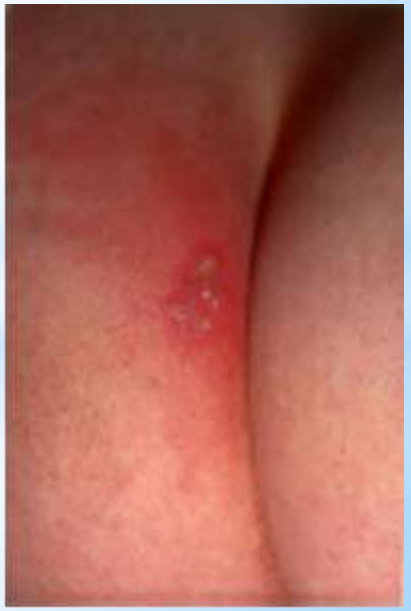
- **Follow your doctor's wound care instructions.** Taking good care of your wounds can help prevent infection and scarring. Your doctor may have recommendations for over-the-counter creams that help control pain.
- **Gently wash your skin.** Use mild soap and apply moisturizer afterward.
- **Protect your skin.** Avoid activities that may hurt the skin.
- **Avoid certain foods.** Blisters in your mouth could be triggered or irritated by spicy, hot or abrasive foods.
- **Minimize sun exposure.** Ultraviolet light may trigger new blisters.
- **Talk with your dentist about maintaining good oral health.** If you have blisters in your mouth, it may be difficult to brush your teeth properly. Ask your dentist what you can do to protect your oral health.

*Viral disoders of the skin

* The group of skin viral infections characterized by formation of blisters (vesicles), which appearance is caused by the degeneration of epidermal cells, includes herpes simplex and herpes zoster.

Herpes simplex

* Herpes simplex viruses (HSVs) are DNA viruses that cause acute skin infections and present as grouped vesicles on an erythematous base. Rarely, these viruses can cause serious illness and can affect pregnancy, leading to significant harm to the fetus. Most infections are recurrent and tend to reappear at or near the same location. Herpes labialis is the most common infection caused by HSV type 1 (HSV-1), whereas genital herpes is usually caused by HSV type 2 (HSV-2). Other clinical manifestations of HSV infection are less common.



Herpes simplex. Pathophysiology

* Herpes simplex virus belongs to the family of Herpesviridae, subfamily Alphaherpesvirinae type Simplexvirus. There are two antigenic serotypes of HSV* first (HSV-1) and second (HS V-2).
* Transmission of HSV-1 usually occurs in childhood, through a direct contact with a HIV-sick or infected person. This causes frequent localization of orofacial herpes lesions caused by HSV-1, in particular on skin areas around mouth (herpes labialis), nose (herpes nasalis), seldom on cheeks, eyelids and ears. In addition to skin, mucous membranes of the mouth (herpes stomatitis) may also be affected. Transmission of HSV-2 occurs mainly through sexual contact. HSV-2 is dominant in causing genital herpes infection (herpes genitalis) with the localization of lesions on skin and mucous membranes of the external genital organs of men and women. However, there is no stable relationship between antigen serotypes of HSV and localization of herpetic
* lesions on skin and visible mucous membranes (genital, extragenital). This is confirmed by the fact that about 20% of cases of genital herpes are caused by HSV-1
* In the pathogenesis of herpes simplex virus, the development of chronic persistent infection in sensory ganglia is crucial. Penetrating through the mucous membranes of the oropharynx, conjunctiva, urethra, cervix, rectum, or skin micro-cracks in the process of initial infection, HSV reaches nerve endings and moves to sensory ganglia through the retrograde axon, where there occurs an acute infection, when the virus replicates in the cells of sensitive ganglion. Further, virus enters into the state of persistence, which provokes the latent course of herpes. Under certain conditions (primarily, due to the lack of immune control), there occurs activation of the virus; from ganglion, the activated virus migrates along the axon of the peripheral nerve and replicates in the epithelial cells. Except general weakening of the immune control, reproduction of virus is caused by a violation of local immunity in the area of the epidermis.

*Clinic

* Herpes can be primary and simplex recurrent. The disease begins with itching or burning, accompanied by the formation of groups of small strained vesicles amid a slightly edematous limited congested spot. The content of vesicles is transparent, becomes thick in 2-3 days. Vesicles feature a tendency to merge. After 3-5 days, vesicles dry up and form yellowish-gray crusts. After 6-8 days, crusts fall off, while secondary pigmentation is left in their place, which then disappears with no trace.

Primary herpes simplex

* Primary herpes simplex. Primary infection with HSV-1 occurs mainly in young children. In most cases, the primary manifestations ofherpes simplex are minor (redness, itching) and remain undetected. However, children infected with HSV-1 may develop primary herpetic gingivostomatitis. The disease is developed suddenly, with an increase in body temperature to 39-40 ° C and intoxication. Mucous membranes of cheeks, gums, lips, tongue, and throat are tonsils are covered with painful grouped vesicles. After their destruction, there occur painful erosions prone to a merge. Clinical manifestations of the inflammation subside in two to three weeks.
* Primary genital herpes. The primary episode of genital herpes occurs after an incubation period of 1 -7 days. In men, herpes rash is usually localized on the head and shaft of the penis and foreskin, while in women it is localized on small and large labia, vagina, clitoris, cervix, perineum, thighs and buttocks. On the background of significant erythema and edema, there develop grouped vesicles, first with clear, and then thick contents. On the ruins of vesicles, erosions, sometimes ulcers and cracks are formed. Subjectively, the rash is accompanied by a sensation of pain and itching. There develops painful bubonadenitis. Unlike further relapses, primary clinical episode of genital herpes features more severe and prolonged course (4-5 weeks).

Recurrent herpes simplex

* Recurrent herpes simplex and recurrent genital herpes. In most cases, the initial clinical episode ofherpes simplex is followed by clinical recovery. However, virus (HSV-1, HSV 2) is stored in the body in a latent form throughout a person's life, not causing any clinical symptoms. Approximately 90% of people infected with HSV are virus carriers. Under the influence of a series of factors that reduce protective capacity of the body, which include hypothermia, overheating, infectious diseases, especially colds, etc., there occur recurrences ofherpes simplex. Unlike primary clinical episode of the disease, clinical episode of recurrent herpes simplex virus features milder course. In recurrent herpes simplex, typical location of the lesion includes lips, face, cornea and conjunctiva of the eye, buttocks. At these sites, there develop grouped vesicles with clear content, accompanied by itching and burning. In further, painful erosions are formed, which may merge. On the surface of the erosion, exudate dries in the form of a crust. After the removal of crust, secondary spots are left. Clinical recurrences ofherpes simplex may occur over many years and decades, with varying frequency - from one or two a year to two to four per month.
* Compared with the initial episode, recurrences of genital herpes are also characterized by a mild course. Rash on skin and mucous membranes is rather sparse. Typical for herpes, lesions are located on skin and mucous membranes of the vulva.
* Genital herpes can cause diverse complications, including reproductive disorders, miscarriage, intrauterine infection of fetus, and be transmitted to a baby during childbirth. In case of transplacental infection, a newborn may develop growth retardation, encephalitis, chorioretinitis. In addition, due to chronic recurrent genital herpes patients may experience significant psychosomatic disorders.

*Treatment

* All currently existing methods and tools for treatment of herpes do not allow achieving complete elimination of pathogens (HSV-1, HSV-2) from the human body. Approaches to treatment of herpes simplex are determined by a clinical picture of the disease, severity of clinical course, frequency of relapses, as well as availability of comorbidity. In the antiviral therapy of herpes infections, preparations of acyclic nucleotides that have an ability to disrupt interaction of virus and cells, in particular inhibit reproduction of the virus through its virostatic action, play the major role.
* For treatment of infections caused by herpes simplex viruses, the drugs from a group of acyclic purine nucleosides are used: acyclovir, valacyclovir (valine aether of acyclovir) and famciclovir (pro-forma of penciclovir). In the form of topical preparations (cream), acyclovir is prescribed to reduce the intensity and duration of the recurrent episode of herpes simplex. Systemic prescription of purine nucleoside analogs (internal or parenteral) is used for treatment of primary manifestations of herpes simplex virus, as well as treatment of relapse (for active clinical manifestations). With frequent recurrences of skin herpes and genital herpes, acyclovir and valacyclovir may be prescribed in long continual courses (so-called long-term suppressive therapy). For a healthy sexual partner of a patient with recurrent herpes, prophylactic or preventive treatment has no medical meaning, since existing antiviral drugs are unable to eliminate the virus from a human body. In some countries, particularly Ukraine, Russia and Belarus, recombinant interferons and interferon inducers are used as a part of comprehensive treatment of the disease.

Discussion questions

1. Differential diagnosis with the viral exanthema of child age.
2. Etiological, pathogenetic and epidemiological features
3. Principle of classification
4. Differential diagnosis
5. The main approaches to the general and local treatment

Questions?