Ulcerative, Vesicular, and Bullous Lesions

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Dermatologic lesions are classified according to their **clinical appearance**
Frequently used terms that are applicable in the oral mucosa are:

- **1. *Macules*.** These are lesions that are **flush with the adjacent mucosa** and that are noticeable because of their **difference in color from normal** skin or mucosa. They may be **red due to increased vascularity or inflammation**, **or pigmented due to the presence of melanin**, **hemosiderin, and foreign materials** (including the breakdown products of medications).
- A good example in the oral cavity is the **melanotic macule.**
- **2. *Papules*.**
- These are lesions **raised above the skin or mucosal surface that are smaller than 1.0 cm in diameter** (some use 0.5 cm for oral mucosal lesions).
- They may be slightly domed or flat-topped.
- Papules are seen in a wide variety of diseases, such as **the yellow-white papules of pseudomembranous candidiasis**.

- **3. *Plaques***. These are **raised lesions that are greater than 1 cm in diameter**; they are **essentially large papules.**
- **4. *Nodules*.** These lesions are present within the dermis or mucosa. The lesions may also **protrude above the skin or mucosa forming a characteristic dome-shaped structure.** A good example of an oral mucosal nodule is the **irritation fibroma.**

5. Vesicles.

These are small blisters containing clear fluid that are **less than 1 cm in diameter**.

6. Bullae.

These are elevated blisters containing clear fluid that are **greater than 1 cm** in diameter

7. Erosions. These **are red lesions** often caused by **the rupture of vesicles or bullae**, or **trauma**. May also **result from thinning or atrophy of the epithelium in inflammatory** diseases such as **lichen planus**. These should not be mistaken for ulcers that are covered with fibrin and are yellow although erosions may develop into ulcers.

8. Pustules. These are **blisters containing purulent material and appear yellow**.

9. Ulcers.

These are **well-circumscribed, sometimes depressed lesions** with an **epithelial defect** that is **covered by a fibrin clot**, resulting in a yellow-white appearance. e.g. aphthous

10. Purpura. reddish to purple discolorations caused by **blood from vessels leaking into the connective tissue**.

These lesions **do not blanch when pressure is applied and are classified by size as petechiae** (less than 0.3 cm), **purpura** (0.4–0.9 cm), or **ecchymoses** (greater than 1 cm)

1. The Patient with Acute Multiple Ulcers

2. The Patient with Recurring Oral Ulcers

3. The Patient with Chronic Multiple Ulcers

4. The Patient with Single Ulcers

1. The Patient with Acute Multiple Ulcers

1. Herpes Simplex Virus Infections
2. Varicella-Zoster Virus Infections
3. Cytomegalovirus Infections
4. Coxsackievirus Infection - CV Infections
5. Necrotizing Ulcerative Gingivitis and Necrotizing Ulcerative Periodontitis
6. Erythema Multiforme
7. Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis
8. Plasma Cell Stomatitis and Oral Hypersensitivity Reactions

1. Herpes Simplex Virus Infection

Etiology and Pathogenesis

- **The primary infection**, which occurs on initial contact with the virus, is acquired by inoculation of the mucosa, skin, and eye with infected secretions.

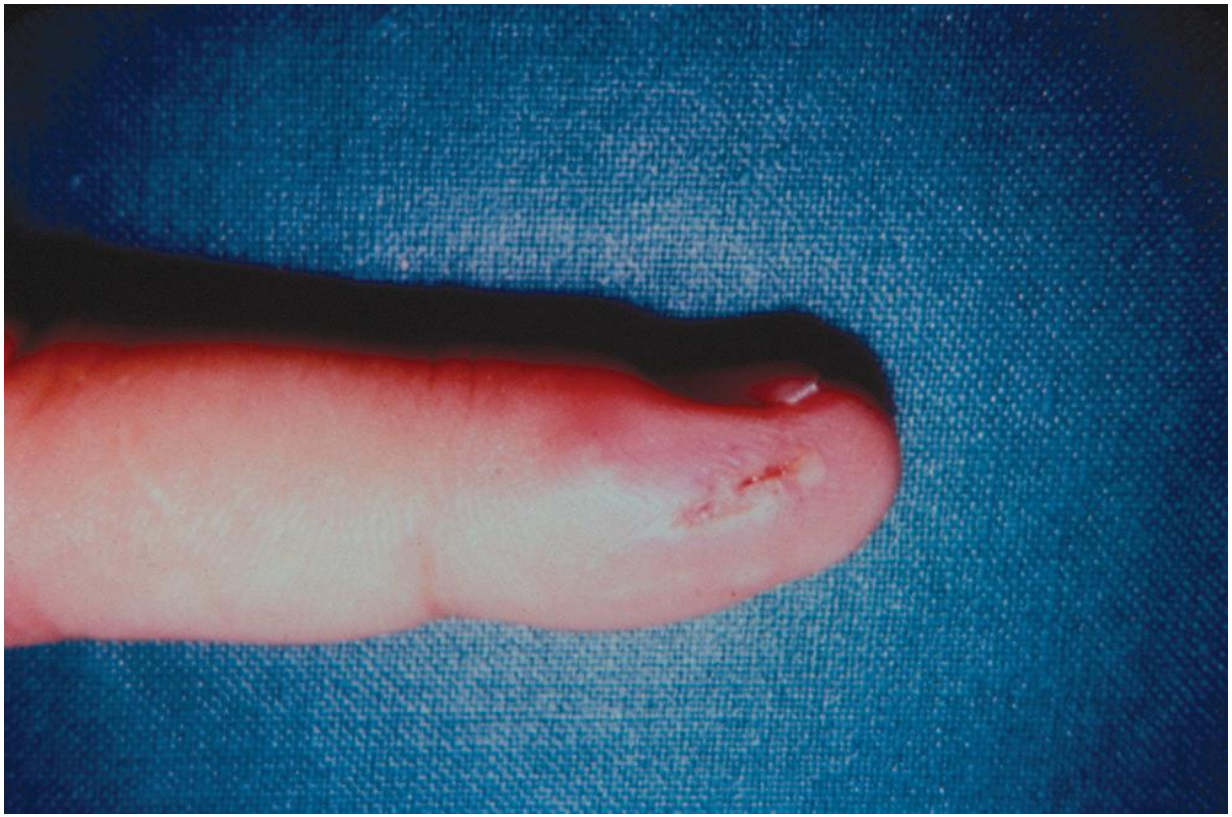
The virus then **travels** along the sensory nerve axons and establishes chronic, latent infection in the sensory ganglion (trigeminal ganglion).

Extraneuronal latency (i.e., HSV remaining latent in cells other than neurons such as the epithelium) may play a role in recurrent lesions of the lips.

Recurrent HSV results when HSV **reactivates at latent sites** and travels centripetally to the mucosa or the skin, where it is directly cytopathic to epithelial cells, causing recrudescent HSV infection in the form of localized vesicles or ulcers.

The most common sites of infection are the **oral** and **genital** mucosa and the **eye**

- HSV infection of the cornea (keratitis) is a major cause of blindness in the world.
- HSV-1 or -2 may cause **herpes whitlow**, an infection of the fingers when virus is inoculated into the fingers through a break in the skin .
- This was a common occupational hazard (including within the dental profession) before the widespread use of gloves.



Other HSV-1 infections include

1. Herpes gladiatorum (infections of the skin spread through the sport of wrestling), herpes encephalitis, HSV esophagitis,
2. HSV pneumonia and neonatal and disseminated infection.
3. HSV is an important etiologic agent in erythema multiforme,
4. HSV has been recovered in the endoneurial fluid of 77% of patients with Bell palsy.

{**endoneurium** a layer of delicate connective tissue around the myelin sheath of each myelinated nerve fiber. Its component cells are called **endoneurial}**

Treatment with antiviral therapy resulted in better outcomes, further supporting the concept of HSV involvement in the pathogenesis of Bell palsy.

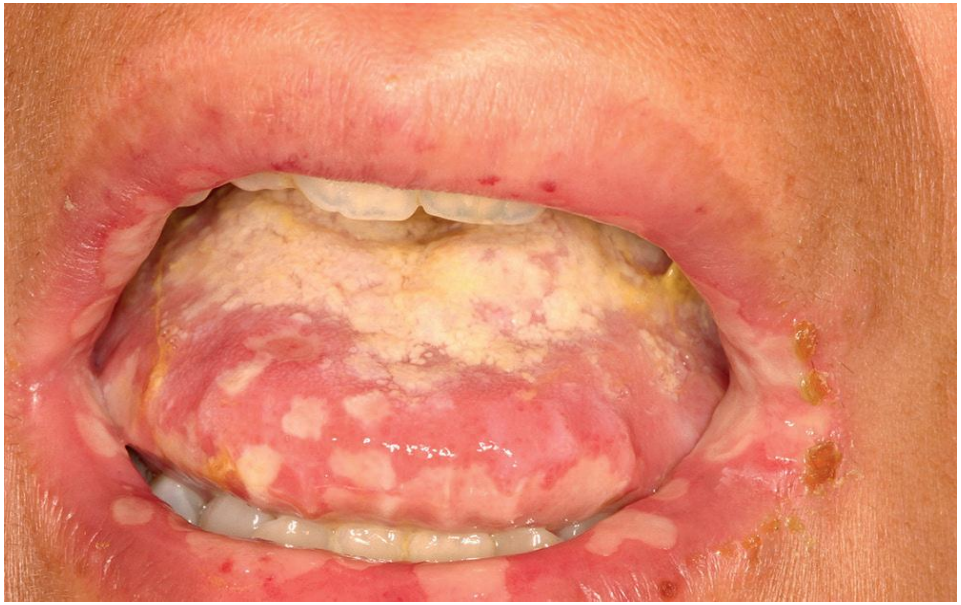
Primary Gingivostomatitis
Clinical Manifestations

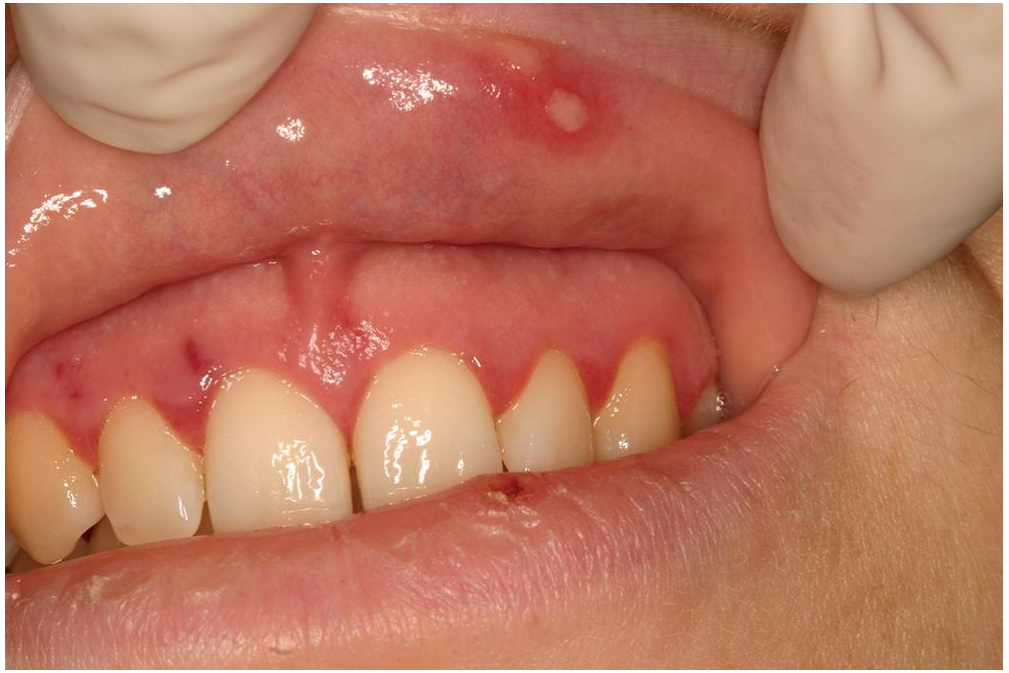
- The majority of primary HSV-1 infections are subclinical and generally occur in **children** and **teenagers**, and **young Adults**
- There is a one- to three-day viral prodrome of fever, loss of appetite, malaise, and myalgia that may also be accompanied by headache and nausea.
- Oral pain leads to poor oral intake, and patients may require hospitalization for hydration.
- The disease is self-limiting in otherwise normal patients and resolves within 10–14 days, typical for a viral illness.

Oral Findings

- Within a few days of the prodrome, erythema and clusters of vesicles and/or ulcers appear on the keratinized mucosa of the hard palatal mucosa, attached gingiva and dorsum of the tongue, and the nonkeratinized mucosa of the buccal and labial mucosa, ventral tongue, and soft palate.
- Vesicles break rapidly down to form ulcers that are usually 1–5 mm and coalesce to form larger ulcers with scalloped borders and marked surrounding erythema.
- The gingiva is often erythematous, and the mouth is extremely painful, causing difficulty with eating. Pharyngitis causes swallowing difficulties.

Primary HSV infection in adults follows a similar pattern





Recrudescent (renewing) Oral HSV Infection

❖ **Reactivation** of HSV may lead to asymptomatic shedding of HSV, in the saliva and other secretions, an important **risk factor** for transmission; it may also cause ulcers to form.

- Asymptomatic shedding of HSV is not associated with systemic signs and symptoms and occurs in 8-10% of patients following dental treatment.

❑ Reactivation of **HSV-1** on the oral mucosa is common and usually **asymptomatic**. However, **HSV-1** is rarely found in tears and nasal mucosa. Frequent oral **shedding** of **HSV-1** may increase the risk for transmitting the virus to both oral and genital mucosa of sexual partners

❖ The term ***recrudescent HSV*** should be used to refer to the actual ulcerations caused by reactivated virus.

❖ Fever, ultraviolet radiation, trauma, stress, and menstruation are important triggers for reactivation of HSV.

❖ Recrudescent HSV on the lips is called recurrent herpes labialis (RHL) and occurs in 20- 40% of the young adult population

- These are associated with a prodrome **of itching, tingling, or burning** approximately 50% of the time, followed by the appearance of papules, vesicles, ulcers, crusting, and then resolution of lesions
- Pain is generally present only within the **first two days**.
- **There is a suggestion that patients who do not experience a prodrome develop lesions from extraneural latent HSV within the epithelium and these lesions are less responive to topical therapy**.

Recrudescent intraoral HSV (RIH) in the immunocompetent host

- Occurs chiefly on the **keratinized mucosa** of the hard palatal mucosa, attached gingiva, and dorsum of the Tongue
- They present as **1–5 mm** single or clustered painful ulcers with a bright erythematous border .
- One common presentation is the complaint of pain in the gingiva **one to two days** after a scaling and prophylaxis or other dental treatment.
- Lesions appear as **1–5 mm** painful vesicles but more often ulcers on the marginal gingiva.

HSV in Immunocompromised Patients

- In immunocompromised patients (such as those undergoing chemotherapy, who have undergone organ transplantation, or who have acquired immune deficiency syndrome [AIDS]),
- may occur at any site intraorally and may form ulcers that may be
- **several centimeters in size** and may **last several weeks or months** if undiagnosed and untreated
- Single RIH ulcers are clinically indistinguishable from recurrent aphthous ulcers if they occur on a nonkeratinized site.
- These ulcers are painful and similar to those seen in immunocompetent patients **except** that they may be larger and often occur on nonkeratinized sites.
- They appear slightly depressed with raised borders.
- The presence of 1–2 mm vesicles or satellite ulcers at the edges of the main ulcer is a helpful sign.

If undiagnosed and left untreated, RIH infection may disseminate to other sites and cause severe infections in the immunocompromised population.

This is a particular problem in patients undergoing **hematopoietic stem cell transplantation**, where reactivation of HSV occurs in approximately 70% of patients.

Laboratory Diagnosis

HSV isolation by cell culture is the gold standard test for the diagnosis since it **grows readily in tissue culture**.
A single swab of the oral ulcers is performed.
More recently, **polymerase chain reaction (PCR)** from **swabs** has been shown to detect HSV antigen **3 to 4 times** more often than culture
real-time PCR has also been shown to be highly sensitive and specific.

- Primary HSV infection is associated with elevated immunoglobulin (Ig)M titers that occur **within days**, followed several weeks later by permanent IgG titers, that indicate previous infection but confer no protection against reactivation.

- **Recurrent infection** is associated with a rise in **IgG antibody titer** in acute and convalescent sera, but a fourfold rise (a criterion that indicates active infection) is seen in only 5% of patients.

- The assay for HSV IgM is not particularly reliable for diagnostic purposes, and overall, the use of serology alone to diagnose recurrent infection is not advised.

HSV lesions **are not generally biopsied** because the clinical appearance and history are characteristic, and infection is readily confirmed with a culture or cytology specimen when necessary.

Management

Primary HSV Infection

Management is directed toward

1. Pain control,
2. Supportive care,
3. Definitive treatment.

In the past, healthy patients with primary herpetic gingivostomatitis were treated only with hydration and supportive measures.

However, since the **acyclovir family** of drugs is inexpensive, safe, and readily available, it is appropriate to treat even primary infections definitively because it **reduces viral shedding and infectivity.**

Acyclovir **inhibits viral replication** and is activated by virally produced **thymidine kinase**.

As such, it has little activity against nonvirally infected cells.

The use of acyclovir at **15 mg/kg five times a day in children** reduces the duration of fever, reduces HSV shedding, stops the progress of lesions, improves oral intake, and reduces the incidence of hospital admissions.

Valacyclovir, a prodrug of acyclovir, has 3 to 5 times the bioavailability of acyclovir and, together with famciclovir, is now widely used.

Recrudescent HSV

Recurrent herpes labialis can often be suppressed by reducing tissue damage, such as using sunscreen. Although RHL is self-limiting, the use of topical antiviral medications reduces shedding, infectivity, pain, and the size and duration of lesions.

Topical antiviral medications such as **5% acyclovir cream**, **1% penciclovir** cream, and **10% docosanol** cream are efficacious if applied **5 to 8 times a day at the first prodrome or sign of a lesion.**

Systemic therapy with valacyclovir (2 g every 12 hours for one day) or famciclovir (1500 mg single dose) are both effective in treating active lesions of RHL

For intraoral lesions, treatment is with 500–1000 mg valacyclovir three times a day or 400–800 mg of acyclovir for 7–10 days.

Suppression of HSV infection in patients who develop **Frequent Episodes, Large Lesions, Or Erythema Multiforme** is effected with variable doses of acyclovir, valacyclovir, and famciclovir.

Similar **suppressive regimens** can be used for patients susceptible to recrudescent HSV **after dental procedures**.

HSV in Immunocompromised Patients

- HSV infections should be treated with systemic antivirals to prevent dissemination to other sites (e.g., HSV esophagitis) or systemically.
- The primary pathogen for herpes encephalitis&herpes pneumonitis is HSV-1.
- For patients undergoing hematopoietic cell transplantation, antiviral therapy such as acyclovir or valacyclovir at suppressive doses should be initiated for all patients who are HSV seropositive (acyclovir 400 mg three times a day or 500 mg valacyclovir twice a day).
- Acyclovir-resistant HSV is most frequently seen in this group of patients, where the virally derived thymidine kinase that activates acyclovir is mutated.
- In such cases, foscarnet or cidofovir is effective.

The dosage of the acyclovir family of drugs should be adjusted for Age and Renal Health.

A number of vaccines and new therapies against HSV are currently under development.

2. Varicella-Zoster Virus Infection

Etiology and Pathogenesis

- Primary infection with varicella zoster virus (VZV), an α-herpesvirus, leads to varicella
- **(chicken pox).**
- The virus then becomes latent, usually in the **dorsal root ganglia or ganglia of the cranial nerves.**
- **Reactivation** produces herpes zoster infection (HZI), commonly called **shingles.**
- The incidence of HZI **increases with age** and the degree of **immunosuppression**. this increases to **10 per 1000** in those older than the age of 75 years.
- **Therefore, it is not uncommon to see HZI**
- **in the elderly**,
- **in patients undergoing cancer chemotherapy**,
- **in patients on chronic immunosuppressive drug therapy and in patients with AIDS**.

As with HSV, this virus is cytopathic to the epithelial cells of the skin and mucosa, causing blisters and ulcers.

Transmission is usually by the respiratory route, with an incubation period of **2 to 3 weeks.**

Post herpetic neuralgia,

a morbid sequela of HZI, is a neuropathy resulting from peripheral and central nervous system injury and altered central nervous system processing.

Clinical Findings

- ✓ **Primary VZV infection** generally occurs in the **first two decades of life**.
- ✓ The disease begins with a low-grade fever, malaise, and the development of an intensely pruritic, maculopapular rash, followed by vesicles that have been described as "**dewdrop-like."**
- ✓ These vesicles turn cloudy and pustular, burst, and scab, with the crusts falling off after one to two weeks.
- ✓ Lesions begin on the trunk and face and spread centrifugally.
- ✓ Central nervous system involvement may result in cerebellar ataxia and encephalitis.
- ✓ Other complications of varicella include **pneumonia**, **myocarditis**, and **hepatitis**.

Immunocompromised hosts usually experience more severe disease with more blisters, a prolonged course, and, not infrequently, involvement of the lungs, central nervous system, and liver; **there is a significantly higher mortality rate.**

Secondary bacterial infection by gram-positive cocci may have severe septic consequences

HZI of the skin (shingles) occurs in adults and starts with a prodrome of deep, aching, or burning pain. There is usually little to no fever or lymphadenopathy. This is followed within **2 to 4 days** by the appearance of **crops of vesicles** in a dermatomal or "zosteriform" pattern. This pattern describes the unilateral, linear, and clustered distribution of the vesicles, ulcers, and scabs in a dermatome supplied by one nerve. **Thoracic/lumbar** dermatomes are the most frequently involved, **followed by the craniofacial area.**
Lesions heal within **2 to 4 weeks,** often with **scarring and hypopigmentation**. Occasionally, HZI may occur without the appearance of dermatomal lesions

(zoster sine eruptione or zoster sine herpete), which makes the diagnosis of this condition challenging; these patients often present with facial palsy.

- VZV has been detected in up to 20% of patients with Bell palsy.
- A serious and occasional side effect of HZI is **acute retinal necrosis**.

One of the most important complications of HZI is **postherpetic neuralgia**, defined as pain that remains for 120 days after the onset of the acute rash

- patients older than age 50, up to 70% developed postherpetic neuralgia and up to 50% have debilitating pain, usually of a sharp, stabbing, burning or gnawing nature lasting more than one month.

- Some unfortunate patients experience pain for years.

- Predisposing factors include older age, prodromal pain, and more severe clinical disease during the acute rash phase.

Immunocompromised patients often experience more severe VZI that may appear atypical, be bilateral, and involve multiple dermatomes; retinitis, pneumonitis, and encephalitis have been reported as complications in this patient population.

On rare occasions, HZI may involve not just the dorsal root ganglion but also the anterior horn cells, leading to paralysis.

Oral Manifestations

- Primary VZV infection presents as acute-onset ulcerations in the mouth that often pale
- In recurrent VZV infection, the ophthalmic division of the trigeminal (V) nerve is the cranial nerve **most often affected** (herpes zoster ophthalmicus);
- Corneal involvement may lead to blindness.
- Involvement of this nerve (V) leads to lesions on the upper eyelid, forehead, and scalp with V; midface and upper lip with V; and lower face and lower lip with V. With the involvement of V, patients experience a prodrome of pain, burning, and tenderness, usually on the palate on one side.

This is followed **several days later** by the appearance of painful, clustered 1–5 mm ulcers (rarely vesicles, which break down quickly) on the hard palatal mucosa or even buccal gingiva, in a distinctive unilateral distribution.

These ulcers heal within **10–14 days**, and post herpeticneuralgia **in the oral cavity is uncommon.** Involvement of V results in blisters and ulcers on the mandibular gingiva and tongue.

Laboratory Findings

As with HSV infection, an oral swab for viral isolation using cell culture is still the best way to confirm a diagnosis of VZV infection, although VZV is more difficult to culture, but this does not distinguish between HSV and VZV.

Direct fluorescent antibody testing using a smear has greater sensitivity. This test uses a **smear** obtained by scraping the lesion and staining it with antibody against VZV conjugated to a fluorescent compound.

The use of PCR and real-time PCR to detect viral antigen is expensive and highly sensitive, but the presence of VZV antigen does not always equate with active infection.

In HZI, there is inflammation of peripheral nerves leading to demyelination and **wallerian degeneration**, as well as degeneration of the dorsal horn cells of the spinal cord.

Management

Management of oral lesions of varicella and HZI is directed toward

- ❑ pain control (particularly, the prevention of postherpetic neuralgia),
- ❑ supportive care,
- ❑ hydration
- ❑ definitive treatment to minimize the risk for dissemination, particularly in immunocompromised patients.

- ➢ **Aspirin use**, especially in children with VZV infection or influenza, may be associated with the development of **Reye syndrome**, which is potentially fatal, and is contraindicated; characterized by fatty degeneration of the liver and encephalopathy.
- ➢ **ibuprofen is the preferred analgesic**.

Treatment of primary VZV infection includes the use of :

- Acyclovir (800 mg five times a day).
- This reduces infectivity, severity of lesions, and hospitalization for complications. However, acyclovir has poor bioavailability.
- Valacyclovir (1000 mg 3 times a day)

or Famciclovir (500 mg) 3 times a day) **for 7 days** is effective in treating HZI and should be started **within 72 hours of disease onset**.

These drugs also reduce the incidence of postherpetic neuralgia compared with acyclovir.

The first line of treatment for postherpetic neuralgia is

- Gabapentin,
- 5% lidocaine patch,
- and 0.025%–0.8% topical capsaicin,

The second line of treatment

- Opioid analgesics
- Tricyclic antidepressants.

The use of **corticosteroids and antiviral** therapy together in an attempt to reduce post herpetic neuralgia has not proved effective, although early treatment with **famciclovir or valacyclovir** may prevent it.

Other modalities of treatment in Case reports suggest that

- botulinum toxin may provide relief.
- attenuated vaccine for the prevention of VZV infection has been shown to reduce the incidence of varicella outbreaks.
- **Vaccination of older adults** with this vaccine causes an increase in antibody levels, boosts cell-specific immunity, and reduces the incidence and/or severity of subsequent HZI and postherpetic neuralgia.

3. Cytomegalovirus Infection

Etiology and Pathogenesis

- 60–70% of the adult population has been exposed.
- Primary infection may be asymptomatic or cause an infectious mononucleosis–like disease.
- Manifestations of infection and disease are most evident in the immun-compromised population
- It is the most common cause of pneumonia within the first 120 days after hematopoietic stem cell transplantation.
- Once exposed to CMV, this virus establishes latency within the connective tissue cells, such as the endothelium of blood vessels, mononuclear cells, and white blood cells.
- CMV within endothelial cells may contribute to vascular inflammation, vascular occlusion, and end-organ damage.

Transmission is by direct transfer of infected white blood cells through intimate contact and through blood products.

In organ transplant recipients, CMV in the donor organ leads to CMV infection in the recipient.

Clinical Findings

Primary CMV infection

- presents similarly to infectious mononucleosis with marked lymphocytosis;
- 20% of patients with infectious mononucleosis–like symptoms have CMV rather than EBV infection.
- Unlike the more common EBV-associated infectious mononucleosis, there is fever but little lymphadenopathy or splenomegaly.
- **Serious complications include** meningoencephalitis, myocarditis, and thrombocytopenia.

- Approximately 90% of patients with AIDS have circulating antibodies against CMV. In these 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 in the immunocompromised patient tends to present as **a single large 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.
- **Up to one-third** of such ulcers are coinfected with other viruses of the herpes family, especially HSV and VZV.

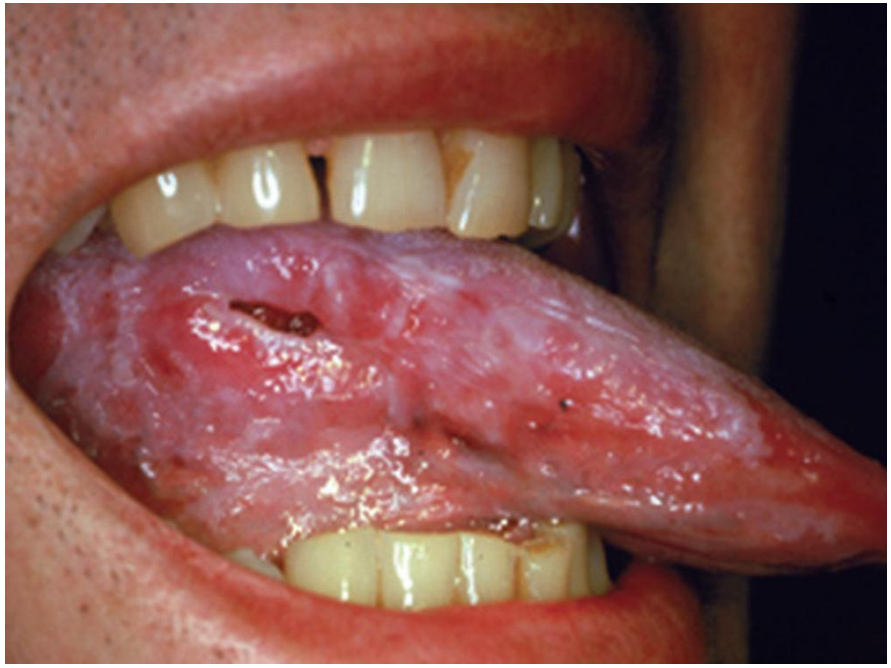
- There have been occasional reports of mandibular osteomyelitis and tooth exfoliation associated with CMV and VZV infection.

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

Management

- Pain is managed with **topical anesthetics** and **systemic analgesics** as needed, with appropriate **dietary modifications and good hydration**.

- CMV infection is treated with **ganciclovir, valganciclovir** (a valine ester and oral prodrug of ganciclovir with approximately 10-fold bioavailability of ganciclovir)



- **A CMV vaccine is currently under development.**

4. Coxsackievirus Infection

- Coxsackie (CV), a ribonucleic acid (RNA) virus, most are type A(CVA), and some type B (CVB).
- More than **90% of infections** caused by the **nonpolio enteroviruses** are either asymptomatic or result in nonspecific febrile illness.
- The viruses replicate first in the mouth and then extensively in the lower gastrointestinal tract, where they shed.

- **Transmission** is therefore primarily by the **fecal-oral route**, although some shedding occurs **in the upper respiratory tract**.

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

(a sharp pain in the side usually located in the intercostal muscles)

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

- **Enteroviruses have been implicated in the pathogenesis of type 1 insulin-dependent diabetes mellitus.**

In the oral cavity, CV infections lead to three disease entities:
HFM disease, herpangina, and lymphonodular pharyngitis.
HFM disease, as with many CV infections, including herpangina, tends to be seasonal (usually summer), occurs in epidemic clusters, and has high transmission rates. Atypical HFM disease exhibits widespread oral and skin involvement and onychomadesis (separation of the nail plate from the nail bed) and is caused by **CVA6**.

Clinical Findings

HFM disease usually afflicts children younger than 10 years in **summer**.
Patients have a low-grade fever and sore mouth; 75-100% 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

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.
Lesions are usually located on the tongue, hard and 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

Clinical Findings

Children younger than 10 years are usually afflicted, and outbreaks usually occur in epidemics in summer. Patients develop fever, headache, and myalgia that usually last only one to three days.

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 2–4 mm ulcers and these persist for 5 -10 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.

Laboratory Tests

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

Management

CV infections are self-limiting
Uunless complications arise or the patient is immunocompromised, and 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.

5. Necrotizing Ulcerative Gingivitis & Necrotizing Ulcerative Periodontitis

- Formerly known as acute necrotizing ulcerative gingivitis and its more severe counterpart, NUP, were reclassified in 1999 by the American Academy of Periodontics under the category of "Necrotizing Periodontal Disease."
- Acute ulcerative-inflammatory conditions of the gingiva and periodontium,
- Was dubbed "trench mouth" since it was frequent among the soldiers in the trenches.
- Both with strong associations with immune suppression (especially AIDS), debilitation, smoking, stress, poor oral hygiene, local trauma & contaminated food supply.
- Diabetes may also be a risk factor.
- It is unclear if NUG is a indication of NUP, but they are often seen in patients with AIDS.
- Both NUP and noma thrive in communities characterized by a large low-socioeconomic class and extreme poverty.

Etiology and Pathogenesis

Treponema* species,** *Prevotella intermedia*, ***Fusobacterium *nucleatum*, are the most common.

The tissue destruction

- Gingiva and adjacent tissues is most probably a result of the production of endotoxins and/or immunologic activation
- Patients show reduced neutrophil chemotaxis and phagocytosis, resulting in poor control of infection.
- Some have identified herpesviruses within the crevicular fluid, but such viruses shed readily in oral secretions, particularly in areas where there is tissue destruction
- If there is underlying systemic illness, NUG and NUP can spread rapidly from the gingiva to the periodontium and into the soft tissues, giving rise to **cancrum oris, noma, or orofacial gangrene.**
- This is particularly devastating in children who are malnourished and live in poverty and is seen not infrequently in Africa. **Fusobacterium necrophorum** is likely to play an important role in the progression of NUP to cancrum oris because this organism produces a **dermonecrotic toxin**, **hemolysin**, **leukotoxin**,and **proteolytic enzymes**, all leading to extensive tissue destruction.

Clinical Findings

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

Oral Manifestations

- ❑ 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, usually on the interdental papillae, although any part are of the marginal gingiva may be affected .
- ❑ There is accompanying malodor, and there may be gingival bleeding.

- ➢ Because of the **pain** associated with the gingivitis, there is usually abundant buildup of dental **plaque** around the teeth because it may be too painful to perform **effective oral hygiene**.

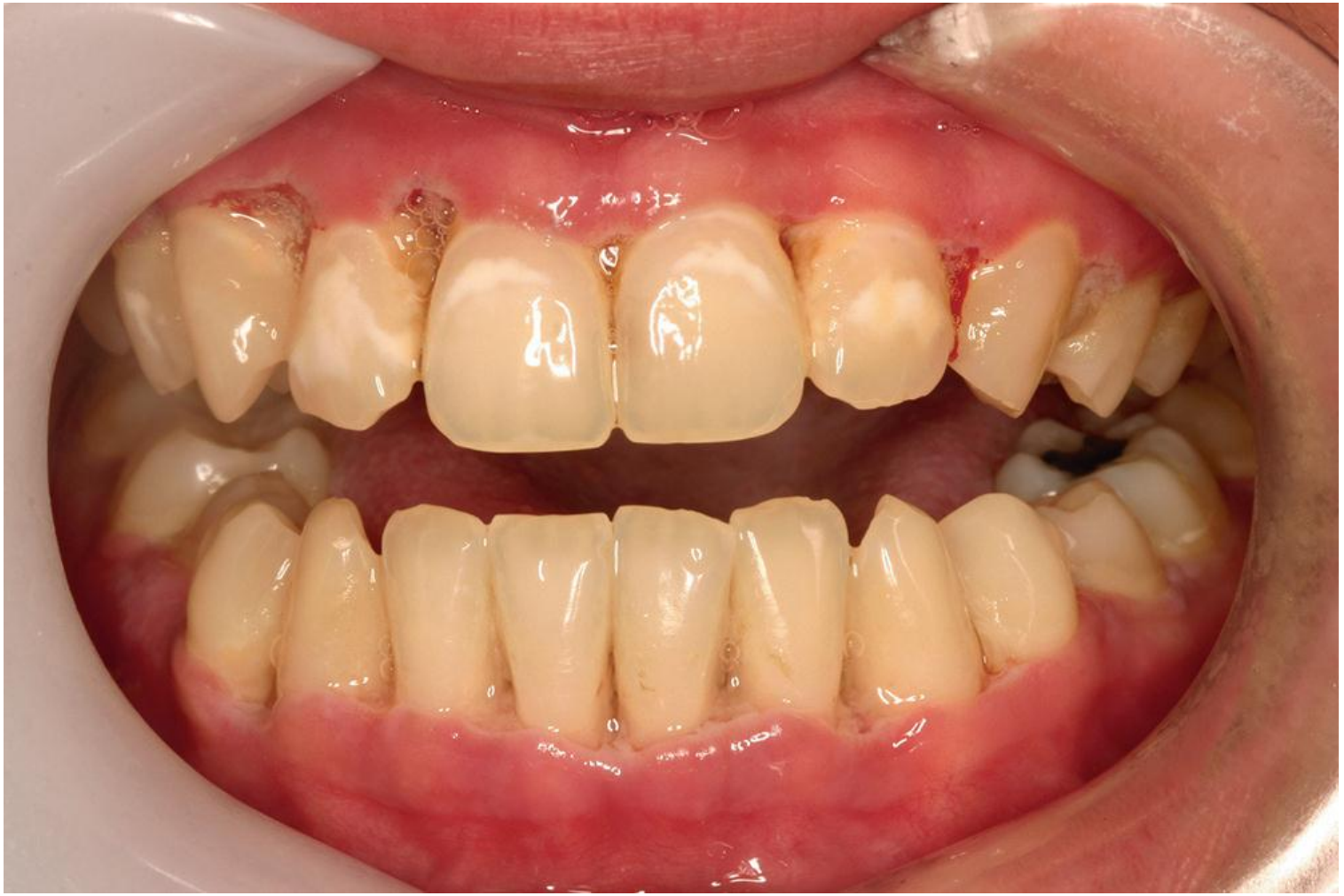
Risk factors

- ➢ **immunocompromised** and **neutropenic** are prone to developing such lesions.

- In patients with **AIDS**, the prevalence of NUP is approximately **6%** and is strongly predictive of a **CD4 count less than 200 cell/mm**, leading to **osteonecrosis or necrosis** of the soft tissues

- In patients who have **severe immunodeficiency or are malnourished**, NUG and NUP may **progress** to **noma** The overlying skin becomes discolored, and perforation of the skin ensues.

- The **orofacial lesions cone shaped**, with the base of the cone within 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 –90%.**



Management

- Definitive treatment of NUG and NUP consists of **gentle debridement** to remove as much of the debris and plaque as possible; this is best accomplished with **topical anesthesia** during the first few visits.
- The use of **chlorhexidin**e digluconate mouthrinse led to resolution in **>90%** of cases.
- Patients with more extensive disease and/or systemic symptoms may require **antibiotics active against gram-negative anaerobes**, such as β-lactams. Interestingly, **metronidazole**,
- Once the **acutely painful episodes** have resolved, **scaling and root planing** to completely remove all residual plaque and calculus are indicated.
- **Periodontal surgery** may be necessary to correct gingival and periodontal defects.
- It may be appropriate to test the patient for HIV or other immunosuppressive conditions, such as blood dyscrasia.
- **Cases of noma** need aggressive treatment with nutritional supplementation, antibiotics, and tissue debridement.

6. Erythema Multiforme

- ❑ 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.
- ❑ It represents a hypersensitivity reaction to infectious agents or medications.
- ❑ There is still controversy over how best to classify EM
- ✓ EM is classified as **EM minor** if there **is less than 10%** of skin involvement and there is **minimal to no** mucous membrane involvement,
- ✓ whereas ***EM major*** has **more extensive** but still characteristic skin involvement, with the oral mucosa and other mucous membranes affected.
- ✓ However, there is likely a subset of EM that affects the **oral mucosa** only without skin involvement.

Historically, fulminant forms EM were labeled Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN [Lyell disease]).

Clinical Findings

- EM affects ages 20 and 40 years, with 20% occurring in children.
- Patients with recurrent EM have an average of **six episodes a year** (range 2–24), with a mean duration of 9.5 years; remission occurred in 20% of cases.

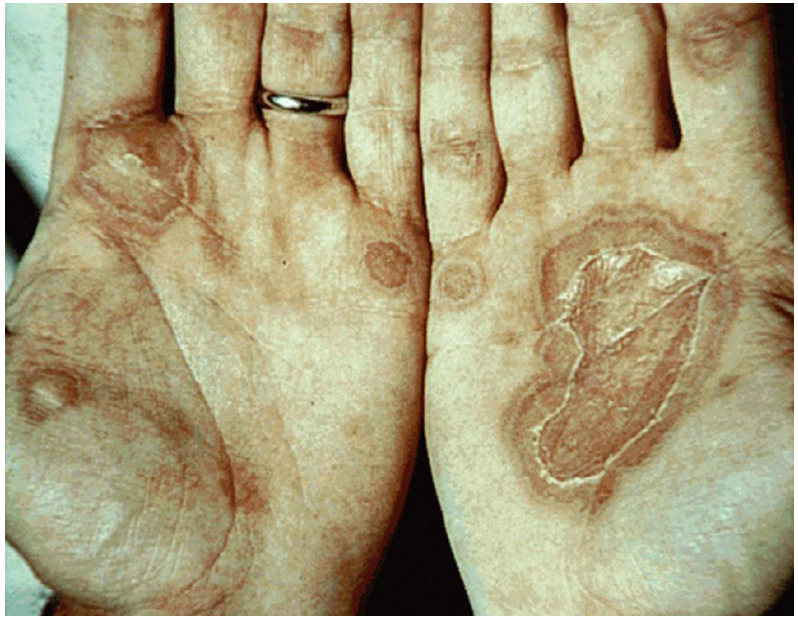
Episodes usually last several weeks.

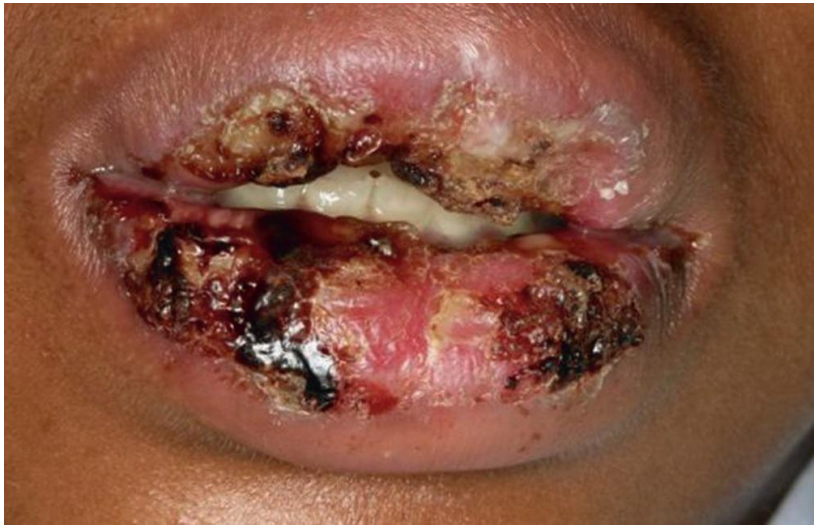
- There may be a prodrome of fever, malaise, headache, sore throat, rhinorrhea, and cough.
- These symptoms suggest a viral (especially respiratory tract) infection, and this is not surprising since infectious agents are known to trigger EM.
- Skin lesions appear rapidly over a few days and begin as red macules that become papular, starting primarily in the hands and moving centripetally toward the trunk in a symmetric distribution.
- The most common sites of involvement are the upper extremities, face, & neck.
- The skin lesions may take several forms—hence the term *multiforme*.
- The classic skin lesion consists called typical “target” or “iris” lesion that is pathognomonic of EM; variants are called “atypical target” lesions.
- The skin may feel itchy and burnt.
- Post inflammatory hyperpigmentation is common in dark-skinned individuals and may be worsened by sun exposure

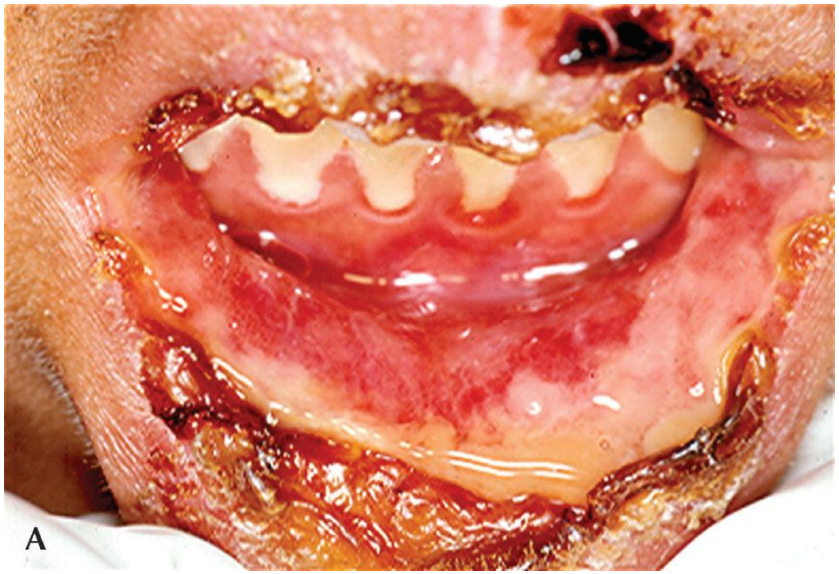
Oral Findings

- The oral findings in EM range from mild erythema and erosion to large painful ulcerations,
- severe, large ulcers, causing difficulty in eating, drinking, and swallowing,
- patients with severe EM may drool blood-tinged saliva.
- Extensive lip involvement with inflammation, ulceration, and crusting is common.
- Oral lesions are present in 23–70% of patients with recurrent EM.
- The most commonly affected sites are the **lips** (36%), **buccal mucosa** (31%), **tongue** (22%), and **labial mucosa** (19%), **Genital** 25% and **ocular** sites are 17%.

- Crusting and bleeding of the lips are common, but not always present



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Etiology and Pathogenesis

- EM is a hypersensitivity reaction, and the most common inciting factors are infection, particularly with HSV, mycoplasma and Chlamydia pneumonia.
- **Drug reactions** to NSAIDS, anticonvulsants, or other drugs play a smaller role.
- Cases of oral EM **precipitated by benzoic acid**, a food preservative, have been reported.
- Studies show that recurrent EM is associated with **HSV infection** in 65–70% of cases, both by history of HSV infection one to three weeks before onset of EM,
- Using PCR techniques, HSV gene products have been identified in 71–81% of cases of recurrent EM For non-recurrent EM, this falls to 27%.
- Cytotoxic T cells, natural killer cells, and/or cytokines destroy the epithelial cells.
- More recently, it has been suggested that CD34+ cells, Langerhans cell precursors, carry fragments of HSV DNA to the skin where it incites EM.

Management

- ✓ Mild oral EM can be managed with systemic or topical analgesics **for pain** and supportive care since the disease is self-limiting and resolves within a few weeks.
- ✓ More severe cases are usually managed with systemic corticosteroids
- ✓ **Topical steroids** may also help resolve lesions.
- ✓ Cases suspected of having **HSV-associated EM** should be treated with **antiviral medications.**
- ✓ Treatment with acyclovir at the first sign of disease in recurrent EM controls disease in approximately **half of patients**
- ✓ Other treatment modalities include dapsone, hydroxychloroquin, mycophenolate mofetil, azathioprine, colchicines, methotrexate, and intravenous immunoglobulin.
- ✓ Continuous acyclovir at 400 mg twice a day prevents development of EM in most patients with HSV-associated disease, whereas EM not related to HSV responded well to azathioprine (100–150 mg/d).
- ✓ Other studies have also shown good suppression of recurrent HSV-associated EM using **500 mg of valacyclovir twice a day** or 250 mg of famciclovir twice daily.
- ✓ **Dapsone** (100–150 mg/d) and antimalarials are partially successful in suppressing recurrent outbreaks

7. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

- Studies done within the last 10 to 15 years now support the concept that Stevens-Johnson Syndrome (SJS) is a less severe variant of Toxic Epidermal Necrolysis (TEN) and separate clinically and etiopathogenetically from EM.
- Although all three are hypersensitivity reactions and give rise to oral bullae, erosions, ulcers, and crusted lips, 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.”
- **SJS** is much more likely to be associated with medication use and *Mycoplasma pneumoniae* infection (especially in children) and rarely with HSV infection, **whereas EM is** much more likely to be associated with HSV infection.
- some cases of **Mycoplasma pneumonia** are associated with EM.
- The more common inciting drugs include **antibacterial sulfonamides, penicillin, anticonvulsants, and NSAIDs in children**, and **allopurinol, oxicams, and nevirapine in adults**.
- In Han Chinese, development of SJS/TEN to the aromatic anticonvulsants; carbamazepine, phenytoin

- ✓ The mucosal surfaces of the eye, genitalia, and mouth are almost always severely affected by SJS/TEN, always with skin involvement.
- ✓ The typical oral manifestation is extensive oral ulceration with hemorrhagic crusts on the vermilion and oral and other mucosal surfaces.
- ✓ These lesions resemble oral lesions of PNPP, which are long-standing and associated with malignancy as well as EM.

- ➢ Histopathologically, most of the disease is localized in the epidermis, presumably this being the site where the drug or its metabolite is bound, with less inflammation in the dermis.

- ➢ **Because of the severity of this condition**, treatment is generally with intensive supportive care because of loss of skin barrier, intravenous immunoglobulin, systemic steroids, cyclosporine, plasmapheresis, cyclophosphamide, and TNF-α inhibitor

8. Plasma Cell Stomatitis and Oral Hypersensitivity Reactions

Etiology and Pathogenesis

Oral hypersensitivity reactions may take the following forms:

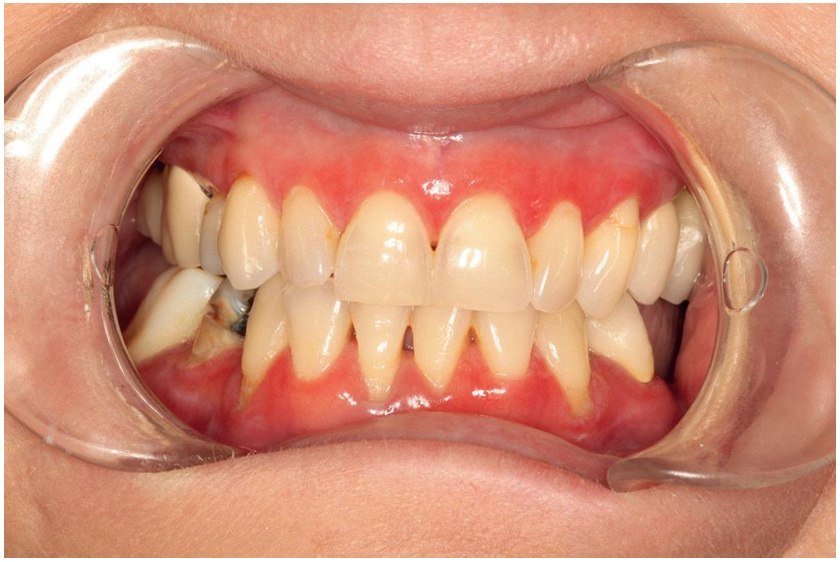
1. Acute onset of ulcers such as in oral EM
2. Red and white reticulated lesions of a lichenoid hypersensitivity reaction
3. Fixed drug eruption
4. Marked erosions and erythema especially on the gingiva with or without ulceration called plasma cell stomatitis (PCS).
5. Swelling of the lips/angioedema
6. Oral allergy syndrome that presents mainly with symptoms of itching with or without swelling of the oral structures and oropharynx

PCS is a hypersensitivity reaction that was first described in the late 1960s and early 1970s and was likely a contact stomatitis to a component of chewing gum. Since then, cases have continued to be reported, and these are all likely caused by a sensitizing contactant, whether or not the contactant is identified.

These include khat (*Catha edulis*),components of toothpaste, mint candies, and household cleaners.

- Because of the intense plasma cell infiltration, it is believed that this is a B cell–mediated disorder, with T cells augmenting the response.

- Some believe that this is caused by components of plaque bacteria, although this is not a universally accepted concept.



Clinical Findings

- PCS occurs within days of exposure to the contactant, with most signs and symptoms limited to the oral cavity.
- Some lesions may affect the periorificial tissues or the oropharynx, leading to upper airway symptoms of hoarseness, dysphagia, and mild airway obstruction.
- Endoscopy may reveal erythematous and thickened mucosa, often with a cobblestoning pattern from the edema. An obvious allergen/contactant is not always identified.

Oral Manifestations

- PCS occurs within a few days of exposure.
- It presents as brightly erythematous macular areas of the oral cavity, almost always involving the marginal and attached gingiva or alveolar mucosa and often involving other soft tissues, such as the maxillary and mandibular sulcus or buccal mucosa.
- Ulcers may be present & there may be epithelial sloughing and desquamation.
- The gingiva may also be swollen and edematous.
- Patients may complain of pain and sensitivity & bleeding of the gingiva on brushing.
- Angular cheilitis with fissuring and dry atrophic lips have been reported.
- Some cases reported as PCS consisted of a very localized area of erythematous gingiva, usually around a single tooth and measuring usually <1 cm. .

Laboratory Findings

- ✓ Patch testing to identify an allergen may be helpful.
- ✓ A biopsy is the most useful diagnostic test for this condition.

A biopsy of the gingiva in PCS shows parakeratosis, epithelial hyperplasia, neutrophilic exocytosis, and numerous spongiotic pustules in the absence of *Candida*.

- ✓ **The most significant finding is dense sheets of plasma cells in the lamina propria; many dilated capillaries lie close to the surface, accounting for the marked erythema.**
- ✓ Eosinophils are not seen usually.
- ✓ Immunoperoxidase stains will invariably show the plasma cell infiltrate to be polyclonal, typical for a reactive/inflammatory process, and not monoclonal, which typifies neoplastic lesions

Management

- PCS is self-limiting and will generally, but not always, regress if the contactant is identified and removed.
- **pain control and anti-inflammatory agents** may be helpful during the healing process .
- **Topical steroids** may help reduce inflammation and speed healing.
- Some lesions have resolved with **intralesional triamcinolone injections**, although the gingiva is a particularly difficult location for such injections.
- Cases have also responded well to **prednisone.**
- **Gingivectomies** may be needed to recontour lesions that are long-standing and more fibrotic.
- One case showed improvement with **2% fusidic acid.**

The Patient with Recurring Oral Ulcers

- Recurring oral ulcers are among the most common problems seen by **clinicians** who manage diseases of the **oral mucosa**.
- several diseases that should be included in the differential diagnosis of a patient with a history of recurring ulcers of the mouth, including:

1. **RAS (recurrent aphthous stomatitis),**
2. **Behçet Disease(Behçet syndrome)**
3. **recrudescent HSV infection, and recurrent oral EM.**

1. Recurrent Aphthous Stomatitis

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

- **Hematologic deficiencies, immune disorders, and connective tissue diseases** may cause oral aphthous-like ulcers clinically similar to RAS.
- These ulcers **resolve** when the underlying systemic condition resolves.
- RAS **affects** approximately **20%** of the general population, but when ***specific ethnic or socioeconomic groups*** are studied, the incidence ranges from **5 to 50%.**
- RAS is classified according to **clinical characteristics**: **minor** ulcers, **major** ulcers (Sutton disease, periadenitis mucosa necrotica recurrens), and **herpetiform** .
- There are cases in which a clear distinction between minor and major ulcers is blurred, particularly in patients who **experience severe discomfort from continuous episodes of ulcers**. These lesions have been referred to as **"severe" minor ulcers**

Etiology and Pathogenesis

- ✓ It was once assumed that RAS was a form of recurrent HSV infection, and there are still clinicians who mistakenly call RAS “herpes.”
- ✓ Many studies done during the **past 40 years** have confirmed that RAS is not caused by HSV.
- ➢ The major **factors presently linked** to RAS include **genetic factors**, **hematologic** or **immunologic abnormalities**, and **local factors**(trauma and smoking).
- ➢ There is increasing evidence **linking local immune dysfunction** to RAS
- ➢ 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.**
- ➢ More recent research has centered on dysfunction of **the mucosal cytokine network.**
- ➢ Further evidence for the **inherited nature** of this disorder results from studies in which genetically specific human leukocyte antigens (HLAs) have been identified in patients with RAS, particularly in certain ethnic groups.

- Recent studies by Bazrafshani and colleagues **linking minor RAS to genetic factors associated with immune function**.

- **Hematologic deficiency**, particularly of **serum iron, folate, or vitamin B_{12}, appears to be an etiologic factor in 5%–10% patients** with aphthous-like ulcers although these sometimes occur on keratinized mucosa.

Aphthous-like ulcers may also be seen in celiac disease.

- It was initially reported in the 1960s that there is a **negative correlation between RAS and a history of smoking**, and many clinicians have reported that RAS is exacerbated when patients stop smoking.

- A study measuring **a nicotine metabolite** present in the blood of smokers confirmed that the incidence of RAS is significantly lower among smokers.

The nicotine metabolites are believed to decrease levels of proinflammatory cytokines and increase anti-inflammatory cytokines.

- Other factors that have been reported associated with RAS include anxiety, periods of psychological stress, localized trauma to the mucosa, menstruation, upper respiratory infections, and food allergy.

Oral Findings

- The first episodes of RAS most frequently begin during the second decade of life.
- The lesions are confined to the oral mucosa and begin with prodromal burning or the sensation of a small bump in the mucosa 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 48–72 hours.
- The individual lesions are round, symmetric, and shallow (similar to viral ulcers), but no tissue tags are present from ruptured vesicles, which helps distinguish RAS from diseases that start as vesicles, such as pemphigus, and pemphigoid.

- Multiple lesions are often present, but the number, size, and frequency vary considerably.
- The buccal and labial mucosae are most commonly involved.
- Lesions rarely occur on the heavily keratinized palatal mucosa or gingiva.
- In mild RAS, the lesions reach a size of 0.3–1.0 cm and begin healing within a few days. Healing without scarring is usually complete in 10–14 days.
- Most patients with RAS have between one and six lesions at each episode and experience several episodes a year.
- The disease is an annoyance for the majority of patients with mild RAS, but it can be painfully disabling for patients with severe RAS and RAS major.

- Patients with major ulcers develop deep lesions that are larger than 1 cm in diameter and last for weeks to months.
- In the most severe cases, large portions of the oral mucosa may be covered with large deep ulcers that can become confluent, and are extremely painful, interfering with speech and eating.

These patients may require *hospitalization for intravenous feeding* and treatment with **systemic corticosteroids.**

- The lesions may *last for months* and sometimes be misdiagnosed as squamous cell carcinoma, granulomatous disease, or blistering disease. The lesions heal slowly and leave scars that may result in decreased mobility of the uvula and tongue.

The least common variant of RAS is the herpetiform type, which tends to occur in adults.

The patient presents with more than 10 small punctate ulcers, measuring <5 mm, scattered over large portions of the oral mucosa.

Laboratory Findings

Laboratory investigation should be ordered when patients do not follow the usual pattern of RAS, for example,

- when episodes of RAS become more severe,
- begin past the age of 40,
- or are accompanied by other signs and symptoms.

Biopsies are only indicated when it is necessary to exclude other diseases, particularly granulomatous diseases such as Crohn disease, sarcoidosis, or blistering diseases such as pemphigus or pemphigoid.

Patients with severe minor aphthae or major aphthous ulcers should be investigated for systemic disorders, including: connective tissue diseases and hematologic abnormalities, such as reduced levels of serum iron, folate, vitamin B12, and ferritin. Patients with abnormalities in these values should be referred to an internist for further management.

HIV-infected patients, particularly those with CD4 counts below $100/mm_3$, may develop major aphthous ulcers, and, occasionally, such oral ulcers are the presenting sign of AIDS.

Biopsies reveal only a superficial ulcer covered by a fibrinous exudate with granulation tissue at the base and a mixed acute and chronic inflammatory infiltrate.

Management

- Pain relief with a topical anesthetic agent such as benzocaine or lidocaine.
- In more severe cases, the use of a 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.

The effectiveness of the topical steroid is partially based on good instruction and patient compliance regarding proper use.

- The **steroid gel** should be applied directly to the lesion after meals and at bedtime two to three times a day or mixed with an adhesive such as Orabase™ prior to application.
- Larger lesions can be treated by placing **a gauze sponge** containing the topical steroid on the ulcer and leaving it in place for 15–30 minutes to allow for longer contact of the medication.

Other topical preparations that have been shown to decrease the healing time of RAS lesions include amlexanox paste and a topical tetracycline or doxycycline, which can be used either as a mouthrinse or applied as a paste directly to the lesions.

Intralesional steroid injections can be used to treat large indolent major RAS lesions. It should be emphasized that no available topical therapy reduces the frequency of new lesions.
When patients with major aphthae or severe cases of multiple minor aphthae do not improve sufficiently with topical therapy, use of systemic therapy should be considered.

Drugs that have been reported to reduce the number of ulcers in selected cases of major aphthae include colchicine, pentoxifylline, dapsone, short bursts of systemic steroids, and thalidomide.
Each of these drugs has the potential for side effects, and the clinician must weigh the potential benefits versus the risks.

Thalidomide, a drug originally marketed as a nonaddicting hypnotic in the 1950s, was withdrawn from the market in the early 1960s due to its association with multiple, severe, deforming, and life-threatening birth defects

Further investigation demonstrated that thalidomide has significant anti-inflammatory and immunomodulatory properties and is useful in treating a number of diseases, including erythema nodosum leprosum, discoid lupus erythematosus, graftvs- host disease, multiple myeloma, and Behçet disease.

The drug has also been shown to reduce both the incidence and severity of major RAS in both HIV-positive and HIV-negative patients. The use of thalidomide for RAS should be reserved for management of severe major RAS where other less toxic therapies, including high-potency topical steroids, colchicine, and pentoxifylline**, have failed to control**

women during childbearing years owing to the potential for severe life-threatening and deforming birth defects. All clinicians prescribing thalidomide in the United States must be registered in the REMS (Risk Evaluation Mitigation Strategy) program for thalidomide and patients receiving the
drug must be thoroughly counseled regarding effective birth control methods that must be used whenever thalidomide is prescribed. For example, two methods of birth control must be used, and the patient must have a pregnancy test monthly. Other side effects of thalidomide include peripheral neuropathy, gastrointestinal complaints, drowsiness and deep vein thrombosis. Monitoring patients taking long-term thalidomide for the development of peripheral neuropathy with periodic nerve conduction studies is also recommended

2. (Behçet Syndrome)

was initially described by the Turkish dermatologist Hulusi Behçet as **a triad of** symptoms including **recurring oral ulcers, recurring genital ulcers, and eye** involvement.

- BD is now understood to be a **multisystem disorder** with many possible manifestations.
- The highest incidence of BD has been reported in eastern Asia, the Middle and the eastern Mediterranean, particularly Turkey and Japan, where BD is a leading cause of blindness in young males; however, cases have been reported worldwide, including Europe and North America.
- BD is more **severe** in **younger patients** and patients with **eye and GI** involvement.

Etiology and Pathogenesis

BD is a systemic vasculitis characterized by hyperactivity of neutrophils with enhanced chemotaxis and elevated proinflammatory cytokines IL-8 and IL-17, with TNF-α playing a major role in the pathogenesis.

The HLA-B51 genotype is most frequently linked to BD, especially in patients with severe forms of the disease in Asia.

Clinical Manifestations

1. The highest incidence is in young adults 25 and 40 years , with the oral mucosa as the most common site of involvement.
2. The genital area is the second most common site of involvement and presents as ulcers of the scrotum and penis in males and ulcers of the labia in females.
3. The eye lesions consist of uveitis, retinal vasculitis, vascular occlusion, optic atrophy, and conjunctivitis.
4. **Blindness** is a common complication of the disease, and periodic evaluation by an ophthalmologist is necessary.

- **Systemic** involvement occurs in over 50% of patients with BD.
- Skin lesions resembling erythema nodosum or large pustular lesions occur in over 50% of patients with BD.
- These lesions may be precipitated by **trauma**, and it is common for patients with BD to have a cutaneous hyperreactivity to intracutaneous injection or a needlestick (pathergy).
- **Arthritis** occurs in greater than 40% of patients and most frequently affects the knees, ankles, wrists, and elbows(red and swollen)

- In some patients, central nervous system involvement is the most distressing component of the disease (brainstem syndrome, involvement of the cranial nerves, or neurologic degeneration resembling multiple sclerosis that can be visualized by magnetic resonance imaging of the brain)
- Other reported signs of BD include thrombophlebitis, intestinal ulceration, venous thrombosis, and renal, cardiac, and pulmonary disease.
- Both pulmonary involvement and cardiac involvement are believed to be secondary to vasculitis. Involvement of large vessels is life threatening because of the risk of arterial occlusion or aneurysms.

BD in children, which most frequently presents 9 and 10 years, has similar manifestations to the adult form of the disease, but oral ulcers are a more common presenting sign in children, whereas uveitis is less common.

Oral lesions are seen **more than 95% of children** with BD.
A variant of BD, characterized by mouth and genital ulcers with inflamed cartilage, is associated with relapsing polychondritis.

Oral Findings

- The most common site of involvement of BD is the oral mucosa.
- Recurring oral ulcers appear in more than 90% of patients; these lesions cannot be distinguished either clinically or histologically from RAS.
- Some patients experience mild recurring oral lesions; others have deep, large, scarring lesions characteristic of major RAS.
- These lesions may appear anywhere on the oral or pharyngeal mucosa

Laboratory Findings

BD is a clinical diagnosis based up the criteria described above. Laboratory tests are used to rule out other diseases, such as connective tissue (lupus erythematosus) and hematologic diseases causing severe neutropenia

Management

The management of BD depends on the severity and the sites of involvement.

- Patients with sight-threatening eye involvement or central nervous system lesions require more aggressive therapy with drugs, with a higher potential for serious side effects.

1. Azathioprine and other immunosuppressive drugs combined with prednisone have been shown to reduce ocular disease as well as oral and genital involvement.
2. Pentoxifylline, which has fewer side effects than immunosuppressive drugs or systemic steroids, has also been reported to be effective in decreasing disease activity, particularly of oral and genital lesions.

3. Dapsone, colchicine, and thalidomide have also been used effectively to treat mucosal lesions of BD.

4. Therapy with monoclonal antibodies such as infliximab and etanercept are playing an increasing role in therapy of BD particularly in patients who do not respond to anti-inflammatory and immunosuppressive drugs.

The Patient With Chronic Multiple Ulcers

1. Pemphigus Vulgaris
2. Paraneoplastic pemphigus PNPP
3. Pemphigus Vegetans
4. Subepithelial Bullous Dermatoses
5. Bullous Pemphigoid
6. Mucous Membrane Pemphigoid (Cicatricial Pemphigoid)
7. LAD and Chronic Bullous Disease of Childhood
8. EBA

Pemphigus

Pemphigus includes a group of autoimmune, potentially life-threatening diseases that cause blisters and erosions of the skin and mucous membranes, characterized by intraepithelial acantholysis.

The predisposition to develop the autoantibodies that cause pemphigus is genetically determined, but the triggering mechanism that initiates the immune response is unknown

Desmoglein 1 (DSG1), a glucoprotein adhesion molecule, is primarily found in the skin, whereas **desmoglein 3** (DSG3) is chiefly detected in *mucosal epithelium* and individuals genetically susceptible to pemphigus harbor desmoglein reactive B and T cells.

The immune reaction against these glycoproteins causes a loss of cell-to-cell adhesion, resulting in the separation of cells and the formation of intraepithelial bullae.

Pemphigus Vulgaris

Etiology and Pathogenesis

- ✓ It is the most common form of pemphigus, accounting for more than 80% of cases.
- ✓ The underlying mechanism responsible for causing the intraepithelial lesion of PV is the binding of IgG autoantibodies to DSG3, a transmembrane glycoprotein adhesion molecule present on desmosomes.
- ✓ The loss of this glycoprotein results in loss of cell- to-cell adhesion resulting in intra-epithelial blisters.
- ✓ Patients with PV mainly involving the mucosa have antibodies primarily against DSG3, but patients with PV involving both the skin and mucosa will have antibodies against both DSG3 and DSG1.
- ✓ PV has been reported coexisting with other autoimmune
- ✓ Several cases of pemphigus have been reported in patients with other autoimmune disorders or those with neoplasms such as lymphoma.

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

- A characteristic sign of the disease may be obtained by applying pressure to an intact bulla.
- In patients with PV, the bulla enlarges by extending to an apparently normal surface.
- Another characteristic sign of the disease is that pressure to an apparently normal area results in the formation of a new lesion.

This phenomenon, called the Nikolsky sign, results from the upper layer of the skin pulling away from the basal layer.

- Any mucosal and skin surface may be involved, and in severe cases, the conjunctival, pharyngeal, and laryngeal mucosa may be involved, along with extensive skin lesions.
- Patients with oral lesions of pemphigus may also have esophageal lesions, and if esophageal symptoms are present, endoscopic examination should be performed to determine the severity of the lesions.

Oral Findings

1. Up to 80- 90% of patients with PV develop oral lesions sometime during the course of the disease, and in 60% of cases, the oral lesions are the first sign.
2. The oral lesions may begin as the classic bulla on a non inflamed base; more frequently, the clinician sees shallow irregular erosions and ulcers because the bullae rapidly break.
3. A thin layer of epithelium peels away in an irregular pattern, leaving a denuded base.
4. The edges of the lesion continue to extend peripherally over a period of weeks until they involve large portions of the oral mucosa.
5. Most commonly, the lesions start on the buccal mucosa, often in areas of trauma along the occlusal plane.

The palatal mucosa and gingiva are other common sites of involvement.

It is common for the oral lesions to be present for months before the skin lesions appear.

6. Frequently, however, the initial diagnosis is missed, and the lesions are misdiagnosed as HSV infection or candidiasis.

7. The average time from the disease onset to diagnosis may often take over five months, and coexisting candidiasis may mask the typical clinical picture of the pemphigus lesions.

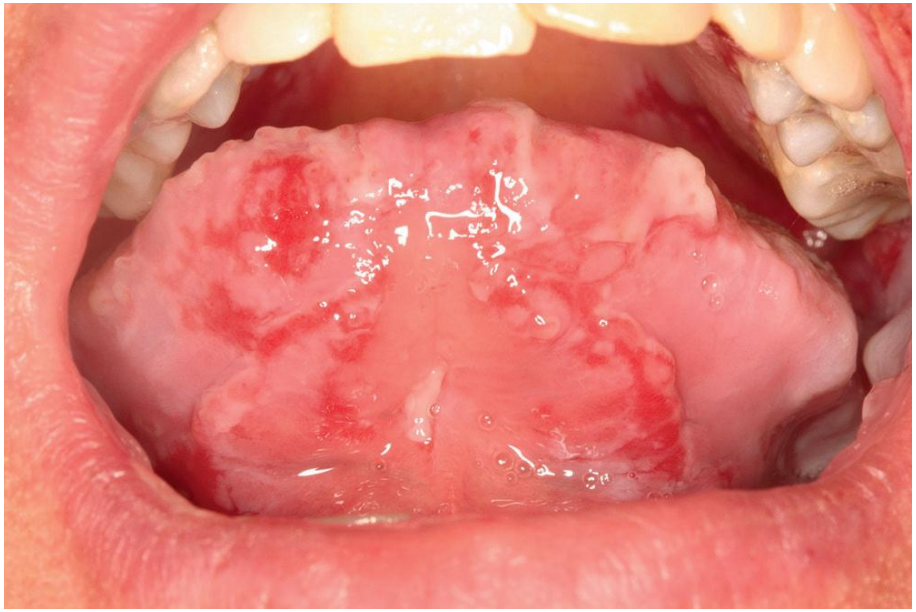
8. There is a small subgroup of pemphigus patients whose disease remains confined to the oral mucosa.

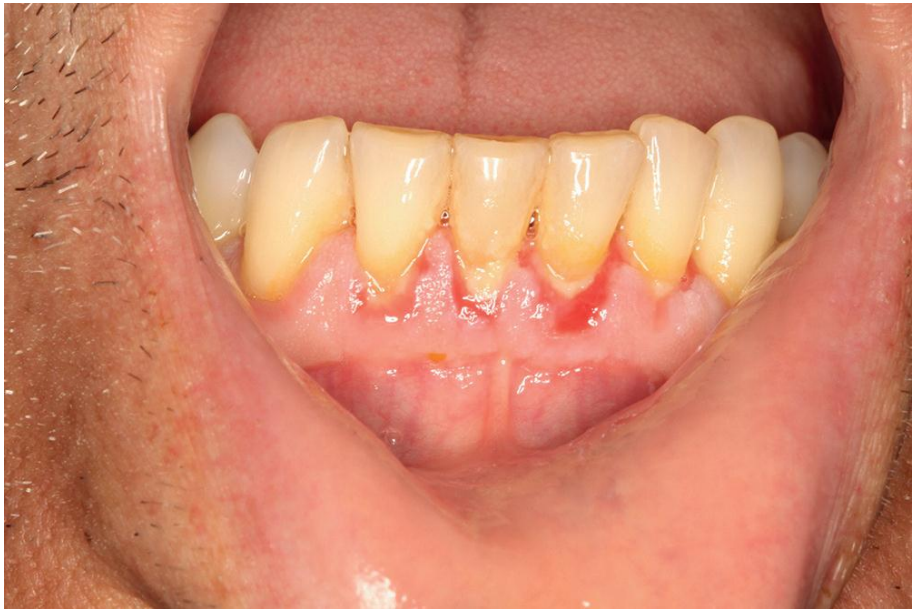
9.These patients often have negative results on indirect and direct immuno-fluorescence testing.

Laboratory Findings and Pathology

PV is diagnosed by biopsy and biopsies are best done on intact vesicles and bullae less than 24 hours old. However, because intact lesions are rare on the oral mucosa, the biopsy specimen should be taken from the advancing edge of the lesion, where areas of characteristic suprabasilar acantholysis may be observed by the pathologist.

Specimens taken from the center of a denuded area are nonspecific histologically.
Sometimes more than one biopsy is necessary before the correct diagnosis is rendered.





Management

- early diagnosis, lower doses of medication can be used for shorter periods of time to control the disease.
- Management varies according to several factors, including the severity of the disease and the speed at which the disease progresses.
- The mainstay of treatment remains high doses of systemic corticosteroids, usually given in dosages of **1–2 mg/kg/d**.
- When substantial doses of steroids must be used for long periods, 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, cyclophosphamide, and cyclophosphamide pulse therapy.
- Prednisone is used initially to bring the disease under control, and once this is achieved, the dose of prednisone is decreased to the lowest possible maintenance levels.
- Patients with only oral involvement also may need lower doses of prednisone for shorter periods, so the clinician should weigh the potential benefits of adding adjuvant therapy against the risks of long- term immunosuppression, such as blood dyscrasias and an increased risk of malignancy.

- There is no one accepted treatment for PV **confined to the mouth**, but one five-year follow-up study of the treatment of oral PV showed ***no additional benefit of adding*** cyclophosphamide or cyclosporine to prednisone versus prednisone alone.

- Most studies of PV of **the skin** show a decreased mortality rate when adjuvant therapy is given along with prednisone.
- The need for systemic steroids may be lowered further in cases of oral PV by combining topical with systemic steroid therapy, either by allowing the prednisone tablets to dissolve slowly in the mouth before swallowing or by using high-potency topical steroid creams.
- **Dapsone** has been shown to be effective.
- Recalcitrant cases are treated with rituximab and intravenous immunoglobulins.

Rituximab is presently being used and evaluated as a first line treatment although some studies demonstrated a high rate of infection.

Bullous Pemphigoid

Etiology and Pathogenesis

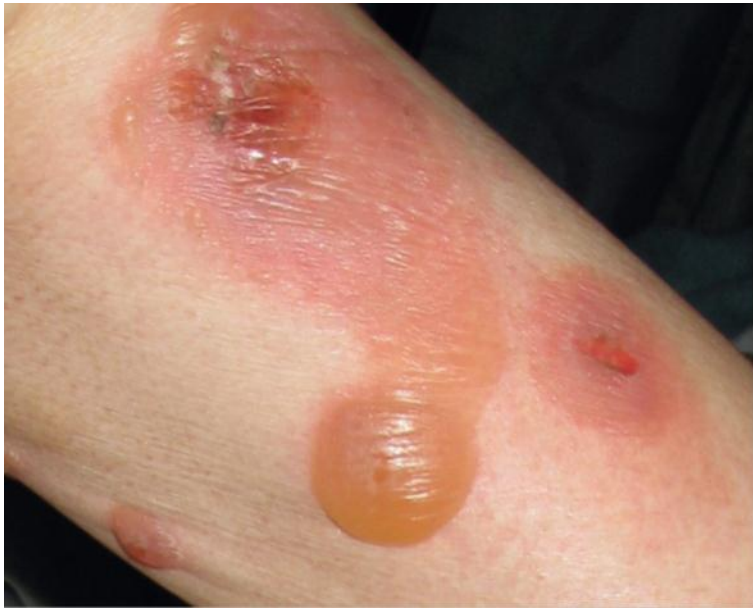
- BP is the most common of the subepithelial blistering diseases,
- occurs chiefly in adults older than the age of 60 years; it is self-limited and may last from a few months to five years.
- BP may be a cause of death in older debilitated individuals.
- A thorough evaluation for an underlying malignancy is recommended for patients with severe or recalcitrant BP.

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 BP 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**.

Clinical Manifestations

- The characteristic skin lesion of BP is a tense blister on an inflamed base accompanied by urticarial plaques in the scalp, abdomen, extremities, axilla, and groin.
- Pruritus is a common feature of the skin lesions,
- The disease is self-limiting but can last for months to years without therapy.
- Patients with BP may experience one episode or recurrent bouts of lesions.
- Unlike pemphigus, BP is rarely life threatening since the bullae do not continue to extend at the periphery to form large denuded areas,
- 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 occurs in 10–20% of BP patients.
- The oral lesions of BP are smaller, more slowly, and less painful than in PV; the often extensive labial involvement seen in PV 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 MMP.

Laboratory Findings

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

Management

- ✓ localized oral lesions of BP may be treated with high-potency topical steroids, such as clobetasol or betamethasone, whereas patients with more extensive disease require use of systemic corticosteroids alone or combined with immunosuppressive drugs such as **azathioprine**, **cyclophosphamide, mycophenolate, or rituximab**.
- ✓ Patients with **moderate levels** of disease may minimize the use of systemic steroids by the use of **dapsone or tetracycline, doxycycline, or minocycline,** which may be combined with niacinamide.

Mucous Membrane Pemphigoid -MMP
(Cicatricial Pemphigoid)

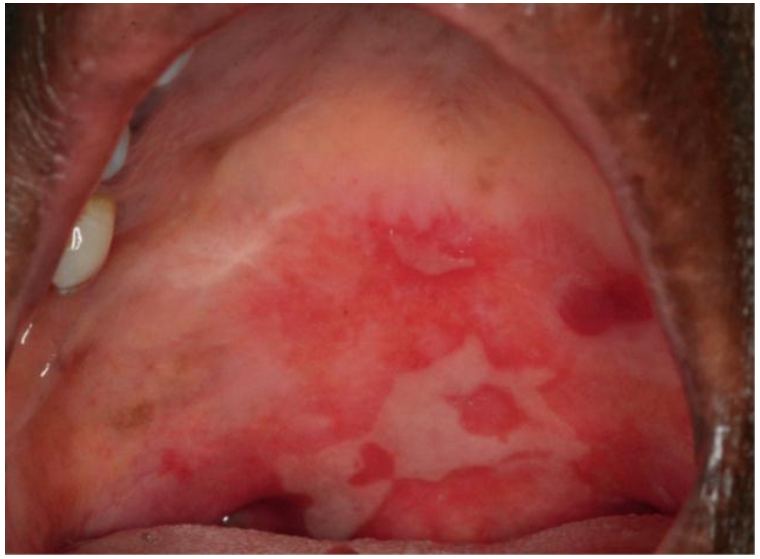
Etiology and Pathogenesis

- ✓ is a chronic autoimmune subepithelial disease that primarily affects the mucous membranes of patients older than the age of 50 years, resulting in mucosal blistering, ulceration, and subsequent scarring in some organs.
- ✓ The disease **occurs twice as frequently in women**.

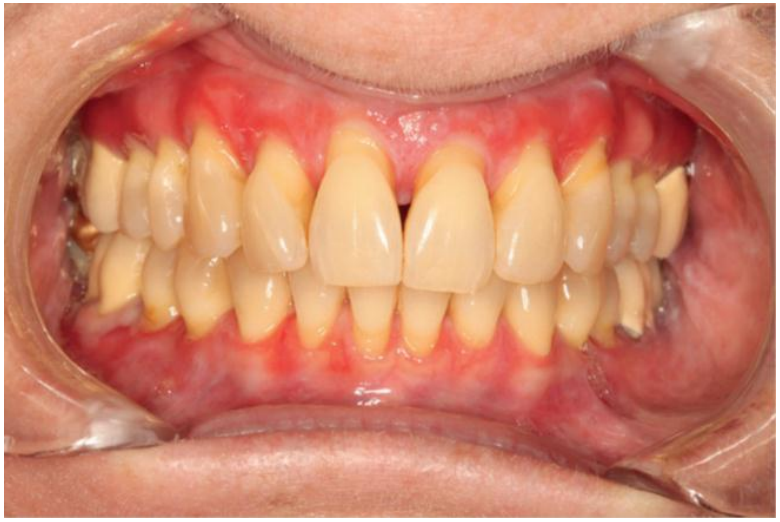
- ➢ The primary lesion of MMP occurs when autoantibodies directed against proteins in the basement membrane zone, acting with complement (C3), cause a subepithelial split and subsequent vesicle formation.
- ➢ Antibodies against basement membrane antigens have been identified in cases of MMP.
- ✓ The antigens are most frequently present in the **lamina lucida** portion of the basement membrane, but the **lamina densa** may be the primary site of involvement in some cases.

Oral Findings

- ✓ Oral lesions occur in more than 90% of patients.
- ✓ Desquamative gingivitis is the most common manifestation and may be the only manifestation of the disease appearing bright red.



- ✓ **Since these desquamative lesions resemble the lesions of erosive lichen planus and PV, all cases of desquamative gingivitis should be biopsied and studied with both routine histology and DIF for definitive diagnosis**.
- ✓ Lesions may present as intact vesicles of the gingival or other mucosal surfaces, but more frequently they appear as nonspecific-appearing erythema and erosions.
- ✓ Unlike ocular pemphigoid, oral MMP rarely results in scarring.



Laboratory Findings

Patients with suspected MMP should have biopsy specimens taken for both routine and DIF studies. **The specimen for routine histology and DIF should be taken from the edge of an ulcer, vesicle, or erythema and tissue**. Histopathology reveals subepithelial clefting with preservation of basal cells and variable inflammation

Management

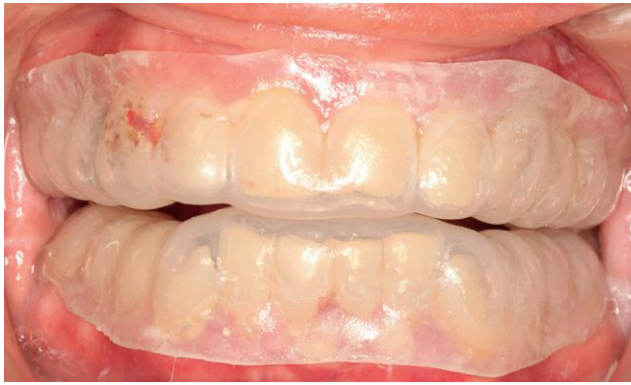
Management of MMP depends on the severity of symptoms and site of involvement.

- When the lesions are confined to the oral mucosa, use of systemic corticosteroids should only be considered for short periods for severe outbreaks until steroid-sparing therapy can be instituted.
- Unlike PV, MMP rarely a fatal disease, and long-term use of systemic steroids for oral lesion involvement alone is seldom indicated.
- Patients with **mild oral disease** may be treated with **topical and intralesional steroids.**

steroid-sparing therapy

❑ Desquamative gingivitis

can often be managed with topical steroids in a soft dental splint that covers the gingiva, although the clinician using topical steroids over large areas of mucosa must closely monitor the patient for side effects such as candidiasis and effects of systemic absorption



- When **topical or intralesional therapy is not** successful, use of a tetracycline, such as doxycycline or minocycline is often 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, immunosuppressive drug therapy or rituximab.

Since **dapsone** causes hemolysis and methemoglobinemia, **glucose-6-phosphate dehydrogenase** deficiency must be ruled out, and the patient's hemoglobin must be closely monitored.

Epidermolysis Bullosa Acquisita

Patients with EBA have **IgG 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, which results in a lesion of the basement membrane with little inflammation,
or the inflammatory form, which includes a significant infiltration of neutrophils.

Clinical Manifestations

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**.
Oral lesions present as erythema, erosion, ulcers and desquamative gingivitis.

Management

- depending on the extent and severity of the clinical lesions.
- The **classic form** of the disease tends to be resistant to treatment, whereas the inflammatory form often responds well to **dapsone**.
- Systemic corticosteroids, immunosuppressive or intravenous IG may be required to control the lesions in severe widespread EBA

Patient with Single Ulcers

1. Traumatic Injuries Causing Solitary Ulcerations
2. Traumatic Ulcerative Granuloma

(Eosinophilic Ulcer of Tongue)

3. Infectious Ulcers

Traumatic Injuries Causing Solitary Ulcerations

Etiology and Pathogenesis

- Single mucosal ulcers may be caused by
  - direct physical/ mechanical,
  - thermal,
  - chemical trauma to the mucosa
  - or even vascular compromise, causing tissue damage and ulceration.

Acute bite injuries, an example of direct physical/ mechanical trauma, occur often in the oral mucosa

Traumatic injuries may also result from malocclusion, ill-fitting dental prostheses, overzealous toothbrushing and flossing, self-injurious habits, and oral piercings.

Thermal injuries including electrical burns are infrequently seen in children who inadvertently chew on electrical wiring.

More commonly, thermal burns occur on the palatal mucosa from ingesting hot foods and beverages (such as hot pizza or coffee).

An iatrogenic cause of thermal injury is from a heated dental instrument

Chemical trauma is caused by patients or dentists placing noxious and caustic substances directly on the mucosa or chewing medications formulated to be swallowed (such as aspirin or oral bisphosphonates) may also lead to severe oral ulcers.

- Mouthwashes or other oral care products with high alcoholic content, hydrogen peroxide, or phenols used too frequently or undiluted can cause mucosal ulcerations
- Some over-the-counter medications for treating aphthous ulcers contain high concentrations of silver nitrate, phenols, or sulfuric acid and should be used with caution.
- Ulcers have also resulted in the use of denture cleansers as an oral rinse.
- Prolonged contact of methacrylate monomer on the mucosa may also lead to necrosis of the mucosa.
- **Necrosis of the bone** and mucosa has been reported from chemicals used in endodontics if these are pushed **past the apices** of teeth.

Vascular compromise leads to oral ulcers and two main patterns are identified.

necrotizing sialometaplasia where there is local infarction of the salivary gland tissue leading to overlying ulceration, exfoliation of the necrotic tissue, and healing.

Many etiologies have been identified including vasoconstrictors, sustained pressure and bulimia and the most common location for this condition is the hard palatal mucosa although any location that contains salivary glands may be affected.

Another is systemic vasculitis, where inflammation of vessels leads to thrombosis and infarction.

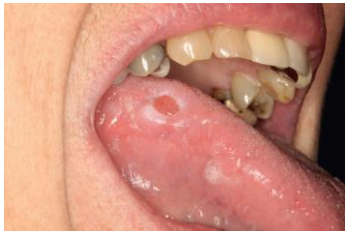
Tongue necrosis is a particularly well-documented aspect of giant cell (temporal) arteritis.

Management

1. Smaller lesions heal on their own once the irritant is removed.
2. Pain can be achieved with topical anesthetics (viscous lidocaine).
3. Topical steroids or intra-lesional steroid injections may be useful..
4. Dentists also should be more aware of taking protective measures when using caustic substances and heated instruments.
5. Electrical burns are generally deep and more extensive, and healing often results in scarring and contracture.

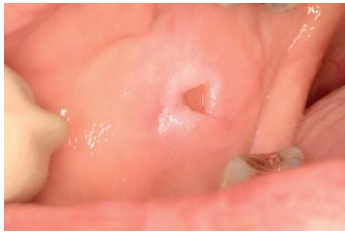
If the corners of the mouth are involved, microstomia may result.
Children benefit from the use of microstomia prevention devices during this healing period, although surgical correction may still be required to restore function and esthetics.
Antibiotics may be necessary to prevent a secondary infection since these burns often take several weeks to heal.
Necrotizing sialometaplasia heals on its own while ulcers of vasculitic origin will generally require treatment with systemic corticosteroids.

Traumatic Ulcerative Granuloma (Eosinophilic Ulcer of Tongue)

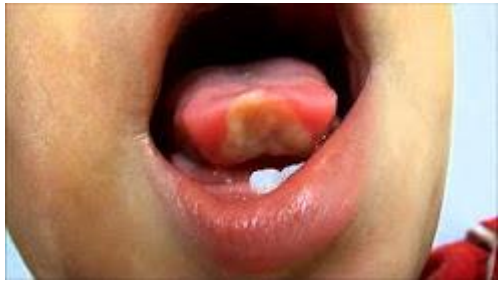


Etiology and Pathogenesis

- This ulcerative condition of the oral cavity is considered traumatic in nature, although less than 50% of patients recall a history of trauma.



- It is likely that the penetrating nature of the inflammation results in myositis that leads to chronicity.
- other acute or chronic ulcerative conditions left untreated may become deep and penetrating.
- Similar lesions are seen on the ventral tongue in infants caused by the tongue rasping against newly erupted primary incisors, a condition known as **Riga–Fede disease**.



- Patients with familial dysautonomia and other conditions, such as Riley–Day syndrome and Lesch–Nyhan syndrome, who have congenital incapacity to sense pain often also develop similar ulcerative and necrotic ulcers because they are unaware of the self-inflicted injury.

Clinical Manifestations

bimodal age distribution

- first two years of life associated with erupting primary dentition.
- adults in the fifth and sixth decades.

Oral Findings

❖ **In children**, the ulcers are always on the anterior ventral or dorsal tongue associated with erupting mandibular or maxillary incisors, respectively.

❖ **The tongue** is the site of involvement in approximately 60% of adult cases, usually on the posterior and lateral aspects.

❖ An ulcer develops that may not be painful in two-thirds of cases and may persist for months.

❖ A history of trauma is 20–50% of cases.

❖ The ulcer generally appears cleanly punched out, with surrounding erythema and keratosis if present for weeks or months.

- A single, chronic, painless ulcer with induration raises the suspicion for squamous cell carcinoma (especially if it is on the tongue), salivary gland malignancy or lymphoma.

Management

1. A careful history is important to rule out continued trauma to the site.
2. Intralesional steroid injections performed over a few weeks will often resolve these lesions.
3. Wound debridement also often leads to complete resolution, in 1/3 of cases
4. The use of a nightguard on the lower teeth may help reduce nighttime trauma.

Infections Causing Solitary Ulcers

1. **Viral infections** such as CMV and EBV of the herpes family may cause single ulcers that **last for weeks or months** in the immunocompromised or immunosenescent patient
2. The deep mycoses were uncommon causes of oral lesions prior to HIV infection, myelosuppressive cancer chemotherapy, and immunosuppressive drug therapy.
3. **The dentist must** consider this group of diseases in the differential diagnosis whenever **isolated ulcerative oral lesions develop in known or suspected immunosuppressed patients.**

If there is reactive epithelial hyperplasia to the organism, lesions may appear as fungating masses resembling squamous cell carcinoma.

Biopsy of suspected lesions, accompanied by a request for appropriate stains, is necessary for early diagnosis. Newer molecular-based diagnostic tests are also available.