Sri Aurobindo College of Dentistry

Indore, Madhya Pradesh

INDIA

MODULE PLAN

TOPIC : VESICULOBULLOUS LESIONS

SUBJECT: OMDR

TARGET GROUP: UNDERGRADUATE DENTISTRY

MODE: POWERPOINT – WEBINAR

PLATFORM: INSTITUTIONAL LMS

PRESENTER: DR.TUSHAR PHULAMBRIKAR

CONTENT

The patient with acute multiple lesions:

- Herpes Simplex Virus Infections
- Varicella-Zoster Virus Infections
- Cytomegalovirus Infections
- Coxsackievirus Infections
- Erythema Multiforme
- Stevens Johnson Syndrome

The Patient with Chronic multiple lesions

Pemphigus

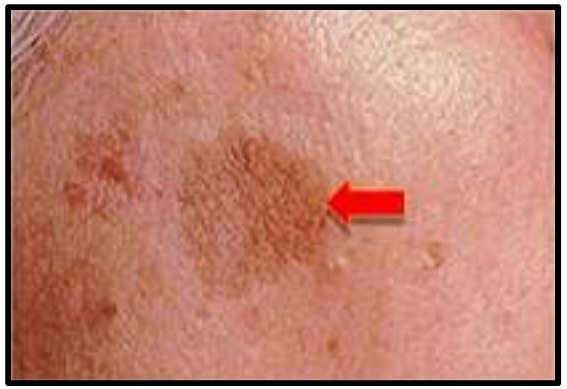
- Pemphigus Vulgaris
- Pemphigus Foliaceus,
- Para-neoplastic Pemphigus (PNPP), and Drug-related Pemphigus.

Sub-Epithelial Bullous Dermatoses

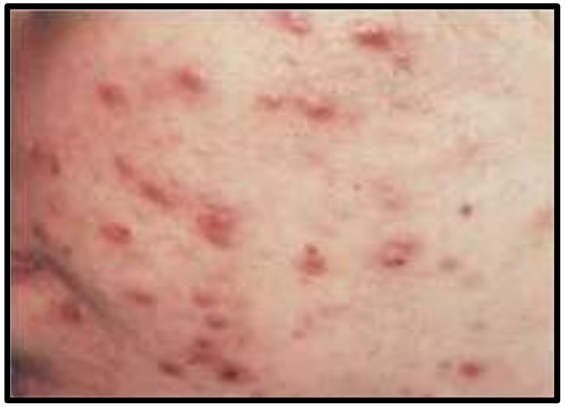
- Bullous Pemphigoid,
- Mucous Membrane Pemphigoid.

Different dermatologic lesions are as follows:

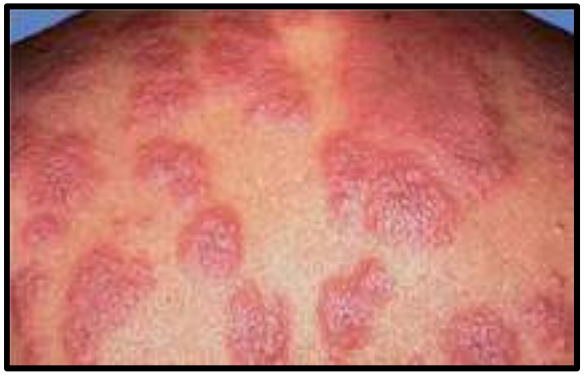
Macules: These are well circumscribed, flat lesions that are noticeable because of their change from normal skin color.

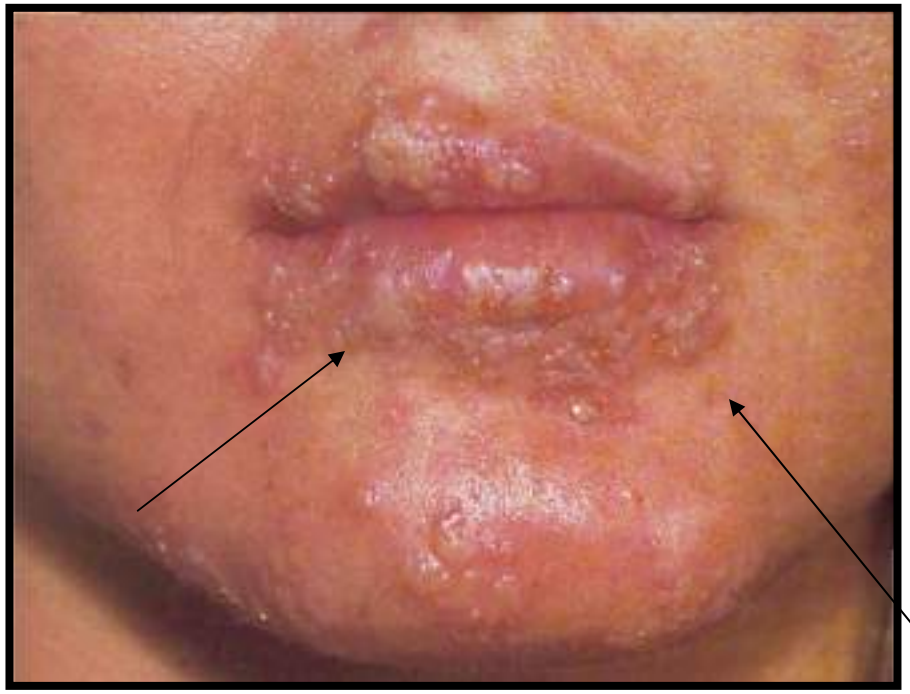


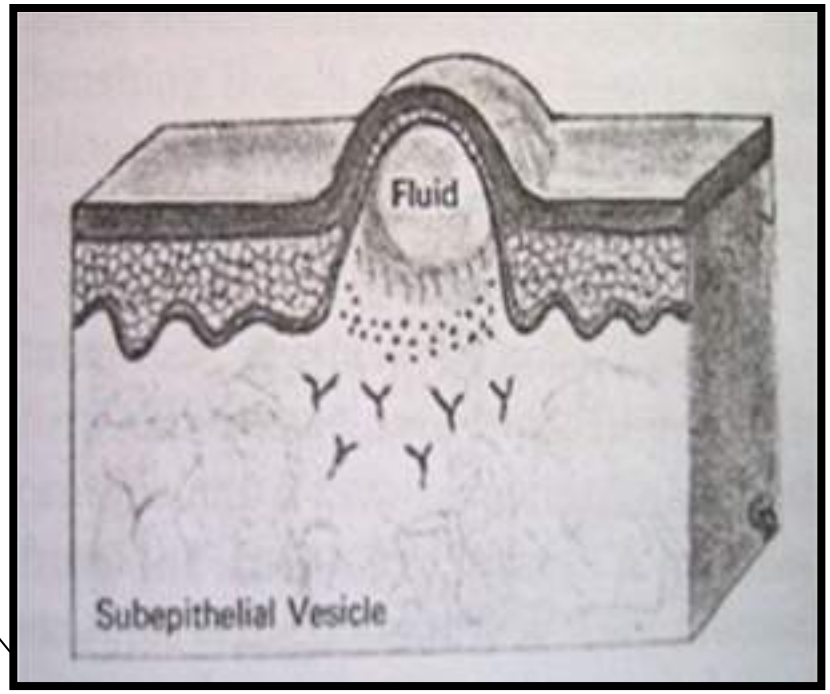
Papules: These are solid lesions raised above the skin surface that are smaller than 1 cm in diameter.



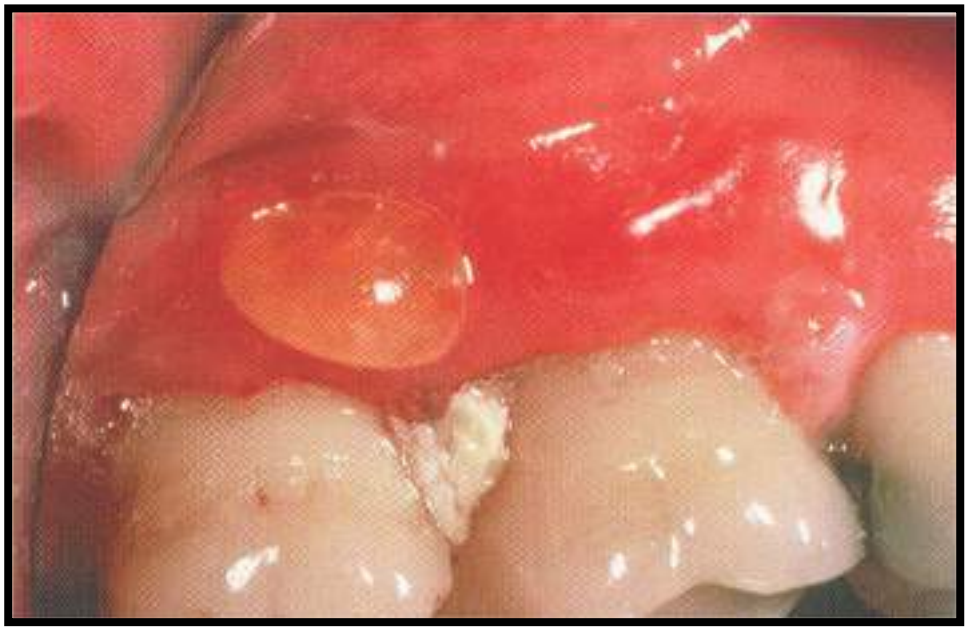
Plaques: These are solid raised lesions that are over 1 cm in diameter; they are large papules.



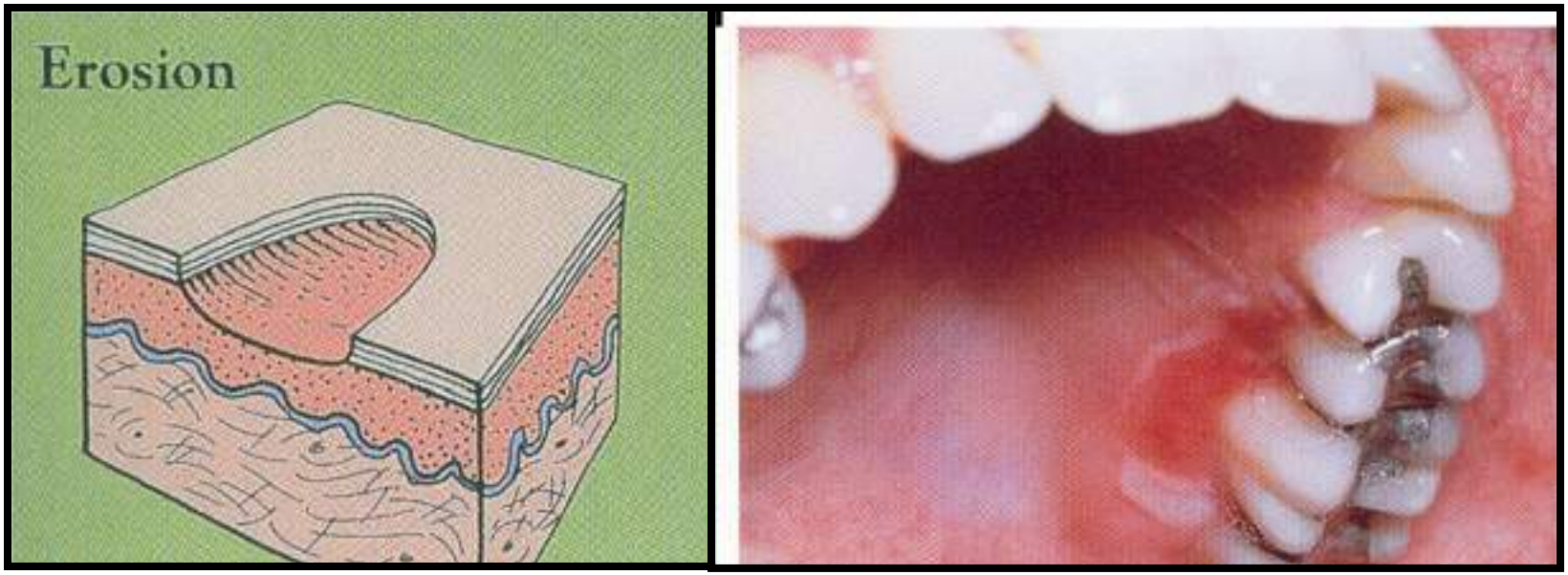




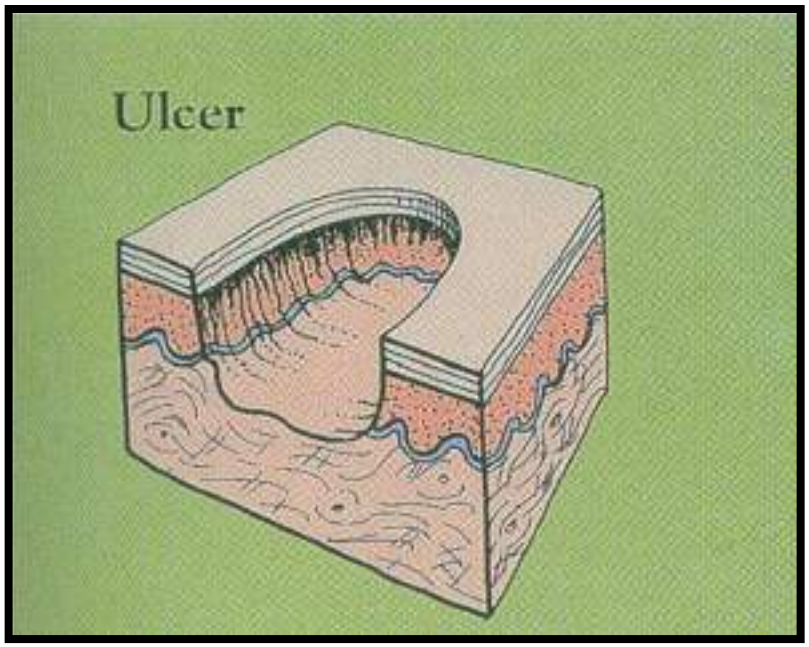
Vesicles: These are elevated blisters containing clear fluid that are less than 1 cm in diameter.

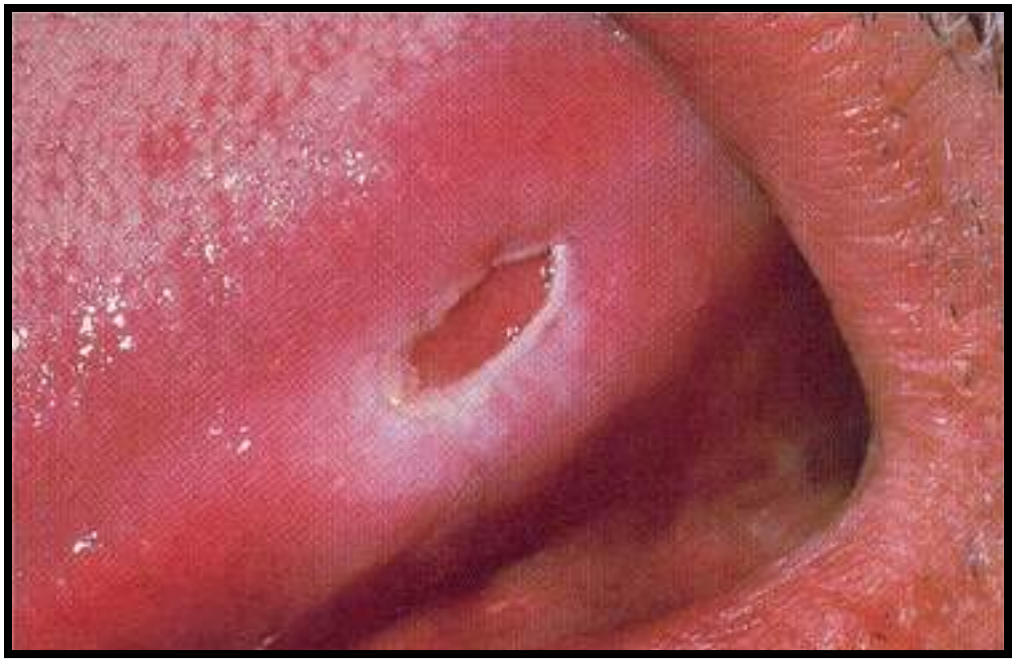


Bullae: These are elevated blisters containing clear fluid that are greater than 1 cm in diameter.



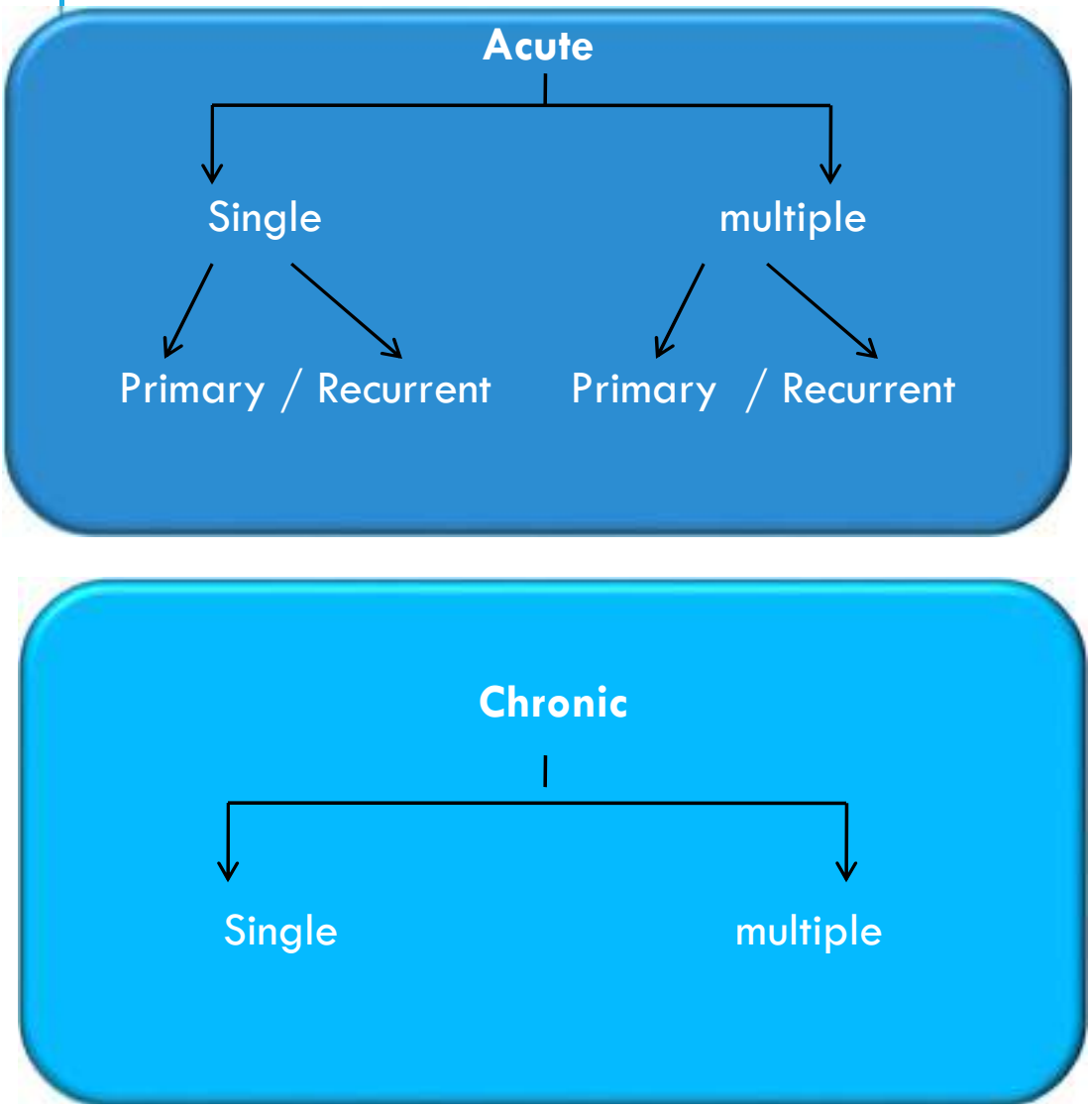
Erosions: These are red lesions often caused by the rupture of vesicles or bullae or trauma and are generally moist on the skin.





Ulcers: These are well-circumscribed, often depressed lesions with an epithelial defect that is covered by a fibrin clot, causing a yellow-white appearance.

CLASSIFICATION OF VESICULOBULLOUS AND ULCERATIVE LESIONS INVOLVING THE ORAL MUCOSA



Acute Multiple Lesions

1. Primary Herpes Simplex Virus Infections
2. Varicella-Zoster Virus Infections
3. Necrotizing Ulcerative Gingivitis and Necrotizing Ulcerative Periodontitis
4. Erythema Multiforme
5. Stevens Johnson Syndrome and Toxic Epidermal Necrolysis(Lyell Disease)
6. Oral Hypersensitivity Reactions
7. Recurrent Apthous Ulcer

Recurrent Lesions

1. Recurrent Herpes stomatitis
2. Behchet Disease(Behcet syndrome)

Patient with Chronic Multiple Ulcers

1. Pemphigus Vulgaris
2. Subepithelial Bullous Dermatoses
3. Bullous Pemphigoid

Patients with Single Ulcers

1. Traumatic Injuries
2. Traumatic Ulcerative Granuloma
3. Infectious Ulcers

HERPES SIMPLEX VIRUS (HSV) INFECTION

HERPESVIRIDAE FAMILY

1. Herpes Simplex Virus Types 1 and 2 [HHV1 And HHV 2]
2. Varicella-zoster Virus [HHV-3]
3. Epstein-barr Virus [HHV-4]
4. Cytomegalo Virus [HHV-5]
5. Human Herpes Virus 6 [HHV-6]
6. Human Herpes Virus 7 [HHV-7]
7. Kaposi's Sarcoma—associated Herpes Virus [HHV-8]

NOTE- They are **DOUBLE STRANDED DNA VIRUS** and have **LIPID ENVELOP.**

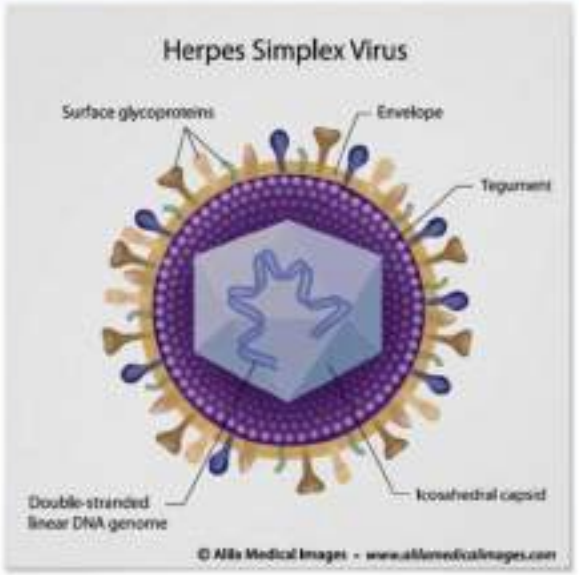
HERPES SIMPLEX VIRUS (HSV)

Herpes simplex viruses (HSV-1, HSV-2; *Herpes virus hominis*) produce a variety of infections involving mucocutaneous surfaces, the central nervous system (CNS), and on occasion visceral organs.

The viral genome is packaged i regular icosahedral protein shell (capsid).

The outer covering of the virus is a lipid-containing membrane (envelope).

Between the capsid and lipid bilayer of the envelope is the tegument.

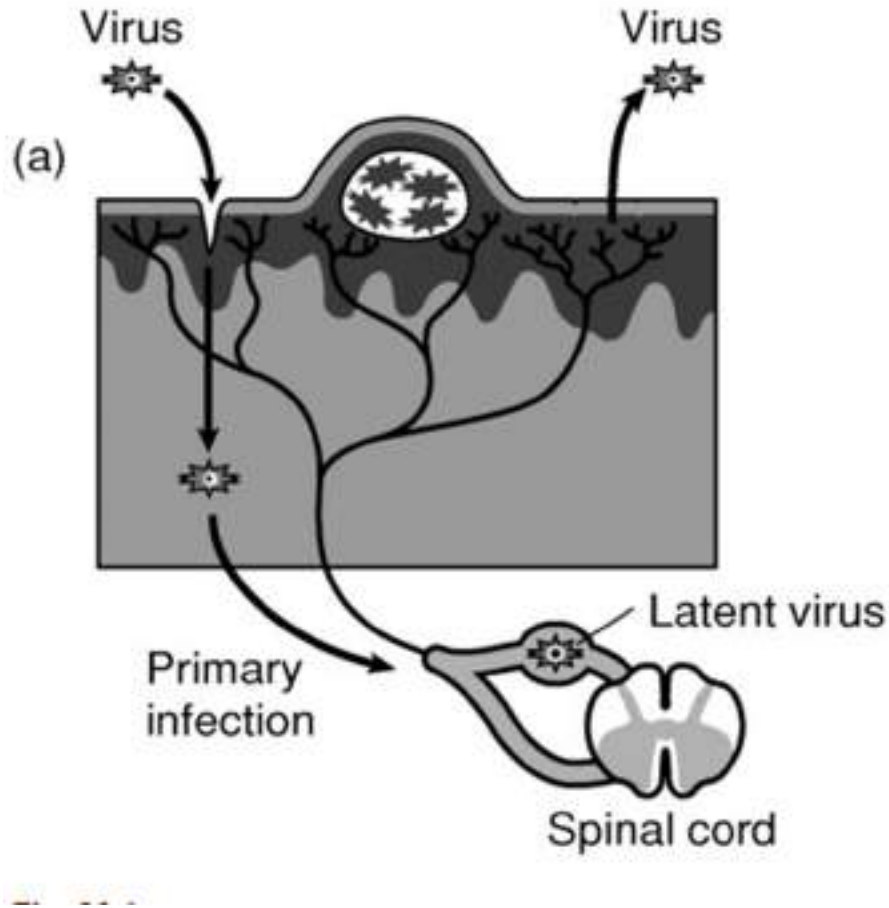


xposure to .

. ucosal surfaces or abraded skin sites

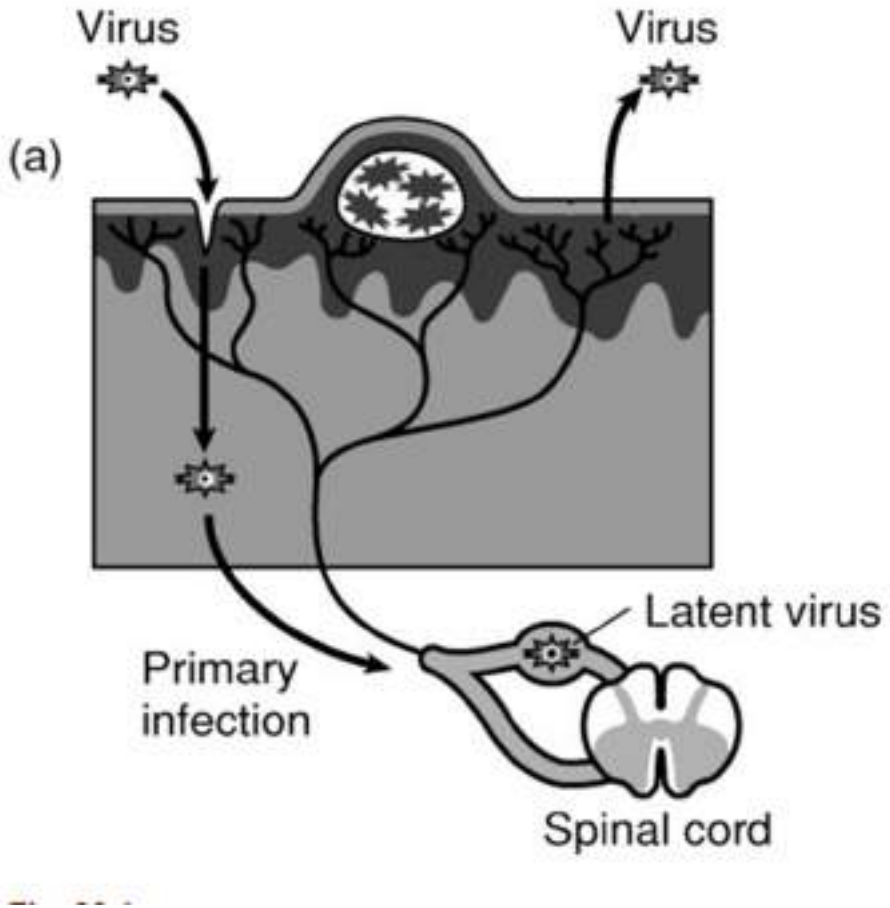
ntry of the virus into cells of the epidermis and dermis

viral replication

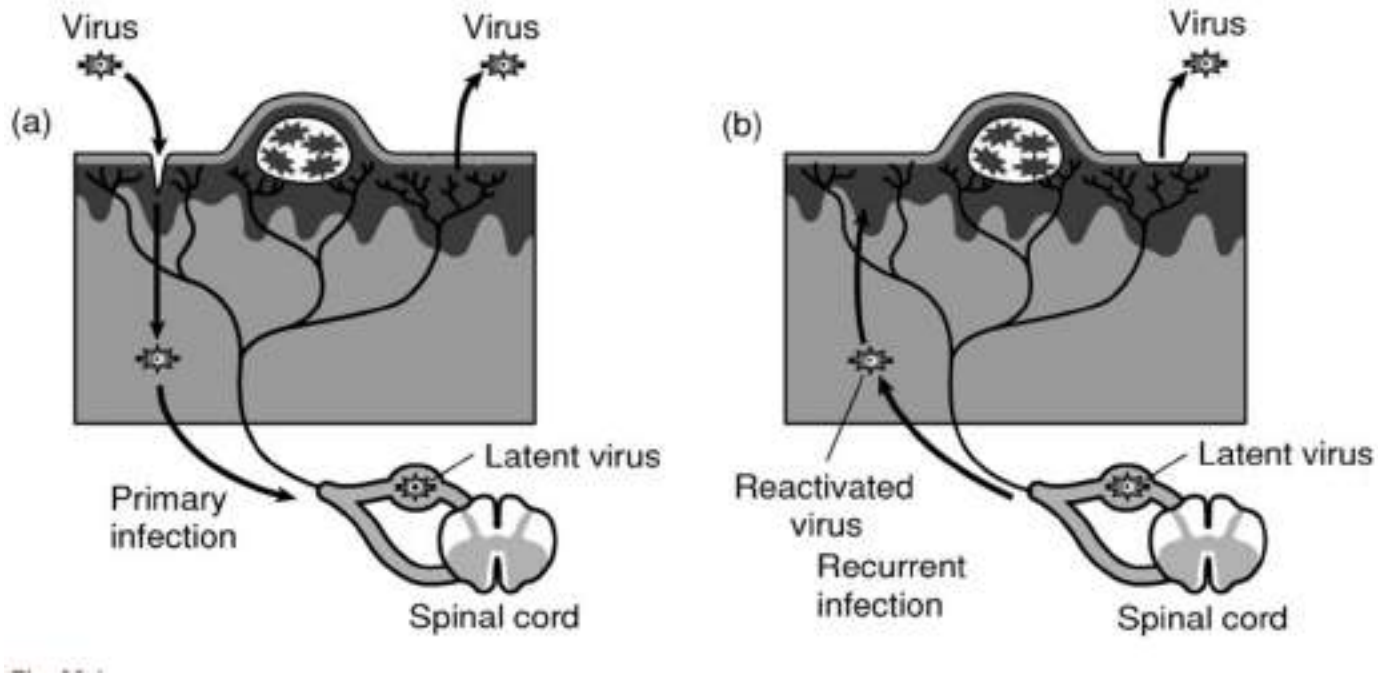


HSV infections are usually acquired sub-clinically. Whether clinical or subclinical, HSV acquisition is associated with sufficient viral replication to permit infection of either sensory or autonomic nerve endings.

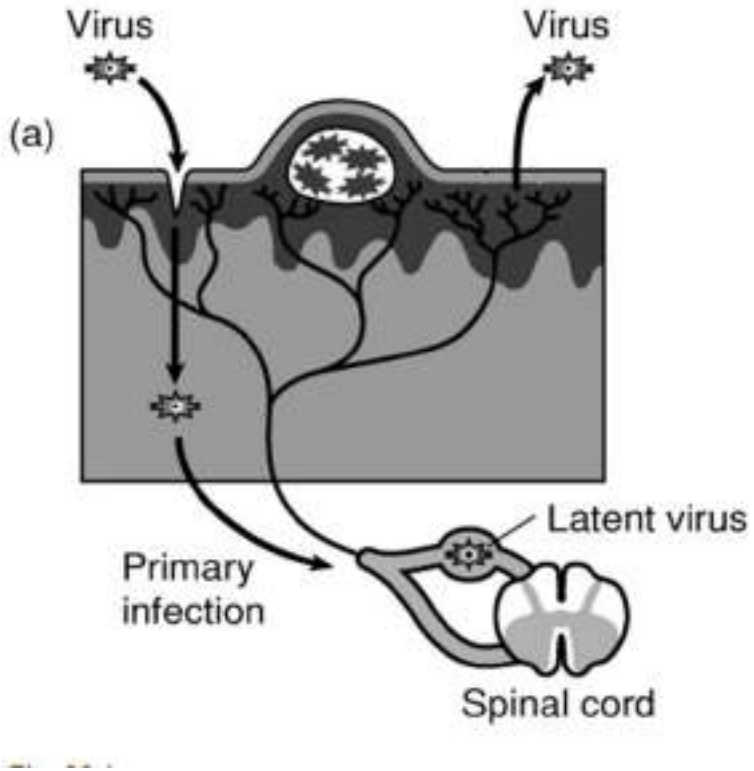
On entry into the neuronal cell, the virus or, the nucleocapsid is transported intra-axonally to the nerve cell bodies in ganglia.



During the initial phase of infection, viral replication occurs in ganglia and contiguous neural tissue.



Virus then spreads to other mucocutaneous surfaces through centrifugal migration of infectious virions via peripheral sensory nerves.



This mode of spread helps explain the large surface area involved, the high frequency of new lesions distant from the initial crop of vesicles that is characteristic in patients with primary genital or oral-labial HSV infection.

HSV viremia — it is another mechanism for extension of infection throughout the body—in 30–40% of persons with primary HSV-2 infection.

For HSV-1 infection, trigeminal ganglia are most commonly infected, it may also extends to the inferior and superior cervical ganglia.

In genital infection, sacral nerve root ganglia (S2–S5) are most commonly affected.

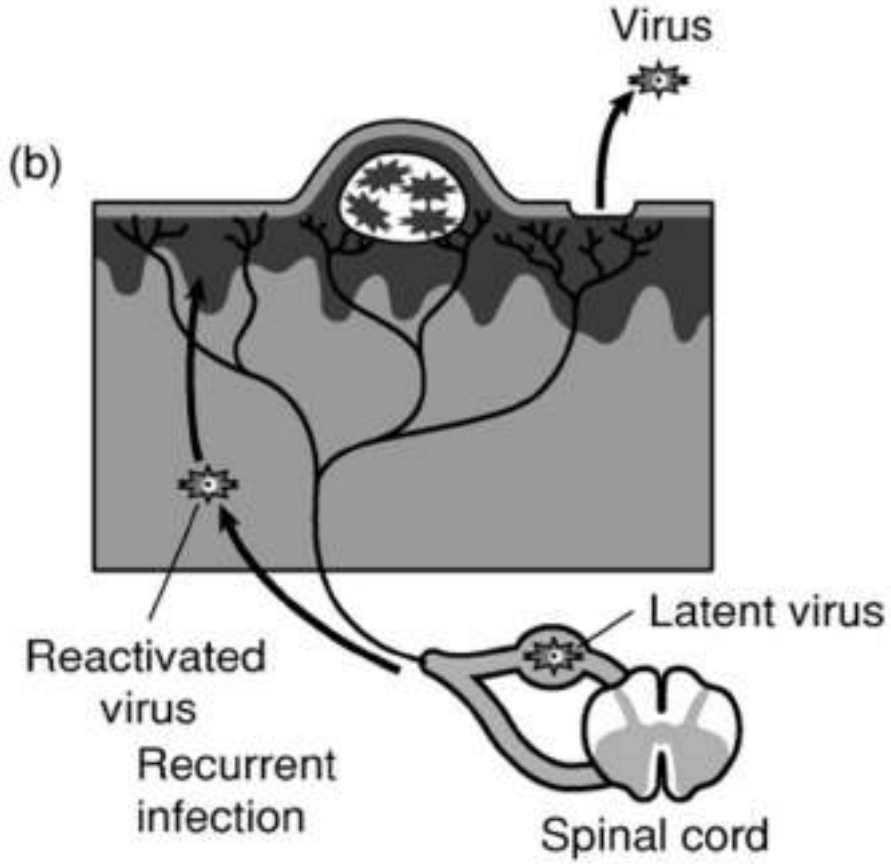
They are triggered by Ultraviolet light, systemic and local immune-suppression, and trauma to the skin or ganglia.

The frequency and severity of HSV reactivation is influenced by Host T cell responses at the ganglionic and peripheral mucosal level.

After resolution of primary disease, infectious HSV can not be cultured from the ganglia.

However, latent infection, persists in 2–11% of ganglionic cells in the anatomic region of the initial infection.

The mechanism of reactivation from latency is unknown.



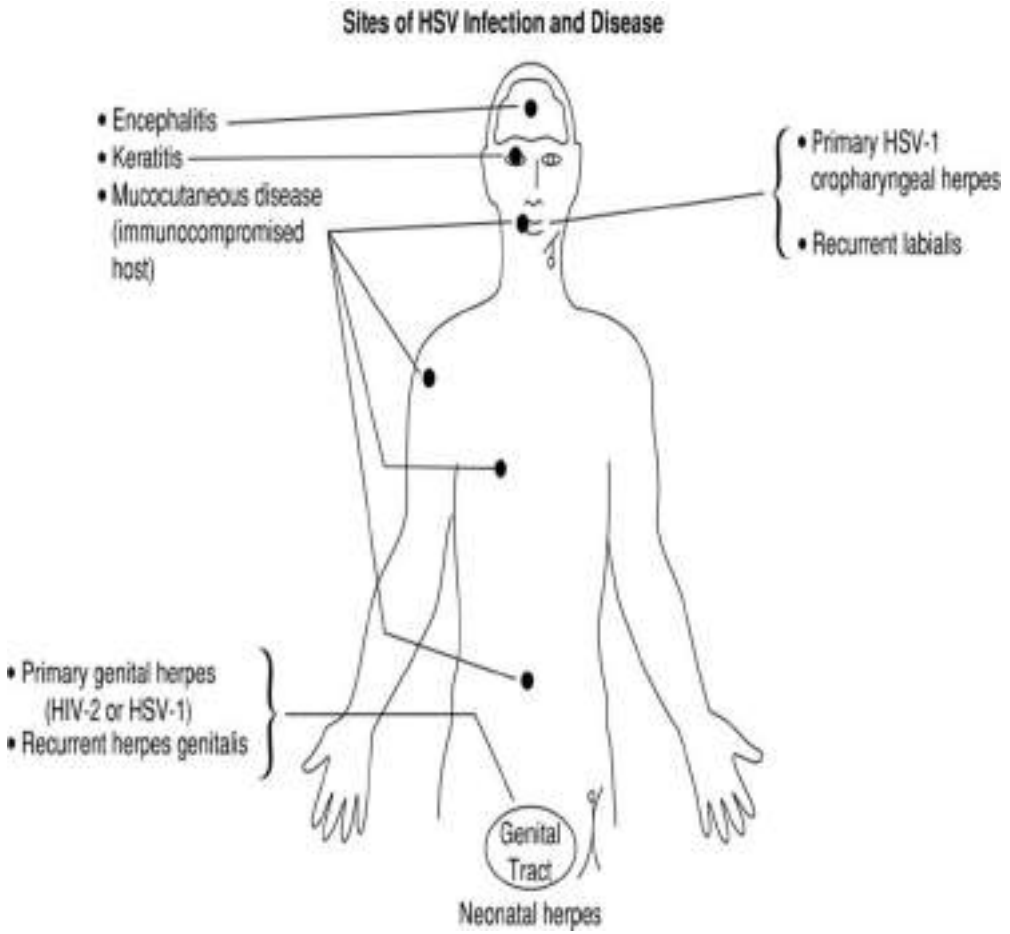
CLINICAL MANIFESTATION

The clinical manifestations and course of HSV infection depend on :-

Anatomic site involved,

The age & immune status of the host,

Antigenic type of the virus.

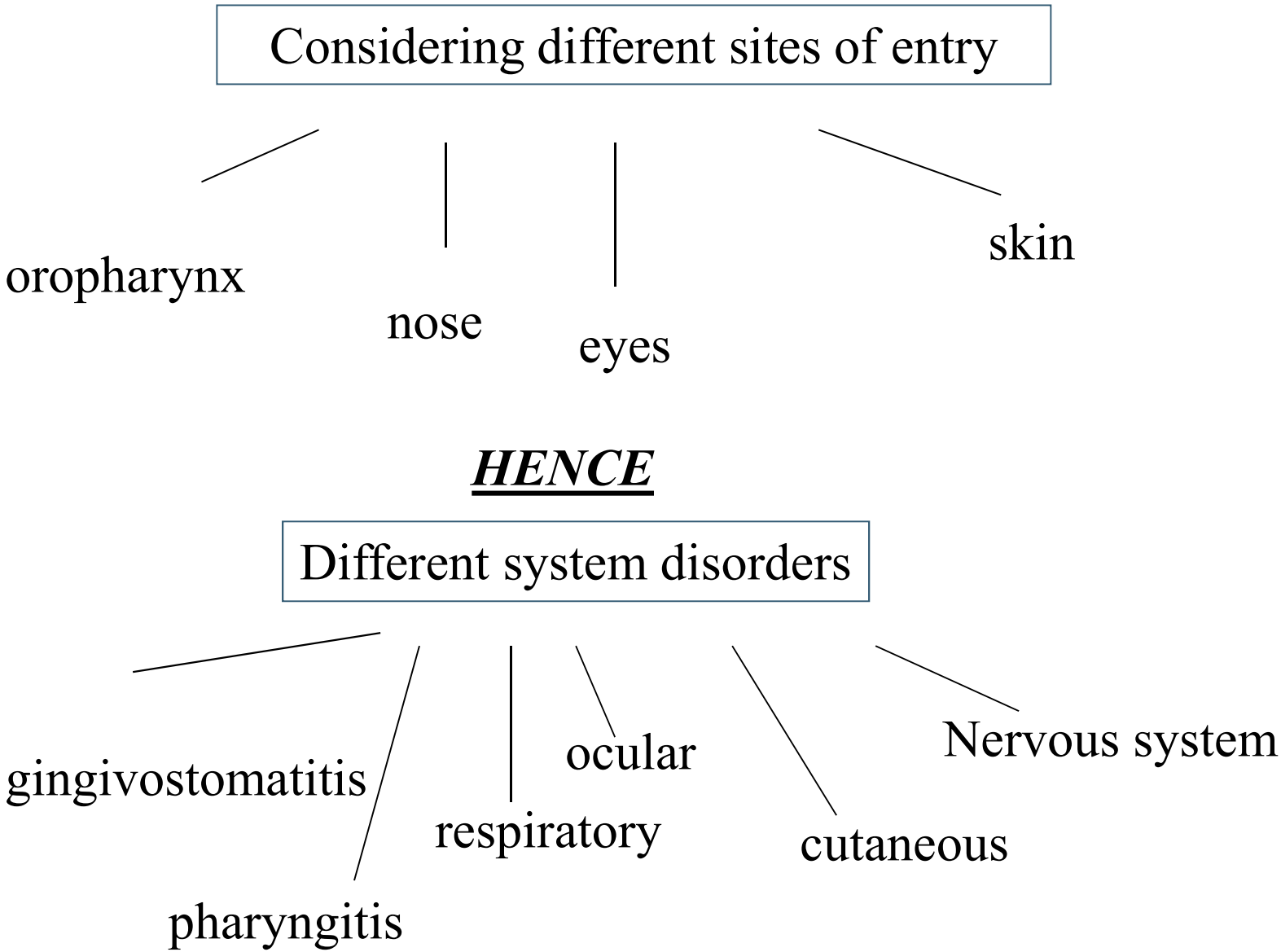


Primary HSV infections (i.e., first infections with either HSV-1 or HSV-2 in which the host lacks HSV antibodies in acute-phase serum) are frequently accompanied by systemic signs and symptoms.

Compared with recurrent episodes, primary infections, are characterized by a longer duration of symptoms

The incubation period ranges from 1 to 26 days (median, 6–8 days).

Both viral subtypes can cause genital and oral-facial infections, and the infections caused by the two subtypes are clinically indistinguishable.


Considering different sites of entry
oropharynx
nose
eyes
skin
HENCE
Different system disorders
gingivostomatitis
pharyngitis
respiratory
ocular
cutaneous
Nervous system

ORAL-FACIAL INFECTIONS

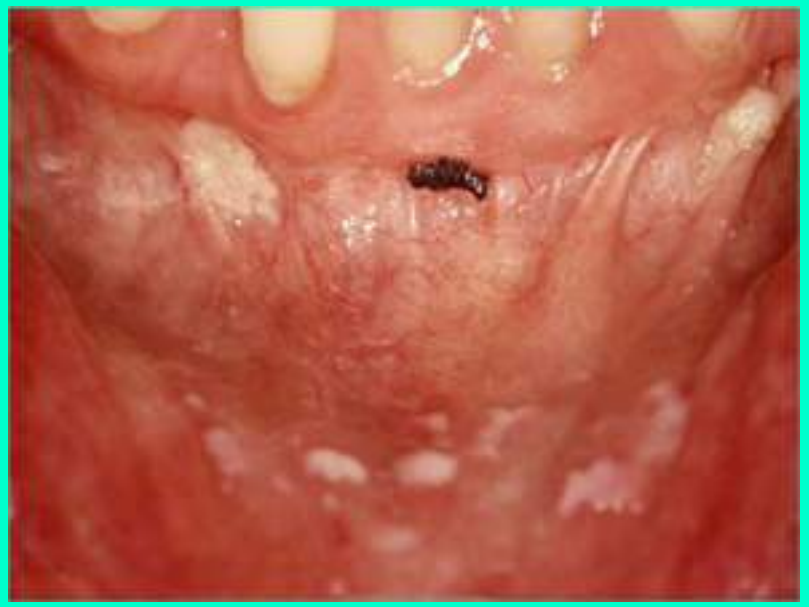
Gingivostomatitis and Pharyngitis are the most common clinical manifestations of first-episode HSV-1 infection.

While Recurrent Herpes Labialis is the most common clinical manifestation of reactivation HSV-1 infection.

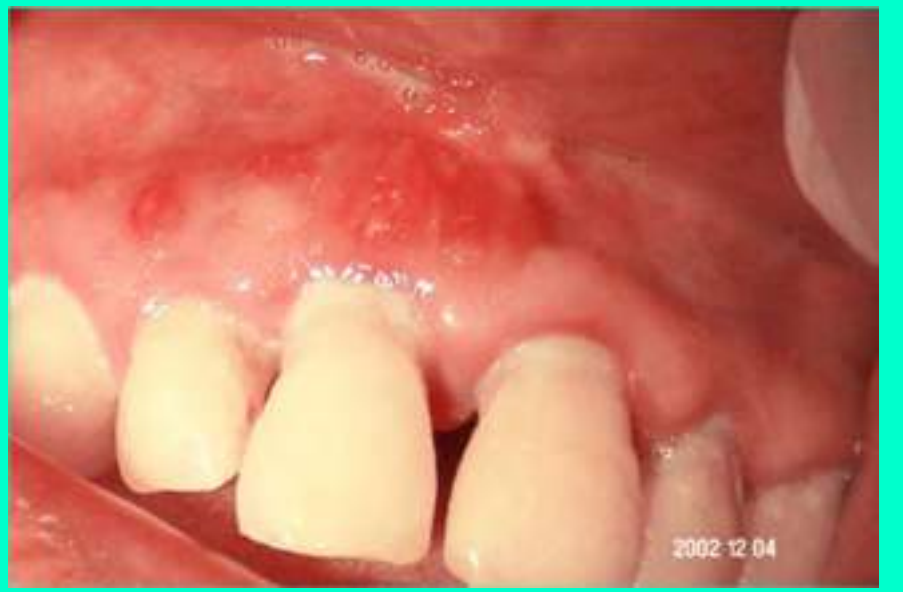
Recurrent HERPES LABIALIS

HSV pharyngitis and gingivostomatitis commonly seen among children and young adults.

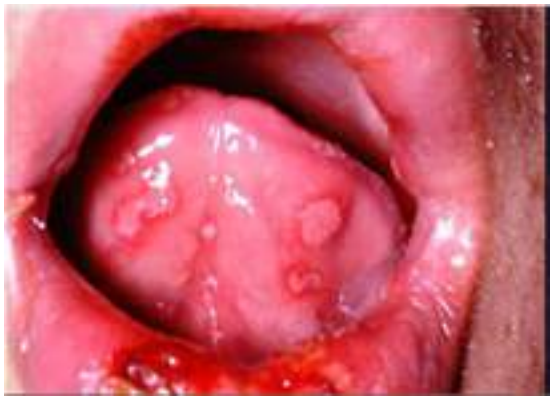
Clinical symptoms and signs includes fever, malaise, myalgias, inability to eat, irritability, and cervical adenopathy, and last for 3–14 days.

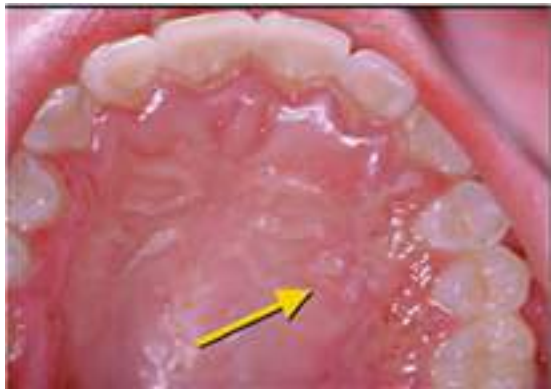


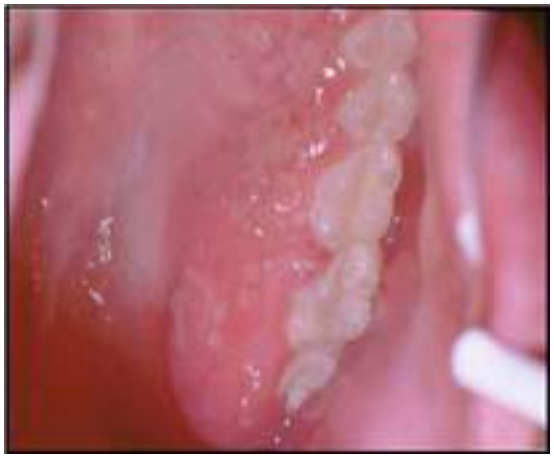
HSV infection

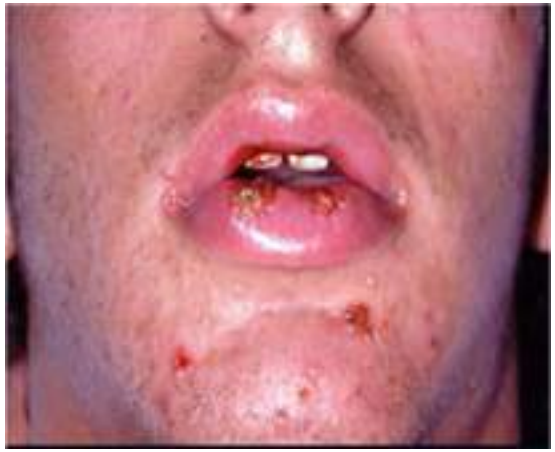


Recurrent Intraoral Herpes Involving Gingiva









HSV-1 or HSV-2 infection of the pharynx usually results in exudative or ulcerative lesions of the posterior pharynx and/or tonsillar pillars. Fever lasting 2–7 days and cervical lymphadenopathy are common.

Appearance - Erythema and clusters of vesicles and/or ulcers appear on the keratinized mucosa of hard palate, attached gingiva and dorsum of tongue, and the non keratinized mucosa of buccal and labial mucosa, ventral tongue, and soft palate.

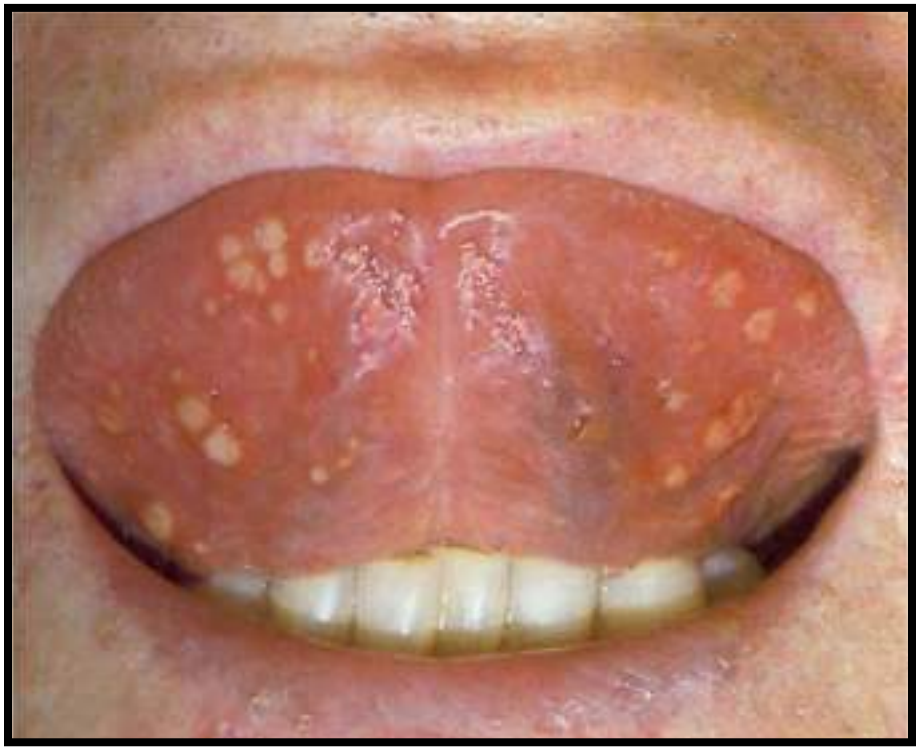
Vesicles break down to form ulcers that are usually 1-5 mm and coalesce to form large ulcers with scalloped borders and marked surrounding erythema.

The gingiva is often fiery red, and the mouth is extremely painful, causing difficulty with eating.

Reactivation of HSV from the trigeminal ganglia may be associated with asymptomatic virus excretion in the saliva, development of intraoral mucosal ulcerations, or herpetic ulcerations on the vermilion border of the lip or external facial skin.

•small vesicles appear on all oral mucosa including gingiva

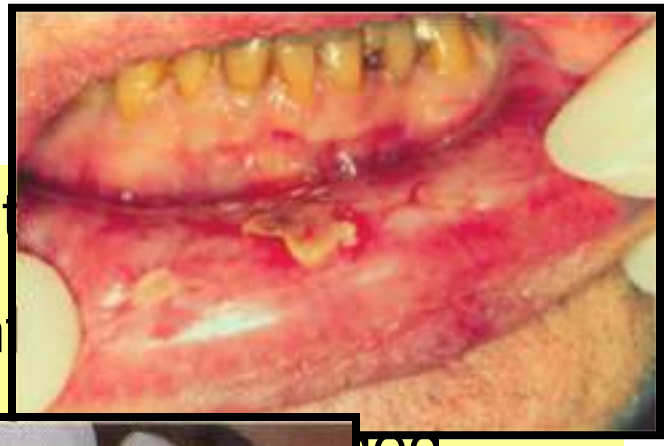
•vesicles burst quickly to form shallow round ulcers surrounded by an inflammatory base



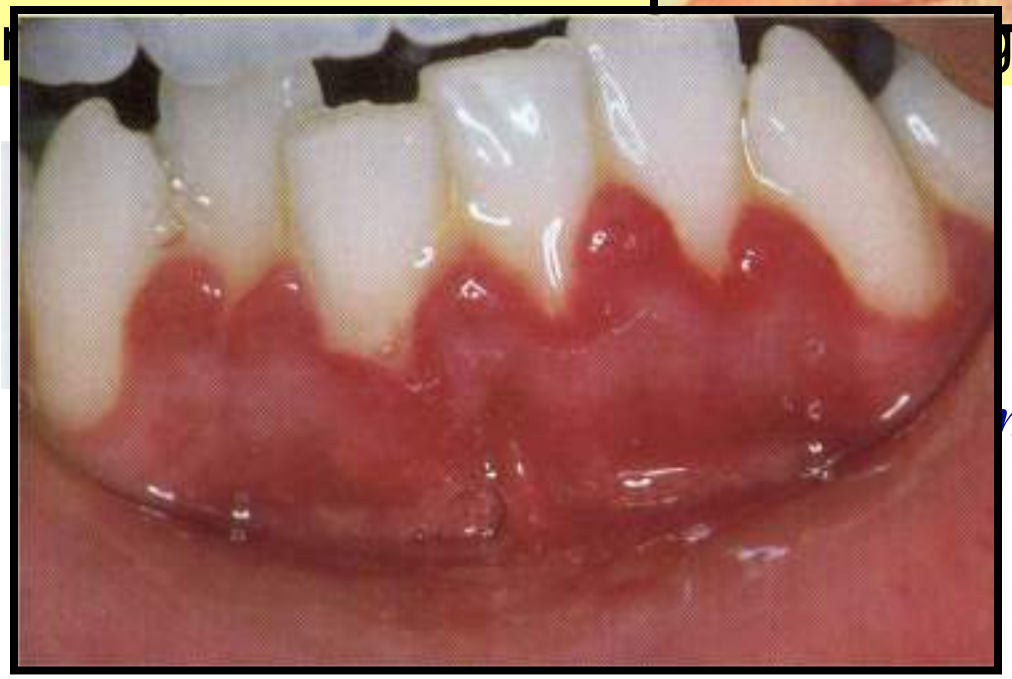
Oral l

•general ingivit

•entire g nd in



•Round ulce ged borders



Discrete ulcers

mucosal

WHEN IT OCCURS ?

About 50–70% of sero-positive patients undergoing trigeminal nerve-root decompression and 10–15% of those undergoing dental extraction develop oral-labial HSV infection a median of 3 days after these procedures.

In Immuno-suppressed patients, HSV infection may extend into mucosal and deep cutaneous layers. Friability, necrosis, bleeding, severe pain, and inability to eat or drink may result.

In AIDS , Persistent ulcerative HSV infections are the most common infections . HSV and Candida infections often occur concurrently.

In early phases of transplantation or induction chemotherapy, frequency of reactivation of HSV is high **(50–90%).**

In Atopic Eczema severe oral-facial HSV infections (eczema herpeticum) may occur, which may rapidly involve extensive areas of skin and occasionally disseminate to visceral organs.

In Erythema Multiforme, HSV infection is the precipitating event in ***75%*** of cases of cutaneous erythema multiforme.

HSV-1 and varicella-zoster virus (VZV) have been implicated in the aetiology of Bell's palsy (flaccid paralysis of the mandibular portion of the facial nerve).

HERPETIC WHITLOW

Infection of the finger—

- ✓ May occur as a complication of primary oral or genital herpes by inoculation of virus through a break in the epidermal surface.

- ✓ By direct introduction of virus into the hand through occupational or some other type of exposure.

HERPETIC WHITLOW

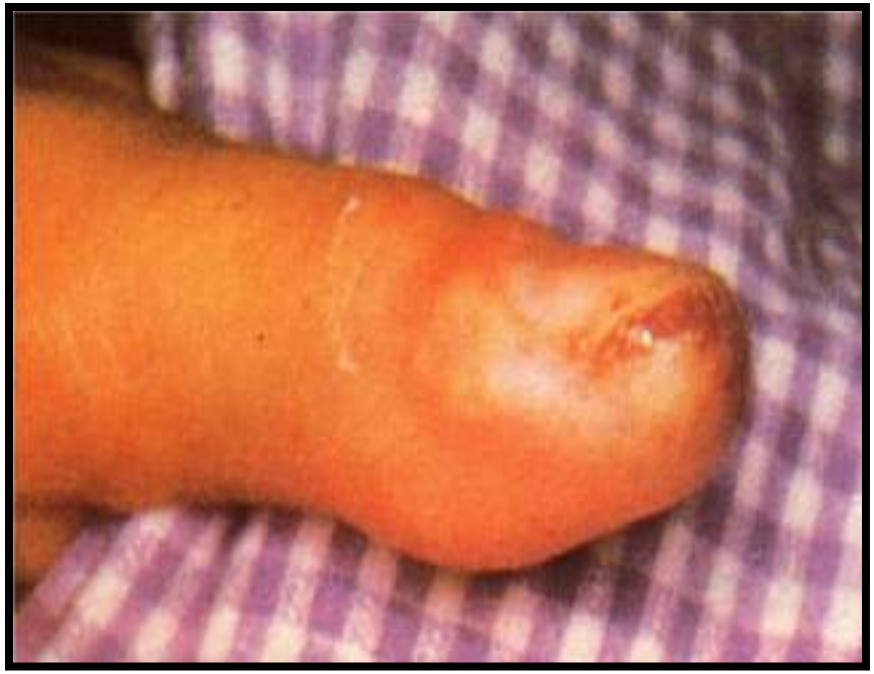
Clinical signs and symptoms

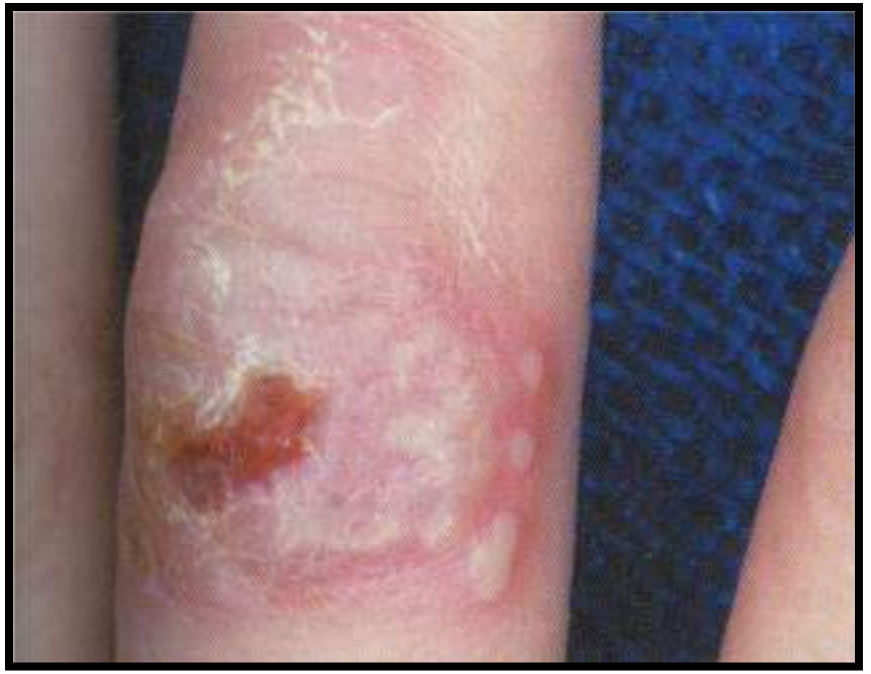
Abrupt-onset edema, erythema, and localized tenderness of the infected finger.

Vesicular or pustular lesions of the fingertip that are indistinguishable from lesions of pyogenic bacterial infection are seen.

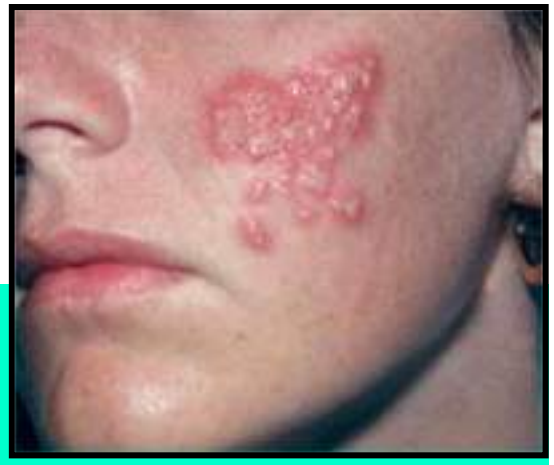
Fever, lymphadenitis, and epitrochlear and axillary lymphadenopathy are common. The infection may recur.

Antiviral therapy is given.





S GLADIATORUM



HSV may infect almost any area of skin.

Mucocutaneous HSV infections of the thorax, ears, face, and hands have been described among wrestlers. Transmission of these infections is facilitated by trauma to the skin sustained during wrestling.

DIFFERENTIAL DIAGNOSIS

HSV

HSV typically has a prodrome of fever and malaise before vesicle and ulcer eruption.

HSV infections usually present with associated gingival erythema, which is uncommon with recurrent aphthous stomatitis.

Recurrent aphthous stomatitis

It generally does not have the same prodromal symptoms before ulcer formation.

Rarely occur on gingiva.

Primary lesion	**RIH**	**RAS**
Mature	Shallow, punctate ulcer	Ulcer with erythematous halo
Location	Attached gingiva, hard palate, vermilion border of lip	Buccal mucosa, Floor of the mouth,oropharynx, tongue.
Number and size	Few to several, .5-2cm	One to few,
Duration of lesion	1-3 weeks	1-2 weeks
Etiology	Viral	Unclear
Prevalance	70-80%	66%
Mucosa involved	Keratinized	Non keratinized and gland wearing tissues.

Primary lesion	**RIH**	**RAS**
Healing	Crusting during healing – 96 hrs Pain resolution – 96-120 hrs Healing – 8-10 days.	10-14 days

VARICELLA ZOSTER VIRUS INFECTION

VARICELLA ZOSTER VIRUS INFECTION

Varicella-zoster virus (VZV) causes two distinct clinical entities: varicella (chickenpox) and herpes zoster (shingles).

Chickenpox, extremely contagious infection, is usually a benign illness of childhood characterized by an exanthematous vesicular rash.

With reactivation of latent VZV (common after the sixth decade of life), herpes zoster presents as a dermatomal vesicular rash, usually associated with severe pain.

ETIOLOGY

VZV is a member of the family Herpes viridae.

It has a lipid envelope surrounding a nucleocapsid with icosahedral symmetry.

Total diameter - 180–200 nm

Double-stranded DNA that is centrally located .

PATHOGENESIS

PRIMARY INFECTION

Transmission occurs by the respiratory route;

The virus starts replication at an undefined site (mainly nasopharynx)

leads to seeding of the reticuloendothelial system and ultimately to

the development of viremia.

Viremia is reflected in form of diffuse and scattered nature of the skin lesions.

Infection may involve localized blood vessels of the skin, resulting in necrosis and epidermal hemorrhage.

Later, the vesicular fluid becomes cloudy because of the recruitment of polymorphonuclear leukocytes and the presence of degenerated cells and fibrin.

Ultimately, the vesicles either rupture and release their fluid (which includes infectious virus) or are gradually reabsorbed.

Recurrent Infection

The mechanism of reactivation of VZV that results in herpes zoster is unknown.

Presumably, the virus infects dorsal root ganglia during chickenpox, where it remains latent until reactivated.

The nerves most commonly affected with HZ are **C-3, T-5, L-1, and L-2.**

EPIDEMIOLOGY

Humans are the only known reservoir for VZV.

Chickenpox is highly contagious, with an attack rate of at least 90% among susceptible (seronegative) individuals.

Persons of both sexes and all races are infected equally.

The virus is endemic in the population at large; however, it becomes epidemic among susceptible individuals during seasonal peaks—late winter and early spring in the temperate zone.

The incubation period of chickenpox ranges from 10–21 days but is usually 14–17 days.

Vesicular rash occurs after 48 hrs of infection.

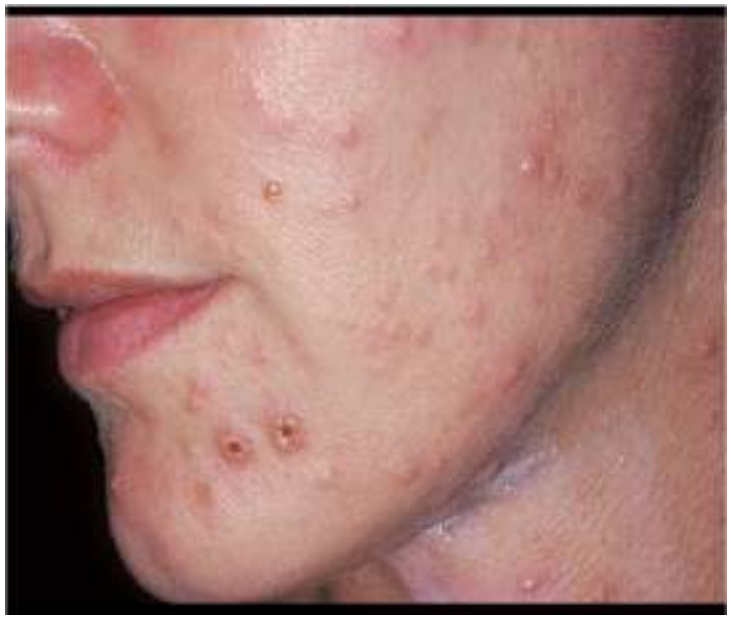
CLINICAL MANIFESTATIONS

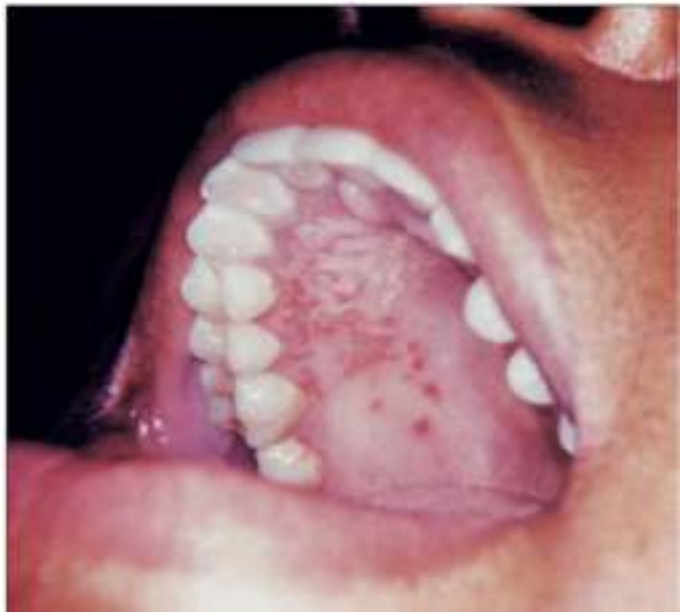
Clinically, chickenpox presents with a rash, low-grade fever, and malaise, although a few patients develop a prodrome 1–2 days before onset of the exanthema.

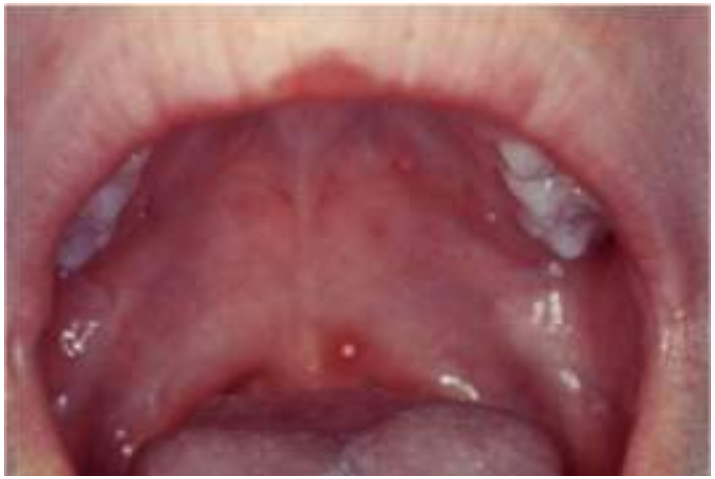
The skin lesions—the hallmark of the infection—include maculopapules, vesicles, and scabs in various stages of evolution .

Successive crops appear over a 2- to 4-day period. Lesions can also be found on the mucosa of the pharynx.

INTRA-ORALLY THE BUCCAL MUCOSA, TONGUE, PALATE, GINGIVA AND PHARYNGEAL MUCOSA ARE AFFECTED.







COMPLICATIONS

The most common infectious complication of varicella is secondary bacterial super-infection of the skin, which is usually caused by Streptococcus pyogenes or Staphylococcus aureus, including strains that are methicillin-resistant.

The most common extra-cutaneous site of involvement in children is the CNS.

HERPES ZOSTER

Herpes zoster (shingles) is a sporadic disease that results from reactivation of latent VZV from dorsal root ganglia.

Herpes zoster occurs at all ages, but its incidence is highest (5–10 cases per 1000 persons) among individuals in the sixth decade of life and beyond.

Recurrent herpes zoster is exceedingly rare except in immune-compromised hosts, especially those with AIDS.

Herpes zoster is characterized by a unilateral vesicular dermatomal eruption, often associated with severe pain.

The dermatomes from T3 to L3 are most frequently involved.

The onset of disease occur by pain within the dermatome, which may precede lesions by 48–72 h; an erythematous maculopapular rash evolves rapidly into vesicular lesions

In the normal host, these lesions may remain few in number and continue to form for only 3–5 days.

The total duration of disease is generally 7–10 days; however, it may take as long as 2–4 weeks for the skin to return to normal.

Patients with herpes zoster can transmit infection to sero-negative individuals, with consequent chickenpox.

13% of patients present with infections involving any of the three branches of the trigeminal nerve[1].

Involvement of maxillary and mandibular branches is less.(1.7% of cases)[2].

1. Millar EP, Troulis MJ. Herpes zoster of the trigeminal nerve: the dentists' role in diagnosis and treatment. J Can Dent Assoc 1994;60:450–3.

2. RagozziuoMW,Melton LJ, Kudand LT, Chu CP, Perry HO. Population based study of herpes zoster and its sequelae. Medicine 1982;61:310–16.

ORAL MANIFESTATION

Primary VZV infection presents as minor acute ulcerations in the mouth.

In recurrent VZV infection, the ophthalmic division of the trigeminal nerve is most often affected (herpes zoster ophthalmicus).

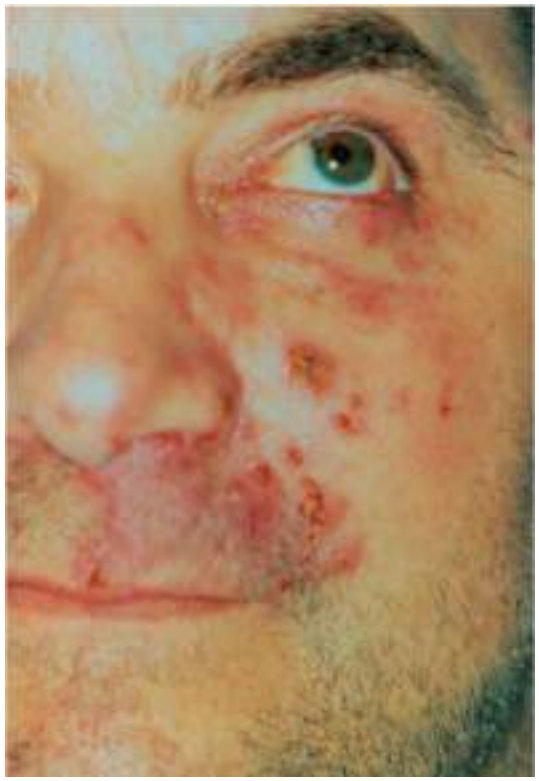
Involvement of this nerve (V) leads to lesions on the upper eyelid, forehead, and scalp with V1; midface and upper lip with V2; and lower face and lower lips with V3.

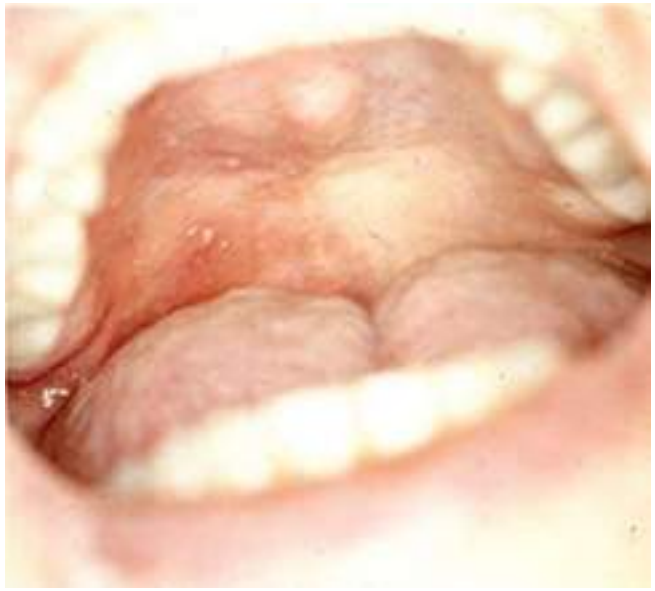
With involvement of V2, patients experience a prodrome of pain, burning, and tenderness, usually on the palate on one side.

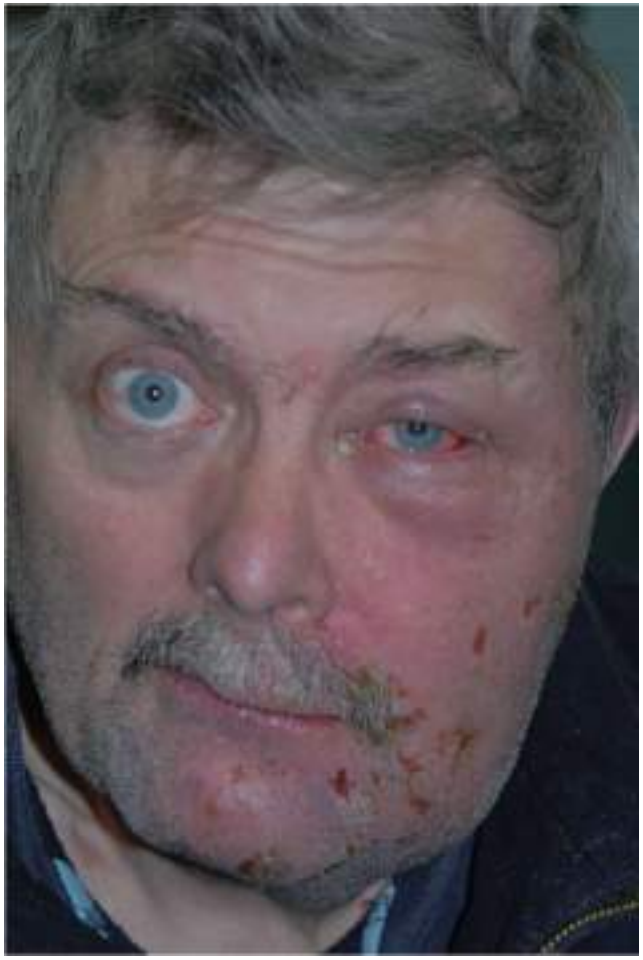
This is followed by the appearance of painful, clustered 1 to 5 mm ulcers (rarely vesicles, which break down quickly) on the hard palate or even buccal gingiva, in a distinctive unilateral distribution.

Ulcers often coalesce to form larger ulcers with a scalloped border. These ulcers heal within 10 to 14 days.

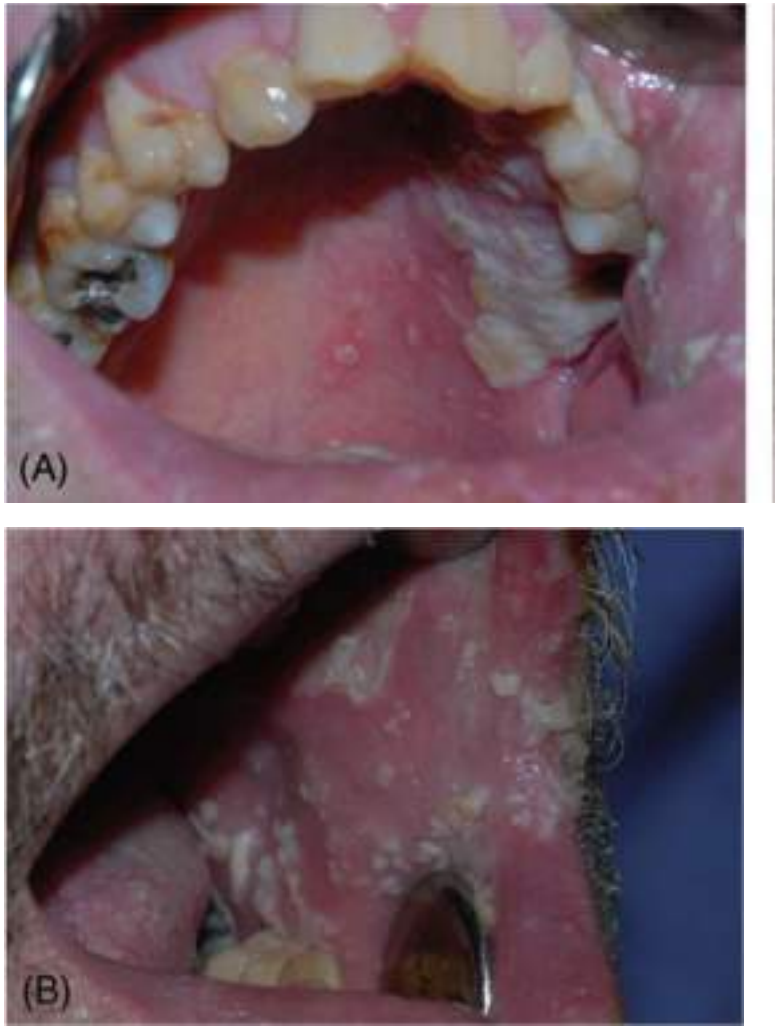
Post-herpetic Neuralgia in the oral cavity is uncommon.







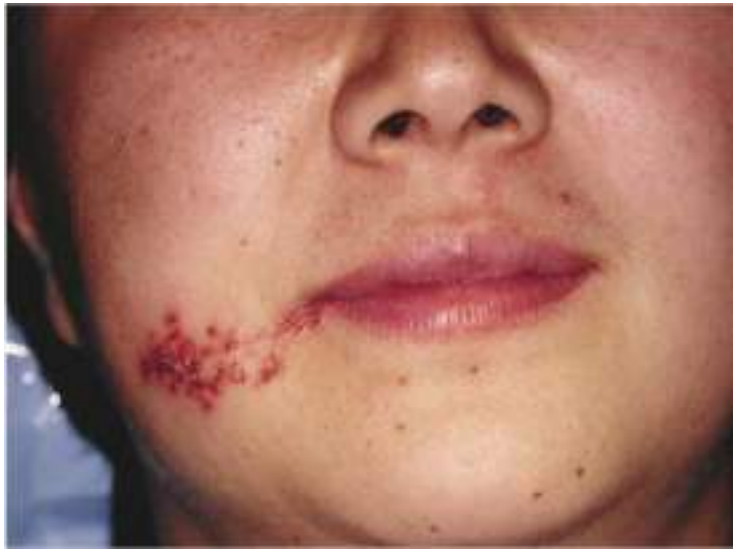
Clinical photograph demonstrating facial swelling with erythema and crusting over the distribution of the left maxillary and mandibular branches of the trigeminal nerve.

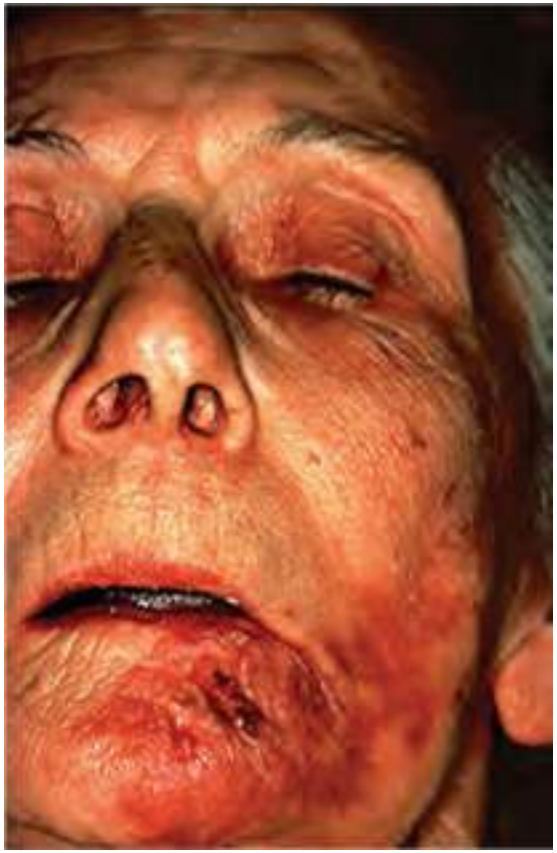


Intra-oral clinical photographs showing unilateral vesicles, ulceration, erythema, scaling and crusting affecting the hard palate (A) and buccal mucosa (B).

N. Pattni, P. HudsonJ&.M. Yates. Herpes zoster, odontalgia and nephropathy: a case report and review. Oral Surgery 4 (2011) 35–38.

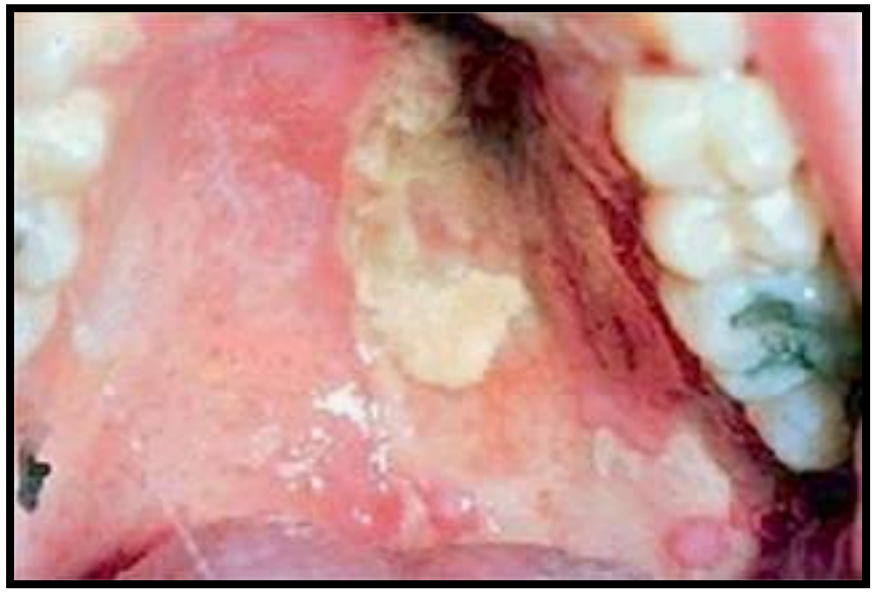
Involvement of V3 results in blisters and ulcers on the mandibular gingiva and tongue.

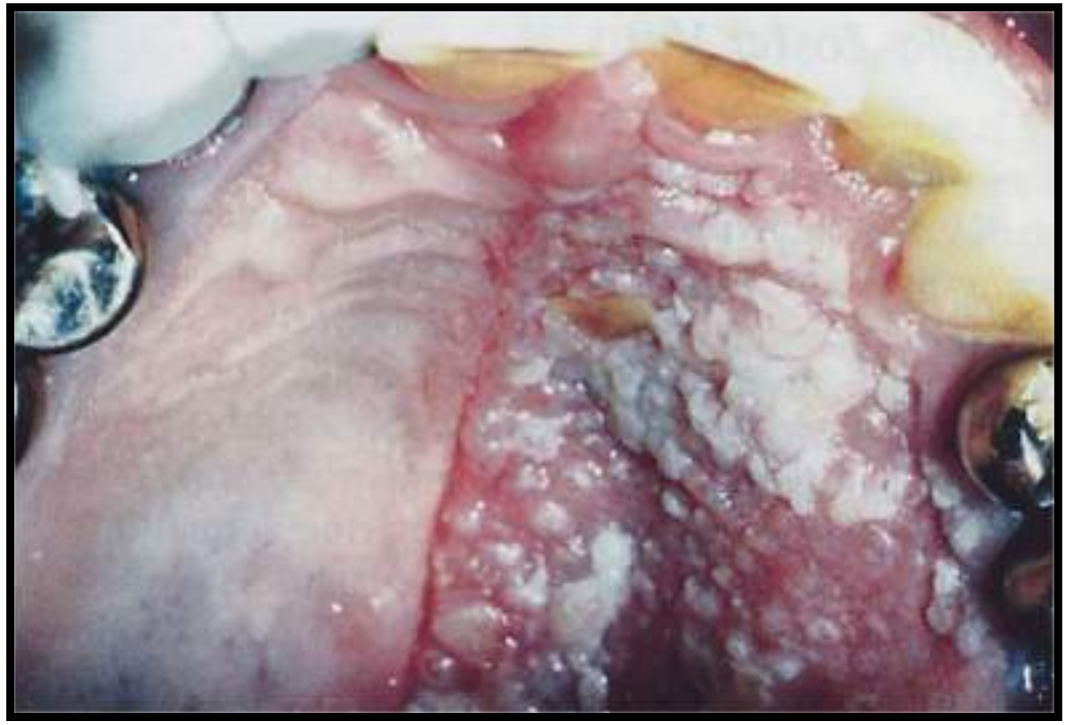


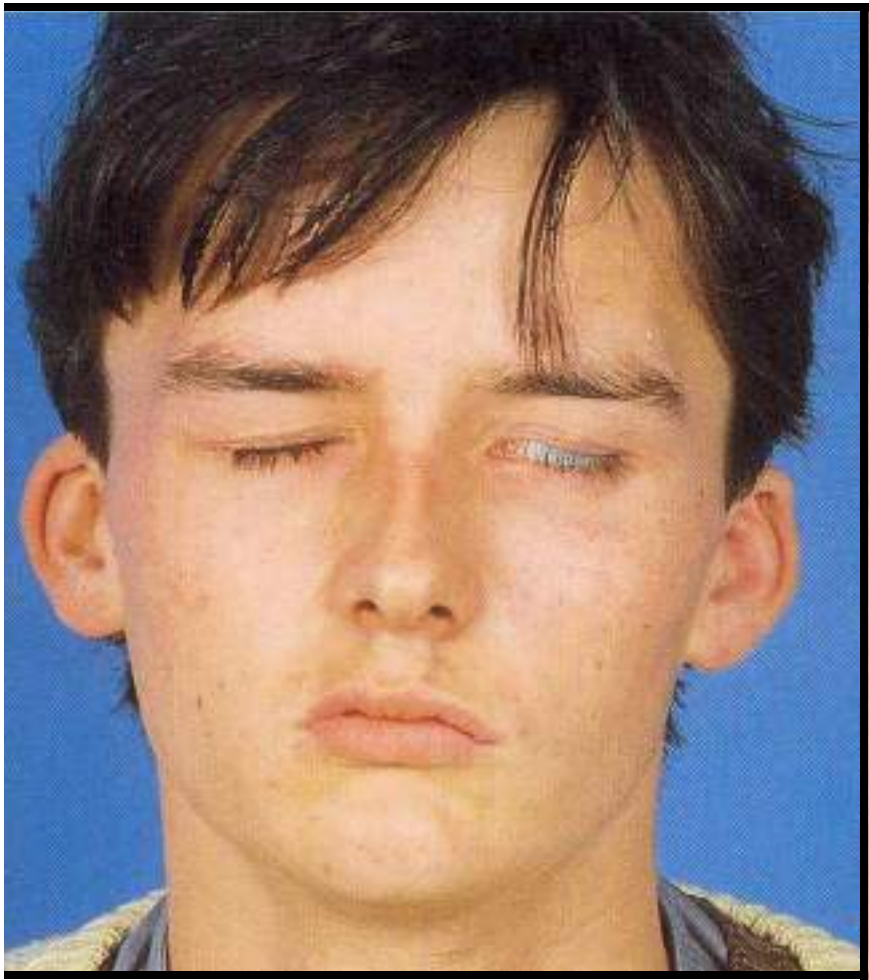


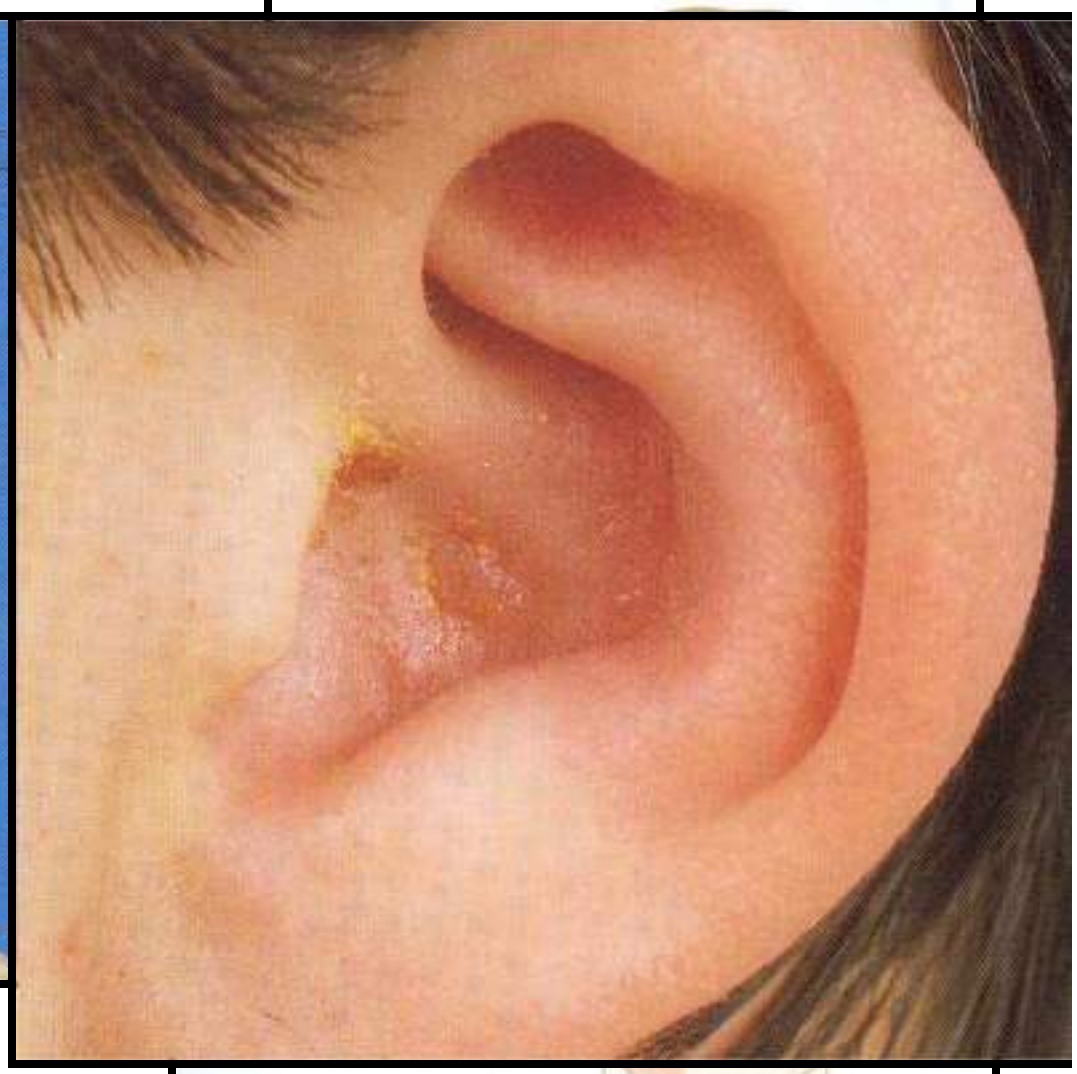
Herpes zoster infection involving the mandibular branch (V3) of the trigeminal nerve

Oral features









Mandibular

COMPLICATION

In both normal and immune-compromised hosts, the most debilitating complication of herpes zoster is pain associated with Acute Neuritis and Post-herpetic Neuralgia.

An uncommon complication of HZI involving the geniculate ganglion is Ramsay Hunt Syndrome.

Patients develop Bells Palsy, vesicles of the external ear, and loss of taste sensation in the anterior two-thirds of the tongue.

HZI has been reported to cause resorption and exfoliation of teeth and osteonecrosis of the jaw bones, especially in patients with HIV disease.

Zoster Sine Herpetica - In a few patients, characteristic localization of pain to a dermatome with serologic evidence of herpes zoster in the absence of skin lesion.

POST HERPETIC NEURALGIA

Most common complication of herpes zoster. It occurs in approximately 30 percent of patients older than 80 years and in approximately 20 percent of patients 60 to 65 years.

It is rare in patients younger than 50 years. Women are at greater risk of Post Herpetic Neuralgia.

Additional risk factors include older age, moderate to severe rash, moderate to severe acute pain during the rash, ophthalmic involvement, and history of prodromal pain.

Post Herpetic Neuralgia may persist from 30 days to more than six months after the lesions have healed, and most cases resolve spontaneously.

Replication of the Varicella zoster virus in the basal ganglia destroys the nerves, leading to pain in the affected dermatome.

LABORATORY DIAGNOSIS FOR HSV & HZV

Laboratory tests are require to diagnose atypical presentations of HSV infections.

These tests should be used when evaluating immune-compromised patients with atypical lesions.

For HZV diagnosis is made clinically however, atypical presentations may require laboratory testing for confirmation of VZV.

LABORATORY DIAGNOSIS FOR HSV & HZV

HSV	HZV
TZANCK SMEAR – show multi-nucleated giant cells or intra-nuclear inclusions. (SENSITIVITY – LOW < 30%)	**TZANCK SMEAR** multinucleated epithelial cells.
It does not distinguish between HSV or VZV.	It can not distinguish between HSV and VZV.
BIOPSY - Infected epithelial cells exhibit acantholysis, nuclear clearing, and nuclear enlargement, known as ballooning degeneration. Intercellular edema, intraepithelial vesicle formation.	**BIOPSY**- VZV is cytopathic to epithelial cells and therefore it results in multinucleated epithelial cells. It is not diagnostic test and not required.

LABORATORY DIAGNOSIS FOR HSV & HZV

HSV	HZV
Polymerase chain reaction	**Polymerase chain reaction**
It can detect HSV antigen three to four times more often than culture.	Detect viral antigen,
Expensive and detects antigen and not whole infectious particles, so a positive PCR test for HSV does not equate with active infection	Costly, available in few labs

LABORATORY DIAGNOSIS FOR HSV & HZV

HSV

Direct fluorescent antigen detection test

Specimen is incubated with fluorescein isothiocyanate–labeled HSV type-specific monoclonal antibody .

More accurate than routine cytology.

Sensitivity is 80%, the specificity is 98% to 100%.

HZV

Direct fluorescent antigen detection test

This test uses a smear obtained by scraping the lesion and staining it with antibody against VZV conjugated to a fluorescent compound.

It have greater sensitivity.

LABORATORY DIAGNOSIS FOR HSV & HZV

HSV

Antibody titre - Elevated Ig M titers followed several weeks later by permanent Ig G titers that indicate previous infection but confer no protection against reactivation.

Recurrent infection is associated with a rise in Ig G antibody titer in acute and convalescent sera, but a four fold rise (a criteria that indicates active infection) is seen in only 5% of patients.

The assay for HSV Ig M is not particularly reliable for diagnostic purposes and routinely not done.

HZV

Antibody titre–After primary infection, the patient seroconverts and Ig G against VZV is detectable in the serum. HZI causes a transient

Rise in Ig M and an increase in levels of Ig G, but these are not reliable for diagnostic purposes.

LABORATORY DIAGNOSIS FOR HSV & HZV

HSV

Cell Culture - HSV isolation by cell culture is the gold standard test for the diagnosis for HSV-1 infections.

Advantages:-

High sensitivity and specificity

Allows for amplification of virions, sub-typing.

Testing for sensitivity to antiviral drugs.

Disadvantages:-

Needs specialized equipment,

Expensive,

Take up to several days for a final result.

May give false positive results.

HZV

Cell Culture – same as HSV

Confirmatory diagnostic test.

MANAGEMENT OF HSV & HZV

Management is directed toward pain control, supportive care, and definitive treatment .

Pain Control and Supportive Care Measures

2% viscous lidocaine (swish and spit out 5 mL 4–5 times/d)

Liquid diphenhydramine (swish and spit out 5 mL 4–5 times/d)

Combination of viscous lidocaine, diphenhydramine, and a covering agent (such as Kaopectate or Maalox) in 1:1:1 ratio

0.1% diclonine hydrochloride

Benzydamine

Supportive care

Hydration

Ice chips

Soft bland diet

FOR HSV

Recommended dosages of antiviral medication for treatment of **RHL**

	Acyclovir	Valacyclovir
Dose	400 mg	2000 mg
Frequency	4/day	2/day
Duration	5 days	1 days

Recurrent HSV in immune-compromised patients: Famciclovir - 125 mg bid for 5 d

TREATMENT: VARICELLA-ZOSTER VIRUS INFECTIONS

For immunologically normal host-

Good hygiene includes daily bathing and soaks.

Secondary bacterial infection of the skin can be avoided by meticulous skin care, particularly with close cropping of fingernails.

Pruritus can be decreased with topical dressings or the administration of antipruritic drugs.

Tepid water baths and wet compresses are better than drying lotions for the relief of itching.

Aluminum acetate soaks for soothing and cleansing

Administration of aspirin to children with chickenpox should be avoided because of the association of aspirin derivatives with the development of Reye's syndrome.

Acyclovir (800 mg by mouth five times daily),

Valacyclovir (1 g three times daily),

Famciclovir (500 mg three times daily) for 5–7 days is recommended for adolescents and adults with chickenpox of 24 h duration

For severely Immuno-compromised hosts

IV Acyclovir 10 mg/kg every 8 h for 7 days

For low-risk Immuno-compromised hosts, oral therapy with Valacyclovir or Famciclovir appears beneficial.

Along with the anti-virals, pain control measures should be given in debilitating pain of acute herpes zoster.

Mild to moderate pain may be controlled with acetaminophen or non-steroidal anti-inflammatory drugs, alone or in combination with a weak opioid or tramadol (Ultram).

Moderate to severe pain requires scheduled opioids (e.g., oxycodone, morphine).

If does not respond to opioids, adjunctive therapy should be considered. Nortriptyline (Pamelor), gabapentin (Neurontin), and pregabalin (Lyrica) have been recommended.

For management of Post-Herpetic Neuralgia

Pain reduction during the acute phase of herpes zoster may stop the initiation of the mechanisms that cause chronic pain, thus reducing the risk of Post Herpetic Neuralgia.

Julia Fashner, Amanda L.Bell; American Family Physician; Volume 83, Number 12, 2011.

Class	Medications	Doses
Anticonvulsants	Gabapentin (Neurontin)	1,800 to 3,600 mg per day
	Pregabalin (Lyrica)	150 to 600 mg per day
Opioids	Controlled-release oxycodone (Oxycontin)	Variable
	Long-acting morphine	Variable
	Tramadol (Ultram)	100 to 400 mg per day
Topical agents	Capsaicin 0.075% cream (Zostrix)	Applied three or four times per day
	Lidocaine 5% patch (Lidoderm)	Maximum three patches per day
Tricyclic antidepressants	Amitriptyline	Up to 150 mg per day
	Desipramine (Norpramin)	Up to 150 mg per day
	Nortriptyline (Pamelor)	Up to 150 mg per day

Julia Fashner, Amanda L.Bell; American Family Physician; Volume 83, Number 12, 2011.

PREVENTION OF HZV

First, a live attenuated varicella vaccine (Oka) is recommended for all children >1 year of age (up to 12 years of age) who have not had chickenpox and for adults known to be sero-negative for VZV.

For >60 years of age, a VZV vaccine with 10 times the viral content of the Oka vaccine is used.

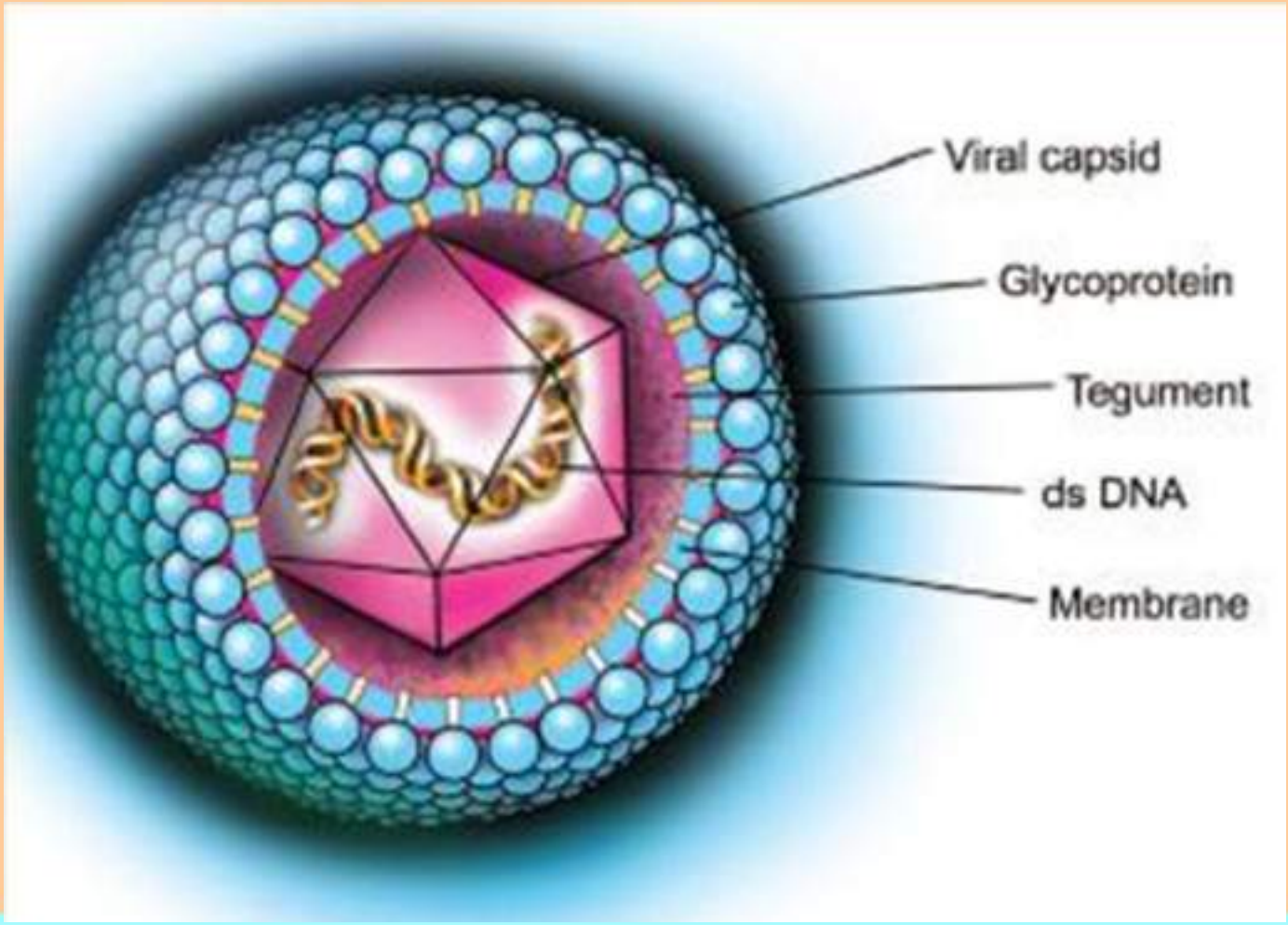
It decreases the incidence of shingles by 51% & the incidence of Post Herpetic Neuralgia by 66%.

Harrision 's principles of internal medicine. 18th edi.

CYTOMEGALOVIRUS (CMV) INFECTION

CYTOMEGALOVIRUS

B-herpesvirus, Double-strand DNA, Four species of m RNA, protein capsid, and lipoprotein envelope



EPIDEMIOLOGY

Communal living and poor personal hygiene facilitate early spread.

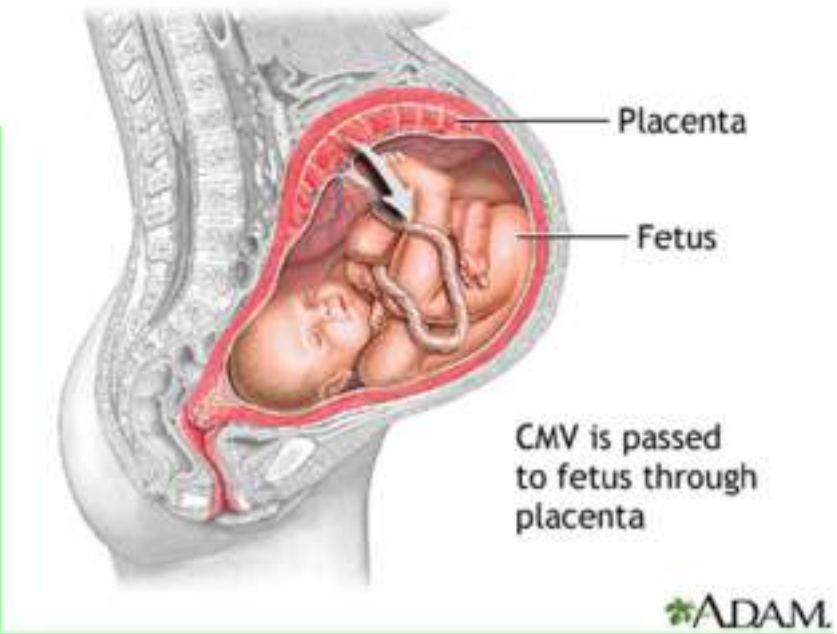
It is common in Peri-natal and early childhood.

CMV may be present in breast milk, saliva, feces, urine, semen, cervical secretions.

Transmission

Transmission occurs among young children in day-care centers.

From Infected child to family members.



It does not readily spread by casual contact but rather requires repeated intimate exposure for transmission.

Sexual transmission also occurs, and asymptomatic carriage is common.

Reactivation

Once infected, an individual generally carries CMV for life.

The infection usually remains silent and establishes latency within the connective tissue cells, such as the endothelium of blood vessels, mononuclear cells, white blood cells, and epithelial cells.

Reactivation occur when T lymphocyte–mediated immunity is compromised.

Like after organ transplantation, in association with lymphoid neoplasms and acquired immune-deficiencies

It is the most common cause of pneumonia within the first 120 days after hematopoietic stem cell transplantation

CLINICAL FINDINGS

Primary CMV infection

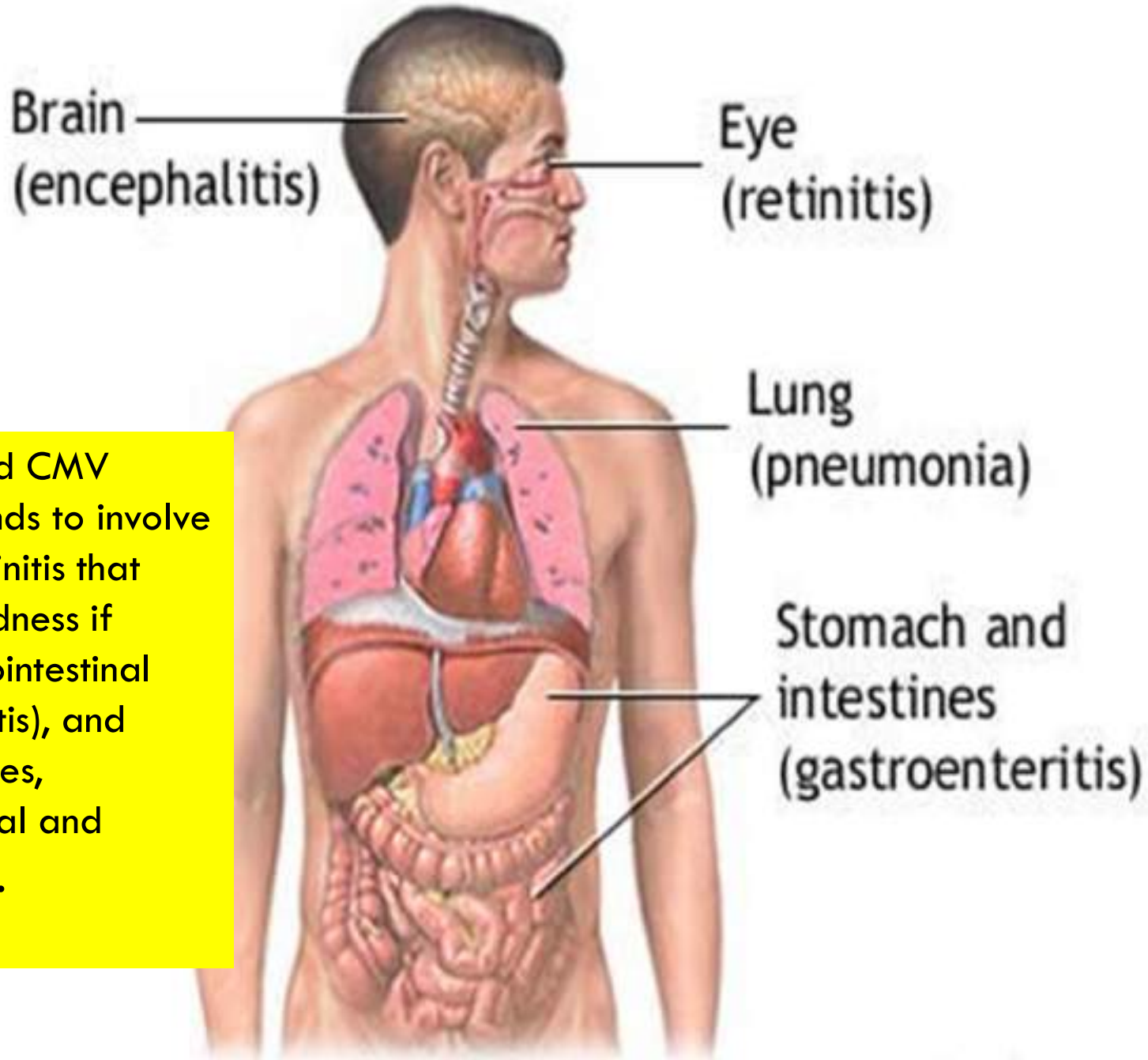
In healthy children and adults, it is asymptomatic.

Clinical symptoms include fever, myalgia, cervical lymphadenopathy, and mild hepatitis, lymphocytosis.

20% of patients with infectious mononucleosis–like symptoms have CMV rather than EBV infection.

Serious Complications include meningoencephalitis, myocarditis, and thrombocytopenia.

In AIDS associated CMV patients, CMV tends to involve the eye (CMV retinitis that may result in blindness if untreated), gastrointestinal tract (CMV enteritis), and mucocutaneous sites, especially perianal and perigenital areas.



ORAL MANIFESTATIONS

CMV infection in the mouth occur in the immune-compromised patient.

It present as a single large necrotic ulcer and less often as multiple ulcers.

They are usually painful and may have been present for weeks or months. Any site may be involved.

One-third are co-infected with HSV and VZV.

Co-infection of oral ulcers with both HSV and CMV has been reported in AIDS patients.

In immune-compromised adults, salivary gland enlargement is a common finding with this disease.

Cases of mandibular osteomyelitis and tooth exfoliation associated with CMV and VZV infection are been reported.

- ✓ Both viruses are associated with vasculopathy and thrombosis, which may be the underlying etiopathogenesis.

Reports indicate that genomes of CMV are frequently detected in several different types of periodontal disease

Eric T. Stoopler.Oral herpetic infections (HSV 1–8). Dent Clin N Am 49 (2005) 15–29

DIFFERENTIAL DIAGNOSIS

HSV or VZV infections in the Immuno-compromised patients.

In patients with (HIV)/AIDS, infections with mycobacteria, fungi, and other organisms

Squamous cell carcinoma

Traumatic ulcerative granuloma

Ulcerated benign or malignant salivary gland tumor or soft tissue tumor.

Burket 11th edition

LABORATORY TESTS

Cell culture – may or may not be positive

Because CMV infections of the oral cavity presenting as ulcers tend to be deep with viral particles residing in endothelial cells and tissue monocytes.

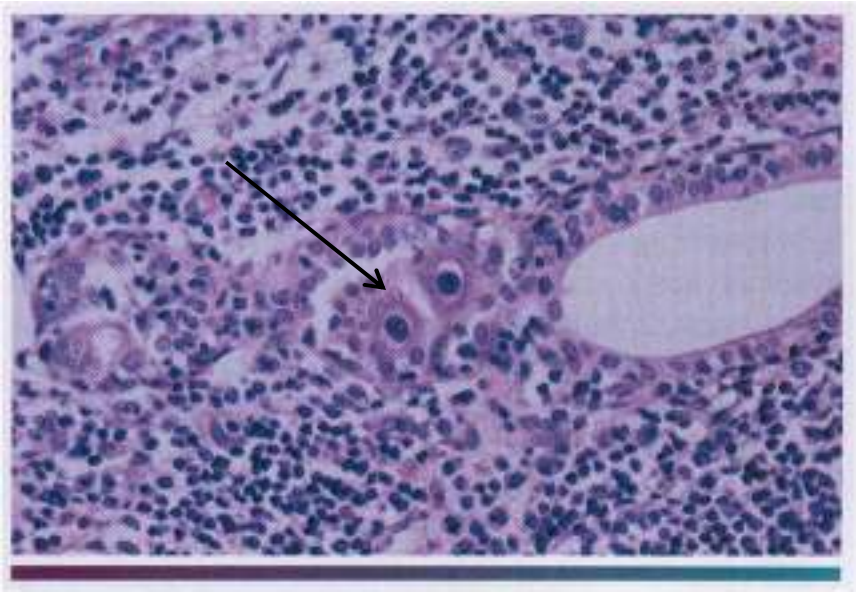
Systemic infection are detected by blood culture using “shell vials” of cultured cells in which CMV antigens are detected through the use of monoclonal Antibodies .

BIOPSY

Biopsy of intraoral CMV lesions shows changes within the vascular endothelial cells.

Scattered infected cell are extremely swollen showing both intracytoplasmic and intranuclear inclusions and prominent nucleoli.

This enlarged cell has been called an "owl eye" cell.



Salivary ductal epithelium with owl eye appearance

Neville 2nd edition
DCNA- 2005

MANAGEMENT

For Pain topical anaesthetics and systemic analgesics, with appropriate dietary modifications and good hydration are advised.

Ganciclovir, Valganciclovir or cidofovir.[5 mg/kg weekly for 2 weeks]

COXSACKIEVIRUS INFECTION

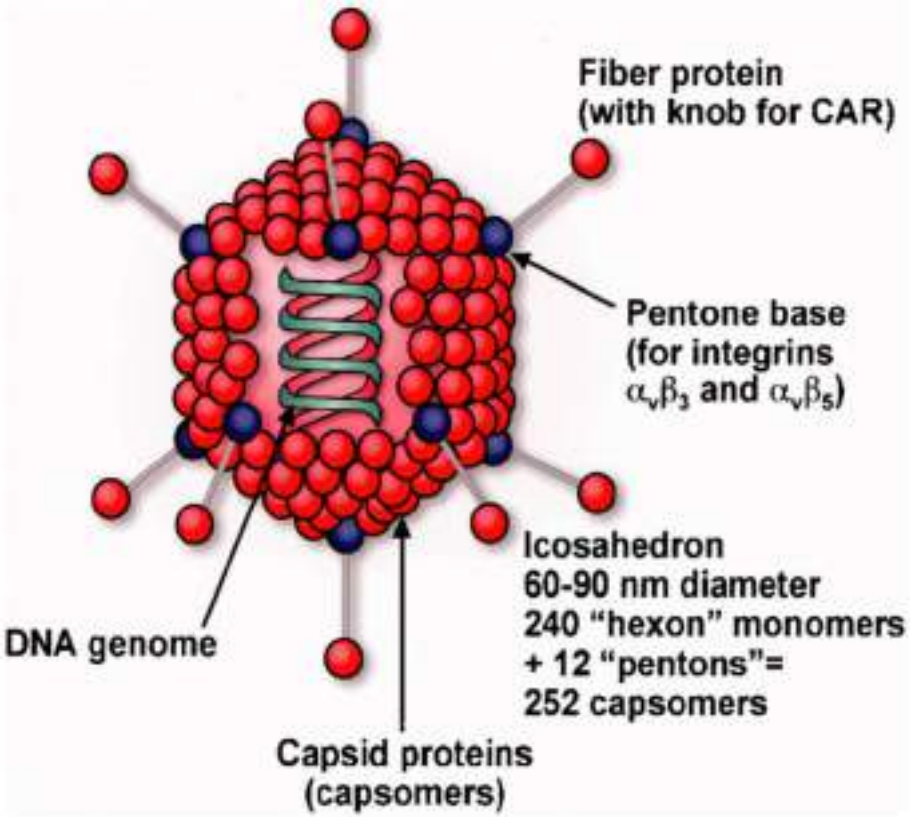
COXSACKIE VIRUS

RNA virus,

Genus – Enterovirus

Family – Picornaviridae

Human enteroviruses contain a single-stranded RNA genome surrounded by an icosahedral capsid comprising four viral proteins.



Enteroviruses encompass 96 human serotypes:

3 serotypes of poliovirus,

23 serotypes of coxsackievirus A,

6 serotypes of coxsackievirus B.

These viruses have no lipid envelope and are stable in acidic environments, including the stomach.

They are susceptible to chlorine-containing cleansers but resistant to inactivation by standard disinfectants (e.g., alcohol, detergents) and can persist for days at room temperature.

The viruses replicate first in the mouth and then in the lower gastrointestinal tract, where they shed.

TRANSMISSION OF COXSACKIE VIRUS

The viruses replicate first in the mouth and then extensively in the lower gastrointestinal tract, where they shed.

Therefore. transmission is by the fecal-oral route, and some shedding occurs in the upper respiratory tract.

CVA & CBV

CVA infection is implicated in paralytic disease, a cold-like illness and upper respiratory tract infection that is usually febrile, and pleurodynia.

CVB (in particular CVB4) infection is associated with the development of aseptic meningitis, sometimes complicated by encephalitis, carditis, and disseminated neonatal infection.

CBV has been implicated in the pathogenesis of type 1 insulin-dependent diabetes mellitus.

One theory suggests direct destruction of the pancreatic islets by the virus, whereas another focuses on the viral infection triggering an autoimmune destruction of islet cells because of similarity between viral and islet cell antigens.

CVB4 has also been implicated in the pathogenesis of primary Sjögren syndrome.

Enteroviral capsid protein VP1 was identified in the salivary gland samples with primary but, not in secondary Sjögren syndrome.

ORAL CAVITY

In the oral cavity, Coxsackie Virus infections lead to three disease entities:

Hand Foot & Mouth disease (HFM),

Herpangina, and

Lymphonodular pharyngitis.

HAND-FOOT-AND-MOUTH DISEASE (HFM)

Enterovirus (EV)71 related to CVA 16 is a common cause of HFM disease and has been seen in large outbreaks in Southeast Asia.

HFM disease, herpangina, are seasonal (usually summer), occurs in epidemic clusters, and has high transmission rates.

CLINICAL FINDINGS - HFM

HFM disease affects children <10 years in summer.

Low-grade fever and sore mouth; 75 to 100% of patients have a skin rash, especially on the hands and feet (dorsa, palms and soles) and 30% on the buttocks.

The rash is first red and macular and then becomes vesicular.

ORAL MANIFESTATIONS- HFM

Patients are febrile and complain of a sore mouth and throat.

Lesions begin as erythematous macules that become vesicles and quickly break down to ulcers.

Site- Tongue,

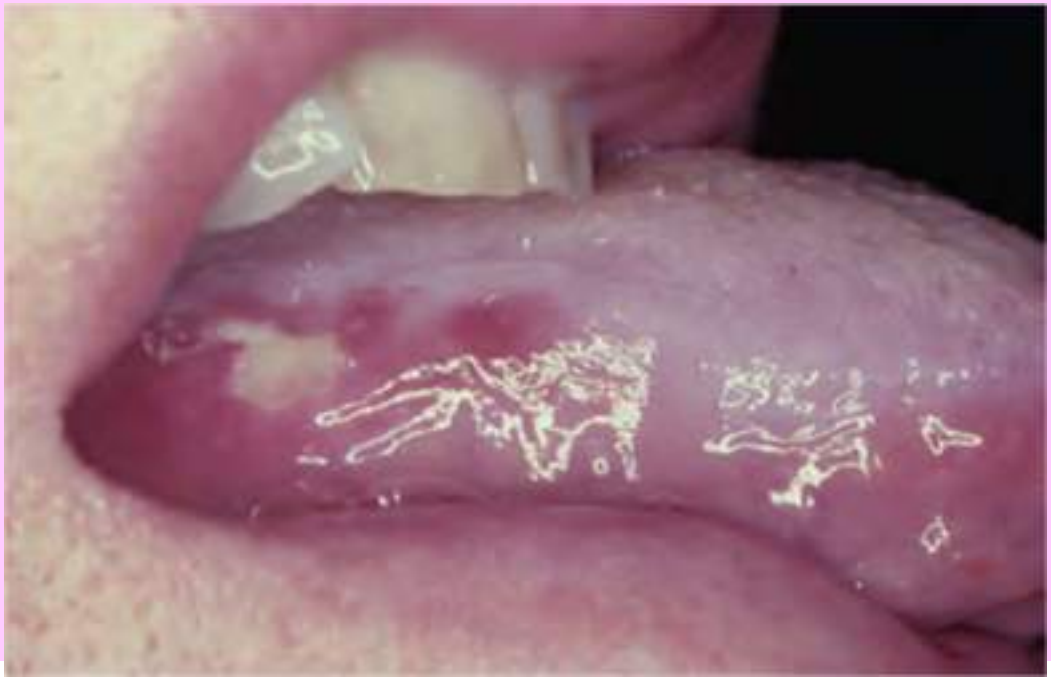
hard & soft palate,

and buccal mucosa

but can present on

any oral mucosal

surface.



HERPANGINA

The word herpangina derives from herpes, meaning "vesicular eruption," and angina, meaning "inflammation of the throat."

CVA (serotypes 1–10, 16, and 22) are the most common viruses isolated from this disease. But C VB1 echoviruses, and E V71 have also been identified in this condition.

CLINICAL FINDINGS- HERPANGINA

As with all CV infections, children under 10 are usually affected and outbreaks usually occur in epidemics in summer.

Patients develop fever, headache, and myalgia that usually last only 1 to 3 days.

Lymphonodular pharyngitis is considered a variant of herpangina and is associated with CVA10.

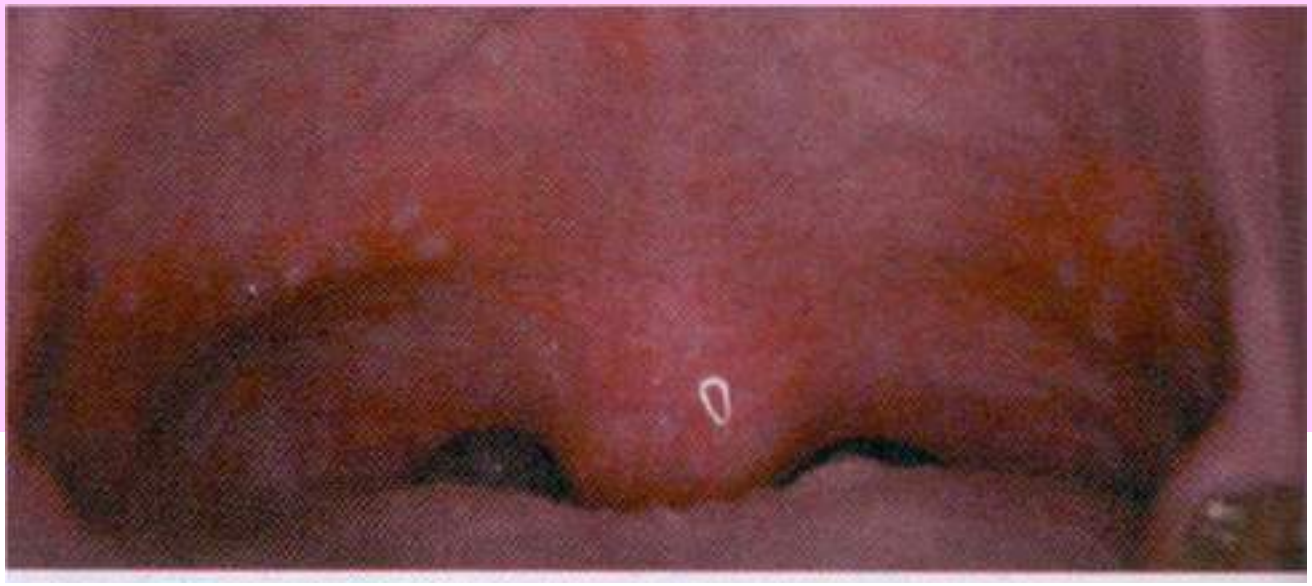
Patients report a sore throat, but rather than presenting with vesicles that break down to ulcers, patients develop diffuse small nodules in the oropharynx.

ORAL MANIFESTATIONS

The first oral symptoms of herpangina are sore throat and pain on swallowing.

There may be erythema of the oropharynx, soft palate, and tonsillar pillars.

Small vesicles form, but these rapidly break down to 2 to 4 mm ulcers. These persist for 5 to 10 days .



LABORATORY TESTS

CVB infections may be diagnosed by culture (usually from the throat or feces), but only CVA9 and CVA16 grow readily.

C VA is best identified by inoculation into newborn mice.

Serum IgM to CVB can be detected early on but is not serotype specific.

Reverse transcriptase PCR is also sensitive and rapid way of identifying viral RNA in clinical specimens.

Diagnosis is usually made on clinical findings, and culture and biopsies are rarely necessary for diagnosis.

Skin biopsies of HFM disease and herpangina show intraepidermal vesicles with a mixed lymphocytic and neutrophilic infiltrate, degeneration of epidermal cells, and dermal edema.

Biopsy of lymphonodular pharyngitis shows hyperplastic lymphoid nodules.

MANAGEMENT

Self-limiting (unless complications arise or the patient is immunocompromised),

Management is directed toward control of fever and mouth pain.

Supportive care, and limiting contact with others to prevent spread of the infection.

Effective antiviral agents for CV are not available.

ERYTHEMA MULTIFORME

ERYTHEMA MULTIFORME (EM)

EM is an acute, self-limited, inflammatory mucocutaneous disease that manifests on the skin and often oral mucosa, although other mucosal surfaces, such as the genitalia, may also be involved.

EM is classified as

- ***EM minor*** - if there is less than 10% of skin involvement and there is minimal to no mucous membrane involvement,

- ***EM major*** - It has more extensive but still characteristic skin involvement, with the oral mucosa and other mucous membranes affected.

ETIOLOGY

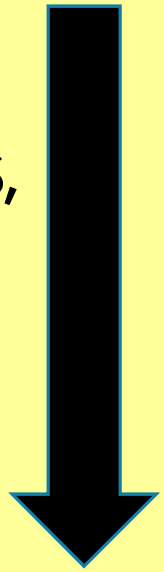
EM is a hypersensitivity reaction, and the most common inciting fac

It is

bac

LIST OF DRUG

SULFONAMIDES;
TRIMETHOPRIM-SULFAMETHOXAZOLE,
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS,
PENICILLINS,
ANTI-CONVULSANTS :-
BARBITURATES AND CARBAMAZEPINE,
HYDANTOINS,
VALPROIC ACID,
ALLOPURINOL, AND
TERBINAFINE



Recurrent EM is associated with HSV infection in 65 to 70% of cases.

It is postulated that HSV antigens incite a T cell–mediated delayed-type hypersensitivity reaction that generates interferon-c, with the amplified immune system.

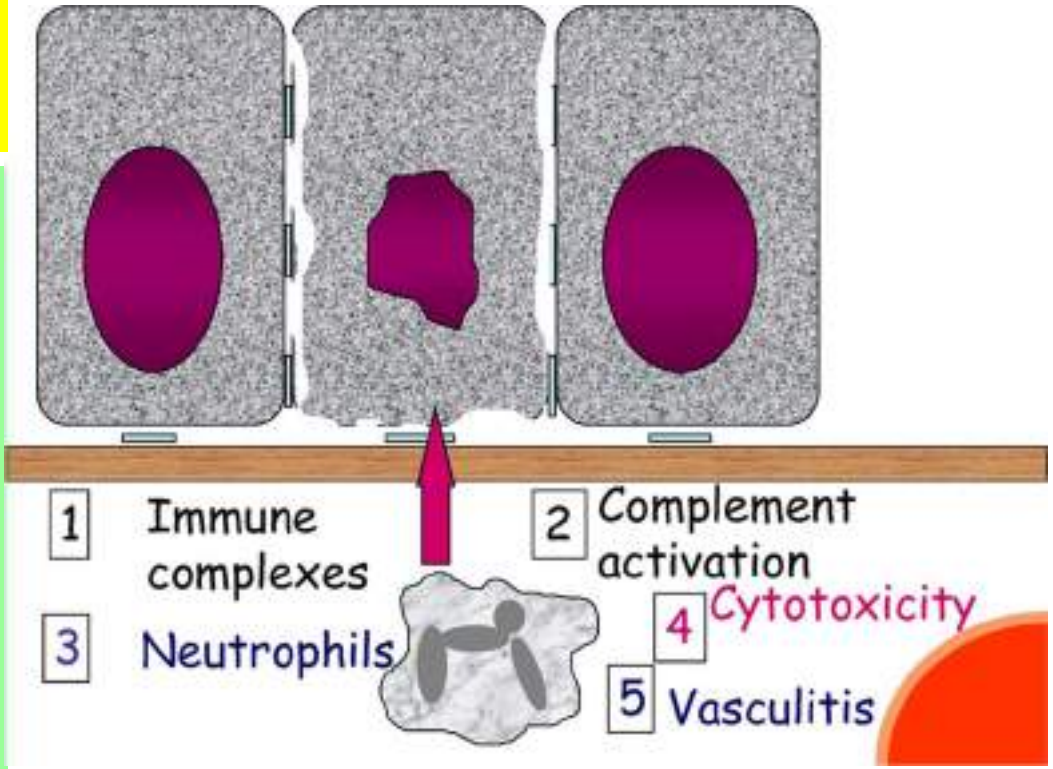
That recruit more T cells to the area. Cytotoxic T cells, natural killer cells, and/or cytokines destroy the epithelial cells.

In contrast to EM, drugs precipitate 80% to 95% of the cases of TEN and more than 50%of cases of SJS

Pathogenesis

EM result from a T-cell-mediated immune reaction.

It leads to a cytotoxic immunological attack on keratinocytes that express non-self antigens, with subsequent sub-epithelial and intra-epithelial vesiculation; this leads to widespread blistering and erosions.



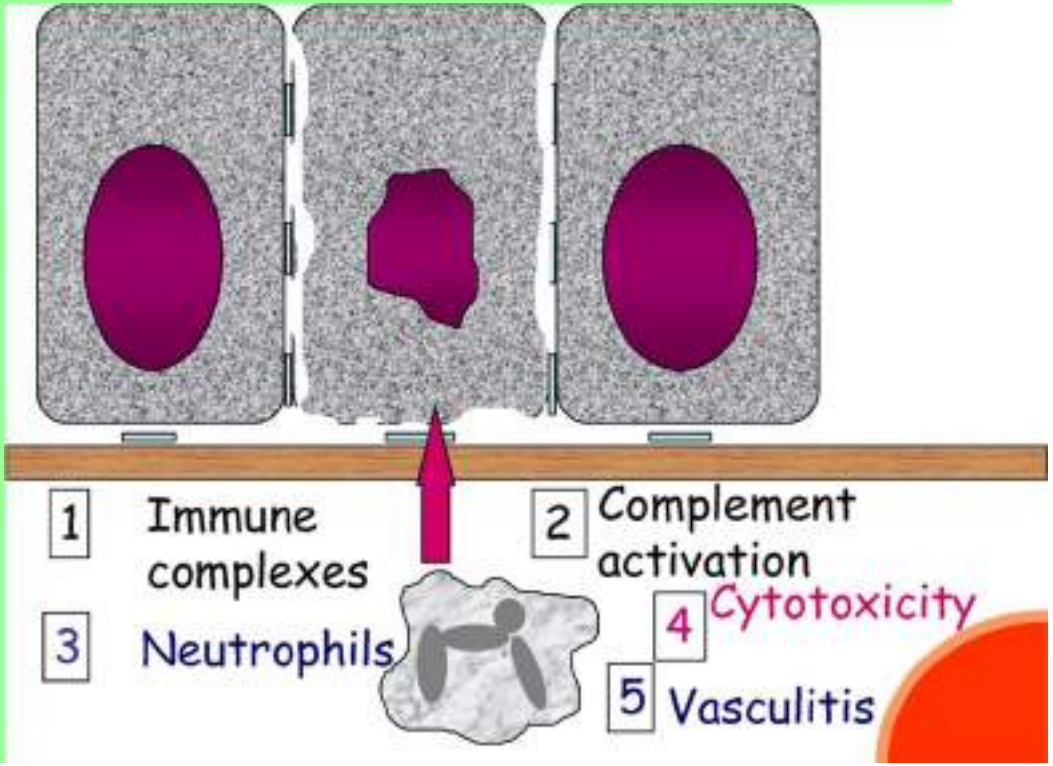
Pathogenesis

The pathogenesis is divided into three steps:

1. The formation of antigen-antibody complex in circulation,

2. The deposit of immune complex in numerous tissues, and

3. The appearance of inflammatory reaction in many parts of the body.

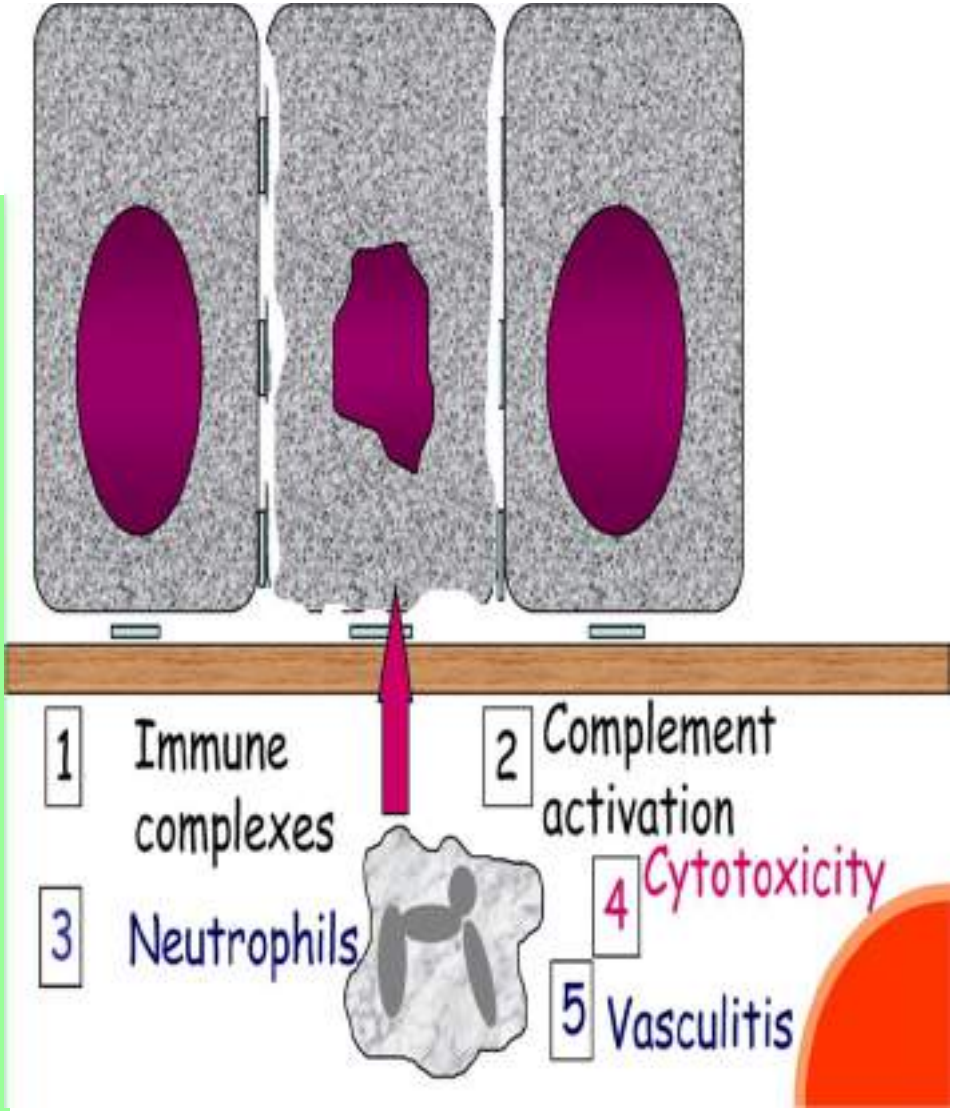


Pathogenesis

First stage, when antigen enters the body, specific antibody will be produced. And then in the circulatory system these two form antigen-antibody complex.

If the antigen could not be eliminated or phagocyte cells fail to do its function, antigen will be in the circulation for a longer time.

This situation can also be caused by malfunctioned macrophage, leading to deposition of immune complex in many parts and causing **vasculitis**

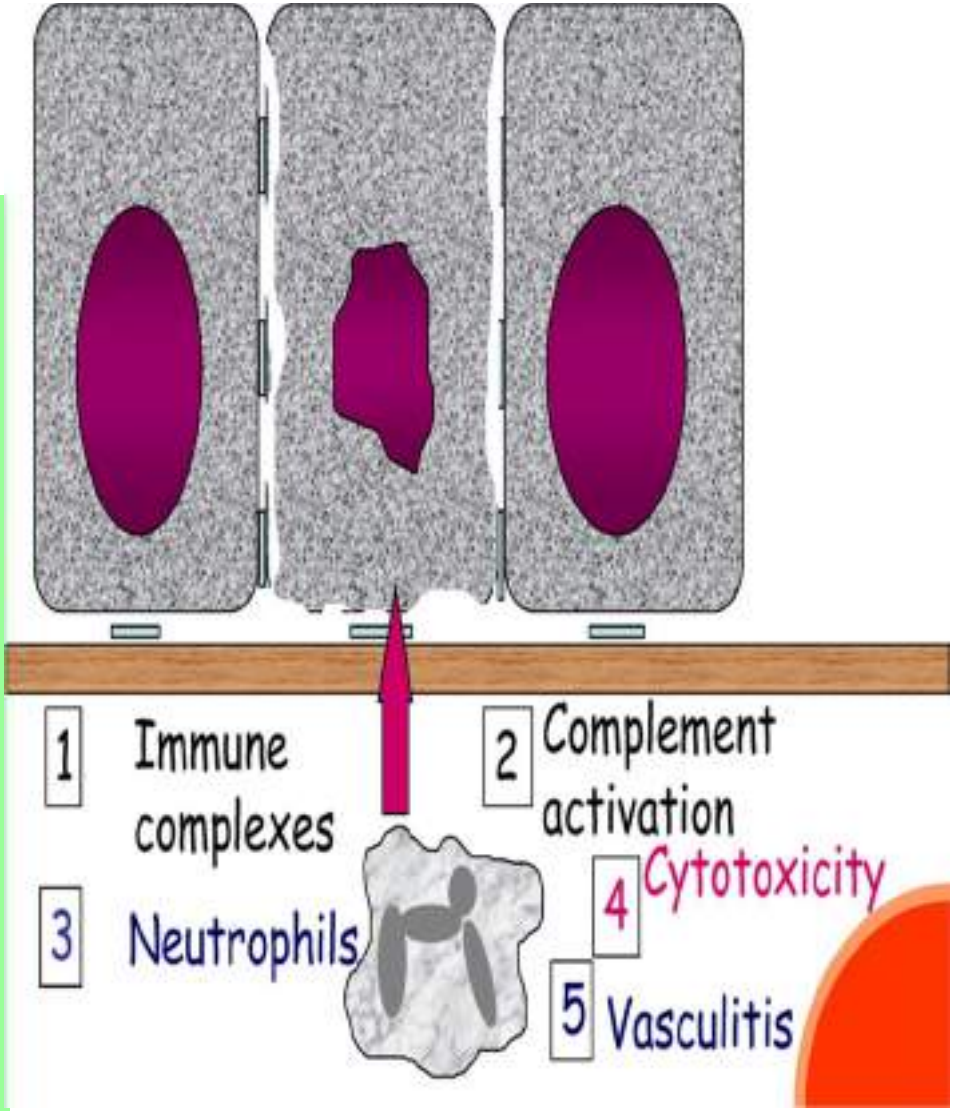


Maharani Laillyza Apriasari and Retno Pudji Rahayu. Dent. J. (Maj. Ked. Gigi), Vol. 42. No. 4 October–December 2009: 159-

Pathogenesis

Immune complex which leave circulation and deposit inside or outside blood vessel wall, will cause the increase of blood vessel permeability.

This condition is marked by immune complex which bound with inflammatory cells through Fc and C3b receptors and trigger the release of vasoactive and cytokine mediators.



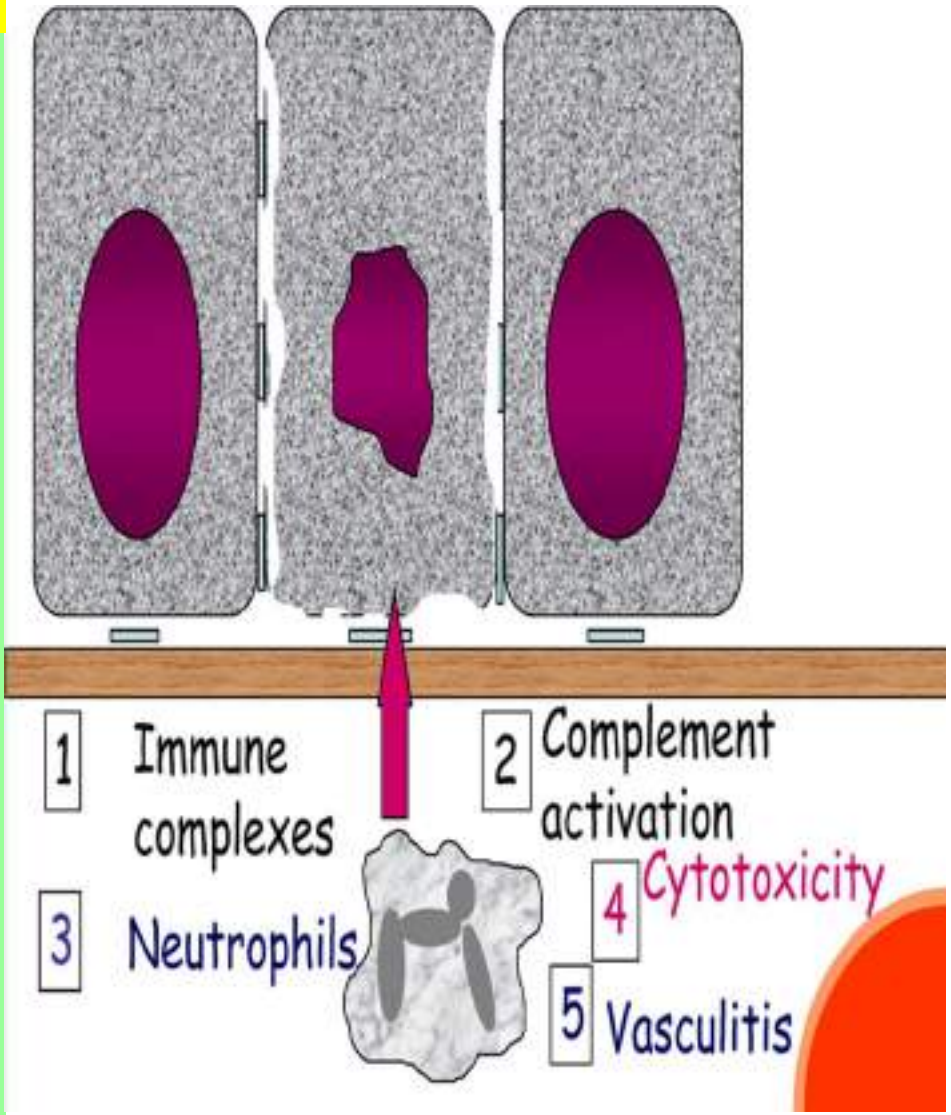
Maharani Laillyza Apriasari and Retno Pudji Rahayu. Dent. J. (Maj. Ked. Gigi), Vol. 42. No. 4 October–December 2009: 159-

Pathogenesis

Sometimes, when immune complex deposit within the tissues, third inflammatory reaction occurs.

In this stage symptoms such as fever, urticaria, arthralgia, and lymphoid gland expansion occurs.

It happens in the beginning of erythema multiforme to quickly appear its clinical manifestation, but the prodromal symptoms which precede it may not as severe as in diseases of viral infections.



Severe erythema multiforme (major type) is mostly caused by autoimmune process.

The formation of autoantibody could happen through several mechanisms.

They are cross reaction, virus, drugs, synthetic error or abnormal lysosome which modify body constituent molecule into autoantigen.

HAEM & Drug-induced EM

HAEM - it is most likely that HSV—DNA fragments in the skin or mucosa precipitate the disease. CD4+ cells transport fragments of HSV to the epithelium, and T cells accumulate in response to HSV antigens and damage cells.

Drug-induced EM - it is thought that reactive drug metabolites induce the disease. And keratinocyte apoptosis is induced by tumour necrosis factor alpha (TNF) that is released from keratinocytes, macrophages, and monocytes causes the tissue damage.

CLINICAL FINDINGS

Age – 20 – 40 years with 20% occurring in children

Patients with recurrent EM have an average of 6 episodes a year (range 2–24), with a mean duration of 9.5 years; remission occurred in 20% of cases.

Symptoms- Prodrome of fever, malaise, headache, sore throat, rhinorrhea, and cough. This suugest the viral etiology.

Oral lesions are present in 23 to 70% of patients with recurrent EM.

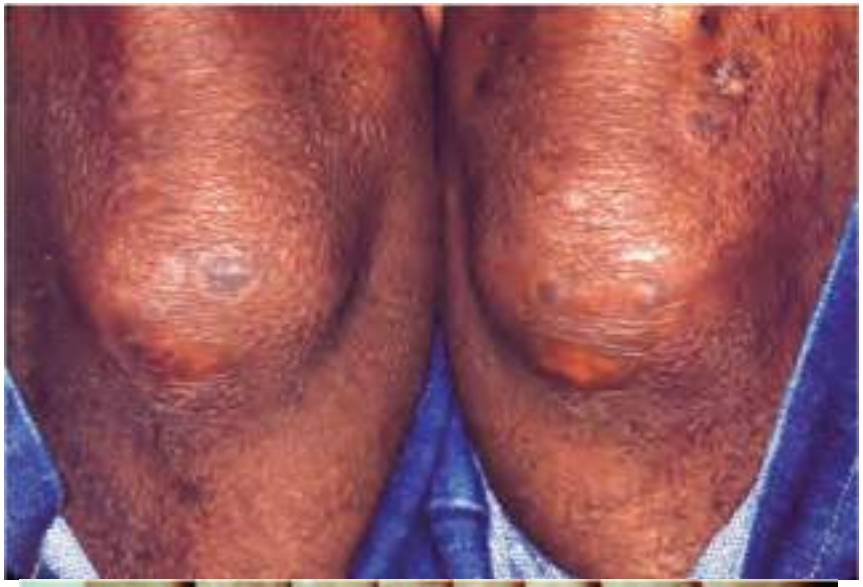
The most commonly affected sites are the lips (36%), buccal mucosa (31%), tongue (22%), and labial mucosa (19%).

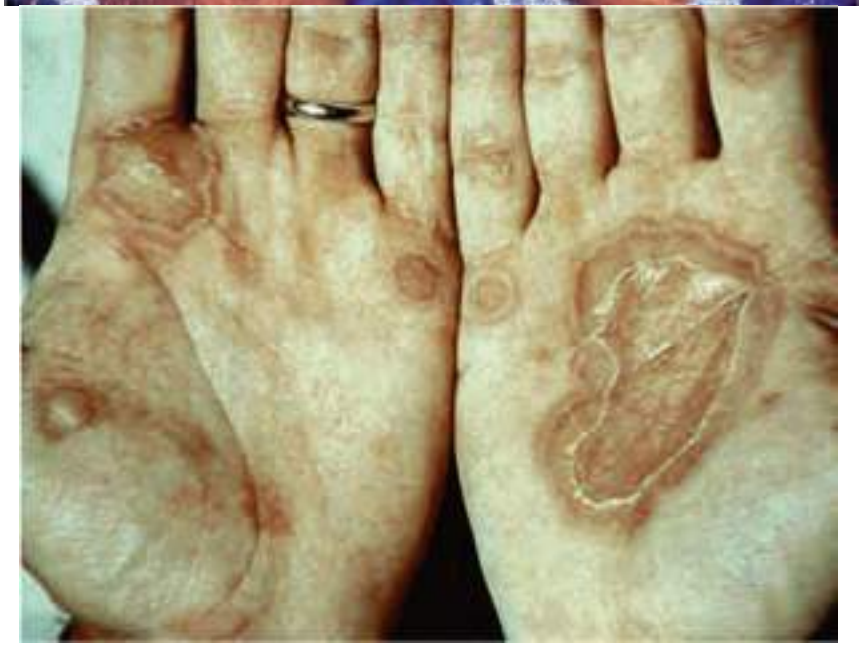
Genital and ocular sites are affected in 25 and 17% of cases, respectively

Cases of oral EM alone have also been reported.

Skin lesions appear rapidly over a few days and begin as red macules that become papular, starting primarily in the hands and moving centripetally toward the trunk in a symmetric distribution.

The classic skin lesion consists of a central blister or necrosis with concentric rings of variable color around it called typical "target" or "iris" lesion that is pathognomonic of EM; variants are called "atypical target" lesions.





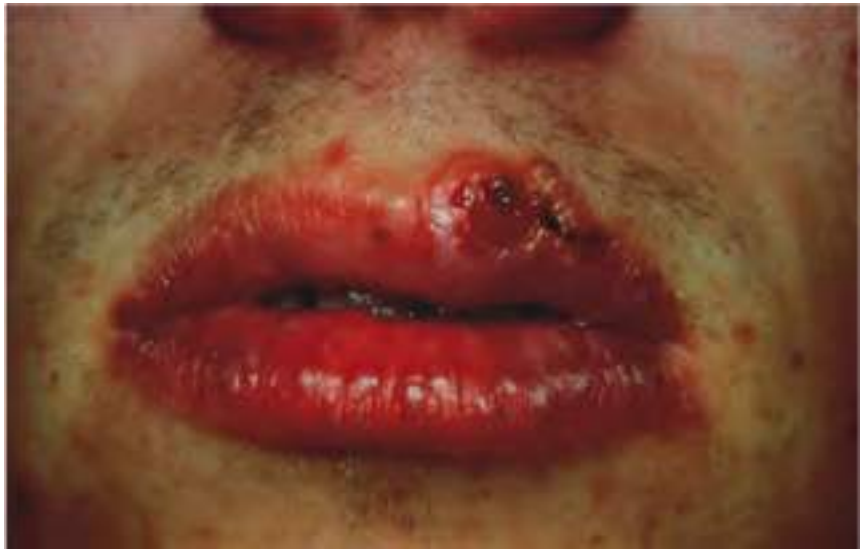
NDINGS

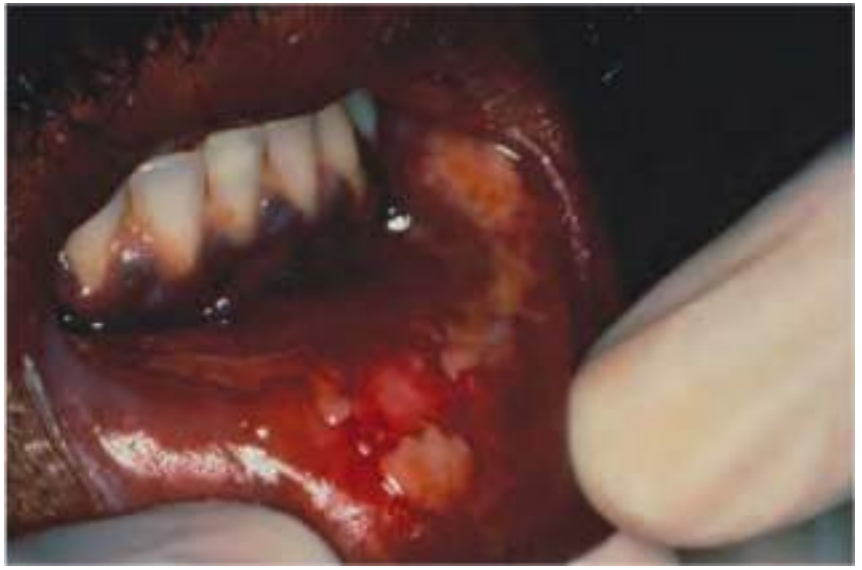
Mild erythema and erosion to painful ulcerations.

Intraoral lesions are irregular bullae, erosions, or ulcers surrounded by extensive areas of inflammation.

Severe crusting and bleeding of the lips are common.

Patients with severe EM may drool blood-tinged saliva.





DIFFERENTIAL DIAGNOSIS

Herpetic gingivostomatitis-

In erythema multiforme ulcers have white pseudomembrane on oral mucosa.

This white pseudomembrane is fibrin formed by vasculitis bleeding and the crusts on lips with bleeding, while these are not occurred in primary herpetic stomatitis.

The location of ulceration differs, erythema multiforme do not always occur on gingival, while primary herpetic stomatitis often occur on gingiva.

Prodromal symptoms starting erythema multiforme are not as severe as in primary herpetic stomatitis,

Pemphigus and pemphigoid

Skin lesions are bullous in nature and not maculopapular

They are chronic, slowly progressive diseases, whereas em heals within weeks.

Recurrent aphthous ulcers

In the absence of skin findings, EM may be be confused with recurrent aphthous ulcers but aphthous ulcers present as discrete lesions, whereas lesions of EM are more diffuse.

Paraneoplastic pemphigus

In severe EM hemorrhagic crusts form on the lips same as in paraneoplastic pemphigus.

PNP are usually present for months

Associated with malignancy and with severe conjunctival and skin lesions.

There are no specific laboratory tests that are useful.

Diagnosis is made primarily on clinical findings or exclusion of other diseases.

Histopathological examination & immunostaining – It is characteristic but not pathognomic.

Intraepithelial oedema and spongiosis early on, with satellite cell necrosis (individual eosinophilic necrotic keratinocytes surrounded by lymphocytes), vacuolar degeneration of the basement membrane zone, and severe papillary oedema with sub-epithelial or intra-epithelial vesiculation.

There is intense lymphocytic infiltration at the basement membrane zone and perivascularly, and non-specific immune deposits of IgM, C3, and fibrin at these sites.

MANAGEMENT

Mild EM – systemic and topical analgesics and supportive care.

It is self limiting and resolves within a few weeks.

Severe cases – systemic corticosteroids

HSV associated EM - Acyclovir

EM not associated with HSV - Azathioprine – 100-150 mg/d.

Dapsone and antimalarials are partially successful in suppresing recurrent outbreaks but may be assiciated with significant side effects.

STEVENS JHONSON SYNDROME (SJS) AND TOXIC EPIDERMAL NECROLYSIS (TEN)

SJS is a less severe variant of TEN and separate clinically and etiopathogenetically from EM.

SJS/TEN exhibits much more widespread necrosis of the epidermis and little vascular inflammation of the dermis.

There is a remarkable absence of significant lymphocytes around the vessels.

As drug antigens are expressed only on the keratinocytes, not the blood vessels.

Whereas, In EM there is a perivascular infiltrate of CD4 and CD8 lymphocytes surrounding swollen blood vessels in the upper dermis.

TEN, especially, shows a lack of inflammatory cells but a predominance of macrophages and dendrocytes in the dermis and epidermis.

There is overproduction of tumor necrosis factor-a (TNF-a) in the epidermis than in EM (TNF ¥)

The skin lesions of SJS and TEN are different from EM.

They are more severe and tend to arise on the chest rather than the extremities on erythematous and purpuric macules; these lesions are called “atypical targets.”

The mucosal surfaces of the eye, genitalia, and mouth are severely affected by SJS/TEN, always with skin involvement.

Treatment - High doses of systemic corticosteroids, intravenous immunoglobulin, and thalidomide

NECROTIZING ULCERATIVE GINGIVITIS (NUG) AND PERIODONTITIS (NUP)

NUG, formerly known as Acute Necrotizing Ulcerative Gingivitis (ANUG).

More severe counterpart was called as Necrotizing Ulcerative Periodontitis (NUP).

These were reclassified in 1999 by the american academy of periodontics under the category of "necrotizing periodontal disease."

These are acute ulcerative-inflammatory conditions of the gingiva and periodontium, respectively, that are associated with polymicrobial infection.*Burket 11th edition.*

Acute necrotizing ulcerative gingivitis (ANUG) is an endogenous oral infection that is characterized by necrosis of the gingiva.*Burket 1oth edition.*

It is also known as trench mouth or vincent infection.

During World War I , NUG was known “trench mouth” since it was frequent among the soldiers in the trenches.

Vincent and Plaut had first identified fuso-spirochete nature of ANUG in 1890.

Vincent identified Borrelia Vincentii (a spirochete) and Bacillus Vincentii (a fusiform) as pathognomic of lesion.

Therefore, lesions were formerly known as Vincent’s disease.

ETIOLOGY AND PATHOGENESIS

Treponema species,

Prevotella intermedia,

Fusobacteria nucleatum,

Peptostreptococcus micros

Porphyromonas gingivalis,

Selenomonas species, and Campylobacter

Prevotella intermedia

Porphyromonas gingivalis

Fusobacterium necrophrom

The Journal of Contemporary Dental Practice, Volume 5, No. 3, August 15, 2004

Burket 11th edi

M.O. Folayan

ANUG & AIDS

Classic ANUG in patients without an underlying medical disorder is found most often in those between the ages of 16 and 30 years, and it is associated with three major factors:

1. Poor oral hygiene with pre-existing marginal gingivitis or faulty dental restorations
2. Smoking
3. Emotional stress

Systemic disorders associated with ANUG are diseases affecting neutrophils (such as leukemia or aplastic anemia),

ANUG & AIDS

In AIDS, the prevalence of NUP is approximately 6% and is predictive of a CD4 count below 200 cell/mm3.

In AIDS, the host response in the gingival crevice is altered.

Levels of proinflammatory cytokines such as interleukin- 1 β are increased in the gingival crevice of patients with (HIV), which alters the regulation of neutrophils.

This alteration in neutrophil function is responsible for the increase in NUP-related organisms including fusobacteria and Candida, which leads torapid necrosis of gingival tissues.

Burket 10th ed

ANUG & AIDS

There are three forms of periodontal diseases observed in patients with (AIDS): linear gingival erythema (LGE), necrotizing ulcerative gingivitis (NUG), and necrotizing ulcerative periodontitis (NUP).

LGE is an intense red band involving the marginal gingiva that does not resolve with standard oral hygiene procedures.

NUG and NUP are clinically similar to ANUG;

the term “NUG” is used when the disease involves only the gingiva, and “NUP”involves a loss of periodontal attachment

CLINICAL FEATURES

NUG and NUP may or may not be associated with fever and malaise, although submandibular lymphadenopathy is usually present.

NOMA generally is accompanied by fluctuating fever, marked anemia, high white cell count, general debilitation, and a recent history of some other systemic illness, such as measles.

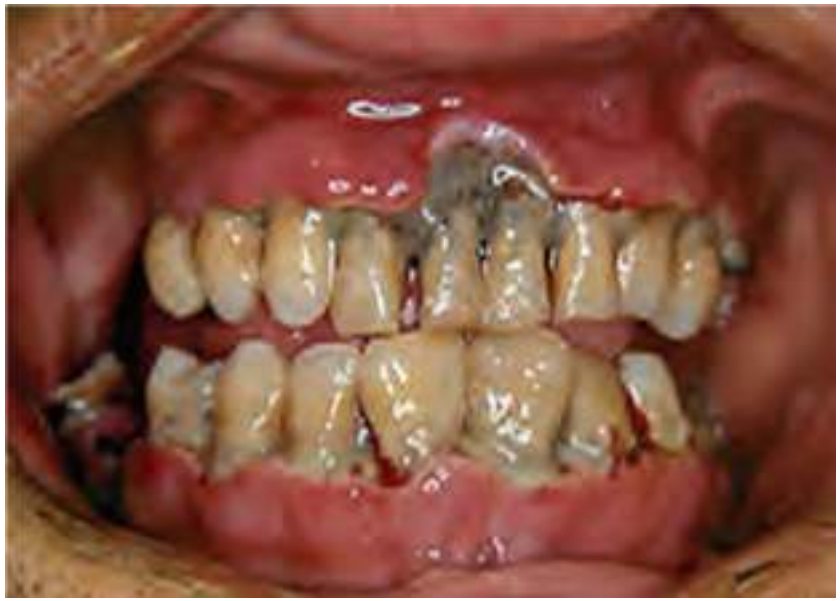
ORAL MANIFES TATIONS

NUG has a rapid and acute onset.

The first symptoms include excessive salivation, a metallic taste, and sensitivity of the gingiva.

This rapidly develops into extremely painful and erythematous gingiva with scattered punched-out ulcerations, mainly on the interdental papillae, & other part of the marginal gingiva may be affected.

Malodor, and gingival bleeding may be present



In patients in whom there is severe immunodeficiency or malnutrition, NUG and NU P may progress to noma.

The overlying skin becomes discolored, and perforation of the skin occurs.

The orofacial lesions are cone-shaped, with the base in the oral cavity and the tip at the skin aspect.

There is sloughing of the oral mucosa followed by sequestration of the exposed, necrotic bone and teeth.

Without treatment, the mortality rate is 70 to 90%.

DIFFERENTIAL DIAGNOSIS

Primary herpetic gingivostomatitis - The acute onset of erythematous and ulcerated gingiva of NUG

Desquamative gingivitides (such as mucous membrane (cicatricial) pemphigoid, pemphigus vulgaris, lichen planus, and hypersensitivity reaction) may present primarily on the gingiva, with no skin findings.

However these are chronic and progressive lesion with inflammation not the necrosis.

DIFFERENTIAL DIAGNOSIS

Deep fungal infection – single large necrotic ulcer of ANUG may mimmic as fungal infection.

Herpes and CMV infection in immunocompromized patient may have single large ulcer.

Squamous cell carcinoma.

LABORATORY TESTING

- **Bacterial culture** - Secretions from the gingival sulcus grow mixed flora but in particular will be culture positive for Treponema species, P. intermedia, F. nucleatum, and other.

Necrotizing gingival lesions may also be caused by microbes other than fusospirochetes, such as pseudomonas aeruginosa.

- **Biopsy** – not confirmatory

Can be used to rule out other diseases with similar presentation.

Biopsy shows ulceration, extensive necrosis, leukocytoclasia, histiocytic vasculitis with luminal fibrin clots, and a prominent infiltrate of large atypical cells

MANAGEMENT

This is directed toward supportive care and pain control, definitive treatment, and identification of underlying predisposing factors.

In patients who are malnourished, nutritional rehabilitation is essential to halt the progress of gingival lesions to noma.

Definitive treatment of NUG and NUP

Gentle debridement to remove as much of the debris and plaque as possible using topical anesthesia during the first few visits.

The use of chlorhexidine digluconate mouthrinse led to resolution in >90% of cases.

In cases of extensive disease and systemic symptoms, antibiotics active against gram-negative anaerobes, such as b-lactams, metronidazole, should be given.

After resolution of painful episodes, scaling and root planing to completely remove all residual plaque and calculus are indicated.

Periodontal surgery to correct gingival and periodontal defects.

RECURRENT APHTHOUS STOMATITIS (RAS)

RAS is a disorder characterized by recurring ulcers confined to the oral mucosa in patients with no other signs of disease.

RAS is considered a diagnosis of exclusion since hematologic deficiencies, immune disorders, and connective tissue diseases may cause oral lesions clinically similar to RAS.

RAS affects approximately 20% of the general population, but when specific ethnic or socioeconomic groups are studied, the incidence ranges from 5 to 50%.

Activities of daily living affect the prevalence of RAS.

RAS prevalence was higher (male, 48.3%; female, 57.2%) among professional-school students than in the same subjects 12 years later when they had become practicing professionals.

Stress during student life is a major factor in RAS

EPIDEMIOLOGY

Approximately 20% of the general population is affected by RAS,

But incidence varies from 5% to 50% depending on the ethnic and socioeconomic groups studied.

Epidemiologic studies have shown that the prevalence of RAS is influenced by the population studied, diagnostic criteria, and environmental factors.

DCNA 2005

In children, prevalence of RAS may be as high as 39% and is influenced by the presence of RAS in one or both parents.

Children with RAS-positive parents have a 90% chance of developing RAS compared with 20% in those with RAS-negative parents.

In children of high socioeconomic status, RAS is five times more prevalent and represents 50% of oral mucosal lesions in this cohort.

DCNA 2005

PREDISPOSING ETIOLOGIC FACTORS

UNKNOWN

Several local, systemic, immunologic, genetic, allergic, nutritional, and microbial factors have been proposed as causative agents.

Local	Trauma
	Smoking
	Dysregulated saliva composition
Microbial	Bacterial: streptococci
	Viral: varicella zoster, cytomegalovirus
Systemic	Behçet's disease
	Mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome
	Crohn's disease
	Ulcerative colitis
	HIV infection
	Periodic fever, aphthosis, pharyngitis, and adenitis (PFAPA) or Marshall's syndrome
	Cyclic neutropenia
	Stress, psychologic imbalance, menstrual cycle
Nutritional	Gluten-sensitive enteropathy
	Iron, folic acid, zinc deficiencies
	Vitamin B_1, B_2, B_6, and B_{12} deficiencies
Genetic	Ethnicity
	HLA haplotypes
Allergic/immunologic	Local T-lymphocyte cytotoxicity
	Abnormal CD4:CD8 ratio
	Dysregulated cytokine levels
	Microbe-induced hypersensitivity
	Sodium lauryl sulfate sensitivity
	Food sensitivity
Other	Antioxidants
	Nonsteroidal anti-inflammatory drugs
	Beta blockers

PATHOGENESIS

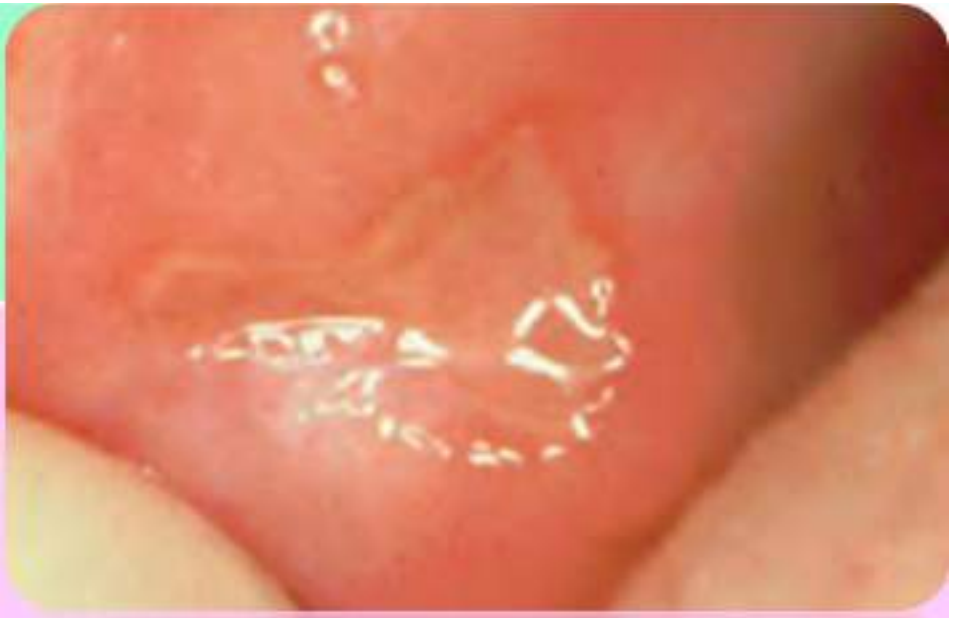
There is increasing evidence linking local immune dysfunction to RAS , although the specific defect remains unknown.

During the past 30 years, research has suggested a relationship between RAS and lymphocytotoxicity, antibody-dependent cell mediated cytotoxicity, defects in lymphocyte cell subpopulations, and an alteration in the CD4 to CD8 lymphocyte ratio.

The work of Buno and colleagues suggests that an **abnormal mucosal cytokine cascade** in RAS patients leads to an exaggerated cell-mediated immune response, resulting in localized ulceration of the mucosa.

The work of Buno and colleagues suggests that an abnormal mucosal cytokine cascade in RAS patients leads to an exaggerated cell-mediated immune response, resulting in localized ulceration of the mucosa.

ORAL FINDINGS



Age - The first episodes of RAS most frequently begin during the Second decade of life.

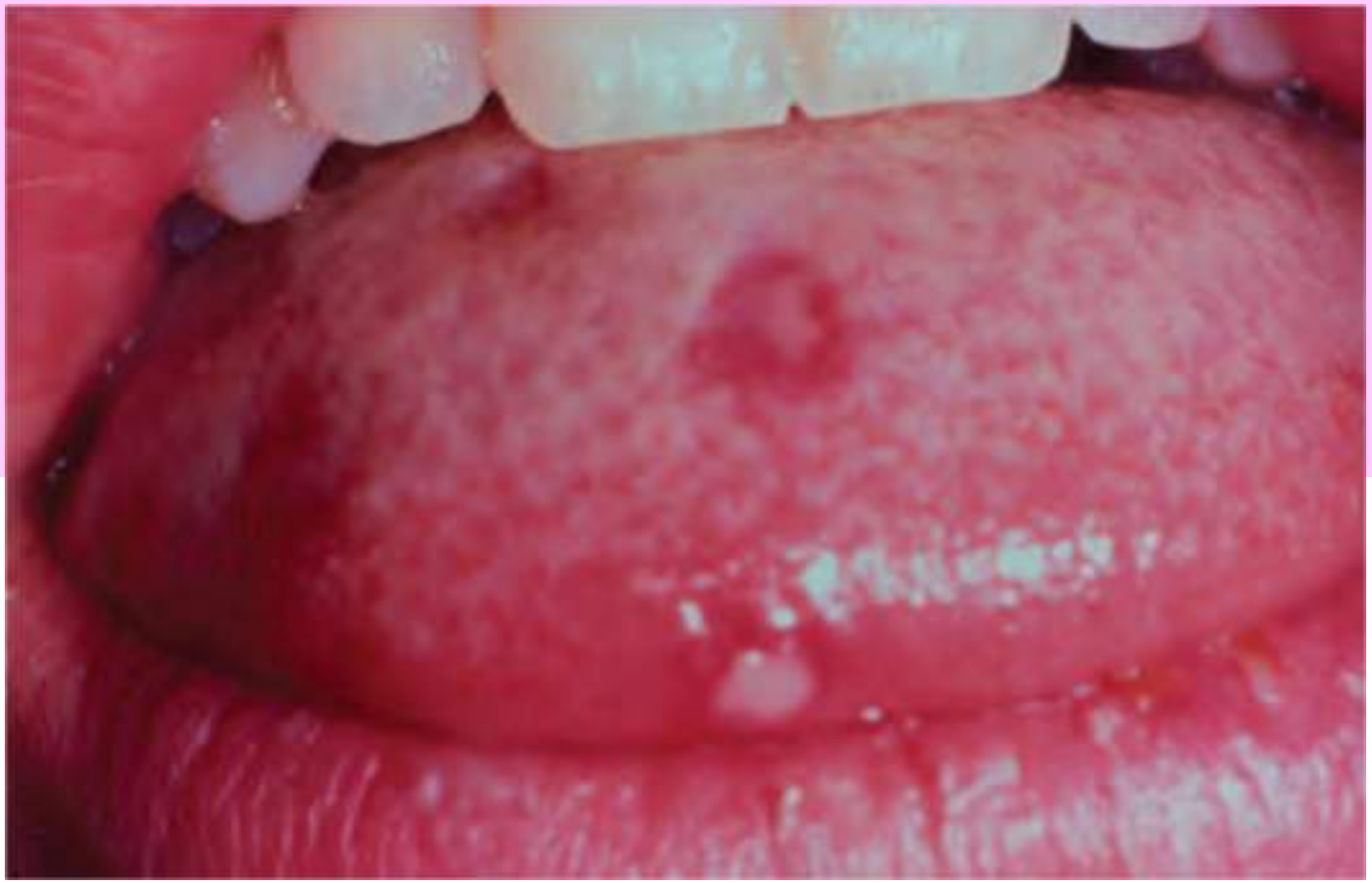
Site- keratinized mucosa : commonly labial and buccal mucosa

Sign & symptoms - Begin with prodromal burning any time from 2 to 48 hours before an ulcer appears.

During this initial period, a localized area of erythema develops.

Within hours, a small white papule forms, ulcerates, and gradually enlarges over the next 48 to 72 hours.

The individual lesions are round, symmetric, and shallow (similar to viral ulcers), but no tissue tags are present, which helps distinguish RAS from vesiculobullous diseases.



\. is classified according to clinical characteristics:

minor ulcers

Less than 1 cm in diameter
Heal without scars

major ulcers

Over 1 cm in diameter
Take longer to heal
Often scar

herpetiform ulcers

<1 cm in diameter.
crops of dozens of small ulcers
"severe" minor ulcers.

Sutton disease,
Periadenitis mucosa
Necrotica recurrens

BURKET 11TH EDITION

Characteristic	Minor	Major	Herpetiform
Gender predilection	M=F	M=F	F> M (usually)
Age of onset (years)	5–19	10–19	20–29
Number of ulcers	1–5	1–10	10–100
Size of ulcers (mm)	<10	>10	1–2 (larger if coalesced)
Duration (days)	4–14	>30	<30
Recurrence rate (months)	1–4	<1	<1
Site predilection	Lips, cheeks, tongue, floor of mouth	Lips, cheeks, tongue, palate, pharynx	Lips, cheeks, tongue, pharynx, palate, gingiva, floor of mouth

DCNA 2005

LABORATORY INVESTIGATIONS

Biopsy - The preulcerative lesion demonstrates subepithelial inflammatory mononuclear cells with abundant mast cells connective tissue edema, and lining of the margins with neutrophils.

Damage to the epithelium occurs in the basal layer and progresses through the superficial layers, leading eventually to ulceration and surface exudate.

The presence of extravasated erythrocytes around the ulcer margin, subepithelial extravascular neutrophils, numerous macrophages loaded with phagolysosomes, and the nonspecific binding of stratum spinosum cells to immunoglobulins and complements may be a result of vascular leakage and passive diffusion of serum proteins.

The proper treatment of RAS depends on the

Frequency,

Size, and

Number of the ulcers.

Patients who experience occasional episodes of minor aphthous ulcers , topical therapy should be given.

Protective emollient such as Zilactin or Orabase , used either alone or mixed with a topical anesthetic such as benzocaine.

Other topical agents are diclofenac, a nonsteroidal anti-inflammatory drug.

Amlexanox paste – Amlexanox 5% paste applied to ulcers 2–4 times

- Reduce the healing time and patient discomfort.

DCNA 2005

Topical glucocorticoid - In more frequent or more severe disease,

It reduces size and healing time of the ulcers, especially when the medication is used early in the developing stage of the lesion.

DCNA 2005

High potency topical steroid preparation, such as fluocinonide, betamethasone, or clobetasol, placed directly on the lesion, shortens healing time and reduces the size of the ulcers.

BURKET 11TH EDITION

Larger lesions can be treated by placing a gauze sponge containing the topical steroid on the ulcer and leaving it in place for 15 to 30 minutes to allow for longer contact of the medication.

Intralesional steroids can be used to treat large indolent major RAS lesions.

BURKET 11TH EDITION

DOSES

Beclomethasone (QVAR oral inhaler) - 50–100 µg sprayed bid onto oral lesion

Betamethasone (Diprolene) - 0.1% cream or

- 0.05% gel applied thinly bid;
- 0.5 mg 2-4 times daily as a mouthwash

Clobetasol (Temovate)- 0.05% cream or gel applied thinly bid

Halobetasol (Ultravate) - 0.05% cream or gel applied thinly bid

Fluocinonide (Lidex) - 0.05% cream applied bid

Topical antibiotics - Tetracycline mouth rinses have been reported to decrease both the healing time and the pain of the lesions in several trials, but the association of these rinses with oral candidiasis and reports of allergic reactions have limited the use of this form of therapy.

It has both antibacterial and the anti-inflammatory effects

When ulcers do not heal by topical therapy systemic therapy should be considered. These include:

Colchicine,

Colchicine has anti-inflammatory activity and inhibits cell-mediated
Response.

Dapsone - a sulfone derivative which is used to manage
a

atitis

ity of

- ✓Thalodimide thalidomide has significant antiinflammatory and immunomodulatory properties.
- ✓Used for erythema nodosum leprosum, discoid lupus erythematosus, graftversus-
host disease, multiple myeloma, and Behçet syndrome.
- ✓It reduce both the incidence and severity of major RAS in both HI V-positive and HIV negative.
- ✓It is indicated in severe major RAS where other less toxic therapies, including high-potency topical steroids, colchicine, and pentoxifylline, have failed to control the disease.

DOSES

Systemic Corticosteroids –

Prednisone (Deltasone)

1. 30–40 mg daily after breakfast for 4–5 d
2. 1–2 mg/kg/d after breakfast until disease controlled
3. 1–2 mg/kg/d, then maintenance of 2.5–15 mg daily.
4. 20–40 mg daily for 7–10 d at onset of lesions or until lesions resolve
5. 60 mg daily for 2 d, 50 mg daily for 2 d, 40 mg daily for 2 d, 30 mg daily for 2 d, 20 mg daily for 2 d, 10 mg daily for 2 d

After 2 weeks gradual tapering is required.

DOSES

Colchicine - 500 µg three times daily

Monitor for agranulocytosis and aplastic anemia

Pentoxifylline – (Trental, Pentoxil) - 400 mg three times daily

Monitor for blood pressure in patients taking antihypertensives.

Thalidomide – (Thalomid) - 100–300 mg daily at bedtime

Monitor for baseline nerve conduction studies and after 10 gm of drug.

Levamisole

Levamisole is an immunopotentiating agent that has demonstrated the ability to normalize the CD4+ cell/CD8+ cell ratio and improve symptoms in RAU patients.

Levamisole was once described as an effective treatment for RAS, but five RCTs reported no significant benefit, and four suggested that.

It reduces neutophill phagocyte function.

150 mg/day × 3 days every 2 wk for 4 mo

It might reduce the duration, number, size, and frequency of ulceration.

The adverse effects nausea, hyperaemia, dysgeusia and agranulocytosis

Crispian Scully , Stephen Porter. Oral mucosal disease: Recurrent aphthous stomatitis. British Journal of Oral and Maxillofacial Surgery 46 (2008) 198–206.

Adalimumab

Adalimumab is an anti-TNF- monoclonal antibody that is used to treat severe, recalcitrant, RAS.

Crispian Scully , Stephen Porter. Oral mucosal disease: Recurrent aphthous stomatitis. British Journal of Oral and Maxillofacial Surgery 46 (2008) 198–206.

ORAL HYPERSENSITIVITY REACTIONS/CONTACT ALLERGY

Contact allergy results from a delayed hypersensitivity reaction that occurs when antigens penetrate the skin or mucosa of susceptible individuals.

These antigens combine with epithelial-derived proteins to form haptens that bind to Langerhans' cells in the epithelium.

The Langerhans' cells migrate to the regional lymph nodes and present the antigen to T lymphocytes, which become sensitized and undergo clonal expansion.

After re-exposure to the antigen, sensitized individuals develop an inflammatory reaction confined to the site of contact.

The incidence of contact stomatitis is unknown, but it is believed to be significantly less common than contact dermatitis for the following reasons:

1. Saliva quickly dilutes potential antigens and physically washes them away and digests them before they can penetrate the oral mucosa.

2. Since the oral mucosa is more vascular than the skin, potential antigens that do penetrate the mucosa are rapidly removed before an allergic reaction can be established.

3. The oral mucosa has less keratin than does the skin, decreasing the possibility that haptens will be formed.

Causative agents

Contact stomatitis may result from contact with dental materials, oral hygiene products, or foods.

Food - cinnamon or peppermint, which are frequently used flavoring agents in food, candy, and chewing gum.

Oral hygiene products such as toothpaste, mouthwash and dental floss.

Dental material - mercury in amalgam, gold in crowns, free monomer in acrylic, and nickel in orthodontic wire.

Note - Pyrophosphates and zinc citrate, which are components of tartar control toothpaste, cause superficial peeling of the mucosa in some users, but this reaction is believed to be caused by physical irritation rather than an allergic reaction.

CLINICAL MANIFESTATIONS

Signs and Symptoms –

Nonspecific and are frequently difficult to distinguish from physical irritation.

The reaction occurs only at the site of contact and includes a burning sensation or soreness accompanied by erythema, and occasionally the formation of vesicles and ulcers.

Burning sensations without the presence of lesions is not a result of contact allergy, and obtaining allergy tests for patients with burning mouth syndrome with normal-appearing mucosa is not indicated.

Other clinical manifestation include - lichenoid reaction, plasma cell gingivitis.

Plasma cell gingivitis, which is characterized by generalized erythema and edema of the attached gingiva, occasionally accompanied by cheilitis and glossitis.

The histopathology shows as sheets of plasma cells that replace normal connective tissue. Some cases have been related to an allergen present in toothpaste, chewing gum, or candy, whereas other cases remain of unknown etiology even after extensive allergy testing.

Pemphigus

- Pemphigus vulgaris (vegetans)
- Pemphigus foliaceus (erythematosus)
- Paraneoplastic pemphigus (PNPP)
- Drug-related pemphigus.

Subepithelial Bullous Dermatoses

- Bullous pemphigoid,
- Mucous membrane pemphigoid,
- Linear IgA disease,
- Epidermolysis bullosa aquisita
- Chronic bullous dermatosis of childhood.

PEMPHIGUS

- First described by Hippocrates and Galen as early as in the 4th and 3rd centuries B.C.

- Pemphigus - the Greek word *Pemphix* (bubble or blister)

- It has been described for a group of potentially life threatening autoimmune mucocutaneous diseases characterized by epithelial blistering affecting mucocutaneous surfaces.

The major variants of pemphigus are

1. Pemphigus vulgaris
   Pemphigus vegetans
2. Pemphigus foliaceus,
   Pemphigus erythematosus
3. Paraneoplastic pemphigus (PNPP),
4. Drug-related pemphigus

- Pemphigus vulgaris
  - PEMPHIGUS VEGETANS
- Pemphigus foliaceous
  - PEMPHIGUS ERYTHEMATOSUS
- Paraneoplastic pemphigus
- Pemphigus herpetiformis
- IgA pemphigus

Diet

- **Garlic**

Drugs

- **Thiol drugs or SH drugs eg ; pencillamine and captopril**
- **Non Thiol drugs eg ; phenol drugs, rifampicin, diclofenac, ACE inhibitors**

Viruses

- **Herpes virus**

tiology

Other factors

- **Higher exposure to pesticides**
- **Estrogen**

Association with other disorders

- **Rheumatoid arthritis**
- **Myasthenia gravis**
- **Lupus erythematosus**
- **Pernicious anaemia**

Epidemiology

There are 0.1 to 0.5 cases reported each year per 100,000 population.

Commonly occurrs in the fifth and sixth decades of life.

Although rare cases have been reported in children and the elderly.

Pemphigus occurs more frequently among Ashkenazi Jews.

The DR6 and DQ5 haplotypes are more common in non-Jewish patients.

Epidemiology

PV is the most common form of pemphigus, 80% of cases of pemphigus are of pemphigus vulgaris.

It may be the commonest autoimmune blistering disease in Eastern countries, such as India, Malaysia, China and the Middle East.

In South Africa, pemphigus vulgaris is commoner in Indians than in Black or Caucasian races.

Pemphigus is less common in the West.

Pemphigus

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Subepithelial Bullous Dermatoses

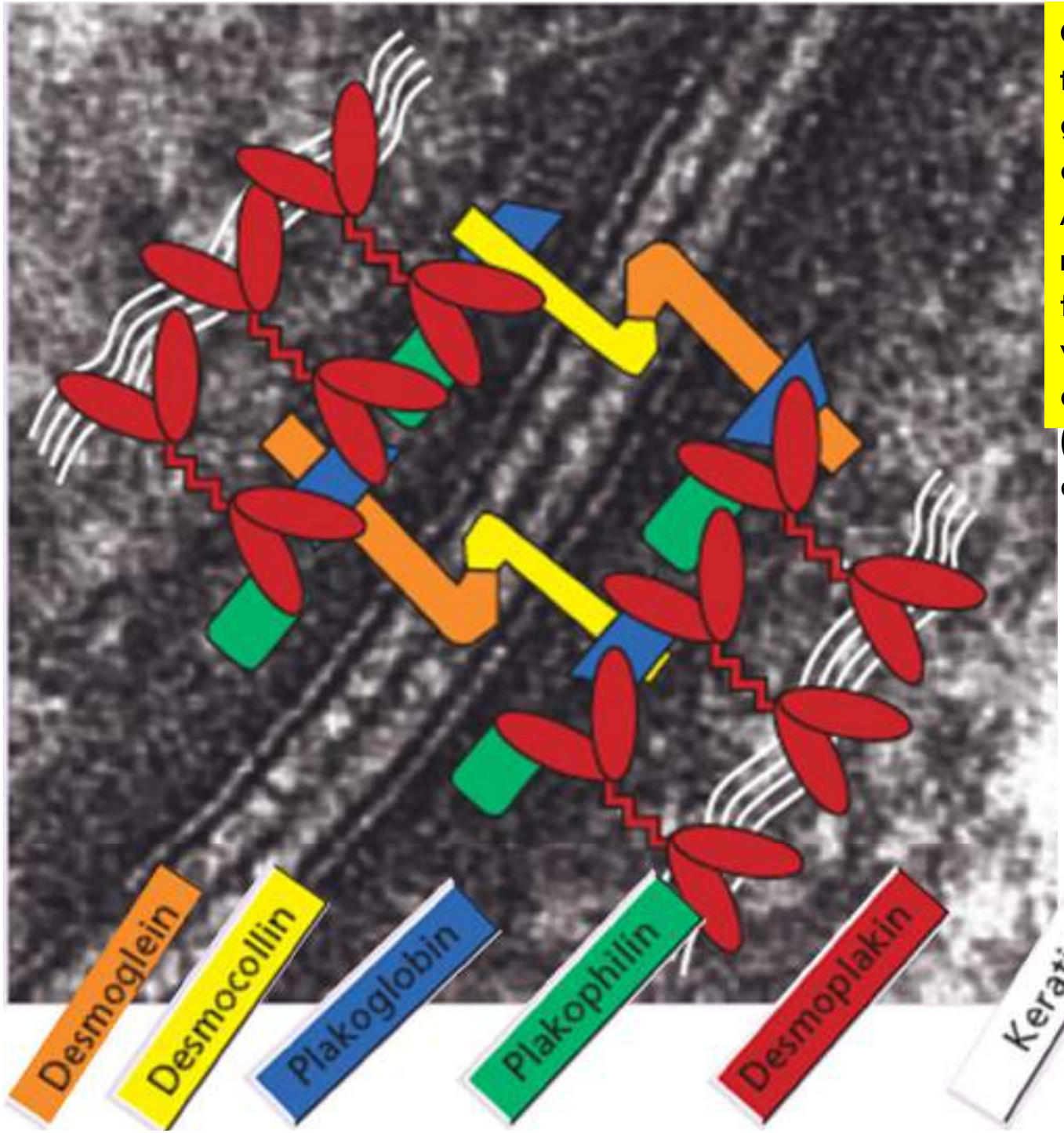
- Bullous pemphigoid,
- Mucous membrane pemphigoid,
- Linear IgA disease,
- Epidermolysis bullosa aquisita
- Chronic bullous dermatosis of childhood.

PEMPHIGUS VULGARIS (PV)

PV is the most common form of pemphigus, 80% of cases of pemphigus are of pemphigus vulgaris.

The underlying mechanism responsible for causing the intraepithelial lesion of PV is the binding of IgG autoantibodies to DSG 3

Pathogenesisc



Cells are connected via transmembranous cadherin glycoproteins (desmogleins and desmocollins). Attachment of these molecules to the keratin fi lament cytoskeleton occurs via a network of desmosomal plaque proteins (desmoplakin, plakoglobin and plakophilin).

Macromolecular composition of desmosomes linking adjacent keratinocytes

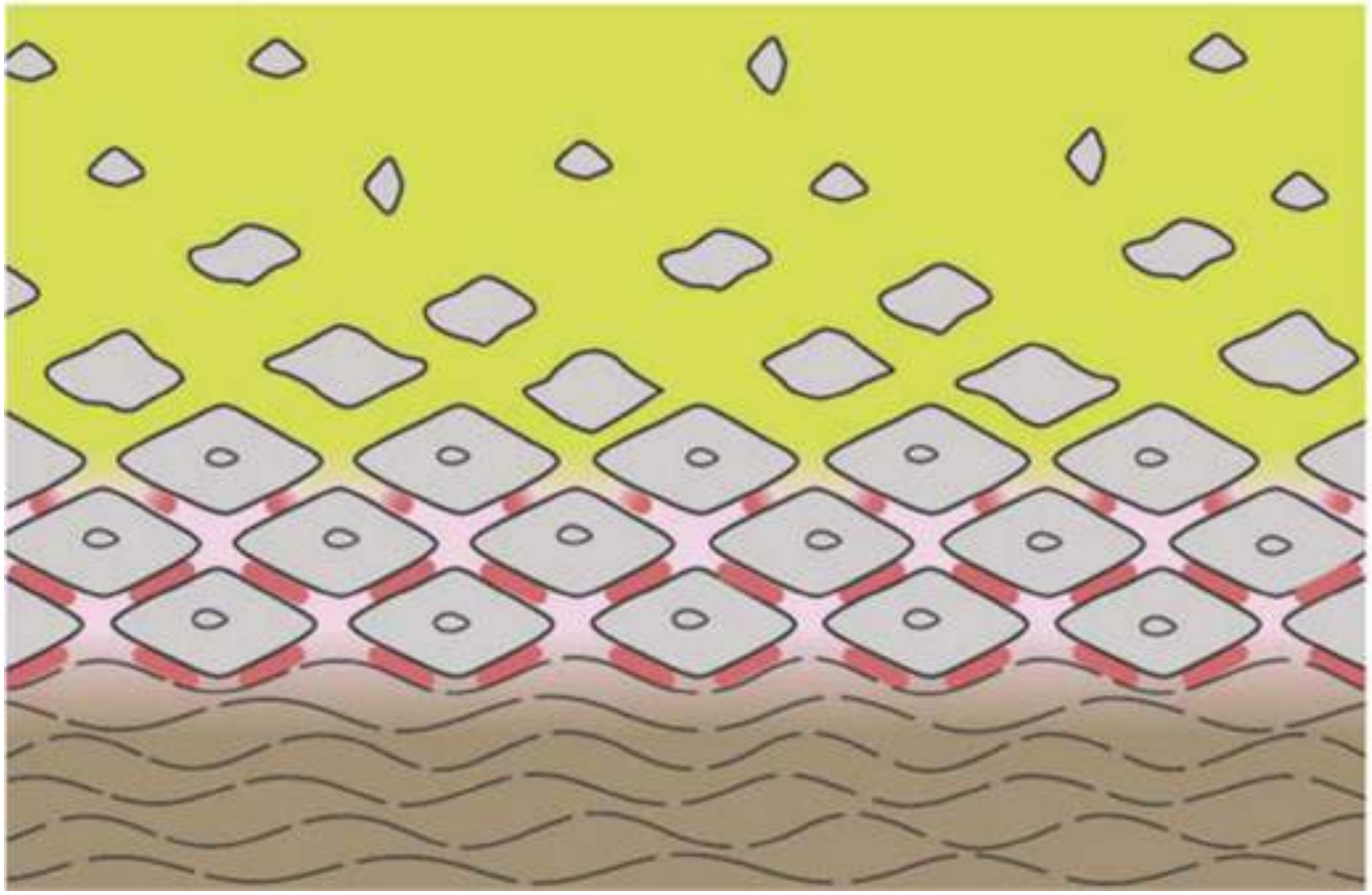
DSG3

DSG3 is a transmembrane glycoprotein adhesion molecule present on desmosomes.

This glycoprotein strengthens the intercellular connection.

In pemphigus, antibody antigen reaction weakens and finally breaks the connection between epithelial cells, resulting in blisters and desquamation.

Acantholysis: Loss off cell cohesion in the superficial layers of mucoepidermal tissue



Binding of antibodies to desmosomal components is associated with acantholysis in pemphigus.

1. **Ettlin/ Dent Clin N Am 49 (2005) 107–125**

MECHANISM OF ACANTHOLYSIS

- Binding of pemphigus vulgaris antibody

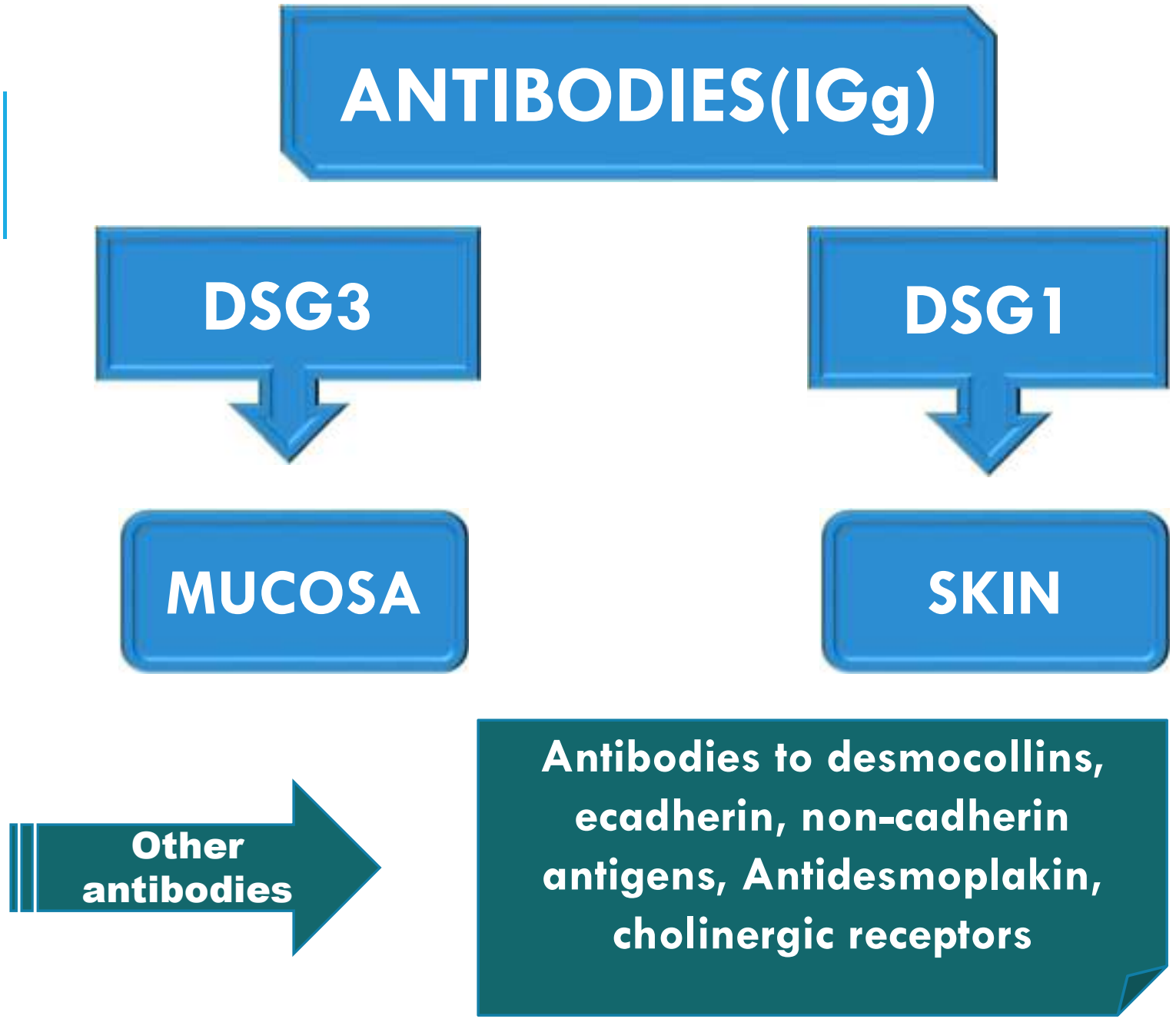
- Activation of a variety of intracellular signalling pathways with phosphorylation of keratinocyte proteins, including activation of EGF receptor and phosphorylation of its downstream substrates (p38 mitogen-activated protein kinase (p38MAPK), Fas apoptotic cascade).

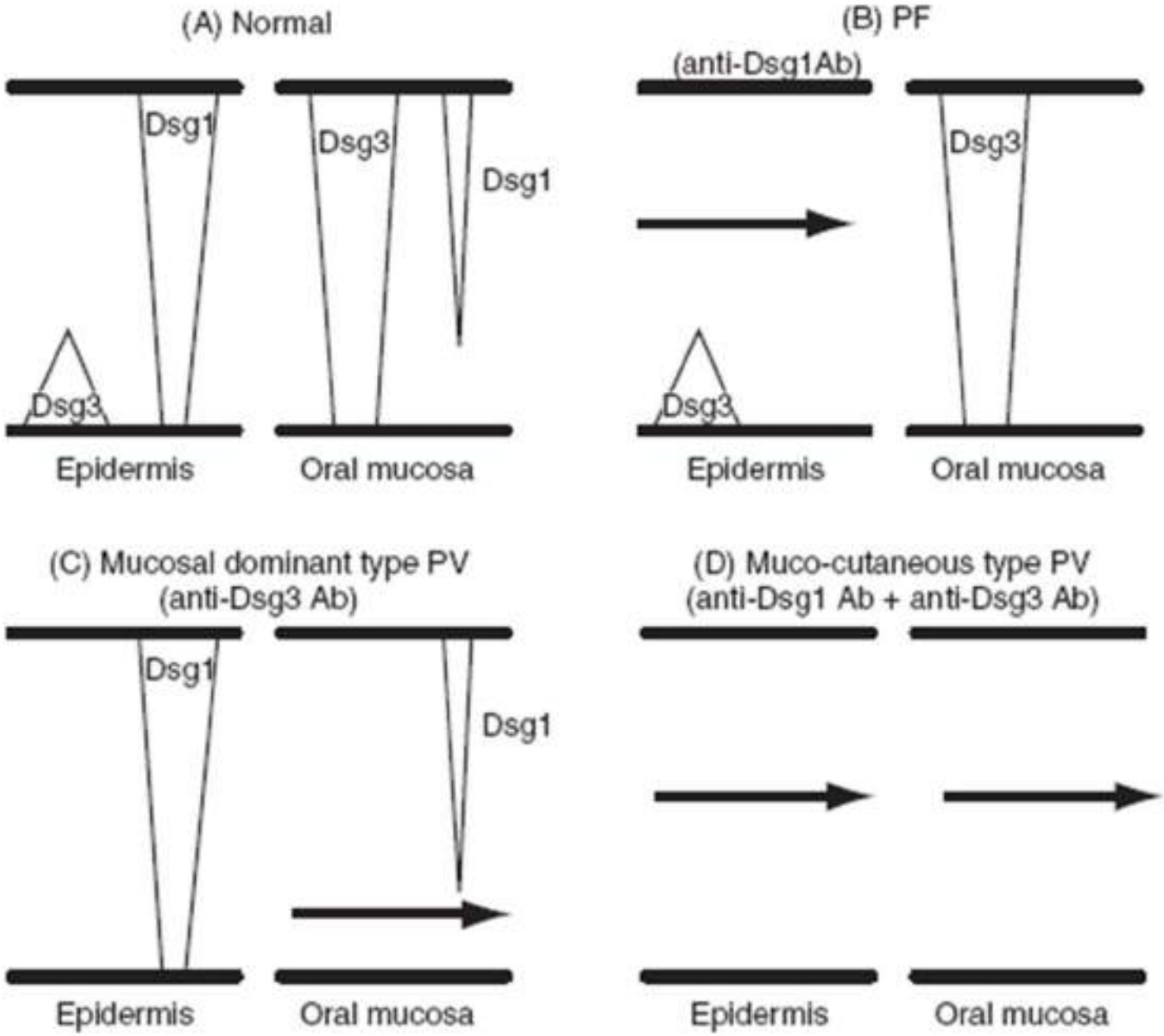
- Binding of antibody activated the complement system
  - IL-1, thromboxane B2 and leukotriene B4 are present in blister fluid

IL1,
TNF-ɠ

- TNF-α and IL-6 are found in serum and lesional skin of pemphigus patients and can induce plasminogen activators and plasmin activity

- Infliximab, monoclonal antibody to TNF-α, produces rapid, short-lived, reduction of blistering in pemphigus cases.


ANTIBODIES(IGg)
DSG3
DSG1
MUCOSA
SKIN
Other antibodies
Antibodies to desmocollins, ecadherin, non-cadherin antigens, Antidesmoplakin, cholinergic receptors


(A) Normal
Dsg1
Dsg3
Dsg3
Dsg1
Epidermis
Oral mucosa
(B) PF
(anti-Dsg1Ab)
Dsg3
Dsg3
Epidermis
Oral mucosa
(C) Mucosal dominant type PV
(anti-Dsg3 Ab)
Dsg1
Dsg1
Epidermis
Oral mucosa
(D) Muco-cutaneous type PV
(anti-Dsg1 Ab + anti-Dsg3 Ab)
Epidermis
Oral mucosa

ASSOCIATION WITH OTHER DISEAES

Other autoimmune diseases, particularly myasthenia gravis.

Thymoma

Lymphoma

Death occurs most frequently in elderly patients and in patients requiring high doses of corticosteroids who develop infections and bacterial septicemia(*Staphylococcus aureus*).

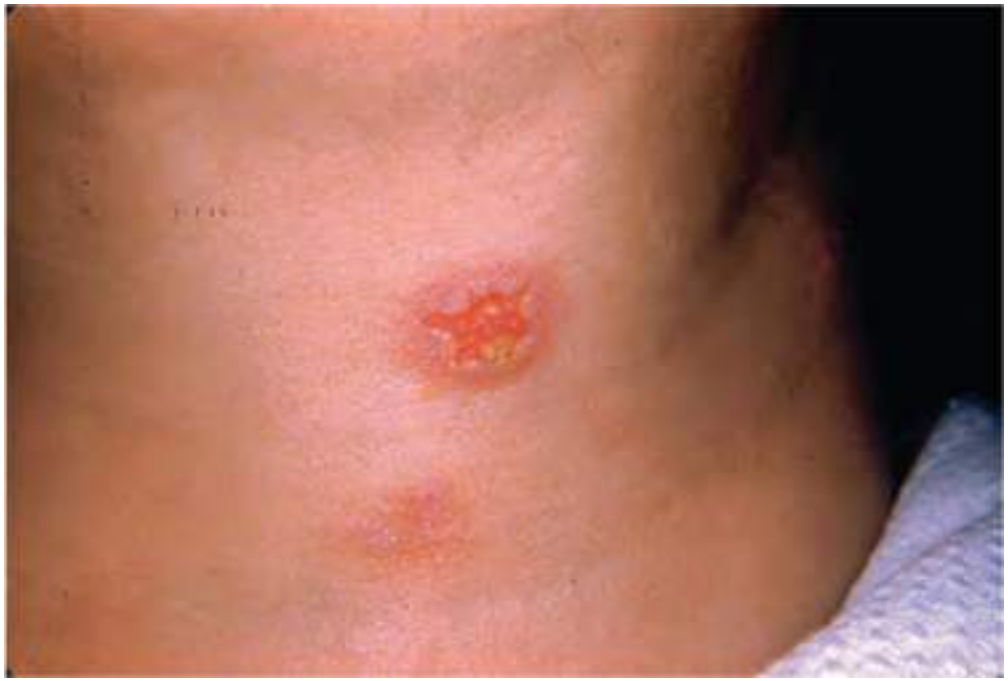
CLINICAL MANIFESTATIONS

The classic lesion of pemphigus is thin walled bullae over the skin or mucosa.

The bullae rapidly break but continues to extend peripherally, eventually leaving large areas denuded of skin.

CHARACTERISTIC SIGN

Esboe hansen sign- On application of pressure to an intact bulla, bulla enlarges by extension to an apparently normal surface



NIKOLSKY'S SIGN

Pressure to an apparently normal area results in the formation of a new lesion.

It results from the upper layer of the skin pulling away from the basal layer.

It is most frequently associated with pemphigus but may also occur in other blistering disorders.

Other diseases having Nikolsky's sign positive

- Paraneoplastic pemphigus
- Oral lichen planus
- Mucous membrane pemphigoid
- Epidermolysis bullosa
- Linear iga disease
- Lupus erythematosus
- Dermatomyositis
- Chronic erythema multiforme
- Graft versus- host disease

Surfaces involved - Any mucosal and skin surface

Sites involved, including

Conjunctiva

Nasal,

Pharynx

larynx,

Oesophagus

Urethra,

Vulva

Cervix

Scalp,

Face, axillae, groins and pressure points

Flaccid blisters filled with clear fluid either arise on normal skin or an erythematous base.

The contents become turbid or the blisters rupture, producing painful erosions.

Nail dystrophies, acute paronychia and subungual haematomas have been observed in pemphigus.

Severe pemphigus in pregnancy may be associated with fetal prematurity and death, but it is difficult to separate the effects of treatment from those of the disease.

ORAL FINDINGS

80% to 90% of patients with PV develop oral lesions sometime during the course of the disease.

In 60% of cases, the oral lesions are the first sign.

The oral lesions may begin as the classic bulla on a noninflamed base which immediately rupture forming shallow irregular ulcer.

The edges of the lesion continue to extend peripherally over a period of weeks until they involve large portions of the oral mucosa.

COMMON ORAL SITES

Buccal mucosa, palate, gingiva.

Oral lesions are preceded by skin lesions commonly.

Therefore, treatment instituted at this time results in disease contrrol.

PEMPHIGUS VEGETANS

DEFINITION

PEMPHIGUS VEGETANS IS A RARE VARIANT OF PEMPHIGUS VULGARIS WHICH IS CHARACTERIZED BY VEGETATING EROSIONS, PRIMARILY IN FLEXURES.

Two subtypes

Severe ⟷ mild

- Neumann pemphigus vegetans
- Hallopeau pemphigus vegetans

PATHOGENESIS

Accounts for 1-2% of pemphigus cases.

Antigen - 130 kDa pemphigus vulgaris antigen.

Other antigen- desmocollins 1 and 2 (Hallopeau type).

Pemphigus vegetans is present with marked cutaneous infiltration of neutrophils and eosinophils which may be due to Complement fixation .

CLINICAL FEATURES

Middle-aged adults

Neumann type

Early lesions are same as pemphigus vulgaris with bullae and denuded area.

These areas attempt healing by developing vegetations of hyperplastic granulation tissue.

Hallopeau type –

Less aggressive

Pustules rather than vesicles are the early lesions

These soon progress to vegetating plaques.

These areas attempt healing by verrucous hyperkeratotic vegetations

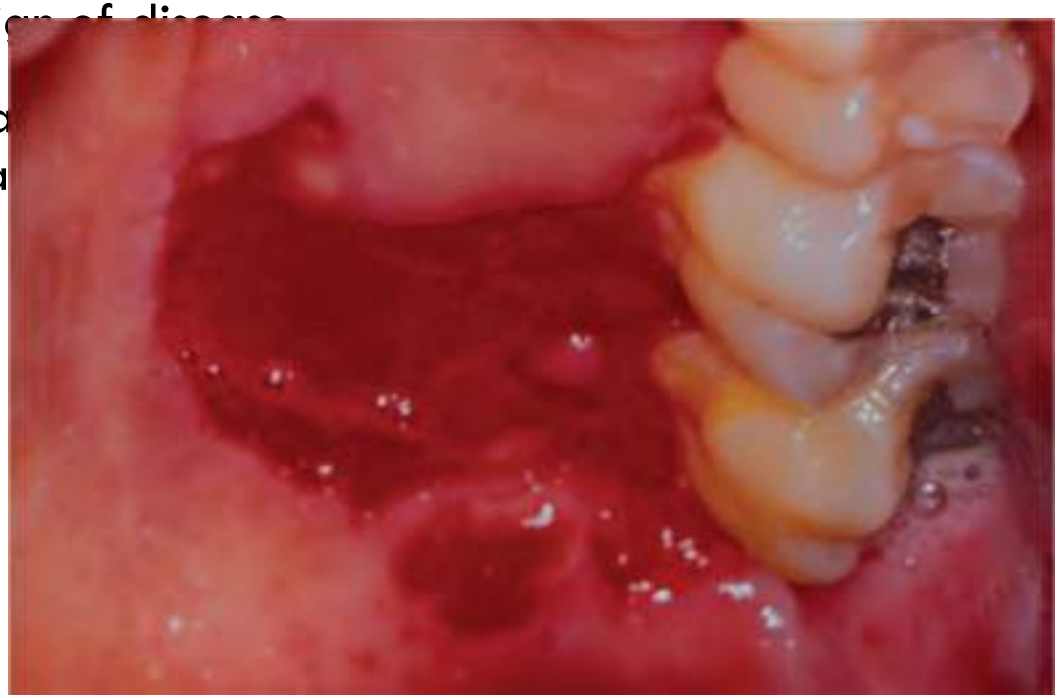
ORAL FINDINGS

Common in both forms

In 60-80% of all cases, the oral mucosa is affected.

Oral lesions May be initial sig

Gingival lesion are present a
on a red base or have a gra



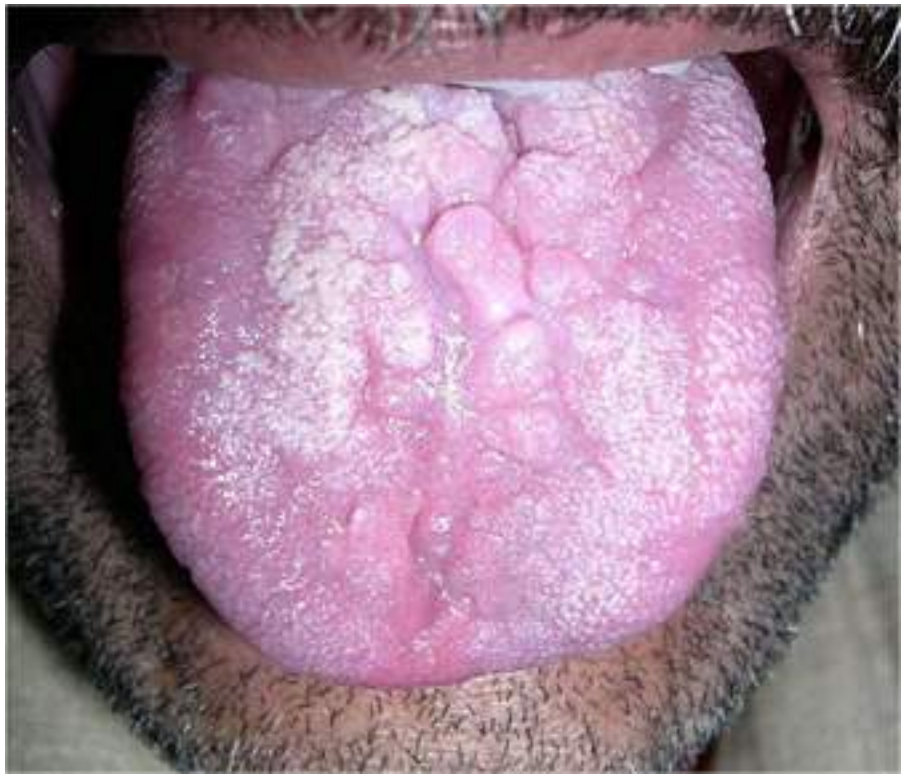
Chronic palatal lesion
of pemphigus vegetans

Burket 11th edition

Neumann type - deep fissures between the vegetations on the vermilion border of the lips.

Hallopeau type – pappilomatous hyperplasia on same location

cerebriform tongue



Amrinder J. Kanwar, Dipankar De; Pemphigus in India; Indian Journal of Dermalogy, Venerology, and Leprology; 2007:77(4)

Pemphigus

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DRUG INDUCED PEMPHIGUS

Sulphydryl group (thiol drugs)

Such as penicillamine and captopril

Non thiol may also induce pemphigus.

ACE inhibitors (enalapril , ramapril , fosinopril)

Angiotensin ii receptor blockers(candesartan and telmisartan)

Nifedipine, penicillins, cephalosporins, pyrazolon derivatives, chloroquine, hydoxychloroquine,

Rifampicin,

Montelukast and

Interferon

tiology

Clinical features

Pemphigus foliaceus or pemphigus erythematosus are the most common patterns of pemphigus induced by drugs.

Drug-induced pemphigus vulgaris and pemphigus vegetans are rare.

Most patients have circulating autoantibodies with the same antigenic specificities as in other forms of pemphigus

PATHOGENESIS

Alleles of HLA-DR4 predispose to pemphigus vulgaris and a susceptibility allele is also carried by individuals with drug-induced pemphigus .

Perhaps drugs act to trigger disease in genetically predisposed individuals.

An active amide group in the molecule of non-thiol drugs may be responsible for inducing disease.

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PARANEOPLASTIC PEMPHIGUS

PNPP is a severe variant of pemphigus.

It is associated with an underlying neoplasm, most frequently non-Hodgkin's lymphoma, chronic lymphocytic leukemia, or thymoma.

Castleman disease and Waldenstrom macroglobulinemia

are also associated with cases of PNPP.

The damage to the epithelium in PNPP is due to both an autoimmune reaction with epithelial cells and cell-mediated cytotoxicity

CLINICAL FINDINGS

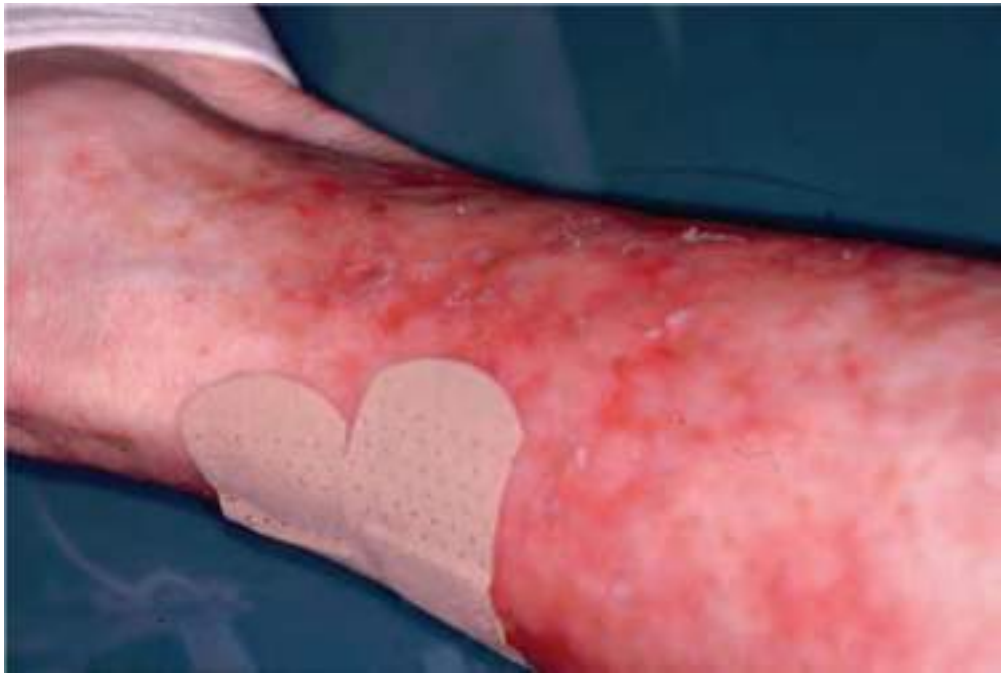
The onset of the disease is often rapid.

Mucocutaneous involvement.

oral and conjunctival lesions are common and present as severe blistering and erosions of the mucous membranes and skin.

These lesions may resemble the inflammatory lesions of a drug reaction, lichen planus, or EM, TEN.

Progressive pulmonary involvement occurs in up to 40% of cases.



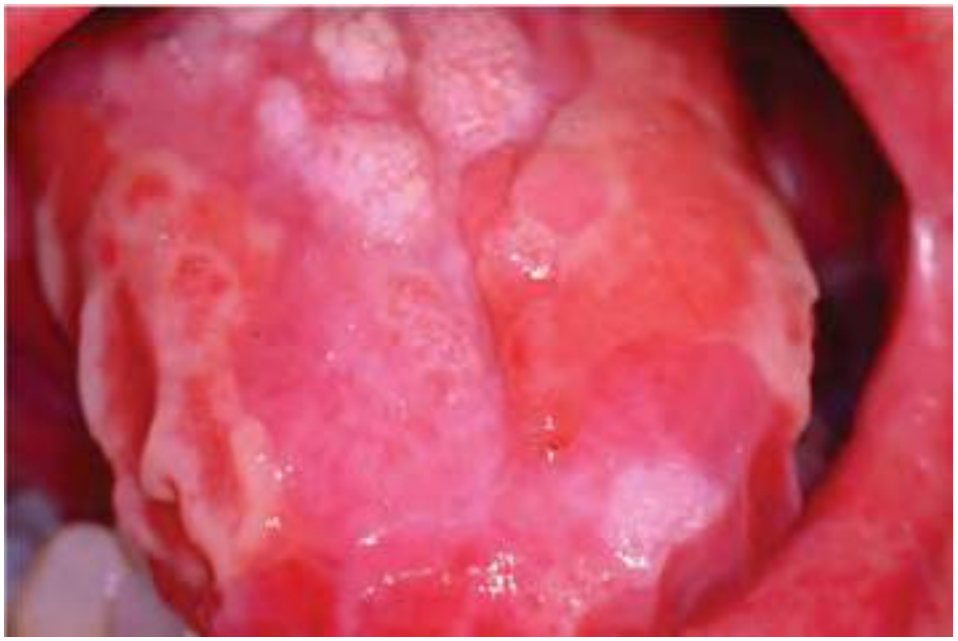
PNP IN HODGKIN LYMPHOMA PATIENT

ORAL MANIFESTATIONS

PNP commonly involve the oral mucosa.

Oral involvement is frequently extensive and painful.

The lesions are frequently inflamed and necrotic, with Large erosions covering the lips, tongue, and soft palate.



Extensive erosion of the tongue in PNP

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SUBEPITHELIAL BULLOUS DERMATOSES

The subepithelial bullous dermatoses are a group of mucocutaneous blistering diseases that are characterized by an autoimmune reaction that weakens a structural component of the basement membrane.

THIS GROUP INCLUDE

1. Bullous pemphigoid,
2. Mucous membrane pemphigoid,
3. Linear IgA disease,
4. Epidermolysis bullosa aquisita,
5. Chronic bullous dermatosis of childhood.

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BULLOUS PEMPHIGOID (BP)

Most common of the subepithelial blistering diseases.

Adults over the age of 60 years

Self-limiting .

May last from a few months to 5 years.

Bp has occasionally been reported in conjunction with other diseases, particularly multiple sclerosis and malignancy, or drug therapy, particularly diuretics

PATHOGENESIS

BP is an autoimmune disease caused by the binding of autoantibodies to specific antigens found in the lamina lucida region of the basement membrane on the hemidesmosomes of epithelial basal cells.

These antigens are glycoproteins referred to as bullous pemphigoid antigens, BP 180 and BP 230.

Binding of antibody to antigen activates both leukocytes and complement, causing localized damage to the basement membrane, resulting in vesicle formation in the subepithelial region.

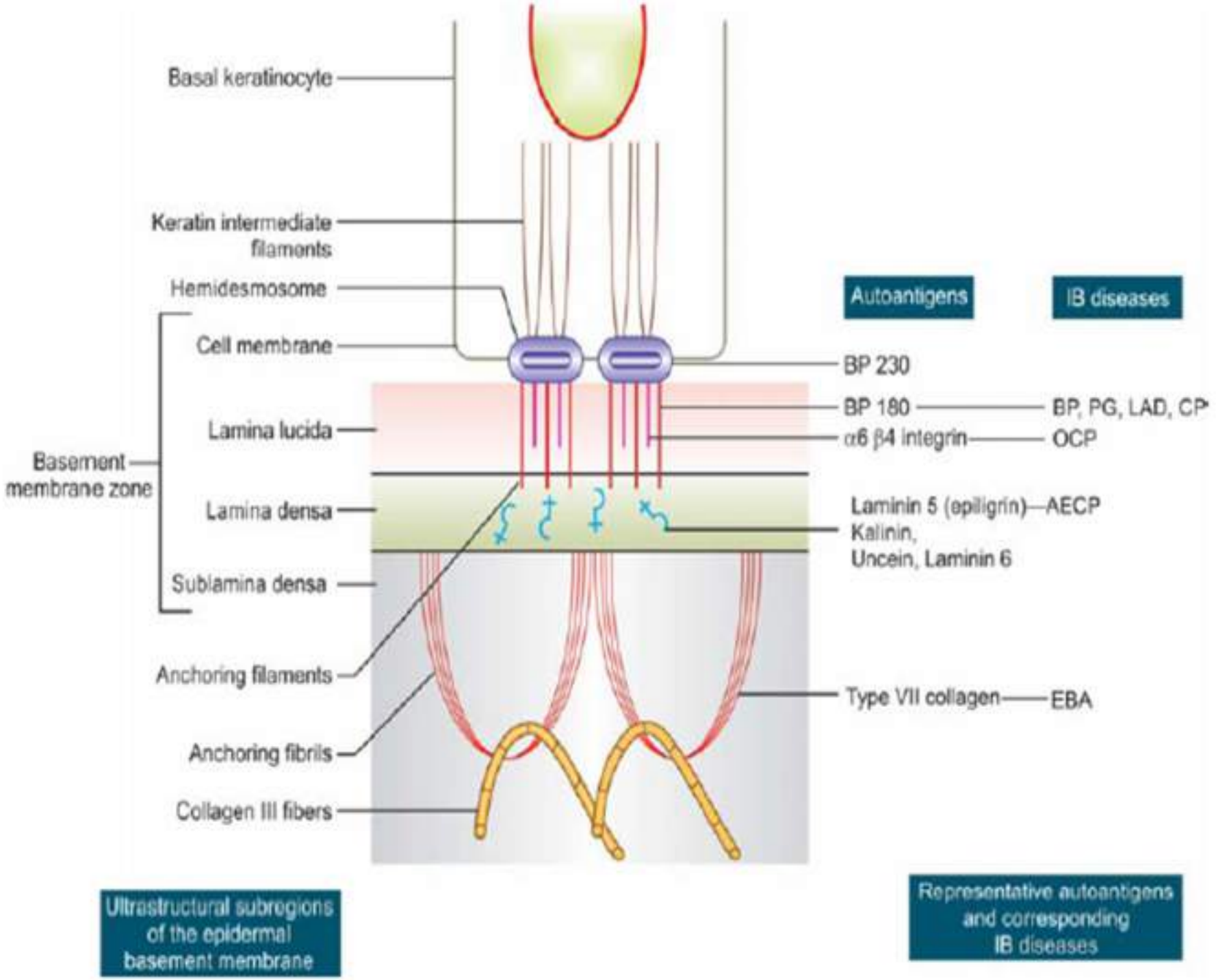

Basal keratinocyte
Keratin intermediate filaments
Hemidesmosome
Cell membrane
Basement membrane zone
Lamina lucida
Lamina densa
Sublamina densa
Anchoring filaments
Anchoring fibrils
Collagen III fibers
Autoantigens
IB diseases
BP 230
BP 180
BP, PG, LAD, CP
α6 β4 integrin
OCP
Laminin 5 (epiligrin)—AECP
Kalinin,
Uncein, Laminin 6
Type VII collagen—EBA
Ultrastructural subregions of the epidermal basement membrane
Representative autoantigens and corresponding IB diseases

Table 1: Immunofluorescence findings in immunobullous disorder[46,47]

Subepidermal bullous disorders	*Antibodies*					*Target antigen*	*Structural target*	*Immunofluorescence patterns*
	IgG	*IgM*	*IgA*	*C3*	*Fibrin*			
Bullous pemphigoid	+ve	-ve	-ve	+ve	-ve	BP230 BP180	Hemidesmosome anchoring filament complexes	Homogenous linear band at the BMZ
Cicatricial pemphigoid	+ve	-ve	-ve	+ve	-ve	BP180, laminin, alpha 4 and beta 6 subunits of integrin	Basement or hemidesmosome	Linear deposition of IgG and C3 along the BMZ
Epidermolysis bullosa acquisita	+ve	+ve	+ve	+ve	-ve	Collagen 7		Linear IgG and/or C3 at BMZ
Linear IgA bullous dermatosis	-ve	-ve	+ve	-ve	-ve	LAD 285, BP180	Hemidesmosome-anchoring filament complexes	Linear deposition of IgA at BMZ

CLINICAL MANIFESTATIONS

The characteristic skin lesion of BP is a blister on an inflamed base.

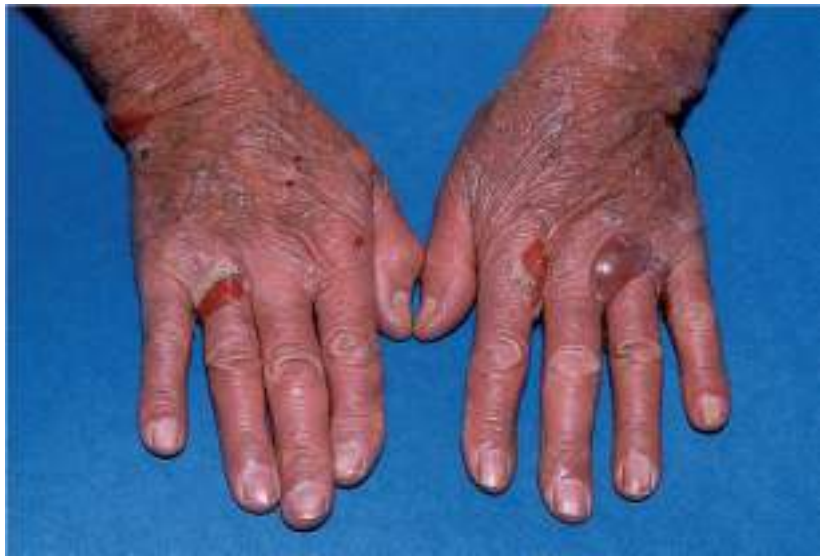
It mainly involves the scalp, arms, legs, axilla, and groin.

Pruritis is a common feature of the skin lesions, which may initially present as macules and papules.

The disease is self-limiting but can last for months to years without therapy.

Unlike pemphigus, BP is rarely life threatening since the bullae do not continue to extend at the periphery to form large denuded areas.

Although death from sepsis or cardiovascular disease secondary to long-term steroid use has been reported to be high in groups of sick elderly patients.



ORAL FINDINGS

Oral involvement is common in BP, occurring in 30 to 50% of patients.

The oral lesions of BP are smaller, form more slowly, and are less painful than those seen in PV, and the extensive labial involvement seen in pemphigus is not present.

Desquamative gingivitis has also been reported as the most common oral manifestation of BP and the gingival lesions may be the only site of oral involvement.

The gingival lesions consist of generalized edema, inflammation, and desquamation with localized areas of discrete vesicle formation.

The oral lesions are clinically and histologically indistinguishable from oral lesions of mucous membrane pemphigoid, but early remission of BP is more common.

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MUCOUS MEMBRANE PEMPHIGOID [MMP (CICATRICIAL PEMPHIGOID)]

MMP is a chronic autoimmune subepithelial disease that primarily affects the mucous membranes .

The primary lesion of MMP occurs when autoantibodies directed against proteins in the basement membrane zone, acting with complement (C3) and neutrophils, cause a subepithelial split and subsequent vesicle formation.

PATHOGENESIS

The antigens associated with MMP are most frequently present in the lamina lucida portion of the basement membrane.

But an identical antigen is not involved in all cases, and the lamina densa may be the primary site of involvement in some cases.

The majority of cases of MMP demonstrate IgG directed against antigens on the epidermal side of the salt-split skin, which have been identified as BP 180 (also called type XVII collagen); however, cases of MMP have also been identified where the antigen is present on the dermal side of the split.

CLINICAL FEATURES

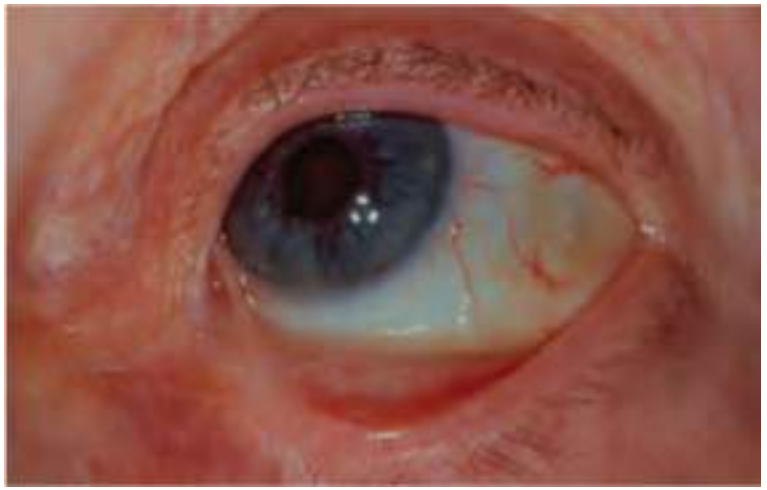
Age - Commonly occurs at age of 50.

Gender - The disease occurs twice as frequently in women.

Site – oral mucosa, conjuctiva, gentital, laryngeal, oesophageal.

It present as mucosal blistering, ulceration, and subsequent scarring.

When conjuctiva is involved adhesions develops between the bulbar and palpebral conjunctiva called symblepharon.



Corneal damage is common, and progressive scarring leads to blindness in close to 15% of patients.

Genital involvement causes pain and sexual dysfunction.

Laryngeal involvement causes pain, hoarseness, and difficulty in breathing.

Esophageal involvement may cause dysphagia, which can lead to debilitation and death in severe cases.

ORAL FINDINGS

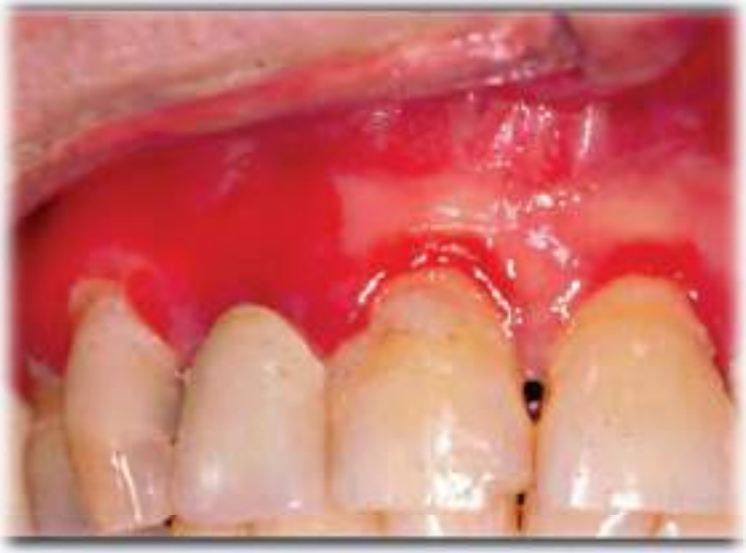
Mucous Membrane Pemphigoid

Oral lesions occur in over 90% of patients with MMP.

Desquamative gingivitis is the most common manifestation.

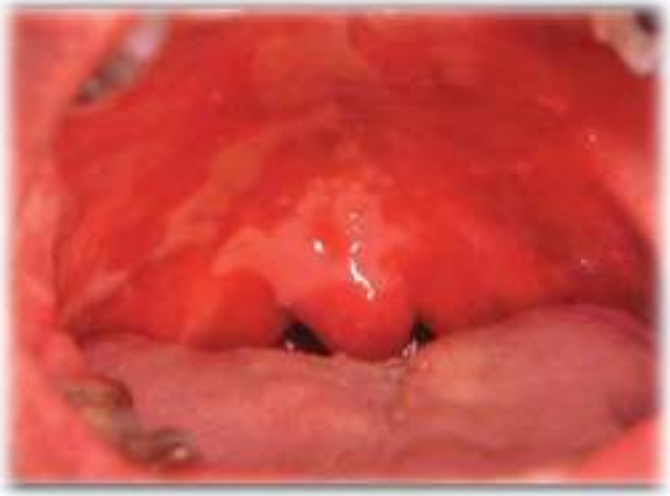
Lesions may present as intact vesicles of the gingival or other mucosal surfaces, but more frequently they appear as nonspecific-appearing erosions.

The erosions typically spread more slowly than pemphigus lesions and are more self-limiting.

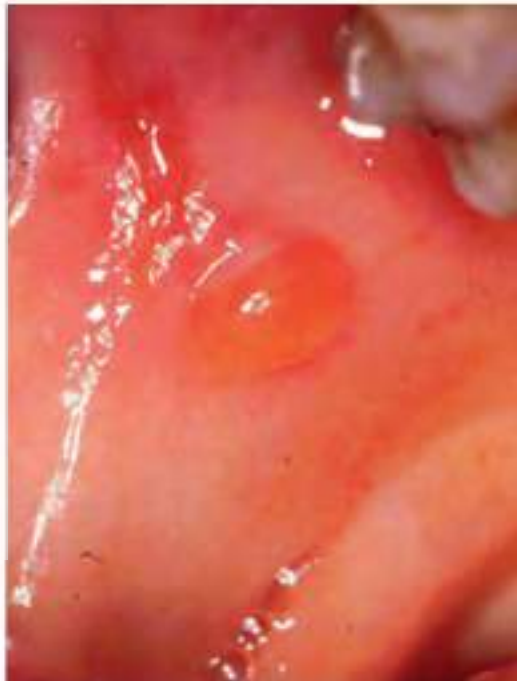


Desquamative Gingivitis in MMP

Intact vesicle in MMP



Lesions on soft palate



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LINEAR IGA DISEASE (LAD)

LAD is a subepithelial disease characterized by the deposition of IgA rather than IgG in the basement membrane.

The clinical manifestations may resemble either dermatitis herpetiformis or pemphigoid.

The cause of the majority of cases is unknown, but some reported cases have been drug induced or associated with systemic diseases, including hematologic malignancies, or connective tissue diseases, such as dermatomyositis.

As in MMP, the antigens associated with LA D are heterogeneous and may be found in either the lamina lucida or lamina densa portions of the basement membrane.

CLINICAL MANIFESTATIONS

The skin lesions of LAD resemble to dermatitis herpetiformis.

Which are characterized by pruritic papules and blisters at sites of trauma such as the knees and elbows.

Other patients have bullous skin lesions similar to those seen in patients with BP. The oral mucosa and conjunctiva are also commonly involved.

ORAL FINDINGS

Oral lesion (70% of patients) are common in LAD.

These lesions are clinically indistinguishable from the oral lesions of MMP.

Blisters and erosions of the mucosa frequently accompanied by desquamative gingivitis.

Desquamative gingivitis alone can be present as in MMP.

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EPIDERMOLYSIS BULLOSA AQUISITA (EBA)

Patients with E BA have I gG autoantibodies directed against type VII collagen, a component of the anchoring fibrils of the basement membrane.

There are two forms of EBA:

The classic form - lesion of the basement membrane with little inflammation,

The inflammatory form - significant infiltration of neutrophils.

The clinical course of EBA can resemble BP or MMP with widespread skin lesions or primary involvement of the oral mucosa, genital mucosa, conjunctiva, and larynx.

CHRONIC BULLOUS DISEASE OF CHILDHOOD (CBDOC)

CBDC is a subepithelial blistering disorder.

It mainly affects children below the age of 5 years.

It is characterized by the deposition of IgA antibodies in the basement membrane zone.

CLINICAL MANIFESTATIONS

The onset of the disease may be precipitated by an upper respiratory infection or drug therapy.

The characteristic lesion of CBDC is a cluster of vesicles and bullae on an inflamed base.

The genital region is commonly involved, and conjunctival, rectal, and oral lesions may also be present.

CBDC is self-limiting and resolves prior to puberty.

ORAL FINDINGS

Oral mucosal involvement is present in up to 50% of cases, and the oral lesions are similar to those observed in patients with MMP.

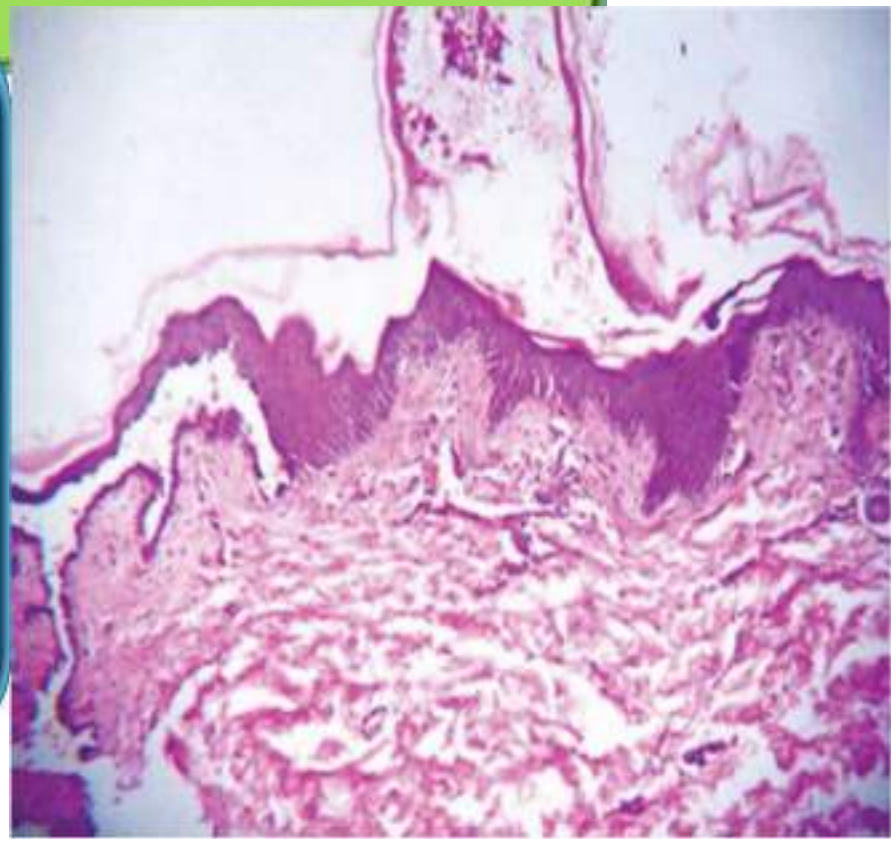
Lesions of the perioral skin are common in CBDC.

PEMPHIGUS

LABORATORY FINDINGS

Tzank prepration shows acantholytic cells, mixed inflammatory infiltrate with few eosinophils .

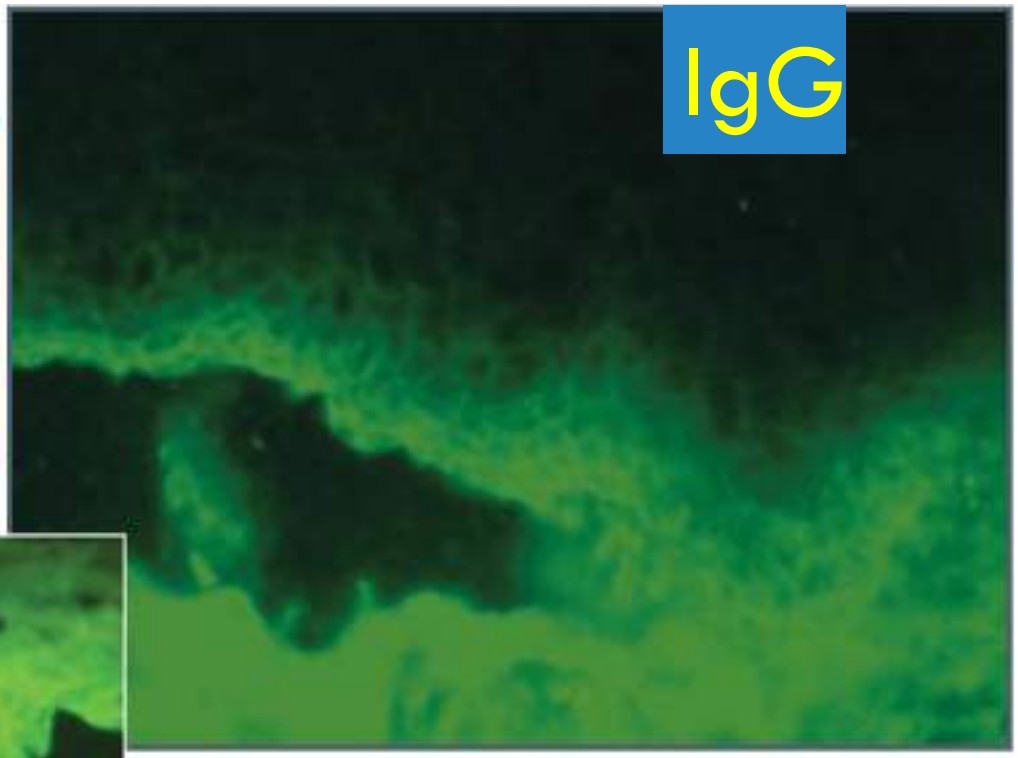
BIOPSY shows acantholytic cells in vesicular space.sometimes entire superficial layers of epithelium are stripped away, leaving only basal cells,which is known as "row of tomb-stones" as basal cells are firmly attached to the basement membrane by hemidesmosomes.

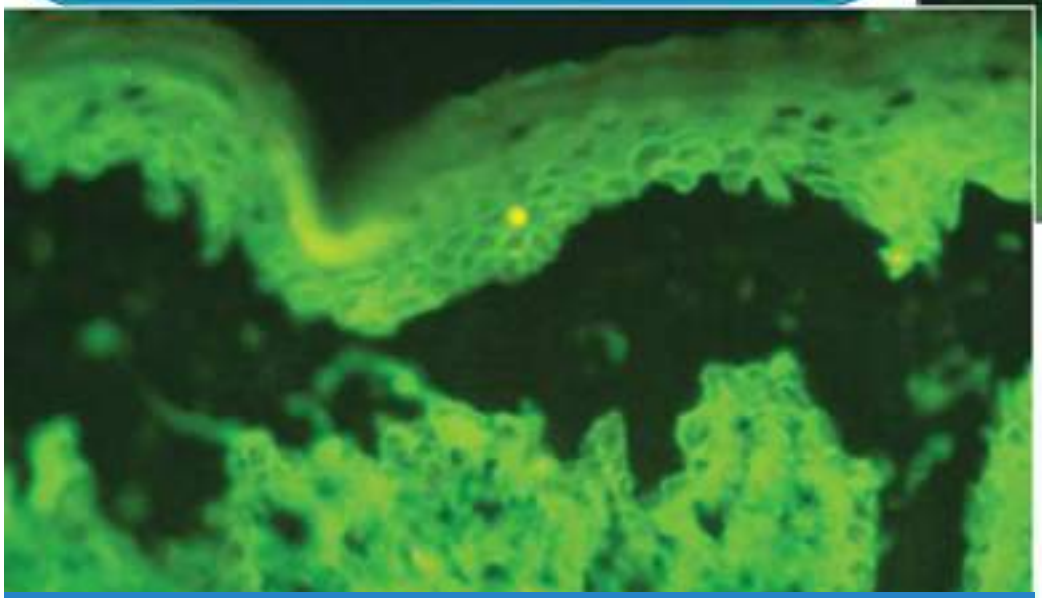


PEMPHIGUS

LABORATORY FINDINGS

DIF - IgG and complement, Bound to the surface of the keratinocytes





C3 BUT PRESENT WITH LESS FREQUENCY AND INTENSITY

PEMPHIGUS

Indirect immunofluorescence circulating autoantibodies (IgG4) are detected.
However, same antibodies are present in thermal burns , toxic epidermal necrolysis, penicillin reactions , staphylococcal scalded skin syndrome and in first-degree relatives of relatives of pemphigus patients

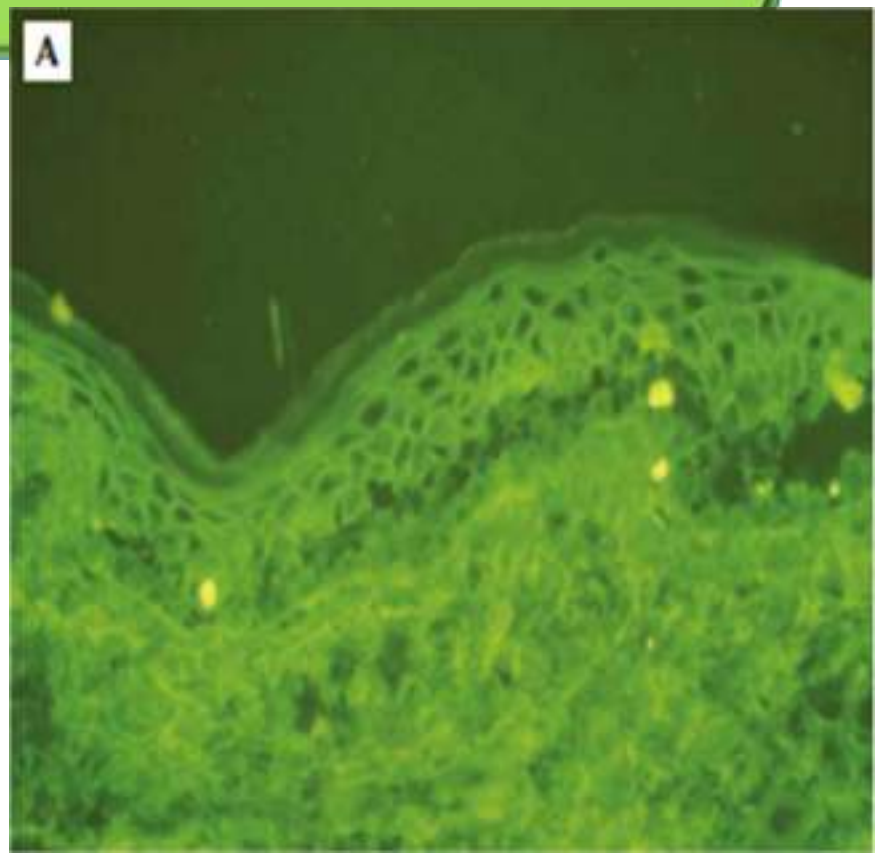
	Electron microscopy widening of the intercellular space, splitting of the desmosome junctions. cytokeratin tonofilaments retraction around the nucleus, the disappearance of desmosomal plaques

LABORATORY FINDINGS

PNPP

Biopsy is suggestive of EM, lichen planus, pemphigoid and pemphigus. There is inflammation at the dermal-epidermal junction and keratinocyte necrosis in addition to acantholysis.

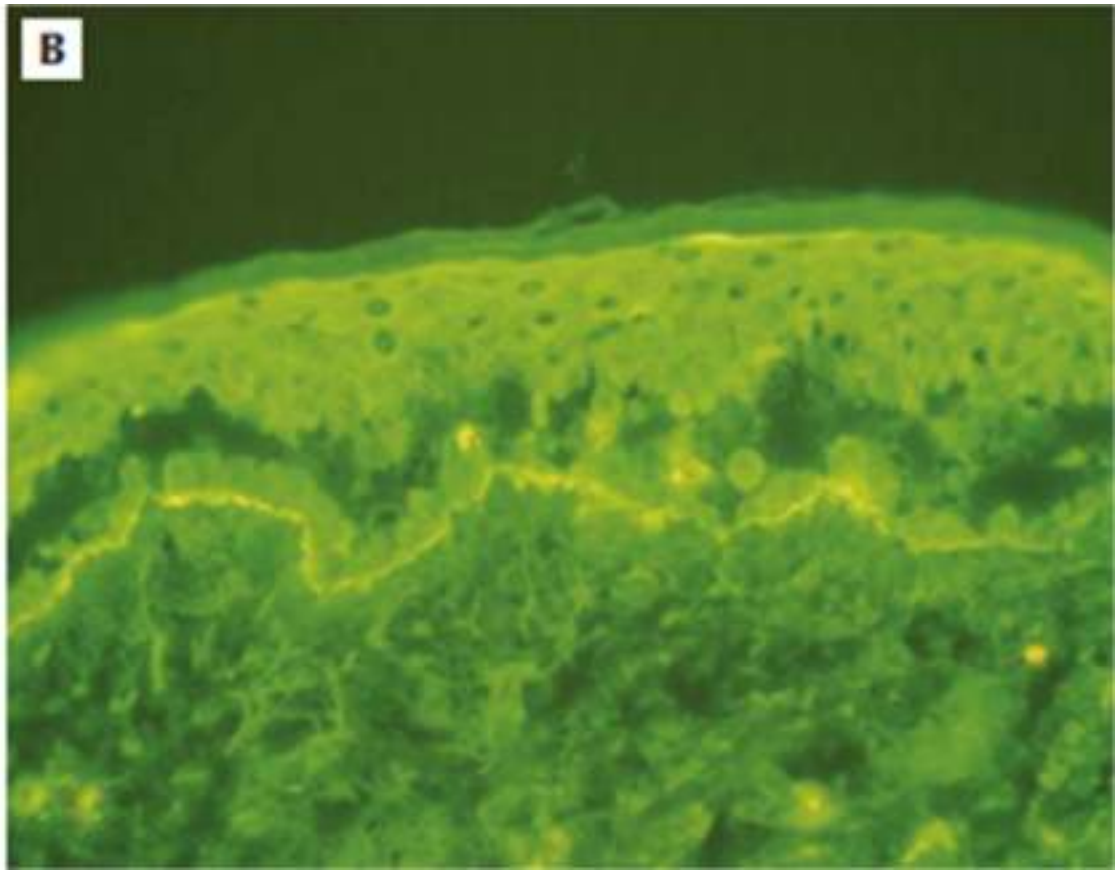
DIF shows deposition of IgG and complement along the basement membrane as well as on the keratinocyte surface in an intercellular location



PNPP

IIF demonstrates antibodies that not only bind to epithelium but to liver, heart, and bladder tissue as well.
(it targets multiple antigens)

Of four classes of IgG, IgG1 is main indicator for PNPP.

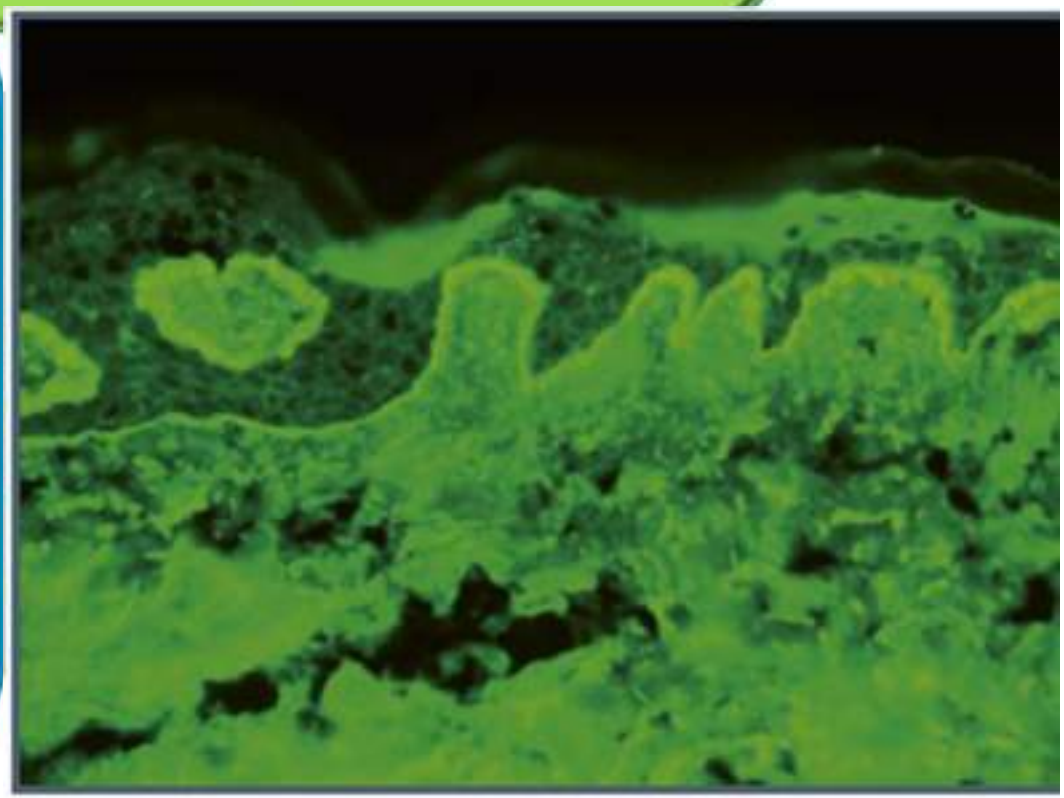


LABORATORY FINDINGS

Bullous Pemphigoid (BP)

Routine histology of a biopsy specimen demonstrates separation of the epithelium from the connective tissue at the basement membrane zone and an inflammatory infiltrate that is usually rich in eosinophils, particularly in skin biopsies.

DIF study of a biopsy specimen taken from perilesional inflamed tissue demonstrates deposition of I gG and C 3 bound in a linear band to the basement membrane.



IIF study of serum obtained from patients with BP demonstrates IgG antibodies bound to the epidermal side of salt-split skin. The salt-split skin test is particularly useful in distinguishing BP from EBA that has IgG antibodies localized to the dermal side of the salt-split skin (floor of the blister). IIF is not a reliable test for BP.

LABORATORY FINDINGS

Mucous Membrane Pemphigoid

Routine histology demonstrates a lesion in the subepidermal basement membrane, which is frequently accompanied by an inflammatory infiltrate.

DIF demonstrate positive fluorescence for immunoglobulin (IgG) and complement (C3) in the basement membrane zone in 50 to 80% of patients. Splitting the biopsy specimen at the basement membrane zone with 1 M NaCl prior to DIF, the salt-split skin technique, increases the sensitivity of the test.

Only 10% of MMP patients demonstrate positive II F for circulating antibasement membrane zone antibodies; however, use of salt-split skin as a substrate increases the sensitivity of this test.

LABORATORY FINDINGS

Linear igA disease

Routine histology demonstrates a lesion in the subepidermal basement membrane, which is frequently accompanied by an inflammatory infiltrate.

DIF study will show deposition of I gA rather than I gG.

IIF is usually negative, but when positive, it will demonstrate circulating I gA antibodies against a basement membrane antigen.

LABORATORY FINDINGS

Routine histology demonstrates a lesion in the subepidermal basement membrane, which is frequently accompanied by an inflammatory infiltrate.

DIF study will show deposition of I gA rather than I gG.

IIF demonstrates circulating I gA in 80% of cases

Management

- **Topical therapy**
- Intralesional injections of corticosteroids
- Topical anticholinergic gel (pilocarpine)
- Oral infection – topical nystatin, amphotericin or imidazoles
- Cutaneous infection – topical antiseptic and potassium permagnate

ORAL CORTICOSTEROIDS

High doses of systemic corticosteroids (Prednisone) are the mainstay of treatment.

Dosages - 1 to 2 mg/kg/d.

When pemphigus is confined to oral cavity prednisone alone can be given with greater effect.

However when skin lesions are present, combined therapy is usually given to reduce the mortality rate.

When steroids are used for long periods of time, adjuvant therapy is recommended to reduce the steroid dose and their potential serious complications.

The most commonly used adjuvants are immunosuppressive drugs such as mycophenolate mofetil, azathioprine, or cyclophosphamide.

Clinical improvement may be seen within days of starting steroids.

On average, cessation of blistering takes 2-3 weeks. (*Lever1984, Ratnam1990*)

Full healing takes 6-8 weeks. (*Lever1963*)

K.E.Harman, S.Albert And M.M.Black; Guidelines for the management of pemphigus vulgaris; British Journal of Dermatology 2003; 149: 926–937.

Doses-

Bystryn suggested a modified regimen for dosing schedule.

- Mild diseases - prednisolone 40-60 mg/day
- Severe diseases- 60-100mg/day.

If no response with in 5-7 days,the dose should be increased in 50 – 100 % increments untill the disease control.

If >100 mg is required than pulse therapy should be considered.

Once remission is induced and maintained with healing of majority of lesions, the dose can be tapered.

Initially reduce by 5-10 mg weekly and more slowly below 20 mg prednisolone daily.

K.E.Harman, S.Albert And M.M.Black; Guidelines for the management of pemphigus vulgaris; British Journal of Dermatology 2003; 149: 926–937.

PULSED INTRAVENOUS CORTICOSTEROIDS

Dexmethasone Cyclophosphosphamide pulse therapy (DCP) was Introduced by Pasricha et al in 1981.

The treatment is divided into four phases

Amrinder J. Kanwar, Dipankar De; Pemphigus in India; Indian Journal of Dermalogy, Venerology, and Leprology; 2007:77(4)

PHASE I

1. 100mg of dexamethasone dissolved in 500 ml of 5% dextrose by slow iv infusion over 2 hour on 3 consecutive days.
2. 500 mg of cyclophosphophamide in the infusion on day 2.
3. in between patient recieve 50 mg of oral cyclophosphophamide daily.

Amrinder J. Kanwar, Dipankar De; Pemphigus in India; Indian Journal of Dermalogy, Venerology, and Leprology; 2007:77(4)

PHASE II

Monthly DCP therapy

Daily oral cyclophosphosphamide 50 mg for 6 or 9 months.

Amrinder J. Kanwar, Dipankar De; Pemphigus in India; Indian Journal of Dermalogy, Venerology, and Leprology; 2007:77(4)

PHASE III

Only oral cyclophosphamide is continued for 9 or 12 months.

Amrinder J. Kanwar, Dipankar De; Pemphigus in India; Indian Journal of Dermalogy, Venerology, and Leprology; 2007:77(4)

PHASE IV

Treatment free follow up period for for early detection of relapses.

Amrinder J. Kanwar, Dipankar De; Pemphigus in India; Indian Journal of Dermalogy, Venerology, and Leprology; 2007:77(4)

Recently in other countries ; UK , South Africa, Serbia (*Zivanovic 2010, Saha 2010, Shaik 2010*) have found it useful.[1]

Sharma et al 2013 have found reduced time to remission, low cumulative corticosteroid dose, and lower rate of relapse when cyclophosphamide prednisolone therapy is used comparing with oral corticosteroids.[2]

Amrinder J. Kanwar, Dipankar De; Pemphigus in India; Indian Journal of Dermalogy, Venerology, and Leprology; 2007:77(4)

Sharma VK, Khandpur S; Evaluation of cyclophosphamide pulse therapy as an adjuvant to oral corticosteroid in the management ofpemphigus vulgaris; Clin Exp Dermatol. 2013 Aug;38(6):659-64.

Flushing (53.4%), weakness (55.4%) are the common complications.

Other immediate side effects include palpitations, hiccup, numbness of feet, psychosis.

Long term side effects include rise of blood sugar, sleep disorder, arthralgia, blurring of vision,loss of hair,discoloration of nails

ADJUVANT DRUGS

Generally slower in onset than steroids, so rarely used alone to induce remission.

Commonly used in conjunction with corticosteroids for their steroid sparing actions.

AZATHIOPRINE

Commonly used in combination with corticosteroids for steroid sparing action.

Complete remission rate 28-45%.

Mortality rate 1.4 – 7%.

Dose – 1-3 mg/kg

Should be avoided in low TPMT (thiopurine methyl transferase) level.

Side effects - Myelosuppression and hepatotoxicity

K.E.Harman, S.Albert And M.M.Black; Guidelines for the management of pemphigus vulgaris; British Journal of Dermatology 2003; 149: 926–937.

ORAL CYCLOPHOSPHAMIDE

Studies have reported the steroid sparing effect of cyclophosphamide at doses of 50-200 mg/day.

Can be used as an alternative to azathioprine.

Side effects – haemorrhagic cystitis, carcinoma of bladder

K.E.Harman, S.Albert And M.M.Black; Guidelines for the management of pemphigus vulgaris; British Journal of Dermatology 2003; 149: 926–937.

MYCOPHENOLATE MOFETIL

Can be used for recalcitrant cases where cyclophophamide and azathioprine is unsuitable.

Dose – 2-2.5 gm in two divided doses daily with prednisolone.

MMF monotherapy has been reported beneficial in two cases. (*Bredlich and Grundmann-Kollmann1999*)

RITUXIMAB

The rationale for the use of rituximab in patients with PV is based on its ability to deplete CD20+ B cells that presumably produce pathogenic Antibodies

Its use in pemphigus is off label.[1]

1. Gurcan HM, Keskin DB, Stern JN, et al. A review of the current use of rituximab in autoimmune diseases. Int Immunopharmacol. 2009;9:10–25.

A meta-analysis of published prospective and retrospective studies on rituximab in pemphigus, showed

- overall efficacy of 65%.
- Serious infections in 7%

(*Feldman 2011*)

OTHER DRUGS

Gold, dapsone ,Methotrexate, Ciclosporin, Tetracyclines and nicotinamide.

IV IG

Can be used as possible adjuvant maintenance agent for recalcitrant cases failed on other regimens.

Severe cases to induce remission while slower acting drugs take effect.

PLASMA EXCHANGE

No benefit over and above steroids. (*Guillaume1988)*

Some case reports suggest steroid sparing effect. (*Turner 2000*).

Not recommended as routine but may be considered for difficult cases in combination with steroids and immunosupressants.

EXTRACORPOREAL PHOTOPHERESIS

Have shown efficacy in recalcitrant cases reducing steroid and immunosuppressive doses.

MANAGEMENT OF PNPP

PNPP secondary to localized tumors such as Castleman disease - surgical removal of the tumor.

Patients with PNPP resulting from lymphoma, have a poor prognosis.

They usually die within 2 years from a combination of the underlying disease, respiratory failure, and extensive mucocutaneous involvement.

Use of a combination of prednisone and immunosuppressive drug therapy may help control the severity of the skin lesions, but the oral, conjunctival, and pulmonary disease is frequently resistant to treatment.

MANAGEMENT OF BP

Localized oral lesions of BP - high-potency topical steroids, such as clobetasol or betamethasone.

Moderate cases - systemic steroids may be avoid by use of dapsone or tetracycline, doxycycline, or minocycline, which may be combined with niacinamide.

whereas patients with more extensive disease require use of systemic corticosteroids alone or combined with immunosuppressive drugs such as azathioprine, cyclophosphamide, or mycophenolate.

MANAGEMENT OF MMP

Depends on the severity of symptoms and site of involvement.

When the lesions are confined to the oral mucosa, use of systemic corticosteroids should only be considered for short periods of time for severe outbreaks.

Patients with mild oral disease should be treated with topical and intralesional steroids.

Unlike pemphigus, MMP is rarely a fatal disease, and long-term use of systemic steroids for oral lesion involvement alone is seldom indicated.

Desquamative gingivitis can often be managed with topical steroids in a soft dental splint.

When topical or intralesional therapy is not successful, tetracycline, doxycycline, or minocycline is helpful in controlling desquamative gingivitis and other oral lesions.

When there are severe oral lesions, conjunctival or laryngeal involvement, dapsone therapy is recommended as the next choice before considering long-term systemic steroids or immunosuppressive drug therapy.

- Side effects - hemolysis and methemoglobinemia
- Therefore, monitor - glucose-6-phosphate dehydrogenase deficiency, hemoglobin

MANAGEMENT OF LINEAR IGA DISEASE

Any subepithelial blistering disease, the possibility of an underlying drug reaction or malignancy should be suspected.

The oral lesions of LAD may be managed with the use of topical steroids.

But it is not as effective as in MMP to either topical or systemic steroid therapy alone.

Dapsone is often effective when topical steroids alone are insufficient.

Sulfapyridine or tetracycline, which may be combined with niacinamide, is also effective.

Severe cases - systemic corticosteroids + immunosuppressive drug therapy.

MANAGEMENT OF EPIDERMOLYSIS BULLOSA AQUISITA (EBA)

The treatment is similar as described for MMP and LA D.

The classic form of the disease tends to be resistant to treatment.

Whereas the inflammatory form often responds well to dapsone.

Some patients with an inadequate response to dapsone have obtained remission with colchicine.

Systemic corticosteroids and immunosuppressive drugs are often required to control the lesions in severe widespread EBA.


Thank You