**INFECTIONS OF ORAL MUCOSA**

### a. viral

- Laboratory confirmation rather long → diagnosis based mainly on clinical features
- → Basic diagnostic methods:
  1. Culture of viral particles;
  2. Morphologic changes and IHC techniques;
  3. Serologic studies
- Main viral infections include:

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**HERPETIC STOMATITIS**

- The most common;
- Caused by DNA virus:
  - HSV type 1 (skin and oral mucosa)
  - Type 2 (genital area)
- → Primary infection of HSV type 1 → Primary herpetic gingivostomatitis
- Mainly in children and young adults

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**HERPETIC STOMATITIS**

- Inoculation → Incubation period (about 5 days)
  → Prodromal symptoms (fever and malaise)
  → 1-2 days latter many small vesicles on any part of oral mucosa and lips
  → Ulceration of vesicles and secondary infections
  → Lymphadenitis
  → In next 6 days symptoms subside and oral lesion resolve in about 10-14 days
- In recurrent infection
  - Predisposing factors: UV, stress, common cold, febrile infections, mechanical trauma, menstruation
  - Prodromal symptoms occur for about few hours and the crusted vesicles become healed within a week.

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**CHICKENPOX AND HERPES ZOSTER (SHINGLES)**

- Both caused by varicella-zoster virus (VZV)
- DNA virus
- Chickenpox lesions may be found on the soft palate and fauces (vesicles → partially ulcerated)

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**CHICKENPOX AND HERPES ZOSTER (SHINGLES)**

- Zoster is a reactivation of latent VZV hidden in sensory ganglia
- Clinically:
  - Unilateral involvement in the distribution of the sensory nerves precede by 2 weeks of pain and paresthesia
  - The course of the disease is about 14 days
  - The most distressing complication is post-herpetic neuralgia (perineural fibrosis ?)
  - Sometimes zoster causes lower motor neuron-type facial paralysis → Ramsay-Hunt syndrome
HERPANGINA
- various coxackieviruses A, RNA virus
- mainly children

Clinically:
- mainly in children with symptoms of:
  - fever, anorexia, dysphagia, and sore throat
  - 1-2mm vesicles with ulcerations mainly on tonsils, soft palate and uvula (oropharyngitis)
  - symptoms persist for 2-3 days only

HAND, FOOT, AND MOUTH DISEASE
- various coxackieviruses A (type 16), RNA virus
- mainly children

Clinically:
- 2-8 mm ulcers on the gingiva, tongue, cheeks, and palate
- (!!) with parallel lesions on palms and soles
- disease persists up to 2 weeks

INFECTIOUS MONONUCLEOSIS (GLANDULAR FEVER)
- EBV, herpes-group, DNA virus
- mainly teenagers and young adults (transmitted by kissing)

Clinically:
- lymph node enlargement + fever + pharyngitis
  - sometimes prolong malaise (months) may occur
  - oral symptoms such as hemorrhages at the soft and hard palate junction (→ unspecific)

MEASLES
- various coxackieviruses A (type 16), RNA virus
- mainly children

Clinically:
- appearance of Koplik’s spots (buccal mucosa opposite the molar teeth) pin-point bluish white spots against an erythematous background
  - from few to hundreds
  - could be overlooked

BACTERIAL
- acute ulcerative gingivitis
  - AUG
  - acute necrotizing ulcerative gingivitis
  - Vincent’s gingivitis
- rather common
- young adults (M > F)
### ACUTE ULCERATIVE GINGIVITIS

- Clinically:
  - crater-like, punched-out ulceration of the interdental papillae of sudden onset
  - the ulcers are covered with greyish-green pseudomembrane demarcated from the surrounding mucosa by a linear erythema
  - NOMA (cancrum oris)
    - found in some undeveloped countries, especially in children
    - rapid spread of necrosis

### acute streptococcal stomatitis

- Clinically:
  - generalized erythema of the oral mucosa
  - marked acute gingivitis,
  - submandibular lymphadenitis,
  - and mild degree fever and malaise

### ACTINOMYCOSIS

- most commonly *Actinomyces israeli*
  - non-spore-forming bacteria
  - Gram-positive
  - do not secrete toxins
  - anaerobe

- normal reservoir:
  - oral cavity
  - GI

### ACTINOMYCOSIS

- Cervicofacial actinomycosis *(Lumpy jaw)*
  - hard, woody induration of the skin
  - an intense fibrocytic reaction
  - sinus tract formation
  - metastatic infection (chiefly skin)

### SYPHILIS (LUES)

- Caused by *Treponema pallidium*
- Inoculation
  - open lesion → mucous membranes; abraded skin
- transmission:
  - (a) sexual contacts
  - (b) bacterial laden secretions
  - (c) transplacental
- inoculation
  - multiplication (local)
  - pass to regional lymph nodes
  - dissemination throughout the body

### SYPHILIS (LUES)

- Delayed-type hypersensitivity
  - Insufficiency in killing spirochetes:
    - lack of outer immunogenic molecules
    - down regulation of T helper cells
- In all stages
  - obliterative endarteritis
    - *T. pallidium* binds to endothelial cells; through fibronectin molecules
  - plasma cell-rich mononuclear infiltrates
Primary syphilis

Macro:
- chancre (1 week - 3 months; last 3-12 weeks)
  - penis/scrotum
  - cervix
  - vaginal wall
  - anus
- solitary papula
- firm raised border
- non-tender
- erodes (shallow ulcer)

Micro:
- intense infiltration of plasma cells
- scattered macrophages, lymphocytes
- obliterative endarteritis
- treponema visible in silver/immunofluorescent techniques
- luetic vasculitis - proliferation of endothelial cells, thickened wall (swelling; lymphocytes and fibrous tissue)

Secondary syphilis (few days-months)

Macro:
- skin*
  - rash or macules (2 weeks - 6 months after chancre heals)
  - mostly on palms and soles
- mucous membranes**
  - white oral lesions
- lymph nodes (lymphadenopathy)***
- meninges irritation (headache; stiff neck)
- stomach
- liver
- arthritis
- and in addition: fever
- lesions resolve spontaneously

* - follicular syphylids (papular lesions)
- nummular syphylids

** - mucous patches
- contain treponemas, very infectious
- condylomata lata (exudative plaques)

*** - follicular hyperplasia
- increase number of plasma cells, macrophages
- luetic vasculitis
- thickened capsules

Tertiary syphilis (after years)

- formation of the gumma
- focal lymphatic necrosis secondary to obliterative endarteritis (infiltration by lymphocytes and plasma cells)

  A) syphilitic aortitis
  - necrosis of aortic media (- aneurism; dilatation of aortic ring)

  B) neurosyphilis
  - meningeal syphilis
  - tabes dorsalis
  - general paresis

  C) gumma formation:
  - skin
  - subcutaneous tissue
  - bones
  - joints
  - liver

CANDIDIASIS (moniliasis, trush)

- caused by yeast-like fungus: **Candida albicans**
  - a common inhabitant of the oral cavity
  - in about 50% of population is asymptomatic
  - found also in the GI and vagina
  - but could be also cased by **Candida tropicalis, Candida pseudotropicalis, Candida krusei**

- oral candidiasis most common in patients:
  - with immunocompromised state
  - diabetics
  - and with AIDS (40-90%)

- the relationship between commensal and pathogenic state of **Candida albicans** includes local factors:
  - dentures,
  - oral hygiene,
  - perturbations of the normal oral microflora by antibiotics
  - and systemic factors (endocrine milieu, immunocompetence)

- basic morphology:
  - white, slightly elevated, soft patches (composed mainly by fungal hyphae)
  - could be also presented as:
    - pseudomembranous
    - hyperplastic
    - or erythematous lesions
TRUSH
(pseudomembranous candidiasis)
• very common in AIDS patients;
• may occur in:
  – neonates,
  – young infants,
  – debilitated,
  – elderly patients
• symptoms from minimal to severe burning and tenderness
• lesions (often multiple) are located mainly on buccal mucosa, oropharynx, and lateral edges of tongue’s dorsum
• the pseudomembrane:
  – consists of fungal yeast, squamous cells, keratin debris, inflammatory cells, bacteria, Foreign Route
  – creamy, easily wiped off to expose an erythematous, eroded, and tender mucosa

Denture-induced stomatitis
• mainly women,
• on the palate
• causes:
  – tight-fitting dentures,
  – and also ill-fitting
  – as well as failure to remove them at night
  → improper exposure to saliva
• usually asymptomatic
• candida microorganisms + inflamed acanthotic mucosa

Angular stomatitis
(angular chalitis, perlèche)
• especially in patients with deep grooves at the angles of the mouth or those who lick their lips
  → circumoral candidal dermatitis
• mainly in elderly
  → sagging facial tissue permit the exposure of the skin to infected saliva
• differential diagnosis:
  – iron deficiency
  – and Staphylococcus aureus infection

Candidal leukoplakia
(chronic hypertrophic candidiasis)
• usually asymptomatic
• healthy middle-aged adults
  (could be associated with cigarette smoking)
• the plaque is tightly adherent
• when the dorsum of the tongue is involved
  → "median rhomboid glossitis" (lozengeshaped area of depapillation)

Chronic mucocutaneous candidiasis
• early age of onset (in most cases),
• several types
  – diffuse type of mucocutaneous candidiasis
    → most severe, and rather rare
    – includes severe candidiasis of the skin, nails, and mucous membranes (oral, vaginal, conjunctiva) + bacterial infections of the skin and respiratory tract
  – familial (limited) mucocutaneous candidiasis
    → autosomal recessive and associated with sideropenia, starts in infancy with trach → leukocytosis candidiasis, later dental and vaginal infections (nwd)
  – endocrine candidiasis syndromes
    → hypoparathyroidism, DiGeorge’s syndrome
  – late onset mucocutaneous candidiasis
    → associated with thymoma, myasthenia gravis, pure red blood cell aplasia, and defective cell-mediated immunity

ORAL NEOPLASIA
EPIDEMIOLOGY
General terms (1)

• Precancerous Lesion (Precancer, Premalignancy)
  → benign, morphologically altered tissue which has a greater than normal risk of transforming to a microscopic focus of cancer at diagnosis or of transforming into a malignancy after diagnosis.

• Precancerous Condition
  → a disease or patient habit which does not necessarily alter the clinical appearance of local tissue but is known to have a greater than normal risk of precancer or cancer development.

• Malignant Potential
  → the risk of cancer being present in a precancerous lesion or condition, either at the time of initial diagnosis or at a future date. The potential for mucosa without precancerous lesions or conditions is termed "normal".

General terms (2)

• Leukoplakia → a chronic white mucosal macule which cannot be scraped off, cannot be given another specific diagnostic name, and does not typically disappear with removal of known etiologic factors

General terms (3)

• Leukoplakia, then, is a clinical diagnosis which has the unusual attribute of being dependent not so much on definable appearances as on the exclusion of other lesions which present as oral white plaques. Such lesions as:
  – lichen planus
  – chronic cheek bite
  – frictional keratosis
  – tobacco pouch keratosis
  – nicotine palatinus
  – leukoedema
  – white sponge nevus
  – and other must be ruled out before a diagnosis of leukoplakia can be made.

General terms (4)

• Oral leukoplakia usually affects persons over 40 years of age
• Prevalence increases rapidly with age, especially for males
• While fewer than 1% of males prior to 30 years of age have lesions, an alarming 8% of males beyond 70 years of age are affected
• This may have grave implications for the practice of dentistry as the U.S. population ages
• The average age of affected persons, 60 years, is similar to the average age for oral cancer patients, although some studies have found it to occur about five years earlier than cancer.

Etiology of leukoplakia (1)

• Tobacco smoking → is quite strong correlation
  → BUT Not all leukoplakia patients have such a habit, only 70-90%
  → and 73% of lesions either completely disappear (59%) or regress within 12 months after smoking cessation
  → Importantly: 70-90% of lesions remaining after habit cessation or in patients who have never smoked may have a higher risk of malignant transformation than leukoplakias in smokers.

• Ultraviolet radiation is another accepted etiologic factor for leukoplakia but only for those associated with actinic cheilitis or "farmer's lip"

• Significantly, 2/3 of all lip vermilion carcinomas are associated with leukoplakia. This is the strongest association for any cancer of the upper aerodigestive tract.

• Chronic mechanical irritation is no longer considered important to the production of precancerous leukoplakia. Such obvious traumatic lesions as linea alba and chronic cheek bite have never been reported to have transformed into malignancies → While TRCs produced by mechanical irritation are best considered as frictional keratoses, which have no potential for malignant transformation.
Etiology of leukoplakia (2)

- Microorganisms have been implicated in leukoplakia etiology for more than a century, beginning with the classic dorsal leukoplakia of syphilitic glossitis.
  - Today, tertiary syphilis is rare, but a fungus, Candida albicans, is ubiquitous and is so often found in thick or homogeneous lesions that the terms candida epithelial hyperplasia and candida leukoplakia are commonly used to describe them. It is not known whether this yeast produces dysplasia or secondarily infects previously altered epithelium, but some leukoplakias have disappeared or become altered to a lower risk level after topical antifungal therapy.
- Recently developed molecular biology and virology techniques have allowed investigators, for the first time, to identify HPV in leukoplakia and oral cancer.
  - Detection rates are similar to normal oral epithelium, however, and such techniques have not yet been applied to large numbers of followed patients. It is, nevertheless, very significant that HPV type 16, a type demonstrated in oral leukoplakias and carcinomas, has been shown to induce dysplasia in squamous epithelium in an otherwise sterile in vitro environment.

Leukoplakia treatment

- Conservative surgical excision remains the treatment of choice for small leukoplakias.
  - Electrocautery, cryosurgery and laser ablation appear to be equally effective, although thermal excision tends to hinder a pathologist’s ability to evaluate extension and degree of dysplasia.
- The key is long-term follow-up after removal, because recurrences are frequent and additional leukoplakias occur. Clinical evaluation every six months is recommended, every 2-3 months for high risk lesions.
- Treatment sites remaining disease free for three years need no longer be followed, but any patient with residual leukoplakia should be followed for a lifetime. Multiple biopsies of high risk areas of large, multiple, or recurrent lesions are essential and should be followed by removal of all dysplastic tissue identified.
  - Even moderate epithelial dysplasias should be removed, as recent research from laryngeal keratosis has identified a significant risk of malignant transformation.

General terms (5)

**Erythroplakia**
- A chronic red mucosal macule which cannot be given another specific diagnostic name and cannot be attributed to traumatic, vascular or inflammatory causes.

**Smokeless Tobacco Keratosis**
- A chronic white or gray/translucent mucosal macule, in an area of smokeless tobacco (ST) contact, which cannot be scraped off and disappears with cessation of the ST habit.

Erythroplakia

- This lesion has been called “the dangerous oral mucosa” because:
  - It typically presents as carcinoma in situ.
  - It superficially invades carcinoma under the microscope.
  - In very high risk settings, such as oral floor lesions in heavy smokers and alcohol abusers, 80% of these red patches already may contain focal areas of microinvasive cancer at the time of initial biopsy.
- Follow-up studies are not available for erythroplakia, but its usual microscopic counterpart, carcinoma in situ, has been shown to transform into invasive carcinoma in approximately one of every four cases.
  - This malignant transformation occurs despite the fact that carcinoma in situ lesions are routinely treated by conservative surgical removal or laser ablation.
- Without therapy this disease transforms into invasive carcinoma in 60-90% of the cases within 5-10 years after initial diagnosis.