Section

I

Oral Medicine

Chapter 1

Case History, Diagnosis and Systemic Considerations

DEFINITION (AAOM)

Oral medicine is the specialty of dentistry that deals with the diagnosis and management of diseases that are non-surgical in nature, that may occur only in the oral cavity or may be an oral manifestation of systemic disease.

Oral cavity can reflect majority of systemic illness in children as well as adolescents. Oral health is integral factor of overall general health to which a clinician should be oriented while aiming at proper diagnosis and management.

Case history is defined as the data concerning an individual and his or her family and environment, including the individual's medical history that may be useful in analyzing and diagnosing his or her case or for instructional purposes. *(Grossman 13th Edition)*

History taking is an art, which a doctor learns over the years by repeated practice and experience. *(PJ Mehta)*

First interaction with the doctor can influence patient to answer every necessary leading question. It is advisable to consider patient's psyche as well, and not only the status of the disease.

IMPORTANCE OF HISTORY

- To aim at diagnosis
- To develop rapport with patient
- To know the psycho-social, economical, educational and health status of the patient so as to help in treatment planning.

Assessing patient's health, obtaining and evaluating history meticulously is mandatory for oral diagnostician. This method of history recording is divided into 4 major steps.

Steps:

1. Obtaining relevant information
2. Deriving provisional diagnosis
3. Carrying out necessary test to get final diagnosis
4. Formulating an accurate treatment plan.

Obtaining a patient's consent is another significant segment of case history taking.

A good case history should have the following information in a systematic manner.

a. **Demographic details:** This includes patient's name, age, sex, address, occupation, religion and marital status.
b. **Chief complaint:** This narrates about complaint with which patient has visited to doctor. These complaints should be recorded in chronological order along with duration.
c. **History of present illness:** This is related to complaints which patient had been dealing with, with all the symptoms right from initial days to present. Details of each symptom must be recorded separately. Associated symptoms must

be inquired and recorded. Similar illness in the past, duration and sequelae should be asked.

d. **Personal history:** It includes patient's appetite, diet, bowel and bladder habits, sleep cycle and associated habits of tobacco, kharra, betel nut, alcohol, snuff, khaini, smoking, etc.
e. **Family history:** The state of health of family members like, parents, grandparents, siblings should be noted. That history may include chronic and serious illness.
   - Few diseases run in family, so family history is of significance when a clinician deals with patient, e.g. X-linked recessive diseases—hemophilia, G6PD deficiency
   - Autosomal dominant disorders—neurofibromatosis familial hyperlipidemias
   - Autosomal recessive disorder—sickle cell anemia, beta thalassemia
f. **Menstrual and obstetric history:** Menstrual history is important to know, as it can be co-related with hormonal cycle and pregnancy.

GENERAL EXAMINATION

Includes following details:

In general examination we observe whether patient is conscious, cooperative and well-oriented with time, place and person, along with it we examine all vital parameters.

1. Built
2. Body proportions
3. Nutrition
4. Decubitus
5. Clubbing
6. Cyanosis
7. Jaundice
8. Pallor
9. Lymphadenopathy
10. Edema
11. Skin, hair and nails, vertebral column
12. Temperature
13. Pulse
14. Blood pressure
15. Respiratory rate

1. **Built:** It is the skeletal structure in relation to age and sex compared to a normal person. Conditions where altered built can be observed are:
   - *Tall:* Gigantism, hyperpituitarism, Marfan's syndrome
   - *Shrot:* Genetic, malnutrition, skeletal deformities, renal diseases.
2. **Body proportions**
   - *In adults:* Upper segment is equal to the lower segment
   - *In infants:* Upper segment is greater than the lower segment.
   - Due to genetic disorders this ratio can be altered, e.g. Marfan's syndrome, Klinefelter's syndrome
3. **Nutrition:** Proteins, fats, carbohydrates, vitamins and minerals are important for nourishment of human body. Deficiency of any of the nutritional factor should be observed and mentioned in the history, e.g. iron deficiency can cause pallor, koilonychia, calcium can cause tetany.
4. **Decubitus:** It is posture of the patient which he adapts when lying in bed, e.g.
   - *Hemiplegia:* One side of patient is immobile
   - *Tetanus:* The patient has neck stiffness.
   - *Pneumonia:* The patient is uncomfortable on lying on the affected side.
5. **Clubbing:** It is bulbous enlargement of soft parts of the terminal phalanges with both transverse and longitudinal curving of the nails. This occurs due to interstitial edema and dilation of the arterioles and capillaries.
   - Conditions leading to clubbing are: Tuberculosis, infective endocarditis, Crohn's disease, myxedema, etc.
   - *Schamroth's sign:* When two fingers are held together with nails touching each other, a diamond-shaped space is seen, which is lost in case of clubbing.

- Hypoxia is considered as possible cause for causing clubbing

6. **Cyanosis:** It is bluish discoloration due to reduced hemoglobin in capillary blood
   - Types of cyanosis are central, peripheral and mixed.
   - Causes of cyanosis can be, congestive cardiac failure, chronic obstructive lung disease, exposure to high altitude or cold, etc.
   - *Cause of cyanosis:* When the amount of reduced hemoglobin exceeds 5 gm% in the capillaries, the blood appears dark, giving the tissue a bluish hue.
7. **Jaundice:** It is a symptom complex which is characterized by yellow discoloration of tissue and body fluids due to increase in the bile pigments. Jaundice can be positive in intra-corpuscular defects, extra-corpuscular defects, disturbance in bilirubin transport and hepatocellular diseases. Normal serum bilirubin: 1 mg% (total)
8. **Pallor:** Pallor is paleness of skin and mucous membrane due to circulating red blood cells or diminished blood supply. Causes of pallor can be anemia, shock and peripheral vascular disease.
9. **Lymphadenopathy:** It is an inflammatory or non-inflammatory enlargement of lymph nodes.There are various causes of lymphadenopathy like inflammatory diseases, neoplastic diseases, and neurological diseases. It can be categorized as generalized or regional lymphadenopathy. For oral and maxillo-facial infections regional lymph nodes are commonly enlarged or show changes.
10. **Edema:** It is a collection of fluid in the interstitial spaces or serous cavities. It may occur due to increased capillary permeability like, in acute inflammation, increased capillary pressure, e.g. cardiac failure or decreased osmotic pressure of the blood in hypoproteinemia. So, various cardiac, renal, hepatic endocrinal and nutritional disorders are responsible for edema.
11. **Vertebral column, skin, hair, nails.**
    - **Vertebral column** has no lateral curvature. It should be examined for any abnormality, angular deformity, swelling or tenderness.
    - Patient can be asked to bend forwards, backwards, and sideways to evaluate changes in vertebral column, which maybe a result of scoliosis, kyphosis, gibbus, lordosis.
    - **Skin** can be examined for its color, pigmentation, eruptions, macule, vesicle, hemorrhage. Types of skin are dry, moist, thick, thin, and pinched.
      To deal with history of **hair**, various details can be obtained as, falling of hair (typhoid), patent hair loss, loss of eyebrows or excessive growth (Cushing's syndrome).
    - **Nails** should be examined for shape, size, pallor and relation to nail bed. Conditions that affect nails are: anemia, tuberculosis, cyanosis or clubbing due to systemic diseases, hemorrhagic condition.

Vital Parameters

12. **Temperature:** Fever is associated with release of endogenous pyrogens which activate T cell and shows active host defense. It refers to body temperature mechanism of the viscera and tissue of the body. It can be best recorded by mercury thermometer and is recorded in axilla as a chair-side method but can also be recoded by keeping thermometer orally or rectally(kids).
    Normal range of temperature; 36°–37°C or 98°–99°F. Fever is an increase of more than 1°C or any rise above normal temperature.
    Probable causes of fever can be infections, neoplasms, vascular diseases, trauma, immunologic diseses, endocrinal diseases, metabolic diseases, etc.
13. **Pulse:** The normal pulse with regular intervals has normal range of 60–100/minute.

Pulse can be *anacrotic pulse, dicrotic pulse, pulsus bisferiens, pulsus parvus of tardus, pulsus alternans, pulsus paradoxus, thread pulse, and water hammer pulse*.

14. **Blood pressure:** BP is measured in terms of systolic and diastolic. Systolic BP is controlled by stroke volume of heart and stiffness of the arterial vessels, whereas diastolic BP is controlled by peripheral resistance.
    Variation in BP can be due to emotional alteration, exercise, meals, alcohol, tobacco, bladder distension, pain or temperature rise. Also circadian rhythms, age and face can influence BP.
    Measuring BP can aid in diagnosis of hypertension, hypotension, pulsus paradoxus, pulsus alternans, and aortic incompetence.
15. **Respiratory rate (RR):** Normal rate of respiration is 16–20/minute.
    - Increased RR (tachypnea) is evident in a few conditions like, exertion and excitement, fever, anorexia, and anemias while decreased RR (bradypnea) can be seen in poisoning like narcotic drugs and brain tumor.
    - Dyspnea is breathlessness, which can be seen with congestive cardiac failure, asthma, pneumonia, COPD.

BODY SYSTEMS: EVALUATION FOR SYMPTOMS (PAST MEDICAL HISTORY)

Obtaining accurate past medical history (PMH) is also important in history taking as it helps to identify oral manifestation of systemic disorders, in diagnosing and treating the condition and sometimes in handling relevant medico-legal issues.

- **Respiratory system:** Chest pain, wheezing, dyspnea, cough, hemoptysis.
- **CVS:** Chest pain, dyspnea, edema, claudication
- **GIT:** Appetite, dysphagia, nausea, vomiting, hematemesis, indigestion, pain, diarrhea, constipation, bloating, jaundice.
- **Genito-urinary:** Urinary frequency, dysuria, hematuria, nocturia, incontinence, discharge.
- **Endocrine:** Polyuria, polydypsia, pigmentation, temperature intolerance.
- **Hematologic:** Spontaneous gingival bleeding, long bleeding time, easy bruising, epistaxis.
- **Dermatologic:** Pruritus, rashes, pigmentation, eruptions, allergy.
- **Musculoskeletal (spasm of muscles of TMJ and accessory muscles of mastication):** Changes in range of motion of joint, joint swellings, joint deformities, pain of muscles or joint, joint sounds.
- **Lymphatic system:** Enlarged nodes, mobility.
- **ENT:** Oropharynx, nasopharynx, voice changes.

EXTRAORAL EXAMINATION

It includes examination of head, facial symmetry, TMJ, lymph nodes, ears, nose, eyes.

Examination is carried out in a dental chair with the head completely rested or supported. This aids in accurate extraoral examination of the patient.

This examination in dental office is restricted to the superficial tissues of the oral cavity, head and neck.

- **Facial symmetry:** This can guide towards uniformity of facial structures, bilaterally. It can be examined under two headings—symmetrical or asymmetrical.
  Face can be asymmetrical due to swelling, genetic disorder, trauma, etc.
- **TMJ:** Joint is examined for range of motion, swelling, pain of muscles, joint, palpation of muscles and joint or any other obvious abnormality (detail examination of TMJ is covered in chapter on TMJ diseases)
- **Ear, nose:** Examined for observable pathology, bleeding and pain.
- **Lips:** Lips are examined for presence of lip seal. Swelling, painful ulcer, gingival enlargement, etc. can alter competency of lips.

- **Eye:** Eyes are examined for intercanthus and eyeball distance, vision or other developmental abnormalities.
- **Neck (lymph nodes):** Regional lymph nodes are cervical group of lymph nodes (submental, submandibular, parotid, post-auricular, pre-auricular, occipital, and others are superficial, deep and anterior cervical nodes).

Nodes are examined under the headings of group of lymph nodes, mobility, side enlargement, dimension, tenderness, number, discharge, fixity to underlying structure, consistency and overlying skin.

Lymph node examination: For submandibular LN clinician stands behind the patient. With fixed neck, clinician uses tip of the first two fingers placing them medial to the body of mandible to palpate the nodes.

Cervical group of LN can be palpated anteriorly and posterior to the sternocleidomastoid (SCM) muscle. (By rotation of neck to opposite side, SCM becomes prominent which facilitates LN examination). There are many clinical conditions causing lymphadenopathy like local or systemic. Most common causes include infections of odontogenic origin, tuberculosis, malignancy, lymphomas or other non-specific lymphadenopathy, etc.

In acutely inflamed ulcers, the regional lymph nodes become enlarged, tender and show signs of acute lymphadenitis. Later on the nodules become soften to form an abscess.

In malignant ulcers, the nodes are stony hard and may be fixed to the neighboring structures in the later stages.

INTRAORAL EXAMINATION

Hard tissue and soft tissue examinations are covered in this section of history.

Hard tissue involves teeth while soft tissue includes all mucosae, tongue, gingiva, oropharynx, faucial pillars, uvula hard palate.

- **Lips:** Normal is pink, smooth and moist. It shows minor salivary glands.
- **Cheeks:** Moist and pink, Fordyce's granules, salivary gland opening (parotid)
- **Floor of mouth:** Lingual frenum, sublingual fold, sublingual carbuncle.
- **Tongue**
  - *Dorsum:* Papilla present and median furrow.
  - *Ventral surface:* Lingual frenum attached and varicosities
  - *Movements*
  - *Lateral borders*
- **Palate (soft/hard):** Minor salivary glands and their opening.
- **Gingiva**
  - Coral pink in color.
  - Firm and resilient in consistency.
  - Stippling present with orange peel appearance.
- **Orifice of salivary ducts**
  1. Parotid gland: Parotid duct
     - The duct opens into the mouth on the inner surface of cheek usually opposite to the maxillary 2nd molar.
  2. Submandibular gland: Wharton's duct
     - It opens by narrow opening on the summit of a small papilla at the side of frenum on the tongue.
  3. Sublingual gland: Bartholins's duct
     - The sublingual glands are drained by 8–20 excretory ducts known as duct of Rivinus.
     - Most of the remaining small sublingual ducts open into the floor of the mouth.
- Tonsillar pillar
- **Hard tissue:** Teeth

  Hypoplasia
  - Enamel hypoplasia
  - Dentin dysplasia
  - Fluorosis
- **Caries:** Initial/moderate/deep/pulp involvement
- Missing
- Filled
- Endodontically treated

- **Mobile**
  - Periodontitis
  - Pulpal infection
  - Trauma
  - Malignancy
  - Trauma from occlusion (TFO)
- Wasting disease
- **Over retained**
  - Ankylosis of tooth
  - Incomplete resorption of primary tooth
- **Supernumerary teeth**
  - Cleidocranial dysplasia
  - Familial adenomatous polyposis
  - Trichorhinophalangeal syndrome,
  - Type I: Rubinstein-Taybi syndrome
  - Nance-Horan syndrome
  - Opitz BBB/G syndrome
  - Oculofaciocardiodental syndrome
  - Autosomal dominant Robinow syndrome.
- Malposed
- Malformed
- Root stumps
- **Discolored/non-vital**
  - Trauma, physical/chemical injuries, caries, etc.
- **Fractured**
  - Trauma, malocclusion, dysplastic teeth, abrasion, erosion, etc.
- **Impacted**
  - Various syndromes are associated with impacted teeth which are either pathogenic or genetic (cleidocranial dysplasia, Gardner's syndrome, Down syndrome, etc.)
- **Migration**
  - Pulpal or periodontal infections
  - Pathogenic cause like cyst, tumors, etc.
- Removable partial denture
- **Edentulous jaw:** Roots pieces, bone spicules, tori, etc.
- **Deposits:** Stains
  - Calculus
  - Plaque
- Periodontal status

TABLE 1.1: Causes of stains

Extrinsic	*Intrinsic*
Remnant of Nasmyth membrane Poor oral hygiene Existing restoration Gingival bleeding Plaque and calculus Eating habits: Tea, coffee, stains, etc. Tobacco chewing habit Chromogenic bacteria Mouthwashes: Chlorohexidine	Hereditary disorders Medication Excess fluoride High fever associated with early childhood illness and other types of trauma. Stains located inside enamel and dentin.

Gingiva Examination

- Color, contour
- Consistency
- Bleeding on probing

TABLE 1.2: Clinical signs of pulpitis, periodontitis and gingivitis

Signs of pulpitis	*Signs of periodontitis*	*Signs of gingivitis*
No sensation to cold and hot temperature Sharp shooting, piercing and lancinating pain (due to involvement of delta nerve fibres) or dull, boring, gnawing and excruciating (C-fibres). Often localized to apex, with a fistulous tract. Mobility of the tooth may or may not be present. Often severe and difficult to localize. Tooth may have large restoration. Problem related to apex.	Tooth sensitive to hot or cold stimuli. Presence of periodontal pocket. Presence of bleeding on probing. Presence of recession Mobility Malodour Teeth migration Dull aching pain on mastication	Tooth sensitive to hot or cold stimuli. Presence of gingival pocket. Presence of bleeding on probing Reddish discoloration and swelling in the marginal gingival. Increase in gingival crevicular fluid.

- Enlargement
- Recession
- Surface texture
- Interdental papillae
- Irritation from prosthesis or overhanging restoration.

Examination of Swelling (Extraoral)

Inspection

- Site, number
- Extent
- Shape
- Surface texture
- Color
- Edge
- Pulsation
- Overlying skin
- Surrounding tissue
- Limitation of movement
- Sinus/fistula discharge

Palpation

All inspectory findings are confirmed by palpation

- Temperature
- Tenderness
- Consistency
- Fixity to underlying structure
- Translucency
- Compressibility
- Pulsatile
- Fixity to overlying structures
- Blanching effect

Examination of Swelling (Intraoral)

Intraoral Inspection

- Site
- Number
- Size
- Shape
- Surface texture
- Color
- Edge
- Number
- Pulsation
- Limitation of movement
- Surrounding tissue

Palpation

All the inspectory findings are confirmed on palpation.

- Temperature
- Tenderness
- Consistency
- Fixity to underlying structures
- Translucency
- Compressible
- Pulsatile
- Fixing to underlying tissue

ULCER EXAMINATION

Inspection

- Size, shape and color
- Number
- Site
- Edge (raised/sloping/punched out/undermined/rolled out/everted.)
- Floor
- Discharge
- Surrounding area

Palpation

- Tenderness
- Edge
- Base
- Depth
- Bleeding
- Relation to deeper structures
- Surrounding area

Intraoral Inspection

- Size and shape
- Number
- Position
- Edge

Provisional diagnosis: After detailed history taking and critical clinical examination, the signs and symptoms collected can guide to arrive at a diagnosis which is known as provisional diagnosis.

Differential diagnosis: Similar disorders, or diseases with overlapping features are rearranged as a list with most probable lesion

ranked at the top and least probable at the bottom.

Chair Side Clinical Investigation

Vitality Test

- Thermal tests
- Electric pulp testing (EPT)
- Bite test
- Anesthesia testing
- Test cavity
- Laser-Doppler flowmetry
- Pulse oximetry
- Dual wavelength spectrophotometry
- **Thermal:** Heat, cold, electric pulp testing
- Aspiration

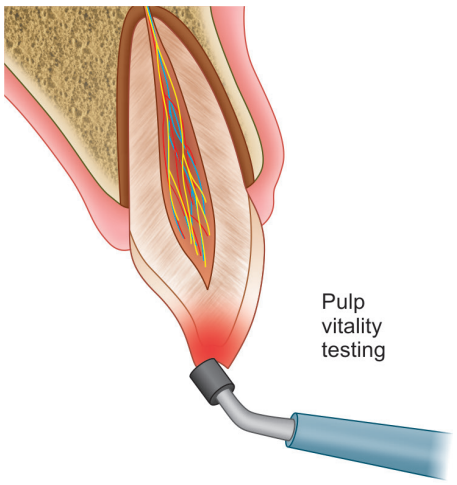


Fig. 1.1: Electronic pulp test



Fig. 1.2: The brand Vital Ice for cold test

Radiographic Investigations

This includes conventional (intraoral and extraoral) and advanced imaging modalities used to arrive at final diagnosis.

Conventional radiographic investigations: PA view or any other advanced imaging investigations include CT, MRI, VSG, scintigraphy, PET scan.

Laboratory investigations like routine hemogram, ESR, calcium, blood sugar, etc. are suggested related to the case to be diagnosed.

Special Investigations

1. **Blood test**
   - To detect any systemic disorder.
   - Total and differential count of WBC, hemoglobin, RBC count, ESR should be done.
2. **Examination of urine**
   - Particularly sugar estimation, to exclude diabetes, is important.
3. **Bacteriological examination of the discharge**
   - It is particularly important in inflamed and spreading ulcers.
   - This will not only give a clue as to the type of organism present in the ulcer, but also its sensitivity to a particular antibiotic.
4. **Biopsy**
   - Very important in malignant ulcers.
   - Biopsy is generally taken from edge of the ulcer, taking apportion of surrounding health tissue.
   - Biopsy material is then examined histologically to know the type of tumor, its invasiveness and whether differentiated or anaplastic.

Other tests include, scrape cytology, staining techniques and culture sensitivity tests.

- Final diagnosis
- Treatment plan
- Drugs/prescription
- Prognosis

Examination of Ulcer

An ulcer is a break in the continuity of the covering epithelium, skin or mucous membrane. It may either follow molecular death of the surface epithelium or its traumatic removal.

History

1. Mode of onset
2. Duration
3. Pain
4. Discharge
5. Associated disease

Local Examination

1. **On inspection**
   - i. *Size and Shape*
     - *Oval:* Generally seen in tuberculous ulcers.
     - *Circular:* Seen in syphilitic ulcers.
     - *Irregular:* Seen in carcinomatous.
   - ii. *Number*
     - *Multiple ulcers:* Herpetic ulcers
     - *Usually single:* Syphilitic and tuberculous ulcer
   - iii. *Floor:* This is the exposed surface of the ulcer.
     - *Red granulation tissue:* Healing ulcer.
     - *Pale and smooth granulation tissue:* Slow healing ulcer.
     - *Watery granulation tissue:* Tubercular ulcer.
   - iv. *Edge:* 5 common types of edges:
     - a. Undermined edge is most commonly seen in tuberculous ulcer.
       - The overhanged skin is thin, friable, reddish blue and unhealthy.
     - b. Punched out edge is most commonly seen in a gummatous ulcer or in a deep trophic ulcer.
       - The edge drops down at right angle to the skin surface as if it has been cut out with a punch.
     - c. Sloping edge is mostly seen in healing traumatic or venous ulcers.
       - Every healing ulcer has a sloping edge, which is reddish purple in color and consists of new healthy epithelium.
     - d. Raised and pearly-white beaded edge is a feature of rodent ulcer.
       - This type of edge develops in invasive cellular disease and becomes necrotic at the centre.
     - e. Rolled out (everted) edge is a characteristic feature of squamous cell carcinoma.
   - v. *Discharge:* The character of discharge and its amount should be noted.
     - *Scanty serous discharge:* Healing ulcer
     - *Purulent discharge:* Spreading inflamed ulcer
     - *Blood:* Malignancy.
   - vi. *Surrounding area*
     - If the surrounding area of an ulcer is glossy, red and edematous, the ulcer is acutely inflamed.
     - All the findings of inspection are confirmed on palpation.
       - a. *Tenderness*
         - *Exquisitely tender:* Acute inflamed ulcer
         - *Slightly tender:* Chronic ulcers like tuberculous
         - *Never tender:* Neoplastic
       - b. *Edge and margin*
         - *Edge* is the area between the margin and the floor of the ulcer.
         - *Margin* is the junction between normal epithelium and ulcer, so it is the boundary of the ulcer.
       - c. *Base:* It is on which the ulcer rests.
         - If an attempt is made to pick up the ulcer between the thumb and the index finger, the base will be felt.
         - *Slight indurations*: Chronic ulcer.
         - *Marked indurations*: Squamous cell.
       - d. *Depth*
         - It can be recorded in mm.

- Trophic ulcers may be as deep to reach even the bone.

e. *Bleeding*
- Whether the ulcer bleeds to touch or not?
- Commonly seen in malignant ulcer.

f. *Relation with deeper structures.*
- The ulcer is made to move over the deeper structures to know whether it is fixed to any of these structures.
- Malignant ulcer is fixed to the deeper structure by infiltration.

g. *Surrounding skin*
- Increased temperature and tenderness of the surrounding skin indicates the ulcer to be of acute inflammatory origin.
- Fixity to deeper structures indicates the malignant nature of the lesion.

vii. *Position*

EXAMINATION OF SWELLING

Definition

1. Swelling is an abnormal enlargement of a part of body, typically as a result of an accumulation of fluid
2. Swelling is a vague term which denotes any enlargement or protuberance in the body due to any cause.

1. Inspection

a. Site
- Exterior angular dermoid: Lateral end of eyebrow
- Meningocele: Back in midline

b. Size (in cm)
c. Shape
d. Surface
- Smooth: Sebaceous cyst
- Modular: Multinodular goiter

e. Skin
- Pigmentation / ulceration / discharge

f. Surrounding area
- Pigmentation / edema / discoloration

g. Others
- Number
- Color
- Edges
- Extent
- Visible parameters

2. Palpation

a. Temperature
- Increase in inflammation

b. Tenderness
- Swelling related to nerves

c. Inspectory findings
- Size, shape, surface
- Edge and extent
- Depth

d. Consistency
e. Fluctuations
- Fluid or gas
- Hydrocele

TABLE 1.3: Types of swellings

Congenital	*Inflammatory*	*Traumatic*	*Neoplastic*	*Miscellaneous*
▪ Dermoid cyst ▪ Hemangioma	▪ Abscess (pyogenic, pyemic, cold abscess) ▪ Boil ▪ Carbuncle ▪ Erysipelas ▪ Cellulitis	▪ Implantation dermoid	▪ Fibroma ▪ Lipoma ▪ Lymphangioma ▪ Neurofibroma ▪ Malignant (basal cell carcinoma, squamous cell carcinoma, malignant melanoma, sarcoma)	▪ Sebaceous cyst ▪ Warts ▪ Condyloma ▪ Keloid/hyper-trophic scar ▪ Keratoacanthoma ▪ Callosity/corn

f. Translucency (transmission of light through swelling)
- Positive: Clear fluid and their transparent walls.
- Negative: Wall thick, turbid liquid (blood or pus or lymph)

g. Reducibility: Can disappear completely and reappears by straining or coughing.
- Hernia
- Varicocele

h. Compressibility (swelling on pressure reduces in size, but only partially. It does not disappear completely).
- Hemangiomas

i. Pulsatility

j. Fixity to skin
- Fixed to skin cannot be lifted.
- Skin moves over swelling.

3. Percussion

Not needed

4. Auscultation

Look for any bruit over pulsating swelling.

a. **Color**
- Arterial haemangioma: Bright red
- Venous haemangioma: Purple
- Malignant melanoma: Black
- Benign naevus: Black
- Ranula: Bluish

b. **Skin overlying swelling**
- Red and edematous: Inflammatory
- Black punctum: Sebaceous cyst
- Pigmentation: Moles, naevi
- Scar
- Ulcers

c. **Surface**
- Smooth: Cystic swelling
- Lobular: Lipoma
- Nodular: Multinodular
- Matted: Lymph nodes
- Irregular: Carcinoma

d. **Edge**
- Well-defined and irregular: Benign neoplasm
- Well-defined and irregular: Neoplasm
- Ill-defined and diffuse: Inflammatory swelling

e. **Consistency**
- Soft: Lipoma
- Cystic: Chronic abscess
- Firm: Fibroma
- Bony hard: Osteoma
- Variable consistency: Malignancy

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Chapter 2

Clinical Investigations and Diagnostic Aids in Oral Medicine: An Overview

INTRODUCTION

Oral medicine as a speciality deals with a diagnosis and management of a vast variety of oral and systemic disorders that affect the oral cavity. Thorough recording of the patient's history, proper clinical examination remains the basis for arriving at a correct diagnosis and proper patient management. At the same time the importance of valid laboratory investigations and diagnostic aids cannot be undermined. It is of prime importance that the oral diagnostician be well aware of the relevant tests and investigations required when posed with a diagnostic challenge.

The pertinent laboratory investigations and diagnostic aids in oral medicine may broadly be classified under the following:

- Hematological investigations
- Biochemical investigations
- Histopathology and cytology
- Adjunct diagnostic aids for oral cancer and precancer
- Investigations for auto-immune disorders of the oral cavity
- Diagnostic microbiology
- Tests for allergy

HEMATOLOGICAL INVESTIGATIONS

Complete Blood Counts (CBC)

The basic test performed on the peripheral blood is the "Complete Blood Count" (CBC). It is one of the most informative investigations, expressing the health and disease status of the body. CBC is a comparatively inexpensive but powerful diagnostic tool in a variety of hematological and non-hematological disease conditions. It provides a myriad of valuable information about the blood and partly about the bone marrow. Over the past 3 decades, hematology analyzers have evolved by leaps and bounds, i.e. from semiautomated to fully automated ones.

The CBC is useful informative tool for various clinical situations like:

- Diagnosis of anemias (etiological and morphological types) and hemoglobinopathies (thalassemia, sickle cell anemia, and hemolytic anemia)
- Nutritional deficiencies (iron, vitamin B_{12}, folic acid)
- Parasitic infections (malaria, filaria, leishmania)
- Thrombocytopenia [primary (due to nonproduction), secondary (due to

peripheral destruction) and bleeding disorders]
- Diagnosis of infections, leukocytosis, leukopenias, eosinophilia, monocytosis, lymphocytosis, etc.
- Hematopoietic malignancies like leukemias, various dysplasias like myelodysplastic syndrome, spillage of lymphoproliferative solid tumors, metastatic malignancies
- Diagnosis of effects of various drugs including chemotherapy and radiation therapy and effects of various toxins and chemicals.

Components

A complete blood count (CBC) is a series of tests used to evaluate the composition and concentration of the various cellular components of blood. It consists of the following tests:

- Red blood cell (RBC) count, white blood cell (WBC) count, and platelet count and parameters.
- Measurement of hemoglobin and calculation of hematocrit and red blood cell indices.
- White blood cells (WBC) total and differential count.
- Presence of parasites

Tests for bleeding and clotting disorders.

A range of screening and confirmatory tests are recommended for disorders affecting the coagulation pathway, broadly stated as bleeding and clotting disorders.

Table 2.1 shows the normal values for various blood component counts, hematological indices, and bleeding and clotting investigations and the conditions affecting them.

TABLE 2.1: Normal values for various blood component counts, hematological indices, and bleeding and clotting investigations and the conditions affecting them

Sr. no.	*Parameter*	*Normal value*	*Increased*	*Decreased*
1.	• Red blood cell count	• Male: 4.5 to 6.0 million/mm^3 • Female: 4.0 to 5.5 million/mm^3	• Polycythemia vera • Congenital heart disease • Anabolic steroids • Kidney tumors due to erythropoietin overproduction	• Anemia • Bone marrow depression • Leukaemia • Thalassemia • Erythropoietin deficiency due to chronic renal disease
2.	• Hemoglobin %	• Male: 13.5 to 17.5 g/dl • Female: 12 to 16 g/dl	• Same as above	• Same as above
3.	• Packed cell volume (hematocrit) • It gives the cell volume in a given quantity of blood	• Male: 41 to 53% • Female: 36 to 46%	• Dehydration • Low availability of oxygen (smoking, high altitude, pulmonary fibrosis) • Congenital heart diseases	• Anemia • Leukaemia
4.	• Mean corpuscular volume (MCV)	• 80–94 fl (femtolitres)/cell	• Macrocytic anemia	• Microcytic anemia

Contd.

TABLE 2.1: Normal values for various blood component counts, hematological indices, and bleeding and clotting investigations and the conditions affecting them (*Contd.*)

Sr. no.	*Parameter*	*Normal value*	*Increased*	*Decreased*
5.	▪ Mean corpuscular hemoglobin (MCH)	▪ 27–32 pg/cell	▪ Macrocytic anemia	▪ Microcytic anemia
6.	▪ Mean corpuscular hemoglobin ▪ Concentration (MCHC)	▪ 31–37 gm/dl	▪ Macrocytic anemia	▪ Microcytic anemia
7.	Reticulocyte count	▪ Infants at birth: 2–6% ▪ Children up to 5 years: 0.2–5% ▪ Adults: 0.2–2%	▪ Iron supplementation ▪ Megaloblastic anemia ▪ Hemolytic anemia	▪ Myelosclerosis ▪ Aplastic anemia ▪ Thalassemia ▪ Erythroleukemia ▪ Sideroblastic anemia
8.	Erythrocyte sedimentation rate ▪ The rate at which red blood cells settle out when anticoagulated whole blood is allowed to stand ▪ It is a non specific measure of inflammation	*Westergren's method* ▪ Men under 50 years old: <15 mm/hr ▪ Men over 50 years old: <20 mm/hr ▪ Women under 50 years old: <20 mm/hr ▪ Women over 50 years old: <30 mm/hr *Children* ▪ Newborn: 0–2 mm/hr ▪ Newborn to puberty: 3–13 mm/hr	▪ Inflammation ▪ Pregnancy ▪ Anemia ▪ Autoimmune disorders (such as rheumatoid arthritis and lupus) ▪ Infections ▪ Malignancies such as lymphoma and multiple myeloma	▪ Polycythemia vera ▪ Sickle cell disease ▪ Congestive heart failure
9.	WBC	Total: 4000–11000/mm^3 Differential: ▪ Neutrophils: 35 to 73% ▪ Lymphocytes: 23 to 33% ▪ Monocytes: 2 to 6% ▪ Eosinophils: 1 to 3% ▪ Basophils: 0 to 1%	▪ Infection ▪ Inflammation ▪ Tissue damage from burns ▪ Myeloproliferative disorders ▪ Acute or chronic leukaemia	▪ Old age ▪ Low immunity states—HIV infection ▪ Autoimmune conditions ▪ Bone marrow depression ▪ Chemotherapy and radiotherapy ▪ Malnutrition.
10.	Platelet count	150,000–400,000/ mm^3	▪ Essential thrombocythemia (due to bone marrow hyperactivity)	▪ Leukemia ▪ Aplastic anemia ▪ Viral infections, such as hepatitis C or HIV

Contd.

TABLE 2.1: Normal values for various blood component counts, hematological indices, and bleeding and clotting investigations and the conditions affecting them (*Contd.*)

Sr. no.	*Parameter*	*Normal value*	*Increased*	*Decreased*
			▪ Reactive thrombocytosis (due to infection, anemia, malignancy, splenectomy)	▪ Drugs (heparin, quinine, chemotherapeutic agents, sulfa containing antibiotics, anticonvulsants) ▪ Heavy alcohol consumption ▪ Pregnancy ▪ Auto-immune diseases—rheumatoid arthritis, lupus
11.	Bleeding time (the time taken to arrest bleeding after puncture is made on the skin surface allowing free flow of blood)	1 to 9 min (Ivy method)	*Hereditary causes* ▪ von Willebrand disease ▪ Glanzmann thrombasthenia ▪ Bernard-Soulier syndrome ▪ Connective tissue diseases *Acquired causes* ▪ Medications (NSAIDs, penicillins, TCA, anticoagulants) ▪ Vitamin C deficiency ▪ Alcohol intoxication ▪ Uraemia ▪ Liver failure ▪ Leukemias ▪ Myelodysplastic syndrome ▪ Amyloidosis ▪ Disseminated intravascular coagulations (DIC)	
12.	Clotting time: This is the time taken before a specimen of blood clots	4 to 9 min (Lee-White)	▪ Hemophilia ▪ Anticoagulant therapy ▪ Vitamin K deficiency ▪ DIC	

Contd.

TABLE 2.1: Normal values for various blood component counts, hematological indices, and bleeding and clotting investigations and the conditions affecting them (*Contd.*)

Sr. no.	*Parameter*	*Normal value*	*Increased*	*Decreased*
13.	Prothrombin time ▪ This is the time taken to clot citrated plasma sample in the presence of thromboplastin (tissue factor—TF) and calcium ions. ▪ It reflects the integrity of the extrinsic and common pathways of the coagulation system	▪ 9.5–13.5 seconds	▪ Warfarin use ▪ Vitamin K deficiency from malnutrition, biliary obstruction, malabsorption syndromes, or use of antibiotics ▪ Liver disease ▪ Deficiency of VII, X, II/prothrombin, V, or fibrinogen ▪ Disseminated intravascular coagulopathy (DIC) ▪ Fibrinogen abnormality ▪ Massive blood transfusion due to dilution of plasma clotting proteins ▪ Hypothermia	▪ Vitamin K supplementation ▪ Fresh frozen plasma transfusion
14.	International normalised ratio (INR) ▪ The INR was devised to standardize the result of the prothrombin time as the results may vary according to the analytical system used. ▪ The INR is typically used to monitor patients on warfarin or related oral anticoagulant therapy	▪ Normal individuals: 0.8–1.2 ▪ For people on warfarin therapy an INR of 2.0–3.0 is usually targeted.		

Contd.

TABLE 2.1: Normal values for various blood component counts, hematological indices, and bleeding and clotting investigations and the conditions affecting them (*Contd.*)

Sr. no.	*Parameter*	*Normal value*	*Increased*	*Decreased*
15.	• Activated partial thromboplastin time (APTT) • The APTT is typically used to monitor heparin therapy	• 30–40 seconds (more than 70 seconds signifies spontaneous bleeding)	• Congenital deficiencies of intrinsic system clotting factors such as factors VIII, IX, XI, and XII, including hemophilia A and hemophilia B. • von Willebrand's factor • Hypofibrinogemia • Liver cirrhosis • Heparin therapy • Vitamin K deficiency • DIC • SLE, rheumatoid arthritis due to circulating antibodies against coagulation factors	• Early stages of DIC; due to circulating procoagulants. • Malignancies with metastasis • Immediately after acute hemorrhage.

BIOCHEMICAL INVESTIGATIONS

One important aspect of oral medicine is the diagnosis and management of oral manifestations of systemic diseases. Hence, it is important for the oral physician to be aware of the biochemical investigations that help in diagnosis of systemic diseases. Biochemical investigations in oral medicine may broadly be subdivided into analysis of blood/serum, urine and saliva.

Blood and Serum Analysis

Blood and serum analysis is useful for assaying the levels of glucose, minerals, trace elements, vitamins, enzymes, proteins, lipid profile, hormones and antibodies. These tests need to be prescribed as indicated to rule out underlying systemic disease. Specific enzymes and parameters are defined for assessing kidney and liver functions, a complete description of which is beyond the scope of this textbook. Important tests and their values that have implications particularly in oral disorders are described in Table 2.2.

Urine Analysis

A urine analysis is a group of physical, chemical, and microscopic tests used to detect several substances in the urine, such as byproducts of normal and abnormal metabolism, cells, cellular fragments, and bacteria. It is indicated to diagnose and/or monitor several diseases and conditions, such as kidney disorders or urinary tract infections (UTIs) and metabolic disorders like diabetes mellitus. Table 2.3 summarizes the normal findings of a urine analysis and clinical implications.

TABLE 2.2: Important serum tests of relevance in oral medicine

S.no	*Parameter*	*Normal range*	*Increased in*	*Decreased in*
1.	Blood glucose	▪ Fasting: 72 to 99 mg/dl (4.0 to 5.4 mmol/L) ▪ Post-prandial: Up to 140 mg/dl (7.8 mmol/L) 2 hours after eating. ▪ Random: 79–160 mg/dl (4.4–8.9 mmol/L)	▪ Uncontrolled diabetes mellitus ▪ Acute stress ▪ Pancreatitis ▪ Drugs—corticosteroids, TCA ▪ Endocrinal causes: Acromegaly, Cushing's syndrome, hyperthyroidism ▪ Chronic renal failure	▪ Insulin overdose, insulinoma ▪ Adrenal insufficiency ▪ Drugs: Acetaminophen ▪ Endocrinal causes: Hypopituitarism, hypothyroidism ▪ Liver disease ▪ Starvation
2.	Serum calcium	▪ 8.5 to 10.5 mg/dl	▪ Hyperparathyroidism ▪ Bony metastasis ▪ Multiple myeloma ▪ Hypervitaminosis D ▪ Ectopic production of PTH-like substance ▪ Milk-alkali syndrome ▪ Sarcoidosis	▪ Hypoparathyroidism ▪ Osteomalacia ▪ Rickets ▪ Decreased intestinal absorption of calcium ▪ Renal insufficiency
3.	Serum phosphorus	▪ Adults: 3.0–4.5 mg/100 ml ▪ Children: 4.0–7.0 mg/100 ml	▪ Hypoparathyroidism ▪ Chronic renal disease ▪ Healing bone fracture ▪ Growth hormone excess ▪ Hypervitaminosis D	▪ Hyperparathyroidism ▪ Osteomalacia ▪ Rickets ▪ Antacid drugs
4.	Serum parathyroid hormone	▪ 10–65 ng/L	*Primary hyperparathyroidism* ▪ Pathology of parathyroid gland (adenoma, hyperplasia or malignancy) *Secondary hyperparathyroidism* ▪ Vitamin D deficiency ▪ Renal failure *Tertiary hyperparathyroidism* ▪ Unregulated autonomously functioning parathyroid gland following longstanding secondary hyperparathyroidism	▪ Injury to the parathyroid glands during thyroid or neck surgery ▪ Radioactive iodine treatment for hyperthyroidism ▪ Very low magnesium level in the blood ▪ Autoimmune destruction ▪ DiGeorge syndrome ▪ Familial hypoparathyroidism
5.	Serum alkaline phosphatase	▪ 1–4 Bodansky units ▪ 3–13 King Armstrong units	▪ Osteitis deformans (Paget's disease) ▪ Hyperparathyroidism ▪ Osteogenic sarcoma ▪ Infectious mononucleosis ▪ Metastatic bone tumor	▪ Hypophosphatasia ▪ Hypothyroidism ▪ Scurvy

Contd.

TABLE 2.2: Important serum tests of relevance in oral medicine (*Contd.*)

S.No	*Parameter*	*Normal range*	*Increased in*	*Decreased in*
		▪ 30–110 IU	▪ Granulomatous or infiltrative disease of liver	
6.	Serum acid phosphatase	▪ 2 ng/ml	▪ Osteopetrosis ▪ Prostate gland pathologies	
7.	Serum iron	▪ Males: 55–160 g/dl ▪ Females: 40–155 g/dl	▪ Hemochromatosis ▪ Hemosiderosis caused by excessive iron intake (e.g., multiple transfusions, excess iron administration) ▪ Hemolytic anemia ▪ Pernicious anemia ▪ Aplastic or hypoplastic anemia ▪ Thalassemia	▪ Iron deficiency anemia ▪ Nephrotic syndrome (loss of iron-binding proteins) ▪ Chronic renal failure ▪ Active hematopoiesis ▪ Malnutrition
8.	Thyroid profile T3, T4, TSH	▪ TSH: 0.40–4.2 mIU/L ▪ T4: 4.6–12 µg/dl ▪ T3: 80–180 ng/dl	▪ Congenital hypothyroidism ▪ Primary hypothyroidism ▪ TSH—secreting pituitary tumors (uncommon) ▪ Pituitary resistance to thyroid hormone (uncommon) ▪ Drugs: Dopamine antagonists, chlorpromazine, haloperidol, iodine-containing drugs ▪ Amiodarone	▪ Hyperthyroidism ▪ Pituitary (secondary) hypothyroidism ▪ Nonthyroid illness ▪ Drugs: Exogenous thyroxine, glucocorticoids, dopamine, levodopa
9.	▪ Antinuclear cytoplasmic antibodies (ANCA) ▪ Perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA)		▪ Rheumatoid arthritis ▪ Ulcerative colitis ▪ Glomerulonephritis ▪ Vasculitis/polyangiitis	

Salivary Analysis

Saliva is a biofluid composed of water (99.5%), electrolytes (0.5%) and a number of organic compounds. The electrolytes found in saliva include sodium, potassium, calcium, magnesium, bicarbonate, and phosphates. The organic compounds present in saliva are immunoglobulins (IgA, IgG and IgM), proteins, enzymes, mucins, and nitrogenous products, such as urea and ammonia. Normal unstimulated salivary flow is 0.25–0.35 ml/min, whereas the stimulated salivary flow is 1–3 ml/min.

In addition to its normal constituents, a number of analytes that may be detectable are steroid hormones, cytokines and chemokines, growth factors, nucleic acids and certain drugs. Hence, salivary analysis that was earlier restricted to disorders affecting the salivary glands (xerostomia, Sjögren's syndrome, etc.) now encompasses

TABLE 2.3: Urinalysis normal findings and clinical implications

S. No.	*Parameter*	*Normal finding*	*Clinical implication*
1.	Color	Straw yellow to amber	▪ Red/dark brown: Hemoglobinuria/ hematuria/porphyria ▪ Bright yellow: Bilirubin ▪ Green: Medications like amitriptyline, propofol ▪ Orange: Pseudomonas infection
2.	pH	4.7 to 8.0 (mean, 6.3)	▪ Very alkaline urine > 8: Strict vegetarian diet; diuretic/ alkali therapy; infection with a urea-splitting organism, such as *P. mirabilis*, vomiting ▪ Acidic pH <4.5: Metabolic acidosis
3.	Volume	1500 ml/day	▪ Less than 400 ml: Oliguria; in dehydration, kidney disease ▪ Excess of 2000 ml: Polyuria; in diabetes mellitus and diabetes insipidus
4.	Specific gravity	1.016 to 1.022	▪ It reflects the ability of kidney to concentrate the urine. ▪ Increased in patients with diabetes mellitus and in individuals on multiple medications ▪ Decreased in diabetes insipidus ▪ Same as plasma in kidney failure.
5.	Glucose	Negative	▪ Glycosuria is an indicator of diabetes mellitus; ▪ When blood glucose levels rise above 160 mg/dl, glucose will be present in the urine.
6.	Protein	Negative	▪ Presence indicates kidney disorder
7.	Ketones	Negative	▪ Presence indicates: Type I diabetes mellitus, pregnancy, glycogen storage diseases
8.	Bilirubin	Negative	▪ Presence indicates hepatic disease or hepatobiliary obstruction
9.	Blood	Negative	Presence of blood may be seen in: ▪ Excessive red cell destruction ▪ Glomerular disease ▪ Kidney or urinary tract infection ▪ Urinary tract injury or malignancy.
10.	Erythrocytes	0 to 2/ high-power field	▪ Same as above (blood)
11.	Leucocytes/ Pus cells	0 to 5/ high-power field	▪ Increased amount suggests urinary tract infection
12.	Leucocyte esterase	Negative	▪ Presence indicates urinary tract infection
13.	Nitrite	Negative	▪ A positive test for nitrite indicates the presence of bacteria including staphylococci, Proteus, Salmonella, Pseudomonas
14.	Urobilinogen	0–2 Ehrlich units	▪ Increased in prehepatic jaundice ▪ Hepatitis and hepatic necrosis
15.	Cellular casts and abnormal crystals	Absent on microscopic examination	▪ Kidney disease

a wide range of conditions. It is useful for diagnosis and monitoring of patients with both oral and systemic diseases and drug monitoring as well. Saliva is biofluid that is easily collected, stored and is ideal for early detection of diseases as it contains specific soluble biological markers. Thus, contemporary salivary diagnostics has gained profound importance in the diagnosis of oral squamous cell carcinoma, understanding the pathogenesis of dental caries and periodontitis as well as the diagnosis of fungal and viral diseases of the oral cavity.

HISTOPATHOLOGICAL INVESTIGATIONS

Oral Biopsy

The phrase "biopsy" originates from the Greek terms *bios* (life) and *opsis* (vision): Vision of life. Biopsy is the removal of a tissue sample from a living body with the objective of providing the pathologist with a representative, viable specimen for histopathologic interpretation and diagnosis. Biopsies are an important diagnostic tool for the diagnosis of lesions ranging from simple periapical lesions to malignancies.

Indications for Oral Biopsy

- Any lesion that persists for more than 2 weeks with no obvious etiologic basis.
- Any inflammatory lesion that does not respond to the treatment even after 2 weeks.
- Clinical suspicion of malignancy, such as an enlarging mass, hyperkeratotic lesion with areas of erythema, chronic ulceration, tissue friability, induration on palpation or persistence of mucosal changes despite removal of local irritants.
- New or enlarging pigmented lesions, especially those with an irregular border and nonhomogenous coloration.
- Clinically benign or reactive (e.g. pyogenic granuloma, mucocele osseous lumps or fibrous hyperplasia interfering with oral function) may be excised for esthetic or functional reasons.
- Anesthesia or paresthesia and pain associated with lesions of unclear etiology.
- Lichen planus, mucous membrane pemphigoid, pemphigus vulgaris and other immune-mediated disorders may be biopsied for definitive diagnosis.
- Labial, buccal, or lingual muscles showing interstitial lesions.

Contraindications for Biopsy

- Vascular lesion—caution must be exercised in the biopsy of any lesion with red, purple or blue coloration or with blanching or pulsation on palpation.
- When acute, virulent, pyogenic infection is present.

Caution and Concerns

- Location of the lesion in an esthetic region (e.g. vermilion border of the lip), referral to a specialist should be considered in such cases.
- Oral sites, such as the floor of the mouth, may be challenging to access, difficult to provide hemostasis and risks damage to anatomic structures (e.g. submandibular duct).
- Obtain medical clearance the case of medically compromised patients, including those with severe or poorly controlled systemic diseases such as coronary artery disease, renal or hepatic impairment, and various endocrinopathies immune-compromised states and patients with significant risk of hemorrhage due to underlying bleeding diatheses.
- Patients undergoing bisphosphonate therapy or radiotherapy may be predisposed to osteonecrosis if the biopsy procedure exposes bone.

Types of Oral Biopsies

Scalpel Biopsy

Depending on the technique employed, biopsies can be classified as *incisional or excisional*.

The incisional technique involves the removal of a representative portion of the target lesion and of a part of healthy tissue. Such an approach is indicated in the case of suspected malignancy or precancerous lesions and lesions greater than 2 cm in size.

An excisional biopsy in turn involves total removal of the lesion, with slight peripheral and in-depth safety margins. It is indicated in lesions, less than 2 cm in diameter. Such biopsies play a diagnostic and therapeutic role, since complete removal of the lesion is carried out, ensuring the inclusion of a peripheral margin of normal tissue.

Punch Biopsy

The punch biopsy technique is an alternative to the traditional incisional biopsy. Essentially the punch comprises a circular blade attached to a plastic handle (Fig. 2.1). Diameters of two to ten millimetres are available. This removes a core of tissue the base of which can be simply and atraumatically released using curved scissors. Alternatively, the specimen can be lifted from the mucosal surface and the base undermined with a scalpel. The resultant wound may not require suturing if using the smaller diameter punches.



Fig. 2.1: An oral biopsy punch

Other Methods

- Surgical tissue removal by cautery or a high-frequency cutting knife
- Soft tissue laser

An elliptical incision is preferred as it is easier to suture (Fig. 2.2).

Frozen Section Biopsy

It is performed while surgery for a malignant lesion is in progress to get an immediate histological report. It is done to ascertain if the entire lesion has been removed. The tissue obtained from the lesion is kept in deep freezer. The frozen tissue is sectioned, stained, studied and report immediately. In this type of biopsy slides cannot be preserved for future reference.

Exfoliative Cytology

Surface cells from the epithelium are constantly being exfoliated and these can

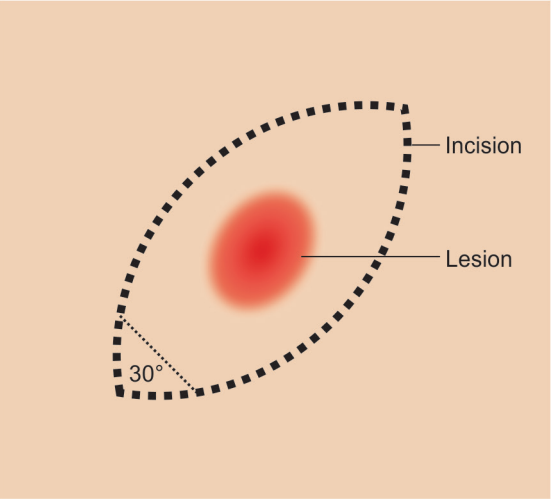


Fig. 2.2: An elliptical biopsy incision (*Image Source*: http://img.medscapestatic.com/pi/meds/ckb/80/10280tn.jpg)

be collected by scraping of the surface epithelium and examined microscopically.

Exfoliative cytology is the study of cells which exfoliate or abrade from the body surfaces. When the epithelium becomes seat of any pathological condition, the cells may lose their cohesiveness, and cells in the deeper layer may shed along with the superficial cells. These exfoliated cells as well as cells which are scrapped off by means of specific instruments, can be studied quantitatively or qualitatively. Considerable interest has developed in the use of exfoliative oral

cytology for the diagnosis of oral mucosal lesions. It is a quick, simple, painless and bloodless procedure.

Indications

- This technique is of utmost value in evaluation of suspected malignancies. (a Papanicolaou stained smear is used generally for this purpose).
- Follow-up detection of recurrent carcinoma in previously treated cases.
- In the diagnosis of certain specific cells in diseases like herpes simplex infection, herpes zoster, pemphigus vulgaris, benign familial pemphigus, keratosis follicularis, hereditary benign intraepithelial dyskeratosis, white sponge nevus, and pernicious and sickle cell anemia.
- Also, studies have been done to determine antioxidant levels and gender determination from exfoliated cells, recently.

Procedure

- The surface of oral lesion is cleaned of debris and mucus.
- The mucosa is stretched and the scraper (metal spatula, moistened tongue blade, cytobrush) is placed on the lesion, pressed firmly and the surface is scraped until a visible quantity of material is collected.
- The collected material is transferred onto a microscopic slide, spread evenly and fixed in a mixture of alcohol and ether before the specimen dries.
- The smear is then stained and examined under the microscope.

Interpretation

The cytologic smear will usually be reported by the cytologist as falling into one of five classes:

- **Class I (normal):** Indicates that only normal cells were observed
- **Class II (atypical):** Indicates the presence of minor atypia but no evidence of malignant changes
- **Class III (indeterminate):** This is an in between cytology that separates cancer from noncancer diagnosis. The cells display wider atypia that may be suggestive of cancer, but they are not clear-cut and may represent precancerous lesions or carcinoma *in situ*. Biopsy is recommended.
- **Class IV (suggestive of cancer):** A few cells with malignant characteristics or many cells with borderline characteristics. Biopsy is mandatory.
- **Class V (positive for cancer):** Cells that are obviously malignant. Biopsy is mandatory.

Aspiration/Fine Needle Aspiration Cytology

This is the procedure whereby small amount of tissue / cells / fluid (in case of cystic lesions) are aspirated from a lesion with the help of a small bore (usually 22 gauge) needle.

Advantages

- It is a safe, economical, outpatient procedure that does not require anesthesia.
- Less traumatic than the conventional biopsy.
- Results can be obtained within an hour
- The procedure is easier to repeat.

Disadvantages

- Not suitable in many non-neoplastic conditions where detailed examination of tissue architecture is necessary for the diagnosis.
- The procedure may produce complications, e.g. bleeding, infection, seeding of tumor cells.

Indications

- Cystic lesions
- Clinically suspicious lymph nodes
- Evaluation of salivary gland tumors.

Procedure

The skin / mucosa above the area is sterilised with an antiseptic solution. A needle of very fine diameter 22–25 gauges on a syringe

TABLE 2.4: Enlists the type of aspirate that may be found in some oral lesions

S. No.	*Lesion*	*Aspirate characteristics*
1.	Radicular cyst	Straw color fluid; it may appear shimmering due to the presence of cholesterol crystals; total protein content between 5 and 11 g/dl
2.	Dentigerous cyst	Straw colored fluid; the total protein content in the dentigerous cyst is usually 4–8 g/100 ml
3.	Odontogenic keratocyst	Dirty white cheesy material with Keratin squames; Total protein content is <5 gm/100 ml; the ratio of soluble protein to total protein content is lower than that in serum
4.	Mucocele/ranula	Mucous aspirate
5.	Anuerysmal bone cyst	Blood tinged sero-sanguinous fluid/no aspirate
6.	Dermoid cyst	Thick sebaceous material
7.	Stafne's cyst	Empty cavity
8.	Solid tumor mass	No aspirate
9.	Unicystic ameloblastoma	Amber colored fluid
10.	Salivary gland tumors	Lesional tissue/fluid

is passed into the swelling. The plunger is withdrawn slowly in stages thus aspirating the fluid/tissue material from the lesion. The needle is withdrawn and the aspirate is spread on a glass slide, fixed, stained and studied (in case of tissue aspirate) or examined for its physical characteristics and chemical analysis (in case of cystic fluid) (Table 2.4).

IMMUNOHISTOCHEMISTRY

Immunohistochemistry is a histopathological technique that involves the application of monoclonal or polyclonal antibodies to determine the tissue distribution of an antigen of interest in health and disease. It is widely used for diagnosis of cancers and tumors because specific tumor antigens are expressed *de novo* or up-regulated in certain cancers.

Principle

IHC requires the availability of tissue sections that are incubated with an appropriate antibody. The site of antibody binding is visualized under an ordinary or fluorescent microscope by a marker such as fluorescent dye, enzyme, radioactive element, or colloidal gold, which is directly linked to the primary antibody or to an appropriate secondary antibody.

Advantages

- It affords a significant advantage in the diagnosis of difficult and equivocal tumors.
- Immunohistochemistry has also provided insight into tumor histopathogenesis. Predictable tumor expression of many of the same antigens (a macromolecular protein or polysaccharide that can bind to an antibody molecule) as their cells of origin or normal tissue counterparts validate the principle of tumor classification by immunohistochemistry.
- Application of immunohistochemistry in distinguishing undifferentiated oral neoplasms of different origins was achieved through the detection of tumor antigens using known antibodies. Thus, immunohistochemistry is important in diagnosis, investigation, and determining the behavior and pathogenesis of oral tumors (Table 2.5).

TABLE 2.5: Describes the tissue specific general IHC markers

S. No.	*Markers*	*Diagnostic applications*
1.	Cytokeratins	Epithelial tumors
2.	Vimentin	Mesenchymal tumors
3.	Desmin	Muscle tumors, muscle lesions
4.	S-100 protein	Nerves, Schwann cells, chondrocytes, melanocytes, Langerhans cells, APUD cells
5.	Neuron-specific enolase	Melanoma, neuroendocrine tumors, neuroblastoma, Wilms' tumors.

ADJUNCT DIAGNOSTIC AIDS FOR ORAL CANCER AND PRECANCER

Brush Biopsy

This technique is an advanced variation of the exfoliative cytology.

- The oral brush biopsy, also known as "oral CDx brush test system" (Fig. 2.3), consists of a method of collecting a trans-epithelial sample of cells from a mucosal lesion with representation of the superficial, intermediate and parabasal/basal layers of the epithelium.



Fig. 2.3: Oral CDx brush (image source www.cdxdiagnostics.com)

- This test was specifically designed for lesions with low-risk clinical features.
- A specially designed brush is used for epithelial cell collection. Samples are fixed onto a glass slide, stained with a modified Papanicolaou test and analyzed microscopically via a computer-based imaging system.
- Results are reported as "positive" or "atypical" when cellular morphology is highly suspicious for epithelial dysplasia or carcinoma or when abnormal epithelial changes are of uncertain diagnostic significance respectively. Results are defined as negative when no abnormalities can be found. The test is considered an intermediate diagnostic step as a scalpel biopsy must follow when an abnormal result is reported (atypical or positive).
- Current data show that Oral CDx's cytologic test is highly sensitive and specific in detecting dysplastic changes in high-risk mucosal lesions.

Vital Staining

Supravital staining has long been used as an adjunct in the early diagnosis of malignant lesions. The technique has been applied in the oral setting for over 30 years by means of the dye toluidine blue. Apart from toluidine blue, other stains such as methylene blue (MB), Lugol's iodine, and acetic acid have also been tried in the diagnosis of cancerous lesions.

Toluidine Blue Staining

TB was first used by Richart in 1963 to stain uterine cervical carcinoma *in situ* and dysplasia.

Properties

TB chemically is referred to as *tolonium chloride*. It is an acidophilic dye of the thiazine group that selectively stains acidic tissue components, including deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). It has the staining property of metachromasia,

which is due to the presence of repetitive phosphate groups in the nucleic acids and is dependent on temperature and the pH. The recommended pH is 6.0–7.0. The temperature should not exceed 30°C above which the metachromatic property diminishes in strength. The TB solution can be prepared in the laboratory or it is also available commercially as ready to use kit, which consists of three component systems. One component is 1% TB solution and the other two are the pre- and post-rinse solutions consisting of 1% acetic acid.

Principle

- The dye attaches to phosphate bonds and the extent of binding depends on the amount of DNA, which is related to number and size of nuclei present in the superficial layers.
- Its use *in vivo* is based on the fact that dysplastic and anaplastic cells contain quantitatively more nucleic acids than normal tissues, shows loss of cell cohesion and increased mitosis.
- In addition, malignant epithelium may contain wider intracellular canals; a factor that enhances penetration of the dye.
- It stains to the depth of 2–10 cell layers, and hence just reflects only the epithelial changes, the invasion into the underlying connective tissue, or the changes in the submucosa cannot be appreciated.

TECHNIQUE OF STAINING

TB can be used in two forms. It is either applied to the site of the lesion with a cotton applicator or it is used as mouth rinse. The procedure of staining is as follows:

- Oral examination
- Rinsing the mouth twice with water for 20 s to remove the debris
- Application of 1% acetic acid for 20 s to remove any ropey saliva
- Application of 1% TB solution for 20 s either with cotton swab when a mucosal lesion is seen or given as a rinse when no obvious lesion is detected
- Application of 1% acetic acid to reduce the extent of mechanically retained stain
- Rinsing oral cavity with water
- Oral examination and recording of the stained areas.

Interpretation

A dark blue (royal or navy) stain of either the entire lesion or a portion of it is considered as positive stain, lack of color absorption by the lesion as negative stain, and light or pale blue staining as doubtful. These cases are usually due to mechanical surface retention or inadequate removal of the stain. False positive dye retention may occur in inflammatory and ulcerative lesions, but false negative retention is uncommon.

Advantages

- TB staining is a simple, quick, noninvasive, and highly cost effective procedure.
- It is used as an adjunctive aid in the detection of premalignant and malignant lesions.
- In selecting biopsy site and in the screening of second primaries of the oral cavity
- And multicentric tumors.
- In obtaining the marginal control of carcinoma, and during the follow-up of treated lesions.

Lugol's Iodine

Lugol's iodine is a solution of elemental iodine. Lugol's solution consists of iodine and potassium iodide.

Principle

- The basic principle with iodine staining is its affinity for carbohydrates and starch in the tissues.
- As the malignancy is associated with reduction in the glycogen content of the tissues, the malignant tissue remains unstained and on the contrary, the normal epithelium gets stained brown or black.

- This selective staining delineates the inflammatory and carcinomatous epithelium from the normal epithelium.
- Iodine infiltrates and reacts with the glycogen mainly in the upper superficial layer of the nonkeratinized epithelium.
- Glycogen content is inversely related to the degree of keratosis, suggesting a role of glycogen in keratinization. Throughout the oral mucosa, the content of glycogen varies with the type of keratinization of the mucosa. This may limit the use of Lugol's iodine in keratinized lesions and in such case its uptake should be assessed carefully.
- This technique also cannot be used for the detection of subepithelial infiltrating tumors.

Double Staining

- Studies have been done wherein a few authors have used combination of two dyes to aid in the assessment of oral malignant diseases.
- The combination of toluidine blue and Lugol's iodine has been used.
- TB will stain the abnormal epithelium, whereas Lugol's solution binds to glycogen present in the normal epithelium.

Other stains used for vital tissue staining are methylene blue and acetic acid.

Chemiluminescence (ViziLite)

This technique involves the use of a chemiluminescent light that is shone inside the mouth to detect areas that may harbour premalignant and malignant changes. Under this light the abnormal tissue glows differently from the normal tissue thus demarcating it.

Components of the ViziLite system (Fig. 2.4)

1. ViziLite rinse (1% acetic acid solution)
2. ViziLite capsule (chemiluminescent light stick)
3. ViziLite retractor (sheath and handle)

Principle

- Normal epithelium absorbs ViziLite and appears dark, whereas abnormal epithelium reflects ViziLite and appears white.
- As a cell becomes more dysplastic, nucleus becomes larger compared with the neighbouring normal cells. The enlarged nucleus reflects light and thus appears white.



Fig. 2.4: The ViziLite kit [Image available via license: CC BY-NC-SA 3.0]

Fluorescence (VELScope: Visually Enhanced Lesion Scope)

The VELscope® System (Fig. 2.5) is a revolutionary hand-held device that provides the oral health care professionals, an easy-to-use adjunctive mucosal examination system for the early detection of abnormal tissue. It can also aid the surgeon to identify diseased tissue around a clinically apparent lesion and thus help in determining the appropriate margin for surgical excision.



Fig. 2.5: The VELscope [*Image source* https://ledapteryx.com]

Principle

- It is based on the direct visualization of tissue fluorescence and the changes in fluorescence that occur when abnormalities are present.
- The VELscope® System Handpiece emits a safe blue light into the oral cavity, which excites the tissue from the surface of the epithelium to the basement membrane and into the stroma beneath, causing it to fluoresce.
- The clinician is then able to immediately view the different fluorescence responses to help differentiate between normal and abnormal tissue
- Under examination with the VELscope® System, abnormal tissue typically appears as an irregular, dark area that stands out against the otherwise normal, green fluorescence pattern of surrounding healthy tissue.

Investigations for Autoimmune Disorders of the Oral Cavity

Immunofluorescence is an immunohistochemical method used to demonstrate the presence of antigen and antibodies in the tissues or serum. It is an auxiliary diagnostic tool for the autoimmune bullous and inflammatory disorders. It detects the *in situ* and circulating immune deposits that are involved in the pathogenesis of immunobullous diseases.

Fluorescence is the property of absorbing light rays of one particular wavelength and emitting rays with a different wavelength. Fluorescent dyes show up brightly under ultraviolet light as they convert ultraviolet light into visible light. In 1941 Coons and Kaplan showed that these fluorescent dyes can be conjugated with antibodies and they are called labeled antibodies. These labeled antibodies can be used to locate and identify antigens in the tissues.

The most commonly used fluorochromes are:

- Fluorescein isothiocyanate (FITC) which produces apple-green color
- Tetramethylrhodamine isothiocyanate with a red color of fluorescence
- Phycoerythrin which also shows red fluorescence.

2 basic types of IF technique

- **Direct IF (DIF):** DIF is the earliest form of immunohistochemistry. In this direct technique, the antigen is reacted directly with a fluorescein-conjugated antibody specific for the material sought within the tissue. Patients tissue biopsy is used (Table 2.6).
- **Indirect IF (IIF):** Indirect IF (IIF) is a two-step serological technique for detecting the circulating antibodies in the body fluids. It uses serial dilution of patients serum applied to the section of suitable tissue substrate.[1] Conjugated antihuman IgG is then applied to localize the autoantibodies from the patient's serum that are bound in the tissue substrate. Patients serum is used.

Nikolsky's Sign

The Nikolsky's sign is a well-described clinical sign seen in some vesiculobullous disorders which manifest as dislodgement of intact superficial epidermis by a shearing force. The pathophysiology associated with Nikolsky's sign is the acantholysis[8], i.e. loss of coherence between epidermal cells due to the breakdown of their intercellular bridges. It is characteristically seen in intraepidermal bullous disorders; whereas in subepidermal VB diseases, the sign is generally absent.

Elicitation of the Nikolsky's Sign

When a tangential pressure is applied on apparently normal skin/mucosa, or on peri-lesional skin/mucosa or on affected skin/mucosa with the thumb or finger, the resulting is a shearing force dislodges the upper layers of epidermis from the lower epidermis resulting in formation of new blister.

TABLE 2.6: Direct immunofluorescence appearance of some vesiculobullous lesions

Disease	*Antigenic self-protein, autoantibody and location in direct immunofluorescence*
Pemphigus vulgaris	• Antibodies are formed against desmoglein 3 and 1, the intercellular cementing substance, resulting in the formation of intra-epithelial blisters (Fig. 2.6). • DIF shows intercellular deposits of IgG and C3, the latter are predominantly located in the lower layers of the epithelium. Chicken wire, fish net appearance (Fig. 2.6A)
Paraneoplastic pemphigus	• Autoantibodies target desmoglein 3, desmoplakins and basement membrane zone [BMZ] antigens. • DIF shows similar pattern to that of PV, along with linear, intercellular and intraepithelial deposition of IgG in the basement membrane. • One way to differentiate PNP from PV is to perform IIF.
Bullous pemphigoid	• Antibodies are formed against BP 180 and 230 • Deposition of C3, IgG or both at the BMZ. • Deposition of C3 with significantly higher intensity than IgG strongly favors the pemphigoid group of diseases (Fig. 2.6B)
Cicatricial pemphigoid	• Antibodies are formed against BP 180 and laminin V • Linear deposits of C3, IgG, and IgA at the dermal epidermal junction, "shore line appearance" (Fig. 2.6C)
Epidermolysis bullosa acquisita	• Antibodies are formed against type VII collagen • Deposition of IgG, IgA and lesser amounts of C3 at the basement membrane zone
Linear IgA disease	• Antibodies are formed against desmoglein 3, desmocolin 1 and 2 • Linear IgA deposits in the basement membrane.
Dermatitis herpetiformis	• Antibodies are formed against tissue transglutaminase • Granular deposition of IgA and C3 in the papillary dermis and along the BMZ is diagnostic of dermatitis herpetiformis • Deposition of IgG or IgM or both is less frequent and less intense (Fig. 2.6D)
Erythema multiforme	• Antibodies are formed against desmoplakins • Granular deposits of IgG, C3, IgM and fibrinogen around dermal vessels and at the dermal-epidermal junction
Systemic lupus erythematosus	• Anti-nuclear antibodies are formed • Deposits of IgG, C3, IgM at the basement membrane zone and around blood vessels; "positive lupus band test" (Fig. 2.6E)

Applications of the Nikolsky's Sign

Nikolsky's sign is also useful in differentiating various blistering diseases. It is usually positive in intraepidermal blistering disease, while in subepidermal blistering disease such as bullous pemphigoid, the sign is usually absent. Nikolsky's sign is positive in pemphigus vulgaris, pemphigus foliaceous, chronic erythema multiforme, epidermolysis bullosa acquisita, Stevens-Johnson syndrome, toxic epidermial necrolysis.

It is of prognostic significance also in the treatment of pemphigus vulgaris as the sign is positive in the active phase and becomes negative with response to the immunosuppressive therapy.

DIAGNOSTIC MICROBIOLOGY

Infectious diseases of the oral cavity may be bacterial, viral or fungal in origin. The most common means of bacterial isolation and identification is culture of an appropriate bacterial specimen (pus, exudate, sputum or blood). Other methods of bacterial identification include methods like phage

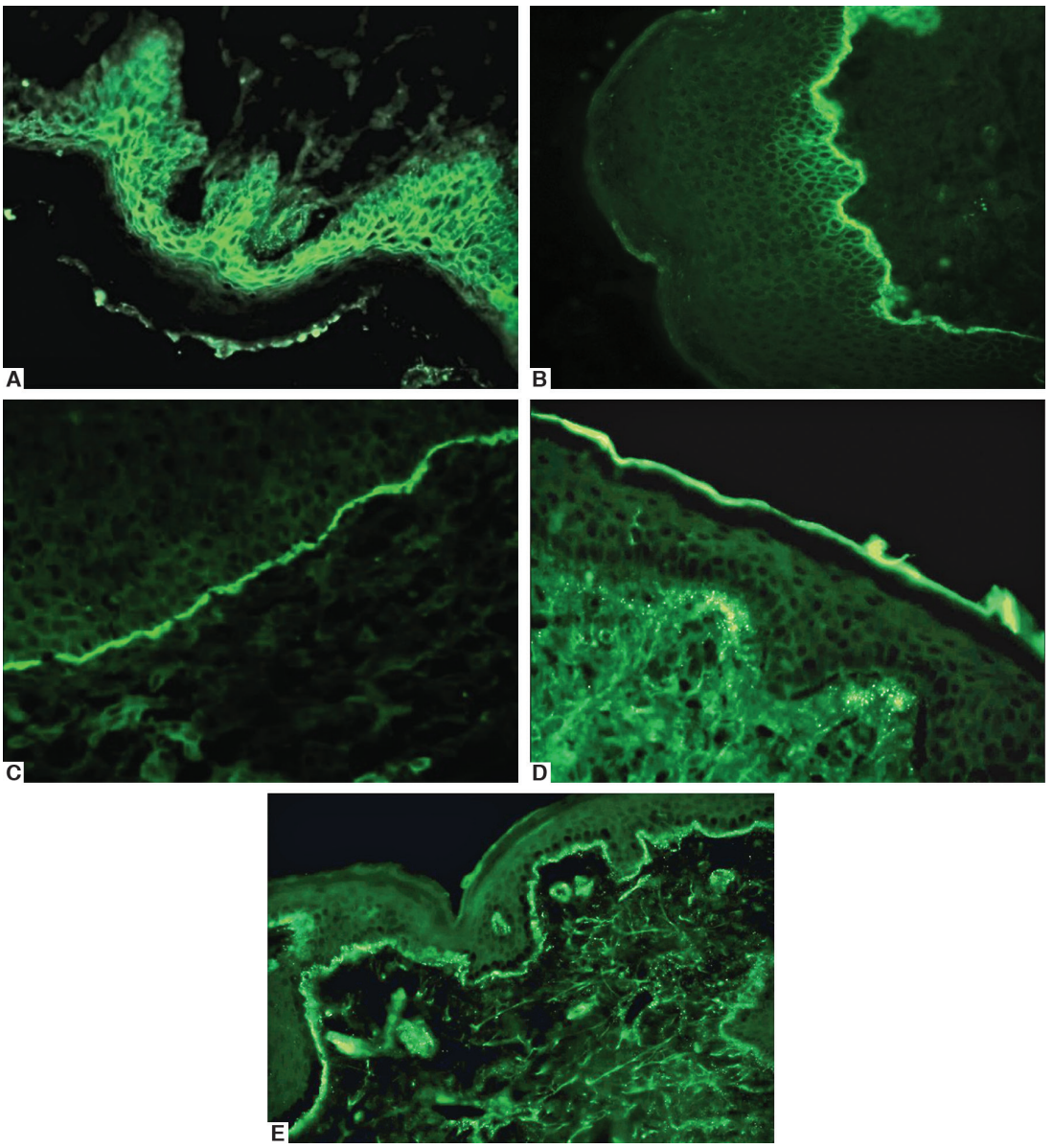


Fig. 2.6: Direct immunofluorescence patterns in: (A) Pemphigus vulgaris; "fishnet appearance"; (B) Bullous pemphigoid; (C) Cicatricial pemphigoid 'shore-line appearance'; (D) Dermatitis herpetiformis; (E) SLE 'positive lupus band' [*Image source:* http://www.ijdvl.com/text.asp?2012/78/6/677/102355]

typing, bacterial PCR, and identification of antibodies to bacteria (ELISA, precipitation assays, etc).

Most oral infections are of a mixed nature, so both aerobic and anaerobic cultures may be necessary.

Table 2.7 delineates the commonly used culture media for infections that may affect the oral cavity.

Table 2.8 shows the recommended tests for bacterial infections that may have oral manifestations.

Fungal Infections

Candidiasis is the most common fungal infection of the oral cavity.

Laboratory Investigations for Candida

- Potassium hydroxide (KOH) wet mount for direct demonstration of fungal hyphae under microscope.
- Periodic acid–Schiff (PAS) stain and methenamine silver stain
- Fungal culture with Sabouraud's dextrose agar, corn meal agar
- **Serology:** Serum (1,3) β-D-glucan and mannan detection assays (these are fungal cell wall components).

Viral Infections

Herpes simplex viruses (1 and 2), human papillomaviruses (HPV) and human immunodeficiency virus (HIV) are the common viruses implicated in viral diseases of the oral cavity (Table 2.9).

TABLE 2.7: Commonly used culture media for infections that may affect the oral cavity

S. No.	*Culture media*	*Organism*
1.	Nutrient agar (1 to 2% agar)	Basal media in microbiology Supports the growth of all non-fastidious organisms
2.	Blood agar	Staphylococcal and streptococcal infections
3.	Robertson's cooked meat broth	Anaerobic culture
4.	MM10 sucrose blood agar	Ideal medium for normal and disease-associated dental plaques
5.	Lowenstein-Jensen medium	Selective media for isolation of *Mycobacterium tuberculosis* from sputum and other samples
6.	Mannitol salt agar	Selective and indicator media for *S. aureus*
7.	Polymyxin B, neomycin, fusidic acid media (PNF)	Selective media for *S. pyogenes* (or β-hemolytic Streptococcus)
8.	Mueller-Hinton agar	Performing antimicrobial susceptibility for bacteria

TABLE 2.8: Recommended tests for bacterial infections that may have oral manifestations

S. no.	*Infection*	*Tests*
1.	Tuberculosis	• Mantoux tuberculin skin test • Acid-fast bacilli (AFB) smear and culture • PCR for *M. tuberculosis* specific DNA • Interferon gamma release assay
2.	Syphilis	*Screening:* • Venereal Disease Research Laboratory (VDRL) test, • Rapid plasma reagin (RPR). *Confirmatory:* • Fluorescent treponemal antibody-absorption (FTA-ABS), microhemagglutination assay-*T. pallidum* (MHA-TP), • *T. pallidum* particle agglutination (TPPA) test
3.	Leprosy	• Acid-fast bacilli (AFB) smear and culture • Serologic assay to detect phenolic glycolipid-1 (specific for *M. leprae*)
4.	Actinomycosis	• Examination of "sulphur granules" • Anaerobic culture

TABLE 2.9: Various tests recommended for the laboratory diagnosis of these conditions

S. No.	*Virus*	*Diseases*	*Diagnosis*
1.	HSV 1 and 2	▪ Acute herpetic gingivostomatitis ▪ Herpetic labialis and whitlow	▪ Viral isolation in tissue culture ▪ Tzanck smear ▪ Detection of viral DNA by polymerase chain reaction (PCR) ▪ Direct fluorescent antibody staining ▪ Serum antibody titres.
2.	Epstein-Barr virus	▪ Infectious mononucleosis	▪ Paul-Bunnel test ▪ Monospot test
3.	HIV 1 and 2	▪ HIV infection and AIDS	▪ Screening: ELISA to detect antibodies to the virus ▪ Confirmatory: Western blot ▪ Antigen detection assay: Done for p24 antigen (for early testing) ▪ CD4+ counts—for disease surveillance ▪ Viral load assessment by PCR—therapeutic monitoring.

ALLERGY TESTING

A possible allergic reaction to a drug or dental medicament is a significant cause of concern for the dentist. An anaphylactic shock is a severe kind of allergic reaction that could be potentially life-threatening, that could be encountered in a dental setting. Allergies include hypersensitivity reactions could be immediate or delayed.

1. Skin Tests

Useful for both immediate and delayed hypersensitivity reactions.

Skin tests for allergy include:

Intradermal injection: The test involves injection of a small amount of the suspected allergen into the superficial layer of the dermis with a fine bore needle (26 or 27 gauge). The amount of quantity injected is approximately 0.05 ml or the amount that causes a visible weal. The preferred sites for intradermal injection are the flexor aspect of forearm or the back. A control (e.g. normal saline) must also be injected at a comparable site. After about 20 minutes the area is examined for a reaction at the site. A typical reaction looks like a small hive with swelling and redness. Examples are tuberculin test, sensitivity testing for Xylocaine. Resuscitation equipment and 1 in 1000 epinephrine should be available in case of any untoward allergic reaction.

Prick test: This is a modification of the intradermal injection. A small amount of test solution is placed on the skin and a shallow prick is made through it with a sharp needle. Care should be taken to avoid inducing any bleeding. The size of the visible flare is measured after 15 to 20 minutes. The concentration of prick test solutions is higher than those used for intradermal testing.

Patch test (epicutaneous test): Patch tests are used to detect contact allergy of the delayed hypersensitivity type. It involves applying patches with test substances in small chambers or discs to a person's back. The patches are secured with hypoallergenic tapes. They are usually read at 48–72 hours and again at 1 week. A positive patch test reaction will produce an area of active dermatitis, which is itchy, in the area of application.

2. Serum Tests

These tests require a small sample of blood (about 5 ml) from which the serum is obtained. The different serum assays used for allergy testing include:

1. **Histamine release assay:** For immediate hypersensitivity reactions
2. Assay for the concentration of IgE antibodies against a specific allergern
3. **Lymphocyte proliferation and lymphokine production assay:** For delayed hypersensitivity reaction.

Frequently asked questions

1. Pathergy test
2. Biopsy
3. Nikolsky sign
4. Toluidine blue staining

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Chapter

3

Dental Therapeutics

The scope of this chapter is limited to the clinical practice of dentistry and does not cover alternative medicines. The dosages and drug preparations described in this chapter are based on the Indian Standard Pharmacopeia (ISP). The reader is cautioned to use the information provided based on their diagnosis and sound pharmacological knowledge. Drug interactions and adverse effects should be considered before prescribing any medications.

GENERAL PRINCIPLES OF DENTAL THERAPEUTICS

A budding dentist usually ponders if he/she is eligible to prescribe all those drugs which was taught in the graduate course. Indeed, the author of this chapter has been asked the same query by many colleagues and students. It should be understood that the subject of pharmacology has been taught and tested in the course of BDS programme which makes a dentist eligible to prescribe drugs with certain exceptions. Diseases which are not in the scope of dentistry should not be treated by a dentist alone.

How to prescribe?

Any prescription has to follow the basic principles taught in the subject of pharmacology (Fig. 3.1). Both written and electronic prescriptions need to be signed by the licensed dentist with his official stamp. However, prescriptions through social media, text messages or telephonic conversations, commonly known as e-pharmacy is better to be avoided. The Drugs Controller General of India (DCGI) has banned the sale of medicines through e-pharmacies on 30th December, 2015[1].

What are over-the-counter medications?

Some of the medications commonly used for oral care are available as over-the-counter (OTC) medications and do not need any prescriptions. NSAIDs like paracetamol and ibuprofen, toothpastes, mouthwashes containing chlorhexidine or chlorine dioxide are a few examples for the OTC products.

Are there any legal issues in drug prescription?

Yes. Any authorized prescription is a legal document and can be used as a piece of evidence by the law of the land. It is a good practice to maintain copies of prescriptions in the patient records. Prescriptions for sedatives, hypnotic agents and opioid analgesics should be for short duration only. If necessary, new prescriptions are issued. These precautionary measures are to safeguard patient's health and avoid any misuse of prescriptions.

Prescriptions are valid from the date of issue to the number of days the drug is prescribed. No prescription can be reused and loses its legal validity if done so.

Faculty of dentistry, Xxxxxxxxxxxxxxxxxxxxxxxx
xxxxxxxxxxxxxxxxxxxxxxxxx

Mr. Yyyyyyy
Folder number: 899898
OPD number: XYZGHKIL

Diagnosis: Periapical abscess
Age: 27 yrs

℞

1. Caps Amoxycillin 500 mg x tid for 5 days
   (to be taken 30 minutes after food only)

2. Tab Ibuprofen 400 mg sos—maximum one tablet per 8 hours
   (to be taken 30 minutes after food only)

Dr. XYZ
Annual practice registration number: 12345678
Date:

Fig. 3.1: Model prescription

Self-prescription is not a valid prescription and does not have any legal validity. It is not illegal to self-prescribe (including immediate family members) most of the medications (except for controlled drugs). However, such practices should be avoided.

Are there any cultural and religious issues related to drug prescriptions?

A dental practitioner should develop the cultural competence so that the values and beliefs of patients are taken into consideration during a drug prescription. Halal drugs, medications containing animal products, IV fluid administration during religious fasting are a few common issues that needs to be understood by the reader.

Should we prescribe trade name or generic name of the drug?

According to the circular of Medical Council of India (2017)[2] 'every physician should, as far as possible, prescribe drugs with generic names legibly and preferably in capital letters and he/she shall ensure that there is a rational prescription and use of drugs'. The circular also states the provision for disciplinary action against defaulters.

Antibiotics

Any chemical produced by microbial organisms used against other microbial organisms are known as antibiotics and can be an antibacterial or antifungal drug. For the sake of convenience, in this chapter we have used antibiotic terminology for antibacterial and antifungal is used separately.

General guidelines for antibiotic prescription:

- Antibiotics is always a prescribed drug
- Complete dosage of antibiotic should be prescribed
- Start with an extended spectrum antibiotic and if therapeutic target is not achieved, should not hesitate to advise culture and sensitivity and followed by a narrow spectrum antibiotic.
- Seldom, antibiotics are prescribed for longer duration (>10 days) in the field of dentistry.

- Prophylactic antibiotics should be based on the standard guidelines rather than any speculation of infection without a clinical evidence.
- Local delivery of antibiotics should be restricted to periodontal treatment procedures and special cases like a dry socket.
- A standard drug duration of 5, 7 or 10-day regimen should be followed and should be based on the clinical judgement.
- Antibiotics are always combined with dental treatment procedures like RCT or extraction or curettage.

Dentoalveolar Infections

Majority of the dentoalveolar infections can be controlled using extended spectrum penicillin like amoxicillin and ampicillin[3]. 30% of these infections are caused by resistant strains to penicillin. Clavulanic acid in combination with amoxicillin is preferred in such cases.

To avoid development of antibiotic resistance to these drugs, a 3-day regimen has been advised[4]. However, the authors believe in the traditional school of thought, i.e. first 3 days of antibiotics are to kill the bacteria and next 2 days to kill the spores, thus making it a minimum of 5 days of prescription.

The traditional amoxicillin piggy backed with metronidazole can increase the effectiveness in treating dentoalveolar infections to 99%[5].

Periodontal and Pericoronal Infections

Periodontal infections are anaerobic infections or mixed infections and thus to be treated with combination drugs like amoxicillin and metronidazole or drugs which are excreted in gingival crevicular fluid like doxycycline.

As a guidance, Table 3.1 gives an overview of antibiotics for common dentoalveolar and periodontal infections.

Cephalosporin group of drugs and ciprofloxacin are commonly not advised in dental infections. However, such prescriptions are valid when supported with culture and sensitivity reports.

Osteomyelitis

Amoxicillin and clavulanic acid combination with metronidazole for 2–3 weeks, or ciprofloxacin combined with clindamycin in penicillin allergic patients are usually advised in jaw osteomyelitis patients. Newer antibiotics like linezolid are good for

TABLE 3.1: An overview of antibiotics for common dentoalveolar and periodontal infections

Infection	*Antibiotic*	*Cost*	*Comments*
Localised, no penicillin allergy	Amoxicillin 500 to 750 mg *tid* for 5 days	Economical	Good compliance
Localised, allergic to penicllin	Clindamycin 300 mg, *bid* for 5 days	Expensive	Avoid in patients with h/o colitis
	Doxycycline 100 mg *bid* on first day and *od* for 4 days	Economical	No interference with food
Spreading, no penicillin allergy	Augmentin 625 mg *bid* for 5 to 7 days	Expensive	Causes diarrhea
Spreading, allergic to penicillin	Azithromycin, 500 mg *bid* for 5 to 7 days	Expensive	For patients with history of diarrhea after taking antibiotics
Alternative drugs	Metronidazole 400 mg *tid* for 5 days	Economical	Should be used with amoxycillin, no alcohol, side effect like colitis

methicillin-resistant strains and vancomycin for nosocomial infections.

Common adverse events related to antibiotics:

A 5 days course of antibiotics such as amoxicillin and augmentin can sometimes result in diarrhea. A prior information of such a possibility should be provided to patients. This is a transient adverse effect which can be treated with probiotic tablets containing *Lactobacillus acidophilus*. Agents like metronidazole, tinidazole and ornidazole can result in metallic taste, xerostomia and fixed drug eruptions. These agents are also known for their 'disulfiram like' effect and hence a warning to avoid alcoholic drinks should be printed in the prescription. Tetracycline and ciprofloxacin should be avoided in pregnant patients and children less than 12 years.

Antifungals

Commonly used topical antifungal agents are clotrimazole, nystatin and miconazole. Resistant infections and deep fungal infections are treated with systemic antifungals like fluconazole, ketoconazole and amphotericin-B.

In denture stomatitis patients, topical antifungal agents are to be applied both on the lesion and on the denture-tissue surface. Topical antifungals are also used as first line of treatment for non-scrapable white lesions.

Table 3.2 describes the commonly used topical and systemic antifungal agents.

Antiviral Agents

In this section we have described antiviral agents commonly used for orofacial viral infections. Antiretroviral drugs are not in the scope of this chapter.

Antiviral agents prescribed in a dental office are acyclovir, famciclovir and penciclovir for herpetic infections. Table 3.3 describes the various conditions and the dosage of antiviral agents used.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Unlike antibiotics, there is no rigid course for NSAID prescription. These drugs are always given 'as and when needed (*SOS*)'. However, appropriate drug should be chosen based on the severity or duration of pain. Table 3.4

TABLE 3.2: Commonly used topical and systemic antifungal agents

Infection	*Antifungal agent*	*Dosage*	*Adverse reactions*
Denture stomatitis, angular cheilitis and non-scrapable white lesions	• Clotrimazole • Nystatin	• 10 mg lozenges five times/day for two weeks or 1% solution *tid*/day topical for 2–4 weeks • 100,000 units qid/day topical for two weeks	• Erythema, stinging, irritation • Nonspecific myalgia, bronchospasm, tachycardia
Resistant oral candidiasis	• Fluconazole • Ketoconazole • Amphotericin-B oral suspension	• 50 to 150 mg/day for two weeks • 200 to 400 mg/day for 2 weeks • 1 ml of 100 mg/ml oral suspension or 10 mg lozenges or 100–200 mg tablets *qid*	• Diarrhea, flatulence, taste disturbance • Adrenal insufficiency, GI disturbances, photophobia are seen • Local irritation, pruritus and skin rash
Deep fungal infections like blastomycosis, cryptococcosis and rhinosporidiosis	• Amphotericin-B	• 250 µg/kg/day up to 1 mg/kg/day	• Pain at injection site, renal toxicity, peripheral neuropathy

TABLE 3.3: Various conditions and the dosage of antiviral agents used

Condition	*Antiviral agent*	*Dosage*
Primary herpes simplex	Acyclovir	200 mg five time/day for 10 days
Recurrent herpes labialis	Acyclovir cream Penciclovir cream	5% five time/day for 1–2 weeks 1% five time/day for 2 weeks
Recurrent herpes simplex	Acyclovir	400 mg bid/day for 5–10 days
Herpes zoster	Acyclovir Famciclovir	800 mg five times/day for 10 days or IV 5 mg/kg 8 hourly 500 mg *tid* for 7 days
Prophylaxis of herpes simplex in immunocompromised patients	Acyclovir	200–400 mg qid/day for 1–2 weeks

TABLE 3.4: Appropriate choice of NSAIDs for dental practice

Condition	*NSAID*	*Cost*	*Comments*
Dentoalveolar infection with swelling and fever	Paracetamol 650 mg	Economical	▪ Not safe in patients with liver disorders. ▪ Preferred drug in children, pregnant patients and asthmatics
Dental extraction	Diclofenac sodium 50 mg Ibuprofen 400 mg	Economical	▪ Can cause gastric irritation
TMJ pain	COX-2 inhibitors like valedicoxib 10 mg or etoricoxib 60 mg	Expensive	▪ Not indicated in patients with liver impairment
Dental infections with fever in children	Mefenamic acid 250 mg	Economical	▪ Not indicated in asthmatic patients

describes the appropriate choice of NSAIDs for dental practice.

It should be noted that there is no therapeutic advantage of using COX-2 inhibitors to treat acute dental pain compared to Ibuprofen[6].

Opioid Analgesics

Indications for opioid analgesics in the field of dentistry is limited. Chronic pain in head and neck cancer patients, facial trauma and patients undergoing minor oral surgery might need these drugs. However, the addiction possibility, misuse of drug and side effects related to opioids need to be taken care in such cases.

Opioid analgesics are contraindicated in patients with cardiac problems, head injury and hypotension. They are not safe to be prescribed in pregnancy, children and teenagers.

Commonly prescribed drugs are tramadol, buprenorphine, pethidine, fentanyl, codeine and pentazocine (Table 3.5). Readers should update themselves with the regulations related to these drugs before any prescriptions are given.

Sedatives and Hypnotics

Alprazolam, barbiturates, clonazepam, diazepam and midazolam are the commonly used sedatives and hypnotics. Alprazolam is used in stress-related disorders leading to chronic orofacial pain. Clonazepam and diazepam are used as central muscles

TABLE 3.5: Commonly prescribed drugs

Type of opioid analgesic	*Dosage*	*Indications*	*Adverse reactions*
Tramadol	50 to 100 mg	Acute and chronic pain	Dizziness, vomiting and fatigue
Buprenorphine	200 to 400 mcg sublingual	Moderate to severe pain Medication assisted treatment	CNS depression, hallucinations and vertigo
Pethidine	50 to 150 mg IV	Moderate to severe acute pain	Hallucinations, dependence
Fentanyl	100 µg sublingual	Chronic pain	Bronchoconstriction, hypotension
Codeine	15 to 60 mg	Mild to moderate pain	Miosis, anorexia, confusion
Pentazocine	25 mg	Mild to moderate pain	Urinary retention and disorientation

relaxants. Topical clonazepam is used in burning mouth syndrome cases. Midazolam is used as a preoperative sedative agent for treating pediatric dental patients.

These group of drugs should be prescribed for short duration and related adverse effects should be informed to the patients.

Instructions to be given to patients on sedatives or hypnotics:

1. Follow the recommended dose.
2. Your medications can induce drowsiness. Please take such medications only before bed and do not drive / work after ingestion of such medications.
3. After taking these medications, do not work with fire, electric appliances and sharps.
4. These medications might cause dry mouth which is a temporary side effect.
5. Do not re-use the prescription.
6. Dispose remnant medications.
7. Keep the medications away from children.

Muscle Relaxants

Central muscle relaxants are more commonly used compared to peripheral ones. These drugs are mainly used for TMDs along with NSAIDs. Chlorzoxazone, orphenadrine, tizanidine, baclofen and thiocolchicoside are commonly used oral muscle relaxants. Other than these drugs, sedative agents like clonazepam and diazepam can be used as muscle relaxants.

We have not covered parenteral muscle relaxants in this section as it is not in the scope of this book. Table 3.6 describes the dosage, indications and key adverse reactions of these drugs.

TABLE 3.6: Dosage, indications and key adverse reactions of these drugs

Type of muscle relaxant	*Dosage*	*Indications*	*Adverse reactions*
Baclofen	5 to 10 mg	Severe chronic spasticity	Dry mouth, taste alterations, dizziness
Chlorzoxazone	250 mg	Painful muscle spasm	Altered liver function test, drowsiness
Orphenadrine	100 mg	Muscle spasm	CNS depression, tachycardia, euphoria, increased intraocular pressure
Thiocolchicoside	4 to 8 mg	Muscle spasm	Photosensitivity reactions
Tizanidine	2 mg	Spasticity and painful muscle spasm	Drowsiness, fatigue, dizziness, insomnia

Corticosteroids

In this textbook, corticosteroid is used as an equivalent terminology to glucocorticoid. We have not covered anabolic steroids and mineralocorticoids in this chapter.

In the field of dentistry, short and medium acting steroids are more commonly used compared to long-acting steroids. Table 3.7 shows the classification of corticosteroids with examples.

TABLE 3.7: Classification of corticosteroids with examples

Types	*Examples*
Short-acting (8–12 hours)	Hydrocortisone, cortisone
Medium-acting (12–36 hours)	Prednisolone, prednisone, methyl-prednisone, triamcinolone
Long-acting (36–72 hours)	Betamethasone, dexamethasone, deflazacort

Other than these, some of the glucocorticoids are used as topical agents only and belong to short-acting category. For example, budesonide, beclomethasone, clobetasone, fluticasone and mometasone.

In the field of dentistry, majority of corticosteroid prescriptions are topical. Corticosteroids are available in market as ointment, cream, paste and gel. It is advisable to use either gel or cream due to the presence of saliva in oral cavity. Because of saliva, ointment may not get absorbed through oral mucosa.

It should be noted by the reader that we seldom have the luxury of getting a topical corticosteroid manufactured for intraoral usage. Thus, we have to depend on the preparations marketed for skin lesions. Such topical preparations have warnings mentioned on the package prohibiting intraoral or intraocular usage. These warnings can panic a patient who has been advised to use the same intra orally. It is a good practice to explain these issues to the patients and take their consent or prescribe specific intraoral usage agents like Kenacort® with Orabase®.

Topical agents have the advantage of lesser systemic effects and lesser adverse event rate. However, there are many limitations which should not be overlooked. Challenges like standardized dispensing of steroid gel, consumption of food or fluids diluting the effect of the drug, unpleasant taste and flavor, messy application methods and difficulty in applying to posterior oral cavity can influence the overall drug effectiveness.

To handle lesions on the posterior parts of the oral cavity, topical prednisolone solution used as mouth rinse is comparatively more acceptable to patients in author's experience, except for its bitter taste. Local drug delivery systems like mucosal patch have yielded promising results[7].

Table 3.8 shows the WHO classification of topical corticosteroids[8].

TABLE 3.8: WHO classification of topical corticosteroids

Types	*Examples*
Ultra high potency	Clobetasol proprionate cream 0.05%
High potency	Flucinonide gel 0.05%
Moderate potency	Triamcinolone acetonide cream 0.1%
Low potency	Hydrocortisone acetate 1%

Systemic corticosteroids are prescribed either in the form of oral tablets or intralesional injections. Most commonly prescribed oral tablets are either prednisolone or prednisone. It is advisable to restrict the prescription of oral tablets up to 30 mg per day in any dental practice due to associated complications and the possible immunosuppression. Cases which need higher dosage should be managed as an inpatient or internal medicine specialist consultation would be needed.

Systemic steroids dosages prescribed in dose of >20 mg/day and/or >3 weeks are usually tapered gradually to allow the adrenal glands to resume their normal function. For patients under systemic steroid

therapy presenting with oral infections, steroid dosage should be increased to combat the stress. It should be noted that despite steroid being an immunosuppressive agent, it is not withdrawn in cases of infection[9]. However, antibiotics and local treatment procedures to combat infection should be done simultaneously.

Intralesional corticosteroids are used specifically for managing trismus in oral submucous fibrosis cases, major aphthae, TMJ osteoarthritis, long-standing mucocele and large central giant cell granulomas. Complications such as local infection, scarring secondary to injections are not uncommon in such cases.

Pulse therapy is a special type of corticosteroid administration in conditions like erythema multiforme in which infusions of methylprednisolone is given in dose of 20–30 mg/kg to a maximum of 500 mg over 2–3 hours on consecutive days.

Prophylactic corticosteroids are used in 3rd molar surgery, edema reduction in trauma cases before open reduction of fractures and in pre-prosthetic surgeries. Although there are some conflicting effects, there is current evidence for such usage in 3rd molar surgery[10].

Occlusive therapy using custom trays are used to localize topical steroid medications on the gingival tissues in cases of desquamative gingivitis. Systemic complications like increase in blood glucose levels can be seen in such cases, which is unusual with conventional topical application of corticosteroids.

Other clinical scenarios where corticosteroids are used with varying success rates are to manage postoperative edema and pain, pulp capping agent, cavity liner, dry socket, Bell's palsy, Melkersson-Rosenthal syndrome, infectious mononucleosis and Behçet's syndrome.

Immune Modulators

Immune modulators can be immunosuppressors or immunoactivators. Although, corticosteroids are potent immunosuppressors, in this section we will limit the discussion to non-steroidal drugs.

Immune suppressors are usually prescribed in autoimmune disorders and have grave clinical implications as the recipient is vulnerable for opportunistic infections. It is best practice to discuss such therapies with an internal medicine specialist beforehand and necessary follow-ups and prophylactic measures should be considered.

Agents such as azathioprine, cyclosporine, methotrexate, sirolimus, tacrolimus and thalidomide are documented in the dental literature for management of autoimmune disorders affecting oral cavity. Oral PUVA therapy is combination of oral psoralen tablets with UV-type A rays for management of resistant type of oral lichen planus.

Some of these immune suppressors are also otherwise known as 'disease modifying anti-rheumatoid drugs (DMARDs)'. Nonbiologic DMARDs are hydroxychloroquine, sulfasalazine, minocycline, methotrexate and leflunomide[11]. Biologic DMARDs are etanercept, adalimumab, infliximab, certolizumab pegol, and golimumab which are related to tumor necrosis factors[11].

Immune activators like levamisole, interferons, interleukin-2, BCG injections and thalidomide have been used in management of aphthous ulcers, oral submucous fibrosis, oral premalignant and malignant lesions. However, there is a clear lack of evidence to ascertain the clinical advocacy of these drugs in these oral disorders.

Dentifrices

Two types of dentifrices are used for dental care, viz. antiplaque or anti-decay toothpaste and desensitizing toothpaste.

Antiplaque toothpastes, if fluoridated, have to declare the fluoride concentration on the label[12] and can range from 1000 to 1500 ppm. The maximum fluoride content in the toothpaste varies between countries. There are non-OTC high fluoride concentration

toothpastes available in some countries. However, the recently published Cochrane review suggests that there is no evidence to choose toothpastes containing fluorides more than 1500 ppm[13].

Non-fluoridated toothpastes are available for both adults and children in India. As toothpastes with higher fluoride content can increase the risk of enamel defects because of fluorosis in children, some countries have restricted the usage of fluoridated toothpastes up to certain age. There is moderate-certainty evidence that 1500 ppm fluoride toothpaste reduces caries increment compared to non-fluoride toothpaste in primary dentition of young children[13]. Readers are advised to further read the American Academy of Pediatric Dentistry recommendations to make decisions related to the use of fluoride toothpaste[14].

Commonly used desensitizing toothpastes in India contain potassium nitrate, sodium fluoride, strontium ion or arginine bicarbonate. These toothpastes should be used for longer duration to see clinical benefits and should be applied with finger and wait for a few minutes before brushing. As these desensitizing agents cannot be combined with the common detergent used in toothpastes (sodium lauryl sulphate), there is comparative lack of freshness and foaming with these toothpastes.

Sodium lauryl sulphate, a detergent and foaming agent, presents in toothpastes can cause recurrent aphthous stomatitis in some individuals. Such patients can be prescribed toothpastes which contain alternative detergents such as non-ionic polyethylene glycol ethers of stearic acid[15].

Mouthwashes

Mouthwashes are antiseptic solutions used after brushing. Whereas, a mouthrinse is used before brushing to freshen the breath. However, these two terminologies are used synonymously in majority of the literature. In this chapter, we have used the terminology 'mouthwash' which includes both mouthwash and mouthrinse.

Antiseptic mouthwashes contain different agents like 0.12% chlorhexidine gluconate, 0.2% chlorhexidine gluconate, hydrogen peroxide, cetyl peridium chloride, chlorine dioxide, povidine-iodine, benzethonium chloride, essential oils or alcohol either as a stand-alone content or in combination. These mouthwashes are used for 1–2 weeks to establish any therapeutic effect. However, there are no evidence-based guidelines for the prescription duration.

Fluoride mouthwashes are used for its anti-cariogenic effect. These mouthwashes are prescribed to patients with high caries risk and post-orthodontic de-bonding cases.

Anodyne mouthwashes are used to reduce burning sensation or pain due to oral ulcers in patients undergoing cancer treatment. These mouthwashes contain benzydamine 0.15% or ketamine or morphine sulphate 2% or doxepin 0.5% and have shown promising results in pain reduction. Mouthwashes containing local anesthetic agents such as lignocaine and benzocaine are usually combined with diphenhydramine and magnesium aluminum hydroxide and dispensed as 'magic solution'. Antacid solutions can be used effectively to control pain or burning sensation in such patients. As a cleansing and debriding mouthwash, carbamide peroxide (10–15%), hydrogen peroxide (3%), or sodium bicarbonate solutions are used with varying success rates in aphthous ulcer patients. Antihistamine syrups such as Benadryl® are successfully used to manage allergic stomatitis.

Miscellaneous Drugs

Topical Agents

Amlexanox 5%, a potent inhibitor of inflammatory mediators, in the form of oral paste is used for aphthous ulcers to reduce pain and healing time. Hyaluronic acid is used topically in cases of oral ulcers including aphthous. 25% podophyllin resin is used to treat oral hairy leukoplakia along with antiviral medications. Preparations

containing choline salicylate are regularly used in managing oral ulcers, inflamed mucosa and teething pain.

In cases of xerostomia, artificial saliva or oral humectants such as Biotene® gel or gels containing aloe vera can be prescribed. Systemic drugs (parasympathomimetic drugs) like pilocarpine, cevimeline, anetholetrithione have severe adverse effects and should be weighed over benefit before prescribing.

In case of leukoplakia, topical vitamin A preparations like retinoic acid, tretinoin, isotretinoin are used if no dysplasia is found in the biopsy reports. In case of dysplasia, topical bleomycin 1% cream is recommended.

Systemic Agents

It is recommended to prescribe H2 blockers like ranitidine or cimetidine or proton-pump inhibitors like pantoprazole or lansoprazole to reduce the gastric irritation along with long-term prescriptions of NSAIDs.

In cases of allergic manifestations, antihistamines such as cetirizine hydrochloride or diphenhydramine can be prescribed. However, in cases of type I anaphylactic reaction, IM administration of hydrocortisone is preferred drug of choice.

Neuralgias can be managed with carbamazepine, oxycarbazepine, phenytoin sodium, gabapentin or baclofen as first-line of treatment. These drugs can be given in combinations depending on the tolerance of the patient.

In potentially malignant conditions as oral submucous fibrosis, antioxidants like beta carotene, vitamin C, vitamin E, lycopene, manganese, selenium are prescribed as chemo-preventive agents. Intralesional injections of antioxidants, especially placental extracts are traditionally used along with local anesthetics and steroids.

Other than these medications, there are disease-specific agents like obtundants, mummifying agents, disclosing agents, denture cleansers, bleaching agents and cauterization solutions. These are explained in detail in the specialty textbooks and hence not covered in this chapter.

Pediatric Dose Calculation

An example is shown here:

A parent brought a 5-year-old boy, who was weighing 17 kilograms to the dental clinic who had pain in his decayed upper front teeth. He was examined and was diagnosed with acute periapical abscess in #51, #61. Prescribe appropriate drugs in the standard format.

In this case, the pediatric drug dose can be calculated either using Young's formula or Clark's rule.

Young's formula: Adult dose × Age / Age + 12 = Child's dose

500 mg × 5 / 5 + 12 = 147 mg

Clark's rule: Adult dose × Weight (in pounds) / 150 = Child's dose

500 × (17 x 2.2*) / 150 = 125 mg

Note: Amoxycillin syrup is sold in the concentration of 125 mg/5 ml. So, the dosage of amoxicillin in this case will be ~5 ml (125 mg).

Similarly, Ibuprofen syrup is sold in the concentration of 100 mg/5 ml. So, the dosage of ibuprofen in this case will be ~6 ml (125 mg)

*1 kilogram = 2.2 pounds (In Clark's rule, body weight of the child has to be in pounds).

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Chapter 4

Physiotherapy in Dentistry

INTRODUCTION

Physiotherapy, a treatment in orofacial dysfunction, is considered to be an estranged abstract to dentist as well as people. This novel method is an important adjunctive therapy used in dentistry based on the traditions of orthopedics concerned with the management and rehabilitation of the patient. Postoperative physiotherapy is essential for the prevention or management of temporomandibular joint hypermobility or ankylosis. People with muscle weakness of mouth may benefit from facial strengthening exercises. Various oral motor exercises may be used as an aid in the management of Bell's palsy, trismus, oral submucous fibrosis. This non-invasive, reversible, and cost effective therapeutic modality is a major part of the comprehensive management of patients with orofacial disorders. The concept of physiotherapy goes way back to immemorial times of Hippocrates, deemed as the great Father of Medicine, who acknowledged that movement of body parts promotes good blood circulation necessary for a patient's recovery.

DEFINITION

World Confederation for Physical Therapy (WCPT) defines physical therapy as "Physical medicine and rehabilitation specialty that remediates impairments and promotes mobility, function and quality of life through examination, diagnosis, prognosis and physical intervention using mechanical force and movements".

—Oxford Textbook of Palliative Medicine

Treatment modalities of physiotherapy are broadly classified into:

- **Physical therapy:** Massage, deep tissue massage, trigger point therapy, spray and stretch, physical activity.
- **Electrotherapy:** Transcutaneous electric nerve stimulation (TENS), electronic galvanic stimulation (EGS), electro-accupuncture, diathermy, ultrasonography, lasers, iontophoresis.
- **Thermal therapy:** Hot packs, ice pack.

PHYSICAL THERAPY

Physical therapy refers to light physical activities that help in the release of endorphins for a sense of physical mental and social well-being. It stimulates muscle spindles for contraction and Golgi tendons for stretching, to maintain the normality of tissues.

Massage

It is mechanical manipulation of tissue with rhythmical pressure. Massage reduces pain and restores the proper length and flexibility

of the muscles. It stimulates parasympathetic activity which in turn reduces stress and anxiety. Deep massage assists in mobilizing tissues, increasing blood flow to the area, and eliminating trigger points. It is most effective when it follows 10–15 minutes of preparation of the tissues with deep moist heat which tends to relax the muscle tissue, decreasing pain. Commonly used in cases of masticatory muscle pain.

Spray and Stretch Technique

Vapocoolants ethyl chloride or fluoromethane spray prior to stretching the muscles provides a temporary anesthesia effect to the muscles, so a more intense stretch can be achieved without pain. Sudden cold and the tactile stimulation provided by the vapocoolant spray, inhibit the pain and the reflex motor, and autonomic responses in the central nervous system. When the pain stimuli subside or suppress, an effective relaxation takes place that allows the gently stretching and lengthening of the muscle. The muscle is stretched and vapocoolant is applied in parallel sweeps in one direction till pain reference area. Commonly used in cases of masticatory muscle pain.

Physical Activity

Physical activity can be achieved by:

I. Soft Tissue Mobilisation

It is accomplished by superficial and deep massage which helps in mobilizing the tissues, increase blood flow to the area, and eliminate trigger points. Soft tissue therapy (STT) is the assessment, treatment, and management of soft tissue injury, pain, and dysfunction primarily of the neuromusculoskeletal system.

II. Joint Mobilisation

Distraction is accomplished by placing the thumb in the patient's mouth over the lower second molar area on the side to be distracted. With the cranium stabilized with the other hand, a downward force is applied on the molar with the thumb as the rest of the same hand pulls up on the anterior portion of the mandible. It is not indicated in inflammatory joint disorder. It inhibits pain, reduces muscle spasm and improves range of motion.

III. Muscle Conditioning

There are exercises that can help restore normal function and range of movement of the orofacial musculature. Four types of exercises can be instituted:

a. **Mobilization exercise:** Mobilizing the temporomandibular joints, the exercise aims to improve flexibility and extensibility of muscles, muscle fascia, tendons, and ligaments of masticatory muscles, as well as the facial muscles around the mouth so as to result in pain relief.
   - *Passive muscle stretching:* Instruct the patient to slowly and deliberately open the mouth until the pain is felt. While observing in a mirror patient is encouraged to open on a straight opening pathway.
   - *Assisted muscle stretching:* It is used when there is a need to regain muscle length. Instruct the patient to apply stretching force gently and intermittently to the elevator muscle with the fingers. If pain is elicited, then the force should be decreased or the exercise is stopped completely.

b. **Muscle-strengthening exercise (resistance exercises):** The patient is instructed to place the fist under the chin and open the mouth gently against the resistance. These exercises are repeated 10 times each session, six sessions a day. If they elicit pain, they should be discontinued. It is used to strengthen the power of targeted muscles.

c. **Coordination exercise:** Open-close or lateral movements of the mandible are effective to obtain coordination of

muscle activity in masticatory muscles. It improves imbalanced muscle activity of painful muscles by repetitive alternate movements and thus relieve the muscle pain.

d. **Postural training:** In temporomandibular disorder (TMD) patients with muscle pain who also have a forward head posture, training the patient to keep the head in a more normal relationship with the shoulders may be helpful in reducing the TMD symptoms. Postural exercise includes head posture correction, correction of mandibular position including tongue postural exercise, and myofascial release.

Exercise for Facial Musculature

- **Facial-strengthening exercises:** Wide open the lips, puckering of the lips and moving from one side to the other, smiling by showing the teeth and gums, tightly closing the lips, puffing of cheeks 'O' exercise.
- **Tongue exercises:** Straight tongue the stretch, side tongue stretch, up and down stretch, by sliding the tongue along the outside of the teeth and gums, making circles in the mouth, pushing the tongue against the inside of the cheek, etc.

Tongue Exercises

Employed in cases of temporomandibular joint disorders, clicking related intracapsular

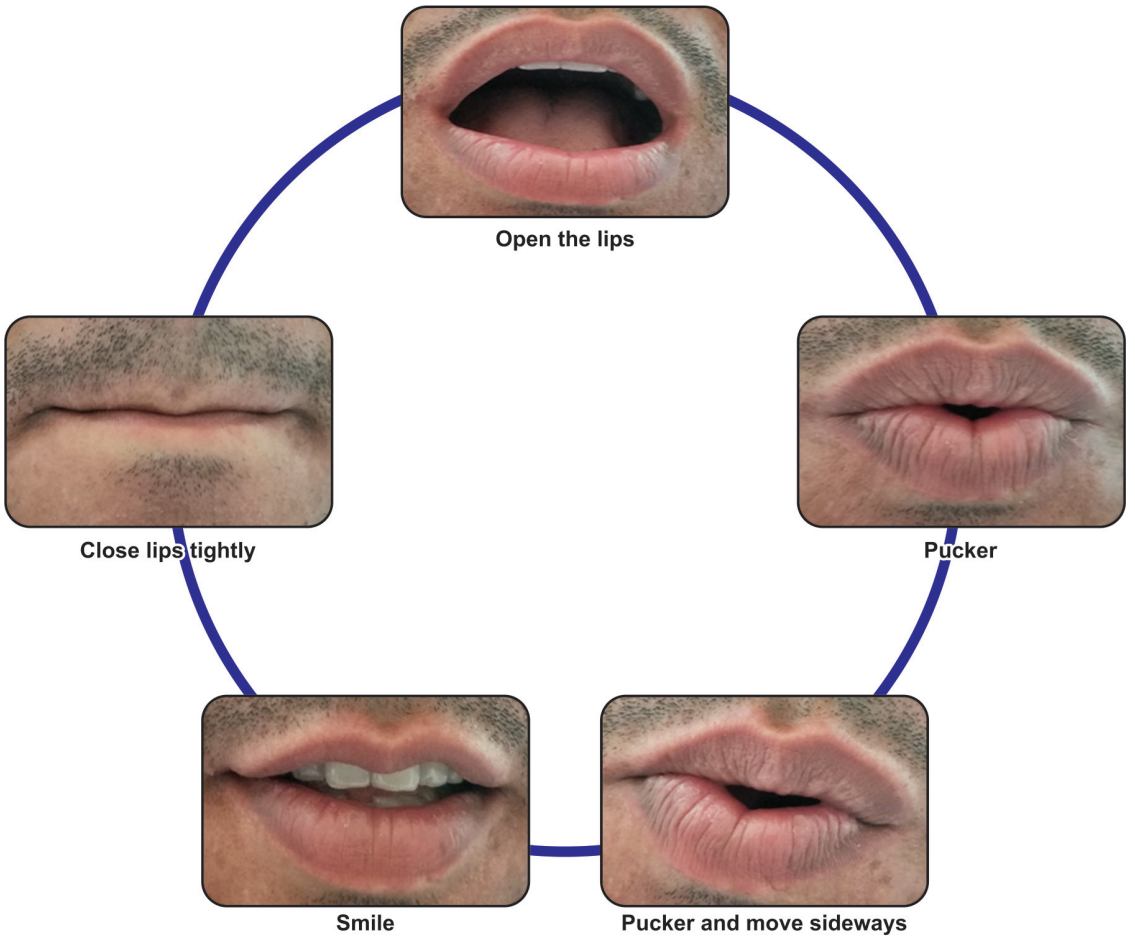


Fig. 4.1: Lip exercises

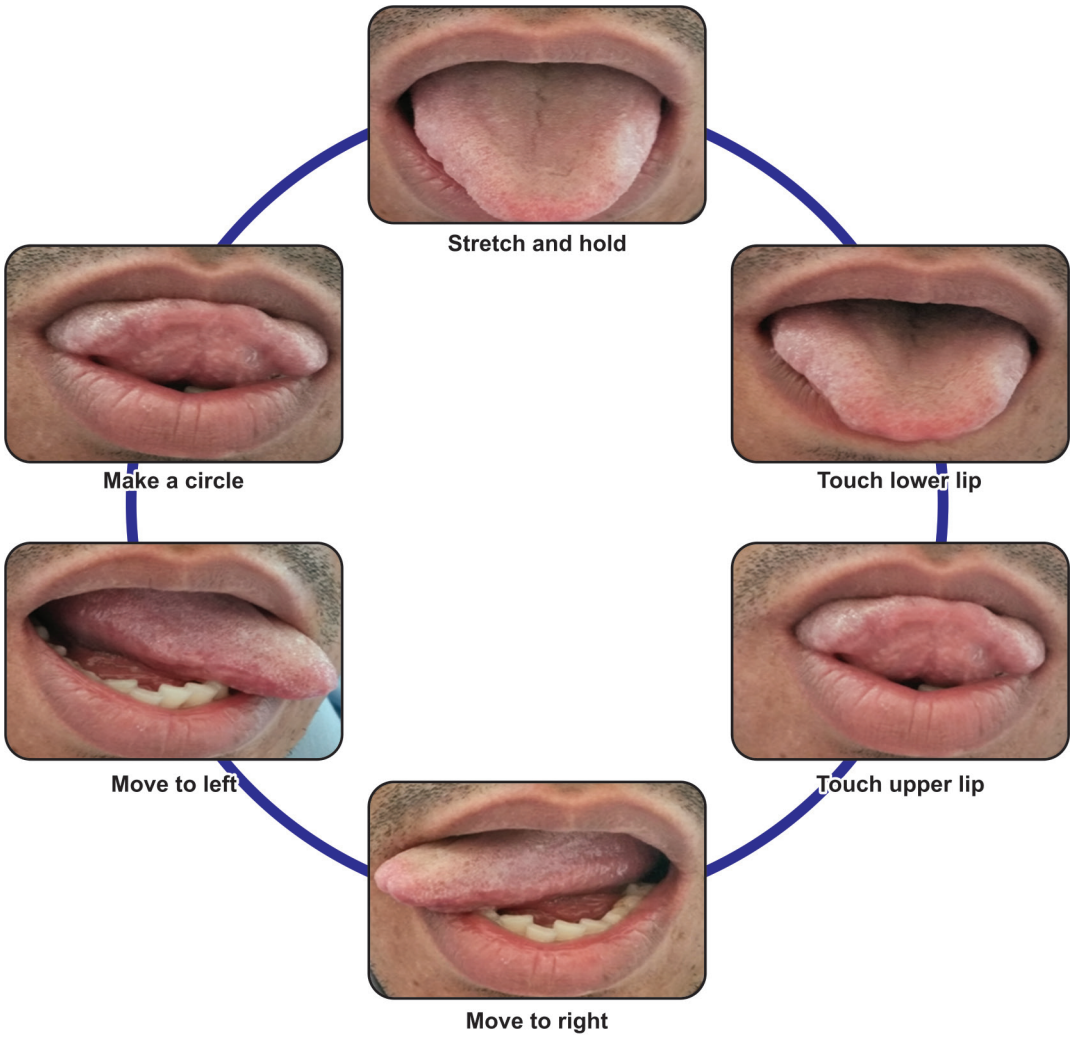


Fig. 4.2: Tongue exercises

joint disorder, acute lock, trauma-induced joint pain, chronic closed lock, capsulitis, hypermobility, hypomobility and oral submucous fibrosis.

ELECTROTHERAPY

Electrotherapy creates an electric field to stimulate or alter healing process, resulting in pain relief and tissue regeneration.

- **Transcutaneous electrical nerve stimulation:** It utilizes a high frequency (50–100 Hz), but very low intensity electric current which stimulates the nociceptive A-beta cutaneous afferents that activate the descending pain-inhibitory mechanism. It is perceived as a tingling or vibratory sensation with phasic muscle/no phasic muscle contraction. It is useful in acute pain, chronic intractable pain, trigeminal neuralgia, peripheral nerve injuries, myofascial pain dysfunction syndrome, post-TMJ surgery and causalgia.

Contraindications listed by manufacturers include pregnancy, infection, malignancy, and pacemaker.

Serious adverse events are rare although skin irritation and contact dermatitis beneath electrodes are erupt.

- **Electrogalvanic stimulation therapy:** A rhythmic electrical impulse of high-voltage, low-amperage is applied to the muscle, creating repeated involuntary contractions and relaxations resulting in the break-up of the muscle spasm as well as increases the blood flow to the muscles. Commonly employed in cases of masticatory muscle pain and post-TMJ surgery cases.
- **Electroacupuncture:** Acupuncture involves the insertion of small, solid needles, stainless steel needles that uses the body's own anti-nociceptive system to decrease the levels of pain felt. Stimulation of acupuncture points appears to cause the release of endorphins which effectively block the transmission of noxious impulses and thus reduce the sensation of pain. Electroaccupuncture requires a current of sufficient intensity to cause pain and muscle contraction. Used in cases of Bell's palsy, masticatory muscle pain, and temporomandibular joint disorders.
- **Diathermy:** Uses short wave (wavelength 3–30 m, frequency 10–100 MHz) or microwave (wavelength 0.001–1 m, frequency 300 MHz–300 GHz) electromagnetic radiation to produce heat within body tissue through conversion. Results in selective heating of epithelial connective tissue that results in physiofibrinolysis. Commonly employed in cases of oral submucous fibrosis.
- **Ultrasonography:** Use physiotherapy in the form of penetrating heat to increase the blood flow in deep tissues and increases the flexibility and extensibility of connective tissue. The frequency range of therapeutic ultrasound is 0.75 to 3.3 MHz. Used in cases of oral submucous fibrosis, TMDs, and masticatory muscle pain.
- **Cold laser:** LASER (Light Amplification by Stimulated Emission of Radiation) is monochromatic, coherent and highly directional light. Low level lasers with red and near-infrared wavelength reduce the transmission of neurotransmitters resulting in decreased stimulation and thus reducing the pain. Act on trigger points by reducing the vascularity and thus diminishing the number of trigger points. Used in masticatory muscle pain and temporomandibular disorders.
- **Iontophoresis:** Local anesthetics and anti-inflammatory agents are placed in a pad and the pad is placed on the desired tissue area. Then a low electrical current is passed through the pad that drives the medication into the tissue. Scientific studies suggested iontophoresis can deliver dexamethasone between 8 and 17 m deep and long duration application of 3 hours via low current is more effective. Employed for TMDs and intracapsular joint disorders.

THERMOTHERAPIES

- **Humans** are warm blooded and their tissues are affected by the application of heat or cold.
- **Superficial mild heat** is used in thermotherapy to increase circulation, soft tissue extensibility, enhance healing, control pain, metabolic, neuromuscular, and hemodynamic activity.
- **Cold application** reduces pain and body temperature, anesthetize an area, control hemorrhage, and growth of bacteria and reduce inflammation.
- **Thermotherapy:** A hot, moist towel is applied over the symptomatic area for 20 minutes, two to three times a day at tolerant temperature. Heat causes vasodilation, increased circulation to the area, and reduces symptoms.
- **Coolant therapy:** Ice is directly applied to the affected area and is moved in a circular motion without pressure on the tissues for a period of 5–7 minutes. When numbness begins, ice should be removed. Types of cryotherapy include cold packs (–12°F), ice packs vapor coolant (cools at 5°C at 2 cm

depth), chemical gel packs, vapocoolant spray, controlled cold compression units, and cold water immersion.

- **Alternate fomentation:** Studies suggest that superficial heat and cold application have similar positive effects in relieving pain because of similar action. Cold therapy has a rapid analgesic effect, reduces acute inflammation and prevents edema in acute injury, whereas thermal therapy increases tissue extensibility thus causing relaxation. Alternate hot and cold fomentation, results in accelerated local circulation and stimulate healing. During the warming period in between applications, it increases the blood flow. Stimulation of cutaneous nerve fibers occur which in turn shuts down the smaller pain (C) fibers. Used in cases of muscle and joint stiffness. Cryotherapy should precede thermal therapy.
- Employed in cases of temporomandibular joint disorders, clicking related intra-capsular joint disorder, acute trauma induced joint pain, chronic closed lock, capsulitis, hypermobility, hypomobility, and masticatory muscle spasm.

Summary

Applications in orofacial conditions:

- Temporomandibular joint disorders
- Intracapsular joint disorders (clicking and clicking-related jaw incoordination as a result of disc displacement)
- Intracapsular joint disorders (trauma-induced acute pain, chronic closed lock, capsulitis and arthritic change)
- Masticatory muscle pain
- Hypermobility and hypomobility
- Post-orthognathic surgery
- Post-TMJ surgery
- Oral submucous fibrosis
- Bell's palsy

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Chapter 5

Ulcerative Vesiculobullous Lesions

TERMINOLOGIES

1. **Ulcer:** A defect in the epithelium; it is well-circumscribed depressed lesion over which epidermal layers have been lost with molecular necrosis. It is also described as break in the continuity of epithelium due to molecular necrosis, e.g. aphthous ulcer, traumatic ulcer, herpetic ulcer.
2. **Macule:** Well-circumscribed, flat lesions that are noticeable because of their change from normal skin color. May be red due to the presence of vascular lesions or inflammation, or pigmented due to presence of melanin, hemosiderin, drugs, e.g. hemangioma, oral melanotic melanoma.
3. **Papule:** Solid lesions, raised above the skin surface that are smaller than 1 cm diameter, e.g. erythema multiforme, rubella, lupus erythematosus, papules of pseudomembranous candidiasis.
4. **Plaque:** Solid raised lesions that are over 1 cm in diameter; they are larger papules, e.g. leukoplakia.
5. **Vesicle:** Raised fluid-filled lesions containing clear fluid with diameter less than 1 cm, e.g. pemphigus, erythema multiforme.
6. **Bulla:** Elevated blister-like lesions containing clear fluid that are over 1 cm in diameter, e.g. pemphigus.
7. **Nodule:** These lesions are present deep in the dermis and the epidermis can be easily move over them. They protrude above the skin or mucosa, e.g. lipoma.
8. **Pustule:** Raised lesions containing purulent material.
9. **Erosion:** Moist red lesions often caused by the rupture of vesicles or bullae as well as trauma, e.g. oral lichen planus.
10. **Purpura:** Reddish to purplish discolorations caused by leakage of blood and varies in size from 0.4 to 0.9 cm which do not blanch on pressure.

The oral mucosa is thin and friable leading to rapid rupture of vesicles and bullae forming ulcers and erosions. A patient presenting with ulcerative or vesiculobullous lesions should be asked the following important questions:

1. **Since when:** Duration (acute/chronic)
2. **How many:** Number (single/multiple)
3. **Recurrent or first time:** Primary or recurrent
4. Presence of fever or systemic complaints, joint pains
5. History of eye, genital or skin lesions

CLASSIFICATION

1. Classification of Vesiculobullous Lesions (Fig. 5.1)

i. **The patient with acute multiple lesions**
- Herpesvirus infection

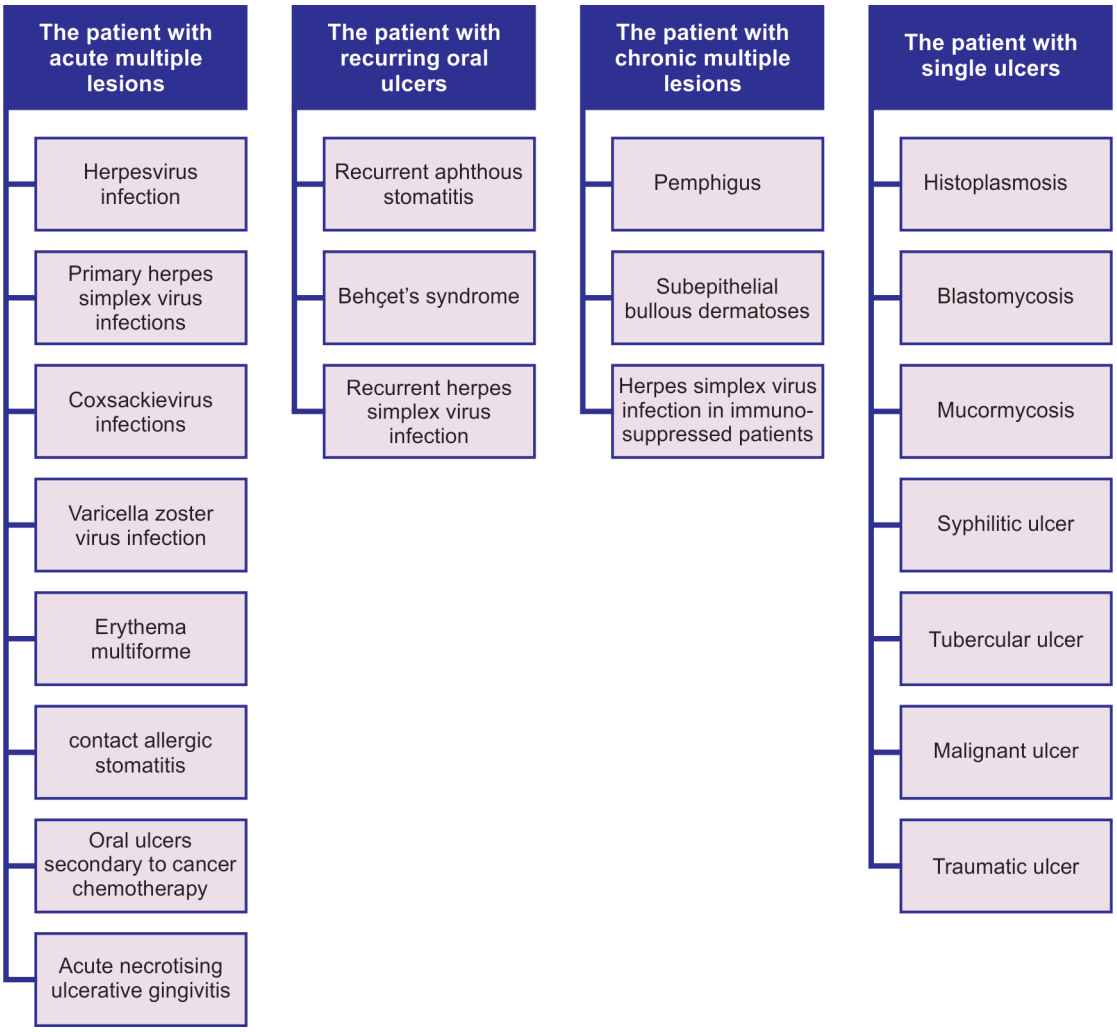


Fig. 5.1: Classification of vesiculobullous lesions based on clinical presentation

- Primary herpes simplex virus infections
- Coxsackievirus infections
- Varicella zoster virus infection
- Erythema multiforme
- Contact allergic stomatitis
- Oral ulcers secondary to cancer chemotherapy
- Acute necrotising ulcerative gingivitis

ii. **The patient with recurring oral ulcers**
- Recurrent aphthous stomatitis
- Behçet's syndrome
- Recurrent herpes simplex virus infection

iii. **The patient with chronic multiple lesions**
- Pemphigus
- Sub-epithelial bullous dermatoses
- Herpes simplex virus infection in immunosuppressed patients

iv. **The patient with single ulcers**
- Histoplasmosis
- Blastomycosis
- Mucormycosis
- Syphilitic ulcer
- Tubercular ulcer
- Malignant ulcer
- Traumatic ulcer

2. Classification of Ulcerative, Vesiculo-bullous Lesions based on Etiology

1. **Traumatic**
   - Mechanical irritation
   - Chemical irritants
   - Thermal burns
   - Radiation burns
2. **Infections**
   A. *Viral infection*
   - Herpes simplex infection
   - Herpes zoster
   - Hand-foot-and-mouth disease
   - Herpangina
   - Measles
   - Infectious mononucleosis
   - HIV-AIDS

   B. *Bacterial infection*
   - Syphilis
   - Tuberculosis
   - ANUG
   - Gonorrhea
   - Leprosy
   - Actinomycosis
   - Noma
   - Scarlet fever
   - Diphtheria

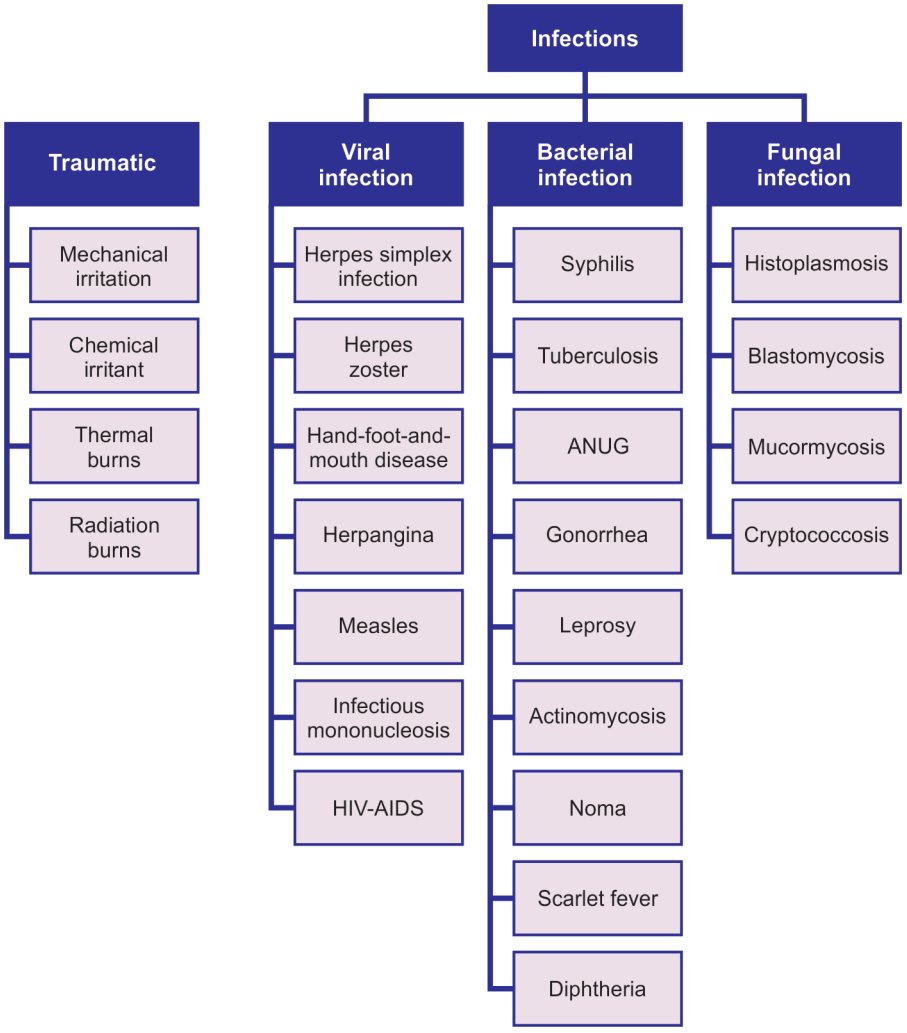


Fig. 5.2: Classification of ulcerative, vesiculobullous lesion based on etiology

C. *Fungal infections*
- Histoplasmosis
- Blastomycosis
- Mucormycosis
- Cryptococcosis

3. **Neoplasms**
- Squamous cell carcinoma
- Malignant melanoma
- Non-Hodgkin's lymphoma

4. **Systemic disorders**

Blood disorders
- Agranulocytosis
- Leukemia
- Aplastic anemia

5. **Nutritional deficiency**
- Scurvy
- Riboflavin deficiency
- Inflammatory bowel disease

6. **Conditions associated with immunologic dysfunction**
- Aphthous ulcers
- Behçet's syndrome
- Reiter's syndrome
- Erythema multiforme
- Lupus erythematosus
- Drug reactions
- Contact allergic stomatitis
- Wegener's granulomatosis
- Chronic granulomatous disease
- Cyclic neutropenia

A. **Intraepithelial vesicles:** The lesion is formed within the epithelium
- *Acantholytic vesicles:* This is because of the breakdown of specialized attachments called the desmosomes, e.g. pemphigus

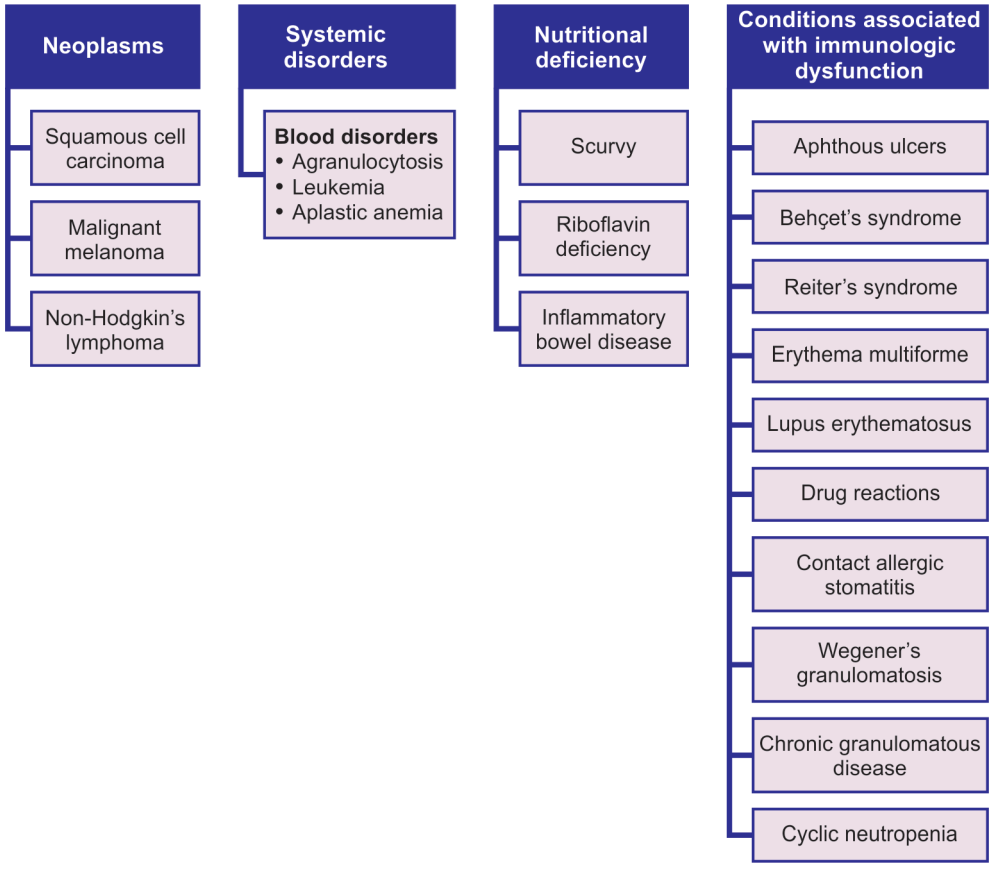


Fig. 5.3: Classification based on various conditions

- *Non-acantholytic vesicles:* It is usually seen in viral infections because of the death or the rupture of the group of cells

B. **Sub-epithelial vesicles:** Lesions formed between the epithelium and the lamina propria, e.g.
- Erythema multiforme
- Pemphigoid
- Epidermolysis bullosa

Acute Multiple Vesiculobullous Lesions

Human herpesvirus infection: Seven types of herpesvirus are known to be pathogenic for humans, with six of them linked to head and neck region.

The Herpesviridae family of viruses contain nine different viruses that are pathogenic in humans. These are:

1. Herpes simplex virus 1
2. Herpes simplex virus 2
3. Varicella zoster virus
4. Cytomegalovirus
5. Human herpesvirus 6
6. Human herpesvirus 7
7. Human herpesvirus 8
8. Simian herpesvirus
9. Epstein-Barr virus

HERPESVIRUS INFECTION

HSV-1 causes infections above the waist and HSV-2 causes infections below the waist. Primary herpes infection is acquired by inoculation of the mucosa, skin and eyes with infected secretions. The virus then travels along the sensory nerve to establish a chronic latent infection in the sensory ganglion.

Two types of HSV: HSV-1 and HSV-2.

HSV-1 affects oral, facial and ocular areas. The pharynx, intraoral sites, lips, eyes and skin above the waist are involved. It can cause:

- Acute herpetic gingivostomatitis
- Herpetic eczema
- Keratoconjunctivitis
- Meningoencephalitis
- Herpes labialis

HSV-2 involves genitalia and skin below the waist. It can cause genital herpes.

Predisposing Factors

- Sunlight
- Trauma
- Menstruation
- Fever
- Immunosuppression
- Decompression of the trigeminal nerve
- Irritation by dental instruments.

Clinical Features

It manifests in two forms: Primary infection and recurrent/recrudescent form

1. **Primary HSV/primary herpetic gingivostomatitis**

Primary infection may be manifested only by a few and mostly the individuals experience a subclinical state. HSV exhibits latency in the trigeminal ganglion, nodosa ganglion of vagus nerve, dorsal root ganglia, sympathetic ganglia and brain. Reactivation of virus by various predisposing factors causes secondary or recurrent infection. The newborn are protected by placentally transferred antibodies and mostly affects children from 6 months to 6 years. Generalized prodromal symptoms like fever, malaise, irritability, headache and cervical lymphadenopathy are mostly accompanied with the infection.



Fig. 5.4: Primary herpes clinical presentation

The vesicles tend to appear in clusters on skin, vermilion border of lips and keratinized oral tissues like palate and gingiva. Thin-walled vesicles (***drops of dew appearance***)

TABLE 5.1: Types of HHV

Type of human herpesvirus (HHV)	*Primary infection*	*Recrudescent lesions in healthy hosts*	*Recrudescent lesions in Immunocompromised hosts*
Herpes simplex virus 1 (HHV-1)	Gingivostomatitis, kerato-conjunctivitis, genital and skin lesions	Herpes labialis ("cold sores" "fever blisters"), intraoral ulcers, kerato-conjunctivitis, genital and skin lesions	Ulcers at any mucocutaneous site, usually large and persistent; disseminated infection
Herpes simplex virus 2 (HHV-2)	Genital and skin lesions, gingivostomatitis, kerato-conjunctivitis, neonatal infections, aseptic meningitis	Genital and skin lesions, gingivosto-matitis, aseptic meningitis	Ulcers at any mucocutaneous site, usually large and persistent; disseminated infection
Varicella-zoster virus (HHV-3)	Varicella (chickenpox)	Zoster (shingles)	Disseminated infection
Cytomegalovirus (HHV-4)	Infectious mononucleosis, hepatitis, congenital disease		Retinitis, gastroenteritis hepatitis, severe oral ulcers
Epstein-Barr virus (HHV-5)	Infectious mononucleosis like hepatitis, encephalitis		Hairy leukoplakia, lympho-proliferative disorders, mucocutaneous ulcers
HHV-6	Roseola infantum (affects children below 3 years), exanthema subitum, otitis media, encephalitis		Fever, bone marrow suppression
HHV-7	Roseola infantum		
HHV-8	Infectious mononucleosis like febrile exanthema		Kaposi sarcoma, lympho-proliferative disorders, bone marrow suppression

affecting any part of the oral mucosa, rupture to form painful, **s**mooth, **r**ound, **s**hallow, **s**ymmetrical and small ulcers with surrounding tissue tags (***moon crater appearance***). The ulcers heal without scarring in 1 to 2 weeks. There is erythematous involvement of marginal gingiva which is characteristic of herpes infection. It may be associated with pharyngitis and there is cervical lymphadenopathy.



Fig. 5.5: Intraoral herpes infection

2. **Secondary or recurrent herpes simplex infection**

Predisposing factors cause reactivation of virus and the patient experiences prodromal symptoms of tingling, burning or pain at the site. Clusters of vesicles form, which often go unreported by the patient, since they soon rupture and coalesce to form large ulcers. Vesicular lesions mostly occur only on the lips and are referred as recurrent herpes labialis (RHL). Sometimes ***clusters of***

smooth, round, shallow, symmetrical ulcers along with marginal gingivitis occur mostly on keratinized mucosa (gingival and hard palate) and is described as recurrent intraoral herpes infection [RIOH].

Recurrent lesions in immunocompromised patients like HIV/malignancy are very severe and large. Infection of the thumbs or fingers may occur in health professionals during treatment of infected patients or as a result of self-inoculation in children with orofacial herpes and is called ***herpetic whitlow***. Recurrences on the digits may result in paresthesia and permanent scarring.

Primary cutaneous herpetic infection in areas of previous epithelial damage is called ***herpes gladiatorum or scrumpox.***

Diagnosis

Clinical examination is most commonly the diagnostic feature of the lesion caused by HSV.

1. **Cytology:** HSV can be identified from the scrapings from the base of the lesions smeared on to the glass slides. These can be stained with Wright's Giemsa (Tzanck test) or Papanicolau staining to demonstrate the characteristic multinucleated giant cells or intranuclear inclusions of herpesvirus.
2. **HSV isolation** by cell culture is the gold standard test for the diagnosis for HSV-1 infections since it grows readily in tissue culture. The advantage of a culture is that it has high sensitivity and specificity and allows for amplification of virions subtyping and testing for sensitivity to antiviral drugs.
   Disadvantage: It needs specialized equipment, is expensive, and may take upto several days for final result.
3. **Recently PCR (polymerase chain reaction)** from swabs has been shown to detect HSV antigen.
4. **Recurrent infection** is associated with rise in IgG antibody titre in acute sera but a fourfold rise is seen in only 5% patients.

Management

RHL is usually self-limiting. Treatment is directed at promoting lesion healing and providing palliation. Adequate food and fluid intake should be ensured. Patients should restrict contact with active lesions to prevent spread and should avoid contact with children. Topical anesthetic agents like dyclonine hydrochloride 0.5 to 1% as oral rinse provides palliation. NSAIDs like ibuprofen can be given for fever.

Antivirals can be given for severe lesions. Topical acyclovir in cream or suspension in a rinse and swallow technique. Systemically acyclovir can be given as 200 mg five times daily in very severe lesions, as in severe immunosuppression.

Penciclovir cream 1% during prodromal stage prodrome and then every 2 hours.

Differential Diagnosis

- **Hand-foot-and-mouth disease:** Hands, feet and oral.
- **Herpangina:** Oropharyngeal and soft palate involvement. It affects children in

TABLE 5.2: Differential features of HSV and EM

HSV	*EM*
SSSR	LIDB
Prodromal symptoms Period: 2 to 8 days	Fever may sometimes accompany No prodromal symptoms
Fever before	Sudden acute explosive onset
Age: Older	Age: Younger <50 years
Etiology: Viral	Hypersensitivity reaction
Marginal gingivitis	No gingival involvement Lips prominently involved
Cervical lympha-denopathy: +nt	–1 nt
No target/ bull's eye lesion	Target/bull's eye lesion
Rx: Antiviral steroids are contraindicated	Rx: Steroids

late summer and early monsoon season on soft palate and facial area with fever and malaise.

TABLE 5.3: Differential features of HSV and HZV

HSV	*HZV*
Lesions do not heal by scarring	Scarring + nt
No osteonecrosis	In severe—osteonecrosis
HSV: 1° and 2° – RHL and RIOH	VZ: 1° Chickenpox and HZ
Bilateral	Unilateral
Prodromal symptoms; fever, malaise	Prodromal symptoms shooting pain, burning paraesthesia and tenderness along the nerve area—C_3, T_5, L_1, L_2
No pain only tingling	No h/o fever
Cytology: Tzanck cells	Non-specific cytology
Rx: Acyclovir 200 mg 5 times a day	Rx: Acyclovir 800 mg 5 times a day

TABLE 5.4: Differential features of HSV and herpangina

HSV	*Herpangina*
Severe	Mild
Non-epidemic	Epidemic
Anterior portion of mouth especially gingiva	Posterior portion
Gingivitis	No gingivitis
Larger SSSR	Smaller lesions Macule, papule, vesicles, ulcers
DNA virus	RNA virus
HSV	A4 coxsackie
Cytology shows multinucleated Tzanck cells	Absence of multinucleated giant cells
Rx: Specific antiviral for HSV	Self-limiting and supportive Rx.

- **Aphthous stomatitis:** No stomatitis, no general systemic symptoms and lesions are less numerous and more oftenly found in adults.
- **Bullous lichen planus:** It is painful condition characterized by large blister on tongue and cheek which rupture and undergo ulceration.
- Erythema multiforme
- Acute necrotizing gingivostomatitis
- Thermal burns
- CMV infection

COXSACKIE VIRUS

Coxsackie virus is a RNA virus and causes following infections

1. Herpangina
2. Hand-foot-and-mouth disease
3. Acute lymphonodular pharyngitis

Herpangina

It is caused by coxsackie group of virus with type 1 through 6, 8, 10, 16 and 22. Herpangina is derived from herpes and angina.

Herpes: Vesicular eruptions and angina: Inflammation of throat.

Infection occurs through ingestion, direct contact, or through droplet spread and multiple cases in a single household are common. It occurs in epidemic with highest frequency from June to October.

Clinical Features

Majorly affected are young children aged 3 to 10 years, and adults are only occasionally affected. Herpangina is chiefly a summer disease, and many children may actually harbor the virus at this time without exhibiting clinical manifestation of the disease. The incubation period is 2–10 days.

Generalized symptoms: Mild and of short duration. It begins with sore throat, cough, rhinorrhea, low-grade fever, headache, sometimes vomiting, prostration, and abdominal pain.

Oral Manifestations

The first oral symptoms of herpangina are sore throat and pain on swallowing. Commonly occur on the anterior faucial

pillars and sometimes on the hard and soft palates, posterior pharyngeal wall, buccal mucosa and tongue. Small vesicles form and persist for short duration which rupture to form crops of ulcers with a gray base and inflamed periphery. The ulcers less painful, although dysphagia may occur.

Symptoms resolve within a few days. Ulcers generally heal within 7–10 days.

Recurrence: Children have been affected several times in one season by infection with different strains of coxsackie virus. A permanent immunity to the infecting strain usually develops rapidly and most adults have neutralizing antibodies against numerous strains.

Laboratory Findings

1. Viral isolation

Differential Diagnosis

1. Herpangina and primary HSV

Treatment

No treatment is necessary, since the disease usually appears to be self-limiting and presents with a few complications.

Hand-Foot-and-Mouth Disease

Hand-foot-and-mouth disease is an epidemic infection, caused by the enterovirus coxsackie A16 and has been reported to be cause less frequently by types A5 and A6, and occasionally even by B2, B6 or enterovirus 71. Despite the similarity in names, it bears no relationship to hand-foot-and-mouth disease, another viral disease with an animal vector.

Clinical Features

It primarily affects young children between age of 6 months and 5 years. It is characterized by the appearance of maculopapular, exanthematous, and vesicular lesions of the skin, particularly involving the hands, feet, legs, arms, and occasionally the buttocks. There is anorexia, low-grade fever and sometimes lymphadenopathy, diarrhea and vomiting.

Oral Manifestations

The oral lesions are usually located on hard palate, tongue and buccal mucosa and sometimes involving the lips, gingival, pharynx and the tonsils. The patient complains of sore mouth with difficulty to eat. This is due to small, multiple vesicular and ulcerative oral lesions that are more numerous than seen in herpangina. The tongue may also become red and edematous.

Laboratory Findings

Intracytoplasmic viral inclusions can sometimes be demonstrated in vesicular scrapings of the lesions. Viral isolates may usually be obtained from vesicular fluid itself. There is rise in acute or convalescent serum antibody titre to coxasackie A16.

Differential Diagnosis

- **Herpetic gingivostomatitis:** Entire oral cavity is affected. No hand and feet involvement.
- **Varicella zoster infection:** Segmental distribution along the anatomical location of nerve (unilateral lesions)
- **Herpangina:** Affect children mostly in late summer and early monsoon and lesions are common on soft palate and facial area with fever and malaise.
- **Allergic stomatitis:** Sudden appearance, no prodromal symptoms with itching and noticeable erythema.
- **Chickenpox:** In addition to intraoral changes, polymorphic exanthematous lesions on the entire body and severe lesions.

Measles (Rubeola, Morbilli)

It is an acute, contagious, dermotropic viral infection, primarily affecting children, and occurring many times in epidemic form.

It is caused by paramyxovirus 'which' belongs to the family paramyxoviridae, which is an RNA virus.

Transmission

Spread of disease occurs by direct contact with a person or by droplet infection, the portal of entry being the respiratory tract.

Epidemiology

It is contagious from first or second day even before the onset of serious illness or appearance of rash.

It is transmitted mainly through respiratory secretions and also through direct contact of droplets.

The incubation period is generally from 8–12 days. It is mainly transmitted in large families, crowded homes and slums.

It is a self-limiting disease in healthy immune competent children, but morbidity and mortality is high in malnourished and immunocompromised individuals.

Pathogenesis

Upon invasion of respiratory epithelium it reaches reticuloendothelial system through blood stream and thereby infects skin, respiratory tract, and other organs.

The invasion of T-lymphocytes and increased levels of suppressive cytokines leads to transient suppression of cellular immunity. Monocyte is mainly infected.

Symptoms show mainly due to the infection of the entire respiratory epithelia and the secondary infection with bacteria.

Viremia develops, but specific antibodies are not developed before the onset of rash. Cellular immunity plays a major role in host defense against measles.

Clinical Features

- **Incubation period:** It is 8 to 10 days.
- **Symptoms:** It is characterized by the onset of fever, malaise, cough, conjunctivitis, photophobia, lacrimation, and eruptive lesions of the skin and oral mucosa.
- **Skin:** It usually begins on the face, in the hair line and behind the ears, and spreads to the neck, chest, back and the extremities. These appear as tiny red macules or papules which enlarge and coalesce to form blotchy, discolored, irregular lesions which blanch upon pressure and gradually fade away in four to five days with a fine desquamation.

Oral Manifestations

Oral lesions are prodromal, frequently occurring two to three days before the cutaneous rash, and are pathognomonic of this disease.

- **Site:** The most common site is on buccal mucosa.
- **Koplik's spot:** Intraoral lesions are called Koplik's spots and occur in 97% of cases. Immune reaction to the virus in the endothelial cells of dermal capillaries plays a role in the development of spots. The spots disappear after the onset of rash.
- **Appearance:** They are small, irregularly shaped flecks which appear as bluish white specks surrounded by bright red margins. These macular lesions increase in number rapidly and coalesce to form small patches. Palatal and pharyngeal petechiae as well as generalized inflammation, congestion, swelling and focal ulceration of the gingival, palate and throat may also occur.

Complications

Measles is a disease which lowers the general body resistance and for this reason often leads to complications.

- Bronchial pneumonia
- Encephalitis
- Otitis media
- Noma

In addition, measles has an immunosuppressive effect through impairment of cell-mediated immunity, so delay in wound healing. It may also cause induction of remission of leukemia and Hodgkin's disease. The disease is rarely fatal except in the case of secondary complications.

Differential Diagnosis

- **Smallpox:** High fever, monoform exanthema.

- **Chickenpox:** Typical exanthema that follows the intraoral lesion. The diagnosis can be established microscopically (blister swab) and virologically.

Control Measures

Measles vaccines are available as single or in combination (MMR).

In Asian countries 'typically' in India, the Edmonton Zagrd (EZ strain) 5 ml of vaccine is given subcutaneously. Studies have suggested the age for vaccination as nine months. A second dose should be given in the form of MMR at 15–18 months for adequate immunity.

Management

- The patient should be isolated, if possible.
- Antiviral drug
- Vitamin A should be given.

Varicella Zoster Virus Infections

Varicella zoster virus (VZV) is responsible for 2 major clinical infections:

1. Chickenpox (Varicella) and
2. Herpes zoster (Shingles / Zona)

Primary infection: 'Chickenpox' is a generalized primary infection that occurs the first time an individual contacts the virus and is accompanied with fever and malaise. It generally occurs in first two decades of life. Lesions begin on trunk and spread centrifugally. It is characterized by intensely pruritic maculopapular rash followed by vesicles which are described as '*Dew Drops on Rose Petals*'. The vesicles turn into scab and crust in 7–10 days.

After the primary disease is healed, VZV becomes latent in the dorsal root ganglia of cranial nerves. There is involvement of C3, T5, L1, L2. The varicella zoster virus may get reactivated due to: Stress, trauma, malignancy, radiotherapy, chemotherapy, immunosuppressive therapy or underlying malignancy.

Herpes zoster virus infection: Herpes zoster is an acute infectious viral disease of extremely painful and incapacitating nature. It is characterized by inflammation of the dorsal root ganglion. It is associated with vesicular eruptions of skin and mucous membrane of the area supplied by the affected sensory nerve. Transmission is through respiratory route.

Clinical Features

It affects adults and there is no sex predilection. Prodromal period of 2 to 4 days in which shooting pain, paraesthesia, burning and tenderness appear along the course of affected nerve. The reason for shooting pain is occurrence of active ganglionitis with resultant neuronal necrosis and severe neuralgia. The pain is present in the area supplied by the affected nerve (dermatome). There may be altered sensation of hypoesthesia or hyperesthesia. Nerves commonly affected are C3, T5, L1, L2 and first division of trigeminal nerve. It may affect motor nerves also. Zoster ophthalmicus results when ophthalmic branch of trigeminal nerve is involved and can lead to acute retinal necrosis.

Unilateral vesicles on an erythematous base appear in clusters, chiefly along the course of nerve and giving picture of a single dermatome involvement. This is called '***zosteriform***' pattern. Thoracic and lumbar dermatome are most commonly involved followed by craniofacial area. Lesions do not cross midline and heal by crustation. ***Zoster sine eruptione or zoster sine herpete*** is the zoster infection without the appearance of dermatological lesion, making diagnosis difficult. Cutaneous zoster infection of the side of tip of nose is termed ***Hutchinson sign***:

Syndrome associated: ***Ramsay Hunt syndrome*** [triad of ipsilateral facial paralysis, ear pain and vesicles on face and ear, loss of taste sensation is typical presentation]. There is involvement of geniculate ganglion of facial nerve.

Oral Manifestations

Varicella zoster virus causing herpes zoster involving 2nd and 3rd divisions of trigeminal nerve leads to oral manifestation. Involvement of 2nd division leads to lesion of midface and upper lip and involvement of 3rd division leads to lesion of lower face and lower lip. It may be found on buccal mucosa, tongue, uvula, pharynx and larynx. Presence of pain, burning, tenderness usually on the palate on one side. After a few days of pain, intact vesicles appear (***drops of dew on rose petals***) which soon rupture leaving tissue tags (***moon crater appearance***) to leave areas of erosion.

HZ has been associated with dental anomalies and severe scarring of the facial skin when trigeminal HZ occurs during tooth formation. Pulpal necrosis and internal root resorption have also been related to HZ. Necrosis of the underlying bone and exfoliation of teeth may be seen in immunocompromised patients. In immunocompromised patients the disease is more severe and last for about three weeks.

Complication

1. **Post-herpetic neuralgia:** Pain of herpes zoster may continue for weeks to months, even after the lesions have healed. The pain that lingers on for more than 120 days even after lesions have healed is called post-herpetic neuralgia. It usually occurs in elderly persons due to inflammation, fibrosis and scarring of the nerve and may cause severe pain which is sharp, stabbing, burning or gnawing in nature.
2. **Tooth extirpation** associated with osteonecrosis.
3. **Involvement** of ophthalamic division leads to corneal scarring and sometimes blindness.
4. **Immunocompromised patient** may experience atypical involvement of multiple dermatome, retinitis, encephalitis and even sometimes bilateral lesions.

Diagnosis and Investigations

1. **Clinical diagnosis:** *Unilateral* lesions along the distribution of the nerve will give clue to the diagnosis.
2. **Cytology:** A simple smear stained with a standard laboratory stain would reveal the presence of multinucleated epithelial cells, it is a rapid method of evaluation.
3. **Fluorescent antibody** stained smears using fluorescein monoclonal antibodies: More reliable than routine cytology.
4. **Viral isolation in tissue culture:** More expensive and results take days rather than hours. It is *the best way to confirm the diagnosis.*
5. **PCR:** Used to detect viral antigen. *Expensive and highly sensitive.*

Treatment

- **Antiviral drugs:** Systemic acyclovir 800 mg 5 times daily / famciclovir (500 mg 3 times daily) for 7 days and topical acyclovir application 5 times daily. Antiviral drugs should be started within 72 hours of onset of infection.
- **Symptomatic treatment:** Antipyretics along with antipruritics (diphenhydramine), aspirin especially in children with viral infection may be associated with development of Reye syndrome causing liver damage.
- To prevent post-herpetic neuralgia prednisone 40 to 60 mg daily for 1 to 2 weeks may be given.
- Gabapentin, topical anesthetics, topical capsaicin 0.025% 4 times a day for treatment of post-herpetic neuralgia.
- Steroid injection can be given in a patient with age more than 60 years, for the treatment of post herpetic neuralgia.
- Antidepressants like amitriptyline, other tricyclic antidepressant and opoid analgesics have been used to minimize painful sequelae of this infection for post-herpetic neuralgia.
- Sympathetic nerve block and chemical and surgical neurolysis for post-herpetic neuralgia.

- Botulinium toxin also been suggested for post-herpetic neuralgia.

Differential Diagnosis

1. **Herpes simplex infection:** Patient will have history of generalized prodromal symptoms (fever, headache, malaise, nausea, vomiting) that precede the lesions by 1 or 2 days. Lesions may not be unilateral (Fig. 5.6)
2. **Herpangina:** Acute infection, posterior part of oral cavity is affected and occur in seasonal epidemics.
3. **Hand-foot-and-mouth disease:** Oral lesions accompanied with maculopapular and vesicular lesions on hand and foot.
4. **Erythema multiforme:** Local lesions and systemic symptoms appear together.
5. **Pemphigus and pemphigoid:** Chronic lesions and do not present unilaterally.

ERYTHEMA MULTIFORME

It is an acute inflammatory mucocutaneous disease that can occur in both the genders at any age. It causes a variety of lesions, hence the name *multiforme*. Initiated either by deposition of immune complexes in thesuperficial microvasculature of skin and mucosa or cell-mediated immunity.

Etiology and Predisposing Factors

It is immunologically mediated disease in which there is deposition of immune complexes in the blood vessels of skin and oral mucosa. It is hypersensitivity reaction to infectious agents or medications.

- **Infections** (mainly HSV and sometimes tuberculosis, histoplasmosis mycoplasma pneumoniae).



Fig. 5.6: Herpes zoster

- **Drugs** (Barbiturates and sulfonamides, phenytoin, carbamazepine, penicillin, anticonvulsants oxicam NSAIDs and allopurinols).
- **Other factors:** Malignancy, vaccination, autoimmune disease, radiotherapy and ultraviolet light.

Immunologic attack by CD8+ cytotoxic effector cells on the 'HSV' expressing keratinocytes. The CD8+ cells induce apoptosis of these keratinocytes causing necrosis in lesions. There may be history of recurrent episodes (in the spring and autumn). Recurrent erythema multiforme (EM) is preceeded with recurrent HSV infection.

Clinical Features

Mostly occurs in young adults (30–40 years) and affects both sexes equally. There may be prodromal symptoms if associated with HSV. There may be a prodrome of fever, malaise, headache, sore throat, rhinorrhea, and cough. These symptoms suggest a viral (especially respiratory tract) infection.

It is characterized by sudden, acute, explosive onset. Skin lesions appear rapidly over a few days and begin as red macules that become papular, starting primarily in the hands moving centripetally towards the trunk area. There are erythematous discrete macules/papules or occasional vesicles and bullae in the skin and oral cavity. It appears as concentric zones with a central blister surrounded by a ring of pale edematous area and another concentric ring of erythematous halo. This lesion appears ***as target, iris or bull's eye.***

PART OF ORAL MANIFESTATIONS

Oral Manifestations

The oral lesions are large ulcers, which are irregular in shape and deep and thus they often bleed. There may be blood tinged saliva. The oral lesions heal without scar formation. It is not characterized by *lymphadenopathy*. **The oral lesions start as bullae on an erythematous base, but intact bullae are rarely seen by the clinician because they break rapidly into irregular ulcers.** There is characteristic ***hemorrhagic crusting*** of the vermillion borders ***of the lips*** it is most common in the lips and gingival involvement is rare. In fully blown clinical cases, lips are extensively eroded and large portions of the oral mucosa are denuded of epithelium.

There is difficulty in eating, swallowing and drooling of blood tinged saliva, within 2 or 3 days lateral lesions begin to crust, healing occurs in 2 weeks.

Types

EM is classified as

- **EM minor** if there is less than 10% skin involvement and there is minimal to no mucous membrane involvement, whereas
- **EM major** has more extensive but still characteristic skin involvement with mucous membrane affected.
- Historically, the fulminant forms of erythema multiforme were labelled as *Steven Johnson Symdrome and Toxic Epidermal Necrolysis* (TEN/Lyell's disease).

SJS is a less severe variant of TENs 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 TENs 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".

Clinical Features

EM is characterized by

- Sudden acute explosive onset.
- Large, irregular deep ulcers with bleeding.
- Characteristic iris/bull's eye lesion.
- Involvement of vermillion border of lip with crustation.
- There may be history of preceding HSV infection

Histopathlogically, most of the lesion is localized in the epidermis presumably this being the site where the drug or its metabolites are bound, with less inflammation in the dermis. The primary cytokine involved is tumor necrosis factor-alpha. There is lymphocytic infiltration in epidermal dermal junction, necrosis of basal keratinocytes and degeneration of basal cell layer.

Differential Diagnosis

The differential diagnosis includes:

- Herpes simplex (Refer to Table 5.5 in HSV)
- Pemphigus vulgaris.
- Benign mucous membrane pemphigoid.
- Bullous lichen planus.
- Recurrent aphthous ulcers

Treatment

- **Mild:** Topical anesthetic mouthwashes, topical steroids and soft/liquid diet.
- **Moderate to severe:** 30–50 mg/day of prednisolone for several days which is then tapered.
- **Recurrent cases:** Dapsone, azathioprine, levamisole or thalidomide.

TABLE 5.5: Differential features of HSV and EM

HSV	*EM*
SSSR	LIDB
• Prodromal symptoms • (Period: 2 to 8 days) • Fever before	• Fever may sometimes accompany (no prodromal symptoms) • Sudden acute explosive onset
• Age: Older	• Age: Younger <50 years
• Etiology: Viral	• Hypersensitivity reaction
• Marginal gingivitis	• No gingival involvement • Lips prominently involved
• Cervical lymphadenopathy: + nt	• –nt
• No target/bull's eye lesion	• Target/bull's eye lesion
• Rx: Antivirals • Steroids are contraindicated	• Rx: Steroids

• Pemphigus	• EM
• Large, irregular ulcers, but no bleeding present	• Large, irregular deep and bleeding
• No prodromal symptoms	• Fever may sometimes accompany (no prodromal symptoms) • Sudden acute explosive onset
• Age: Older	• Age: Younger <50 years
• Etiology: Auto-immune	• Hypersensitivity reaction (drug/HSV)
• No bloody lip crustation	• Lips are extensively eroded and large portions of the oral mucosa are denuded of epithelium. • Lips show bloody crustation
• Chronic	• Acute
• No target/ bull's eye lesion	• Target/ bull's eye lesion
• Rx: Steroids to be given for long duration	• Rx: Steroids for short duration

TABLE 5.6: Differential features of pemphigoid and EM

Pemphigoid	*EM*
• Large irregular ulcers, but no bleeding present	• LIDB
• Prodromal symptoms absent • Chronically present	• Fever may sometimes accompany (no prodromal symptoms) • Sudden acute explosive onset
• Age: Older	• Age: Younger <50 years
• Etiology: Autoimmune	• Hypersensitivity reaction
• Desquamative gingivitis present	• No gingival involvement • Lips prominently involved
• No target/ bull's eye lesion	• Target/bull's eye lesion
• Rx: Steroids are for long term	• Rx: Steroids are for short duration

TABLE 5.7: Differential features of RAS and EM

RAS	*EM*
SSSR (smooth, round, shallow, symmetrical)	LIDB (large, irregular, deep and bleeding)
Acute but recurrent	Sudden acute explosive onset
Age: Older	Age: Younger <50 years
Etiology: Autoimmune, hematological, etc.	Hypersensitivity reaction to a drug or HSV
No lip crustations present	Lips prominently involved
No target/ bull's eye lesion	Target/bull's eye lesion
Rx: Steroids are for short term	Rx: Steroids are for short duration

Antiviral drugs (acyclovir) in HSV associated EM patients.

- Hydroxychloroquine, mycophenolate-mofetil, azathioprine, colchicines, methotrexate, and intravenous immunoglobulin are the other drugs which can be given.

ALLERGIC STOMATITIS

Also known as allergic contact stomatitis, or allergic contact gingivostomatitis. It is basically a type IV delayed hypersensitivity reaction that occurs in susceptible atopic individuals when allergens penetrate skin or mucosa or it is described as an inflammatory reaction of the oral mucosa by contact with irritants or allergens.

Pathogenesis

- Allergens which may be different for different individuals combine with



Fig. 5.7: Healed iris lesions

epithelial derived proteins forming haptens which bind with Langerhans cells in the mucosa, which in turn present the antigen on their surface to T lymphocytes, sensitizing them to that antigen and causing to produce many specific clones. The second time that specific antigen is encountered an inflammatory reaction is triggered at that site of exposure.

- Most common allergens that may cause allergic stomatitis in some individuals include:
  - Cinnamaldehyde, balsam of Peru, peppermint, mercury, gold, pyrophosphates, zinc citrate, free acrylic monomer, and nickel, fluoride and sodium lauryl sulfate.
- These allergens may originate from many sources, including various foods and drinks, chewing gums, toothpaste, mouthwash, dental floss, dental fillings, dentures, orthodontic bands or wires and many other sources.

Allergic oral reactions to systemic drugs are termed stomatitis medicamentosa and those to topical agents like toothpaste, acrylic resin, strongly flavoured foods, cosmetics and topical medications and chemicals are termed stomatitis venenata.

Clinical Features

Clinically it may be characterized by:

- Erythematous plaques
- Vesiculation
- Ulceration and/or hyperkeratosis
- Pain, burning sensation or itchiness

Oral hypersensitivity reaction may be of various forms:

1. Acute ulcer in erythema multiforme
2. Lichenoid drug reaction, a variant of allergic contact stomatitis, brought about by direct contact with the oral mucosa of certain metals in dental restorations.
3. Fixed drug eruptions
4. Plasma cell gingivitis and stomatitis
5. Angioedema of lips
6. Oral allergy syndrome without swelling.

- The features of allergic contact stomatitis are neither clinically nor histopathologically specific, so the diagnosis is usually presumptive and can only be confirmed by resolution of the inflammation after withdrawal or removal of suspected causative allergen.
- When allergic contact stomatitis is suspected but an allergen cannot be identified, *patch testing* is necessary.

Differential Diagnosis

Plasma cell gingivitis resembles desquamative gingivitis in pemphigoid and lichen planus and chronic granulomatous gingivitis.

Allergic contact stomatitis resembles chronic atrophic candidiasis

Treatment

- In persistent cases, topical corticosteroids are treatment of choice.
- For severe cases and extensive lesions, systemic corticosteroid and systemic antihistamines may be indicated.



Fig. 5.8: Healed lesions of EM

ACUTE NECROTIZING ULCERATIVE GINGIVITIS

- Vincent's infection, trench mouth, acute ulceromembranous gingivitis, phagedenic gingivitis, fusospirochetal gingivitis.
- It is an acute, ulcerative lesion of gingiva and periodontal tissues. It was also called trench mouth since it was very frequent

among soldiers living in trenches during World War I.

Etiology and Pathogensis

Plaut and Vincent were the first who reported that ANUG is caused by specific bacteria like fusiform bacilli and spirochetes. Other microbes include Treponema species, *Prevotella intermedia*, *Fusobacteria nucleatum*, *Peptostreptococcus micros* and *Porphyromonas gingivalis Selenomonas* species, and *Campylobacter*. The tissue destruction is most probably result of production of endotoxins or immunological activation and subsequent destruction of gingiva and adjacent tissue.

It has strong association with immune suppression (AIDS), debilitation, smoking, stress, poor oral hygiene and diabetes.

Clinical Findings

ANUG may not be associated with fever and malaise, although lymphadenopathy may be present.

Oral Manifestations

It has rapid and acute onset. The gingiva is tender, erythematous and there is presence of pseudomembrane. The patient may experience excessive salivation, metallic taste, malodor, gingival bleeding. It rapidly develops into extremely painful and erythematous gingiva with scattered punched out crater like ulcerations, usually on the interdental papilla. Linear gingival erythema.

When ANUG progresses to involve mucogingival junction, it is called necrotising ulcerative periodontitis it may be characterized by sloughing of oral mucosa followed by sequestration of exposed necrotic bone. Necrotising ulcerative stomatitis may also accompany the lesions on gingiva.

Complications

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. The overlying skin becomes discolored, and perforation of the skin ensues. The orofacial lesions are cone shaped, with the base of the cone within the oral cavity and the tip at the skin aspect.

Fusobacterium necrophorum is likely to play an important role in the progression of NUP to cancrum oris because this organism produces toxins, leading to extensive tissue destruction. Noma is generally accompanied by fluctuating fever, marked anemia, high white cell count, general debilitation, and a recent history of some other systemic illness, such as measles.

Lab Findings

Secretions from the gingival sulcus grow mixed flora but in particular will be culture positive for *Treponema* species, *Prevotella intermedia*, *Fusobacterium nucleatum*, it may be appropriate to test the patient for HIV or other immunosuppressive conditions, such as blood dyscrasia.

Differential Diagnosis

- **Primary herpetic gingivitis:** It is a viral infection caused by herpes simplex virus.
- **Desquamated gingivitides** (cicatricial pemhigoid, pemhigus vulgaris, lichen planus) no acute course, no bad breath, whitish changes and skin symptoms.
- **Neutropenic ulcers** in patients on cancer chemotherapy may appear similar, leading to extensive ulceration and necrosis of the marginal gingiva and other mucosal surfaces.
- **Chronic periodontitis**

Management

- **First visit:** Instruct the patient to rinse with 3% of hydrogen peroxide H_2O_2 with equal volume of warm water every 2 hrs.
- **Antibiotics:** Amoxycillin 500 mg 6 hrly for 10 days if allergic, erythromycin 400 mg 6 hrly for 10 days and metronidazole 400 mg BD for 7 days.

- Ultra super soft toothbrush with bland dentifrice twice daily.
- **NSAIDs:** Ibuprofen SOS as required for pain relief.
- No scaling and root planing is to be done on 1st visit. Patient is called after 2 days.
- **2nd visit:** Once the acutely painful episodes have resolved, scaling and root planing to completely remove all residual plaque and calculus are indicated. Supragingival scaling is done
- Re-evaluation of patient.
- Patient is called after 5 days.
- **3rd visit:** Plaque control measures—3% H_2O_2 stopped.
- 0.12% chlorhexidine twice a day for 2–3 weeks.
- Scaling and root planing is repeated if required.
- Copious amount of fluid consumption
- Gingivoplasty and periodontal surgery may be necessary to correct gingival and periodontal defects.

B. Recurrent Oral Ulcers

The following present with recurrent ulcer:

1. Recurrent aphthous stomatitis
2. Behçet syndrome
3. Recurrent HSV infection
4. Recurrent oral EM

RECURRENT APHTHOUS STOMATITIS/ CANKER SORES

The term aphthous was given by Hippocrates and was first described by von Mikulicz and Kümmell in 1888. Recurrent aphthous stomatitis (RAS) is a common disorder characterized by recurring ulcers confined to the oral mucosa in patients with no other systemic disorder. It affects 20% of the general population.

Classification:

Lehner has classified it as follows:

Etiology: The major factors include:

1. *Genetic factors:* Genetic factor is considered as the main cause. Patients with RAS have HLA B_{12}, DR2, DR7, CW7 and B5.
2. *Immunological abnormalities:* Humoral and cell-mediated immunity. Research has suggested a relationship between RAS and lymphotoxicity, antibody-dependent cell-mediated cytotoxicity defects in lymphocyte cell subpopulation, and alteration in CD4 to CD8 lymphocyte ratio. There is exaggerated cell-mediated immune response resulting in ulceration of mucosa.
3. Hematological deficiency of iron, folate, vit. B_1, B_{12}
4. *Bacterial cause:* Allergy to *Helicobacter pylori*

Predisposing factors: Stress, anxiety, local trauma, food allergies and menstrual cycle, upper respiratory infections, food allergy. Aphthous like ulcer may be seen in celiac disease.

Clinical Features

They have been classified according to the clinical manifestations.

1. **Recurrent aphthous minor:** Also called Mikulicz ulcer. Most common disease and referred as canker sores. <1 cm, lasting 7–14 days, no scarring
2. **RA major**: Most severe form. Also called Sutton's disease, periadenitis mucosa necrotica recurrens, more than 1 cm, lasting for weeks, often with scarring.
3. **Recurrent herpetiform ulcerations:** Has clusters of ulcerations resembling herpetic lesions. <1 cm, >10 ulcers present continuously

Most common in 2nd decade of life. It is characterized by burning sensation, erythema, generalized edema of oral cavity, with no evidence of lymphadenopathy.

Oral Manifestations

The lesion begins at the oral mucosa with prodromal burning or a sensation of a papule in mucosa 1 to 2 hours before the ulcer develops. During initial period there's localized erythemataus, within hours, a small white papule forms, ulcerates and gradually enlarges over the next 48–72 hours.

TABLE 5.8: Types of RAS

Characteristics	*Major*	*Minor*	*Herpetiform*
Sex incidence	Females more than males	Females more than males	Females more than males
Age of onset	After puberty	Childhood or adolescence	Adulthood
Areas involved	Mostly labial mucosa, soft palate, lips, tongue, faces	Buccal and labial mucosa, tongue, soft palate, pharynx (mucosa not bound to perio-steum)	Non-keratinized movable mucosa
Number of ulcers per episode	1–10	1–5	Many, may even be 100 (may coalesce to form large irregular ulcers)
Size of each ulcer	1–3 cm (large)	3–10 mm (small)	1–3 mm (tiny)
Ulcer duration	2–6 weeks	7–14 days	7–10 days
Rate of recurrence	May be in waves lasting 20 years or more	Episodes per month to one year	Remissions short
Ulcer healing	Scar formation	No scarring	No scarring
Pain	Present	May be severe	May be severe
Prodormal symptoms	Localised itching, burning sensation	Burning, itching, stinging	----------

The lesions are round, symmetrical, shallow, without tissue tags and develop mostly on non-keratinized mucosa like labial and buccal mucosa and tongue. In most severe cases, the ulcers become confluent, and are extremely painful, interfering with speech and eating. Patients experience multiple ulcer over several episodes in a year.

RA major: Develop ulcers that are deep and larger than 1 cm in diameter. Lesions last for weeks to months.

Lab Findings

Lab tests should be done when RAS becomes severe or occurs at the age past 40 years.

With other signs and symptoms

1. Investigations for systemic diseases.
2. Hematological tests for reduced levels of vit. B_{12}, Se. iron, folate, ferritin
3. Biopsy only to differentiate from diseases like Crohn's, sarcoidosis, etc.
4. CD4 counts in immunodeficients

Differential Diagnosis

1. Viral stomatitis, herpetic stomatitis is associated with prodromal symptom of fever, malaise, lymphadenopathy and commonly affects the keratinized mucosa like gingiva and palate.
2. Erythema multiforme
3. Chronic multiple lesions, e.g. pemphigus, pemphigoid: Lesions remain in the same site from week to months in contrast to RAS in which lesions heal and reoccur at a different site.
4. Lupus erythematosus
5. Traumatic ulcers
6. Herpangina
7. Erosive lichen planus

Management

1. Protective emollient such as orabase to promote healing
2. Topical anaesthetics such as benzocaine or lidocaine (for minor lesions) to provide pain relief.



Fig. 5.9: RAS

3. High potency topical steroids such as clobetasol, betamethasone, fluocinonide placed directly over the lesion (shortens the healing time and reduces the size of the ulcer).
4. Amlexanox paste, topical doxycycline, tetracycline can be used with a guaze over a lesion in larger-sized ulcers.
5. Thalidomide, though 1st being the drug of choice, has to be given very cautiously due to its prominent side effects such as phocomelia, teratogenicity, gastrointestinal complaints, DVT.
6. Levamisole has also been found useful to manage the disease.
7. Pentoxyfylline has also been tried in management of aphthous stomatitis.

BEHÇET'S DISEASE (BEHÇET'S SYNDROME)

Behçet's disease (BD) is a multisystem disorder with many possible manifestations. It was first described by Turkish dermatologist Hulusi Behçet. It is also known as Silk route disease and is known to involve areas around Mediterranean sea.

Behçet's disease (BD) presents with triad of symptoms including recurring oral ulcers, recurring genital ulcers, and eye involvement. 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 pro-inflammatory 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

The highest incidence of BD is in young adults around 25 to 40 years of age.

Oral involvement followed by genital lesions and eye involvement (uveitis, retinal vasculitis, vascular occlusion, optic atrophy, and conjunctivitis) mainly comprises the BD. Blindness is a common complication of the disease. Skin lesions resembling erythema nodosum or large pustular lesions occur in patients with BD. It is common for patients with BD to have a cutaneous hyperreactivity to intracutaneous injection or a needlestick **(pathergy).**

BD causes red and swollen joints as in rheumatoid arthritis, but with involvement of small joints.

- In some patients, central nervous system involvements causing brainstem syndrome, involvement of the cranial nerves and neurologic degeneration.
- 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.
- BD in children, which most frequently presents between the ages of 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.
- It is characterized by mouth and genital ulcers with inflamed cartilage and is associated with relapsing polychondritis (MAGIC syndrome).

Oral Findings

The most common site of involvement of BD is the oral mucosa with recurrent

oral aphthous ulcers. Some patients may have large, scarring lesions of major RAS. Lesions may appear anywhere on the oral or pharyngeal mucosa.

Differential Diagnosis

The following diagnostic criteria based on a point system where 4 or more points is strongly associated with BD: Oral, ocular, and genital lesions score 2 points each, while skin lesions, and neurologic and vascular manifestations score 1 point each. Positive pathergy test is an optional test but also scores 1 if positive.

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

Management

Prednisolone, azathioprine and other immunosuppressive drugs have been shown to reduce ocular disease as well as oral and genital involvement.

Pentoxifylline, which has fewer side effects than immunosuppressive drugs or systemic steroids, has also been reported to be effective. Dapsone, colchicine, and thalidomide have also been used effectively to treat mucosal lesions of BD.

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.

CHRONIC ULCERATIVE LESIONS

These lesions are present in the patients from weeks to months and are usually misdiagnosed as recurrent ulcerative lesions. Careful history will reveal that the patient has new lesions which heal and recur at a different site. However, the chronic lesions are present at the same site from weeks to months. The following lesions are included in the list of chronic ulcerative lesions.

1. Pemphigus vulgaris
2. Bullous and cicatricial pemphigoid
3. Erosive oral lichen planus
4. Herpes simplex infection in immunocompromised patients.

Pemphigus

It is an autoimmune disease. Derived from Greek word 'pemphix' means bubble or blister.

Etiology

Autoimmune: Unknown triggering mechanism predispose genes to form autoantibodies.

It occurs more commonly in Ashkenazi Jews in whom a strong genetic association is present with HLA-DR4 and DQ8 haplotypes. In pemphigus there are antibodies against desmoglein 1 and 3 which are adhesion molecules in the epithelium of skin and oral mucosa respectively resulting in acantholysis and intraepithelial bulla formation. PV has been reported coexisting with other autoimmune diseases, particularly myasthenia gravis and thymoma, lymphoma.

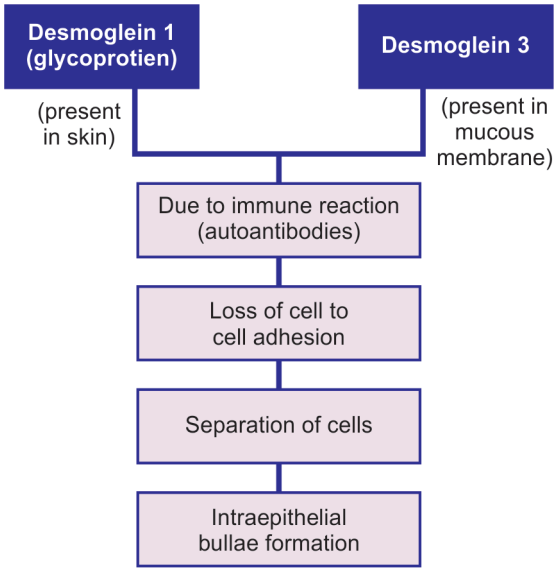


Fig. 5.10: Pathogenesis of pemphigus vulgaris

Drugs like penicillin, phenylbutazone, d-penicillamine and captopril are associated with drug-induced pemphigus.

Pemphigus foliaceous and erythematous affect desmoglein 1, hence there are no oral lesions in these forms.

Pemphigus foliaceous has blisters in superficial granular cell layer, whereas in pemphigus vulgaris it is present deep but above basal cell layer.

Clinical Features

Age: 50 to 60 years

Gender predilection: Male = Female

The subsets of pemphigus include:

- Pemphigus vulgaris
- Pemphigus vegetans (variant of pemphigus vulgaris)
- Pemphigus foliaceous
- Pemphigus erythematosus (variant of foliaceous)
- Paraneoplastic pemphigus
- Drug-related pemphigus

Sites: Oral mucosa and other mucosa involved are those of conjunctiva, cervix, urethra, penis, anus, pharyngeal, laryngeal and esophageal mucosa.

Pemphigus vulgaris has a classical thin-walled bulla which rapidly breaks to form ulcers and continue to extend which eventually leave denuded areas of skin. The bullae soon rupture to form large irregular asymmetric ulcers. Most of the lesions develop very slowly taking weeks to months.: 'Nikolsky sign' is the characteristic sign of disease in which application of lateral pressure on unaffected area results in formation of new lesion and it occurs due to pulling of upper layers of skin from basal layer.

Oral Findings

Oral lesions may be the first sign of the disease and may precede skin lesions. Initially, there is formation of bullae on non-inflammed base which breaks rapidly and there is formation of shallow irregular ulcers.

Thin epithelium layer peels away in irregular pattern and leaves denuded base which continue to extend covering large area. The lesion usually starts on buccal mucosa, gingiva and palate. 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.

Differential Diagnosis

Recurrent aphthous stomatitis: Lesion is severe but heal and recur, but in pemphigus lesion continues to extend, is not round and symmetrical like RAS but is shallow and irregular.

Erythema multiforme: It has an acute sudden explosive onset in contrast to pemphigus which is chronic in onset.

- Mucous membrane pemphigoid
- Erosive lichen planus

Lab Findings

Biopsy: Best on intact vesicles and bullae in <24 hours and is taken from advancing edge of lesion.

Positive Nikolsky's sign

Direct immunofluorescence: Presence of IgG in combination with C3 , IgA , IgM in epithelium of lesion or clinically normal epithelium of lesion.

Indirect immunofluorescent (iif) antibody tests performed on a patient's serum are helpful in distinguishing PV from pemphigoid.

An enzyme-linked immunosorbent assay (ELISA) can distinguish anti-DSG1 antibodies from anti-DSG3 in serum samples. The ELISA test results combined with results from direct and IIF are the most accurate method to confirm a diagnosis of PV.

For the **Ashboe-Hansen sign**, lateral pressure on the edge of a blister may spread the blister into clinically unaffected skin.

Management

It varies according to the severity of disease and rate of progression of disease.

- High dose corticosteroids 1–2 mg/kg/day
- The most commonly used adjuvants are immunosuppressive drugs such as mycophenolate mofetil, azathioprine, cyclophosphamide, and cyclophosphamide pulse therapy.
- When disease is under control, adjunct therapy like immunosuppressants are given to decrease the steroid dose as it causes serious complications.
- But studies show that there is no benefit of adding immunosuppressants to it as it increases the risk of malignancy and blood dyscrasias.
- If patient is having only oral involvement, low dose of prednisolone (topical+systemic) is given for short period.
- Other therapies like parentral gold therapy and dapsone is beneficial.
- May be treated with IV immunoglobulins, extracorporeal photophoresis or plasma exchange.
- Rituximab is presently being used and evaluated as a first line treatment although some studies demonstrated a high rate of infection.

Pemphigus Vegetans

- Uncommon variant of pemphigus vulgaris
- Benign variant because patient has ability to heal denuded areas. It has 2 types:
  - Neumann type (flaccid bullae and erosions)
  - Hallopeau type (pustules)
  - Neumann type is more common, whereas Hallopeau type is less aggressive and has verrucous hyperkeratotic lesions
- Both heal by hyperplastic granulation tissue.

Oral Findings

Gingival lesions may be lace like ulcer with purulent surface on red base or have granular or cobblestone appearance.

Characteristic feature is 'cerebriform tongue' with pattern of sulci and gyri on dorsum of tongue.

Lab Findings

Biopsy: Suprabasilar acantholysis, hyperkeratosis, pseudoepitheliomatous hyperplasia.

Immunofluorescence: Same as pemphigus vulgaris.

Management

Same as pemphigus vulgaris. Pemphigus foliaceus (superficial pemphigus, fogo selvagem).

Paraneoplastic Pemphigus (PNPP)

PNPP is a severe blistering disease, that is, a multiorgan disease associated with an underlying neoplasm, most frequently non-Hodgkin lymphoma, chronic lymphocytic leukemia, or thymoma.

This condition is also referred to as paraneoplastic autoimmune multiorgan syndrome because of the involvement of other systems such as the lungs in particular, and the variable skin findings, namely pemphigus, pemphigoid, EM-like, graft-vs-host disease-like and lichen planus-like.

The damage to the epithelium in PNPP is due to antibodies to desmogleins, plakins and an α-macroglobulin-like-protein.

Pathogenesis

Autoimmune reaction + cell-mediated cytotoxicity with epithelium cells.

Clinical Findings

Age: 7 to 76 years mean age of 60 years

Gender predilection: Male = Female

- Severe blisters and erosions of mucous membrane and skin.
- Has rapid onset and has severe oral and conjunctival lesions.
- The lesions resemble lichen planus, erythema multiforme, inflammatory lesion of drug reaction.
- It may involve respiratory epithelium.

- Nasal ulcers may cause epistaxis.
- In severe cases, the lesions may mimic TEN and often also involve the respiratory epithelium. Unlike EM or TEN, the lesions of PNPP continue to progress over weeks to months.

Oral Manifestations

Common sites are lips, tongue, soft palate, labial, buccal and lingual mucosae.

Lesions are large inflammed, necrotic erosions and are very painful.

The eruptions assume wide variety of morphology like morbilliforme, urticarial, bullous or erythema multiforme like lesions.

Erosions and crustations on vermillion border of lips are typical and is similar to Stevens-Johnson keratinocyte necrosis and acantholyis.

PEMPHIGOID

Pemphigoid is an **autoimmune disease** caused by malfunction of the immune system and results in skin rashes and blistering. It is the most common subepithelial blistering disease and occurs in older adults above 60 years of age.

Etiology

It is an autoimmune disease. Autoantibodies are directed against basement membrane proteins leading to a subepithelial split and subsequent vesicle formation.

Types of pemphigoid:

1. **Cicatricial pemphigoid:** This subepithelial blistering results in ulceration which then undergo scarring.
2. **Bullous pemphigoid**

Cicatricial Pemphigoid

It is an autoimmune disease in which the autoantibodies are directed against one or more components of basement membrane. In this antibodies are directed against basement membrane proteins, causing a subepithelial split resulting in vesicle formation. Antibodies to lamina lucida portion of the basement membrane are present, but antibodies to lamina densa may be sometimes the primary site of involvement. Drugs such as clonidine, d-penicillamine, and l-dopa have been reported as triggers for mucous membrane pemphigoid.

Clinical Features

It is seen in age group of 50–60 years with female predilection. Sites involved are skin, oral, nasal, laryngeal and conjunctival mucosa. Oral mucosa followed by conjunctival mucosa are the most common sites of involvement. Conjunctival involvement leads to scarring and adhesions developing between bulbar and palpebral conjunctiva called symblepharon. **Ocular** lesion includes subconjunctival fibrosis in which the conjunctiva is inflamed and eroded and when it attempts to heal, **scarring occurs** which close the opening of lacrimal glands leading to absence of tears which cause the eyes to become dry and cornea produce keratin causing blindness.

Laryngeal involvement causes pain, hoarseness, difficulty in breathing and may lead to death due to asphyxiation.

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

Skin lesions and genital involvement are also present.

Oral Manifestations

Oral mucosa is involved in more than 80% of cases. Oral lesions begin as **vesicle/bullae** which rupture to form large superficial **ulcerated** area which are **painful** and persist for weeks or months and heals **without scaring.** Gingival lesions are also found**.**

Desquamative gingivitis is the most common manifestation and may be the only manifestation of the disease appearing bright red.



Fig. 5.11: Oral clinical presentation of pemphigus vulgaris

Diagnosis

- **Biopsy** is taken for both routine and immunofluorescent study.
- **Histopathology** shows sub-basilar cleavage.
- **Direct immunofluorescent** technique is excellent for distinguishing cicatricial pemphigoid from pemphigus, it demonstrates positive fluorescence for immunoglobulin and complement in the basement membrane zone in 50–80% of patients. Only 10% patients demonstrate positive *indirect immunofluorescence* for circulating antibasement membrane zone antibodies.
- Using the salt-split skin technique, immunoreactants usually localize to the roof of the split.

Treatment

Topical steroids, intralesional steroids

- Depends on severity of symptoms, lesions confined to oral mucosa are treated by systemic corticosteroids.
- Desquamative gingivitis can often be managed with topical steroids in a soft dental splint that covers the gingiva.
- 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 prescribing it, patient should be tested for G6PD deficiency as it is known to cause hemolysis.

Dapsone is also known to cause hypersensitivity syndrome, idiosyncratic disorder characterized by fever.

Immunosuppressive drugs such as cyclophosphamide, particularly when there is risk of blindness from conjunctival involvement or significant laryngeal or esophageal damage can be used.

Bullous Pemphigoid

It is the most common autoimmune subepithelial blistering condition.

Etiology

Autoantibodies are directed against components of basement membrane. Antigens are referred to as BP antigens, BP 180 and BP 230. The BP antigens are found in lamina lucida regions of basement membrane on the hemidesmosomes of basal epithelial cells. It is seen to be reported with diseases like multiple sclerosis and malignancy, drug therapy like diuretics. This damage to basement membrane results in subepithelial vesicle formation.

Clinical Features

It is seen in old age of about 60–80 years and no sex predilection is seen. The characteristic skin lesion of BP is a tense blister on an inflamed base which ruptures after several days resulting in crust formation which heals without scarring. These lesions are accompanied by pruritis and urticarial plaques involving the scalp, abdomen, extremities, axilla, and groin.

Oral Manifestations

Oral lesions are uncommon which begin as bullae and rupture to form large shallow ulcer. These lesions are less painful and do not involve the mucosa extensively, as in pemphigus. Gingival lesions consist of generalized edema, inflammation and desquamation with localized areas of discrete vesicle formation. 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. Recurrence is more common in BP than mucous membrane pemphigoid.

Diagnosis

- **Biopsy** is done in early stages when clinical differences are not apparent.
- **Histology** shows subepithelial bulla formation.
- **Indirect immunofluorescent** antibody testing demonstrate circulating IgG antibody against basement membrane antigen.
- **Direct immunofluorescent** is more reliable. The salt-split skin test is particularly useful in distinguishing BP from EBA that has IgG antibodies localized to the dermal side of the salt-split skin (floor of the blister).
- **ELISA:** Circulating autoantibodies against pemphigoid antigens BP 180 and BP 230 can be detected in serum samples using ELISA and are useful in both diagnosis and monitoring disease activity.

Differential Diagnosis

- **Erosive form of lichen planus:** The erosive areas and ulcers are surrounded by Wickham's striae.
- **PV:** Unlike the bullae in bullous pemphigoid does not extend at the periphery. The lesions of BP are less painful and do not involve the mucosa as extensively, as in pemphigus. The lesions of BP are shallow as compared to pemphigus. Intact vesicles are rarely seen in pemphigus in contrast to pemphigoid, as they rupture soon because of its intraepithelial location.
- **Subepithelial bullous dermatoses:** MMP, unlike ocular pemphigoid, rarely results in scarring.

Treatment

Topical steroids—clobetasol, betamethasone

TABLE 5.9: Differential features of pemphigus and pemphigoid

Pemphigus	*Pemphigoid*
4 types: P. vulgaris, P. foliaceous, P. vegetans, P. erythematosus	2 types: Cicatriacial pemphigoid, bullous pemphigoid
Intraepithelial bullae formation (antibodies are formed against desmoglein 1 and 3)	Sub-epithelial bullae formation (antibodies to lamina lucida portion of the basement membrane are present)
Oral lesions precede the skin lesions. There is no involvement of conjunctiva	Oral mucosa followed by conjunctival mucosa are the most common sites of involvement. Laryngeal and esophageal, genital involvement has also been seen.
	Desquamative gingivitis is the most common manifestation
Has thin-walled bullae which rupture easily	Has thick-walled bullae which are intact for a period of time compared to pemphigus
Nikolsky sign is positive	Nikolsky sign is not seen
In direct immunofluorescence: Presence of IgG in combination with C3, IgA , IgM in epithelium of lesion or clinically normal epithelium of lesion.	*In direct immunofluorescence:* Positive fluorescence for immunoglobulin and complement in the basement membrane is seen
	Circulating autoantibodies against pemphigoid antigens, BP 180 and BP 230 can be detected in serum samples for bullous pemphigoid



Fig. 5.12: Desquamative gingivitis in patient with pemphigoid

Systemic corticosteroid is usually necessary with lower dose and for short period of time. They may be combined with 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.

ORAL LICHEN PLANUS

Oral lichen planus (OLP) is a common mucocutaneous disease and is thought to affect 0.5–1% of the world's population.

The condition can affect either the skin or mucosa or both.

OLP is considered to be a premalignant condition. Patients with OLP are predisposed to develop oral carcinomas. Ulcerative lesions are suspected to be associated with malignant transformation.

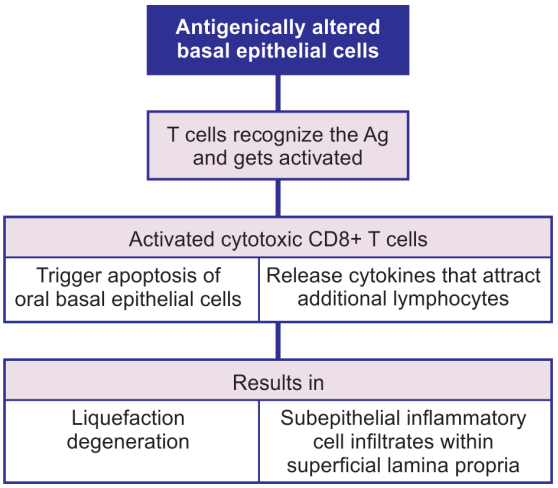
Etiology

- Exact etiology is not known.
- The immune system has a primary role in the development of this disease (immunologically mediated disease).
- Other factors
  - Stress
  - Anxiety

- An association between OLP and hepatitis C virus (HCV). But no comprehensive explanation has been provided regarding this association.

Pathogenesis

Autoreactive T-lymphocytes may be of primary importance for the development of OLP.



Epidemiology

- **Prevalence:** 0.5 – 2.2%
- **Gender:** More common in women than men.
- **Age:** Approximately 55 years

Clinical Manifestations

- Cutaneous lesions in approximately 15% of patients with OLP.
- Skin lesions are classically described as of pruritic, papular, polygonal, plaque, purple. They may be erythematous to violaceous papules that are flat topped.
- **Predilection sites:** Trunk and flexor surfaces of arms and legs. The patient reports relief following intense scratching of the lesions, but trauma may aggravate the disease, which is referred to as a Koebner phenomenon. Lichen planus involving genital mucosa, esophageal mucosa and nails have been reported.

Oral Manifestations and Clinical Classification

- Reticular
- Papular
- Plaque-like
- Bullous
- Erythematous
- Ulcerative/erosive

When mild degree of inflammation is present, it stimulates the epithelium to produce hyperkeratosis, whereas more intense inflammation leads to deterioration of epithelium leading to atrophic, erosive and ulcerative forms of lichen planus.

1. **Reticular form:**
   - Characterized by fine white lines or Wickham's striae and striae may show annular patterns. Found in all regions of the oral mucosa, most frequently observed bilaterally in the buccal mucosa.
   - It may be asymptomatic.
   - Reticular OLP can sometimes be observed at the vermilion border
2. **Papular type**
   - Initial phase of the disease
   - Characterized by small white dots, which in most occasions intermingle with the reticular form.
3. **Plaque type**
   - Homogenous well-demarcated white plaque that occurs in conjunction with striae. It resembles homogenous leukoplakia.
   - It usually presents on dorsum of tongue and patient may experience a feeling of roughness.
4. **Bullous form:** It is usually rare and appears as bullous structures surrounded by a reticular network.
5. **Erythematous OLP**
   - Characterized by a homogenous red area and striae are frequently seen at the periphery of the lesion.
   - Lesions may occur on attached gingiva without any papules or striae and presents as a desquamative gingivitis.

6. **Ulcerative lesions**
   - Most disabling form of OLP in which erythematous zone is surrounded by white striae.
   - Patients complain of severe burning sensations and discomfort on food intake.

Diagnosis

Pathognomonic Wickham's striae help to establish a correct clinical diagnosis. Desquamative gingivitis, plaque-like, erythematous, bullous, or ulcerative forms may exist together with the Wickham's striae.

Biopsy required for an accurate diagnosis of erythematous type of OLP .

Histopathology

1. Areas of hyperparakeratosis or hyperorthokeratosis, often with a thickening of the granular cell layer and a saw: toothed appearance to the rete pegs.
2. "Liquefaction degeneration" or necrosis of the basal cell layer.
3. An eosinophilic band seen just beneath the basement membrane, containing fibrin covering the lamina propria.
4. A dense subepithelial band-shaped infiltrate of lymphocytes and macrophages is also characteristic of the disease.

Management

- Since the etiology behind OLP is unknown, thus all the treatment strategies are aiming at reducing or eliminating symptoms.
- Topical steroids like triamcinolone acetonide 0.1% ointment and clobetasol can be used as the primary therapeutic choice for symptomatic OLP. Topical steroids are used as a mouth rinses or a gel. It can be used by "swish and spit out" method. Apply the drug 2 or 3 times a day during 3 weeks followed by tapering during the following 9 weeks until a maintenance dose of 2 to 3 times a week is reached. When potent topical steroids are used, a fungal infection may emerge, and a parallel treatment with antifungal drugs may be necessary when the number of applications exceeds once a day and antifungal treatment itself may result in significant improvement of symptoms and clinical features. For desquamative gingivitis, steroid gels in prefabricated plastic trays may be used for 30 minutes at each application to increase the concentration of steroids in the gingival tissue.
- Several other topical drugs including calcineurin inhibitors like topical tacrolimus 0.1% ointment, topical cyclosporine and retinoids form the second line of treatment.
- Systemic steroids are used to control symptoms from recalcitrant lesions. 1 mg/kg daily for 7 days followed by a reduction of 10 mg each subsequent day.
- Since half of OLP lesions exhibit candidal infection, antifungal treatment may be used before treatment with steroids. Oral hygiene should be optimized prior to the beginning of steroid treatment.
- Retinoids, levamisole, dapsone, mycophenolate mofetil, cyclosporine, low dose heparin (enoxaprin), efalizumab are other treatment modalities which can be given in recalcitrant cases of oral lichen planus.
- Ultraviolet phototherapy, PUVA, photodynamic therapy and lasers are the non-pharmacological methods for treatment of oral licen planus.
- Relapses are common, and the general approach should be to use steroids at the lowest level to keep the patient free of symptoms.

Differential Diagnosis

1. Lichenoid contact reactions
2. Lichenoid reactions of graft-versus-host disease (GVHD)
3. Oral lichenoid drug eruptions
4. Discoid lupus erythematosus (DLE)
5. Systemic lupus erythematosus (SLE)
6. Homogenous oral leukoplakia (d/d of plaque-type)
7. Mucous membrane pemphigoid (d/d of erythematous type)



Fig. 5.13: Lichen planus involving tongue



Fig. 5.15: Discoid lichen planus



Fig. 5.14: Lichen planus involving gingiva



Fig. 5.16: Plaque type lichen planus



Fig. 5.17: Erosive lichen planus

SINGLE ULCERS

Traumatic Ulcers

Most common cause of single ulcers is due to trauma. It is a frequently encountered ulcerative lesion of mouth.

Causes

- **Direct physical/mechanical:** Acute bite injuries, sharp tooth (most common cause), ill-fitting prosthesis, overzealous toothbrushing, oral piercing.
- **Thermal:** Electrical burns, burns on palate from ingesting hot foods and beverages, reverse smoking, hot instrument (iatrogenic)
- **Chemical:** Placing noxious and caustic substances directly on mucosa such as silver nitrate, phenol, acetylsalicylic acid. Sucking on or chewing medications formulated to be swallowed (such as aspirin or oral bisphosphonates) may also lead to severe oral ulcers. Prolonged contact of methacrylate monomer on the mucosa may also lead to necrosis of the mucosa.
- A positive history about inciting agent helps in confirmation of etiologic agent.

Clinical Features

It can occur in persons of any age, with equal frequency in both the sexes. Appearance depends on the site of injury, the nature and severity of trauma and the degree of secondary infection present. It may persist for a few days and may last for weeks. May be crater-like, generally the result of repetitive trauma over a prolonged period, thereby preventing healing.

Oral Findings

Traumatic ulcer usually present as single, irregular ulcer in proximity of the offending sharp tooth or clasp of dental prosthesis and usually present on lateral borders of tongue. It may persist from many days to weeks. The ulcer may conform to the shape of etiologic agent and may be surrounded by a whitish keratotic area. Sometimes, trauma from natal teeth may present with ulcer in the sublingual area of neonates. These are described **as Riga-Fede's ulcer**.

Electrical burns in particular are caused by high heat, are generally fairly extensive, involve the lips, and are generally seen in young children and toddlers.

Burns from hot foods and beverages are generally small and localized to the hard palatal mucosa or lips and are usually seen in teenagers and adults, usually presents as an area of tenderness and erythema that develops into ulcers within hours of the injury.

Differential Diagnosis

A positive history about inciting agent will help to confirm the diagnosis.

- **Tubercular ulcer:** Undermined flabby borders, usually painless.
- **Primary syphilic lesion:** Painless indurated edema and lymph swelling.
- **Dystrophic ulcer:** Rare ulceration caused by deficient blood supply due to local anesthesia.
- **Malignant ulcer**
- **Recurrent intraoral** herpes infection of palate may resemble thermal burn.

Lab Findings

- Culture may be needed if the areas do not heal well or if suppuration develops, suggesting a secondary bacterial infection.
- A biopsy should be performed if the ulcer does not heal within a few weeks.

Management

- Pain control can be achieved with topical anesthetics (such as viscous lidocaine). Topical steroids or intra-lesional steroid injections may be useful.
- Electrical burns are deep and more extensive, and healing results in scarring and contracture.
- Smaller lesions caused by less severe thermal or chemical injury heal on their own once the irritant is removed.

- Antibiotics may be necessary to prevent a secondary infection.
- Chlorhexidine mouthwash or topical local anesthetics to relieve symptoms of pain.

ULCERS CAUSED BY FUNGAL INFECTIONS

Fungal infections are common and a variety of environmental and physiological conditions can contribute to development of fungal infections. Inhalation of fungal spores or localized colonization of the skin may initiate persistent infections; therefore, fungal infections often start in the lungs or on the skin. Fungal infections are usually confined to the subcutaneous tissues, but in rare cases they become systemic and produce life-threatening disease. Individuals with weakened immune systems, with HIV / AIDS, under steroid treatments, chemotherapy and uncontrolled diabetes tend to develop fungal infections.

Histoplasmosis

It is caused by fungus *Histoplasma capsulatum*, a dimorphic fungus. Primary infection which is mild, from inhaling dust contaminated with droppings, cause pulmonary disease that heals to leave fibrosis and calcification similar to TB. It occurs in immunocompromised states and may be the first sign of AIDS.

Oral Manifestations

Oral involvement is usually secondary to pulmonary involvement. It begins as an area of erythema that becomes a papule and eventually a painful, indurated, granulomatous ulcer appearing on palate, gingiva or tongue. It often resembles squamous cell carcinoma. It is accompanied with cervical lymphadenopathy.

Lab Diagnosis

A rapid diagnosis may be made with the use of a smear of the lesion stained with methenamine silver or a biopsy of the lesion stained with periodic acid–Schiff or methenamine silver, which will reveal the presence of the fungi within granulomas. Cultures should be performed on a portion of tissue removed during the biopsy. Diagnosis of disseminated histoplasmosis occurs by antigen detection via enzyme immunoassay in serum and urine, antibody detection via immmunodiffusion, identification of histoplasma DNA via various PCR techniques.

Differential Diagnosis

Ulcers present for weeks or months may represent other lesions of infectious etiology like deep fungal infections, tuberculous ulcer, traumatic ulcerative granuloma, squamous cell carcinoma, lymphoma, or other malignancy.

Management

- Intravenous amphotericin B
- Itraconazole in AIDS patient
- Systemic ketoconazole for 6 to 12 months in immunocompetent individuals

Blastomycosis

It is caused by blastomyces dermatitidis. Inhalation causes primary pulmonary infection that is acute self-limiting and remains asymptomatic, in some cases it is normal inhabitant of soil so it is more commonly associated with farmers and construction workers. And is not commonly associated with HIV infection.

The skin lesions (usually on exposed surfaces) start as subcutaneous nodules, slowly progressing to well-circumscribed indurated ulcers. If the infection goes untreated, the signs and symptoms may mimic TB and include dyspnea, weight loss, and production of blood-tinged sputum.

Oral Manifestations

Oral lesions are rarely the primary site of infection. Oral lesions are non-specific, painless, verrucous ulcer with indurated borders and is often mistaken for squamous

cell carcinoma. Other oral lesions include hard nodules and radiolucent jaw lesions.

Diagnosis

PCR, antibody identification through enzyme immunoassay, biopsy, and culture on Sabouraud agar.

Management

- Itraconazole therapy is used to manage mild cases of blastomycosis. More advanced cases infections are treated with amphotericin B
- Ketoconazole
- Fluconazole

Mucormycosis (Phycomycosis, Zygomycosis)

It causes opportunistic infections in debilitated patients, patients with decreased host resistance, those with poorly controlled diabetes or hematologic malignancies, post-solid-organ transplantation cancer chemotherapy or immunosuppressive drug therapy. It may occur as a pulmonary, gastrointestinal, or rhinocerebral infection.

Clinical Features

The two most common forms of mucormycosis are pulmonary / sinus and cutaneous. In pulmonary / sinus mucormycosis, spores are inhaled from the environment. It is characterized by arterial invasion and a fulminant course, frequently resulting in death. The hallmark of infection is the formation of emboli with resulting necrosis of involved tissue.

Oral Findings

The most common signs are ulceration of palate, which results from necrosis due to invasion of palatal vessels. Lesions are large and deep, causing denudation of underlying bone. Ulcers have been reported on gingiva, lip and alveolar ridge. More advanced disease with ulcer and palatal perforation may lead to invasion of maxillary sinus and involvement of brain.

Lab Diagnosis

- Biopsy for culture and direct examination must be performed. The histopathology shows necrosis and nonseptate hyphae, which are best demonstrated by a periodic acid–Schiff stain or the methenamine silver stain
- PCR

Management

- Control the predisposing factors such as diabetes.
- Surgical debridement of infected area.
- Systemic administration of amphotericin B

Tuberculous Ulcer

Tuberculosis is an infectious granulomatous disease caused by acid-fast bacilli *Mycobacterium tuberculosis*. Although, oral manifestations of tuberculosis has a rare occurrence, but it has been considered to account for 0.1–5% of all the TB infections. These lesions are usually secondarily inoculated with infected sputum or due to haematogenous spread. Nowadays, oral manifestations are re-appearing as a consequence of the outbreak and emergence of drug-resistant TB. Dental identification of the tuberculosis lesions have the potential of serving as an important aid in the first line of control for this dangerous and often fatal disease.

The following symptoms are common: Chronic cough, moderate fever, night sweats, fatigue, decreased appetite, and weight loss.

Oral Manifestations

Lesions may occur in the oral tissues and the neck lymph nodes. The latter is termed scrofula.

Tongue is the most commonly affected followed by palate, lips, buccal mucosa, and gingiva. It may be preceded by an **opalescent vesicle or nodule**, a result of caseation necrosis which breaks down into an ulcer which is usually superficial or deep and painful. Tubercular ulcers are generally

oval in shape but their coalescence may give an irregular crescentic border.The edge of the ulcer is **undermined** with minimum induration. It tends to be increased slowly in size. The disease spreads in and destroys the subcutaneous tissue faster than it destroys the skin. The overhanging skin is thin, friable, reddish blue and unhealthy.The mucosa is **inflamed** and **oedematous.**

Base: The base of ulcer is pale with scanty granulation tissue.

Floor: The floor of the ulcer is watery / apple jelly appearance.

Differential Diagnosis of Tubercular Ulcer of Oral Cavity

- **Syphilitic ulcer:** Primary lesion is harder and spirochetes are found.
- **Traumatic ulcer:** Short duration and history of trauma.
- **Sarcoidosis:** Tuberculin test negative, the granuloma of sarcoidosis are of non-necrotizing type.
- **Lupus erythematosus:** Histology, causative agent tests negative, skin changes.
- **Leukaemia:** Immature WBCs, prolonged bleeding and clotting time.

Laboratory Diagnosis

The diagnosis of latent disease is initiated by performing a tuberculin skin test (TST) on the forearm with purified protein derivative, a mycobacterial antigen. If a red welt forms within 72 hours, the patient is considered to have been exposed to *M. tuberculosis*. A chest radiograph often reveals pulmonary involvement. Confirmation of active TB involves collecting patient sputum to look for the infecting organism.

Treatment

The patient diagnosed with a latent TB infection is typically treated with one of the following regimens from four to nine months: Isoniazid, isoniazid plus rifapentine, or rifampicin.

Malignant Ulcers

Ulcer can be defined as break in the continuity of the covering epithelium of the skin or mucous membrane. Malignant ulcers include squamous cell carcinoma, basal cell carcinoma, malignant melanoma.

Etiology

- Smokeless tobacco and alcohol
- Genetic changes
- Immunosuppressed patient
- Exposure to UV light
- Chemical and physical irritants, viruses, and hormonal effects

Clinical Features

- Male predominance
- Age above 60 years
- Site = Lower lip, anterior floor of the mouth, lateral borders of the tongue.
- Appearance = Red, white or mixed red-white lesions, change in surface texture, presence of mass or ulcerations
- Ulcers are irregular, indurated with raised everted edges. It may be accompanied with a proliferative growth.
- Superficial and deep lymph nodes affected, enlarged and firm to hard on palpation. There may be pain, discomfort and trismus accompanied with the ulcer.

Differential Diagnosis

- Major aphthous ulcers
- Long standing ulcers in herpes
- Basal cell carcinoma
- Primary syphilitic lesion
- Verrucous carcinoma

Treatment

Surgery and radiation

Syphilitic Ulcers

It is also called lues, caused by *Treponema pallidum*. There are three stages of infection in syphilis and sometimes may develop at the site of inoculation in the oral cavity.

Etiology

- Sexual contact
- Maternal transmission

Primary Syphilis

- **Site:** Most frequently on genitalia, lip, tongue, nostrils and to some extent gingiva and tonsillar area.
- The lesion is called chancre which is highly infectious. The chancre is painless, necrotic, covered with grayish white membrane, and may be painful due to secondary infection. The ulcers are characterized by rolled out borders and lymphadenopathy.

Secondary Syphilis

Commences six weeks after primary syphilis

- **Site:** Tongue, soft palate, cheek, tonsils, buccal mucosa
- **Appearance:** Slightly raised, greyish white, glistening patches on mucous membrane called 'mucous patches'. The mucous patch presents as thickened whitish plaques with necrosis and sloughing. The lesions are accompanied with fever, lymphadenopathy, weight loss.
- **Snail track ulcers:** Mucous patches coalesce to form snail track ulcers. The leions in secondary syphilis are described as interstitial glossitis or leutic glossitis. These lesions constitute a premalignant condition.

Patients with syphilis who are not treated in the secondary stage will develop tertiary syphilis which can cause complications including paralysis and dementia.

Tertiary Syphilis

Site: The lesion in tertiary syphilis is called gumma. It most commonly affects hard palate, soft palate, lips and tongue. Gumma manifests as painless, firm nodular mass with deep, punched out borders.

Gumma begins as small, pale, raised area of mucosa that ulcerate and rapidly progress to large zone of necrosis and denudation of bone in case of palate and may lead to oro-nasal fistula.

Congenital Syphilis

It is characterized by:

Hutchinson's incisors: Screw driver shaped incisors and mulberry molars. In late congenital syphilis, over two years of age, a number of complications develop including Hutchinson's notched incisors, mulberry-shaped molar teeth, corneal keratitis, deafness, frontal bossing, saddle nose, hard palate defects, and swollen joints.

Diagnosis

1. Darkfield microscopy to identify organisms from lesion
2. *Antibody to Treponema:* The more specific fluorescent treponemal antibody absorption test.
3. Venereal disease research laboratory (VDRL) test

Differential Diagnosis

- **Primary syphilis**
  - Ruptured vesicles of herpes simplex
  - Traumatic ulcer
- **Secondary syphilis**
  - Aphthous ulcers
  - Erythema multiforme
  - Lichen planus
  - Malignant ulcer
  - Tuberculous ulcer

Treatment

- Antibiotics

Cytomegalovirus Infection

CMV causes an infectious mononucleosis like disease especially in the immuno-compromised patient such as HIV, organ transplant. CMV remains latent in connective tissue cell and causes vascular inflammation. It is associated with mild fever, lymphadenopathy and splenomegaly. It results in CMV retinitis and CMV enteritis in HIV patients.

Oral Manifestations

In immunocompromised patient CMV is known to cause single large ulcer and rarely multiple which are painful and last for weeks to months.

Differential Diagnosis

- Tuberculous ulcer
- Ulcer caused by fungal infection
- Malignant ulcer
- Traumatic ulcerative granuloma

Treatment

Topical anaesthetics and antiviral drugs

FREQUENTLY ASKED QUESTIONS

1. Write clinical features, differential diagnosis and management of the following:
   a. Herpes simplex
   b. Herpes zoster
   c. Recurrent aphthous ulcers
   d. Pemphigus
   e. Erythema multiforme
2. Define macule, papule, vesicle, bullae

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Chapter 6

Red and White Lesions

INTRODUCTION AND EPIDEMIOLOGY

The oral cavity is a complex anatomical space delimited by structures of different nature and functions. The oral mucosa covering the different oral structures and areas has a different role and may be affected by a plethora of pathologic conditions of variable etiology and significance. Oral soft tissue lesions result from histologic changes occurring at a molecular and microscopic level that affect the oral epithelium and the underlying connective tissue. These changes may lead to a color change of the mucosa, causing red and/or white appearing lesions of the oral cavity.

A white appearance of the oral mucosa may be caused by a variety of factors including an increased production of keratin (hyperkeratosis), an abnormal, benign thickening of stratum spinosum (acanthosis), intracellular and extracellular accumulation of fluid in the epithelium, necrosis of the oral epithelium or microbes, particularly fungi, that produce a whitish pseudomembranous appearance. A red lesion of the oral mucosa may develop as a result of atrophic epithelium, characterized by a reduction in the number of epithelial cells or increased vascularization.

Classification

The red and white appearing lesions on the oral mucosa have a multifactorial etiology. Based on the underlying pathology and etiology, these lesions may be classified as

1. **Potentially malignant disorders**
   - Oral leukoplakia
   - Erythroplakia
   - Actinic cheilitis (cheilosis)
   - Actinic keratosis
   - Oral submucous fibrosis.
2. **Immunologically mediated diseases**
   - Oral lichen planus
   - Drug-induced lichenoid reactions
   - Lichenoid reactions of graft-versus-host disease.
   - Lupus erythematosus.
3. **Infectious disease**
   - Oral candidiasis
   - Hairy leukoplakia
4. **Allergic reactions**
   - Lichenoid contact reactions
   - Reactions to dentifrice and chlorhexidine
5. **Toxic reactions**
   - Reactions to smokeless tobacco
   - Smokers palate.
6. **Reactions to mechanical trauma**
   - Morsicatio
   - Frictional keratosis

7. **Others**
   - Benign migratory glossitis
   - Leukoedema
   - White sponge nevus
   - Pachyonychia congenita
   - Dyskeratosis congenita

POTENTIALLY MALIGNANT ORAL DISORDERS

Oral cancer is one of the most common malignancies in southeast Asia, accounting for 30–40% of all malignancies in India. The survey burden of cancer and their variations across Indian states showed that cancer of the oral cavity and lip accounts for 7.2% cases and was identified as a leading cause of death. SEER data has demonstrated an increase in the incidence of tongue cancer in young individuals (age less than 40 years) from 3–6% over time. The complex association between poverty, education, reduced access to treatment, low prioritization of the disease and the specific cultural and social habits are the main reasons for increased incidence of oral cancer in the Indian population.

Many oral malignancies develop from the premalignant disorders affecting the oral cavity including leukoplakia, erythroplakia, lichen planus, etc. Early detection of premalignant lesions can improve the prognosis and is well proved as an effective aid in disease prevention. The prevalence of potentially malignant disorders varies by geographic location and population ranging from 1 to 5% despite all limitations. Most affected patients are middle aged or elderly men but trends have shifted and men:women ratio has reduced considerably with time. This trend is thought to be the reflection of general acceptance of habits of smoking and drinking by both the sexes. Most commonly affected sites in general are the buccal mucosa, lower gingiva, tongue, floor of the mouth.

In 1978, WHO classified precancer into precancerous lesions and precancerous conditions.

- A precancerous lesion is a morphologically altered tissue in which oral cancer is more likely to occur than its apparently normal counterpart.
- A precancerous condition is a generalized state associated with a significantly increased risk of cancer.

The current Working Group of WHO in its latest monograph (2005) did not favour the subdividing of the precancer to lesions and conditions and the consensus view was to refer to all clinical presentations that carry a risk of cancer under the term 'potentially malignant disorders' to reflect their widespread anatomical distribution.

A proposed definition for potentially malignant oral disorder is:

"It is a group of disorders of varying aetiologies, usually tobacco; characterized by mutagen-associated, spontaneous or hereditary alterations or mutations in the genetic material of oral epithelial cells with or without clinical and histomorphological alterations that may lead to oral squamous cell carcinoma transformation".The suggested definition depicts the molecular nature of the oral potentially malignant disorders along with the possible presence and absence of clinical and histomorphological alterations.

Oral Leukoplakia

Definition

In 1978, WHO defined oral leukoplakia as"A white patch or plaque that cannot be characterised clinically or pathologically as any other disease." The term leukoplakia is unrelated to presence or absence of epithelial dysplasia.In a monograph by WHO (1977) the phrase any other definable disease was replaced by other "definable lesion''. No clarification was provided for this change. In 2005, WHO changed the definition of oral leukoplakia to "A white plaque of questionable risk having excluded other known diseases or disorders that carry no increased risk for cancer". Leukoplakia has been considered a potentially malignant or

precancerous disease and not a lesion since it is well known that cancer development not only occurs in or close to a leukoplakic patch but can also occur at any other site of the oral cavity. A combination of 1978 and 2005 WHO definition has led to the following text:

"A predominantly white patch or plaque that cannot be characterized clinically or pathologically as any other disorder. Oral leukoplakia carries an increased risk of cancer development either in or close to the area of leukoplakia or elsewhere in the oral cavity or the head and neck region."

The diagnosis of leukoplakia mainly denotes that the mucosa is irritated by mechanical, chemical, or galvanic means and the mucosa is trying to adapt to the noxious stimuli by undergoing hyperkeratinisation of its surface.

Classification

Traditionally, two major clinical types of oral leukoplakia (OL) are recognized: Homogenous and Non-homogenous. Figure 6.1 illustrates a simple classification of leukoplakia.

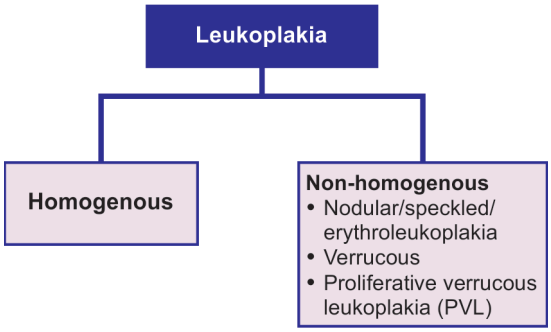


Fig. 6.1: A simple classification of leukoplakia

The homogenous type is characterized by a thin, flat, and homogenous whitish appearance giving the lesion a cracked mud appearance.

The non-homogenous type consists of:

- *Nodular/speckled:* Red and white (erythroplakia)
- *Verrucous*
- *Proliferative verrucous leukoplakia (PVL):* This was introduced by Hansen et al. It may start as simple keratosis at one end to invasive carcinoma at the other.

Epidemiology: Almost all leukoplakias in India occur in tobacco users. A definitive dose—response between leukoplakia and various forms of tobacco use has been demonstrated particularly as smoking.

Etiology

The etiology of oral leukoplakia is multifactorial.

1. **Tobacco:** The habit of tobacco smoking/chewing is associated with leukoplakia. There is a dose response relationship between oral leukoplakia and tobacco. It has been observed that reducing or cessation of tobacco use may result in the regression or disappearance of oral leukoplakia. The smokeless tobacco habit often leads to a clinically distinctive white plaque called "tobacco pouch keratosis" which is not a true oral leukoplakia.
2. **Alcohol:** Alcohol along with tobacco does have a synergistic effect in oral leukoplakia as in cancer. People excessively using mouthrinses with an alcohol content greater than 25% may have greyish buccal mucosal plaques but not true leukoplakia.
3. **Sanguinaria:** Toothpastes or mouthrinses containing sanguinaria may lead to the development of true oral leukoplakia. Sanguinaria associated oral leukoplakia are located in maxillary vestibule or on the alveolar mucosa of the maxilla. The lesions may persist even after the cessation of the use of product.
4. **Ultraviolet rays:** UV rays are causative factor for oral leukoplakia of lower lip vermillion. Immunocompromised persons, especially transplant patients, are prone to the development of leukoplakia and squamous cell carcinoma of lower lip vermillion.
5. **Candida:** Candida can colonize the superficial epithelial layers of the oral mucosa often producing a thick granular

plaque with a mixed white and red color. The term 'candidal leukoplakia or hyperplastic candidiasis' has been used to describe such lesions and biopsy may show hyperplastic histopathological changes. It is not known whether Candida produces dysplasia or secondarily infects altered epithelium. There is reduction or disappearance of these lesions after the use of antifungal therapy.

6. **Human papillomavirus (HPV):** HPV subtypes 16 and 18 have been identified in some oral leukoplakias. HPV 16 has been shown to induce dysplasia like changes in normally differentiating squamous epithelium, particularly with exophytic verrucous leukoplakia.
7. **Trauma:** Several keratotic lesions which were until recently considered as variants of oral leukoplakia are now considered as precancer. *Nicotine stomatitis* is a generalized white palatal hyperkeratotic response to heat generated by tobacco smoking (pipe smoking) rather than a response to carcinogens within smoke. *Frictional keratosis* is a chronic mechanical irritation that can produce a white lesion similar to true oral leukoplakia. Such a lesion can be reversed after elimination of the trauma. Traumatic lesions such as linea alba, morsacatio, toothbrush and gingival abrasion along with denture trauma or masticatory keratosis should be differentiated from groups of precancer.
8. **Nutritional deficiency:** It has been observed that serum levels of vitamins A, B_{12}, C, beta carotene and folic acid significantly decrease in Indian patients of leukoplakia.

Clinical Features

The onset of oral leukoplakia usually starts after the age of 30 years. However, younger age groups between 20 and 30 years have also been reported. Peak incidence is above the age of 50 years. The gender distribution in India is strong male predominance, however other studies have reported 1:1 male to female ratio in the Western world.

Leukoplakias are most commonly encountered on the buccal mucosa, gingiva, floor of the mouth, tongue, lip vermillion. Almost 90% of cases on the tongue, floor of the mouth or lip vermillion will show dysplasia or carcinoma. Early or mild leukoplakias are thin, greyish white plaques, somewhat translucent in appearance, fissured or wrinkled and may disappear on discontinuation of smoking or continue unchanged. These may later become thick and distinctly white appearance, leathery on palpation and fissures may deepen and become numerous. At this stage, the lesions are often called ***homogenous leukoplakia***. These may remain regress or disappear, few may become severe develop surface irregularities and are called verrucous or verruciform leukoplakia.

Speckled leukoplakia/erythroleukoplakia/nodular leukoplakia is a non-homogeneous type of leukoplakia. Speckled leukoplakia (SL) according to WHO, is a leukoplakia with a mix of white and red plaque lesions. It is a form of leukoplakia that is rarely found with very aggressive high risk for transformation into malignancy, and also considered as precursor lesion for squamous cell carcinoma. Clinically the lesion appears in the form of plaque/whitish nodules that have a granular surface against a reddish background. SL is often accompanied by pain and discomfort.

Verrucous leukoplakia appears as an adherent white plaque that has numerous papillary projections on its surface.

A high-risk aggressive form of leukoplakia, ***proliferative verrucous leukoplakia (PVL)*** is characterised by the development of multiple keratotic plaques with roughened surface projections. The multiple plaques of PVL tend to slowly spread and involve other oral mucosal sites. Gingiva is frequently involved with spread to the other sites as well. The PVL lesions begin as simple, flat hyperkeratosis that are indistinguishable from ordinary leukoplakia. PVL exhibits

persistent growth, becoming exophytic and verrucous in nature.These lesions have a strong female predilection (1:4) and minimal association with tobacco use and mostly associated with human papilloma virus. The lesions rarely regress despite therapy.

Severe leukoplakia lesions may become invasive and scattered patches of redness called erythroleukoplakia or speckled leukoplakia. The red areas usually represent sites where epithelial cells are so immature or atrophic that they lose their ability to produce keratin and hence intermixed red and white areas are seen. These lesions frequently represent advanced dysplasia on biopsy.

Diagnostic Procedures

Clinical examination with directed conventional biopsy remains the best means of assessing oral leukoplakia. Biopsy should be taken from the site of symptoms if present or site of redness or induration for the confirmatory diagnosis. Diagnostic methods other than histological examination like supra-vital staining or cytologic listing (brush biopsy) have their limitations when dealing with oral leukoplakia.

Histopathologic Features

Microscopically, leukoplakia is characterized by a thickened surface keratin layer described as hyperkeratosis. The keratin layer may consist of parakeratin (hyperparakeratosis) or orthokeratin (hyperorthokeratosis) or a combination of both. There is thickening of spinous cell layer (acanthosis). Some lesions may show surface hyperkeratosis but may demonstrate atrophy or thinning of underlying epithelium. Subadjacent connective tissue may show variable number of chronic inflammatory cells.

Verrucous leukoplakia has papillary or pointed surface projections, varying keratin thickness and broad blunted rete ridges.

PVL shows a variable microscopic appearance depending on the stage of the lesions. Early PVL appears as a hyperkeratotic lesion with time, the lesion becomes papillary, exophytic, verrucous hyperplasia. In later stages, the papillary proliferation exhibits downgrowth into the epithelium with broad, blunt rete ridges invasion into underlying CT. This stage is similar to verrucous carcinoma. Furthermore, the invading epithelium becomes less differentiated transforming into a full-fledged squamous cell carcinoma (SCC). Due to variable clinical and microscopic appearance, careful correlation of findings is required.

Most leukoplakia lesions demonstrate no dysplasia on biopsy.

Dysplasia

A loss in the uniformity and architectural pattern of the individual cells is termed dysplasia. The dysplastic features typically begin at the basilar or suprabasilar areas of the epithelium and may go on to involve the entire thickness of the epithelium. The dysplastic features include architectural features and cytologic features.

Architectural Features

- Asymmetric epithelial stratification
- An increased number of mitotic figures
- Dyskeratosis
- Drop-shaped rete pegs
- Loss of polarity of basal cells
- Basal cell hyperplasia or anaplasia

Cytologic Features

- Cellular and nuclear pleomorphism
- Increased nuclear cytoplasmic ratio
- Prominent nucleoli
- Hyperchromatism

These dysplastic features could be mild, moderate, or severe depending on restriction of features to lower one-third to two-thirds and more than two-thirds of the epithelium respectively.

Carcinoma *in situ* is the term applied when the entire thickness of epithelium is involved in which the dysplasia extends from the basal layer to the overlying mucosa without invading the underlying connective tissue.

The risk for malignant transformation of oral leukoplakia includes

- Female gender
- Long standing oral leukoplakia
- Oral leukoplakia in non-smokers (idiopathic)
- Location on tongue, floor of the mouth
- Size greater than 200 mm
- Non-homogenous type with presence of Candida infection
- Presence of epithelial dysplasia

Differential Diagnosis

Table 6.1 enumerates the list of lesions affecting the oral mucosa that must be considered in the differential diagnosis of oral leukoplakia and their differentiating points.

TABLE 6.1: Differential diagnosis of oral leukoplakia and their differentiating points

Lichen planus (LP)	• Typical lacy white lesions; • "Wickham's striae" are seen possible presence of concurrent skin lesions • Plaque-like LP lesions are also associated with reticular areas at periphery • LP is commoner in females as opposed to leukoplakia • Biopsy of the lesion helps in making a definitive diagnosis in case of multiple lesions/ co-existing lesions
Leukoedema	• Occurs bilaterally on the buccal mucosa • Disappears on stretching • Appears as a faint milky opalescence as opposed to the definite white appearance of the leukoplakia
Cheek-biting lesion/ *Morsicaio buccarum*	• Buccal mucosa takes on a roughened, whitish lesion with a ragged, eroded surface. • Careful questioning of the patient usually elicits the cause and promotes the proper diagnosis.
Smokeless tobacco lesion	• Lesion often has a more wrinkled pattern and is easily identified by its location in the vestibule and history of tobacco chewing use
Lupus erythematosus	• Leukoplakia-like intra-oral lesions are seen in DLE • Lesions are frequently bilateral • Classic oral lesion in DLE has a central atrophic area with small white dots and a slightly elevated border zone of irradiating white striae. • Concurrent skin lesions and work-up for lupus help to distinguish
Hyperplastic candidiasis	• Occurs as a result of chronic infection of *C. albicans*. • It may be difficult to identify whether the lesion is a primary candidal lesion or a secondarily infected leukoplakia. • Multiple lesions favour the diagnosis of candidiasis.
Hairy leukoplakia	• Occurs usually on the lateral or ventral surfaces of the tongue in HIV-positive patients. • Associated features of HIV infection are present • HIV testing and biopsy of the lesion are helpful in making a definitive diagnosis
Electro-galvanic reactions	• They are keratotic plaque-like lesions similar to leukoplakia that arise due to a microgalvanic current from dissimilar metal restorations on the adjacent mucosa • Lesions disappear when the different metal restorations are replaced or when the teeth are extracted.
White sponge nevus	• Familial pattern • Widespread folded white lesions develop in childhood as opposed to leukoplakia that occurs in older individuals

Treatment

When diagnosed with leukoplakia, the clinician should try to eliminate the possible cause either by stoppage of habit or removal of mechanical irritation. The treatment options for leukoplakia may be broadly subdivided into non-surgical treatment and surgical treatment.

Non-surgical Management

1. The use of beta-carotene in a dose of 60 mg/day for 12 months has been proven to have an effective response in preventing dysplasia in OL.
2. Retinoids are derivative compounds of natural vitamin A (retinol). Both systemic and topical therapies with vitamin A derivatives have been documented.
   Systemic-13-cis retinoic acid: A decrease in the size of oral leukoplakia was reported in patients who were provided systemic (1–2 mg/kg per day) for 3 months. However, systemic vitamin A therapy is associated with significant dose dependant toxicity including skin rash, dryness and bleeding of the nasal mucosa, conjunctivitis, oral mucositis, cheilitis, hypertriglyceridemia, and teratogenic effects.
   Topical vitamin A: Topical therapy has the potential advantages of high local dose with low systemic exposure, limiting the risk of systemic side effects.
   - 0.05% tretinoin gel applied topically 4 times per day has been proved to show complete clinical remission in some cases.
   - Topical 0.1% 13-*cis* retinoic acid (isotretinoin) gel 3 times is also effective in reducing the size of the lesion. Isotretinoin oral lozenges containing 1–5 mg 13-*cis* retinoic acid has been reported to have a similar effect.
3. Lycopene, an antioxidant, protects cells against damage and plays a protective role against progression of dysplasia by inhibiting tumor cell proliferation. 8 mg of lycopene in daily dose is an effective treatment.
4. Topical bleomycin, a cytotoxic antibiotic, has been used in the treatment of OL in dosages of 0.5%/day for 12 to 15 days.
5. Fenretinide (4-HPR) or N-(4-hydroxyphenyl) retinamide is a vitamin A analogue that has also been used in the chemoprevention of oral leukoplakia. 4 HPR has been used in both topical and systemic forms. Systemic use of 4-HPR with 200 mg/day for 3 months has been reported to produce partial clinical resolution of existing lesions.
6. **Photodynamic therapy:** The principle of this therapy is to produce photochemical reaction by using photosensitizer drugs, oxygen and visible light to eradicate the lesion. Drugs like photofrin, 5-aminolevulinic acid (ALA), verteporfin, Foscan have been used.
7. **Cryotherapy:** This method locally destroys the lesional tissues by freezing *in situ*. It has several advantages like bloodless treatment, a very low incidence of secondary infection and a relative lack of scarring and pain. Oral leukoplakia can be treated by direct application of CO_2 snow or liquid nitrogen by spray.

Surgical Treatment

1. In case of moderate to severe dysplasia surgical excision is the treatment of choice. The lesions on the ventral and lateral borders of the tongue, floor of the mouth, soft palate and oropharynx should be completely excised. Close surveillance and follow-up are mandatory for all lesions. Surgical removal is the treatment of choice for PVL.
2. **Laser surgery:** The use of carbon dioxide, Nd:YAG and KTP lasers has been suggested for the vaporization or excision of oral leukoplakia. Their precision allows a conservative and site-specific, minimally invasive surgery with sterilization of the surgical area and minimal intraoperative hemorrhage, with less postoperative swelling and pain with minimal scarring.



Fig. 6.2: Intra-oral photograph showing white patch, with cracked mud appearance on the left buccal mucosa, suggestive of homogenous leukoplakia



Fig. 6.3: Homogenous leukoplakia of lower left commissure and buccal mucosa



Fig. 6.4: Homogenous leukoplakia on the left lateral border of tongue



Fig. 6.5: Speckled/nodular leukoplakia lesion present on the right buccal mucosa, note the intermingled red and white clinical components and severe staining on the teeth due to heavy tobacco use

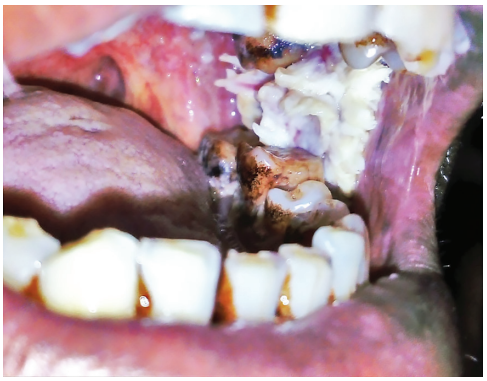


Fig. 6.6: Verrucous leukoplakia with minute projections imparting a warty, "cauliflower" like appearance



Fig. 6.7: An extensive PVL lesion on the right buccal mucosa and buccal vestibule

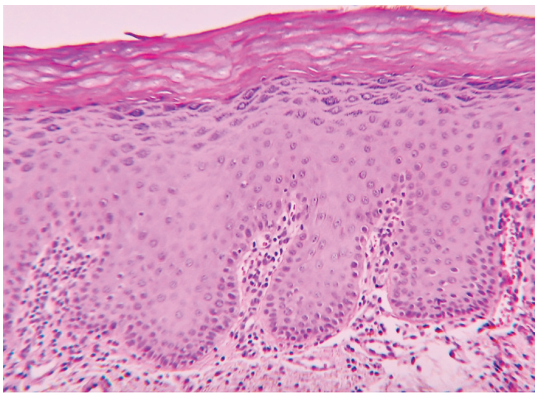


Fig. 6.8: Photomicrograph of an oral leukoplakia. H and E stained section

Erythroplakia (Erythroplasia of Queyrat)

The term erythroplakia is defined as "a red patch that cannot be clinically and pathologically diagnosed as any other condition." Queyrat used the term "erythroplasia" to describe a precancerous red lesion that develops on the penis. Almost all true erythroplakias demonstrate significant epithelial dysplasia, carcinoma *in situ* or invasive SCC. These may occur in conjunction with leukoplakia and has been found with a large proportion of early invasive oral carcinomas.

Clinical Features

Erythroplakia has no sex predilection but most cases are reported in the sixth and seventh decades. The etiology is by and large similar to that of squamous cell carcinoma. The floor of the mouth, tongue and soft palate are the most common sites of involvement and multiple lesions may be present. The altered mucosa appears as a well-demarcated erythematous macule or plaque with a soft velvety texture. It is usually asymptomatic and may be associated with adjacent leukoplakia.

Diagnosis

On histopathologic examination, the epithelium shows lack of keratin production and is often atrophic but it may be hyperplastic. This allows the underlying microvasculature to show through, thereby imparting the red color. The epithelium by far shows dysplastic changes, carcinoma *in situ* or invasive SCC. The underlying connective tissue often demonstrates chronic inflammation. Differentiation of erythroplakia from malignant change can be done by using toluidine blue applied topically or through an oral rinse.

Differential diagnosis: Non-specific mucositis, candidiasis, erosive lichen planus, or vascular lesion may mimic erythroplakia and biopsy is often required.

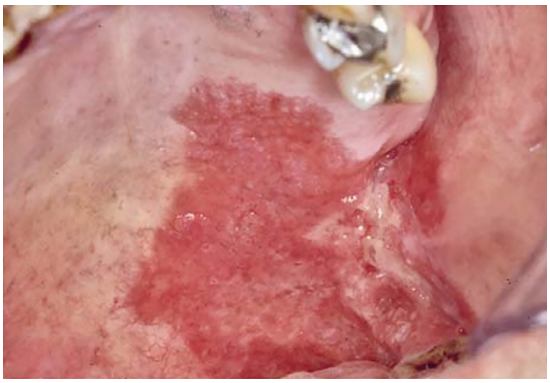


Fig. 6.9: Erythroplakia appearing as a well-demarcated red patch on the left side of the hard and soft palate

Treatment

Red lesions of the floor of the mouth and ventral or lateral tongue should be biopsied. For lesions in other locations, source of irritation, if identified should be removed, then biopsy should be performed if the lesions fail to regress after 2 weeks. As with leukoplakia the treatment of erythroplakia is guided by definitive diagnosis obtained by biopsy. Recurrence and multifocal oral mucosal involvement are common with erythroleukoplakia, hence long-term follow-up is suggested for treated patients.

Actinic Cheilitis (Cheilosis)

This is a premalignant alteration of the lower lip vermillion that results from long-term

exposure to UV light or sunlight with compromised immunity.

Clinical Features

It occurs in older males more than 45 years. MF is 10:1 in some studies. The earliest change includes atrophy of the lower lip vermillion border, characterized by smooth surface and blotchy pale areas. As the lesion progresses it becomes rough, scaly and thicken resembling leukoplakia. Further, focal ulceration may develop at more than one sites finally proceeding to SCC.

Histopathology

There is an atrophic stratified squamous epithelium with marked keratin production. Varying degrees of dysplasia may be encountered.

Differential Diagnosis

Cheilocandidiasis, lip chapping, traumatic ulcer.

Treatment

Carbon dioxide or erbium: YAG laser ablation, photodynamic theory, chemoexfoliation or chemical peel with trichloroacetic acid is done. Long-term follow-up is necessary.

Actinic Keratosis (Solar Keratosis)

This is a premalignant lesion caused by cumulative ultraviolet radiation to sun exposed skin, particularly in fair-skinned people.

Etiopathogenesis

UV light exposure can produce mutations in the p53 tumor suppressor gene. Mutations in the telomerase gene represent delayed apoptosis. Apart from UV light, other potential risk factors include immunosuppression, arsenic exposure, genetic abnormalities like albinism, xeroderma pigmentosum, Cockayne syndrome, Bloom syndrome, Rothmund-Thomson syndrome.

Clinical Features

This is found in older individuals, above 40 years of age. The head, neck, face, scalp of bald-headed men, forearm, dorsum of the hands are the most common sites of occurrence. The lesions are irregular, scaly plaque which vary in color from normal to white, grey, brown superimposed an erythematic background. The lesion may be as small as 7 mm and may reach a size of 2 cm, with minimal elevation above the surface of the skin. Occasional lesions may produce so much keratin that a 'horn' may be seen arising from the central area.

Diagnosis

Histopathologically, there is hyperparakeratosis and acanthosis of epithelium. Tear drop rete ridges of the epithelium with mild epithelial dysplasia are noted. When full thickness dysplasia is noted, then it is termed **Bowenoid actinic keratosis**. Suprabasilar acantholysis with melanosis and lichenoid inflammatory infiltrate is seen. The dermis exhibits band of sun damaged collagen and elastic fibres (solar elastosis) appearing as pale basophilic area. There is increase in elastic fibres seen in this band and thickness may increase with increased exposure to actinic rays.

Differential Diagnosis

Seborrheic keratosis, skin lesions of DLE, Bowen's disease.

Treatment

The lesion is either surgically removed or destroyed by liquid nitrogen cryotherapy, curettage, electrodessication due to its precancerous nature. It is observed that 10% actinic keratosis will progress to SCC over a period of approximately 2 years.

Oral Submucous Fibrosis (OSF)

OSF is a chronic progressive, scarring disease that predominantly affects the south Asians. First described by Schwartz (1952) as

"atropia idiopathica mucosa oris" and was later described by Joshi (1953) in Mumbai, who predesignated the condition as oral submucous fibrosis.

In 1966, Pindborg defined OSMF as an insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx. It is associated with juxtaepithelial inflammatory reaction followed by fibroelastic changes in the lamina propria layer, along with epithelial atrophy which leads to rigidity of the oral mucosa, proceeding to trismus and difficulty in mouth opening.

Other terms such as juxtaepithelial fibrosis, idiopathic scleroderma of mouth, idiopathic palatal fibrosis, sclerosing stomatitis and diffuse OSMF have also been used. It can occur at any age but most commonly it is seen in young adults (2nd–4th decade). Onset of disease is insidious and is often 2–5 years duration. It is more prevalent in southeast Asian and Indian subcontinent. The prevalence rate in India is 0.2–0.5%. The increased prevalence is due to increased use and popularity of commercial products prepared from areca nut and tobacco products like gutkha, paan masala, flavoured supari, etc. The malignant transformation rate of OSMF is almost 7.6%.

Etiopathogenesis

It is multifactorial in origin with main etiological factors being areca nut, capsaicin in chillies, micronutrient deficiencies of iron, zinc, essential vitamins like vitamin A and B_{12}. Autoimmune etiological basis with demonstration of autoantibodies against specific HLA antigens has also been suggested.

Areca nut chewing: Areca nut (betel nut) chewing is one of the most common causes of OSMF. It contains tannins, alkaloids such as arecoline, arecadine, guanacine, guacoline. Arecaidine is an active metabolite in fibroblast stimulation and proliferation, thereby inducing collagen synthesis. With addition of slaked lime, Ca (OH) to areca as seen in Indian subcontinent, causes hydrolysis of arecoline to arecadine making it available in the oral environment. Tannin reduces the collagen degradation by inhibiting collagenase. OSMF is a combined effect of tannins and arecoline which causes excessive production of collagen and reduced degradation.

Lime is a major component of betel quid preparation which alters the oral environment to severely alkaline. Under pH more than 9.5, areca nut releases reactive oxygen species (ROS) and areca phenols (tannins and catechins) undergo auto-oxidation to release superoxide radicals and hydrogen peroxide. Also transition metal ions Cu^{2+}, Fe^{2+}, Fe^{3+}, promote reactive oxygen species (ROS) production by interacting with areca nut constituents. These ROS are capable of formation of mutated cells during replication.

Copper: Areca nut releases copper after chewing which is brought directly in contact with mucosal epithelial cells for prolonged period of time. Uptake of Cu^{2+} ions, by cells is a non-energy, non-enzyme dependent diffusion. Copper causes upregulation of enzyme lysyl oxidase which plays a crucial role in cross-linking of collagen and elastin molecules.

Nutritional deficiency: Deficiency of iron, vitamin B complex, minerals and malnutrition are the promoting factors that disturb the repair of inflamed oral mucosa, thus leading to deranged healing and resultant scarring and fibrosis.The resulting atrophic mucosa is more susceptible to the effects of chillies, betel nuts and other irritants causing burning sensation.

Genetics and immunology: The genes COL1A2, COL3A1, COL6A1, COL6A3 have been linked in the progression of disease. There is polymorphism for gene coding for TNF-α which inhibits collagen phagocytosis. Patients with OSMF have increased frequency of HLA-A10, HLA-B7 and HLAD3. There is increase in autoantibodies directed towards the gastric parietal cells,

thyroid gland, anti-nuclear antibodies and anti-smooth muscle antibodies in OSMF. Humoral immunity may also play a role with increased serum levels of IgG and IgA. Serum-derived antibodies provide a basis for increase in the mucosal permeability and thereby accentuating the existing pathologic condition. A viral origin (HPV, HSV) is also linked with OSMF as decreased immune response is mediated by viral antigens and associated transformation of epithelium.

Various grading/staging classification systems have been documented by various authors in the past, which involves clinical classification, histopathological classification or their combination. A combination of clinical and histopathological classification by Khanna and Andrade is the most referred classification. A newer classification by Passi D et al (2017) includes all the parameters and components of OSMF along with treatment and prognosis. None of the previous classifications includes these features in a single classification. The main drawback of this classification is that it is lengthy and complex to read.

Clinical Features

Early stage: The prodromal symptoms include burning sensation in the mouth when consuming spicy food, appearance of vesicles especially on the palate, labial and buccal mucosa, melanosis, excessive salivation, defective gustatory sensation and dryness of the mouth (xerostomia). There are periods of exacerbation manifested by appearance of vesicles on cheek and palate for 3 months to 1 year. Petechiae are observed in about 22% of OSF cases mostly on the tongue followed by labial and buccal mucosa and soft palate. Submucosal fibres can be palpated with pain in the areas, the mucosa develops blotchy, marble-like pallor. Buccal mucosa, retromolar area, soft palate are the most commonly affected sites.

Advanced stage: As the disease progresses buccal mucosa and lips are affected symmetrically with fibrous bands in buccal mucosa running in the vertical direction. Circular bands can be felt around entire rimaorris (mouth orifice) and more marked around lower lip. There is impairment of tongue movement with significant atrophy of the tongue papillae. The density of deposition of the fibrous bands varies from a slight whitish area on the soft palate to a dense fibrosis causing fixation, shortening and deviation of the uvula and soft palate. The faucial pillars may also show slight to dense fibrosis extending deep into the pillars and causing strangulation of the tonsils. The fibrosis around pterygomandibular raphe, causes varying degrees of difficulty in the mouth opening. Sometimes fibrosis spreads to the pharynx and down to the piriform fossae. Leukoplakia on the surface of the buccal mucosae may be noted. With progressing fibrosis mouth opening reduces, inability to whistle or blow and difficulty in swallowing may be noted. When the fibrosis involves nasopharynx, there is referred pain in the ear and a nasal voice.

Histopathology

Epithelial changes include hyperplasia (early) and atrophy (advanced) changes, associated with an increased tendency for keratinizing metaplasia. Association with parakeratotic leukoplakia and atrophic epithelial changes predisposes OSF to malignancy.

Subepithelial changes

On the basis of H and E stained sections, OSF can be grouped into four clearly definable stages.

Very early, early, moderately advanced and advanced

The criteria depend on:

- Presence or absence of oedema
- Physical state of mucosal collagen
- Overall fibroblastic response
- State of blood vessel
- Predominant cell type in the inflammatory exudate

Vascular response due to inflammation has been noted in OSMF. Normal, dilated

and constricted blood vessels can be seen in combination in the same section. The narrowing of smaller vessels appears first in upper mucosa and with the advancing stage involves larger, deeper vessels. Persistent dilation has been noted in moderately advanced and advanced cases. In earlier stages, mast cells predominate which fall to fewer numbers at a later stage. The inflammatory cells are mainly lymphocytes and plasma cells. In the advanced stage, submucosal connective tissue shows extremely dense and avascular collagenous tissue, variable numbers of chronic inflammatory cells. Epithelial dysplasia without carcinoma may be evident in large number of biopsy tissues (10–15%) with frank carcinoma in at least 5% cases. The excessive fibrosis in the submucosa seems to occur earlier than atrophic changes in the epithelium.

Investigations and Blood Chemistry

There is increased ESR, anemia and eosinophilia, increased gamma globulins, reduction in serum iron, and increase in total iron binding capacity. A significant alteration in the serum copper and zinc ratio is also reported.

Differential Diagnosis

- *Oral manifestations of scleroderma:* Scleroderma can be distinguished by other cutaneous, systemic, and characteristic laboratory findings.
- Subjective symptoms of burning sensation of the oral mucosa may be confused with those caused by oral lichen planus and anemia as the latter are also associated with atrophic oral mucosa.
- Other causes of trismus including TMJ dysfunction, tetanus and localised infection are easily distinguishable by proper history and examination.

Management

The management of oral submucous fibrosis depends on the degree of clinical involvement. If the disease is detected at a very early stage, cessation of the areca nut/tobacco chewing habit along with cessation of smoking, alcohol and restriction of hot and spicy food are sufficient. Moderate-to-severe oral submucous fibrosis is irreversible.

Medical Management

1. *Nutritional supplement and antioxidants:* Lycopene is a tomato extract and one of the most potent carotenoid antioxidants. Lycopene capsules in a daily dose of 8–16 mg have been proven to have a beneficial effect in reducing the OSF associated symptoms and in preventing the disease progress. As an antioxidant it has the highest singlet oxygen quenching capacity with high capability of quenching other free radicals. Lycopene also exerts an anti-inflammatory effect as well as inhibits abnormal fibroblast proliferation in OSF.
2. *Steroids:* Steroids suppress inflammatory reactions, thereby preventing fibrosis by decreasing fibroblastic proliferation and deposition of collagen. Topical applications triamcinolone acetonide 0.1% (kenacort) and betamethasone—0.5% (betnesol) have been reported to reduce the symptoms of burning sensation. Alternatively, injections of dexamethasone 1.5 ml, with hyaluronidase 1500 IU and 0.5 ml lignocaine HCl injected intralesionally biweekly for 4–6 weeks has also been tried and has been reported to produce a definite reduction in burning sensation, blanching of oral mucosa and marginal improvement in mouth opening.
3. *Placental extract:* Placental extract contains growth factors and anti-inflammatory agents and also has antiplatelet activity. It has biogenic stimulator action and is used on the basis of tissue therapy method. It stimulates metabolism, increases the vascularity and promotes regeneration and recovery of the tissue, upon implantation into the body. Submucosal injection of Placentrex (2 ml) are given alone/ in conjunction with intralesional steroids.

4. *Interferon gamma:* IFN-gamma is a known antifibrotic cytokine. IFN-gamma, through its effect of altering collagen synthesis, appears to be a key factor to the treatment of patients with oral submucous fibrosis, and intralesional injections of the cytokine may have a significant therapeutic effect on oral submucous fibrosis.
5. *Peripheral vasodilators:* Vasodilators like pentoxifylline and oral isoxsuprine have vasodilating properties and help in increasing the hampered mucosal vascularity in OSF. Pentoxifylline also suppresses leucocyte function and alters fibroblast physiology and stimulates fibrinolysis. Pentoxifylline in a dose of 400 mg 3 times daily, as coated, sustained release tablets have been used as an adjunct therapy in the management of oral submucous fibrosis.
6. *Herbal extracts:* Several herbal compounds including curcumin (found in turmeric), aloe vera and spirulina have been shown to possess antioxidant and anti-inflammatory properties and have accorded significant relief in subjective symptoms of OSF.

Surgical management

1. *Surgical excision:*
   - Surgical treatment of OSF by excision of the fibrous bands followed by inter-position of local flaps/graft material have been documented in severe cases of OSF.
   - The commonly used extra-oral and intra-oral flaps include the nasolabial flap, temporalis fascia flap, buccal pad of fat, tongue flap, palatal island flap.
   - Grafting materials used are split skin grafts (SSG), collagen membranes and artificial dermis for the mucomuscular defects in the surgical management of OSMF.
   - Adjunctive temporalis muscle myotomy and coroinoidectomy has also been used to maintain the mouth opening achieved.
2. *Laser surgery:* ErCr:YSGG laser and carbon dioxide laser fibrotomy under local anesthesia is a minimally invasive, cost effective, chairside procedure and an useful adjunct in management of moderate OSMF.
3. *Cryosurgery:* Cryosurgery is an efficient method for tissue destruction by means of freezing. It has been used in the management of various oral lesions like the oral submucous fibrosis, oral leukoplakia, pyogenic granuloma, actinic cheilitis, vascular lesions, mucocele, keratoacanthoma, etc.
   - *Advantages:* Absence of bleeding, minimal pain, low incidence of infection, economical and relatively safe in patients with a pacemaker, the elderly, and those with coagulopathies. Useful in cases of multiple and extensive lesions and areas of difficult surgical access.
   - *Procedure:* Cryosurgery is performed using N_2O refrigerant gas and cryoprobe. After placing the cryoprobe over the lesion coolant gas is allowed to flow through the channels in the metal tip of the cryoprobe for duration of about 7 s after which lesion is allowed to thaw to complete one freeze thaw cycle. The hypothermia produced by this procedure resulted in ice crystal formation leading to destruction of the tissue.

Adjuvant modalities

1. *Diathermy:* Diathermy is a selective deep heating therapy. Both shortwave and microwave diathermy have been tried as adjuvant treatment modalities in OSF. Heat therapy acts by fibrinolysis of bands. Microwave diathermy selectively heats only juxtaepithelial connective tissue further limiting the area to be treated. Thus, it is easy to apply with minimum discomfort. A proposed regimen advocates the use of microwave diathermy every day for 20 min at each

site of lesion by means of 20–25 watts of energy to create comfortable warmth.

2. *Ultrasound:* Therapeutic ultrasound is an effective adjuvant along with combination therapy in patients of OSMF. Therapeutic effects obtained by ultrasonic energy are due to increased vascular and fluid circulation, increase in cell permeability, and increase in pain threshold and a break in pain cycle.
3. *Physiotherapy:* This includes muscle stretching exercises and heat therapy. They are helpful in preventing any further reduction in mouth opening.



Fig. 6.10: Blanched, marble-like appearance seen on the buccal mucosa in OSF

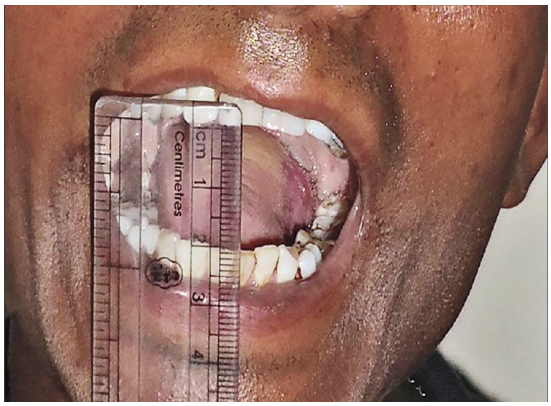


Fig. 6.11: Restricted mouth opening in OSF

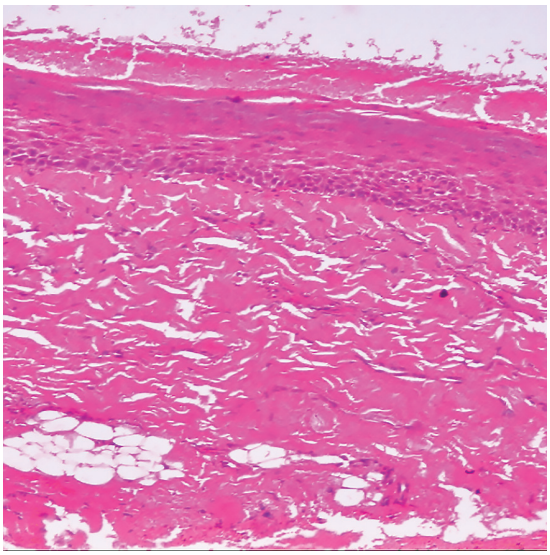


Fig. 6.12: Photomicrograph of H and E stained section showing atrophic epithelium with loss of rete ridges and hyalinization of connective tissue

IMMUNOLOGICALLY MEDIATED DISEASES

Oral Lichen Planus (OLP)

Lichen planus is a chronic mucocutaneous disorder of the stratified squamous epithelium that affects oral and genital membranes skin, nails and scalp. OLP is the mucous counterpart of cutaneous Lichen planus. It is derived from the Greek word *lichen* means tree moss and Latin word *planus* means flat.

History

The disease was first presented by the English physician Erasmus Wilson in 1866. He considered it to be the same disease described by Hebra previously as Lichen ruler. In 1892, Kaposi reported clinical variant of the disease, lichen rubber pemphigoid. In 1895, Wickham noted the characteristic reticulate white lines on surface of lichen planus papules, recognized as Wickham's striae. Darriel is credited with the first formal histopathological description.

Epidemiology

Different prevalence figures have been reported for OLP and vary from 0.5 to 2.2%. The proportion of women affected is higher with age range between 30 and 60 years. OLP occurs more frequently than cutaneous forms and tends to be more persistent and resistant to treatment.

Etiology

The exact etiology is unknown. Some of the factors associated with it are

- **Genetic background:** Familial cases are seen in association with HLA-A3, A11, A26, A28, B3, B5, B7, B8 DR1 and DRW9 have been noted. There is increase in HLA-DRW9 and Te 22 antigens in the Chinese population
- **Dental materials:** Silver amalgam, gold, cobalt, chromium, palladium, cadmium, have been identified as the triggering elements for OLP. Epoxy resins (composites) restorations and prolonged denture usage can also lead to OLP lesions.
- **Drugs:** Lichenoid like reactions may be triggered by systemic drugs, including NSAIDs, beta blockers, sulfonylureas, some anti-malarial ACE inhibitors.
- **Infectious agents:** OLP has been found to be associated with various viral agents such as HPV, EBV, HHV-6 and HIV virus. Epidemiological evidenced worldwide strongly suggest HCV as an etiological factor in OLP. Hepatitis C virus has been reported in the epithelial cells from the mucosa by rt-PCR or *in situ* hybridization. HCV specific CD4 and CD8 lymphocytes were reported in the subepithelial band. These suggest role of HCV in oral lichen planus.
- **Autoimmunity:** Autoreactive T lymphocytes may be of importance in the development of OLP. These cells cannot discriminate between the inherent molecules of the body and the foreign antigens. It may be associated with other autoimmune disorders such as primary biliary cirrhosis, chronic hepatitis, myasthenia gravis and thymoma. Bowel diseases showing concomitant OLP include celiac disease, ulcerative colitis and Crohn's disease.
- **Food allergies:** Food additives such as cinnamon have been found to be associated with OLP.
- **Stress:** Anxiety and stress have revealed the role of psychologic stress in the etiology of OLP
- **Trauma:** Could be a mechanism by which other etiological factors exert their effect.
- **Diabetes and hypertension** have been associated with OLP—'Greenspan syndrome'
- **Malignant neoplasm:** Lichen planus has been observed on the skin or mucosae of patients affected with breast cancer and metastatic adenocarcinoma.

Pathogenesis

OLP is a T-cell mediated autoimmune disease in which the auto-cytotoxic CD8+ T cells trigger the apoptosis of the basal cells of the oral epithelium. The CD+ lesional T cells may recognize an antigen associated with major histocompatibility complex (MHC) class I on keratinocytes. After antigen recognition and activation, CD8+ cytotoxic T Cells may trigger, basal cell apoptosis. Activated CD+T cells and keratinocytes release cytokines that attract additional lymphocytes into the developing lesion, thereby causing a vicious cycle.

Clinical Features

The cutaneous lesions of LP are characterized by 5 Ps—purple, polygonal, pruritic, papules and plaques. Initially evident cutaneous lesion is usually a discrete, flat topped papule that is 3 to 15 mm in diameter coalesce and form larger plaque. Initially, the lesions may appear red but eventually they take on reddish purple or violaceous hue. The centre of the papule may be slightly umbilicated and is surface is covered by characteristic, very fine, greyish white lines, called Wickham's striae. The lesions are seen more on the

flexor surfaces of the limbs, inner aspects of knees and thighs and the trunk. The primary symptoms are severe pruritis. The severity of pruritis varies, some patients may report scalp, genital or nailbed involvement.

Oral Manifestations

The oral manifestations are different from that on the skin and is characterised by bilaterally symmetrical lesions consisting of radiating, white, grey, velvety, thread-like papules in a linear, annular or retiform pattern forming lacy reticular patches, rings and streaks. A tiny elevated white dot is present at the intersection of white lines known as striae of Wickham. Most commonly seen on the buccal mucosa, tongue, lips, gingiva, floor of the mouth palate and may appear weeks or months before appearance of cutaneous lesions. The oral lesions produce no significant symptoms, although patients may complain of burning sensation in the involved areas.

The oral lesions can have a clinically varied presentation (Fig. 6.13).

- **Reticular:** This is the most common clinical form and presents with fine, asymptomatic intertwined lace-like pattern called Wickham's striae in a bilateral symmetric form involving posterior aspect of buccal mucosa.
- **Atrophic:** Appears as smooth, red, poorly defined areas, often with peripheral striae evident on gingiva of postmenopausal women.
- **Ulcerative:** Vesicular or bulla formation may be seen which rupture and erode resulting into frankly ulcerated lesions, irregular in size and shape appears as raw, painful, areas. Despite the erosion of the mucosa, the characteristic radiating striae may be noted on the periphery, of the individual lesions.
- **Plaque-like:** Hypertrophic form appearing as well circumscribed, elevated white lesions resembling leukoplakia mainly on the buccal mucosa and tongue.
- **Papular:** This is a rarely observed form. It presents with small white papules with fine striae in its periphery.

Diagnosis: The history, typical oral lesions, skin and nail involvement are sufficient for clinical diagnosis. A biopsy is recommended to differentiate from the other lesions.

Histopathology

The histopathological findings include hyper para or orthokeratosis with the thickening of granular layer, acanthosis with intercellular edema of spinous layer in some instances or atrophic epithelium where the rete pegs may be shortened pointed giving a characteristic saw-tooth appearance of rete pegs. Band like subepithelial infiltrate consisting of T-cells and histiocytes, increased numbers of intraepithelial T-cells, degenerating basal keratinocytes that form, civatte (hyaline, cytoid) bodies which appear as homogenous eosinophilic globules. Degeneration of basal keratinocytes and disruptions of anchoring fibrils of epithelial basement membrane and basal keratinocytes weakens the epithelium connective tissue interface. As a result, a histologic cleft (Max-Joseph space) may form blisters that can be seen on the oral mucosa. Direct immunofluorescence studies on the oral lichen antibody planus have shown that the antifibrinogenic antibody reacts with the lesions and exhibits strap positive fluorescence that outlines basement membrane zone and numerous irregular extensions into superficial lamina propria.

Differential diagnosis: Lichenoid reactions, oral lesions of graft-versus-host disease (GVHD), leukoplakia, may be confused with reticular and plaque-like varieties. Erosive forms may mimic atrophic candidiasis, pemphigus, cicatricial pemphigoid, and erythema multiforme.

Malignant transformation: The potential of malignant transformation remains small, i.e. 0.3–3.8%. Most of the reported cases have been confined to erosive and atrophic forms.

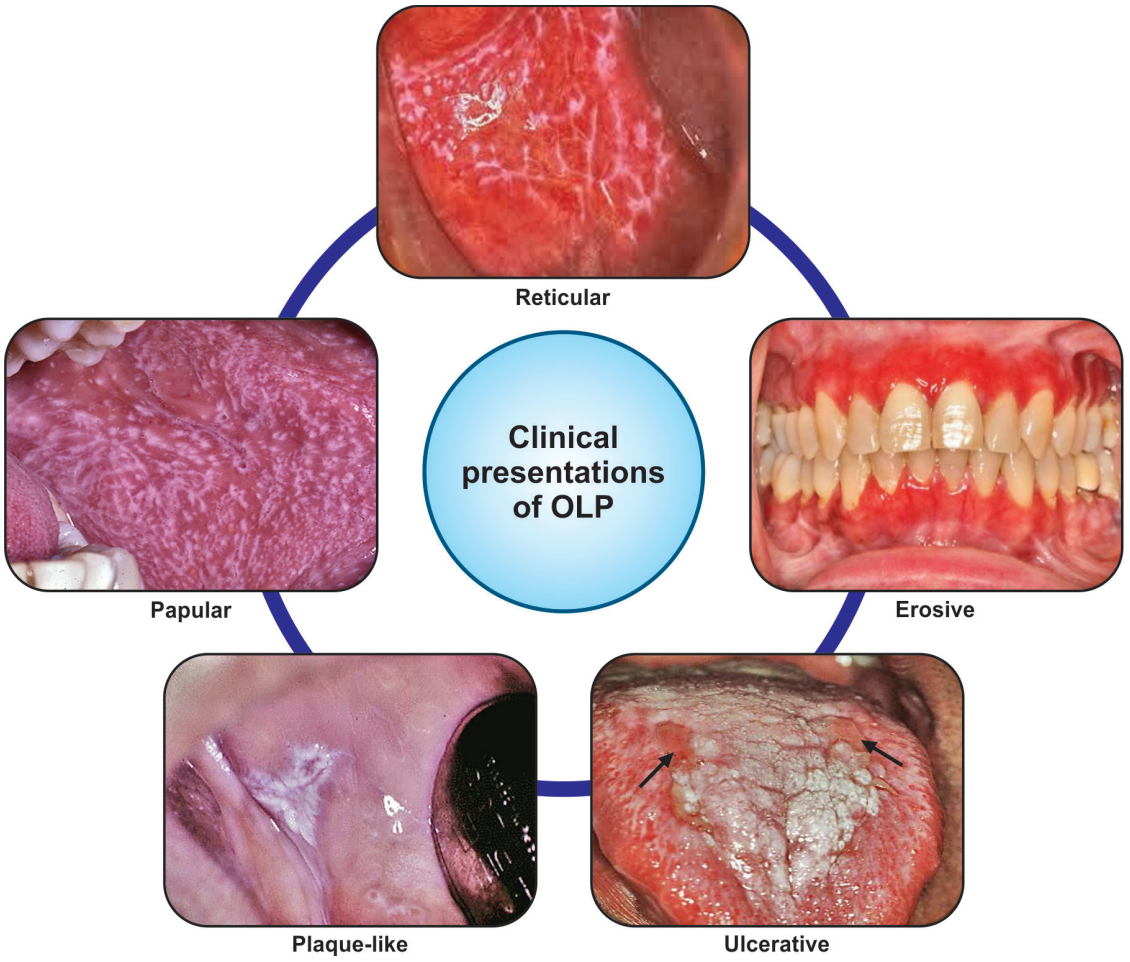


Fig. 6.13: The varied clinical appearances of oral lichen planus

Treatment: The primary aims of oral lichen planus therapy are the resolution of painful symptoms and oral mucosal lesions, the reduction of the risk of oral cancer, and the maintenance of good oral hygiene. In patients with recurrent disease, prolongation of the symptom-free intervals is another management goal. No treatment for oral lichen planus is definitely curative.

General Guidelines

- Eliminate all local exacerbating factors including sharp teeth, broken restorations or prostheses that are likely to cause physical trauma to areas of erythema or erosion.
- Thorough scaling of the teeth to remove calculus deposits.
- Removal and replacement of any dental restoration/drug identified as possible etiological factor for the lesion.
- General measure to reduce stress-like mediation and relaxation training.
- Patient education regarding the potentially malignant nature of the disease.
- Advise complete cessation of tobacco and alcohol consumption and advise a diet rich in fresh fruits and vegetables.

Medicinal Management

1. **Corticosteroids:** Corticosteroids have been the mainstay of management of

OLP. Corticosteroids act by reducing inflammation and immune reponse.

Topical therapy

- Topical midpotency corticosteroids such as triamcinolone acetonide (0.1%), high-potent corticosteroids such as fluocinonide acetonide, disodium betamethasone phosphate, and super-potent halogenated corticosteroids such as clobetasol (0.05%) are used based on the severity of the lesion. The greatest limitation in using topical corticosteroids is their lack of adherence to the mucosa for a sufficient length of time.
- Small and accessible erosive lesions located on the gingiva and palate can be treated by the application of the drug in an adherent paste with the help of a custom tray. This allows for accurate control over the contact time and ensures that the entire lesional surface is exposed to the drugs.
- Patients with extensive OLP lesions may be precribed high-potent and superpotent corticosteroids mouthwashes and intralesional injections.
- Long-term use of topical steroid can lead to the development of secondary candidiasis which necessitates antifungal therapy.

Systemic therapy

- Systemic corticosteroids are reserved for recalcitrant erosive OLP lesions where topical approaches have failed.
- Systemic prednisolone is the drug of choice, but should be used at the lowest possible dosage for the shortest duration. One milligram per kilogram daily for 7 days has been suggested, followed by a reduction of 10 mg each subsequent day. A maintenance dose with topical steroids may be commenced during the tapering of the systemic steroids.

2. **Immunomodulatory agents:** Calcineurin inhibitors
   - *Cyclosporine:* Cyclosporine inhibits lymphokine production and interleukin release, leading to a reduced function of effector T-cells. It is used as a mouth-rinse or topically with adhesive bases in OLP. However, the drug is expensive and should be reserved for highly recalcitrant cases of OLP. It is known to cause dose-related gum hyperplasia which reduces when the drug is withdrawn. Systemically administered cyclosporin has been used in a dose of 150 mg, twice a day in cases of severe recalcitrant erosive lichen planus. Topically, cyclosporine oral solution (100 mg/ml) as a "swish and spit" medication, 3 times daily, each rinse cycle lasting for 5 min has also been tried.
   - *Tacrolimus:* Tacrolimus is a macrolide immunosuppressant. It is 10–100 times as potent as cyclosporine and it has a greater capacity to penetrate the mucosa. It has been successfully used in recalcitrant OLP cases. The immunosuppressive action of tacrolimus is similar to that of cyclosporine. Burning sensation is a common side effect. A potential risk of development of carcinoma from its prolonged use is documented. Hence, its use is recommended for short periods of time. 0.1% ointment is used.
   - *Pimecrolimus* has significant antiinflammatory activity and immunomodulatory capabilities with low systemic immunosuppressive potential. 1% topical cream of pimecrolimus has been successfully used as treatment for OLP.

Retinoids: Topical retinoids such as tretinoin, isotretinoin and fenretinide, with their immunomodulating properties, have been reported to be effective in OLP. Their use should be weighed against their significant side effects like cheilitis, elevation of serum liver enzymes and triglyceride levels and teratogenicity. Doses for these agents are same as used for the treatment of leukoplakia.

Dapsone: It is an antibacterial agent traditionally used in the treatment of leprosy. It is effective in the treatment of lichen planus due to its anti-inflammatory action and inhibition of mast cell activity. Dapsone 100 mg per day for 3 months has been reported to produce a significant improvement in the burning sensation and reduction in size of the erosive areas with minimal side effects (Fig. 6.14).

Others: Mycophenolate mofetil [MMF] (oral administration: Capsules containing 250 mg of MMF, tablets containing 500 mg of MMF, and as a powder for oral suspension, which when constituted contains 200 mg/ml MMF). **Efalizumab** (a monoclonal antibody, once a week as a sub-cutaneous injection)



Fig. 6.14: Papular lichen planus with reticular form at the periphery and areas of hyperpigmentation

Non-pharmacological Modalities

PUVA therapy: PUVA (psoralen and ultra-violet A therapy) uses photochemotherapy with 8-methoxypsoralen and long wave ultraviolet light (PUVA). Psoralens are plant derive compounds that make skin temporarily sensitive to UV radiation. Methoxy psoralen is given orally 0.6 mg/kg, 2 hours before of UV irradiation, intraorally in the affected sites. It has been successfully used in the treatment of severe cases of OLP. Disadvantages of this therapy include nausea and dizziness secondary to psoralen and photosensitivity for up to 24 hours.

Photodynamic therapy: Photodynamic therapy (PDT) is a technique that uses a photosensitizing compound like methylene blue which is activated by laser light of specific wavelengths, to produce oxidizers, which cause cellular damage. PDT is found to have immunomodulatory effects and induces apoptosis in the hyperproliferating inflammatory cells present in lichen planus.

Laser therapy: 980 nm diode laser, CO_2 laser, pulsed diode laser using 904 nm pulsed infrared rays have been tried in the treatment of oral lichen planus. All types of laser destroy the superficial epithelium by protein denaturation. A deeper penetrating beam like the diode laser destroys the underlying connective tissue with the inflammatory component along the epithelium (Fig. 6.15).

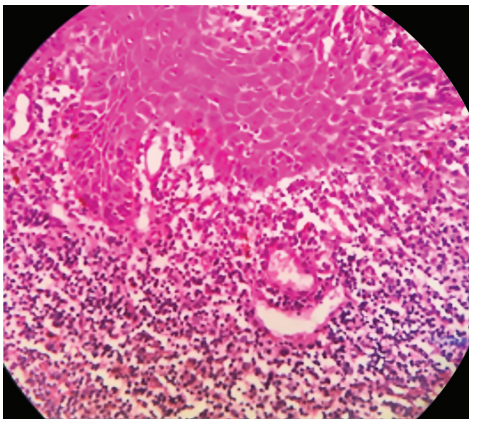


Fig. 6.15: Photomicrograph of lichen planus: H and E stained section

Drug-induced Lichenoid Reactions

Etiopathogenesis

Drug-induced lichenoid reactions are essentially delayed hypersensitivity type of reactions. It has been hypothesized that drugs or their metabolites act as hapten triggers for the lichenoid reaction. Some of the

examples of drugs that cause drug-induced lichenoid reactions are penicillin, gold and sulphonamides. It has been postulated that drug-induced lichenoid reactions may result from poor drug metabolism because of genetic variation of the major cytochrome P-450 enzymes.

Clinical Features

The drug-induced lichenoid reactions are predominantly unilateral in appearance and with an ulcerative reaction pattern along with lesions appearing clinically similar to oral lichen planus.

Diagnosis

Drug-induced lichenoid reactions often pose diagnostic challenge as the condition may be associated with a large number of drugs (Table 6.2). However, diagnosis is easier if a new drug is recently started. Drug-induced lichenoid reactions often may not develop for several months after a new drug is started and may take weeks or months to disappear after withdrawal.

Differential diagnosis: Oral lichen planus, oral lichenoid contact reactions. Careful history and clinical examination help distinguish the drug-induced lesions.

Management

Discontinuation of the drug and topical steroid application are sufficient to treat drug-induced lichenoid reactions. Patient should be educated and made aware about the drug causing the lesion for the prevention of future drug-induced lichenoid reactions.

Graft-versus-host Disease

Etiopathogenesis

This disease occurs mainly in the recipients of allogenic bone marrow transplants for patients suffering from disease of blood or bone marrow. The donor supplies haematopoietic stem cells obtained from bone marrow, peripheral blood or umbilical cord blood. However, to provide the

TABLE 6.2: Drugs implicated to cause oral lichenoid reactions

Drugs known to cause lichenoid reaction	
ACE inhibitors	Mercury (amalgam)
Allopurinol	Metformin
Amiphenazole	Methyldopa
Antimalarials	Metronidazole
Barbiturates	Niridazole
BCG vaccine	NSAIDs
Captopril	Oral contraceptives
Carbamazepine	Oxpronolol
Carbimazole	Para-aminosalicylate
Chloral hydrate	Penicillamine
Chloroquine	Penicillins
Chlorpropamide	Phenindione
Cholera vaccine	Phenothiazines
Cinnarizine	Phenylbutazones
Clofibrate	Phenytoin
Colchicine	Piroxicam
Dapsone	Practolol
Dipyridamole	Prazosin
Ethionamide	Procainamide
Flunarizine	Propranolol
Gaunoclor	Propylthiouracil
Gold	Protease inhibitors
Griseofulvin	Prothionamide
Hepatitis B vaccine	Quinidine
Hydroxychloroquine	Quinine
Interferon	Rifampicin
Ketoconazole	Rituximab
Labetalol	Streptomycin
Levamisole	Sulfonamide
Lincomycin	Tetracycline
Lithium	Tocainide
Lorazepam	Tolbutamide
Mepacrine	Triprolidine

transplant, an HLA-matched donor must be found. Unfortunately, this HLA match is not always exact and despite the use of immunosuppressive drugs such as prednisolone, methotrexate, cyclosporin, the graft is recognized as foreign and the cells start attacking what they perceive as a foreign body and the condition which results is graft-versus-host disease (GVHD).

Clinical Features

The symptoms could be acute and chronic depending on milder disease in patients with better HLA match and age of the individual.

Acute GVHD: It is observed within first few weeks or first 100 days after transplant particularly in bone marrow transplant patients. The skin lesions may range from mild rash to severe sloughing resembling toxic epidermal necrolysis. The associated symptoms are fever, nausea, vomiting, diarrhoea, abdominal pain and liver dysfunction.

Chronic GVHD: It may represent previously diagnosed case of acute GVHD or appear after days. This forms mimics variety of autoimmune condition such as systemic lupus erythematosus, Sjögren's syndrome, primary biliary cirrhosis. Skin lesions may mimic lichen planus or systemic sclerosis.

Oral Manifestations

The lesions appear as a reticular network of white striae resembling OLP. Diffuse pattern of pinpoint white papules is also seen. Burning sensation of oral mucosa is often present along with candidiasis. Atrophy of oral mucosa may be seen.Ulcerations are seen related to chemotherapeutic conditioning and neutropenic state. Ulcers often develop during first 2 weeks of transplant. If they persist longer than 2 weeks than acute GVHD should be considered and differentiated from intra-oral herpes virus or bacterial infection. Xerostomia is a common complaint along with the development of small, superficial mucoceles on palate indicating destruction of salivary gland tissue by immunologic response.

Diagnosis

The diagnosis of GVHD may be difficult because of varied manifestations. However, oral lesions have a highly predictive index in presence of GVHD.

Differential diagnosis: Since oral GVHD may manifest as lichenoid, erosive or ulcerative lesions, these reactions may mimic lichen planus, drug-induced reactions and contact allergies.

Management

Primary strategy of dealing with GVHD is to reduce or prevent its occurrence. Careful HLA matching is performed and patient is given prophylactic immunosuppressive and immune modulating therapy with the combination of prednisone, cyclosporin or tacrolimus. If GVHD develops, then mycophenolate mofetil or azathioprine may be added. Topical steroids may facilitate healing of focal oral ulcerations and OLP like lesions. Use of PUVA therapy, i.e psoralen and UVA has shown to improve these lesions. In case of dentulous patients with xerostomia topical fluorides may be used to prevent xerostomia related caries. Salivary flow can be enhanced by using pilocarpine hydrochloride or cevimeline hydrochloride. Patient's oral health status may be evaluated before transplant to remove potential source of infection. In general, some degree of GVHD often develops after allogenic bone marrow transplant. Prognosis depends on disease progress and control.

Lupus Erythematosus

Etiopathogenesis

Lupus erythematosus (LE) is an immunologically mediated condition. Environmental factors include sun exposure, drugs, chemical substances and hormones which aggravate the disease. Genetic predisposition with

elevated risk for siblings in monozygotic twins has been supported.

It has the following clinical subtypes:

- **Systemic lupus erythematosus (SLE):** SLE is a serious multisystem disease with a variety of cutaneous and oral manifestations. There is an increase in the activity of B-lymphocytes in conjunction with abnormal function of T-lymphocytes. There is an interplay between genetic and environmental factors in development of SLE.
- **Chronic cutaneous LE (CCLE):** It primarily affects skin and oral mucosa. This has fairly good prognosis.
- **Subacute cutaneous LE (SCLE):** It is a third form of disease which is intermediate between those of SLE and CCE.

Clinical Features

SLE: Women are affected 8–10 times more frequently than men. The average age is 31 years. In 40–50% of affected patients, a characteristic rash, having the pattern of a butterfly, develops over the malar area and nose typically sparing the nasolabial folds. Sunlight often worsens the lesions. Kidneys are affected in 40–50% of cases. The complications may ultimately lead to kidney failure. Cardiac involvement with pericarditis being the common complication. There are warty vegetations affecting heart valves in 50% of cases (Libman-Sacks endocarditis). Oral lesions predispose as lichenoid areas on buccal mucosa, gingiva and palate. Involvement of the vermillion border of lip is also seen. Varying degrees of ulceration, pain, erythema and hyperparakeratosis may be present. Xerostomia, candidiasis, periodontal disease, dysgeusia have also been described. Diagnosis can be confirmed by American Rheumatism Association and these include both clinical and laboratory findings (Table 6.3).

Chronic cutaneous lupus erythematosus (CCLE)—discoid lupus erythematosus (DLE): The skin lesions begin as scaly erythematous patches that are frequently distributed on sun exposed skin in head and neck area. The lesions are exacerbated by sunlight. The lesions may heal with time, only to appear in another area. The healing results in cutaneous atrophy with scarring and hypopigmentation of the resolving area. Oral lesions of DLE are similar to erosive lichen planus and seldom occur without skin lesions. An ulcerated or atrophic, erythematous central zone surrounded by white fine, radiating striae characterizes oral lesion of DLE. Sometimes the central zone may show stippling of white dots. The ulcerative oral lesions may be painful.

TABLE 6.3: American College of Rheumatology Criteria for systemic lupus erythematosus

1.	Malar rash
2.	Discoid lesions
3.	Photosensitivity
4.	Presence of oral ulcers
5.	Nonerosive arthritis of two joints or more
6.	Serositis
7.	Renal disorder
8.	Neurologic disorder (seizures or psychosis)
9.	Hematologic disorder (hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia)
10.	Immunologic disorder (anti-DNA, anti-SM, or antiphospholipid antibodies).



Fig. 6.16: DLE lesion involving lower lip

Subacute cutaneous LE: SCLE may be triggered by anyone of a variety of medications (Table 6.4). It is usually seen in the patients with arthritis or musculoskeletal problems. The skin lesions predominate in the sun-exposed areas.

TABLE 6.4: Drugs causing lupus erythematosus-like eruptions

Medications implicated in lupus erythematosus-like eruptions	
Carbamazepine	Etanercept
Chlorpromazine	Ethosuximide
Gold	Hydantoins
Griseofulvin	Hydralazine
Infliximab	Lithium
Isoniazid	Methyldopa
Penicillamine	Procainamide
Primidone	Quinidine
Reserpine	Thiouracil
Streptomycin	Trimethadione

Diagnosis

Histopathology

Skin lesions: There is presence of hyperparakeratosis, with keratin plugging in hair follicles. In all forms of LE, degeneration of the basal cell layer is observed and underlying connective tissue shows patchy to dense aggregates of chronic inflammatory cells. Deeper areas of connective tissue show chronic inflammatory cells surrounding small blood vessels.

Oral lesions: The oral lesions typically mimic oral lichen planus. However, the two conditions can be distinguished by the presence of patchy deposits of PAS deposits materials in the basement membrane zone, subepithelial edema and a more diffuse, deep inflammatory infiltrate often in a perivascular orientation. Differentiation of LE from OLP is best seen by immunofluorescence studies.

Direct immunofluorescence: It shows the deposition of one or more immunoreactants (IgM, IgG or C3) in a shaggy or a granular band at the basement membrane zone. Evaluation of the serum obtained from the patients with SLE have antibodies against multiple nuclear antigens (ANA). Antibodies directed against the double-stranded DNA are noted. Also, antibodies against Sm, a protein that is complexed with small nuclear RNA is very specific for SLE.

Differential diagnosis

- **SLE:** The differential diagnosis for SLE includes sunburn, photosensitivity, rash caused by vitamin deficiency (pellagra), discoid lupus erythematosus, seborrheic dermatitis, dermatomyositis, and drug eruptions.
- **DLE:** The differential diagnosis for DLE includes seborrheic dermatitis, psoriasis, superficial basal cell carcinoma and systemic lupus erythematosus.

Treatment

To obtain relief from oral symptoms, topical steroids may be tried. Immunosuppressive drugs used to treat LE may precipitate opportunistic fungal and viral infections. Oral ulcerations may also occur due to frequent use of NSAIDs. Oral lesions may regress spontaneously but can also persist for months or even years. Table 6.4 delineates the various topical agents used in the treatment of SLE (Table 6.5).

TABLE 6.5: Topical treatment options for oral lesions or lupus erythematosus

	Directions for use
Topical steroids 1. 0.05% fluocinonide gel 2. 0.05% clobetasol gel 3. Dexamethasone elixir (0.5 mg/ml) 4. Triamcinolone acetonide 5 mg/ml	• Place on affected areas twice a day for 2 weeks • Place on affected areas twice a day for 2 weeks • Swish and spit 10 ml 4 times a day for 2 weeks • Intralesional injection

Contd.

TABLE 6.5: Topical treatment options for oral lesions or lupus erythematosus *(Contd.)*

	Directions for use
Topical antifungals 1. 10 mg clotrimazole troches 2. Nystatin suspension (100,000 U/ml)	• Dissolve in mouth, 5 times a day for 10 days • Swish and spit 5 ml 4 times a day for 10 days
Chlorhexidine rinse (0.12%)	Swish and spit 10 ml 2 times a day, until lesions resolve

INFECTIOUS DISEASE

1. Oral Candidiasis

Candidiasis is caused by yeast-like fungus *Candida albicans*. This is one of the commonest oral infections. *C. albicans* are one of the components of the normal oral microflora. There are many types of *Candida* species seen in the oral cavity. These include *C. albicans*, *C. glabrata*, *C. krusei*, *C. guilliermondii*, *C. parapsilosis*, *C. pseudotropicalis*, *C. stellatoidea*, *C. tropicalis*. Candida exists harmlessly in mucous membranes such as eyes, ears, nose, mouth, sinuses, skin, GIT, vagina, etc. It is a beneficial flora, however, if an imbalance of normal flora occurs, it can cause overgrowth of *Candida albicans*. The organism is present in two forms, a trait known as dimorphism. The yeast form is innocuous but hyphae form is associated with the invasion of host tissue. There exists a complex host and organism interaction; Candida infection may range from mild, superficial mucosal involvement to fatal disseminated disease in immunocompromised patients.

Etiology

Pathogen: Infection with *C. albicans* is associated with certain pathogenic variables. Adhesion of fungi to the epithelium is an important step in initiation of infection. This is promoted by certain fungal cell wall components like mannose, C3d receptors, mannoproteins, and saccharine other factors include persistence within the epithelial cells, endotoxins, induction of tumor necrosis factor and proteinases. Phenotypic switching from one morphological form to other depending upon environment has been implicated.

Host Factors

Local

- Impaired salivary gland function leading to xerostomia may predispose to candidiasis.
- Antimicrobial proteins in the saliva such as lactoferrin, sialoperoxidase, lysozyme, histidine-rich polypeptides and especially anti-Candida antibodies prevent overgrowth of Candida.
- Drugs such as inhaled steroids may alter the environment by possibly suppressing cellular immunity and phagocytosis. The local mucosal immunity reverts back to normal on discontinuation of inhaled steroids.
- Dentures predispose to infection with Candida in elderly people wearing full upper dentures. Dentures provide environment with low oxygen, low pH and an anaerobic environment, reduced salivary flow under dentures.
- Other factors include oral cancer and leukoplakias and high carbohydrate diet.

Systemic Factors

- Extremes of life predispose to infection due to reduced immunity. Drugs such as broad-spectrum antibiotics, immunosuppressive drugs, anti-neoplastic agents alter the oral flora, disrupting the mucosal surface and altering the character of the saliva.
- Other factors include smoking, diabetes, Cushing's syndrome, immunosuppressive conditions such as HIV, malignancies, leukaemia, nutritional deficiencies, vitamin B have been implicated.

Classification

The disease is classified as:

Primary oral candidiasis—Group I

- Acute
  - Pseudomembranous
  - Erythematous
- Chronic
  - Hyperplastic
  - Pseudomembranous
  - Erythematous
- Keratinized primary lesions super infected with Candida
  - Leukoplakia, lichen planus, lupus erythematosus
- Candida associated lesions
  - Angular cheilitis
  - Denture stomatitis
  - Median rhomboid glossitis

Secondary oral candidiasis—Group II: Oral manifestations of systemic mucocutaneous as a result of diseases such as thymic aplasia and candidiasis endocrinopathy syndrome.

PRIMARY CANDIDIASIS

The clinical manifestations of clinically important forms of primary candidiasis are described below.

◈ Acute Candidiasis

☛ *Acute Pseudomembranous Candidiasis (Thrush)*

This form is characterized by the presence of adherent white plaques that resemble cottage cheese or curdled milk on the oral mucosa. Sites frequently involved are the tongue, buccal mucosa, labial mucosa, palate. The white mass is composed of entangled hyphae, yeasts and desquamated epithelial cell debris. Scraping them with tongue blade or rubbing them off with a dry gauze sponge can remove these plaques leaving an underlying erythematous area.

This may be seen in patients on long-term, broad-spectrum antibiotics or by impairment of patients' immune system as in HIV infection or leukemic patients. Infants may also be affected due to underdeveloped immunity. Symptoms may be mild causing burning sensation or an unpleasant taste in the mouth described as salty or bitter. The oral surfaces frequently involved include labial and buccal mucosa, tongue, hard and soft palate and oropharynx. The involvement of both oral and oesophageal mucosa is prevalent in AIDS patients. The symptoms of the acute form are rather mild and the patients may complain only of slight tingling sensation or foul taste, whereas the chronic forms may involve the oesophageal mucosa leading to dysphagia and chest pains.



Fig. 6.17: Confluent white scrapable plaques of oral thrush on the retromolar regions, palate and buccal mucosa, that resemble curdled milk



Fig. 6.18: Slightly raised, creamy white patches of acute pseudomembranous candidiasis on the palate in a patient undergoing chemotherapy for carcinoma of gall bladder

Differential diagnosis: A few lesions mimicking pseudomembranous candidiasis could be white coated tongue, thermal and chemical burns, lichenoid reactions, leukoplakia, secondary syphilis and diphtheria.

☛ *Acute Atrophic Candidiasis* (*Antibiotic sore mouth*)

This typically follows a course of broad-spectrum antibiotic therapy. Clinically, it manifests as a painful localized erythematous area.The lesions are seen on the dorsum of the tongue, typically presenting as depapillated areas. The redness is accompanied by pain and burning sensation. Also, patients who suffer from xerostomia for any reason also have an increased prevalence of erythematous candidiasis.



Fig. 6.19: Acute atrophic candidiasis manifesting as redness and depapillation on the tongue

Differential diagnosis: Thermal burns, anemia, erythroplakia, denture stomatitis, erythema migrans.

◈ Chronic Hyperplastic Candidiasis

This condition is also referred to as 'candidal leukoplakia.' Clinically, it may present in two forms.

- Homogenous adherent white plaques
- Erythematous multiple nodular / speckled type

The lesions usually occur bilaterally in the commissural region of buccal mucosa and the tongue. These lesions are non-scrapable associated with smoking and may present with varying degrees of dysplasia. Some cases may be associated with nutritional deficiencies like iron or folate and with defective cell-mediated immunity.

Differential diagnosis: Leukoplakia, lichen planus, angular cheilitis and squamous cell carcinoma.

◈ Candida Associated Lesions

☛ *Denture Stomatitis* (*Chronic Atrophic Candidiasis*)

This condition is characterized by varying degrees of erythema, sometimes by petechial hemorrhages, localized to denture bearing areas of the maxillary arch. It may also manifest as a granular or papillary type. It is seen in almost 50–65% of denture wearers. It is usually asymptomatic but occasionally patients may complain of burning sensation or soreness. Associated factors include poor oral hygiene, ill-fitting dentures with limited salivary flow.



Fig. 6.20: Denture stomatitis manifesting as diffuse erythema of the maxillary alveolus in 11, 21, 22 regions and on the hard palate in a patient wearing removable partial denture

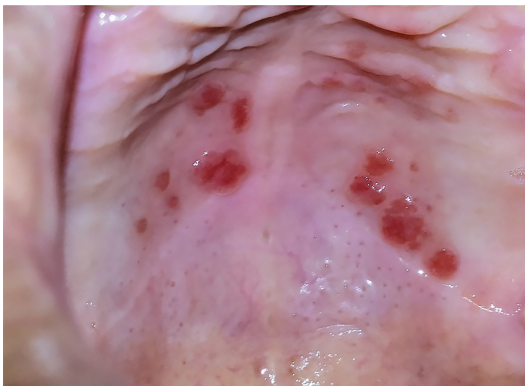


Fig. 6.21: Denture stomatitis of the granular type on the hard palate. Also note the inflamed orifices of the minor salivary glands due to smoker's palate

☛ *Angular Cheilitis (Perleche)*

This condition is characterised by erythema fissuring and scaling seen at commissures of the lip. It is usually seen in older individuals with reduced vertical dimension of occlusion and accentuated folds at the corner of the mouth. It may also be seen in vitamin B_{12} deficiency and in iron deficiency anemia. There is drooling of saliva in these areas, favouring fungal and bacterial growth. Microbiological studies have shown 20% of these cases are caused by Candida alone, by *Staph. aureus* in 20% cases and a combination of the two in the remaining cases.



Fig. 6.22: Angular cheilitis appearing as fissuring at the corner of mouth

☛ *Median Rhomboid Glossitis*

The lesions appear as a well-demarcated erythematous, central papillary atrophy of the tongue and located around the midline of the dorsum of the tongue. The surface may range from smooth to lobulated. The majority of the cases are asymptomatic, some may complain of continuous pain, irritation or pruritis. The lesion is now believed to be a localized chronic infection by *C. albicans*, associated with tobacco smokers and inhalation steroid users.



Fig. 6.23: Median rhomboid glossitis

Linear Gingival Erythema

It was referred earlier as HIV gingivitis because of its occurrence with HIV associated periodontal disease. The lesion manifests as a linear gingival erythematous band of 2–3 mm on the marginal gingiva along with petechial or diffuse erythematous lesion on attached gingiva.

C. dubliniensis has been reported to be the emerging pathogen along with *C. albicans*.

Differential diagnosis: Plaque-related gingivitis, herpetic gingivitis, desquamative gingivitis, granulomatous gingivitis, plasma cell gingivitis, leukemia.

SECONDARY CANDIDIASIS

◈ Mucocutaneous Candidiasis

This consists of a rare group of immunologic disorders known as mucocutaneous

candidiasis. Most cases are sporadic, in some cases autosomal recessive pattern of inheritance has been identified in the families. The immune problem emerges during the first few years of life, with Candida infection of the mouth, nails, skin and other mucosal surfaces. The lesion simulates chronic hyperplastic candidiasis. In some, mutations in the autoimmune regulator (AIRE) gene has been documented with autoantibodies directed against persons own tissues. This immunologic disorder is directed against the endocrine gland, endocrine-candidiasis syndrome, autoimmune polyendocrinopathy-candidiasis syndrome, ectodermal dystrophy syndrome, as well as iron deficiency anemia may develop along with candidiasis. Endocrine disturbances include hypothyroidism, hypoparathyroidism, Addison's disease, diabetes mellitus. Oral cavity involvement is reported in more than 90% cases and the lesions may spread to larynx, pharynx, or oesophagus.

Diagnosis

Fragments of plaque material can be smeared on a microscopic slide, macerated with 20% KOH and examined for typical hyphae. The hyphae can also be appreciated with PAS stain, on exfoliative cytology or biopsy specimen. The PAS method stains carbohydrates contained in abundance on the cell walls. It takes up bright magenta-red color. These hyphae are 2 μm in diameter showing branching along their length. The fungi can be cultured in various media, including blood agar, cornmeal agar and Sabouraud's broth to aid in diagnosis. On histologic sections, Candida hyphae are embedded in the parakeratin layer and rarely penetrate into variable cell layers of epithelium except in extremely immunocompromised patients.

Treatment

General principles

- Early and accurate diagnosis of the infection.
- Correcting the predisposing factors or underlying diseases
- Evaluating the type of Candida infection
- Appropriate use of antifungal drugs, evaluating the efficacy/toxicity ratio in each case which are more effective and have higher salivary concentration and better tolerance for patients with oropharyngeal candidiasis.

Topical antifungals: The topical agents are the treatment of choice for uncomplicated localized lesions in patients with normal immune function. Polyenes are fungicidal drugs that act through binding to ergosterol within fungal cell wall inducing cytoplasmic leakage leading to fungal cell death.

- Nystatin suspension 100,000 units/ml are used for 4–6 ml for 7–14 days.
- Nystatin pastilles 200,000 units each in a dose of 1–4 pastilles a day for 7–14 days.
- Clotrimazole troches 10 mg, 5 times a day for 7–14 days.
- Miconazole can also be used topically and should be used for 1 week also after resolution of symptoms. It also causes altered cell permeability by binding with ergosterol, cytochrome P450 enzyme 14-alpha demethylase. Miconazole in gel form is applied directly to affected area dose 200–500 mg/day 4 times a day. This drug is absorbed by intestine and it inhibits enzyme cytochrome P450, which affects clearance of certain drugs. Mucoadhesive tablets of miconazole are also available, while treating candidiasis four fundamentals should be kept in mind.
- Fluconazole oral suspension in distilled water (10 mg/ml) gives a 95% cure by administering 5 ml daily for 7 to 14 days.

Systemic treatment

- Fluconazole has been used to treat systemic candidiasis because of its efficacy and good tolerability. Dose is 100–200 g daily. This gives good results with immunocompromised patients and cancer patients.
- Itraconazole is used in fluconazole resistant Candida strains.

- The newer antifungal voriconazole (200 mg/day) has been shown to be a potent drug.
- While treating denture stomatitis ketoconazole tablets (200 mg daily with topical 2% ketoconazole have been used but share adverse effects like nausea, vomiting and GIT problems).

Good oral hygiene practices like mechanical cleaning of teeth and dentures with a toothbrush is an effective tool to prevent candidiasis. Oral decontamination using chlorhexidine mouthwashes or cetylpyridinium chloride is equally effective. People using inhalers with corticosteroids should be washing out mouth with water or mouthwash after using inhaler. For susceptible denture wearers, regular cleaning of dentures with removal at night and soaking it in 0.2% chlorhexidine solution helps.

Table 6.6 summarizes the different antifungal medications used systematically.

2. Hairy Leukoplakia

These are white confluent patches of fluffy (hairy) mucosa seen bilaterally, along the lateral borders of the tongue, although other sites may also be involved. It is associated with HIV positive patients and believed to be caused by the Epstein-Barr virus (EBV). It has been less frequently described in immunosuppressed patients following organ transplantation.

Clinical Features

Most often seen in young males. In some instances, the lesion consists of diffuse white plaques with occasional hairy striae. When other sites are involved it may be smooth and homogenous. Most of them are colonised by *C. albicans*. This lesion should be considered as an AIDS prodrome as it is predictive for progression of asymptomatic HIV seropositivity to full-blown syndrome.

Microscopically, the surface parakeratin layer is thickened and colonized with *C. albicans*. The upper spinous layer shows cytopathologically evident altered keratinocytes. The cells show cytoplasmic clearing and nuclear vesiculation with chromatin marginalisation. The spinous layer is of moderate thickness and the submucosa is devoid of inflammation. DNA *in situ* hybridization can be used to detect EBV virions.

Differential diagnosis: Ordinary leukoplakia with Candida infection habit and lichen planus should be considered.

Treatment: As this is a pre-AIDS condition, patients should be referred to ART centres for the treatment and drug therapy.

ALLERGIC REACTIONS

Lichenoid Contact Reactions

There is a subgroup of patients who demonstrate delayed hypersensitivity reaction to

TABLE 6.6: Systemic treatment of oral candidiasis

	Drug	*Dosage*
First line	• Fluconazole (per oral or IV)	• 100–200 mg/day for 7–14 days.
Second line	• Itraconazole solution (PO) • Posaconazole (PO) • Voriconazole (PO or IV)	• 200 mg/28 days • 400 mg daily in divided doses • 200 mg twice daily
Agents used in refractory cases	• Caspofungin (IV) • Micafungin (IV) • Anidulafungin (IV) • Amphotericin B oral suspension • Amphotericin B deoxycholate (IV)	• 70 mg loading dose followed by 50 mg daily • 100–150 mg daily • 100 mg loading dose followed by 50 mg daily • 500 mg every 6 hours • 0.3 mg/kg once.

constituents of dental materials; depicting lichenoid lesions adjacent to either dental amalgam filling or dental metals. On patch testing, majority of these patients react to the offending metal and the lesions resolve rapidly after removal of the adjacent dental material. This pathosis is diagnosed as lichenoid contact stomatitis (LCR) and not a true lichen planus.

Etiopathogenesis

It is based on a delayed hypersensitivity reaction. Most commonly, mercury (Hg) is the contact metal which affects the immune system as Hg is not identified initially by T-cell lymphocytes. A delayed reaction which involves APCs, i.e. Langerhans cells and MHC Class II molecule together containing Hg peptide bind on the antigen-specific T-lymphocytes. This is the first signal in the antigen-presenting process. The second signal comprises further cellular interactions which is decisive for clonal expansion of the Hg peptide-specific T-lymphocytes to take place. These cells will migrate into the blood stream to reach the peripheral tissues. At this stage, patient is sensitized to Hg. Once the oral mucosa of the sensitized individual is further exposed to Hg, Langerhans cells are able to present the peptide conjugated Hg to peripheral T-cells with an appropriate T-cell receptor. This interaction will invoke cytokine production and attract inflammatory cells at the site giving rise to clinical reaction pattern of LCR.

Clinical Features

The most commonly affected sites are the posterior buccal mucosa and the ventral surface of the lateral borders of the tongue. Gingival cuffs adjacent to the subgingival metallic restorations and porcelain fused to metal crowns with metal collars may also be affected. The affected mucosa may be white plaque like or erythematous with or without peripheral striae. The difference between OLP and LCR is the extension of the lesion. LCRs are confined to sites that are regularly in contact with dental materials. Most LCRs are asymptomatic, but when erythematous or ulcerative lesions are present, patient may experience discomfort from spicy and warm food.

Diagnosis

The diagnosis is made from adjacent correlation to dental material along with clinical appearance. Patch test is of a little clinical significance. Histopathology, may not be of any assistance in discrimination between OLP and LCR.

Differential diagnosis: The lesions resemble those of oral lichen planus (OLP), and it is therefore necessary to exclude likely lichenoid contact reactions when making a diagnosis of OLP. OLP is a more widespread condition involving many anatomical sites within the oral cavity with or without concurrent skin lesions. Similar oral lesions can occur as a result of drug-related lichenoid reactions or as graft-versus-host disease (GVHD), discoid lupus erythematosus (DLE), and systemic lupus erythematosus (SLE). Diagnosis is facilitated by detailed history, clinical findings, and immunohistological findings. LCRs caused by hypersensitivity to amalgam or its constituents typically have a clear anatomical relationship to the dental amalgam fillings so they are usually unilateral and not symmetrical.

Management

Replacement of dental materials in direct contact with the lichenoid contact reaction will result in cure or marked reduction in 90% of the cases. Most lesions resolve in 1–2 months.

Reactions to Dentifrice and Chlorhexidine

Delayed hypersensitivity reactions to toothpaste and mouthwashes containing flavour additives such as carvone or cinnamon or preservatives are rare. These flavouring agents may be used in chewing gum and

produce similar forms of gingivostomatitis. The clinical manifestations include fiery red, edematous gingiva, which may include both white lesions or ulcerations. Labial and buccal mucosa and tongue mucosa may also be involved. The lesions heal after withdrawal of the allergen containing agent.

Differential diagnosis: Desquamative gingivitis due to erosive lichen planus, mucous membrane pemphigoid or pemphigus vulgaris, pubertal or pregnancy-induced gingivitis, and leukaemia associated gingivitis.

TOXIC REACTIONS

Smokeless Tobacco Use (Tobacco Pouch Keratosis)

Tobacco pouch keratosis or smokeless tobacco-induced keratosis in the development of a white mucosal lesion in the area of tobacco contact. The term smokeless tobacco is derived from the fact that tobacco is not burned unlike smoking. Table 6.7 depicts the types of smokeless tobacco.

TABLE 6.7: Forms of smokeless tobacco

Types of smokeless tobacco	Methods of consumption and description of ingredients
Chewing tobacco/ spit tobacco	Chewed in the form of leaves. Placed in between the cheek or lip. Once chewed, the saliva is spit.
Spitless tobacco	Finely milled and dissolves orally. The form of tobacco is chewed and spitting is not required; hence referred to as "spitless tobacco".
Snuff tobacco	Snuffed in the form of fine powdered tobacco. Available in dry and moist.

Clinical Features

The most common location is lower anterior vestibule followed by posterior vestibule. Health and addiction hazards are due to ready absorption of nicotine and other molecules through the oral mucosa. The most common local change is painless loss of gingival tissues in the area of tobacco contact. The gingival recession accompanied by destruction of the facial surface of the alveolar bone. Brownish black extrinsic tobacco stains are seen on the enamel and cemental surface of the teeth adjacent to tobacco. Class five cervical caries in cases of cemental wear and halitosis is present in chronic users. The lesion appears thickened and corrugated and as the condition worsens, it becomes leathery. Smokeless tobacco keratosis usually takes 1–5 years to develop. Once the lesion develops keratosis remains unchanged indefinitely unless the daily tobacco contact with the tissue is altered.

Diagnosis

Histopathology of the lesion shows that the squamous epithelium is hyperkeratinized and acanthotic. Parakeratin 'chevrons' may be seen as pointed projections above or in superficial epithelial layers. Increased subepithelial vascularity and vessel engorgement are seen. Occasionally, significant dysplasia or SCC may be present.

Differential diagnosis: Leukoplakia, frictional keratosis.



Fig. 6.24: Tobacco pouch keratosis buccal vestibule and buccal mucosa showing a corrugated surface

Management

It includes complete cessation of tobacco chewing habit and follow-up to assess resolution. In maximum number of patients mucosa is resumed to normal in 2–6 weeks after stopping the habit. A biopsy is to be performed if there is any evidence of erythema or ulceration to rule out dysplasia or low-grade oral malignancy and verrucous carcinoma (snuff dippers carcinoma). Nicotine replacement therapy such as nicotine gum and patches can be delivered to patients which acts as a substitute.

Nicotine Stomatitis (Smokers Palate, Nicotina Palatini)

Nicotina palatini is a white keratotic mucosal change of the hard palate associated with tobacco smoking. It does not have a premalignant nature as it develops in response to heat rather than chemicals in tobacco smoke. Pipe smoking generates more heat on the palate, hence often associated with this habit. Similar changes are seen with long-term use of extremely hot beverages.

In some American and southeast Asian cultures, hard rolled cigarettes and cigar are smoked with the lit end held within the mouth producing excessive heat and pronounced palatal keratosis or so-called reverse smokers' palate. This lesion has a significant potential to develop dysplasia or carcinoma.

Clinical Features

This is commonly found in men older than 45 years of age. With long-term exposure to heat, the palatal mucosa becomes diffusely grey or white, with small nodular excrescences having a central red spot corresponding to the inflamed orifices of the minor salivary glands. The palatal surface may become so keratinized and thickened that a fissured or dried mud appearance is impaired. The white appearance involves marginal gingiva and interdental papilla, sometimes leukoplakia may be seen in buccal mucosa. Heavy brown or black tobacco stains may be present on the teeth.

Diagnosis

Microscopic examination reveals that the epithelium is characterized by hyperorthokeratosis and acanthosis along with patchy chronic inflammation of the subepithelial connective tissue and mucous glands squamous metaplasia of the excretory ducts and an inflammatory exudate with the ductal lumina is often noted. In cases of papular elevation, hyperplastic ductal epithelium may be seen near the orifice.

Differential diagnosis: Oral leukoplakia, Darier's disease, discoid lupus erythematosus, oral candidiasis, oral lichen planus, and denture-induced hyperplasia.

Treatment

This condition is completely reversible after stoppage of habit within 1–2 weeks even if it may be present for decades. Although this is not a precancerous lesion, care should be taken to observe any erythematous, ulcerated areas which are to be suspiciously seen and to be biopsied if, persist even after stoppage of the habit.

REACTIONS TO MECHANICAL TRAUMA

Morsacatio buccarum (Chronic Cheek Chewing)

Morsacatio comes from Latin word *morsus* or bite, chronic nibbling produces lesions that are located on buccal mucosa, lip or lateral border of the tongue. The lesions are found in people under stress or exhibiting psychological conditions. It is more prevalent in women and three times more prevalent after 35 years.

Clinical Features

The lesions could be bilateral on anterior buccal mucosa or unilateral combined with lesions on lips and lateral border of tongue.

There are areas of thickened, shredded white areas with intervening zones of erythema, erosion or focal traumatic ulceration.

Diagnosis

Biopsy reveals extensive hyperparakeratosis in an extremely ragged surface with numerous projections of keratin. Surface bacterial colonization is often seen. Sometimes, clusters of vacuolated cells are seen in the superficial portion of prickle cell layer striking similarity to oral hairy leukoplakia. In most cases the clinical presentation is pathognomonic and rarely requires biopsy. However, lesions on the border of the tongue have to be viewed with suspicion to rule out HIV.

Differential diagnosis: White sponge naevus, leukoplakia, lichen planus.

Frictional Keratosis

Frictional keratosis is a common alteration in areas of recurring mild mechanical trauma or irritation from malposed teeth, dental prosthesis, exuberant tooth brushing with an overly firm toothbrush, constant rubbing of the tongue against the teeth (tongue thrust keratosis) or frequent clenching of the facial muscles, thereby pushing cheek and lips firmly against the dentition.

Clinical Features

Frictional keratosis is usually seen in young adults of both genders. There may be presence of a thin, slightly raised, white keratotic line bilaterally along the occlusal plane of the buccal mucosa. This is called ***linea alba***, a form of frictional keratosis. At times the surface may be quite rough, and irregular and scalloping may be seen on the buccal mucosa, simulating the contours of adjacent teeth.

A similar linear line of excess keratin may be found along the lateral edges of the tongue, often with crenations from chronically pushing the tongue against the teeth; tongue thrust keratosis. Rounded or irregularly shaped white plaques may be seen in retromolar region from trauma due to maxillary posterior teeth

Alveolar keratosis is another form of frictional keratosis which presents as a thick, white verruciform, keratotic plaque often bilaterally on the edentulous mucosa of the alveolar ridge in the retromolar areas of the mandible. The irregular granular plaque is well demarcated from the surrounding mucosa. Alveolar keratosis has shown to have a low frequency of epithelial dysplasia and much lower risk of malignant transformation than verrucous leukoplakia.

Diagnosis

Microscopically, hyperorthokeratosis and acanthosis are the hallmarks of frictional keratosis.

Differential diagnosis: Alveolar keratosis must be distinguished from oral leukoplakia and tobacco pouch keratosis.

Treatment

No treatment is required for frictional keratosis as there is no malignant potential. The white keratotic plaques will completely disappear within a few days or weeks after elimination of chronic trauma. Any keratosis that persists for more than 4 weeks after stoppage of habit or removal of chronic trauma should be considered as true leukoplakia and biopsy be performed.



Fig. 6.25: Linea alba on the right buccal mucosa

OTHERS

Leukoedema

Leukoedema is a variant of the normal mucosa that is more prevalent in Caucasians and Black population. The gender distribution is equal. The etiology is not clear.

Clinical Features

It is a bilateral white veil-like alteration of the oral mucosa that is merely considered as a normal variant. These lesions are more prevalent in the Caucasians and Black population. This condition is encountered bilaterally on the buccal mucosa and sometimes the borders of the tongue. The lesions disappear on stretching the mucosa and reappear on stretching the mucosa and reappear on release of the mucosa. This is characteristic feature of leukoedema.

Histopathology shows hyperparakeratosis, acanthosis with intracellular edema in spinous layer of epithelial cells.

Differential diagnosis: Other white lesions of the oral mucosa including leukoplakia, oral candidiasis, oral lichen planus, white sponge nevus, *Morsicatio buccarum* may be confused with leukoedema but can be easily distinguished from these conditions as leukoedema disappears completely on stretching.

Treatment: As the condition is asymptomatic, no treatment is required.

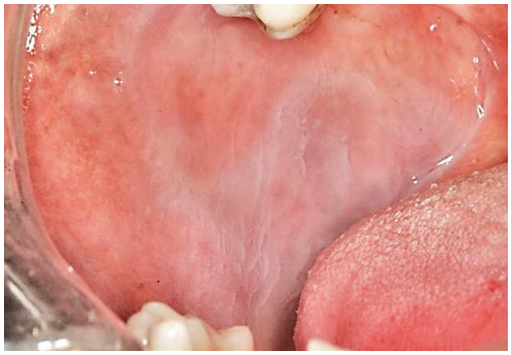


Fig. 6.26: Greyish white veil-like appearance of the right buccal mucosa that characterizes leukoedema

Benign Migratory Glossitis
(Geographic Tongue)

Benign migratory glossitis is a psoriasiform mucositis of the dorsum of the tongue. This is characterized by changing pattern of serpiginous white lines surrounded by smooth, depapillated mucosa. The changing appearance has led to call this as wandering rash or geographic tongue-like continental outlines on a globe. The etiology is unknown but aggravates due to psychological stress and is found with increased frequency in the patients with psoriasis of skin.

Diagnosis

A biopsy taken from prominent serpiginous line at the periphery of a depapillated patch shows thickened layer of keratin infiltrated with neutrophils. These inflammatory cells often produce small microabscess called Munro's abscess in the keratin and spinous layers. Rete ridges are typically thin and elongated with thin layer of epithelium overlying the connective tissue papillae. When rete ridges are not elongated, then

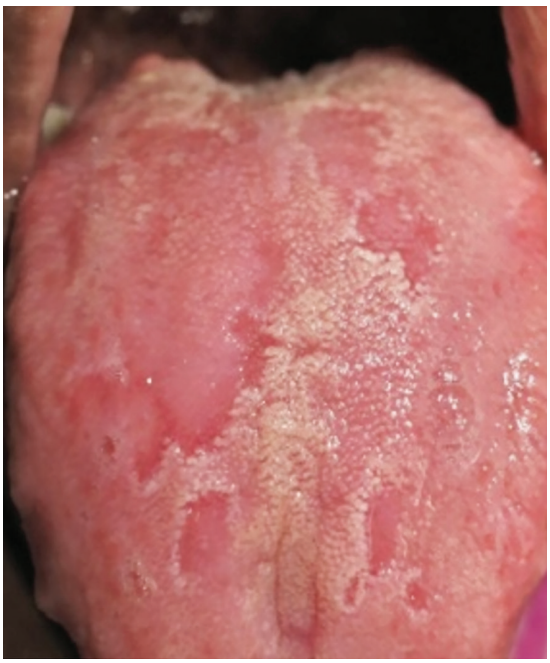


Fig. 6.27: Benign migratory glossitis

Reiter's syndrome could be considered. PAS staining will demonstrate Candida hyphae on the superficial layers of the epithelium. Ulcerations can be seen in Reiter's syndrome.

Differential diagnosis: Red lesions of the mucosa including chemical burns, contact stomatitis, fissured tongue, erosive lichen planus, atrophic candidiasis may be confused with geographic tongue. Proper history taking helps distinguish it from these conditions.

Treatment

No treatment is usually necessary. However, topical prednisolone or topical or systemic antifungal medication can be tried in case of symptomatic lesions and secondary Candida infection.

White Sponge Nevus

This is a rare genodermatosis that is inherited as an autosomal dominant trait with high degree of penetrance and variable expressibility. Mutations in keratin 4 and keratin 13 may be responsible for the clinical manifestations.

Clinical Features

The lesions appear at birth or early childhood, sometimes during adolescence. Symmetrical thickened, white, corrugated or velvety diffuse plaques affect the buccal mucosa bilaterally. Other sites include the ventral surface of the tongue, labial mucosa, soft palate, floor of the mouth. Patients are asymptomatic.

Diagnosis

The microscopic picture is characteristic depicting prominent hyperparakeratosis, acanthosis with the clearing of cytoplasm of the cells in the spinous layer. In some instances, an eosinophilic condensation is noted in the perinuclear region of the cells, in the superficial layers of the epithelium, a feature that is unique to white sponge nevus. No treatment is required for this condition.

Differential diagnosis: Cheek chewing lesion, leukoedema, leukoplakia, pachyonychia congenita, hereditary benign intraepithelial dyskeratosis.

Pachyonychia Congenita

Pachyonychia congenita is a rare genodermatoses inherited as an autosomal dominant trait. Oral lesions are seen only in patients affected by the Jadassohn-Lewandowsky form of the disease (pachyonychia congenita type 1).

Clinical Features

Patients with pachyonychia congenita exhibit characteristic nail changes, either at birth or in the early neonatal period. The free margins of the nails are lifted up because of an accumulation of keratinaceous material in the nail beds. This results in a pinched, tubular configuration of the nails, ultimately leading to nail loss. Other skin changes that may occur include marked hyperkeratosis of the palmar and plantar surfaces, producing thick, callous-like lesions. The oral lesions seen in the Jadassohn-Lewandowsky form consist of thickened white plaques that involve the lateral margins and dorsal surface of the tongue and buccal mucosa.

Diagnosis

Microscopic examination of lesional oral mucosa shows marked hyperparakeratosis and acanthosis with perinuclear clearing of the epithelial cells.

Differential diagnosis: The white keratotic lesions of this condition may be similar to that white sponge nevus and both conditions may be present at birth. However, the presence of the nail anomalies and the skin lesions in pachyonychia congenita distinguishes this entity from white sponge nevus.

Treatment: Because the oral lesions of pachyonychia congenita show no apparent tendency for malignant transformation, no treatment for the oral lesions is required.

Dyskeratosis Congenita

Dyskeratosis congenita is a rare genodermatosis having an X-linked recessive inheritance pattern, and hence a striking male predilection.

Clinical Features

Dyskeratosis congenita usually becomes evident during the first decade of life. A reticular pattern of skin hyperpigmentation develops, affecting the face, neck, and upper chest along with, abnormal, dysplastic changes of the nails. Intraoral, the tongue and buccal mucosa develop bullae, that are followed by erosions and, eventually, leukoplakic lesions. These leukoplakic lesions are potentially malignant. Hematologic complications of thrombocytopenia and aplastic anemia develop in 70 % of the cases.

Diagnosis

Biopsy specimens of the early oral mucosal lesions show hyperorthokeratosis with epithelial atrophy. As the lesions progress, epithelial dysplasia develops.

Differential diagnosis: White sponge nevus, pachyonychia congenita.

Treatment: The discomfort of the oral lesions is managed symptomatically and periodic oral mucosal examinations are recommended to check for evidence of malignant transformation in the leukoplakic lesions. Routine medical assessment is warranted to screen the patient for the development of aplastic anemia.

FREQUENTLY ASKED QUESTIONS

Long Answer Questions

1. Define leukoplakia. Describe the etiology, classification, clinical and dysplastic features of oral leukoplakia. Add a note on its management.
2. Enumerate the potentially malignant disorders of the oral cavity. Describe the etiopathogenesis, clinical features and management of OSMF.
3. Define lichen planus. Describe the etiopathogenesis and the clinical variants of OLP. Add a note on the treatment of oral lichen planus.
4. Classify candidiasis. Describe the etiopathological factors, clinical features and treatment of acute pseudomembranous candidiasis.
5. Classify the red and white lesions of the oral cavity. Describe speckled leukoplakia in detail.

Short Answer Questions

1. Oral thrush
2. Candidal leukoplakia
3. Erosive lichen planus
4. Antibiotic sore mouth
5. Denture stomatitis
6. Proliferative verrucous leukoplakia
7. Speckled leukoplakia
8. Drug-induced lichenoid reactions
9. Smokers palate
10. Hairy tongue
11. Clinical variants of OLP
12. Erythroplakia
13. Systemic lupus erythematosus
14. Angular cheilitis/perlèche

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Chapter 7

Oral Cancer and Radiologic Considerations of Malignant Lesions

INTRODUCTION

Oral cancer (OC) is the commonest cancer in India, accounting for 50–70% of total cancer mortality.

It also accounts for the highest incidence among Asian countries. OC is the sixth most common cancer worldwide. It can affect anterior tongue, cheek, floor of mouth, gingival or any other part of the oral cavity. The incidence of OC is directly correlated with age of subjects. Rates rise dramatically after the age of 40–49 years, and reach a plateau around the age of 70–79 years. OC is more frequent in men than women, and depending on its location within the oral cavity, males are two to six times more likely to be affected than females, largely owing to their higher intake of alcohol and tobacco. Oral cancer can be divided according to the tissue involvement, such as, epithelial cancer—squamous cell carcinoma, verrucous carcinoma, etc., salivary gland cancer—mucoepidermoid carcinoma, acinic cell carcinoma etc., soft tissue cancer— Kaposi sarcoma, hematolymphoid cancer—Burkitt lymphoma, T cell lymphoma, etc., odontogenic carcinoma—ameloblastic carcinoma, primary intraosseous squamous cell carcinoma developed in cysts, etc. and odontogenic sarcomas—ameloblastic fibrosarcoma.

Epidermal	Carcinoma
Connective tissue	Sarcoma
Fibrous	Fibrosarcoma
Vascular	Angiosarcoma, etc.

ORAL CARCINOMA

Etiopathogenesis/Carcinogenesis

Tobacco: It is used either as smokeless tobacco combined with pan, gutkha, or in cigarettes, cigars, pipe and bidi, i.e. smoking hookah and chillum (a clay pipe used to keep the burning tobacco) are other common forms of smoking in some countries of Asia including India. The most important carcinogens in tobacco smoke are the aromatic hydrocarbon benzpyrene and the tobacco-specific/nitrosamines (TSNs), namely 4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) and N′-nitrosonornicotine (NNN).

Alcohol: Alcohol has additive effect. Alcohol causes dehydration of mucosa. It is shown to increase the permeability of oral mucosa producing an alteration in morphology characterized by epithelial atrophy, which in turn leads to easier penetration of carcinogens into the oral mucosa.

Viruses: Viruses are capable of hijacking host cellular apparatus and modifying DNA and

the chromosomal structures and inducing proliferative changes in the cells. **Human papillomavirus** and **herpes simplex** virus (HSV) have been established in recent years as causative agents of OC. The most commonly detected HPV in head and neck squamous cell carcinoma (HNSCC) is HPV-16, which has been demonstrated in 90–95% of all HPV positive HNSCC cases, followed by **HPV-18, HPV-31, and HPV-33**. **Epstein-Barr virus** (EBV), **human herpesvirus-8** (HHV-8) and **cytomegalovirus** have also been reported as risk factors of OSCC in different studies.

Immunosuppression: Immunosuppressed individuals are more prone to develop oral cancers.

Candida

Nodular leukoplakia infected with Candida has a tendency for higher rate of dysplasia and malignant transformation.

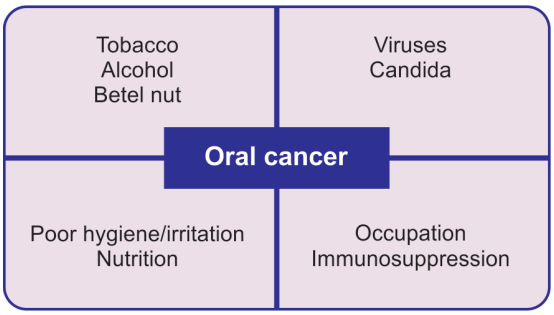


Fig. 7.1: Various predisposing factors for development of oral cancer

Occupational Risks

Occupational risks such as exposure to excessive solar radiation/ultraviolet (UV) light is known to cause lip cancers. UV rays also cause actinic cheilitis which may transform to malignancy. Sulfur dioxide, asbestos, pesticide exposures, and mists from strong inorganic acids and burning of fossil fuels have also been known to cause cancers of posterior mouth, pharynx, and larynx. Certain occupations have been reported to place people at increased risk for the development of salivary gland carcinomas. These include manufacturing of rubber products, plumbing (exposure of metals), and wood working in an automobile industry.

Syphilis

Tertiary syphilis had been known to predispose to the development of oral cancer along with other risk factors such as tobacco and alcohol. However, nowadays, tertiary syphilis is rare in clinical practice as the infection is diagnosed and treated before the onset of tertiary stage.

Dental Hygiene and Related Factors

Poor oral hygiene and prolonged irritation from sharp teeth have been viewed for their possible role in the development of OC. Poor oral hygiene and dental sepsis is thought to promote carcinogenic action of tobacco. This is due to the presence of coexisting risk factors like smoking and alcohol consumption.

Nutritional Factors

Dietary deficiencies are also suggested to play a role in the development of OC. Some researchers have reported lower risk of OC with higher intake of fruits and vegetables.

Pathogenesis: The complete understanding of molecular pathology of OC and its association with causative agent is a complex mechanism. Genetic approach and proteomic approach in recent years have revealed the molecular pathological picture of OC.

The common mechanism for cancer initiation appears to be through damage to DNA resulting in uncontrolled cell proliferation. There are several gene classes involved in carcinogenesis, which are affected by genetic transmission. The major epigenetic modification in tumors is methylation. Changes in the methylation patterns can play an important role in tumor formation.

Genetic susceptibility: Glutathione S-transferase M1 (GSTM1) null genotype appears to be the most consistent polymorphic susceptibility marker for head and neck

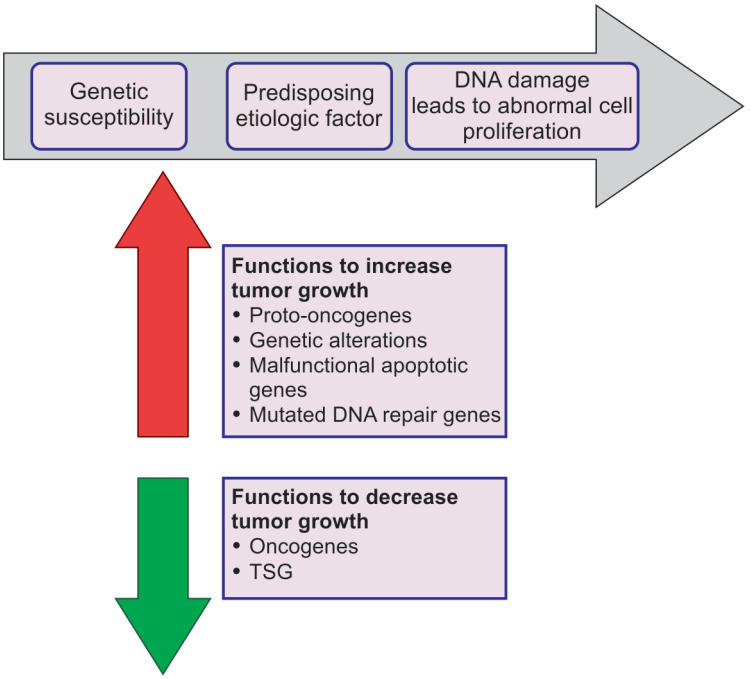


Fig. 7.2: Effects of various genes on oral cancer

cancer including OC. It is found that ALDH1B and ALDH2 (aldehyde dehydrogenase 2) genes were associated with HNSCC and showed significant correlation with alcohol consumption.

Proto-oncogenes increase the cell growth and differentiation and help in carcinogenesis.

Oncogenes act in a positive way in the normal growth regulatory pathway of the cell.

Genetic alterations define molecular basis of carcinogenesis, which includes point mutations, amplifications, rearrangements, and deletions.

Tumor suppressor genes (TSG): Tumor suppressor gene products are involved in the negative control of cell proliferation and differentiation, for example, p53, p16.

Apoptotic genes: The production of tumors includes disturbances of the mechanism that control cell death by apoptosis (cells escape normal aging and death), e.g. myc gene.

DNA repair genes: Mutations in DNA repair genes are known to lead some cancers.

Metastasis genes: Genes involved in metastasis are **nm23-H1 (NME1) and nm23-H2 (NME2).**

Angiogenesis is required for expansion of the primary tumor and new blood vessels penetrating the tumor are frequent sites for entry of tumor cells into the circulatory system. Cells first detach themselves from the primary tumor and circulate in the body.

Clinical Presentations

Sites: High risk oval

A. Buccal mucosa
B. Soft palate
C. Retromolar region
D. Ventral surface of tongue
E. Floor of mouth
F. Lips
G. Tongue lateral borders

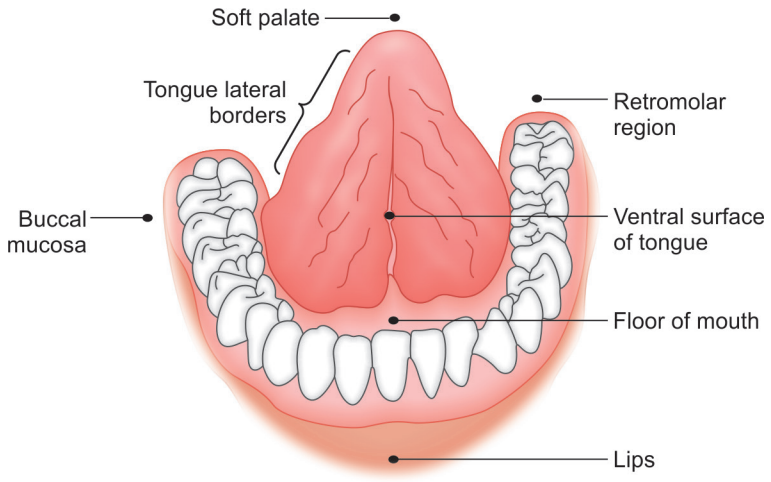


Fig. 7.3: High risk oval

Symptoms

- Lump or swelling/ulcer growth/patch
- Minimally palpable to indurated
- Bleeding
- Loose teeth
- Malfitting denture
- Neck lump or swelling
- Restriction of the tongue movements
- Dysgeusia
- *Change in sensation:* Hyperesthesia, paresthesia, or anesthesia
- Paresis or paralysis
- Chronic cough
- Change in speech
- Change in voice
- Dysphagia
- *Lymphadenopathy:* Submandibular, digastrics and upper cervical nodes

Mode of Spread

- Hematogenous
- Lymphatic

TNM staging: The American Joint Committee on Cancer (AJCC) has developed *tumor nodes metastasis* staging system for cancer. This staging helps clinicians to reflect on prognosis and probable outcome of treatment plan.



Fig. 7.4: Clinical presentation of oral malignancy

Tumor (T) describes the size of the tumor (area of cancer).

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

T1: Tumor 2 cm or less in greatest dimension
T2: Tumor >2 cm, but <4 cm

T3: Tumor >4 cm

T4a: Moderately advanced local disease, means the tumor has grown further than the mouth and oropharynx and into surrounding tissues such as bone, tongue, skin or the facial air cavities (sinuses).

T4b: Very advanced local disease, means the tumor has spread into nearby areas such as the space behind the jaw, the base of the skull, or the area of neck surrounding the arteries (carotid arteries).

Lymph Node (N): Regional Lymph Nodes Affected or Involved

NX: Regional LN cannot be assessed

N0: No regional LN metastasis or there are no cancer cells in the lymph nodes.

N1: Metastasis or cancer cells in 1 lymph node on the same side of the neck (ipsilateral). 3 cm or less in greatest dimension.

N2a: Metastasis or cancer cells in 1 lymph node on the same side of the neck (ipsilateral). >3 cm and <6 cm in dimension.

N2b: Metastasis in more than 1 lymph node on the same side of the neck as the cancer. But none of these nodes are bigger than 6 cm.

N2c: Metastasis in multiple nodes on the opposite side of the neck, or in nodes on both sides. But none of these nodes are bigger than 6 cm.

N3: Metastasis in nodes more than 6 cm.

Metastasis (M): Distant metastasis due to primary tumor.

M describes whether the cancer has spread to a different part of the body.

M0 : Means the cancer has not spread to the other parts of the body.

M1: Means cancer has spread to other parts of the body such as the lungs.

Investigations

There are various diagnostic aids or investigations available for early detection of potentially malignant and malignant lesions of oral cavity. Detail case history with accurate clinical examination is always necessary as an adjunct to investigations.

Toluidine blue: This is a vital tissue staining method. It uses a chromatic dye, which has affinity to bind with DNA. This property is used and the dye is applied directly to suspicious tissue. Positive retention of dye by the lesion helps to identify the site of biopsy.

Fine needle aspiration cytology (FNAC): This diagnostic procedure can be used for neoplastic and non-neoplastic and, for deep seated as well as superficial lesions. It is simple, fairly sensitive and specific procedure, inexpensive and comfortable to the patient. It can be used in conjunction with good clinical and morphological co-relation of the lesion.

Biopsy: Tissue biopsy is gold standard method in detecting malignancy. Incisional or excisional biopsy is performed depending on the criteria of size of the lesion.

Chemiluminescent devices: It involves the use of a hand-held, single-use, disposable chemiluminescent light stick that emits light at 430, 540 and 580 nm wavelengths. The use of the light stick is intended to improve the visual distinction between normal mucosa and oral white lesions. Normal epithelium will absorb light and appear dark, whereas hyperkeratinized or dysplastic lesions appear white. The difference in color could be related to altered epithelial thickness or to the higher density of nuclear content and mitochondrial matrix that preferentially reflect light in the pathological tissues.

Confocal Microscopy

It is an optical imaging technique for increasing optical resolution and contrast

of a micrograph by means of using as partial pinhole to block out-of-focus light in image formation. The identification 3000 technology combines anatomical imaging with fluorescence, fiber optics and confocal microscopy to map and delineate the lesion in the area being screened. The advantage of this device is its small size and easy accessibility to all tissues in the oral cavity.

Optical Coherent Tomography (OCT)

It is one of the light-based diagnostic aids which uses back scattered reflections to create images up to a depth of 1.5–2 mm. OCT is a noninvasive real time imaging modality that helps in obtaining images that can be compared to histopathological sections and hence this procedure is also termed optical biopsy.

Oral CDx Brush Biopsy

It uses the concept of exfoliative cytology to provide a cytological evaluation of cellular dysplastic changes. The oral CDx provides a complete transepithelial sample as the brush extends deep in the epithelial layers. The oral cytological epithelial samples are fixed onto a glass slide, stained with a modified Papanicolaou test and analyzed microscopically via a computer-based imaging system.

Molecular Markers

Most tumor markers are proteins and these markers may be detected within exfoliated or distributed cells, or as circulating agents within the peripheral blood or plasma. Other uses of tumor markers are to assess cancer response to:

- Treatment and to check for its recurrence.
- In some types of cancers, tumor marker levels may reflect the presence of the disease but are not predictive of the stage of the disease.

Imaging

Selection of imaging modality depends on the type and location of suspected tumor. It includes:

- Intraoral periapical radiographs, extraoral radiographs like OPG, PA views, etc.
- Ultrasonography, computed tomography, magnetic resonance imaging, positron emission tomography or PET scan.

Other investigations indicated are routine hemogram, ESR, liver function test, kidney function test, X-ray chest

Common radiographic appearances of oral carcinoma involving bone–

- Floating tooth
- Radiolucency with ragged and vague borders
- Band-like widening of PDL
- Mixed radiolucent—radiopaque lesion with vague pattern
- Sunray appearance from the border of the bone, possible combined changes.
- Periosteal reactions
- Onion skin appearance from the border of the bone

Treatment

- Management of oral cancer is a challenge, as it involves multidisciplinary approach to maintain critical functions like mastication, speech, swallowing as well as esthetics of the patient. Treatment of individual case depends on site, location, stage, histology, node status of the lesion and 4Cs, i.e. complication, compliance of patient, cost, convenience (Shah et al 2009).
- There are three basic modalities practiced for the treatment of oral cancer: Surgery, radiotherapy and chemotherapy.

Surgery and radiotherapy: Curative approach: Initial stage (T1 and T2)

Chemotherapy in combination with surgery and radiotherapy—supportive care approach: Surgery/radiotherapy + chemotherapy—advanced stage

Surgery results in a sacrifice of the structure, which can compromise esthetics and function. Surgery involves removal of the primary tumor that may demand for jaw removal with neck dissection. Surgical excision of dysplastic and malignant lesions can also be accomplished with laser

Surgery and radiotherapy—curative approach—initial stage (T1 and T2)
Chemotherapy—in combination with surgery and radiotherapy—supportive care approach
Surgery/radiotherapy + chemotherapy—advanced stage

Indications for surgery	*Indications for radiotherapy*	*Indications for chemotherapy*
⁎ For tumors involving bone. ⁎ When side effects of surgery are expected to be less significant than those with radiotherapy. ⁎ Radio-resistant tumors	⁎ Radical treatment (medically inoperable cases) ⁎ Post-operative treatment (advanced cases) ⁎ As a palliative therapy	⁎ Chemoradiation—chemotherapy given with radiotherapy in cases where surgery is not a choice of treatment. ⁎ Adjuvant chemotherapy—given after surgery to kill remnant cancer cells. ⁎ Induction chemotherapy—given prior to surgery to shrink the tumor. ⁎ Sometimes chemotherapy is given to cancers that have metastasized and cannot be treated by surgery.

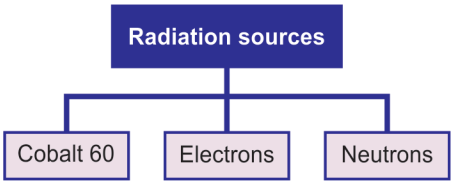
therapy. Recent advances in surgical field are novel approaches of reconstructions of the jaws such as vascularized flaps and free microvascular reconstruction. These methods help to provide stable implant prosthesis, enhance esthetics and function as a component of rehabilitation.

Radiotherapy is based on principle of interaction of radiation with matter or tissues. It kills cells by reacting with water molecules inside them, causing damage to cells. Cancer cells have less potential to repair after damage compared to normal cells and they are more sensitive to radiations due to higher growth fraction. To achieve better effect of radiation therapy, it is delivered only in fractions for planned days (e.g. 5 days/week with 2 days of gap to repair for 5/6 weeks). Due to this method, central hypoxic cells that are less susceptible to radiations become well oxygenated, as peripheral cells are killed with subsequent fractions of radiation. Exophytic and well-oxygenated tumors are more radiosensitive, whereas large invasive tumors with small growth are less responsive.

Radiotherapy can be administered by methods like external beam radiation therapy (EBRT) and brachytherapy.

External beam radiation therapy (EBRT) directs a beam of radiation externally (outside the body) at tumor inside the body. EBRT delivers high-energy rays to tumors, using a special gamma ray machine called a linear accelerator. Special planning is done to use radiations to reach to the contour of the tumor. The machine moves around the body without touching the patient and aims radiation at the tumor.

Radiation can be delivered to a localized lesion by using implants or needles inside the tumor which is known as brachytherapy.



Intensity modulated radiation therapy (IMRT) and image-guided radiotherapy (IGRT) are a few other advance methods of radiotherapy.

Chemotherapy: Chemotherapy refers to the drugs that prevent cancer cells from dividing and growing. It does this by killing the dividing cells. The drug can be administered orally or intravenously depending on the type and stage of malignancy. Commonly used drugs for chemotherapy are 5-Fluorouracil, Cisplatin, Bleomycin, Methotrexate and Taxol.

Complications of Cancer Treatment

Surgery can cause disfigurement of the jaws or face, acute pain, fibrosis due to scarring and neurologic changes. Oral hard and soft tissue structures also respond to radiotherapy and chemotherapy treatment. This occurs due to direct toxicity and secondary bacterial infections occurring in the oral cavity. These oral changes resolve after completion of therapy within a few weeks. Radiation acts by hypovascularity, hypocellularity and hypoxia causing fibrosis and necrosis while chemotherapy suppresses bone marrow activity, which further leads to variable oral manifestations.

TABLE 7.1: Clinical presentation of complication of treatment modalities

Complication	*Signs and symptoms*	*Treatment*
Mucositis	✖ Peripheral erythema ✖ Dysgeusia	✖ Maintenance of oral hygiene ✖ Chlorohexidine gluconate mouthwash.
Hyposalivation/ xerostomia	✖ Dental caries (often rampant caries) ✖ Thirst ✖ Dysphagia ✖ Dysphonia ✖ Acid erosion ✖ Oral candidiasis ✖ Oral dysesthesia	✖ Saliva substitute like mucin spray, mucin lozenge, biotene oral balance gel and toothpaste, etc. ✖ Saliva stimulants such as ascorbic acid, malic acid, parasympathomimetic drugs, etc.
Candidiasis	✖ Burning sensation in oral cavity ✖ Pseudomembrane (blisters) formation ✖ Dysphagia ✖ Dysphonia	✖ Antifungal drugs like nystatin, miconazole, gentian violet, amphotericin B, etc.
Caries	✖ Pain, tooth loss, difficulty in eating. ✖ Demineralization of calcific structures of teeth.	✖ Low sugar diet, tooth brushing, fluoride, flossing.
Soft tissue and osteoradio-necrosis	✖ Pain and swelling. ✖ A sore or ulcer in the mouth or on the jaw. ✖ Difficulty opening the jaw or trismus ✖ An abnormal opening or fistula between the jaw and the surface of the face.	✖ Antiseptic mouthwashes, antibiotics, ultrasonic therapy, hyperbaric oxygen therapy as a conservative management. ✖ Removal of small sequestrate, sequestrectomy, alveolectomy with primary closure, closure of orocutaneous fistula and large resections.
Speech and mastication	✖ Dysphonia ✖ Dysphagia	✖ Restoration and rehabilitation.
Taste and smell impairment	✖ Dysgeusia ✖ Focal seizure ✖ Uremia	✖ Vitamin supplements.
Pain	✖ Patient's discomfort ✖ Anxiety	✖ Administration of analgesics. ✖ Psychological distress, etc.
Mandibular dysfunction	✖ Difficulty in mastication ✖ Dentoalveolar pain ✖ Malocclusion	✖ Mouth opening exercises ✖ Surgical measures to eliminate the cause.
Dentofacial abnormalities	✖ Malocclusion ✖ Difficulty in mastication ✖ Poor esthetics	✖ Restoring the normal occlusion by orthodontic or by surgical means. ✖ Rehabilitation

Update

Laser Capture Microdissection (LCM)

This novel technology offers sample purity and complements gene chips by allowing accurate gene profiling studies.

Promising gene therapy strategies have been reported the use of highly efficient adenovirus vectors to deliver therapeutic genes in advanced cases of HNSCC.

"Irressa" is an orally-active selective epidermal growth factor receptor—tyrosine kinase inhibitor, showing anti-tumor activity in HNSCC, in combination with radiation treatment.

Dealing with case history:
⋆ Positive history of short duration of lesion with involvement of adjacent vital structures. Absence of pain except in case of secondary infection
⋆ History of associated habits
⋆ Sudden weight loss, anorexia and malaise

RADIOGRAPHIC STUDY OF MALIGNANT DISEASES OF THE JAWS AND ORAL CAVITY

Malignant tumor is a genetic disorder in the course of its progression in which visible physical changes take place at cellular level and at tissue level.

Radiographic features of malignant tumors of the jaw will be discussed primarily as follows:

- ⋆ Primary epithelial tumors, i.e. carcinomas
- ⋆ Metastatic [secondary]
- ⋆ Sarcoma and
- ⋆ Malignancy arising from the hematopoietic system (Table 7.2).

General Radiographic Features of Malignant Tumors of Oral Cavity

Squamous cell carcinomas occur in older age group (>50 years), whereas sarcomas occur in younger age group. They are more common among males. Malignant epithelial tumors of the jaw are commonly present in the following sites, i.e. tongue, floor of the mouth, tonsillar area, lip, soft palate or gingiva. They may spread and invade the adjacent areas involving the upper and lower jaws.

- ⋆ Sarcomas are more common in posterior mandible. Some lesions grow in the developing dental follicles and periapical areas of teeth.
- ⋆ Metastatic tumors are more seen in posterior mandible and maxilla.

Clinical Features

These tumors are primarily tumors of soft tissue, extending into the bone and thus

TABLE 7.2: Radiographic differences between benign and malignant lesions

	Benign tumor	*Malignant tumor*
Margins	⋆ Well defined	⋆ Infiltrative and irregular
Effects on surrounding structures	⋆ Displaces the surrounding tissue—no resorption or destruction	⋆ Invades and destroys surrounding tissue. Destruction of cortical outlines.
Effects on surrounding structures	⋆ There may be periosteal reaction	⋆ There is bone destruction and rarely periosteal reaction.
Internal structure	⋆ Radiopaque/radiolucent/mixed	⋆ Mostly radiolucent except osteosarcoma and some metastatic carcinomas.
Effects on teeth	⋆ Displacement and smooth resorption	⋆ Resorption is rare. If present, then spiked root resorption. ⋆ Floating teeth appearance.

causing radiographic changes. The basic understanding of pattern of growth of malignant tumors reflects in its radiographic presentation. Thus, the clinical features of malignant tumors are discussed pertaining to its radiographic presentation:

- **Ulceroproliferative growth/ulcers/exophytic lesion:** It may sometimes mimic a healing socket after tooth extraction, which however never heals. Presents radiographically as a soft tissue mass with adjacent bone resorption.
- **Uncontrolled uncoordinated growth:** Radiographically ill-defined borders with finger-like extensions
- **Non-encapsulated:** Absence of radiolucent capsule
- **Rapid rate of growth:** Rapid bone destruction and floating teeth appearance
- Persists even after cessation of stimulus
- **Invasion of surrounding structures:** Destruction of cortical outlines
- Displacement and mobility of teeth as compared to contralateral side
- **Regional and distant metastasis:** Metastatic radiolucent lesions
- Exposure of underlying bone presents radiographically as pathological fracture
- Paresthesia may present as invasion of inferior alveolar nerve.

Radiographic Features

These tumors are primarily tumors of soft tissue, extending into the bone and thus causing radiographic changes. There may sometimes be no visible radiographic signs of oral malignant lesions specially when there is only involvement of soft tissues. Radiographic investigations help to determine the extent of the disease and to assess osseous involvement.

Typically, borders are ill-defined with lack of cortication and absence of encapsulation. Evidence of mild ragged border on the alveolar ridge may be seen in initial bony invasion of malignancy arising in soft tissue. The borders may show finger-like projections and uneven extensions of bone destruction, which resembles bays and promontories.

Since epithelial cells are not normal constituents of the bone, thus they do not produce bone, instead cause osteolysis. They are typically radiolucent in most cases. Most malignancies are osteolytic, however, there may be residual islands of bone giving a ***salt and pepper appearance*** due to rapid destruction of bone. Malignancy causes invasion of surrounding bone.

Metastatic malignant epithelial tumors may sometimes produce bone. Sarcomas which arise from connective tissue elements from which bone forming cells are derived, tend to produce bone. Some metastatic tumors from breast and prostate can induce bone formation, hence appear radiopaque. Osteosarcoma produces bone and may give a patchy radiopaque appearance. Some lesions may stimulate reactive bone formation (osteoblastic).

Malignancy is mostly destructive and rapidly growing. There is destruction of the cortical boundary with adjacent soft tissue mass. It destroys supporting alveolar bone so that teeth may appear to be ***floating in space.*** Root resorption may be seen. Root resorption is more common in benign tumors, and is smooth. Resorption associated with malignancy is: ***Spiked root resorption.***

It penetrates by means of easiest route like periodontal ligament space and causes irregular widening and destruction. It may grow along inferior neurovascular canal and through mental foramen. There is widening of inferior alveolar canal. Inferior border of mandible may be thinned and destroyed resulting in pathologic fracture. Multifocal lesions located at root apices and in the papilla of developing tooth destroying the crypt cortex and displacing the developing tooth in occlusal direction.

Cortical bone destruction of inferior border of mandible, cortical border of inferior alveolar nerve canal, floor of sinus, lamina dura and developing follicles of teeth.

Periosteal reactions in malignant lesions

Onion skin (laminated periosteal reaction)
Formation of ***Codman's triangle***

- A spiculated sun-ray/hair on end type of periosteal reaction.

Absence of radiographic features is indicative that the lesion has not invaded the bone or an early lesion involving bone. Careful observation may show superficial mild ***surface erosion/cupping*** of surface bone described as a ***saucer-shaped defect***. Evidence of irregular soft tissue mass adjacent to an area of ill-defined radiolucency is highly suggestive of malignancy.

Squamous cell carcinomas affect the jaws in 2 ways:

1. Primary soft tissue tumor: Arises in soft tissue
2. Central variety: Develops within jaw

RADIOGRAPHIC FEATURES OF SQUAMOUS CELL CARCINOMA/ EPIDERMOID CARCINOMA (PRIMARY SOFT TISSUE TUMOR)

Squamous cell carcinomas occur in older age group (>50 years). It occurs most commonly in males. Tongue, floor of the mouth, tonsillar area, lip, soft palate or gingiva are the common sites. Involvement of palate is rare. They may spread and invade the adjacent areas involving the upper and lower jaws. In squamous cell carcinoma of oral mucosa, the malignancy infiltrates the adjacent bone. Thus, the radiographic features are not because of bone tumor, but tumor in bone.

Radiographic Features

Evidence of mild ragged borders on the alveolar ridge may be seen in initial bony invasion of malignancy arising in soft tissue. The borders are ill-defined blending gradually with the normal bone. The borders may show ***finger-like projections*** and uneven extensions of bone destruction, which resembles ***bays and promontories***. There is bone infiltration of tumor in which little bays of bone destruction extend into bone, leaving irregular areas of promontories.

Oral squamous cell carcinoma produces osteolytic lesion which is radiolucent. There may be residual islands of bone giving a ***salt and pepper appearance*** due to rapid destruction of bone. Initial lesions may show ***saucer-shaped*** erosions on the alveolar crest. These osteolytic lesions may sometimes resemble alveolar resorption following tooth removal, delaying the diagnosis. There may be presence of pathological fracture in advanced and aggressive lesions.

Malignancy is mostly destructive and rapidly growing causing destruction of the cortical boundary with adjacent soft tissue mass. Evidence of irregular soft tissue mass



Fig. 7.5: An ulcerative lesion in left cheek region

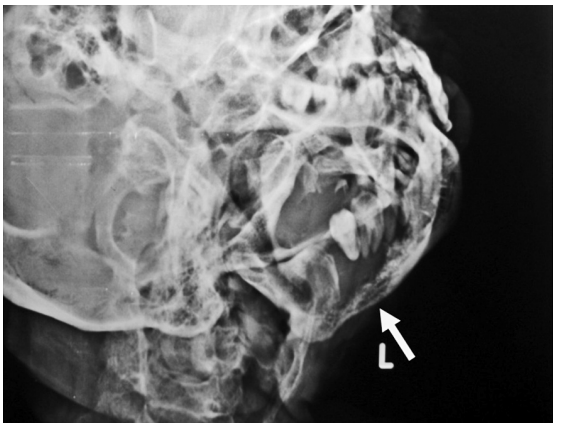


Fig. 7.6: Lateral oblique radiograph of the above case showing floating tooth appearance and ill-defined radiolucent lesion on left side of mandible

adjacent to an area of ill-defined radiolucency is highly suggestive of malignancy. It destroys supporting alveolar bone so that teeth may appear to be ***floating*** in space. The cortical outlines of maxillary antrum and inferior alveolar canal, etc. are destroyed rather than displaced, as in a benign tumor. There may be evidence of the tumor invasion in the maxillary sinus presenting as a diffuse radiopacity within it with loss of cortical outlines.

Root resorption may be seen rarely and is described as spiked root resorption.



Fig. 7.7: Panoramic radiograph showing severe bone destruction up to the lower border of mandible with ill-defined borders and pathologic fracture



Fig. 7.8: Axial CECT of mandible shows a soft tissue enhancing mass in mandibular anterior region causing erosion of labial and lingual surface of mandible



Fig. 7.9: White exophytic lesion on tongue

Differential Diagnosis

Squamous cell carcinoma	*Osteomyelitis*
Clinically presence of ulceroproliferative lesion. No evidence of pus discharge.	Clinically presence of non-vital tooth with pus discharge.
No evidence of periosteal reaction	Presence of periosteal reaction
Paresthesia, pathological fracture may be present.	Paresthesia, pathological fracture may be present.
Destruction of cortical structures like inferior alveolar canal.	Cortical structures may be destroyed later.
Floating teeth appearance	Moth-eaten appearance
The borders of the lesion are ill-defined with finger-like extensions.	Borders are ill-defined with radiopaque sequestrum in radiolucent background.

- In osteoradionecrosis there is previous history of malignancy treated by radiotherapy which resembles osteolytic lesion of squamous cell carcinoma. There may be presence of radiopaque sequestrum.
- Osteosarcoma presents with mixed radiolucent and radiopaque borders. However, there may be some radiographic evidence of sclerotic lesions present. Clinically also, there is no evidence of soft tissue lesion in osteosarcoma.

- **Periodontitis:** The bone destruction in periodontal disease starts at the alveolar crest and extends apically at the root surface. Margins of bone loss in periodontitis are smooth and well-defined as compared to squamous cell carcinoma. Alveolar bone loss in periodontitis is generalized as compared to localized lesion in squamous cell carcinoma. Evidence of mild areas of sclerosis in periodontitis due to chronicity of disease.
- **Langerhans cell histiocytosis:** Epicenter of bone destruction in LCH is in the mid-root region. There is scooped out appearance. It affects patients in younger age group up to 3 decades in contrast to squamous cell carcinoma which affects elderly people.

RADIOGRAPHIC FEATURES OF PRIMARY INTRAOSSEOUS CARCINOMA

Squamous cell carcinoma originating in bone, intra-alveolar epidermoid carcinoma, central squamous cell carcinoma.

The malignant epithelial tumor which arises within the jaw is termed **central or intraosseous carcinoma**. It arises from the intraosseous remnants of odontogenic epithelium like enamel organ or dental lamina, derived from ameloblastoma, odontogenic cysts, etc. It is more common in 4 to 7th decade. It is more common in males.

Mandibular molar region followed by anterior mandible or maxilla is more commonly affected and can occur in the tooth bearing region only.

Radiographic Features

It may be round or irregular in shape with ill-defined periphery and ragged borders.

Internal structure is radiolucent.

Destruction and effacement of adjacent cortical structures and floating tooth appearance.

Differential Diagnosis

Primary intraosseous carcinoma	*Metastatic carcinoma*
Concentrically destructive	No uniform pattern of destruction
Usually appears at a single site	Multifocal
Unilateral	May be bilateral

Infected periapical cyst or granuloma: The adjacent teeth are non-vital. The borders of infected periapical lesion have lost the cortical outline, however, careful observation may depict the presence of some areas of intact cortical lining of the cyst.

Odontogenic tumors: They are slow growing with well-defined borders causing expansion and thinning of cortex, in contrast to destruction and ill-defined borders.

Carcinoma arising in the cyst: There is presence of a few areas of intact cortical lining of the pre-existing cyst, indicating origin from it.

Multiple myeloma: It is a bilateral lesion with multiple well-defined punched out lesions.

RADIOGRAPHIC FEATURES OF MALIGNANCY ARISING IN A CYST

Epithelial lining of periapical cyst, residual, dentigerous and odontogenic keratocyst may sometimes undergo transformation to form malignant neoplasm. As it is arising from odontogenic epithelium of a cyst, it can appear in tooth bearing region. It is more common in mandible.

The smooth and corticated periphery of the cyst is lost. Initial lesions may show the smooth round oval shape of the cyst, which is lost in advanced lesion. The borders become ragged and ill-defined later.

Internal structure is radiolucent. It causes resorption of corticated lining of maxillary sinus or inferior alveolar nerve canal. Loss of lamina dura of adjacent teeth may occur.

Differential Diagnosis

- **Infected dental cyst:** It may show loss of cortical boundary and ill-defined borders of the cyst, however, some remnants of the intact cortical lining is present. History, previous radiographs and histological examination may confirm the diagnosis.
- Metastatic tumor usually resembles this lesion but are multifocal and history of primary malignancy is present.
- In multiple myeloma multiple punched out well-defined radiolucent lesions are present. Solitary lesion of multiple myeloma may resemble malignancy arising in the cyst.

RADIOGRAPHIC FEATURES OF METASTATIC TUMOR

It affects people of older age with no gender predilection. It is more common in mandibular posterior region of jaw, followed by maxillary sinus, anterior hard palate and mandibular condyle. Paresthesia, without any clinical evidence of a lesion, is the commonest presentation of a metastatic malignancy.

The metastatic lesions may produce either osteolytic or osteoblastic radiographic appearances. The osteolytic lesions may produce

i. Frank bony destruction
ii. Salt and pepper appearance
iii. Multiple areas of bone destruction resembling multiple myeloma.

It has a moderately well-demarcated osteolytic lesion but has no cortication or encapsulation at their tumor margins. It may be polymorphous. Thyroid, prostatic and breast lesions may stimulate sclerotic bone formation and may produce a radio-opaque or mixed radiolucent-radiopaque appearance.

Internal structure is mostly radiolucent if sclerotic metastasis is present and patchy sclerosis is seen.

It stimulates a periosteal reaction in a spiculated pattern resembling ***hair on end/ sunburst appearance***. There is effacement of lamina dura, causing irregular increase in width of periodontal ligament. There may be multiple areas of radiolucencies interspersed with patchy radiopacities giving a ***salt and pepper appearance.*** Sometimes there may be extensive bone destruction giving a ***floating tooth appearance.*** In developing teeth there may be effacement of bony crypts. Loss of cortical boundaries of maxillary sinus, nasal fossa, inferior alveolar canal and lower border of mandible.

Differential Diagnosis

Primary squamous cell carcinoma	Metastatic tumor of the jaw
Single lesion is usually present	Multifocal
Clinically presence of exophytic lesion on the alveolar ridge, etc. may be present	Clinically no evidence of pathology in the cavity
Radiographically, presence of soft tissue mass with adjacent ill-defined radiolucent lesion.	Radiographically, multifocal lesions with well-defined borders.
Unilateral	Can be bilateral

Infected odontogenic cyst: It may show loss of cortical boundary and ill-defined borders of the cyst, however, some remnants of the intact cortical lining is present. History, previous radiographs, histological examination may confirm the diagnosis.

Osteomyelitis: Clinical examination, history and presence of infective foci help to rule out. Pus is usually present in osteomyelitis. Moth-eaten appearance, with radiopaque sequestrum, surrounded by involucrum is present.

Squamous cell carcinoma arising in a cyst: There is presence of a few areas of intact cortical lining of the pre-existing cyst, indicating origin from it.

Multiple myeloma: Multiple punched out well-defined lesions.

Periapical lesion: There is periapical periodontal ligament widening in contrast to irregular widening extending up to the side of the root in metastatic carcinoma.The teeth are usually vital in metastatic carcinoma.

Osteopenia and osteoporosis: There is generalized presence of decreased bone radiopacity.

Radiopaque lesions of metastatic malignancy may resemble Paget's disease, however, there is bilateral bony enlargement, which is absent in metastatic malignant lesions.

RADIOGRAPHIC FEATURES OF CENTRAL MUCOEPIDERMOID CARCINOMA

It is a malignancy of the salivary gland, the cells of which are derived from pluripotent cells of odontogenic epithelium or from the lining of a cyst. The tumor behaves like a benign lesion causing displacement of bony walls without destruction. It is more common in mandible, usually in premolar and molar region and occurs above the inferior alveolar canal. It is more common in females.

Radiographically, it appears as a unilocular or ***multilocular*** expansile mass. Borders are well-defined and well-corticated and often crenated or undulating in nature. Internal structure has a ***soap bubble or honeycomb*** *appearance* due to presence of thick or thin cortical septa.

It can cause expansion of adjacent normal bony walls. Teeth are not affected but lamina dura is lost. There is displacement of the mandibular canal inferiorly.

Differential Diagnosis

Radiographically this malignancy resembles multilocular lesions of the jaw-like ameloblastoma, odontogenic myxoma and central giant granuloma which is confirmed histopathologically.

Features of Malignant Ameloblastoma and Ameloblastic Carcinoma

It occurs in middle age up to 6th decade. Males are more commonly affected and more in mandibular posterior region of jaw (premolar and molar).

Well-defined borders with cortication, crenations and scalloping are present. Unilocular or multilocular lesions having ***honeycomb or soap bubble appearance*** with thick septa are present within the lesion.

Tooth displacement and root resorption by tumor are commonly seen. Cortical boundaries may be effaced or breached. Lesions may erode lamina dura and displace normal anatomic boundaries of floor of mouth and maxillary sinus. Inferior alveolar nerve canal may be displaced or cortical boundaries may show resorption.

Differential Diagnosis

- Multilocular benign lesions like ameloblastoma, central giant cell granuloma, odontogenic myxoma, odontogenic keratocyst
- Malignant lesion of central mucoepidermoid tumor.

The diagnosis of the above lesions is confirmed by histopathology.

RADIOGRAPHIC FEATURES OF OSTEOSARCOMA

It is a malignant tumor of the bone characterized by bone formation. It is known to occur secondary to radiation in Paget's disease and fibrous dysplasia. It occurs commonly in males in 3rd to 4th decade. Lesions are known to occur more commonly in mandibular posterior region and tend to cross the midline.

There are three main radiographic features of osteosarcoma

i. Frankly osteolytic
ii. Lesions producing some bone (mixed radiolucent-radiopaque)
iii. Sclerotic osteosarcomas, almost entirely bone forming.

It is characterized by ill-defined borders with no peripheral sclerosis or encapsulation. When the periosteum is displaced, partially destroyed and disorganized, typical ***sun***

ray spicules or hair on end trabeculae may be seen. If the periosteum is elevated and maintains its osteogenic potential, but is breached in the center, a ***Codman's triangle*** is formed.

The internal structure is usually radiolucent, mixed radiolucent-radiopaque or quite radiopaque. Initial radiolucent lesion may give rise to ***moth-eaten appearance.*** Internal osseous structure may appear as granular or sclerotic and the bone appears as ***cotton balls, wisps (sclerotic) or honeycombed*** (mixed appearance). Internal structure may show areas of adjacent bone destruction of the pre-existing osseous architecture. The mixed type produces granular or structureless appearing bone. Sclerotic type produces bone of homogenous density and the trabeculae are not clearly seen.

It may be characterized by symmetrical widening of periodontal ligament space of teeth involved in the lesion. This is described as ***Garrington's sign***. The antral or nasal wall cortices may be lost/ destroyed in maxillary lesion. Mandibular lesions may destroy the cortex of neurovascular canal and adjacent lamina dura. Subperiosteal reaction may sometimes give rise to ***laminated onion peel*** appearance. Pathologic fractures may occur in extensive lesion.



Fig. 7.10: Mild intraoral swelling in maxillary central incisor region showing erythematous area

Differential Diagnosis

Squamous cell carcinoma: Early osteolytic stage of osteosarcoma may resemble squamous cell carcinoma, metastatic carcinoma but can be differentiated by clinical examination and history. There is absence of any soft tissue involvement in osteosarcoma. Sarcoma produces concentric bone destruction as compared to carcinoma.

Chondrosarcoma: It is more common in old age and maxilla.

Osteosarcoma	*Chondrosarcoma*
Rapid growth rate	Slow growth
Young age	Old age
More malignant potential	Less malignant
High metastasis rate	Slower metastasis
More tendency to recur	Less recurrence
More common	Less common
Mandibular posterior	Anterior maxilla and symphysis and angle of mandible

Ossifying fibroma: It is a benign capsulated lesion with well-defined margins.

Fibrous dysplasia: It occurs in younger age.

Osteomyelitis: Clinical examination, history and presence of infective foci help to rule out. Pus is usually present in osteomyelitis.

Sarcoma is usually rapidly growing.

RADIOGRAPHIC FEATURE OF CHONDROSARCOMA

It is a malignant tumor of cartilaginous tissue. It is of two types: Primary which arises directly from the cartilage and secondary in which malignant transformation occurs in chondroma. Chondrosarcoma is a relatively slow growing malignant lesion.

Primary tumor occurs in younger age, whereas secondary occurs in old age. It affects male and female equally.

It occurs with equal frequency in maxilla and mandible. Maxillary lesions occur in anterior region and mandibular lesions are



Fig. 7.11: IOPA and occlusal radiograph show irregular radiopacity in upper anterior region

more common in coronoid process, condylar head and neck and symphysis, where cartilaginous tissue is more.

The lesion is slow growing, round, ovoid or lobulated with well-defined corticated borders. Aggressive lesions have infiltrative ill-defined margins. Some form of calcification within the center is seen giving them a mixed radiolucent-radiopaque appearance. Typically described as ***moth-eaten appearance***. The central radiopaque structure has been described as ***flocculent or snow-like*** features.

Since they are slow growing tumors, hence there is expansion of cortical boundaries rather than destruction. Displacement and mobility of teeth is present. In mandible the inferior border is grossly expanded. Maxillary lesions may push the walls of maxillary sinus or nasal fossa and impinge on the infratemporal fossa. Peripheral new bone formation may resemble ***sun ray or hair on end*** appearance. When condyle is involved, there may be widening of temporomandibular joint space with its remodeling.

Differential Diagnosis

Osteosarcoma: It is relatively more aggressive and has more infiltrative margins.

Fibrous dysplasia: It occurs in younger age with characteristic radiographic appearances.

RADIOGRAPHIC FEATURES OF EWING'S SARCOMA

It mostly affects the long bones and rarely affects the jaw. It is highly invasive tumor with high metastatic potential.

It is more common in mandibular posterior areas and mostly affects in second decade of life. It is common in males.

The borders of the lesion are poorly demarcated and never corticated. Its advancing edge destroys bone in an uneven fashion resulting in ragged borders. The internal structure is entirely radiolucent.

It stimulates the periosteum to produce new bone causing laminar periosteal new bone formation which is described as ***onion skin appearance. Codman's triangle or hair on end appearance*** may also be seen.

It does not cause root resorption but destroys the supporting bone of adjacent teeth causing mobility. Cortical borders of maxillary sinus, inferior alveolar canal and lower border of mandible may be effaced. There is destruction of dental follicle and lamina dura of adjacent teeth.

Differential Diagnosis

Osteomyelitis: Periosteal reaction is seen in osteomyelitis, however, there is a pus discharge and focus of infection present in it. There is presence of radiopaque sequestrum and moth-eaten appearance.

Eosinophilic granuloma: is characterized by well-defined borders, as compared to ragged borders.

Osteosarcoma: Also shows periosteal reaction. It occurs in one end of the bone, whereas Ewing's sarcoma in center of bone.

Radiographic Feature of Fibrosarcoma

This tumor is more common in mandibular molar and premolar region.

The borders are ill-defined and ragged. They are non-corticated and lack any capsule. They tend to elongate through marrow spaces.

RADIOGRAPHIC FEATURES OF MULTIPLE MYELOMA

It is a malignant neoplasm of plasma cells. The single lesions are called plasmacytoma and multiple lesions are called multiple myeloma.

There is a male predilection and affects commonly at 35–70 years of age.

Posterior mandible is the most common site and lesions are mostly bilateral. It is divided into two varieties:

i. Solitary (plasmacytoma)
ii. Multiple

Three main radiographic manifestations are:

i. Multiple lesions
ii. Generalized osteoporotic lesions
iii. Solitary lesions

The borders are well-defined and non-corticated. They may sometimes be infiltrative and ill-defined. Multiple radiolucent lesions are present which resemble ***punched out radiolucencies***. Solitary lesions may sometimes form sausage-shaped lesions with undulating margins. There may be generalized osteopenia in the bone and the teeth appear conspicuous (to stand out) in the radiolucent jaws.

The surrounding structures may be destroyed. Cortical structures of inferior alveolar canal, lower border of mandible and lamina dura may be obliterated. Root resorption not seen. Teeth are grossly displaced. Widening of periodontal ligament space. There may be a ***sun-ray*** appearance.

If a large amount of bone is resorbed, the teeth may appear too radiopaque and may stand out conspicuously from their osteopenic background. Lamina dura is lost. Changes are profound if associated with renal disease.

Differential Diagnosis

Benign giant cell tumor: It occurs anterior to the molars and in young people.

Periapical cyst may resemble a plasmacytoma if it is present at the apex of the tooth. The tooth is however vital.

Malignant lesions like histiocytosis X and metastatic carcinoma can be ruled out by histopathology and biochemistry.

Osteomyelitis shows moth-eaten appearance with radiopaque sequestrum.

Hyperparathyroidism also causes multiple radiolucencies of the jaw and occurs in older patients.

MALIGNANT LYMPHOMA

It is a neoplastic process of lymphopoietic cells of reticuloendothelial system involving the lymphocytes and histiocytes. It is of two types: Hodgkin lymphoma and non-Hodgkin's lymphoma.

Radiographic Features of Hodgkin's Lymphoma

It is characterized by painless enlargement of lymphoid tissues of the body.

Cervical lymph nodes are usually involved first followed by other superficial lymph nodes which are painless and rubbery.

It is characterized by severe pruritis and characteristic Pel-Ebstein fever. There is bimodal age incidence and affects young adults and fifth to sixth decade of life. There is no sex predilection. Borders are ill-defined with irregular borders. Internal structure is radiolucent.

Radiographic Features of Non-Hodgkin's Lymphoma

It is a neoplastic proliferation of B lymphocytes and it affects lymph nodes as well as extra nodal sites involving the maxillary sinus, posterior palatal area, posterior mandible and tonsils.

Mostly occur in lymph nodes. Extra nodal sites include maxillary sinus and posterior mandible. It affects all age groups.

There are three radiographic appearances associated with Hodgkin's disease

1. Bone destruction
2. Bone destruction with bone formation
3. Bone formation alone

The most common lesion is the osteolytic one, producing ill-defined radiolucent areas. Initially it takes shape and form of host bone. It has the capability of destroying overlying cortex. The borders are ill-defined and invasive. There may be multiple areas of destruction. In the sclerotic lesions, radiopaque masses may be seen in the maxillary sinus with ill-defined borders. There may be distinct areas of frank sclerosis filling in the narrow spaces.

It is almost always entirely radiolucent. In maxillary sinus lesions the antral walls may be effaced. Lesions involving mandible destroy the cortex of neurovascular canal. There may be ***floating teeth appearance*** due to destruction of underlying bone. Crypt of dental follicles and lamina dura may be lost. The tumor occurring in younger age group has tendency to shift or displace developing teeth occlusally which may cause their premature eruption and sometimes their exfoliation. There may be a laminated periosteal reaction present.



Fig. 7.12: Clinical presentation of NHL as chronic ulcer in the palate

Differential Diagnosis

Ewing sarcoma has similar osteolytic lesions, however, there may be presence of periosteal reaction in it.

Multiple myeloma: Histopathology and presence of Bence-Jones proteins.

Leukemia and Langerhans cell histiocytosis which occur in younger age group, may displace the teeth occlusally.

Osteomyelitis: It is characterized by pus formation and normal appearing bone adjacent to radiolucent lesion in contrast to absence of acute inflammation in Hodgkin's lymphoma.

Sclerotic areas may resemble metastatic breast or prostate carcinoma.

Radiographic Features of Burkitt's Lymphoma

Burkitt's lymphoma is also known as African jaw lymphoma. It is a B cell lymphoma and is the fastest growing tumor with a tumor doubling time less than 24 hours. The endemic form is known as African type and the non-endemic form is the American type.

African cases may involve one jaw or both and affect its posterior parts. It mostly affects young children. There is no sex predilection. Lesions begin as multiple ill-defined large, non-corticated radiolucencies that coalesce later into larger ill-defined radiolucencies with expansile periphery. This expansion

breaches its outer cortical limits, causing gross ***balloon-like expansion*** with thinning of adjacent structures.

Osteolytic radiolucent lesions are present in almost all cases. It grows rapidly to involve adjacent structures like maxilla, ethmoidal and sphenoidal sinuses, nasal and orbital cavity when involving the upper jaw. The teeth in tumor area are grossly displaced. After tumor involvement of the developing dental structures occurs, root development ceases. Lamina dura of teeth is destroyed and cortical boundaries of maxillary sinus, nasal floor are thinned out. There may be an adjacent soft tissue mass.

Differential Diagnosis

Non-Hodgkin's lymphoma radiographically appears similar and it is more common in older age group.

Cherubism: It is common in children and shows floating tooth appearance and is bilateral.

Ewing's sarcoma: Periosteal reaction may be present.

Osteosarcoma: The osteolytic type resembles lesion of Burkitt's lymphoma.



Fig. 7.13: Extraoral swelling associated with Burkitt's lymphoma

RADIOGRAPHIC FEATURES OF LEUKEMIA

Leukemia is a malignancy of immature neutrophils which increase at the expense of other cells in the bone marrow resembling preapical pathology.

Its manifestations are seen in jaws in areas of tooth development, mostly in the periapical area. Leukemic infiltrates called chloromas (greenish in color) may be present in the skull and facial bones. Leukemic infiltration in bone marrow causes ill-defined radiolucent areas in the jaws which are usually bilateral. The radiolucent areas produce osteopenia in which the teeth appear to stand out conspicuously from their surrounding bone. Patchy radiolucent areas are also seen in the jaws.

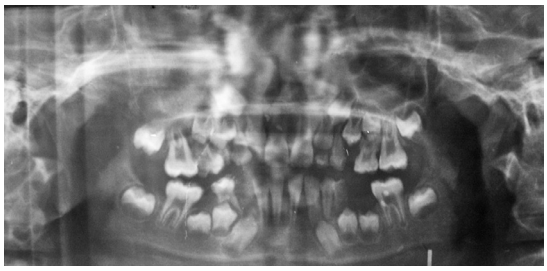


Fig. 7.14: Radiogaraphic presentation of Burkitt's lymphoma

Developing teeth and bony crypts may be displaced occlusally. Premature loss of teeth is seen. Lamina dura and bony outline of dental crypts may be lost. There may be periosteal reaction causing new bone formation without bony expansion.

Differential Diagnosis

Hyperparathyroidism may cause generalized bony radiolucency. Blood investigation may reveal endocrinal imbalance.

Malignant disorders like multiple myeloma and leukemia may cause similar picture on the radiograph.

Radiolucent areas at the apex of tooth may resemble periapical pathology.

Common appearances of malignant lesions involving jaws:

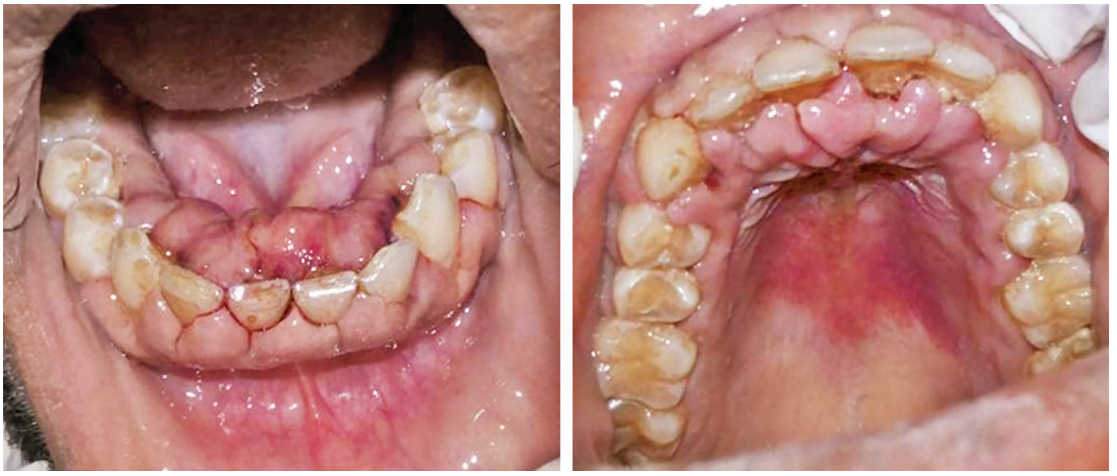


Fig. 7.15: Leukemic gingival enlargement

Sunray / Sunburst appearance
1. Osteosarcoma
2. Hemangioma
3. Thalassemia
4. Sickle cell anemia

Onion peel appearance
1. Ewing sarcoma
2. Osteosarcoma
3. Garre's osteomyelitis
4. Syphilis
5. Infantile cortical hyperostosis

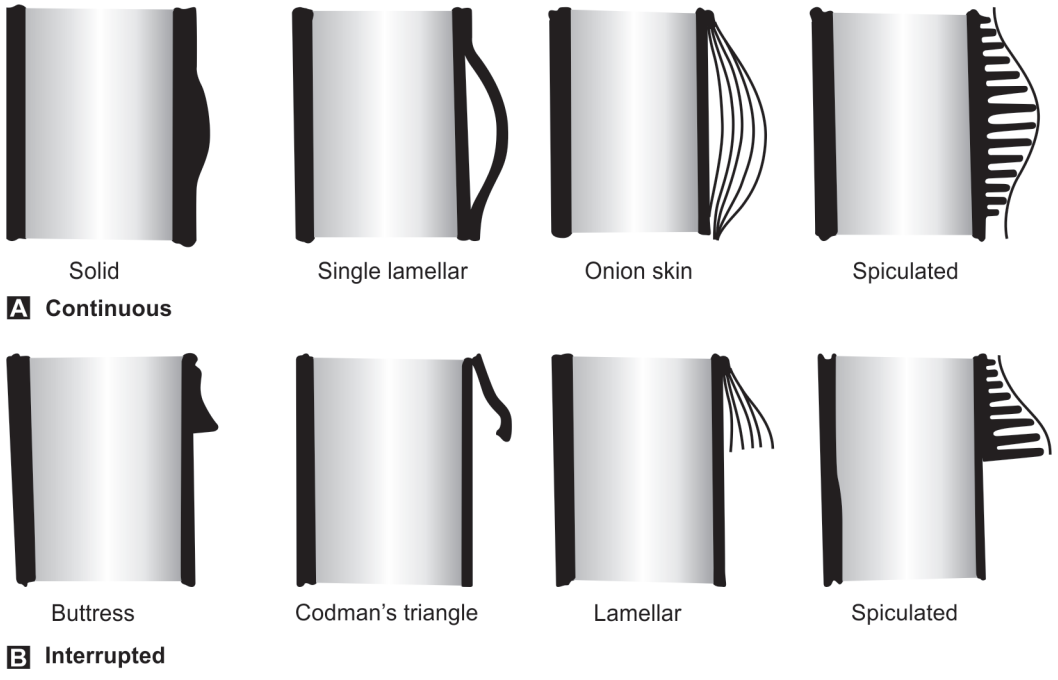


Fig. 7.16: Various types of periosteal reactions

FREQUENTLY ASKED QUESTIONS

1. Write clinical features, radiographic features, investigations and treatment protocols for malignancy / squamous cell carcinoma.
2. Write a note on radiographic features of malignant lesions in maxillofacial region.
   - Notes: TNM classifications
3. Adverse effects of radiotherapy / chemotherapy.
4. Stages of malignancy.

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Chapter

8

Benign Tumors of the Jaw

According to Rupert Willis, neoplasm is

"An abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli that evoked the change."

Neoplasms can be classified as benign and malignant.

General characteristics of benign tumors are:

1. They are insidious in onset, are slow growing and spread by direct extension and not by metastases.
2. They have an unlimited growth potential
3. They are well-defined masses of regular, smooth outline with a fibrous capsule.
4. They usually resemble the tissue of origin histologically.
5. Clinically they show enlargement of the jaws or are found during a radiographic examination.

General Symptoms

1. Benign tumors are painless unless they are secondarily infected and do not metastasize.
2. They produce symptoms due to swelling and pressure effect on the surrounding structures.
3. A slow growing benign lesion towards the lower border of the mandible causes the cortex to expand.
4. Some tumors of the bone invade the adjacent normal bone like ameloblastoma.
5. Roots usually may be resorbed.
6. They sometimes recur as their complete removal is difficult.

General Radiographic Features

1. The tumors have a specific anatomic predilection
   - Odontogenic tumors occur in the alveolar process above the inferior alveolar nerve canal.
   - Vascular and neural lesions may originate inside the mandibular canal.
   - Cartilaginous tumors occur in jaw locations where residual cartilaginous cells lie such as in the condyle.
2. They are usually well defined, corticated or hyperostotic. Some tumors are demarcated by a radiolucent band of soft tissue or capsule at the periphery which separates more mature internal radiopaque portion from the surrounding normal bone.
3. The internal structure may be completely radiolucent, radiopaque or mixture of radiopaque-radiolucent structures.

There radiolucent tumors show various appearances. Some are radiolucent unilocular, multilocular, cystic, honeycomb or soap bubble (ameloblastoma, myxoma, hemangioma, central giant cell granuloma).

Mixed Radiopaque-Radiolucent Lesions

- Curved septae that are characteristics in ameloblastoma represent residual bone trapped into the tumor that has remodeled into curved septa.
- Reactive bone lesions seen in central giant cell granuloma.
- Numerous scattered radiopaque foci of varying size giving a snow-driven appearance seen in CEOT, milky-way lumen appearance seen in AOT.
- Complete radiopaque structures usually represent either residual bone or a calcified material that is being produced by the tumor-like osteoblastoma has an internal granular radiopaque pattern which produced by abnormal bone due to tumor.
- Benign tumors can be odontogenic and non-odontogenic tumors.

TABLE 8.1: Classification according to WHO

A. Benign odontogenic tumors

I. Odontogenic epithelial tumors without ectomesenchymal origin:
   a. Ameloblastoma
   b. Squamous odontogenic tumor
   c. Calcifying epithelial odontogenic tumor (CEOT)/Pindborg tumor.
   d. Adenomatoid odontogenic tumor (AOT)
   e. Keratocystic odontogenic tumor

II. Odontogenic epithelial tumors with ectomesenchymal origin with or without hard tissue formation.
   a. Ameloblastic fibroma
   b. Ameoblastic fibro-dentinoma
   c. Ameloblastic fibro-odontoma
   d. Compound and complex odontoma
   e. Odontoblastoma
   f. Calcifying cystic odontogenic tumor
   g. Dentinogenic ghost cell tumor

III. Odontogenic ectomesenchymal tumors with or without odontogenic epithelium
   a. Odontogenic fibroma
   b. Odontogenic myxoma
   c. Cementoblastoma: It is a solitary, slow growing hamartomatous tumor comprising of disorganized cementum at the apical end of the root. It is more common in males and younger adults, with no racial predilection. The involved tooth is vital and painful without any mobility. The adjacent teeth may get displaced. Cementum-like material or abnormal bone with invasion of root canal is seen in the histopathological sections.

Source: Pathology and Genetics of Head and Neck tumors, edited by Leon Barnes, Published by WHO in 2005.

B. Nonodontogenic tumors

I. Benign epithelial tissue origin
   a. Papilloma
   b. Keratoacanthoma

II. Connective tissue origin
   a. Fibroma
   b. Epulis
   c. Pregnancy tumor

III. Adipose tissue origin:
   a. Lipoma

IV. Cartilage tissue origin:
   a. Chondroma
   b. Chondroblastoma

V. Bone tissue origin:
   a. Osteoma
   b. Torus

VI. Lymphatic and vascular tissue origin:
   a. Hemangioma
   b. Sturge-Weber syndrome

VII. Neural tissue origin:
   a. Neuroma
   b. Neurofibroma
   c. Neuroblastoma

VIII. Muscle tissue origin:
   a. Leiomyoma
   b. Rhabdomyoma

Source: Collected and modified from *Textbook of Oral Pathology*. Shafer, Hine, Levy. Edited by B Sivapathasundaram, 8th edition. 2016. Elsevier Inc.

TABLE 8.2: Differences between benign and malignant tumors

	Benign tumors	*Malignant tumors*
1.	Usually single mass	Multiple masses may be seen
2.	Usually round	Irregular masses
3.	Slow growth	Rapid growth
4.	No necrosis	Necrosis may be seen, so fetid odour
5.	Lymph nodes may not be enlarged	Lymph nodes may be enlarged, fixed
6.	No metastasis	Distant metastasis
7.	Recurrence uncommon	Recurrence common
8.	Good prognosis	Poor prognosis
9.	Tumor cells similar to parent cells	Tumor cells are undifferentiated
10.	Well-defined fibrous capsule present	Fibrous capsule absent
11.	No invasion in connective tissue	Connective tissue invasion seen
12.	Normal nuclei	Abnormal nuclei
13.	No dysplastic changes	Dysplastic changes like abnormal mitosis, increased nuclear–cytoplasm ratio seen
14.	Well capsulated and defined margins	No capsule with ill-defined margins
15.	Root resorption may be seen	Root resorption may not be seen
16.	Displacement of adjacent structures like floor of maxillary sinus, inferior alveolar canal	Invasion of adjacent structures
17.	No floating tooth appearance	Floating tooth appearance due to severe bone destruction
18.	No pathologic fractures	May lead to pathologic fractures

I. EPITHELIAL TISSUE ORIGIN

A. Benign Odontogenic Tumors

I. Odontogenic epithelium tumors without ectomesenchymal origin:

◈ Ameloblastoma

According to Robinson, ameloblastoma is defined as "a tumor of the odontogenic epithelium, which is unicentric, non-functional, intermittent in growth anatomically benign and clinically persistent lesion which does not undergo differentiation to the extent of hard tissue formation."

It arises from remnants of dental lamina and dental organ (odontogenic epithelium).

Clinical features: Ameloblastoma is more commonly seen beyond the age of 40 years, in the molar ramus region. Males are more commonly affected than females. It gives rise to expansion of buccal and lingual cortical plates. Displacement of teeth in the involved region may be seen. Occasionally, pain or paresthesia is noticed. The surrounding bone is thinned out, so on palpation 'egg shell crackling' is felt.

Radiographic features: It is mostly seen in mandibular posterior region in molar-ramus area. The radiolucency is usually well-defined and delineated by a cortical border. In the maxilla it is usually more ill-defined.

Roots of the involved teeth may show resorption.

According to HM Worth, 4 types of appearance are seen.

1. **Unicystic type:** It appears as a unilocular radiolucency resembling the cyst.
2. **Spider variety:** From the center of the lumen, coarse strands of trabeculae radiate peripherally giving size to a *gross caricature of a spider.*
3. **Multilocular radiolucency:** Ameloblastomas which are seen as multilocular radiolucencies have a *soap-bubble appearance.*

4. **Solid ameloblastoma:** Multiple small radiolucencies are seen surrounded by polygonal or hexagonal thick-walled bony cortices giving rise to a *honeycomb* appearance.
   - Tooth displacement is common. An occlusal radiograph may demonstrate cyst-like expansion and thinning of a cortical plates leaving a thin "egg shell" of bone.

Variations

Malignant ameloblastoma is defined as that particular ameloblastoma which has given evidence of truly malignant behavior judged chiefly by the occurrence of metastasis, but in which the metastatic lesions have no significant differences from the primary tumor.

Ameloblastic carcinoma: It is defined as that type of ameloblastoma in which there has been obvious histologically malignant transformation of the epithelial component and in which the tumor has behaved in a malignant fashion, so that the metastatic lesions do not resemble the primary odontogenic tumor.

Mural ameloblastoma: It is unicystic variant arising from the lining of dentigerous cyst.

Recurrent ameloblastoma: Recurrent tumor has typical characteristic appearance of multiple small cyst-like structures with very coarse sclerotic cortical margins.



Fig. 8.1: Radiograph showing ameloblastoma



Fig. 8.2: OPG showing ameloblastoma

Management: Complete resection.

Differential diagnosis:

Residual cyst	History of tooth extraction
Central giant cell granuloma	More common in anterior to premolar region
Dentigerous cyst	Radiolucency surrounds CEJ
KOT	Has curved septae, minimal expansion
Giant cell granuloma	Anterior to molars, younger age
Odontogenic myxoma	Sharp, thin septae

◈ Calcifying Epithelial Odontogenic Tumor (CEOT): Pindborg's Tumor

It is an epithelial odontogenic tumor originating from the reduced enamel epithelium.

Clinical features: The frequent age group affected is adults over 40 years of age. Males are common affected than females. Mandible is twice more affected than maxilla with a predilection for premolar–molar region, the swelling is hard, painless and shows slow expansion of buccal and lingual cortical plates. Sometimes may be associated with impacted tooth.

Radiographic features: The lesion is unilocular or multilocular with a well-defined cortex. Initially the lesion is radiolucent. In the

mixed stage, numerous scattered radiopaque foci are seen giving a *driven snow appearance*. The trabeculae are irregularly arranged in all directions. It may displace erupting tooth or cause impaction.

On CT examination, expansion of the jaw bone with thinning of buccal and lingual cortex may be seen because of the well-defined mass.

Histologically they are not capsulated. Round eosinophilic masses which undergo calcification, in the form of Liesegang's rings are seen within the tumor.

Management: Enucleation and curettage

Differential diagnosis

Dentigerous cyst	Impacted tooth
Ameloblastoma	Middle age, molar-ramus region

◈ Adenomatoid Odontogenic Tumor (AOT)

It is also called adenoameloblastoma. The tumor is a noninvasive hamartoma arising from enamel organ epithelium and is sometimes as a mixed tumor as it contains connective tissue stroma and sometimes calcifications that have been interpreted as enamel like or dentinoid material. It is commonly associated with an unerupted maxillary cuspid.

- **Follicular type:** Associated with impacted tooth
- **Extrafollicular type:** Not associated with impacted tooth

Clinical features: The average age range is 5 to 50 years with an average age of below 20 years with a female predilection. It is slow growing, gradually expanding, and asymptomatic swelling, associated with unerupted or impacted tooth. It is observed in the anterior region of the jaw mostly.

It is most commonly seen in the cuspid region in the maxilla. The cortex may be expanded. This tumor has follicular relationship with an impacted tooth, it often does not attach at the cemento-enamel junction but surrounds a greater part of the tooth. Often a tooth may be missing in the region affected by the tumor.

Peripheral lesions have been observed on the gingiva as painless masses.

Radiographic features: It is associated with impacted tooth, usually canine. The lesion shows a unilocular radiolucency with well-defined corticated borders. The small radiopaque flecks give rise to *milky way lumen* appearance to the lesion. Most commonly AOT shows a pericoronal radiolucency with well-defined margins. Rarely root resorption is seen. The adjacent teeth may be displaced.

Management: Resection

Differential diagnosis:

Follicular cyst	Radiolucency from CEJ
CEOT	Posterior mandible and older age group
Ameloblastic fibro-odontoma	Multilocular, radio-opacities of enamel and dentine seen in radiolucent area.

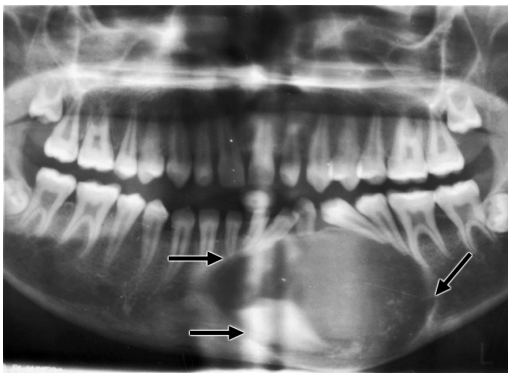


Fig. 8.3: OPG showing AOT associated with impacted canine

◈ Odontogenic Keratocyst (Keratocystic Odontogenic Tumor—KOT)

WHO, in 2005, reclassified KOT as odontogenic tumors from its earlier nomenclature as odontogenic keratocyst which was first explained by Philipsen in 1945. It is also grouped as primordial cyst. It is derived from the remnants of dental lamina. KOTs can be associated with nevoid basal cell carcinoma.

The tumor arises from the dental lamina.

Clinical features: The tumor is more common in 2nd to 3rd decade, with a more male predilection and with a mandibular molar ramus predilection. It is usually asymptomatic. There is minimal swelling and expansion of bone and expands along the bone.

The lumen filled with thin straw colored fluid.

The condition shows high recurrence rate because of:

- Thin epithelium
- Presence of daughter cysts
- No rete pegs in epithelium which is difficult to scrape

Radiographic features: The common site is the posterior mandible, superior to the inferior alveolar canal. The lesion has corticated margins with a scalloped outline. It is smooth, round or oval in shape. It shows radiolucent internal structure with curved septae giving it a multilocular appearance. There is minimal expansion as the tumor grows along the internal aspect of the bone. The roots may get displaced. The inferior alveolar canal may be displaced inferiorly. Radiologically these variations can be noted

- *Envelopmental type:* Envelops an unerupted tooth
- *Replacement type:* Replaces normal teeth
- *Collateral type:* Adjacent to roots of teeth



Fig. 8.4: OPG showing OKC

Management: Marsupialization or enucleation. Carnoy's solution is used to irrigate larger lesions and thus has been observed to reduce the size of the lesion.

Differential diagnosis

Dentigerous cyst	Radiolucency involving the CEJ of unerupted teeth
Ameloblastoma	Expansion of cortex, middle age, no straw colored fluid on aspiration
Primordial cyst	Missing tooth seen
Traumatic bone cyst	Usually unilocular with scalloped margins, mostly positive history of trauma

II. Epithelial tumors with ectomesenchymal origin

◈ Ameloblastic Fibroma

It is a tumor of the odontogenic epithelium of the enamel organ and odontogenic mesenchyme of the primitive dental pulp. It is non-invasive as it is well encapsulated. Histopathologically the epithelium is odontogenic in nature and shows focal areas of calcifications. The connective tissue contains randomly oriented fibroblasts.

Clinical features: It is an asymptomatic, slow growing tumor commonly seen in younger age group with an average of 14 years with no sex predilection. The frequent site is mandibular molar region, often associated with an unerupted tooth.

Radiographic features: They are seen as unilocular or multilocular well corticated radiolucencies with indistinct curved septa. Expansion may be noted with an intact cortex.

Management: Surgical excision.

Differential diagnosis:

- Ameloblastoma—middle age, coarse septa
- Giant cell granuloma—anterior to first molars, granular, ill-defined septa.

◈ Ameloblastic fibro-odontoma

It is an expansile tumor with soft tissue component as fibroma and hard tissue

component as odontoma. It has a higher growth potential with local destruction. Histopathologically, a well-encapsulated lesion, with the epithelium resembling dental lamina with the connective tissue showing fibroblasts is observed. In the adjacent areas, complex odontomas are seen.

Clinical features: It is seen in the first and second decade of life. It is an asymptomatic, slow growing tumor with swelling, commonly seen in the posterior mandible.

Radiographic features: A well-defined, corticated, large unilocular or multilocular, mixed radiopaque-radiolucent lesion is seen. It may be associated with an impacted tooth.

Management: Surgical enucleation.

Differential diagnosis:

- Ameloblastic fibroma—no calcification
- Odontoma—has no radiolucent component

◈ Odontoma

Odontomes are believed to be hamartomas of dental origin which are derived from the primordial odontogenic cysts during the period of tooth development and they do not grow beyond a particular point.

Mixed variety of odontoma can be classified into:

- Compound composite odontoma
- Complex composite odontoma
- Germinated odontoma
- Dilated odontoma: Further classified as (HM Worth)
  - dens in dente
  - root dilation
  - inverted open umbrella
  - fleur-de-lis which resembles the French emblem

Clinical features: Compound odontoma is made up of two or more tooth-like bodies with enamel capped crowns known *as denticles*, whereas the complex odontoma appears as a single mass with haphazard distribution of enamel, dentine and cementum. Most of compound type occur in the anterior maxilla mainly in association with the crown of an unerupted canine. In contrast, 70% of complex odontome are found in the mandibular first and second molars.

Dilated odontoma is seen as a single calcified structure with a more radiolucent central portion that has an overall form similar to a doughnut.

Radiographic features:

- *Compound odontome:* It is more common in anterior maxilla, around crowns of unerupted teeth. It appears as multiple radiopaque bodies surrounded by a radiolucent fibrous capsule which is in turn surrounded by a corticated border.
- *Complex odontome:* It is more common in mandibular molar region. It appears as a dense, irregular radiopaque mass, the density of which is equal to that of the dental tissues. It is surrounded by a radiolucent halo which in turn is surrounded by a corticated well-defined border.

Radiographically dilated odontome shows tooth within a tooth appearance because of enamel lined tract within the tooth.

Management: Simple excision

Differential diagnosis:

Complex odontome:

Cemento-ossifying fibroma	More radiopaque, younger patients
Periapical cemental dysplasia	Multiple, common in lower anterior periapical region, wider uneven sclerotic border
Calcifying epithelial odontogenic tumor	Fleks of calcification seen, less opaque.
Enostosis	Do not have soft tissue capsule

◈ Dentinogenic Ghost Cell Tumor

Dentinogenic ghost cell tumor (DGCT) is a rare odontogenic tumor with a locally invasive behavior. It is proposed that DGCT is a neoplastic variant of calcifying epithelial odontogenic cyst. It was renamed

by Práetorius et al. and more recently categorized as a separate entity in the updated classification of the World Health Organization (WHO).

Clinical features: It usually affects elderly people and 75% occur in males. Two variants have been recognized: Intraosseous (central) and extraosseous (peripheral). Intraosseous lesions show locally invasive behavior and mostly affect the canine to first molar region. Peripheral DGCT usually shows predilection for the anterior portion of the jaw.

DGCT is characterized by a peculiar histology composed of ameloblastoma like islands of epithelial cells in a fibrous connective tissue stroma with variable amounts of keratin production or dentinoid material. Connection between tumor cells and the overlying oral mucosa has been described in the peripheral lesions.

The condition shows a high recurrence rate.

Radiographic features: DGCTs usually appear as unilocular, mixed radiolucent and radiopaque lesions. Usually the lesions show well-defined borders, but poorly defined borders have been observed in cases.

Management: Radical treatment of peripheral or segmental resection

III. Odontogenic ectomesenchymal tumors with/without odontogenic epithelium

◈ Ossifying Fibroma

It is classified as a fibro-osseous lesion. The term cemento-ossifying fibroma was discarded as it was not easy to differentiate between cementum and bone histologically and radiographically.

Peripheral and central variety can be observed.

Peripheral ossifying fibroma: Calcifications or ossifications seen in the hypercellular fibroblastic stroma.

Clinical features: It is more common in young adults, females than males. It is well-demarcated focal mass exclusively on the gingiva, in the interdental papillae region, sessile or pedunculated. It is pale pink or cherry red. The surface may be intact or ulcerated.

Radiologic features: No underlying bone involvement seen. It rarely shows mild erosion.



Fig. 8.5: Odontogenic ectomes enchymal tumors

◈ Central Ossifying Fibroma

Clinical features: It is more common in young adults with equal occurrence males and females and more common in the mandibular premolar molar region. It is asymptomatic. Facial asymmetry may be noted because of the swelling. Displacement of teeth is common.

Radiographic features: It is an expansile lesion with a clearly defined cortical margin which enlarges concentrically. Radio-opaque foci appear in later stages which tend to coalesce. The teeth in the region may get displaced and may get resorbed. It grows into cavities like nasal, antral and destroys surrounding bone. It can be subclassified as:

- Ossifying form
- Cementifying or psammomatoid form
- Aggressive or juvenile form: More aggressive form
- Familial gigantiform fibroma

Management: Surgical enucleation

Differential diagnosis:

Ameloblastoma	Age, location
Central giant cell granuloma	Anterior to molars, granular, ill-defined septae
Odontogenic myxoma	Straight sharp septae

◈ Odontogenic Myxoma

Myxomas are rare benign tumors of mesenchymal in origin occurring only in facial bones. These are not encapsulated and tend to infiltrate into the surrounding tissues.

Clinical features: Myxomas are more common in females, usually occur at younger age between 10 and 30 years. It is a slow growing painless swelling, mainly affects mandible in the premolar–molar region. Teeth involved are loosened.

Radiographic features: A well-defined multilocular lesion associated with impacted tooth. The internal structure is made up of thin, straight bony trabeculae arranged at right angles to the periphery giving rise to a *tennis racket or step ladder like pattern*. The lesion also frequently scallops between the roots of adjacent teeth similar to a simple bone cyst.

Histologically, myxomas show loosely arranged spindle cells with long fibrillary processes, which mix with the odontogenic epithelium.

Management: Resection with wider margins

Differential diagnosis:

Ameloblastoma	Septae are not thin and straight, older age, molar ramus region
Central giant cell granuloma	Common in anterior mandibular region
Central hemangioma	Calcifications in larger lesions, no missing teeth
Odontogenic sarcoma	Cortex not intact

Cementoblastoma

It is a solitary, slow growing hamartomatous tumor comprising of disorganized cementum at the apical end of the root. It is more common in males and younger adults, with no racial predilection. The involved tooth is vital and painful without any mobility. The adjacent teeth may get displaced. Cementum like material or abnormal bone with invasion of root canal is seen in the histopathological sections.

Radiologic features: They are commonly seen in the mandibular premolars or first molars. A well-defined radiopacity with corticated margins surrounded by a well-defined radiolucent rim because of the soft tissue capsule is seen at the apical end of the root obliterating the root outline. The internal structure is amorphous and gives a wheel spoke appearance. The roots may show resorption. Larger lesions cause the cortex to expand. Jaw expansion is seen only in larger lesions.

Management: Extraction of involved tooth

Differential diagnosis

- Focal cemental dysplasia—irregular shaped, not attached to root
- Periapical sclerosing osteitis—no radiolucent rim
- Hypercementosis—surrounding periodontal ligament space is thinner, no root resorption.

B. Non-odontogenic Tumors

I. Epithelial tissue origin

◈ Papilloma

It is a rare neoplasm of respiratory epithelium. The most common site is nasal cavity and para-nasal sinuses. Chronic trauma is a major etiology. Oral papillomas are caused by HPV virus.

Clinical features: It is more common in men, third and fourth decade of life. It is an exophytic, cauliflower-like growth. The

maxillary and ethmoidal sinus are more commonly affected. It can cause unilateral nasal obstruction, nasal discharge, pain and epistaxis. There is usually a history of recurrent sinusitis. The other sites could be tongue, cheek, lip or oesophagus. It rarely grows more than 1 cm. Oral papillomas do not undergo malignant changes.



Fig. 8.6: Papilloma

Radiographic features: It is a small homogeneous mass of soft tissue density. The pressure effect may lead to erosion of bone.

Management: Surgical excision, laser.

Differential diagnosis:

Squamous cell carcinoma	More exophytic appearance.
Verrucous carcinoma	Seen in elderly patients with a history of tobacco smoking habit, flat, wide-based lesion.

◈ Keratoacanthoma

It is a localized lesion, usually found in the sun-exposed region, tar, HPV virus, immunocompromised status. It has a rapid growth. It is fixed to surrounding tissue with a pseudoepitheliomatous periphery and a thick keratin cap. 40% of the lesions regress spontaneously.

Clinical features: It occurs at any age group. Men more commonly affected. The common sites are face, neck and dorsum of upper extremities. The lesions are usually solitary, round or dome-shaped. The surface is shiny with a central keratin plug.

Management: Surgical excision, lasers.

Differential diagnosis:

Oral squamous cell carcinoma	Larger lesions, more exophytic.

◈ Fibroma

It is not a true neoplasm with a limited growth potential. Histologically, it appears as a hypocelluar mass with hyperkeratinized epithelium.

Clinical features: It presents as a rounded, painless, firm non-blanching mass on the intact mucosa. it could be seen on the cheek, lips, lateral border of the tongue. It is referred to as traumatic fibroma if it is secondary to trauma.

Management: Surgical excision

Differential diagnosis: Lipoma—soft in consistency

◈ Lipoma

It is a rare intraoral benign tumor of adipocytes. The etiology could be trauma, chronic irritation, infection and hormonal imbalance.

Clinical features: It is more common in age above 30 with no gender predilection. It has been observed on the tongue, buccal mucosa and floor of the mouth. Two variants are: Superficial and diffuse form.

Superficial form is single, sessile or pedunculated mass and diffuse is a deeper version usually. Lipomas are soft in consistency with a yellowish appearance.

Multiple lipomas in head and neck region are common in neurofibromatosis and Gardner's syndrome.

Histologically, collection of multiple adipocytes, well-demarcated from the surrounding connective tissue is seen. Depending upon the involvement of tissues, the lipoma is defined, e.g. small vasculature-angiolipoma.

Management: Lipomas are excised with no recurrence.

◈ Chondroma

These are extremely rare benign tumors of mature cartilage. Histopathologically, lobulated hyaline cartilage is seen which contains small, regular chondrocytes.

Clinical features: They are seen in the anterior maxilla, nasal septum or the body of mandible. They don't have any sex predilection and are painless.

Radiographic features: They appear as well demarcated radiolucent expansions of the bone. At times, calcification of cartilages is seen as radiopacities.

Management: Surgical excision, if required.

◈ Osteoma

Most common mesenchymal neoplasm of bone and commonly seen in the para-nasal sinuses.

Clinical features: It is more common in males, 2nd–4th decade. It is a slow growing, asymptomatic, bony hard swelling. The mucosa is normal over the swelling. It is more common in frontal and ethmoidal air sinuses. The symptoms depend on extent of the growth. Osteoma of maxillary sinus may cause nasal obstruction, swelling on the face or orbital proptosis.

In the jaws, mandibular posterior region is common and could be exophytic.

Soft tissue osteomas are rare and known as osteoma mucosae.

Radiographic features: It is usually round or lobulated homogeneous radiopacity with sharp-defined margins. Larger lesions can displace adjacent structures.

Histologically, osteomas are composed of dense compact bone or coarse cancellous bone.

Management: Surgical resection

Differential diagnosis:

× Fibrous dysplasia—diffuse borders, homogeneousness of bone differs
× Torus—usually bilateral, diffuse

◈ Torus

A bony overgrowth in the body of the bone is a torus. It is the most common exostosis of bone. It develops due to genetic or environmental factors. It may sometimes obstruct in the making of a denture.

Clinical features: It is more common in females, around 30 years of age. It is asymptomatic and may appear single or multiple, unilateral or bilateral, flat, lobulated, or nodular. The overlying mucosa is normal or may get ulcerated due to trauma. The most common sites in maxilla is hard palate and in mandible is lingual surface of the alveolar ridge.

Radiographic features

Torus palatinus: It is well-defined, homogeneous dense radiopacity attached to the palate. The borders are usually well defined.

Torus mandibularis: It could be unilateral or bilateral, homogeneous radiopacity. It is well-demarcated anteriorly and poorly demarcated in the posterior region.

Management

- × No treatment if asymptomatic
- × Surgical excision if obstructs in denture making or routine activities

Differential diagnosis

Exostosis	Diffuse margins, density of bone

◈ Peripheral Giant Cell Granuloma

It is a reactive lesion of the oral cavity. The etiology could be local irritation, dental plaque, calculus, faulty restoration, ill-fitting dental appliances. Histologically, it is non-capsulated lesion with giant cells resembling osteoclasts in the connective

tissue. Numerous capillaries around the periphery of the lesion.

Clinical features: It occurs at around the 4th to 6th decade. Females are more affected than males. It is usually asymptomatic, has a rapid growth rate. It occurs on gingiva or alveolus anterior to the molars. It is pedunculated or sessile, 0.5 to 1.5 cm, red, vascular and granular in appearance. It may get ulcerated due to trauma.

Radiographic features: It may not show any bony involvement. It shows mild superficial erosion or peripheral cuffing of the bone is seen sometime.

Management: Conservative excision.

Differential Diagnosis:

- Other inflammatory lesions—history, biopsy
- Hemangioma—by birth
- Metastatic carcinoma—has a primary lesion elsewhere

◈ Lymphangioma

It is a benign developmental hamartomatous hyperplasia of lymphatic vessels. It is a developmental malformation of vessels. It can be classified as:

a. Simple lymphangioma
b. Cavernous lymphangioma
c. Cellular or hypertrophic lymphangioma
d. Diffuse systemic lymphangioma
e. Cystic hygroma lymphangioma

Clinical features: Usually present at birth or before the age of 10. Head and neck lymphangiomas are on the lateral side of the neck and termed cystic hygromas which appear as large, diffuse swellings. Intraorally the common sites are tongue, buccal mucosa and lips. Superficial lesions appear papillary with slightly reddish hue, deeper lesions are diffuse nodules without any significant superficial changes. Tongue involvement may show macroglossia.

Histologically, multiple coalesced lymph vessels in a fibrovascular stroma are seen.

Surgical debulking is the typical line of management.

◈ Central Hemangioma

It is a hamartoma. Proliferation of blood vessels is seen. It is rare in the jaws. It could be developmental or traumatic.

Clinical features: The male: female ratio is 1:2. It is more common in the first decade. The mandible is twice more affected than the maxilla. The ramus and body of mandible is the most common location. It is slow growing, painless bony hard expansion. The adjacent teeth may be displaced or loosened. The tumors are sometimes compressible and show bruit on auscultation. Aspiration shows arterial blood.

Types

- *Capillary:* Aggregation of smaller capillaries.
- *Cavernous:* Dilated blood vessels mainly arteries.

Radiographic features: Larger lesions show expansion of cortex. Well-defined corticated margins are seen. A sun-ray appearance is seen because spicules of bone seen coming out of the bony surface. The marrow spaces are enlarged. Coarse, dense, well-defined trabeculae are seen giving a honeycomb appearance. Phleboliths are seen when the soft tissues are involved. Roots are resorbed sometimes. The inferior alveolar canal follows a tortuous course.

Management: *En bloc* resection, use of sclerosing agents to reduce the size of the lesion.



Fig. 8.7: Hemangioma involving upper lip

Differential diagnosis:

Ameloblastoma	Age, location, no calcifications

II. Neural tissue origin

◈ Neuroma

It is not a true neoplasm. There is abnormal proliferation of the peripheral nerve due to mechanical or chemical irritation in an attempt to regenerate.

Clinical features: There is no sex predilection. It is more common in 2nd and 3rd decade. The most common site is inferior alveolar canal. It is a slow growing tumor with swelling, severe pain, paresthesia or neuralgia.

Radiographic features: The mental foramen is the most common location. It is a radiolucent lesion with well-defined corticated margins. There is expansion of the inferior alveolar canal.

Management: Surgical excision along with the proximal portion of the nerve.

◈ Neurofibromatosis: (von Recklinghausen disease)

It is a genetic disorder of the skin. It has two subtypes: Neurofibromatosis 1 (NF-1) and neurofibromatosis 2 (NF-2).

NF-1 is an autosomal dominant condition and appears early in life as 1.5 cm or larger café-au-lait macules in the axilla (axillary freckle sign or Crowe sign) and freckles. These grow in size with age. There could be associated skeletal abnormalities like bone erosion, pigmented hamartomas of the iris or Lisch nodules are observed.

Well-circumscribed, firm growths are seen originating from Schwann cells. In the jaw they may occur in the mandibular canal.

Intraorally, discrete, non-ulcerated nodules are seen on the buccal mucosa, palate, alveolar ridge floor of the mouth and gingiva occurs when tongue is involved.

Diagnostic criteria:

1. Six or more café-au-lait macules
2. Two or more neurofibromas of any type
3. Freckling of axial or inguinal region
4. Optic glioma
5. Two or more Lisch nodules
6. Distinctive osseous lesion
7. Seen in first degree relations.

Shows no or a few peripheral signs. Intracranial or intraspinal neural tumors in the form of schwannomas or meningiomas are seen.

Diagnostic criteria:

- Bilateral VIII nerve tumors OR
- First degree relative OR
- Two of the following criteria:
  - Dermal or subcutaneous neurofibromas
  - Plexiform neurofibromas
  - Schwannoma, glioma
  - Meningioma

Radiographic findings: Unilocular radiolucencies with sharp borders around the nerve region are seen. The nerve canal may show fusiform enlargement.

Differential diagnosis:

Vascular lesions	The whole canal may be enlarged.

Management: Solitary lesions can be surgically excised. Recurrence is observed with malignant transformation in a few cases.

III. Muscle tissue origin

◈ Leiomyoma

It is a benign tumor of the smooth muscles and are uncommon in the oral cavity, except in the blood vessels or excretory ducts of salivary glands.

Clinical features: They are seen in adults over the age of 30 years. It is a slow growing, painless, occasionally pedunculated lesion. It resembles normal mucosal surface.

Management: Surgical excision

◈ Rhabdomyoma

It is a hamartoma rather than a true neoplasm.

Clinical features:

- **Adult type:** It is found in females and older age group. Symptoms are seen depending upon their location. If it occurs on the tongue, it may cause protrusion and if it is seen in the pharyngeal muscles, it may lead to obstruction. The other sites where it could be seen are floor of the mouth or soft palate
- **Fetal type:** It is rare and presents as a painless mass within the muscles usually beneath the intact skin or mucosa
- **Genital type:** It is the rarest and seen as a polypoid mass on the genitalia.

Management: Excision

Differential diagnosis: Lipoma—soft consistency

TABLE 8.3: Differences between cysts and benign tumors

	Cysts	*Benign tumors*
1.	Usually radiolucent	Mixed radiolucency seen usually
2.	Smooth, round, continuous, corticated	Scalloped borders
3.	Trabeculae absent	Trabeculae may be present
4.	Septae may be present	Septae are absent
5.	Buccal expansion may be seen, rarely lingual expansion	Buccal and lingual expansion may be seen
6.	Root resorption uncommon	Root resorption may be seen
7.	Rarely splaying of roots	Splaying of roots common

FREQUENTLY ASKED QUESTIONS

1. Classify benign tumors. Write about clinical features, radiographic features and differential diagnosis of ameloblastoma/AOT/PGCG/ossifying fibroma.
2. Write a short note on fibroma, osteoma, torus.

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Chapter 9

Pigmentation

The oral mucosa and peri-oral tissues can assume a variety of appearances, showing color variations in health and disease. The normal color of gingival tissues has traditionally been described as coral pink, whereas the color of the buccal mucosae and oral vestibules has been described as moist pink. The causes of oral mucosal pigmentations are varied. Broadly stating the oral pigmentations can arise as a result of endogenous or exogenous causes. Endogenous pigmentation arises as a result of intrinsic colored complexes present in the body. Exogenous pigmentation results from extrinsically administered drugs, chemicals, etc. or chromogenic bacteria. Figure 9.1 presents a simple classification of oral pigmentation.

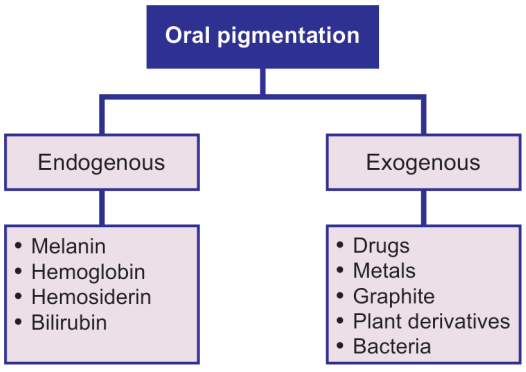


Fig. 9.1: Classification of oral pigmentation

ENDOGENOUS ORAL PIGMENTATION

Colored molecular complexes synthesized within the human body are the causes of endogenous oral pigmentation. Melanin, is a brown-black pigment synthesized by melanocyte, residing near the basal layer of the epithelium. As a general rule, the amount of melanin pigment normally present imparts the skin tone or color. It follows that, any disturbance in the melanin metabolism leads to blackish or brownish appearance of the oral mucosa.

Hemoglobin is a red compound present in the red blood cells. Any factors causing extravasation of blood and lysis of RBCs and vascular overgrowth may hence manifest as reddish / reddish blue appearing lesion on the oral mucosa. Hemosiderin is a hemoglobin-derived granular pigment that is golden yellow to brown and accumulates in tissues when there is a local or systemic excess of iron.

Bilirubin, a yellow orange pigment, is basically a catabolic product synthesized due to the breakdown of hemoglobin. Hyperbilirubinemia causes jaundice, i.e yellowish appearance of skin and mucous membranes.

Table 9.1 enlists in detail the various causes of endogenous oral pigmentation.

TABLE 9.1: Causes of endogenous oral pigmentation (adapted from Burket's Oral Medicine, 11th edition)

Pigment	*Etiology*	*Associated lesion/condition*
Melanin	Physiologic, developmental, idiopathic, neoplastic, reactive, drugs, hormones, genetic, autoimmune, infectious	▪ Ephelis ▪ Melanotic macule ▪ Actinic lentigo ▪ Melanocytic nevus ▪ Malignant melanoma ▪ Physiologic pigmentation ▪ Chloroquine-induced pigment ▪ Lichen planus pigmentosus ▪ Laugier-Hunziker pigmentation ▪ Smoker's melanosis ▪ Peutz-Jeghers disease ▪ Adrenal insufficiency ▪ Cushing's syndrome ▪ Oral submucous fibrosis ▪ HIV/AIDS
Hemoglobin and hemosiderin	Developmental, hamartomatous, neoplastic, genetic, autoimmune, trauma, idiopathic, inflammatory	▪ Varix ▪ Hemangioma ▪ Lymphangioma ▪ Angiosarcoma ▪ Kaposi's sarcoma, ▪ Hereditary hemorrhagic telangiectasia ▪ CREST syndrome ▪ Hematoma, ecchymosis, purpura, petechiae ▪ Vasculitis ▪ Hemochromatosis
Bilirubin	Trauma, alcohol, infection, neoplasia, genetic, autoimmune	▪ Jaundice

MELANIN ASSOCIATED ENDOGENOUS ORAL PIGMENTATION

Melanin is the pigment derivative of the amino acid tyrosine. It is synthesized by the melanocytes, which reside near the basal cell layer of the oral epithelium. Melanin is synthesized within specialized structures known as melanosomes. Melanin is composed of eumelanin, which is a brown-black pigment, and pheomelanin, which has a red-yellow color. The melanocytes present in the skin serve as protection against actinic radiation and act as scavangers against cytotoxic metabolites, however, their role in the oral mucosa is obscure. Light, hormones, and genetic constitution influence the amount of pigment produced. Melanin pigmentation may be physiologic or pathologic. It may be focal, multifocal, or diffuse in its presentation. Figure 9.2 highlights the various causes of oral melanotic hyperpigmentation. Biopsy is definitively mandated whenever a clear-cut cause of oral hyperpigmentation cannot be ascertained.

Focal Melanocytic Pigmentation

Freckle *(Ephelis)*

The cutaneous freckle, or ephelis is a common, asymptomatic, small (1–3 mm), well-circumscribed, tan- or brown-colored macule that is often seen on the sun-exposed regions of the facial and perioral skin.



Focal
- Freckle/ephelis
- Oral/labial melanotic macule
- Oral melanoacanthoma
- Melanocytic nevus
- Malignant melanoma



Multifocal/diffuse
- Physiologic
- Smokers melanosis
- Drug-induced melanosis
- Postinflammatory hypermelanosis
- Melasma



Associated with systemic disease
- Hypoadrenocorticism
- Cushing's syndrome/Cushing's disease
- Hyperthyroidism
- Primary biliary cirrhosis
- Vitamin B_{12} deficiency
- Peutz-Jegher's syndrome
- Café au lait pigmentation
- HIV associated melanosis

Fig. 9.2: Causes of melanotic oral hyperpigmentation

Etiopathogenesis: Freckles are developmental in origin and a genetic basis for their formation has been identified that includes polymorphisms in the ***Melanocortin 1 receptor gene (MC1R)*** and an another freckles-predisposition gene which has been mapped to chromosome ***4q32–q34***.

Clinical features: These innocuous macules are most commonly observed in light-skinned individuals and in red- or light blond-haired individuals. Although the pigmentation itself is focal, most patients have multiple freckles. These are usually more in number and darker in intensity during childhood and adolescence. Freckles tend to become darker during periods of prolonged sun exposure (spring, summer) and less intense during the autumn and winter months. They arise as a result of temporary overproduction of melanin by a normal quota of melanocytes due to stimulation by UV radiation. With increasing age, the number of freckles and their color intensity tends to reduce.

Treatment: No therapeutic intervention is needed as the lesions tend to spontaneously resolve over a period of time.

Oral Melanotic Macule

The oral melanotic macule is defined as a benign, pigmented lesion exclusive to the oral mucosa, with no known dermal counterpart. It is the most common oral lesions of melanocytic origin, that is relatively innocuous in nature.

Etiopathogenesis: The etiology of the melanotic macule remains largely obscure. Trauma has been postulated to be an elucidating factor. In a rare instance, the lesion has also been reported after external beam radiotherapy. However, exposure to sunlight has no role whatsoever in the development of these lesions.

Clinical features: Melanotic macules develop more common in females with a predisposition for the lower lip and gingiva though any intra-oral mucosal site may be involved. It is usually a solitary lesion that occurs mostly in light-skinned individuals. Although the lesion may develop at any age, it generally tends to present in adulthood, mean patient ages being between 31.5 and 44 years. Congenital melanotic macules have also been reported.

The lesions usually present as small (<1 cm), well-circumscribed, oval macules that are uniformly pigmented, brown to black in color (Fig. 9.3). Most of the lesions remain constant in size and do not tend to become malignant. Their size is unaffected by sun exposure. They do not recur after surgical removal. Microscopically, increased melanin is seen in the basal cell layer with many lesions also showing melanin in the lamina propria, some of which is contained in melanophages.

Differential diagnosis: The differential diagnosis includes melanocytic nevus, malignant melanoma, amalgam tattoo, and focal ecchymosis. If such pigmented lesions are present after a 2-week period, ecchymosis can usually be ruled out, and a biopsy specimen should be obtained to secure a definitive diagnosis. Since oral mucosal malignant melanomas have no defining clinical characteristics, a biopsy of any persistent solitary pigmented lesion is always warranted.



Fig. 9.3: Melanotic macule present on the left buccal mucosa

Treatment: The incisional biopsy is diagnostic as well as curative for the lesion.

Oral Melanoacanthoma

Oral melanoacanthoma is a benign, relatively uncommon pigmented lesion of the unique to the oral mucosa. The lesion is innocuous in nature, with many cases showing spontaneous regression. Oral melanoacanthoma is an entity clearly distinct from the melanoacanthoma of skin. The cutaneous melanoacanthoma represents a pigmented variant of seborrheic keratosis and typically occurs in older Caucasian patients.

Etiology and pathogenesis: The oral melanoacanthoma is essentially a reactive lesion. Patients often report a history of acute trauma or a chronic irritation usually prior to the development of the lesion.

Clinical features: Oral melanoacanthoma is seen almost exclusively in the individuals of the negroid race, has a definite a female predilection, and is most common during the third and fourth decades of life. The buccal mucosa is the most common site of occurrence. The lips, palate, gingiva, and alveolar mucosa also may be involved. Most patients exhibit solitary lesions, although

bilateral or multifocal involvement is possible as well. Oral melanoacanthomas typically are asymptomatic; however, pain, discomfort, burning, and pruritus have been reported in a few cases. The lesion may be smooth, flat or slightly raised, and dark-brown to black in color. Lesions often demonstrate an increase in size rapidly, reaching a diameter of several centimeters within a period of a few weeks.The borders are typically irregular in appearance, and the pigmentation may or may not be uniform.

Differential diagnosis: The clinical presentation and a rapid increase in the size of the lesion often gives rise to the suspicion of malignant melanoma. Since, clinically it is not distinguishable from other melanocytic lesions, a nevus and melanotic macule could also be considered in the differential diagnosis.

Treatment: Because of the alarming growth rate of oral melanoacanthoma, incisional biopsy is usually indicated. Microscopically, the oral melanoacanthomas are characterized by a proliferation of benign, dendritic melanocytes throughout the full thickness of an acanthotic and spongiotic epithelial layer. A mild lymphocytic infiltrate with exocytosis is also characteristic. Once the diagnosis has been established, no further treatment is necessary. The biopsy procedure itself may lead to spontaneous regression of the lesion. Recurrence or development of additional lesions has been reported only rarely. There is no potential for malignant transformation. In cases where a source of irritation is present, it must be removed to prevent any future recurrence.

Melanocytic Nevus (Mole)

The term 'nevus' encompasses a varied group of pigmented lesions occurring on the skin or oral mucosa. Nevi could be congenital or developmental in origin. As opposed to ephelides and melanotic macules, which result from an increase in melanin pigment synthesis, nevi arise due to proliferation of melanocytes.

In general, both genetic and environmental factors are thought to play a role in the formation of nevi. Sun exposure is a well-recognized factor for the development of nevi on the skin. The role of genetics in nevogenesis, has been evidenced by the occurrence nevi in a number of inherited diseases, e,g. Turner's syndrome and Noonan syndrome, etc.

Acquired Melanocytic Nevus

The most commonly recognized nevus is the **acquired melanocytic nevus,** or common **mole**—so much so that the simple term *nevus* is often used synonymously for these pigmented lesions. The acquired melanocytic nevus represents a brownish black pigmented lesion of the skin and mucous membrane that arises due to a benign, localized proliferation of the *nevus cells* (Fig. 9.4). The nevus cells are the derivatives of neural crest cells.



Fig. 9.4: A melanocytic nevus on the face in a middle aged Indian man

Clinical features: The development of the acquired melanocytic nevi on the skin usually begins in childhood, and most lesions are present before 35 years of age. There is a slight female predilection for their development. It has also been found that there is an increased occurrence of these lesions in Caucasians. The head and neck region is relatively a common site, with most lesions.

Acquired melanocytic nevi advance through several clinical stages, which tend to correlate with specific histopathologic features. The foremost clinical presentation is that of a sharply demarcated, brown or black macule, typically less than 6 mm in diameter, **the junctional nevus**. As the lesion progresses over time, the nevus cells proliferate to produce a slightly elevated, soft papule with a relatively smooth surface, **the compound nevus.** Further**,** the amount of visible pigmentation becomes less and the lesion appears brown or tan. As time passes, the nevus gradually loses its pigmentation, the surface may become somewhat papillomatous, and hairs may be seen growing from the center**, the intradermal nevus**. Figure 9.5 shows the prototypical clinical appearance of these three types. However, the nevus usually remains less than 6 mm in diameter. Ulceration does not occur usually, unless the nevus is located where it is constantly subjected to irritation by clothing like belts, etc. Many of the acquired melanocytic nevi undergo spontaneous involution and disappear with ageing.

Intraoral melanocytic nevi are relatively uncommon. Common intra-oral locations are the hard palate, buccal mucosa, and gingiva, though any oral mucosal site may be affected. Roughly two-thirds of intraoral examples are found in females and the average age at diagnosis is 35 years. Intraoral lesions progress through same stages as the skin lesions and have a similar appearance, but papillary surface change does not occur even in mature lesions. Some intra-oral nevi may lack clinical pigmentation.

Microscopically, the acquired melanocytic nevus is characterized by a benign, unencapsulated proliferation of small, ovoid cells called the nevus cells. These cells demonstrate a variable capacity to produce melanin, with the pigment primarily evident in the superficial aspects of the lesion. Nevus cells typically lack the dendritic processes that melanocytes possess.

Halo nevus (as the name suggests surrounded by a halo) and spitz nevus (solitary, dome-shaped pink/red nevus typically seen in children) are cutaneous nevi with distinct clinical characteristics.

Treatment and prognosis: No treatment is indicated for a cutaneous melanocytic nevus unless it is needed for esthetic considerations, is chronically irritated by clothing, or shows clinical evidence of a change in size or color. By midlife, cutaneous melanocytic nevi tend to regress. If removal is indicated, then conservative surgical excision is the treatment of choice and any recurrence is unlikely. There have been incidences of skin **melanomas** arising from long standing or irritated nevi of the skin. Overall, the risk of transformation of a particular acquired melanocytic nevus to melanoma is approximately 1 in 1 million.However, because any oral melanocytic nevi clinically can mimic an early malignant melanoma, it is generally advised that biopsy be performed for all unexplained pigmented oral lesions, especially because of the extremely poor prognosis for oral melanoma discovered in its later stages.

Congenital Melanocytic Nevus

Congenital melanocytic nevus as the name suggests affects the newborns. Depending on its size, it is divided into two types: (1) Small (<20 cm in diameter) and (2) large (>20 cm in diameter). Approximately 15% of congenital nevi are found in the head and neck area, although intraoral involvement is quite rare.

Clinical features: The small congenital melanocytic nevus may be similar in appearance to an acquired melanocytic nevus, but it is frequently larger in diameter. The large congenital lesion classically appears as a brown to black plaque, usually with a rough surface or multiple nodular areas. Early lesions are flat and light tan, becoming elevated, rougher, and darker with age. A common feature is the presence of **hypertrichosis** (excess hair) within the lesion, which may become more prominent



Fig. 9.5: Typical clinical appearance of the three types of cutaneous nevi

with age **(giant hairy nevus).** A very large congenital nevus sometimes may be referred to as **bathing trunk nevus** or **garment nevus,** because it gives the appearance of the patient wearing an article of clothing.

The histopathologic appearance of the congenital melanocytic nevus is similar to that of the acquired melanocytic nevus, and some small congenital nevi cannot be distinguished microscopically from the acquired nevus. In addition, congenital nevus cells often are seen intermingled with neurovascular bundles in the reticular dermis and surrounding normal adnexal skin structures (e.g. hair follicles, sebaceous glands).

Treatment and prognosis: Many congenital melanocytic nevi are excised for aesthetic purposes. In addition, 3% to 15% of large congenital nevi may undergo malignant transformation into melanoma. Therefore, whenever feasible, these lesions should be removed completely by conservative surgical excision. Close follow-up is required for lesions not removed. Patients with multiple large congenital nevi also are at risk for developing neurocutaneous melanosis, a rare congenital syndrome in which patients may develop melanotic neoplasms of the central nervous system (CNS), including meningeal melanosis or melanoma. Unfortunately, no effective therapy is currently available for patients with symptomatic neurocutaneous melanosis.

Blue Nevus (Dermal Melanocytoma; Jadassohn-Tièche Nevus)

Blue nevus is an uncommon, benign proliferation of dermal melanocytes, usually deep within subepithelial connective tissue. Two major types of blue nevus are recognized: (1) The **common** blue nevus and the **cellular** blue nevus. The common blue nevus is the second most frequent melanocytic nevus encountered intraorally. The blue color of this lesion can be explained by the **Tyndall effect,** which relates to the interaction of light with particles in a colloidal suspension. In the case of a blue nevus, the melanin particles are deep to the surface, so that the light reflected back has to pass through the overlying tissue. Colors with long wavelengths (reds and yellows) tend to be more readily absorbed by the tissues; the shorter-wavelength blue light is more likely to be reflected back to the observer's eyes. Most common intraoral location is the hard palate.

Malignant Melanoma

Malignant melanoma is a malignancy of melanocytic origin that arises from a benign melanocytic lesion or *de novo* from melanocytes within otherwise normal skin or mucosa. It is the deadliest of all primary cancers of skin.

Etiopathogenesis: The etiopathogenesis of malignant melanoma, like any malignancy is an interplay of both environmental and

intrinsic factors. Damage from ultraviolet radiation and acute sun damage, in the form of history of multiple sunburns especially at a young age are considered a major causative factor. Oral lesions, however, are not related to sun exposure. A positive family of melanoma is also a strong risk factor. Additional predisposing factors include a fair complexion and light hair and a history of dysplastic or congenital nevus.

In recent years, there have been many discoveries regarding recurrent genetic alterations in melanomas, including those involving the *Ras-Raf-ERK,* mitogen activating protein (MAP) kinase, and phosphatidylinositol 3-kinase *(Pl3K)* pathways. Melanoma-prone families have a high incidence of germline mutations in the tumor suppressor genes, CDKNA2 and CDK4 and BRAF, HRAS, and NRAS proto-oncogenes.

Clinical Features

Cutaneous malignant melanoma: Malignant melanomas of the skin occur usually in white individuals living in the sunbelt regions. The age range is 30–80 years with the average age at diagnosis being 55 years. 91% of all melanoma lesions arise on the skin and of all cutaneous lesions, about 25% arise in the head and neck regions. Overall, there is a male predilection, but melanoma is one of the most commonly occurring cancers in women of child bearing age. On the facial skin, the malar region is a common site for melanoma since this area is subject to significant solar exposure. Melanomas may develop either *de novo* or arise from a pre-existing nevus. As many clinical similarities exist between melanoma and its benign counterpart, the melanocytic nevus, an "ABCDE" system of evaluation has been developed. The ABCDE criteria include: A symmetry, irregular borders, color variegation, diameter greater than 6 mm, and evolution or surface elevation.

Four main clinico-pathologic subtypes of melanoma have been described.

1. Superficial spreading melanoma
2. Nodular melanoma
3. Lentigo maligna melanoma
4. Acral lentiginous melanoma

In the first three varieties, the initial growth is characterized by radial extension of the tumor cells **(radial growth phase).** In these lesions, the malignant melanocytes have a tendency to spread horizontally through the basal layer of the epidermis. These lesions have a good prognosis if they are detected early and treated. Eventually, however, the malignant cells begin to invade the underlying connective tissue, thus initiating **the vertical growth phase**. The development of nodularity in a previously macular lesion is often an ominous sign. In the nodular melanoma, the vertical growth phase predominates.

Superficial Spreading Melanoma

Superficial spreading melanoma is the most common variety found on the skin, representing about 70% lesions. The site predilections are, the interscapular area in males and the back of the legs of females. The lesion essentially appears as amacule which may be tan, brown, gray, black, blue, white or pink in color. Usually, the lesion is smaller than 3 cm in greatest diameter at diagnosis, but it may be larger. The lesional surface may show slight elevated. Clinically, invasion is indicated by the appearance of surface nodules or induration. Satellite macules or nodules may develop around the primary lesion.

Lentigo Maligna Melanoma

Lentigo maligna melanoma develops from a precursor lesion called **lentigo maligna (Hutchinson's freckle).** It accounts for 5% to 10% of cutaneous melanomas, lentigo maligna occurs almost exclusively on the sun-exposed skin of fair-complexioned older adults, particularly in the midfacial region. The lesion appears as a large, slowly expanding macule with irregular borders and a variety of colors, ranging from tan, brown, black, and even white.

Acral Lentiginous Melanoma (Mucosal Lentiginous Melanoma)

Acral lentiginous melanoma is the most common form of oral melanoma. It is commonly seen in blacks. The usual sites involved are palms, soles, subungual area, and mucous membranes. It begins as a darkly pigmented, irregularly marginated macule, which later develops a nodular growth phase that is invasive.

Nodular Melanoma

Nodular melanoma represents 15% of cutaneous melanomas, and one-third of such lesions develop in the head and neck area. Nodular melanoma is thought to begin almost immediately in the vertical growth phase; therefore, it typically appears as a nodular elevation that rapidly invades into the connective tissue. Nodular melanoma is usually a deeply pigmented exophytic lesion, although sometimes the melanoma cells are so poorly differentiated that they no longer can produce melanin, resulting in a non-pigmented **amelanotic melanoma.**

ORAL MALIGNANT MELANOMA

Primary mucosal melanomas comprise less than 1% of all melanomas. The majority develop in the head and neck, mostly in the sinonasal tract and oral cavity. The prevalence of oral melanoma is higher among black-skinned individuals and Japanese people. The etiology of the oral malignant melanoma is obscure and mutations in BRAF gene are less common as compared to the skin lesions. A definite male predilection has been reported, with two-thirds of the affected individuals being males. Most patients are older than 50 years of age at the time of diagnosis. The hard palate and the maxillary gingiva are the sites most commonly involved. An oral lesion typically begins as a brown to black macule with irregular borders (Fig. 9.6) though most melanomas are often nodular at the time of diagnosis. The macule



Fig. 9.6: Malignant melanoma of the maxillary anterior region presenting as pigmented patch

extends laterally, and a lobulated, exophytic mass develops once the vertical growth is initiated. Up to one-third of oral melanomas may exhibit a little or no clinical evidence of pigmentation a phenomenon termed amelanosis. Most lesions remain relatively soft to palpation. Other signs and symptoms that may be associated with oral melanoma are nonspecific including ulceration, pain, tooth mobility or spontaneous exfoliation, root resorption, boneloss, and paresthesia/anesthesia may be evident. Underlying or adjacent bone may show radiographic evidence of irregular or "moth-eaten" destruction. The mucosal melanomas are usually diagnosed at a more advanced stage and are much more aggressive than their cutaneous counterpart. Regional lymphatic metastases are frequently identified. Melanoma occasionally affects the parotid gland, usually as a metastatic deposit from a scalp, conjunctival, or paranasal tumor.

In a few cases, oral melanomas may appear as diffuse multifocal areas of pigmentation. This particular appearance can be attributed to the presence of both melanotic and amelanotic areas within a lesion. Lesions of the oral cavity that do not involve the hard palate or gingiva and exhibit amelanosis are more likely to be metastatic lesions from another primary site.

Thus, the clinical differential diagnosis may be quite exhaustive and could

include melanocytic nevus, oral melanotic macule, and amalgam tattoo, as well as various vascular lesions and other soft tissue neoplasms. Hence a biopsy of any persistent solitary pigmented lesion is always warranted. Oral mucosal malignant melanoma usually has a grave prognosis with 5-year survival rates between 15 and 40%.

Histopathologically, oral mucosal melanomas may show a radial or a vertical growth pattern. The radial pattern is often seen in macular lesions wherein clusters of pleomorphic melanocyte exhibiting nuclear atypia and hyperchromatism proliferate within the basal cell region of the epithelium. As the vertical growth into the connective tissue starts, the lesions appear clinically as nodular mass.

Treatment

1. *Surgery:* For primary oral melanomas, ablative surgery with wide margins is the first line of treatment. Adjuvant radiation therapy may also be required.
2. *Chemotherapy and immunotherapy:* Chemo- and immunotherapeutic strategies are often used if metastases are identified and as a palliative measure. Adjuvant interferon-alpha-2B therapy has been approved for the treatment of primary cutaneous melanomas greater than 4 mm in thickness. The role of an anti-tumor vaccine against malignant melanoma is also under exploration owing to its immunogenic nature.

MULTIFOCAL/DIFFUSE PIGMENTATION

Physiologic Pigmentation

Physiologic pigmentation remains the most common source of multifocal oral mucosal pigmentation. It is frequently observed in dark-skinned individuals. Clinically it appears as patchy to generalized hyperpigmentation of the oral mucosal tissues usually involving the gingiva and buccal mucosa (Fig. 9.7). The pigmentation begins in childhood itself. The pigmentation is considered a variation of normal and has no particular clinical relevance. Surgical intervention may be indicated if the pigmentation is compromising the esthetics. Gingivectomy and laser therapy have been used to remove pigmented oral mucosa. However, repigmentation may occur.



Fig. 9.7: Physiologic gingival pigmentation in an Indian female of wheatish complexion

Differential diagnosis: Idiopathic, drug-induced, or smoking-induced pigmentation. Hyperpigmentation associated with endocrinopathic and other systemic disease

Drug-induced Melanosis

Etiology and pathogenesis: Medications may induce oral melanosis or cause oral pigmentation due to the soft tissue deposition of drug metabolites. The later kind of pigmentation is discussed with exogenous pigmentation further in the chapter. Table 9.2 shows the list of drugs commonly implicated in inducing oral mucosal melanosis. Of these, the most common offenders are the antimalarials including chloroquine, hydroxychloroquine, quinacrine. Although the mechanisms by which melanin synthesis is increased remains unknown, one theory is that some drugs may stimulate melanogenesis and others may physically bind to melanin which results in retention of the drug within melanocytes and may contribute to the oral pigmentation.

TABLE 9.2: Drugs that may induce diffuse oral melanosis

Amiodarone	Imipramine
Amodioquine	Ketoconazole
Aziodothymidine	Mepacrine
Bleomycin	Methacycline
Busulfan	Methyldopa
Chloroquine	Minocycline
Chlorpromazine	Oral contraceptives
Clofazamine	Premarin
Cyclophosphamide	Quinacrine
Gold	Quinidine
Hydroxychloroquine	Tacrolimus
Hydroxyurea	

Clinical features: Clinically, the pigmentation can be localized to one mucosal surface, often the hard palate and gingiva (Fig. 9.8), or it can be multifocal and involve multiple surfaces. The diffuse lesions are flat and without any evidence of nodularity (Fig. 9.9). The lesions present on the skin may be exacerbated by sun exposure. Microscopically, there is evidence of basilar hyperpigmentation and melanin incontinence without a concomitant increase in the number of melanocytes.

Diagnosis: In most cases, the pigmentation resolves and subsides within a few months after the offending drug is identified and discontinued. Nonetheless, pigmentation caused by hormone therapy may persist longer.

Differential diagnoses include other causes of diffuse mucosal pigmentation.



Fig. 9.8: Localized gingival pigmentation; patient gave a history of homeopathic medicine used for arthritis

Smoker's Melanosis

Multifocal oral pigmentation involving the anterior maxillary and mandibular gingiva, buccal mucosa, lateral borders of the tongue, hard palate, and floor of the mouth is reported among cigarette smokers (Fig. 9.10). Melanin synthesis is thought to be stimulated by tobacco smoke products. It is also postulated that one or more of the chemical compounds incorporated within cigarettes, along with



Fig. 9.9: Pigmentation seen on the lateral borders of the tongue post-chemotherapy for a case of misdiagnosed breast cancer

the heat generated, rather than the actual tobacco, may be causative.



Fig. 9.10: Grayish black pigmentation of the soft palate in a smoker

Clinical features: The pigmented areas are brown, flat, and irregular or map-like in configuration, prominently during the first year of smoking. Spontaneous resolution is reported with the cessation of the smoking habit. Smoker's melanosis is not a potentially malignant condition. In addition to smoking, alcohol abuse has also been associated with diffuse oral mucosal pigmentation particularly in the posterior regions of the mouth and soft palate. Diffuse patchy pigmentation may also be seen in oral submucous fibrosis caused by areca nut chewing habit.

Histologically, basilar melanosis with melaninin continence is observed.

Postinflammatory Hyperpigmentation

Postinflammatory hyperpigmentation is the presence of focal or diffuse pigmentation in sites that have been subjected to previous injury or inflammation. It is more commonly observed in dark individuals. The areas of healed acne on the face are a relatively common site for this phenomenon.

Postinflammatory pigmentation in the oral cavity has been observed in the following instances:

- **Oral lichen planus (lichen planus pigmentosus):** Pigmentation has been observed along with lesions of oral lichen planus (Fig. 9.11). Upon resolution of these lesions, the pigmentation may or may not disappear. Histologically, along with the typical histopathological changes of lichen planus basilar hyperpigmentation and melanin incontinence are seen.
- The overlying mucosa in a nonmelanocytic malignancy may become pigmented.

Melasma (Chloasma, Pregnancy Mask)

The term 'melasma' is used to describe the hyperpigmentation changes seen on the



Fig. 9.11: Pigmentation associated with reticular lichen planus on buccal mucosae

face that are associated with pregnancy or ingestion of contraceptive hormones in females. It develops as acquired, symmetric areas of diffuse hyperpigmentation on sun-exposed areas of the skin and the face. The forehead, cheeks, upper lips, and chin are the most commonly affected. Melasma tends to evolve rapidly over a period of a few weeks. Sun exposure excerabates the condition further. Rare cases of idiopathic melasma have also been described in females. It is believed that the combination of estrogen and progesterone hormones induces the melanosis. The condition may spontaneously resolve after parturition, or cessation of the exogenous hormones. Biopsy reveals basilar melanosis with no increase in the number of melanocytes.

MELANOSIS ASSOCIATED WITH SYSTEMIC OR GENETIC DISEASE

Hypoadrenocorticism (Addison's Disease)

Hypoadrenocorticism is an endocrinal disorder characterised by a decrease in endogenous corticosteroid levels, which can have grave consequences. The causes of hypoadrenocorticism include autoimmune disease, infection, malignancy, trauma, medications, genetic disease and iatrogenic causes. As a result of low steroid levels, there is a compensatory activation of adreno-corticotropin hormone (ACTH) secretion from the pituitary gland.With persistently low steroid levels, there is a loss of feedback mechanism, resulting incontinuous secretion of ACTH. Along with the ACTH the serum levels of alpha-melanocyte-stimulating hormone also increase. This phenomenon is due to the fact that ACTH and alpha-MSH share the common precursor gene called pro-opiomelanocortin. Both these hormones are also thought to have stimulatory effects on melanocytes.

Clinical features: The first sign of disease may be mucocutaneous hyperpigmentation. Generalized bronzing of the skin and diffuse but patchy melanosis of the oral mucosa are the prototypical features of hypoadrenocorticism. Other important symptoms include weakness, fatigue, and depression. Diffuse hyperpigmentation is more commonly associated with chronic form hypoadrenocorticism. Evaluation of serum cortisol and electrolyte levels is necessary to make a diagnosis of addisonian hyperpigmentation.Treatment consists of exogenous steroid replacement therapy. With appropriate therapy, the pigmentation eventually resolve.

The differential diagnosis includes other causes of diffuse oral pigmentation as discussed earlier.

Cushing's Syndrome/Cushing's Disease

Cushing's syndrome results from high levels of circulating endogenous or exogenous corticosteroids. Causes include injudicious and poorly monitored steroid therapy, pituitary tumor (Cushing's disease), adrenal pathology (hyperadrenocorticism), as well as ectopic secretion of corticosteroids in certain malignancies like small cell lung carcinoma.

Clinical features: Cushing's syndrome is more common in female patients. Signs and symptoms include truncal obesity, weight gain "moonfacies," and diffuse mucocutaneous pigmentation in some cases. Hyperpigmentation is common in patients where the etiology is a primary pituitary neoplasm, that leads to increased ACTH secretion. Oral pigmentation appears similar to as seen in hypoadrenocorticism. Serum steroid and ACTH levels help in the diagnosis, and the pigmentation tends to resolve after appropriate treatment of the underlying cause.

Hyperthyroidism

It has been reported that more than one-third of the patients diagnosed with hyper-thyroidism and thyrotoxicosis present with diffuse mucocutaneous hyperpigmentation. This phenomenon is relatively common

amongst dark skinned individuals. The trigger mechanism in this situation remains largely unexplained, but the pigmentation spontaneously resolves following correction of the thyroid disorder.

Primary Biliary Cirrhosis

Primary biliary cirrhosis is an autoimmune disorders that result from damage to small intrahepatic bile ducts. This condition may cause generalized melanotic as well as non-melanotic hyperpigmentation (yellowish discoloration, due to jaundice). The exact mechanism by which melanosis develops in this condition is unknown.

Vitamin B_{12} (Cobalamin) Deficiency

Vitamin B_{12} deficiency essentially causes megalobastic anemia and various other neurologic deficits. Diffuse mucocutaneous hyperpigmentation is an uncommon manifestation of vitamin B_{12} deficiency. The pigmentation regresses the following correction of deficiency.

HIV infection Associated Melanosis

Hyperpigmentation has been frequently observed as an oral manifestation of HIV infection. This may be due to anti-retroviral/anti-fungal drugs or as a result of adrenocortical destruction by the virus. It has also been reported that the immune dysregulation in HIV infection leads to increased secretion of alpha-MSH from the anterior pituitary gland, which may also stimulate increased melanin synthesis.The buccal mucosa is the most frequently affected site, but the gingiva, palate, and tongue may also be involved.

Peutz-Jeghers Syndrome

The Peutz-Jeghers syndrome is an autosomal dominant disorder. Mutations in the *STK11/LKB1* tumor suppressor gene have been postulated as the cause. Clinical features of this syndrome include multiple intestinal polyposis that have a malignant potential, and multiple, pigmented macules of the lips, perioral skin, and extremities. The macules are usually small measuring <0.5 cm in diameter. The oral and peri-oral pigmentations are quite characteristic. Histologically, these lesions show increased basilar melanin without an increase in the number of melanocytes. The color intensity and number of macules is unaffected by sun exposure. Other syndromes with similar clinical manifestations include Cowden syndrome and Cronkhite-Canada syndrome.

Café-au-lait Pigmentation

Cafe-au-lait ("coffee with milk") macules are discrete melanin-pigmented patches of skin that have irregular margins and a brown coloration. The lesions are noted at birth or soon thereafter and may also be seen in normal children. No treatment is required, but they may be indicative of a syndrome of greater significance. It is obscure how the gene mutations that give rise to the various genetic diseases stimulate melanin production.

Genetic disorders where café-au-lait spots are seen include the following syndromes:

Neurofibromatosis Type I

Individuals with six or more large (>1.5 cm in diameter) café-au-lait macules should be suspected of possibly having neurofibromatosis (NF). Neurofibromatosis type I is an autosomal dominant disease that is associated with the development of multiple neurofibromas of the skin, oral mucosa, nerves, central nervous system, and occasionally the jaw. The genetic abnormality is in the neurofibromin gene located on chromosome 17q 11.2. In addition, the size, number, and age at onset of the cutaneous café-au-lait spots are of diagnostic importance for this disease. Axillary and/or inguinal freckling (Crowe's sign) and pigmented lesions of the iris (Lisch nodules) are also highly characteristic of neurofibromatosis type I.

McCune-Albright Syndrome

This syndrome is characterized by multiple café-au-lait spots, polyostotic fibrous dysplasia and endocrinal disturbances. This sporadic disorder is considered to be strongly associated with mutation of the Gs, alphagene. The café-au-lait spots in McCune-Albright syndrome appear distinct from those associated with neurofibromatosis. The café-au-lait macules of Albright's syndrome tend to be large and unilateral and have irregular borders, whereas in neurofibromatosis, the borders are typically smooth and soft tissue myxomas.

Mazabraud Disease

This entity is genetically and phenotypically similar to McCune-Albright syndrome. It is characterised by polyostotic fibrous dysplasia, café-au-lait pigmentation and soft tissue myxomas.

Microscopically, café-au-lait macules are not particularly remarkable. They generally show excess amounts of melanin in basal keratinocytes and subjacent macrophages. Melanocytes are normal in appearance and may be slightly increased in number.

Noonan's syndrome and the allelic **Leopard syndrome** (multiple lentigines, electrocardiographic-conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensineural deafness) are autosomal dominant disorders that are also associated with pigmented mucocutaneous macules.

IDIOPATHIC ORAL PIGMENTATION

Laugier-Hunziker Pigmentation

The Laugier-Hunziker pigmentation decribed as an acquired, idiopathic, macular hyperpigmentation of the oral mucosal tissues specifically involving the lips and buccal mucosae (Fig. 9.12). In majority of the cases pigmentation of the nail in the form linear melanotic streak is seen (Fig. 9.13). This condition is essentially a diagnosis of exclusion when all other systemic and genetic causes of oral pigmentation have been ruled out after a thorough diagnostic work up. Oral involvement presents as multiple, discrete, brown black macules of varying sizes.

HEMOGLOBIN AND IRON-ASSOCIATED PIGMENTATION

Ecchymosis

Ecchymosis occurs due to extravasation of blood in the submucosal tissues.

Causes of Ecchymosis

Trauma: This is the single most common cause. Traumatic ecchymosis usually occurs on the lips and face. Intraoral ecchymosis due to trauma can be seen in cases of blunt trauma and oral intubation. The lesion appears bright red in cases of fresh trauma and gradually changes to brown in 2–3 days.

Hemorrhagic diasthesis and coagulation disorders: Presence of multiple ecchymotic patches in the absence of trauma should raise a strong suspicion of an underlying hematological disorder.

Anticoagulant therapy, leukaemia, end stage renal disease and cirrhosis of the liver may also be associated with oral ecchymosis.

Purpura/Petechiae

These lesions arise as a result of focal capillary hemorrhages. The difference between the two lies essentially in their size. Petechiae are typically described as pinpoint hemorrhages, whereas purpura as multiple, small 2 to 4 mm collections of extravasated blood. Causes include platelet deficiency and aggregation disorders, viral infections and trauma.

Hemochromatosis

Hemochromatosis is a chronic, progressive disease that is characterized by excessive iron deposition, in the form of hemosiderin in the liver and other organs.



Fig. 9.12: A case of Laugier-Hunziker pigmentation showing multiple macules on upper and lower labial mucosa and vermilion border



Fig. 9.13: Longitudinal melanotic streak on the nail in LH pigmentation

Causes

- Idiopathic
- Neonatal hemochromatosis
- Blood transfusion
- Hereditary

The cutaneous pigmentation is a hallmark of the disease.The oral mucosal though less common, appears as diffuse and brown to gray pigmentation involving the palate and gingiva. Iron deposition within the adrenal cortex may lead to hypoadrenocorticism with its impending complications.

Other sequelae of hemochromatosis may include liver cirrhosis, diabetes, anemia, heart failure, hypertension, and bronzing of the skin. Lower labial gland biopsy has been shown to be an effective method for the diagnosis of hemochromatosis, where golden or brown-colored hemosiderin can be seen diffusely scattered throughout the submucosal and salivary gland tissues, which can be further confirmed by Prussian blue stain for iron.

EXOGENOUS PIGMENTATION

Amalgam Tattoo

Etiology and pathogenesis: Amalgam tattoo is the single most common source of solitary or focal pigmentation in the oral mucosa. It occurs as a result of the inadvertent deposition of amalgam restorative material into the submucosal tissue.

This can occur in several ways.

- Mucosal abrasions can be contaminated by amalgam dust within the oral fluids.
- Broken amalgam fragments can fall off into extraction sites.
- If dental floss becomes contaminated with amalgam particles of a recently placed restoration, then linear areas of pigmentation can be created in the gingival tissues as a result of hygiene procedures.
- Amalgam from endodontic retrofill procedures, accidentally left within the soft tissue at the surgical site.
- Fine metallic particles can be driven through the oral mucosa from the pressure of high speed air turbine drills.

Clinical features: Amalgam tattoos appear small macules that are black, blue or gray in color with borders that may be well-defined or diffuse. The lesions are usually asymptomatic. They may be found on any mucosal surface. However, the gingiva and buccal mucosa are the most common sites. In some cases, the lesions may be slightly raised. Lateral spread may occur for several months after the implantation. In most cases, solitary site is involved, although multiple tattoos in a single patient may be present. The lesions are often found in the vicinity of teeth with large amalgam restorations or crowned teeth that probably had amalgams, around the apical region of endodontically treated teeth with retrograde restorations or obturated with silver points, and in areas in and around healed extract ion sites.

Theoretically, the use of the rubber dam should decrease the risk of amalgam tattoos, however, immediately after removal of the dam, the occlusion often is adjusted with the potential for amalgam contamination of any areas of mucosal damage.

Pathology: Microscopically, pigmented fragments of the metal are seen within the connective tissue. Often a fine brown granular stippling of reticulum fibers is seen with a particular affinity for vessel walls and nerve. The tissue response appears related to particle size and the elemental composition of the amalgam. Large fragments often become surrounded by dense fibrous connective tissue with mild inflammation. Smaller particles typically are associated with a more significant inflammatory response that may be granulomatous or a mixture of lymphocytes and plasma cells.

Differential diagnosis: Intra-oral radiograph may reveal well-defined radiopacity in the involved region, suggestive of the embedded metallic fragments in the soft tissue. For this purpose the radiographic film should be such that it provides high detail, since some fragments are extremely minute. If there is no radiographic evidence of amalgam and the lesion is not in proximity to any restored tooth, a biopsy is necessary. A typical differential diagnosis often includes melanotic macule, nevus, and melanoma. Pigmentation associated with other dental restorative materials like cast alloy, has also been described. Titanium has been associated with pigmentation of the skin, specifically in areas around orthopaedic implants.Thus, it is justifiable that dental implants may also be a potential source of exogenous oral pigmentation.

Management: Amalgam tattoos are innocuous, their removal is not always mandated. Occassionally, the amalgam implantation may occur in a cosmetically objectionable location such as the anterior maxillary facial gingiva. In such cases, conservative surgical excision can be performed; alternatively amalgam tattoos have been removed successfully with Q switched ruby or alexandrite lasers.

Graphite Tattoo

Graphite tattoos mainly result from accidental injury involving pencils, in which graphite from the tip of the pencil is inserted into the oral mucosa. The lesions are most common on the palate. Clinically they appear similar to amalgam tattoos, presenting as a solitary gray or black macule. Since the traumatic event often occurs in childhood,

many patients may not report a history of injury. Thus, a biopsy may be necessary to confirm the diagnosis. Microscopically, graphite particles resemble those of amalgam. Treatment is recommended only in cases with esthetic considerations.

Ornamental Tattoos

Amateur tattooing on the mucosa in the form of designs has gained a considerable amount of popularity. Such tattoo inks are basically composed of simple, carbon particles derived from burnt wood, paper, etc and from a variety of inks, such as India ink, pen ink, and plant-derived matter. Such tattoos are permanent, unless a therapeutic intervention in the form of lasers is sought for to attempt their removal.

In certain tribal cultures, ornamental mucocutaneous tattooing with plant derived pigments is considered an aesthetics enhancing, custom particularly among female members.

A rare South African female tribal custom includes brushing the teeth and gums with a chewed root of the tree *Euclea natalensis*, for its purported antibacterial effects. This plant contains pigmented naphthoquinones that impart a bright orange to the teeth and mucosa. Contrary to the ornamental tattoos, this form of pigmentation is transient and reversible.

Medicinal Metal-induced Pigmentation

Metals and metallic salts are constituents of a number of therapeutic and medicinal agents used for treating a variety of conditions. Oral mucosal pigmentations can result from such treatments in different forms.

Gold: Gold therapy (used for the treatment of rheumatoid arthritis) has been shown to cause diffuse cutaneous pigmentation. Gold-induced pigmentation called chyriasis may appear blue-gray or purple. Chyriasis is uncommon in the oral cavity, nonetheless, oral lichenoid eruptions have been reported with systemic gold therapy. The pigmentation resulting in such instances may be persistent, even after discontinuation of the therapy.

Silver: Oral pigmentation more often results due to ingestion of silver. Colloidal silver is used as a nutritional supplement and has been shown to cause diffuse cutaneous pigmentation. Silver nitrate cautery has been used to treat recurrent aphthous stomatitis. Silver may cause a generalized blue-gray discoloration (argyria).

Salts of metals are also found in topical medications, examples include silver nitrate and zinc oxide, and zinc oxide is a common component of suntan lotions. They have also been associated with focal mucocutaneous pigmentation that often appears grayish black. Bismuth subsalicylate tablets, a commonly used antacid, has also been associated with a diffuse blackish pigmentation of the tongue. Maintenance of tongue hygiene and discontinuation of the bismuth-based antacid are remedial.

Heavy metal pigmentation: Lead, mercury, bismuth, and arsenic have all been shown to be deposited in oral tissue if ingested in sufficient quantities or over an extended period of time. Such a chronic exposure to these heavy metals usually occurs as a result of an occupational and health hazard for individuals who work in certain industrial plants and for those who live in the environment in and around these types of facilities. These ingested metal salts tend to extravasate from vessels in areas of chronic inflammation. Thus, in the oral cavity, the pigmentation is usually found along the free marginal gingiva. This metallic line is a gray to black in color.

Drug-induced pigmentation: Minocycline and methacycline, both tetracycline derivatives, have been implicated in causing oral pigmentation, due to the deposition of the drug complexes within the developing bones, imparting the bone a grayish or brownish color, which is reflected through the overlying mucosa. Minocycline may also cause actual soft tissue pigementation

which appears clinically as patchy or diffuse grayish black hyperpigmentation.

Hairy tongue: Hairy tongue is a fairly common condition of the tongue with no known etiology. A change in the oral microflora due to prolonged antibiotic therapy has been suggested as a possible cause. The discoloration typically involves the dorsum of the tongue. The filiform papillae are severely enlarged and elongated. These hyperplastic papillae then become pigmented by the colonization of chromogenic bacteria, which can impart a variety of colors, including green, brown, or black. Food items and beverages can also contribute to the diffuse discoloration. Smoking of tobacco, cocaine and use of psychotropic medications has also been linked to black hairy tongue. Treatment consists of maintaining the tongue hygiene and limiting the ingestion of color-forming foods and drinks.

Conclusion

Thus oral pigmentation can arise due to multifactorial causes. A thorough clinical examination with proper diagnostic work up and investigations is often necessary to ascertain the right cause behind the pigmented lesion. Treatment is often warranted for cosmetic purposes and in rare cases of malignancy as a life-saving measure.

EXPECTED QUESTIONS

Short Answer Questions

1. Define macule. Add a note on oral melanotic macule.
2. Amalgam tattoo
3. Peutz-Jeghers syndrome
4. Café-au-lait pigmentation
5. Blue nevus
6. Drug-induced pigmentation
7. Amelanotic melanoma
8. Hairy tongue
9. Enumerate two syndromes associated with café-au-lait pigmentation. Describe any one.

Long Answer Question

1. Classify oral pigmentation, enumerate the various causes of endogenous oral pigmentation and describe malignant melanoma in detail.

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Chapter 10

Salivary Gland Disorders—Clinical and Radiologic Considerations

INTRODUCTION

Salivary gland is a secretary gland that secretes tasteless, clear fluid called saliva. Salivary glands can be classified into major and minor. There are three pairs of major salivary glands, namely parotid glands, submandibular salivary gland and sublingual gland in addition to minor salivary glands which are dispersed throughout the oral mucosa. Saliva plays an important role in lubrication of food, integrity of mucosa, prevention of tooth decay, antimicrobial effect and in digestion. The main constituent of saliva is water with organic and inorganic components.

DEVELOPMENT OF SALIVARY GLANDS

The development of salivary gland starts between 4th–6th week of intrauterine life with parotid being first gland to initiate followed by submandibular gland at 6th week and sublingual gland including minor salivary gland at 8th–12th week. Parotid gland is the largest salivary gland which is ectodermal in origin. Submandibular gland and sublingual gland are endodermal in origin.

ANATOMY OF SALIVARY GLANDS

Parotid Gland

It is the largest salivary gland. The parotid lobe lies on the lateral aspect of the ramus of the preauricular region. The parotid gland wedges in between sternocleidomastoid muscle and masseter muscle. The gland is enclosed in deep fascia of neck.

Relations of Gland

a. **Superiorly:** External auditory meatus
b. **Inferiorly:** Lies over the posterior belly of the digastric muscle
c. **Anteriorly:** Ramus of the mandible and masseter muscle
d. **Posteriorly:** Sternocleidomastoid muscle
e. **Medially:** Facial nerve. Retromandibular vein and external carotid artery lies medial to the parotid lobe

The duct of parotid gland, called Stenson's duct, opens into buccal vestibule opposite to upper second molar. The secretion of parotid gland is generally serous (primarily watery) in nature.

Submandibular Gland

Submandibular gland lies medially to the body of mandible with large superficial lobe and small deep lobe. Both the lobes are connected around the posterior aspect of mylohyoid muscle. Superficial lobe is wedged between mandible and mylohyoid muscle and lies within deep fascia of neck. Submandibular gland is separated by parotid gland by stylomandibular ligament.

Relations of the Gland

a. **Superficially:** Platysma and cervical branch of facial nerve.
b. **Deep:** Mylohyoid muscle, lingual nerve and hypoglossal nerve.
c. **Medially:** Deep part or small lobe of gland projects along hyoglossus.

Submandibular gland's duct, called Wharton's duct, opens in floor of the mouth in the midline along the frenulum of the tongue on the summit of sublingual papilla. The secretion of submandibular gland is mixed (serous and mucous) in nature.

Sublingual Gland

Sublingual gland is the smallest salivary gland and is almond-shaped gland which lies deep to the submandibular gland.

Relations

a. **Medially:** Separated from base of the tongue by submandibular duct and lingual nerve.
b. **Laterally:** Sublingual groove on the medial aspect of the mandible.

Its secretions are mainly drained through numerous small ducts called Rivinus duct that opens along the sublingual fold in floor of mouth. Sometimes few anterior ducts may join to form a common duct called Bartholin's duct. Sublingual and minor salivary glands secretion is predominantly mucous in nature.

Saliva

Saliva is produced and secreted by salivary glands out of which submandibular gland secretes approximately 60% of total salivary volume. Total volume of saliva secreted in a day by an adult is 600–1000 ml. In the resting (unstimulated) state, approximately two-thirds of the total volume of the whole saliva is produced by submandibular glands. Upon stimulation, the parotid glands are responsible for at least 50% of the total volume of saliva from the mouth. The average rate of unstimulated whole saliva is 0.3–0.4 ml/min.

TABLE 10.1: Major constituents of saliva

Electrolytes	Sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, thiocynate, and fluoride
Secretory proteins/ peptides	Amylase, proline rich proteins, mucins, histatin, cystatin, peroxidase, lysozyme, lactoferrin, glycoproteins, lysozyme, defensins
Secretory immuno-globulins	IgA, IgG, IgM
Organic constituents	Glucose, amino acids, urea, uric acid, and lipid molecules
Biological active peptides	Leptin, ghrelin and endothelin
Other constituents	Epidermal growth factors, epithelial cells, insulin, cyclic adenosine monophosphate, binding proteins and serum albumin

SIALOGRAPHY

Sialography is a technique where retrograde injection of dye is instilled into the duct of major salivary gland. Following injection a series of radiographs are taken in order to evaluate the salivary glands. Prior to the advent of CT and MRI, sialography is the only technique to assess the ductal and parenchymal tissue of salivary glands. Today MRI has largely replaced sialography in evaluation of salivary glands.

The first sialogram was performed by Carpy in 1902 on isolated parotid gland using mercury as contrast agent. Subsequently,

Arcelin reported the first ever *in vivo* human sialogram using bismuth as contrast agent.

Contrast Agents

The contrast agents used in sialography are either fat soluble or water soluble, containing approximately around 37% of iodine.

Fat soluble media: Fat soluble dyes were used due to its virtue of higher viscosity and excellent contrasting agent, however, higher viscosity requires extra pressure to push the dye into the ductal system. Also, fat soluble dye may remain inside the gland and can initiate inflammatory process leading to change in texture of gland. Some of the fat soluble dyes are lipoidal, ethiodol and pantopaque.

Ethiodol is one of the popularly used fat soluble dyes due to lower viscosity and excellent contrast properties. Ethiodol is insoluble in saliva and not absorbed in the glandular mucosa. That is why it was frequently used as contrast agent. Sooner, fat soluble dye was replaced by water soluble dyes.

Water soluble dyes: The most common water soluble dyes are angiographic dyes.Water soluble dyes are less viscous and can be easily injected into the gland. The major drawback of these dyes is saliva soluble and can be absorbed by the gland. This often results in poor radiographic contrast and suboptimal demonstration of ducts. However, the good quality is liquid-based dyes do not provoke any inflammatory process inside the gland.

Most commonly used liquid-based sialographic dye is **Sinograffin** composed of **Diatrizoate meglumine** and **Iodipamide meglumine**. It is highly viscous dye with sufficient contrast property as it has 38% of iodine content.

Armamentarium for Sialography

Sialography is comparatively easier procedure. It requires following things:

1. Sialographic catheters
2. Lacrimal probes
3. Iodinated contrast agent
4. Dental cotton rolls

Sialographic Procedure

Sialography should ideally be performed under direct fluoroscopy, however, most of the times it is performed without fluoroscopic observation. Thorough examination of salivary gland should be performed before carrying out the procedure. All procedural steps should be explained to the patient and written consent form should be signed by the patient before the start of the procedure.

First step in sialography is dilation of ductal opening using lacrimal probes. The injection containing dye should be given with steady, constant pressure. The injection should be ceased once patient shows discomfort. Normally, parotid can accommodate around 0.5–0.75 ml of contrast and submandibular accommodates 0.3 ml of contrast agent.

Phases of Salivary Gland

Sialography can be divided into three phases

1. Ductal
2. Acinar
3. Evacuation

Ductal phase: The ductal phase starts with injection and terminates on acinar opacification. Ductal opacification is intended to demonstrate abnormalities in ductal system.

Acinar opacification: It starts after ductal opacification and ends at increased density of gland. This phase demonstrates intraglandular and extraglandular masses in parenchyma.

Evacuation and postevacuation phase: This phase shows secretory function of the gland and ductal pathology, if any, present in the gland. Normally all contrast agent leaves the gland during this phase. Any residual dye inside the gland may indicate any pathology in the ductal system.

Indications of Sialography

1. Acute obstructive and/or chronic recurrent sialadenitis

2. Autoimmune sialadenitis
3. Sialosis
4. Post-trauma evaluation
5. Mandibular lesions like Stafne's cyst.

Contraindications of Sialography

1. Acute infection of the gland
2. Hypersensitivity to the iodine dye

Diseases of Salivary Gland

Salivary glands are involved in number of conditions. The diseases of salivary glands can occur from within the gland or can be manifestation of any systemic diseases. Various conditions of salivary gland can be classified as given in Table 10.2.

Developmental Disorders

Aplasia/Agenesis and Related Aberrancy of Salivary Glands

Aplasias/agenesis of major salivary gland is rare finding. It can occur unilaterally or bilaterally, involving either single salivary gland or multiple salivary glands. It can be syndromic or non-syndromic.

Aplasia/Agenesis: Agenesis/aplasia refers to congenital absence of salivary gland(s). The first case of agenesis/aplasia was reported by Gruber in 1885. It is a rare condition of unknown etiology. Usually, it is present bilaterally, however, some cases of unilateral agenesis were also reported in literature. Agenesis/aplasia of parotid gland can occur independently or in association with agenesis of submandibular gland, lacrimal gland, first branchial arch developmental disturbances or any other developmental disturbance. The true incidence of agenesis/aplasia cannot be determined as majority of cases goes unnoticed. Syndromes associated with aplasia/agenesis are **Treacher Collins syndrome, hemifacial microsomia, lacrimo-auriculo-dento-digital syndrome (LADD).**

Atresia: It is a congenital absence/occlusion of salivary gland duct which can lead to mucocele or mucus retention phenomenon.

Aberrancy: It is an anatomic variation where the gland is found at unusual position. Example is Stafne's bone cyst. Stafne's bone cyst is the accumulation of abnormal salivary gland tissue at medial surface of body of mandible causing indentation in the medial aspect of body of mandible.

Clinical features: Often, cases of aplasia/agenesis are asymptomatic due to partial manifestation of the disease. The clinician should look out for ductal openings of major salivary glands in case of suspicion of salivary gland aplasia/agenesis. Thorough history from siblings is mandatory to rule out any familial tendency.

The clinical features of aplasia/agenesis include hyposalivation, frequent dental caries, enamel hypoplasia, occlusal wearing of teeth or congenital absence of teeth, difficulty in swallowing, poor oral hygiene. Besides oral features, ophthalmologic dryness and association of aplasia/agenesis with other syndromes should be considered.

Radiologic features: Radiological examination includes ultrasonography (USG), computed tomography (CT) of parotid and submandibular areas and pertechnetate scintingraphy. USG and CT will reveal partial to complete absence of one or more gland. Scintingraphy will show reduced or no uptake of radioisotope in the major salivary gland areas.

Management: Management of such cases will include periodical dental examinations, salivary substitutes, meticulous home care and frequent fluoride application to prevent dental caries.

Hyperplasia of Salivary Glands

Hyperplasia of salivary glands is a pseudo tumor, generally manifested in minor salivary glands located in hard and soft palate in oral cavity. It is a rare lesion with unknown etiology. Although, some authors think local trauma could be the cause.

Clinical features: It is characterized by localized, indolent swelling in hard and soft

TABLE 10.2: Classification of salivary gland disorders

Developmental	*Functional disorders*	*Inflammatory disorders*	*Autoimmune disorders*	*Non-inflammatory disorders*	*Tumors benign*	*Tumors malignant*
• Aplasia/agenesis and related aberrancy of salivary glands • Hyperplasias	• Xerostomia • Sialorrhea	• Mucocele • Ranula • Salivary duct cyst • Sialolithiasis, sialadenitis *Viral infections* • Mumps • HIV • Subacute necrotizing sialadenitis • Cheilitis glandularis • Necrotizing sialometaplasia	• Sjögren's syndrome • Mikulicz's disease	• Sialoadenosis • Orofacial granulomatosis	• Pleomorphic tumor • Warthin's tumor • Oncocytoma • Canalicular adenoma • Basal cell adenoma	• Mucoepidermoid carcinoma • Acinic cell adenocarcinoma • Malignant mixed tumor • Metastasizing mixed tumor • Adenoid cystic carcinoma

palate. The most common presentation of adenomatoid hyperplasia is painless swelling which may be soft to firm on palpation. It generally occurs in 4th to 6th decades of life. The overlying mucosa may be normal in color. The diagnosis can be confirmed by biopsy.

Management: After confirmation of diagnosis by biopsy, patient should be kept under observation for 6 months. Any change in size or change in color should be investigated further.

Functional Disorders of Salivary Gland

Xerostomia

Xerostomia refers to "dry mouth" which may be associated with decrease in quality or quantity of saliva. Hypofunction means decreased function of saliva. However, both these terms have been used interchangeably. The prevalence of the hypofunction/xerostomia varies in different population as xerostomia is subjective sensation of oral dryness. Hyposalivation refers to decreased flow rate of saliva from salivary glands. The flow rate of saliva varies with daytime so defining the normal rate is difficult. However, salivary rate less than 0.15 ml/min is considered as reference for decreased flow rate. Sometimes patients with decreased salivation have no complaints. Conversely, patients with dry mouth complaints have normal salivary production.

Xerostomia has great impact on one's quality of life. Patients with complains of Xerostomia have difficulty in chewing, speaking, swallowing and wearing dentures. Patients complaining of dry mouth comes with chief complains of need to sip frequently, difficulty in swallowing without water or burning sensation in oral cavity.

Various causes of dry mouth are listed in Table 10.3.

Mouth breathing, tobacco smoking, alcohol use and beverages containing caffeine also cause decrease in salivary production. In the past, aging was considered as reason for decreased salivary secretion, however, recent studies revealed that there is no significant decrease in salivary production as age advances. It might be due to medications taken during old age.

TABLE 10.3: Various causes of dry mouth

Developmental	*Salivary gland aplasia*
Medications	Tricyclic antidepressants, antipsychotic drugs, diuretics, antihistamines, proton pump inhibitors, opioids, benzodiazepines, selective serotonin reuptake inhibitors, anticholinergics
Radiotherapy/ chemotherapy	Radiotherapy to salivary glands and related structures
Autoimmune diseases	Sjögren's syndrome, systemic lupus erythematosus
Infections	Viral infections like HIV, hepatitis C induced salivary diseases
Other systemic diseases	Diabetes mellitus, sarcoidosis, Parkinson's disease, cystic fibrosis, vitamin A deficiency

Clinical Features

Examination of patients with dry mouth demonstrates a reduction in salivary secretion and saliva appears to be 'thick and ropy". The dorsal aspect of tongue is fissured with atrophic filliform papillae. Patients complain of food sticking in oral membranes while eating. The amount of saliva secretion can be determined by assessing stimulated and unstimulated salivary flow.

In xerostomic patients there is increase incidence of caries and oral candidiasis because of reduction in quantity and quality of saliva. The xerostomia related caries commonly occur in cervical and root area.

Various chair side procedures could be done in order to diagnose dry mouth condition. These are:

1. **Lack of pooling** of saliva in floor of the mouth is the basic sign of dry mouth.
2. **Cracker sign:** If patient tells that he was unable to chew cracker without sipping water, then it is indication of decreased salivary secretion.
3. **Lipstick sign:** If lipstick remains adhered to upper incisors in females, indicates dry mouth.
4. **Mouth mirror test:** The clinician places the mouth mirror on buccal mucosa or on dorsal tongue and check for mouth mirror sticking to surface. If it sticks, then clinician can deduce diagnosis of dry mouth.

Radiological features: All patients with dry mouth do not require radiological investigations. Depending upon the cause of dry mouth, radiological investigations should be prescribed. If decreased secretion is due to medication, radiotherapy/ chemotherapy, then apparently there is no need for radiographic investigation. For other conditions, special radiological procedures should be advised. Radionuclide salivary imaging will show reduced uptake of pertechnetate in Sjögren's syndrome. Sialosis usually demonstrates enhanced pertechnetate uptake and in cases of post-radiotherapy patients, there is reduced uptake of radionuclide dye.

Treatment: The treatment of dry mouth is very difficult and unsatisfactory. Artificial saliva and frequent water sipping may help patients with decreased saliva secretion. In addition, sugarless candy or vitamin C candy (limcee, celin lozenges) can be used in order to stimulate saliva. Use of oral hygiene products containing lactoperoxidase, lysozyme and lactoferrin (biotene toothpaste, oral balance gel) should be prescribed to patients.

Systemic pilocarpine 5 to 10 mg three to four times a day may also be given to the patients. Pilocarpine is parasympathomimetic agonist that can be used as sialogogue. Another cholinergic agonist with affinity for M3 receptor is cevimeline hydrochloride which can be prescribed to increase the secretion from salivary glands. Both these drugs are contraindicated in patients with narrow angle glaucoma.

If dryness is secondary to patient's medications, then patient should be asked to consult his/her physician for either modulation of dose or substitution of drug. As patients with dry mouth have increased risk for caries, frequent fluoride applications

are recommended with chlorhexidine mouthwash to minimize plaque accumulation.

SIALORRHEA (PTYALISM)

Sialorrhea or ptyalism is a condition with excessive salivation. Sialorrhea is not only a medical issue but also a social stigma. It generally occurs secondary to any underlying condition. Various causes include neurological disorders, infections, heavy metal poisoning, Wilson's disease, drug-induced, rabies, familial dysautonomia. In most of the patients with neurological disorders, drooling of saliva is not related to increased production of saliva but due to decreased neurosensory control of orofacial muscles to retain saliva.

Minor sialorrhea results from local irritation from new or ill-fitting dentures, aphthous ulcer. Episodic excess salivation or "water brash" occurs as a result from gastrointestinal reflux (GERD). Drugs involved with increased salivation are antipsychotic drugs such as clozapine, cholinergic agonist used in treatment of Alzheimer's disease and myasthenia gravis. Another hypersecretion of saliva of unknown etiology is idiopathic paroxysmal sialorrhea. Individuals with this condition exhibit increased salivation for small burst of time lasting from 2 to 5 minutes. These episodes are usually associated with nausea or vomiting.

Clinical features: Patients with excessive secretion of saliva complain of soiling of clothes and bed linens. In children with decreased intellectual disability or cerebral palsy, uncontrolled salivary drooling may result in maceration sores around mouth, chin or neck that may become secondarily infected.

Treatment: The treatment of sialorrhea depends upon its cause. Transitory or mild sialorrhea does not require any intervention. Patients with increased salivation due to GERD may be referred to physician to manage underlying cause. For persistent severe drooling, therapeutic intervention may be indicated. Anticholinergic medication can decrease salivary production, however, side effects are unacceptable. Intraglandular injection of botulinium toxin has been shown to be successful in decreasing saliva secretion.

Besides, medicinal treatment, surgical interventions like relocation of parotid and submandibular duct, ligation of ducts and bilateral tympanic neuroectomy with sectioning of chorda tympani may help in managing these patients.

INFLAMMATORY DISORDERS OF SALIVARY GLAND

Inflammatory disorders are most common lesions affecting salivary glands. The etiology of these inflammatory conditions can be obstruction, infection, granulomatous disease or unknown. Below is the description of common inflammatory pathology of major and minor salivary glands.

Mucocele (Mucus Extravasation Cyst)

Mucus extravasation cyst is a pesudocyst which results from rupture of salivary gland duct and secretion of gland spills into the surrounding connective tissue. That is why it is called mucus extravasation cyst. The most common cause for development of mucocele is local trauma. However, in some cases trauma could not be found to be the cause.

Clinical features: Mucocele generally occurs in minor salivary glands present on the lower lip (Fig. 10.1). The chance of trauma is more in younger age group and on lower lip that is why it is more common in lower lip with younger age group. However, case reports with involvement of all age groups have been documented in literature. Other sites for mucocele are buccal mucosa, floor of the mouth, ventral tongue, palate and retromolar.

Mucocele typically presents as lesion with 1–2 mm to several centimeters in diameter, dome-shaped with smooth surfaced

(non-ulcerated) and fluctuant swelling. The color of swelling is bluish if it is presented superficially. Deep swelling may have normal mucosal color. The duration of lesion can vary from a few days to several years. Sometimes, patients present with history of recurrent swelling that periodically ruptures and spill its fluid contents.

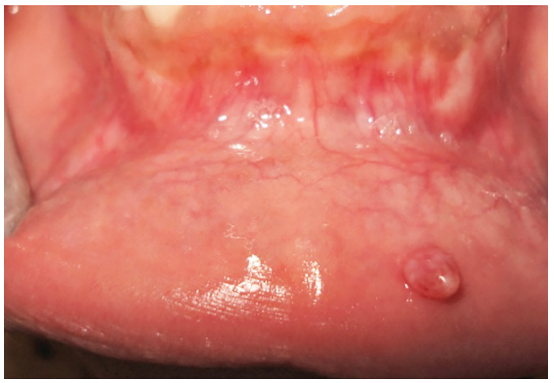


Fig. 10.1: Mucocele of lower lip

Differential diagnosis: Differential diagnosis will include lipoma, mucus producing salivary gland tumor, lymphangioma, hemangioma, vesicobullous lesion like cicatricial pemphigoid. Lipoma would be normal in color and its margins will slip during palpation. Lymphangioma and hemangioma would be present in younger age group and cicatricial pemphigoid would leave scar once it has healed. Also in pemphigoid other systemic features will also be present.

Treatment: Mucocele are chronic in nature, therefore, require surgical intervention. Careful surgical excision with removal of feeding gland should be done as this will decrease the chances of recurrence. Some mucoceles are short spanned that ruptures and heal by its own. The excised tissue should be sent to histopathological examination to rule out the possibility of any tumor.

Ranula

The term **Ranula** is derived from Latin word Rana means "frog". As the swelling resembles the translucent underbelly of frog, the term ranula has been coined. Ranula is the swelling of floor of the mouth, commonly arising from the sublingual gland. Ranula is primarily a mucocele; however, it has been discussed separately due to its bigger size and different characteristics. The etiology of ranula is local trauma or any obstruction or aneurysm of the duct.

Clinical features: The ranula usually presents as dome-shaped, fluctuant swelling with bluish tinge on the floor of the mouth (Fig. 10.2). The size of ranula is much larger than commonly occurring mucocele and it can raise the tongue causing considerable discomfort to the patients. Ranula appears in children and in young adults. The ranula is generally located lateral to the midline, thus can be distinguished from midline dermoid cyst.



Fig. 10.2: Ranula of floor of mouth

A variant of ranula is "**Plunging ranula**" which occurs when leaked mucin divides mylohyoid muscle and produces swelling in the neck which can be seen extra-orally.

Radiological features: Imaging can help in supporting the clinical diagnosis and in determining the origin and extent of the lesion. Computed tomography (CT) and magnetic resonance imaging (MRI) can be taken before surgery. The "tail sign" is

characteristically seen in plunging ranula cases. It is the slight extension of lesion in to the sublingual space.

Treatment: The treatment of ranula/plunging ranula is surgical. Removal of feeding sublingual gland and/or marsupialization can be done for small and superficial ranulas. For larger lesions, the removal of involved gland is important in order to prevent recurrence of the lesion.

Salivary Duct Cyst (Sialocyst)

Salivary duct cyst is true cyst arising from the salivary gland tissue. Unlike mucocele, sialocyst is lined by epithelium and separated from salivary ducts. The cause of occurrence of such cyst is unknown. Some researchers refer such lesions as mucus retention cyst however, it is different from retention cyst.

Clinical features: Salivary duct cyst can occur in major salivary glands and in minor salivary glands as well. Among major salivary glands, parotid gland is commonly involved. Cyst is presented as slowly growing, painless swelling. In minor glands, the swelling can occur in floor of the mouth buccal mucosa and in lips. The consistency of these cysts are same as that for mucocele, however, some cysts are firm in consistency. In some patients multiple sialocysts can also develop which often is presented as painful nodules with dilated ductal orifices on mucosal surface.

Radiological features: Smaller lesions do not require any imaging procedures. Larger lesions in major salivary gland would require CT/MRI to confirm the diagnosis and to see the extent of lesion. Ultrasonography can also be used to see the nature of the lesion.

Treatment: Isolated salivary gland cyst should be treated by conservative surgery. For cysts in major glands partial or total gland removal may be necessary. The chances of recurrence are very minimal. For multiple lesions, only symptomatic lesions should be removed surgically as and when required.

Sialolithiasis (Salivary Calculi: Salivary Stones)

Sialolithiasis is a condition where calcified structures are developed in the salivary ductal system. The cause for formation of sialoliths is still unclear but their formation can be supported by the chronic sialadenitis or partial obstruction. The composition of sialolith may consist of calcium and phosphorus salts which get deposited around the nidus of debris in the ductal system. The debris may include mucin, bacteria, ductal epithelial cells or any foreign body. The development of the sialolithiasis does not have any systemic implication and typically not related with calcium or phosphorous level imbalance.

Clinical features: Sialolithiasis can occur in major and minor salivary glands of which about 80% of sialoliths develop in submandibular gland ductal system. The reason for frequent formation of sialoliths in submandibular salivary gland is its long, tortuous duct with path which is against the gravity, causing stasis of saliva. Also, the secretion of submandibular gland is more mucous and thick.

Sialolithiasis can occur in any age group, however, young and middle-aged affect more often. There is no sex predilection for sialolith formation. Sialolithiasis in major salivary gland is frequently associated with episodic pain and swelling which increases during meal (Fig. 10.3). The severity of the symptoms depends upon the extent of obstruction and amount of resultant back pressure produced on the structures. If the obstruction is partial, then saliva may pass through the obstruction and relieves the symptoms associated.

The stone can be easily palpated in the floor of the mouth if it is present in terminal portion of the submandibular duct. Sometimes, in long standing cases, the ductal opening is also inflamed in sialolithiasis. Chronic obstruction of the saliva may lead to infection, fibrosis or glandular atrophy.



Fig. 10.3: Submandibular gland sialolithiasis

Radiological features: Plain radiography is still a convenient and inexpensive way of confirming diagnosis of sialolithiasis. The stones present in the terminal portion of the duct can be visualized as radio-opaque mass in occlusal radiograph. The submandibular stones which are formed away from the ductal opening can be visualized in panoramic radiographs. They may be superimposed on the mandibular body and should not be confused with any bony pathology.

Multiple parotid gland stones can be seen in PA view, lateral view (Fig. 10.4). These multiple stones should not be confused with calcified lymph nodes which are present in cases of tuberculosis. Sometimes, the obstruction in ductal system may occur due to mucus plug which cannot be seen on radiographs. Radiolucent sialoliths can be diagnosed using sialography. Radiolucent stone appears as filling defect in contrast filled ducts. Sialography can also easily differentiate between radiolucent sialolith and stricture formation.

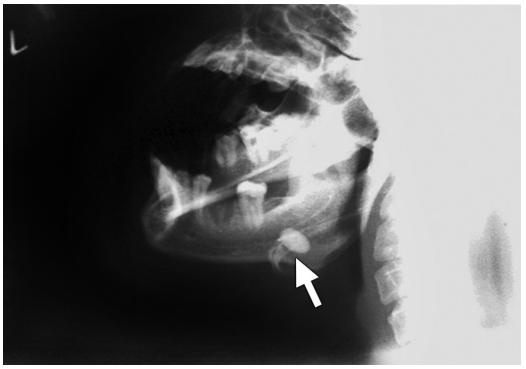


Fig. 10.4: Stone in submandibular gland

Besides sialography, ultrasonography is an effective tool in detecting stones in the ductal system. USG of parotid or submandibular gland can be done as it is non-invasive and non-ionizing. Contrast enhanced CT and MRI can also be advised, however, they should be kept reserved for the cases which could not be diagnosed through plain radiography or USG.

Diagnostic sialoendoscopy is newer tool used in evaluation and diagnosis of ductal obstructions. In this technique, a miniaturized endoscope is introduced into the duct through ductal orifice, allowing direct visualization of ductal system for any stones, strictures or adhesions.

Treatment: The stones present near the ductal opening should be treated conservatively by massage of the gland. Sialogogues (drugs that increase salivary flow) and increased fluid intake may also promote passage of stone. Larger sialoliths should be removed surgically. Extracorporeal shock wave lithotripsy (ESWL) and interventional sialoendoscopy are newer, non-invasive way of removal of stones from the ducts.

Sialadenitis

Sialadenitis is an inflammation of salivary glands, whereas sialodochitis is an inflammation of salivary ductal system. There are various causes of sialadenitis which include bacterial, viral, radiation therapy, Sjögren's syndrome, medications, ductal obstruction, sarcoidosis and congenital anomalies. Viral etiology of sialadenitis is the most common.

Other causes may include recent surgery (especially abdominal surgery) after which acute parotids may develop. Sialadenitis may be acute or chronic depending upon duration.

Bacterial Sialadenitis

Bacterial sialadenitis is common during pre-antibiotic era. However, with the advent of newer and potent antibiotics the incidence of bacterial sialadenitis has decreased. Most bacterial infections result due to ductal obstruction or decreased salivary flow. Sialolithiasis, congenital strictures, compression by adjacent tumor or any surgery can lead to ductal blockade. Decreased salivary flow may result from medications, dehydration, or conditions like diabetes mellitus.

Common bacteria involved in bacterial sialadenitis are *Staphylococcus aureus*, *Streptococcus viridians*, *Strep. pneumonia*, *Escherichia coli*, and *Haemophilus influenzae*.

Clinical features: Acute bacterial sialadenitis most commonly affects parotid gland unilaterally or bilaterally. The affected gland is painful, swollen with raised temperature. Patient may experience mild or low grade fever associated with chills and sweating. A purulent discharge may be seen from the ductal opening when gland is milked (Fig. 10.5). Patient may also complain of limited mouth opening and change in taste sensation.

Chronic or recurrent sialadenitis may result from ductal obstruction or stricture.

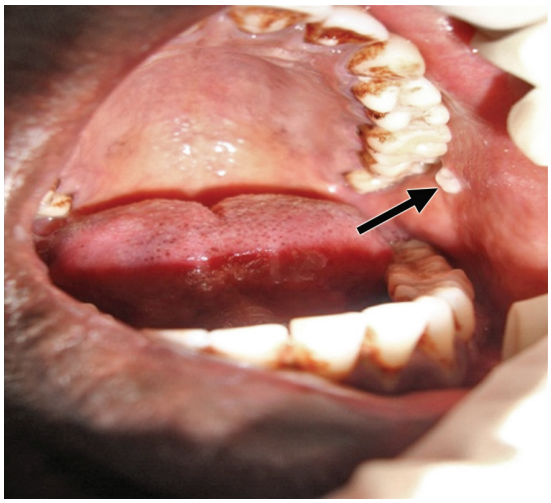


Fig. 10.5: Suppurative parotitis

Periodic swelling and pain may occur in the affected gland which usually increases during meal time. Pain may not be as severe as in acute sialadenitis patients. Generally, chronic adenitis occurs in older age group. Constitutional signs of fever, chills and sweating may be absent. Purulent discharge may or may not be present.

Juvenile recurrent parotitis is the most common condition affecting children in United States and second common worldwide after mumps. It usually affects children with age between 3 and 6 years. The etiology of this condition is unknown; however, congenital malformations, genetic factor or immunological factors are described in literature. Clinically, it manifests as recurring episodes of unilateral or bilateral, non-purulent parotid gland swelling. The condition may resolve around the puberty by its own.

Radiographic features: Patients with sialadenitis should have panoramic radiograph screening to rule out sialolith. Additional imaging studies include sialography, CT and MRI. Sialography is an important tool in diagnosis of sialadenitis and can differentiate chronic obstructive sialadenitis with autoimmune sialadenitis. However, with the introduction of advanced imaging techniques, Sialography is not such popular nowadays.

Acute sialadenitis shows minimal changes on sialography. However, evidence of obstruction might be seen in sialography. The sialographic findings of chronic sialadenitis patients vary with number and severity of previous infections. The sialographic pattern ranges from minimal changed to extensively altered ductal system. The pattern shows multiple areas of focal stricture and dilatation involving main duct (Fig. 10.6). Involvement of secondary duct may occur in advanced cases. Areas of fusiform dilatation and stricturing of main duct shows "sausage" or "string of sausages" like pattern.

On CT sialography studies, sections through the primary duct will demonstrate marked dilatation of primary duct.



Fig. 10.6: Sialography showing chronic recurrent parotitis

Treatment: The treatment includes antibiotic therapy and rehydration. Surgical drainage may be done if required. Treatment of chronic sialadenitis includes various factors like number and times of previous episodes. The treatment ranges from conservative management to surgical intervention. Conservative management includes antibiotics, analgesics, sialogogues, and sometimes, corticosteroids. The cases which develop secondary to ductal blockage should be treated with removal of sialolith.

If strictures are present, then patient might be prone for recurrent inflammation of the gland. Sialoendoscopy and ductal irrigation are employed in such patients in order to eliminate any stasis, sialolith or mucus plug in the duct. If conservative method cannot alleviate the symptom, then gland removal may be done.

Viral Infections

The most common viral infection involving salivary glands is mumps. It is caused by paramyxovirus. Other viruses involved in salivary gland pathology are coxsackie A virus, cytomegalovirus, human immunodeficiency virus (HIV) and parainfluenza virus.

◈ Mumps (Epidemic Parotitis)

Mumps is an infection of exocrine glands like salivary gland, pancreas, choroid plexus and mature ovaries and testes. Among all exocrine glands major salivary glands are affected usually. Mumps is a contagious, self-limiting disease which spreads through respiratory droplets, saliva and urine. The incubation period of this virus is 16–18 days with range of about 2–4 weeks.

Mumps can occur in epidemic form, however, its incidence has been brought down after introduction of two-dose regimen of MMR vaccination.

Clinical features: Mumps is a self-limiting disease with approximately 30% of subclinical cases. It affects adolescence population but recent trend shows more young adults involvement. The disease usually starts with pro-dromal symptoms such as low grade fever, malaise, anorexia and myalgia. Parotid gland is most commonly affected major salivary gland followed by submandibular and sublingual gland. It is presented as unilateral/bilateral parotid painful swelling. The glandular enlargement typically peaks in 2–3 days. Patient complains of difficulty in mouth opening and in chewing food.

Epididymo-orchitis is other common finding in young adult patients. It affects about 25% of males. The testicles are swollen and tender. Unilateral involvement of testes is more common as compared to bilateral involvement. On resolution, testes might show atrophy leading to sub-fertility. The condition may involve other organs also leading to pancreatitis, arthritis, carditis meningoencephalitis and decreased renal function.

The common oral manifestation of mumps is inflammation of Stenson's and Wharton's ductal openings. Apart from this, sublingual gland swelling may lead to bilateral enlargement of floor of the mouth.

The diagnosis of epidemic parotitis can be easily done clinically, however, isolated cases require laboratory confirmation. Mumps specific IgG and IgM titers may be elevated up to four times. The swab from secretion of salivary glands can be used for viral culture or real time PCR.

Treatment: The treatment of mumps is symptomatic. Analgesics and lots of fluid intake is recommended to the affected patients. The children should be immunized using two-dose MMR vaccination.

◈ HIV Infections and Salivary Glands

Another virus which affects salivary gland is HIV. It is evident in 5–10% of HIV affected individuals. The affected individuals have xerostomia which in turn leads to unilateral or bilateral salivary gland enlargement. The underlying pathogenesis may be autoimmune dysregulation and viral opportunistic infection. The incidence of salivary gland disease in HIV individuals is more in homosexuals and in intravenous drug abusers.

Clinical features: Salivary gland swelling is less commonly associated with HIV infection. Bilateral salivary gland swelling with lymphadenopathy is seen in majority of affected individuals. Patient may also complain of dry mouth. Dry mouth may occur either due to disease progression or due to antiretroviral therapy.

Radiographic features: CT and MRI of individuals may show multiple cystic masses in major salivary glands.

Treatment: The treatment of HIV associated salivary gland disease is symptomatic. Patient should be asked to sip water frequently with periodic dental examination. Fluoride application may be undertaken in order to prevent dental caries. Some investigators have reported that use of prednisone and antiretroviral therapy may regress the swelling. Other treatment options are removal of gland or radiotherapy.

◈ Subacute Necrotizing Sialadenitis

Subacute necrotizing sialadenitis is a self-limiting lesion which involves minor salivary glands of hard palate. The cause of subacute necrotizing sialadenitis is unknown, however, some investigators believe it to be allergic or infectious in origin.

Clinical features: Subacute necrotizing sialadenitis typically affects patient in their teens. It is represented as localized palatal swelling covered by erythematous, smooth, intact mucosa. Abrupt pain may be associated with this condition. It can be differentiated from necrotizing sialometaplasia on the basis of smooth surface, whereas latter has ulcerated surface.

Treatment: Though it is a self-limiting disease but the patient should be kept under observation for 2–3 weeks. If it does not heal, biopsy should be taken to confirm the diagnosis.

◈ Cheilitis Glandularis

In 1870 Volkmann first used the term "cheilitis glandularis" to describe a disorder which is suppurative inflammation of lower lip. It is an uncommon inflammatory lesion of minor salivary glands. Although cause for this condition is unknown, but investigators have pointed actinic damage, tobacco, poor hygiene and hereditary as etiologic factors.

Clinical features: Cheilitis glandularis occurs in middle aged and older with male sex predilection. It characteristically involves vermillion border of lower lip. Affected individuals have swollen lower lip with eversion due to hypertrophy and inflammation of minor salivary glands. Secondary infection of inflamed minor salivary glands in lower lip may lead to suppuration and mucopurulent discharge from the ductal openings. Based on its severity, it is classified into three progressive types:

a. Simple
b. Superficial suppurative (Baelz disease)
c. Deep suppurative lesion (cheilitis glandularis apostematosa)

Biopsy may be done in order to confirm the diagnosis of cheilitis glandularis.

Treatment: Depending upon the severity of lesion, the lesion may be treated with topical steroids, intralesional steroids or systemic steroids and antihistaminics. If conservative treatment fails, then surgical treatment with

resection or vermillonectomy should be considered.

Deep suppurative type of cheilitis glandularis has potential to convert into squamous cell carcinoma. This might be due to actinic damage due to solar radiation.

◈ Necrotizing Sialometaplasia

Necrotizing sialometaplasia is a self-healing, local infiltrative, rare inflammatory disorder of the salivary gland. It mainly affects minor salivary glands. The exact cause for lesion is unknown but local ischemia of salivary gland may play role in the etiopathogenesis. Some of the authors have enlisted a few predisposing factors which might play role in its etiopathogenesis. These are traumatic injuries, ill-fitting dentures, dental infections, upper respiratory tract infections, adjacent trauma and previous history of surgery, etc. Necrotizing sialometaplasia mimics squamous cell carcinoma clinically and histopathologically due to its infiltrative nature.

Clinical features: Necrotizing sialometaplasia is a condition which frequently develops in 4th decade of life and older individuals. Males are affected nearly twice as females. The usual site of involvement is palate with hard palate more commonly involved than soft palate. It mainly presents in midline, however, it can also occur unilaterally. Submandibular gland and sublingual glands are rarely affected.

The lesions appear as non-ulcerated swelling in midline palate associated with pain or paraesthesia. In due course, the surface of lesion undergoes necrosis and ulcer-like defect is created which mimic malignant process. The pain may reduce after ulcer formation. Underlying palatal bone might get involved in latter stages.

Radiological features: Computed tomography can be done in order to see any bony resorption and also to differentiate from squamous cell carcinoma. In malignancy, bony destruction with lymph nodes involvement may be seen on CT sections.

Treatment: Since this condition mimics malignancy, biopsy should be done in order to rule out the possibility. Once the diagnosis has been established, patient should be given symptomatic treatment and should be kept under observation as this disease is self-limiting. The lesion may heal on its own in 5–6 weeks.

AUTOIMMUNE DISEASES

Sjögren's Syndrome

Sjögren's syndrome is chronic autoimmune disease affecting salivary gland and lacrimal gland. The population prevalence of primary Sjögren's syndrome is 0.5% with women affecting more as compared to men in ratio of 9:1. About 15% of rheumatoid patients suffer from secondary Sjögren's syndrome. It is the second common autoimmune disease worldwide with prevalence of 1–3%.

The cause of Sjögren's syndrome is unknown. It has been postulated that human histocompatibility antigens (HLA-DRw52, HLA-DR3) might play role in etiopathogenesis of this condition. Additionally some researchers have described the role of viruses like Epstein-Barr virus and human T cell lymphotropic virus, in the pathogenesis of Sjögren's syndrome but substantially it has not been confirmed. The condition is not hereditary disease *per se*. Traditionally, the disease is divided into two forms:

1. **Primary Sjögren's syndrome:** It is also known as sicca syndrome with clinical feature of xerostomia and xerophthalmia meaning dry mouth and dry eyes. Dry eyes are also called keratoconjunctivitis sicca. No other autoimmune disorder is present.
2. **Secondary Sjögren's syndrome (sicca syndrome + autoimmune disorders):** The patients manifest other autoimmune disorders like rheumatoid arthritis, systemic lupus erythromatosus or scleroderma, in addition to sicca syndrome.

Clinical Features

Sjögren's syndrome is a rare condition which occurs in middle-aged individuals. There is preponderance for females. The classification criterion was proposed by American-European consensus group which is being discussed below.

The main symptom which patient presents is oral dryness due to decreased salivary secretion. The salivary acini are destroyed by the lymphocytic infiltration. The patients often find difficulty in chewing, swallowing, speaking, wearing dentures and have altered taste sensation. The tongue may become fissured and exhibits atrophy of papillae. The oral mucosa may become red due to candidal infection. There are increased chances of caries in such patients.

Some patients may exhibit diffuse enlargement of salivary glands unilaterally or bilaterally. The swelling is painless and persistent in nature. More is the severity of disease and more are the chances of appearance of salivary gland swelling. These patients may have possibility of retrograde bacterial sialadenitis due to decreased salivary secretion.

Above described features along with dry eyes are seen in patients with primary Sjögren's syndrome. Keratoconjunctivitis sicca develops as a result of less secretion from lacrimal glands. The lacrimal inflammation causes decrease in water content of tears and makes tears more mucinous. Patient may complain of dry, gritty sensation or perceived presence of foreign body in eyes. The eye problem worsens as day progresses.

Apart from xerostomia and xerophthalmia patient with secondary Sjögren's syndrome may have other connective tissue disorders. The skin is often dry as are the nasal and vaginal mucosae. Lymphadenopathy, primary billiary cirrhosis, Raynaud's phenomenon, interstitial nephritis, intestinal lung fibrosis, vasculitis and peripheral neuropathy may be noticed in patients with secondary Sjögren's syndrome.

TABLE 10.4: European–American consensus group criteria for Sjögren's syndrome

1.	Ocular symptoms (at least 1 of 3) a. Daily dry eyes >3 months b. Recurrent sand or gravel sensation in eyes c. Use of tear substitute for more than 3 times a day
2.	Oral symptoms (at least 1 of 3) a. Feeling of dry mouth >3 months b. Recurrent or persistent swelling of major salivary glands c. Need frequent sipping of fluid during swallowing of food
3.	Ocular signs (1 of 2) a. Schirmer's test performed without anesthesia (≤5 mm in 5 mins) b. Rose Bengal score or other ocular dye score (≤4 according to van Bijsterveld's scoring system)
4.	Histopathology In labial gland biopsy: Focus score ≥1 focus/4 mm^2 of glandular tissue
5.	Salivary gland involvement (at least 1 of the following) a. Unstimulated salivary flow (≤1.5 ml in 15 mins) b. Parotid sialography shows presence of disuse sialectasia without evidence of ductal obstruction c. Salivary scintigraphy shows delayed uptake, reduced concentration and/or delayed excretion of tracer
6.	Autoantibodies: presence of anti-Ro and anti-LA antibodies
7.	Diagnosis of primary Sjögren's syndrome a. Presence of any 4 items out of 6 as long as item 4 and item 6 are positive b. Presence of any 3 out of four items (items 3, 4, 5, 6)
8.	Diagnosis of secondary Sjögren's syndrome a. Presence of item 1 or item 2 with any two items from items 3, 4, 5 is considered positive for secondary Sjögren's syndrome.

Exclusion Criteria

- Past head and neck radiation treatment
- Hepatitis C infection
- AIDS
- Sarcoidosis
- Pre-existing lymphoma
- Graft-versus-host disease
- Use of anticholinergic drugs

Laboratory Tests

In Sjögren's syndrome patients have increased ESR and have high levels of circulating IgG immunoglobulins. Reduction in salivary gland flow using Lashley cups, less than 1.5 ml in 15 mins is considered positive for decreased secretion. Sialochemistry can also be done as there is decreased phosphate concentration and increased sodium concentration in saliva.

Various antibodies are positive in blood, however, none of the test is specific for diagnosis of the disease. The antibodies which are positive in Sjögren syndrome is anti-Ro (SS-A) and anti-La (SS-B), antinuclear antibodies (ANAs) and rheumatoid factor (RF). Occasionally antibodies against salivary gland duct can also be demonstrated.

For keratoconjunctivitis sicca Schirmer's test and Rose Bengal dye test can be performed. In Schirmer's test, a standardized strip of sterile filter paper is placed such that the margin of strip lies over the lower eyelid. Subsequently, the length of wetting is measured after 5 minutes. Values less than 5 mm are indicative of positive Schirmer test.

In Rose Bengal dye test, the cornea of eye is stained with Rose Bengal dye and examined using slit lamp for any ulceration. Histopathologically, labial gland biopsy shows lymphocytic infiltration of minor salivary glands with focus: 1 focus/4 mm^2.

American College of Rheumatology proposed classification criteria for Sjögren's syndrome.

TABLE 10.5: European–American consensus: Patients must have at least two of the following three objectives:

1.	Positive autoantibodies to Ro (SS-A) and/or La (SS-B) antigens, or positive rheumatoid factor and antinuclear antibodies titer ≥1:320
2.	Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with focus score ≥1 focus/4 mm^2
3.	Keratoconjunctivitis sicca with ocular staining score ≥3

Radiographic features: Sialographic examination reveals punctuate, cavitatory or destructive pattern and lack of normal architecture of ductal tissue, demonstrating "fruit laden branchless tree" pattern.

Scintigraphy with radioactive technetium-99m pertechnetate characteristically shows decreased uptake, retention and/or excretion of isotope.

Treatment: The treatment of Sjögren syndrome is primarily supportive. Salivary substitute or sialogogues should be used along with sugarless candies and daily fluoride application to prevent dental caries. Topical antifungal agent such as clotrimazole or miconazole may be used in order to prevent any fungal candidiasis. Pilocarpine or cevimeline may be used to enhance the saliva secretion from unaffected salivary gland.

Artificial tears may be used topically to prevent eyes from drying. Sealing of lacrimal punctum may prevent normal drainage of lacrimal secretion into nose and in turn, helps in keeping eyes moist.

Patients with Sjögren's syndrome have risk of 5 to 15% for developing lymphoma. Recent literature reveals that all salivary gland infiltrates are not benign lymphoepithelial lesions but some of them are low grade non-Hodgkin B cell lymphomas of mucosa associated lymphoid tissue. The detection of immunoglobulin gene rearrangements in labial salivary gland biopsy may serve as useful marker for predicting development of lymphoma.

Mikulicz's Disease (IgG4 Related Disease)

Mikulicz's disease was first described by Johann von Mikulicz-Radecki in late 1800s. Mikulicz's disease is characterized by chronic inflammatory infiltrate in the salivary glands. Histopathologically, some of the lesion's presentation is confusing and same as benign lymphoepithelial lesions associated with Sjögren syndrome. Therefore, these types of

lesions are classified as IgG4 related lesions which are a fibroinflammatory disorder.

IgG4 related diseases are the group of sclerosing inflammatory disorders in which IgG4 levels are elevated in serum along with presence of IgG4 positive plasma cells. Serum levels of IgG4 can shoot up to 25 times greater than normal levels.

Clinical features: IgG4 related diseases may present as unilateral/bilateral salivary gland painless swelling. It affects in middle aged and older individuals in 6th decade of life. After pancreas, head and neck region is second most common region to be affected by this condition. There is slight predilection for men than women. IgG4 related disease affects submandibular gland more frequently. The severity of disease depends upon the site of involvement.

Treatment: IgG4 related diseases should be treated aggressively. Systemic corticosteroid is the mainstay of treatment to avoid further damage of organ. Most of the patients show rapid response to immunosuppressive therapy. Other steroid sparing immunosuppressive drugs are azathioprine, mycophenolate mofetil and methotrexate.

NON-INFLAMMATORY DISORDERS OF SALIVARY GLANDS

Sialadenosis (Sialosis)

Sialadenosis is non-inflammatory, non-neoplastic disorder involving major salivary glands. The condition arises majorly due to any systemic cause like endocrinal, nutritional or neurogenic. Most common systemic conditions which cause sialadenosis are diabetes mellitus, malnutrition, alcoholism and bulimia.

The cause for sialadenosis is believed to be dysregulation of autonomic nervous system supplying salivary glands. The condition leads to excessive accumulation of secretory granules with marked enlargement of acinar cells. In addition, there is atrophy of supporting myofilaments around acinar cells due to reduced innervations of myoepithelial cells.

TABLE 10.6: Conditions associated with sialadenosis

1.	Endocrine disorders a. Diabetes mellitus b. Diabetes insipidus c. Acromegaly d. Hypothyroidism e. Pregnancy
2.	Nutritional a. General malnutrition b. Alcoholism c. Cirrhosis d. Anorexia nervosa e. Bulimia
3.	Neurogenic medications a. Antihypertensive drugs b. Psychotropic drugs c. Sympathomimetic drugs used for treating asthma

Clinical features: Sialadenosis represents as bilateral or unilateral, painless, slow growing swelling. The saliva secretion is decreased. Sometimes, it may present as painful swelling. The most common major gland which is involved is submandibular salivary gland. Minor salivary glands are rarely affected. It may be differentiated from Sjögren syndrome on the basis of systemic history and laboratory tests.

Radiographic features: Sialadenosis generally spares the ductal system and involves acinar tissue of major salivary glands. Therefore, sialography examination reveals "leafless pattern" with splaying of ductal system. CT scan studies demonstrate generalized increase in size and density of parenchyma caused by infiltration of fatty and fibrous tissue.

Treatment: Treatment will include patient reassurance and education. Many times treatment is often unsatisfactory. Underlying cause should be corrected first. Mild swelling of parotid gland does not cause many problems. Bigger swelling is a concern from

cosmetic point of view. Therefore, surgically, partial/complete removal of involved gland can be undertaken. Pilocarpine might be used to increase the secretion in case of salivary output.

Orofacial Granulomatosis

Wiesenfeld introduced the term orofacial granulomatosis in the year 1985 which comprises variety of clinical presentations. Histopathologically, all orofacial granulomatoses share some pictures of non-caseating giant cell granulomas. Various orofacil granulomatosis pathologies are Melkersson-Rosenthal syndrome, cheilitis granulomatosa, Crohn's disease, sarcoidosis and tuberculosis.

Sarcoidosis is a multisystem immune-related disorder primarily affecting lymph nodes. Heart, liver, spleen, bones, kin eyes, parotid gland may also get involved in some patients.

Clinical Features

Painless, asymptomatic or mildly symptomatic enlargement of major salivary gland may be the first sign of sarcoidosis. Facial nerve involvement may present and can be wrongly diagnosed as malignancy. Salivary gland milking may yield delayed response, however, sialometry is normal in this condition. It may also affect other parts of orofacial region such as gingiva, buccal mucosa, floor of the mouth and tongue. Biopsy of lesion should be carried out in order to diagnose sarcoidosis.

Serum angiotensin converting enzyme (sACE) is considered as diagnostic for sarcoidosis. Elevated level of sACE is found in 80–90% of the cases as sACE is secreted by granulomas.

Treatment: Spontaneous regression is seen in most of the patients. Some patients may require systemic corticosteroids. Refractory cases may be treated with azathioprine, mycophenolate mofetil and cyclosphosphamide or methotrexate. Consultation with dentist should be done in order to prevent dental caries and dry mouth.

TUMORS OF SALIVARY GLANDS

General Considerations

1. The annual incidence of salivary gland tumor worldwide is 1.0–6.5/100,000. That means salivary gland tumor is not a rare entity.
2. **Parotid glands:** Around 60–80% of salivary gland tumors occur in parotid gland and relatively low percentage of tumors are malignant in nature. Around 2/3rd to 3/5th parotid tumors are benign in nature. Pleomorphic adenoma is most common tumor occurring in parotid gland followed by Warthin's tumor.
3. **Submandibular gland:** Approximately 8–11% of salivary glands tumors occur in submandibular gland. The incidence of malignant tumor involving submandibular gland is more as compared to parotid gland. Pleomorphic tumor followed by adenoid cystic carcinoma is most common tumors of salivary gland.
4. **Sublingual gland:** The occurrence of tumor in sublingual salivary gland is rare. However, the chances of malignant tumors are more in sublingual gland as compared to other two major salivary glands.
5. **Minor salivary glands:** Minor salivary gland tumor is the second most common site for salivary neoplasia. The frequency of malignant tumors in minor salivary gland is far more common as compared to major salivary gland tumors.
6. Mucoepidermoid carcinoma is the most common malignant tumor of minor salivary gland.
7. Palate is the most common site for salivary gland tumors accounting for about 50% of tumor occurring at this site. The density of minor salivary gland is more in posterolateral hard or soft palate that is why more tumors occur at postero-lateral aspect of palate.

8. Although CT and MRI have replaced the sialography in evaluation of salivary masses, the reader should be aware of some sialographic patterns obtained in cases of neoplasia. In tumors, sialography will show the following patterns:
   a. Ductal splaying or "ball in hand" appearance
   b. Ductal displacement, buckling or cut off
   c. Abrupt ductal irregularities or displacement and contrast spilling within gland
   d. Filling defects on parenchymal opacification.

The above sialographic signs are non-specific and could not be able to differentiate between low grade malignancies and benign tumors. Sialographic pattern suggestive of malignancy is abrupt ductal irregularity and displacement and contrast spilling in tissue parenchyma.

Classification

Benign

- Pleomorphic adenoma (mixed tumor)
- Myoepithelioma
- Basal cell adenoma
- Canalicular adenoma
- Warthin tumor (papillary cyst adenoma lymphomatosum)
- Oncocytoma
- Sebaceous adenoma
- Sebaceous lymphadenoma
- Ductal papillomas
- Sialadenoma papilliferum
- Intraductal papilloma
- Inverted ductal papilloma
- Papillary cyst adenoma

Malignant

- Malignant mixed tumors
- Carcinoma ex pleomorphic adenoma
- Carcinosarcoma
- Metastasizing mixed tumor
- Mucoepidermoid carcinoma
- Acinic cell adenocarcinoma
- Adenoid cystic carcinoma
- Polymorphous low-grade adenocarcinoma
- Basal cell adenocarcinoma
- Epithelial-myoepithelial carcinoma
- Mammary analogue secretory carcinoma
- Salivary duct carcinoma
- Myoepithelial carcinoma
- Cyst adenocarcinoma
- Sebaceous adenocarcinoma
- Sebaceous lymph adenocarcinoma
- Clear cell adenocarcinoma
- Oncocytic carcinoma
- Squamous cell carcinoma
- Malignant lymphoepithelial lesion (lymphoepithelial carcinoma)
- Small cell carcinoma
- Sialoblastoma
- Adenocarcinoma, not otherwise specified (NOS)

BENIGN TUMORS OF SALIVARY GLANDS

Pleomorphic Adenoma

Pleomorphic adenoma is most common tumor of salivary gland. It is also called mixed tumor of salivary gland because it is derived from ductal and myoepithelial elements and microscopically it presents wide variation from one tumor to another. However, it does not originate from more than one germ layer. Cytogenetic analysis revealed that 70% of adenoma primarily involves translocation of pleomorphic adenoma gene 1 (PLAG1) located on chromosome 8q12.

Clinical Features

Pleomorphic adenoma can occur in major and minor salivary glands. It is painless, slow growing, firm mass with well distinct borders. Most common age is between 30–60 years. However, it can develop in any age group. There is slight female predilection.

Parotid gland pleomorphic adenoma presents as swelling on the ramus of mandible. Initially the swelling becomes less movable. In most cases superficial lobe of parotid gland is involved and in about 10% of

cases deep lobe of parotid gland is involved. The lesion does not show fixation either to the deeper tissues or to the overlying skin. Associated features of facial nerve palsy and pain are less evident in literature.

Pleomorphic adenoma of minor salivary gland generally occurs in palate (Fig. 10.7) followed by upper lip and buccal mucosa. It presents as smooth surfaced firm swelling in posterolateral portion of palate. The swelling might get ulcerated if it is traumatized.



Fig. 10.7: Pleomorphic adenoma of minor salivary gland

Radiographic features: Computed tomography will show pleomorphic adenoma as enhancing, well-circumscribed lesions with fibrous capsule around it. The tumors are well-demarcated from sound parenchymal tissue. Lesions smaller than 1 cm usually rounded and lesions above 1 cm are lobulated. To rule out any malignant changes, evaluation of facial nerve involvement is essential. On ultrasonography, lesion are well circumscribed, hypoechoic and non-enhancing masses.

Treatment: Pleomorphic adenomas are best treated by surgical removal. Parotidectomy with identification and preservation of facial nerve is recommended. The prognosis of pleomorphic adenoma is excellent and chances of recurrence are less.

Warthin's Tumor

Warthin's tumor or papillary cystadenoma lymphomatosum, is the second most common tumor of parotid gland. It accounts for about 5–22% of parotid gland tumors. The pathogenesis of the lesion is controversial. One theory believes that it arises from salivary gland tissue found in the parotid lymph node. However, other researchers believe that the tumor may develop from salivary gland duct cells. The incidence of Warthin's tumor is found to be more in smokers than non-smokers.

Clinical Features

Warthin's tumor occurs in older age group between 6th and 7th decades of life. Male preponderance was seen in previous literature (10:1), however, recent studies show frequency of occurrence is similar in female and males. Smoking is considered as one of the important etiological agents and nowadays frequency of smoking is more or less equal in male and female probably, that is why the male and female predilection is similar in recent studies.

Warthin's tumor presents as slow growing, painless swelling in the tail end of parotid gland. Rarely, it can involve sub-mandibular and sublingual gland also. The consistency on palpation is fluctuant or firm. Warthin's tumor can occur bilaterally with one swelling appearing after another.

Radiographic Features

Sialographic studies in Warthin's tumor show indistinguishable features from other benign tumors of salivary gland such as pleomorphic adenoma. It can also occur in inferior aspect of superficial lobe of parotid gland.

Computed tomography examination show tumor as enhancing, rounded and well-demarcated lesion in posteroinferior segment of parotid gland. Radionuclide scan shows increased uptake of radionuclide dye and presents as "hot spot" on the scans. This might be due to the fact that Warthin's tumor is composed of secretory cells not excretory cells so the dye gets accumulated in the gland. Ultrasound studies show hypoechoic

areas with echogenic line and may also demonstrate lobulated outline.

Treatment: Surgical excision is the choice of treatment in cases of Warthin's tumor. Some surgeons excise with minimal surrounding tissue and others prefer parotidectomy. The chances of recurrence are minimal.

Oncocytoma (Oxyphillic Adenoma)

Oncocytoma is a rare, benign tumor of salivary gland mainly composed of oncocytes. The word onco (derived from Greek word onkoustai) means to swell. In this tumor, swollen granular cytoplasm with accumulation of mitochondria is seen in salivary gland cells. Sometimes, metaplasia of ductal and acinar cells is also noted. Besides salivary gland, oncocytes are also seen in other organs like thyroid, parathyroid, and kidney.

Clinical features: Oncocytoma occurs in older age group, around 6th–7th decade of life. It commonly involves parotid gland although, cases involving submandibular gland and minor salivary glands are also reported in literature. The tumor appears as firm, slow growing and painless swelling in parotid gland. It majorly affects superficial lobe of parotid gland and clinicians find it difficult to distinguish it from other benign tumors of parotid gland.

Radiographic features: CT images of oncocytoma usually reports well-circumscribed enhancing lesion in the parotid gland. It can be multifocal or bilateral. MRI usually demonstrates well-circumscribed, low signal intensity on T1 and T2 weighted images. Homogenous enhancement of lesion is seen after intravenous injection of contrast.

Treatment: The oncocytoma is benign in nature, therefore, surgical excision with partial parotidectomy can be done. Facial nerve should be preserved while operating. Oncocytoma affecting submandibular gland should be excised completely with gland removal. The chance of recurrence is rare. Some cases of oncocytoma are locally aggressive and should be considered for low grade malignancy.

Canalicular Adenoma

Canalicular adenoma is an uncommon tumor of minor salivary gland. Histopathologically, it shows uniform pattern, therefore, it is also called monomorphic adenoma.

Clinical Features

Canalicular adenoma occurs in older age group peaking in 7th decade of life with slight female preponderance. Canalicular adenoma is one of the rare tumors that occur on upper lip. The buccal mucosa is the second common affecting site. It usually affects major salivary glands and also predilection for minor salivary gland.

It presents as slow growing, fluctuant, painless swelling with bluish surface. This tumor is often mistaken as mucocele. The mucocele of upper lip is very uncommon, therefore, swelling on the upper lip should be considered for canalicular adenoma.

Radiographic features: CT findings will show well-defined, enhancing, homogenous lesion in the major salivary gland. MRI can also be done revealing same finding as that of CT scan.

Treatment: Local surgical excision is the choice of treatment for canalicular adenoma. Recurrence of the lesion is rare.

Basal Cell Adenoma

Basal cell adenoma is an uncommon tumor accounting for about 1–4% of all salivary gland tumors. As canalicular adenoma, it is also categorized under monomorphic adenoma of salivary gland, however, some histopathological study reveals presence of more than one cell type. Previously canalicular and basal cell adenoma were used synonymously but recent literature termed them different entity.

Clinical Features

Basal cell adenoma is a tumor of major salivary gland with basaloid appearance

microscopically. It may occur in minor salivary glands also. The tumor can occur at any stage of life with peak prevalence of 7th decade of life. Females are more affected than male counterparts (2:1).

Clinically, basal cell adenoma shows features like pleomorphic adenoma. The swelling usually slow growing and painless in nature. Superficial lobe of parotid gland is involved commonly. One subtype, termed membranous basal cell adenoma, is hereditary and often occur with dermal tumors like cylindromas and trichoepitheliomas. Membranous basal cell adenoma bears resemblance to the dermal counterparts microscopically, therefore, termed dermal analogue tumors.

Radiographic features: CT scan shows well-defined, enhancing, homogenous lesion. It may be round to oval in shape. Sometimes, CT findings reveal inhomogenous mass due to presence of cystic spaces within the lesion.

Treatment: Like pleomorphic adenoma, basal cell adenoma is also treated surgically and prognosis is very good with less chance of recurrence.

MALIGNANT TUMORS OF SALIVARY GLAND

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma is the most common malignancy arising from salivary glands. Mucoepidermoid carcinoma may be graded according to aggressiveness of the tumor into low grade, intermediate grade and high grade tumor. The etiopathogenesis of the tumor is not clear, however, some researchers reported radiation exposure as one of the causes. Reciprocal translocation (11:19) is also been reported by some authors in low grade and intermediate type of mucoepidermoid carcinomas.

Clinical Features

Mucoepidermoid carcinomas commonly occurs in parotid gland followed by minor salivary glands on palate (Fig. 10.8), lower lip and floor of the mouth. The tumor may occur during wide age range but it is very rare in first decade. Mucoepidermoid carcinoma generally starts as painless swelling which may involve facial nerve in later stages. The swelling is usually smooth surfaced but may get ulcerated due to secondary trauma.



Fig. 10.8: Mucoepidermoid carcinoma of palate

Clinically, low grade carcinomas are associated with a slower growth rate, longer duration and good prognosis as compared to high grade carcinomas. About two-thirds of mucoepidermoid carcinomas are low grade. Low grade carcinomas generally present as cystic swelling, whereas high grade are more solid in consistency. High grade malignancy may infiltrate surrounding structures and may metastasize to the regional lymph node.

Radiographic features: Clinically suspected case of mucoepidermoid carcinoma should be investigated using contrast enhanced CT. In low grade malignancy CT images will show well-circumscribed mass with cystic degeneration in some areas. More or less, these tumors have appearance like benign mixed tumors. High grade malignancy will show poorly demarcated, solid lesion which is infiltrating locally.

Ultrasonography and MRI studies can also be done. MRI studies may be done in order to rule out perineural spread of tumor into base of skull.

Treatment: Patients with low grade malignancy should be treated surgically with wide excision. Facial nerve may be conserved while operating. Patients with high grade tumor should be treated aggressively. Parotidectomy with wide excision along with facial nerve dissection and neck dissection may be required. Radiotherapy and/or chemotherapy may be done after surgical treatment.

Prognosis for low grade is generally good with survival chance of 90–98%, however, survival rate is reduced in cases with high grade malignancy.

Intraosseous Mucoepidermoid Carcinoma

Intraosseous salivary gland tumors may develop in the jaws and anterior tumor can arise in bone, however, mucoepidermoid carcinoma is most common tumor to arise inside bone. Many theories had been proposed for the intrabony presence of salivary tumor but none has been found to be good enough to explain the reason. Some intraosseous mucoepidermoid carcinoma develops in association with impacted teeth or odontogenic cysts.

Clinical features: Intraosseous mucoepidermoid carcinoma occurs in middle age group with mandible more commonly involved than maxilla. There is slight predilection for females as compared to males. The tumor presents as swelling with cortical expansion, like in benign tumors. The swelling may be associated with pain, trismus and paraesthesia.

Radiographic features: Radiographically, it represents as unilocular or multilocular radiolucency with well-defined borders. However, in some cases ill-defined borders are also noted with osteolytic lesion depending upon tumor's aggressiveness. Contrast enhanced CT scan shows in homogenous enhancement with well-defined borders.

Treatment: Intraosseous carcinomas are treated by surgery first followed by radiotherapy or chemotherapy or both. The recurrence chance is high if surgery with conservative approach is done. Metastasis has also been reported in some cases.

Acinic Cell Carcinoma

Acinic cell carcinoma is low grade malignancy where salivary gland cells undergo serous acinar differentiation. Previously, this entity was considered as tumor and was termed acinic cell tumor. But these tumors can metastasize, recur and can cause mortality. Therefore, now researchers have kept this tumor into low grade malignancy.

Clinical features: Predominately, acinic cell carcinoma occurs in parotid gland. Superficial lobe affects more than deep lobe of parotid gland. Other sites of involvement are submandibular gland, minor salivary gland in buccal mucosa, lip and palate. Majority of cases occur in parotid gland as this is the largest salivary gland and is serous in nature. The tumor occurs in wide age range from 4th–7th decade of life. The tumor usually appears as slow growing mass and can attain large size. Most of the time it is asymptomatic and facial nerve involvement is rare.

Radiographic features: Radiographic features of acinic cell carcinoma are overlapping with benign tumor. CT scan findings show enhancing, irregular lesion which may be associated with necrotic areas.

Treatment: Acinic cell carcinoma is treated by lobectomy if the lesion is confined to superficial lobe and parotidectomy if deep lobe is involved. Submandibular gland tumor may be treated by total gland removal. The prognosis of the patients with acinic cell carcinoma is generally good with some chances of recurrence.

Malignant Mixed Tumors

Malignant mixed tumors present malignant counterpart of pleomorphic adenoma. It is comparatively rare carcinoma comprises 2–4% of all salivary gland tumors. Malignant

mixed tumors are categorized into three categories:

1. Carcinoma ex pleomorphic adenoma
2. Carcinosarcoma
3. Metastasizing mixed tumor

Carcinoma ex pleomorphic adenoma is the most common variant among three. Histopathologically, it shows dysplastic features in the epithelial component of pleomorphic adenoma. Carcinosarcoma is rarest of the three and shows both epithelial and connective tissue component undergoing dysplasia, whereas metastasizing mixed tumor does not show any dysplasia in the epithelial or connective tissue part but metastasize to other parts of body. The microscopic features of metastasize lesion shows benign appearance.

Clinical Features

◈ Carcinoma ex pleomorphic adenoma

This variant develops in long standing cases of pleomorphic adenoma. It commonly occurs in parotid gland and suddenly benign tumor starts to grow at rapid pace. Rapid growth may be associated with surface ulceration. It may be painful or painless. Facial nerve involvement can be seen in this variant. It may also occur in minor salivary glands and palate is the most common site for its occurrence. It generally occurs in middle age group in 6–7th decade of life.

◈ Carcinosarcoma

Carcinosarcoma is one of the rare malignant tumors of salivary gland. It either occurs in long standing pleomorphic adenoma or *de novo*. It most commonly involves parotid gland although cases of submandibular gland are also reported. The clinical signs and symptoms are more or less similar to carcinoma ex pleomorphic adenoma.

◈ Metastasizing mixed tumor

Metastasizing mixed tumor is also rare tumor, commonly occurring in parotid gland. It shows benign nature and frequently metastasizes to bones, lungs, regional lymph nodes, liver and skin. It may develop in previously treated mixed tumor also.

Radiographic features: Both CT and MRI can be done to investigate the malignant mixed tumors. Radiographic findings of malignant mixed tumors are similar to the other malignant tumors. Carcinoma ex pleomorphic adenoma and carcinosarcoma shows large, ill-defined, heterogeneous lesion with infiltrative margins. The tumor may infiltrate into surrounding tissues. Regional lymph node metastasis can also be noted. Metastasizing mixed tumor shows well-defined borders, homogeneous and enhancing lesion. However, other parts like bones, liver, skin, lungs may show similar kind of lesion therefore, whole body CT scan or PET scan should be done in order to see distant lesions.

Treatment: Treatment of carcinoma ex pleomorphic adenoma and carcinosarcoma comprises surgery with radiotherapy and chemotherapy. The excision of the lesion should be done with wide margins with regional lymph node removal. The chances of survival after treatment are not so good in both the tumors. Metastasizing mixed tumor should be treated by surgical excision of primary and secondary tumors.

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma is also called cylindroma. It is the relatively common malignancy of salivary gland. Adenoid cystic carcinoma shows myoepithelial and ductal cells in varied arrangement.

Clinical features: Adenoid cystic carcinoma commonly occurs in minor salivary gland with palate being common site (Fig. 10.9). Male to female ratio is 1:1.4. The age group for this malignancy is 4–5th decade and comparatively rare in age below 20. It presents as slow growing lesion associated with pain and facial nerve involvement. Patients often complain of constant, low

grade, dull ache which increase in intensity as time progress.



Fig. 10.9: Adenoid cystic carcinoma

Radiographic features: CT scan shows enhancing, heterogeneous mass, locally destructured lesion with involvement of palate and maxillary. The borders are ill defined. Regional metastasis to lymph nodes is comparatively uncommon.

Treatment: Surgical resection with wide borders is the treatment of choice for these tumors. As regional metastasis is uncommon, so the need for neck dissection is not indicated. Adenoid cystic carcinoma is prone to local recurrence and distant metastasis. Both these features increase the mortality index in this carcinoma.

FREQUENTLY ASKED QUESTIONS

Long Answer Questions

a. Classify salivary gland tumors. Write in detail about clinical features, radiographic features and treatment of pleomorphic adenoma.
b. Describe in detail about etiopathogenesis, clinical features, laboratory findings and treatment of Sjögren's syndrome.
c. Describe in detail about indications, contraindications, contrast agents and procedure of sialography.
d. Write in detail about causes, clinical features, chair side tests and treatment of xerostomia.

Short Answer Questions

a. Contrast agents in sialography
b. Sialorrhea
c. Causes of xerostomia
d. Bacterial sialadenitis
e. Mumps
f. Sialolithiasis
g. Mucoepidermoid carcinoma
h. Sialosis
i. Necrotizing sialometaplasia
j. Classify salivary gland disorders.

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Chapter

11

Temporomandibular Joint Diseases and Radiologic Considerations

INTRODUCTION

The term *temporomandibular disorders* (TMDs) is a collective term embracing a number of clinical problems that involve the masticatory muscles, the temporomandibular joints (TMJs) and the associated structures or both. These disorders are characterized by facial pain in the region of the TMJs or muscles of mastication, limitation or deviation in mandibular movements, and TMJ sounds during jaw movement and function. This chapter presents a general approach to the diagnostic assessment and nonsurgical management of the most common TMDs.

Functional Anatomy

Temporomandibular joint, the TMJ articulation is a joint that is capable of hinge type and gliding movements.

The bony components are enclosed and connected by a fibrous capsule. The mandibular condyle forms the lower part of the bony joint and is generally elliptical, although variations in shape are common. The articulation is formed by the mandibular condyle occupying a hollow in the temporal bone (mandibular or glenoid fossa).

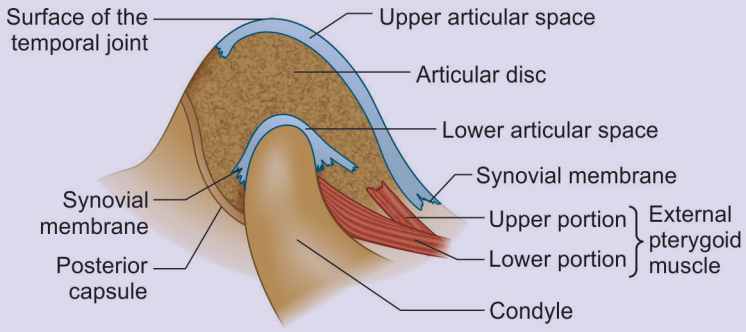
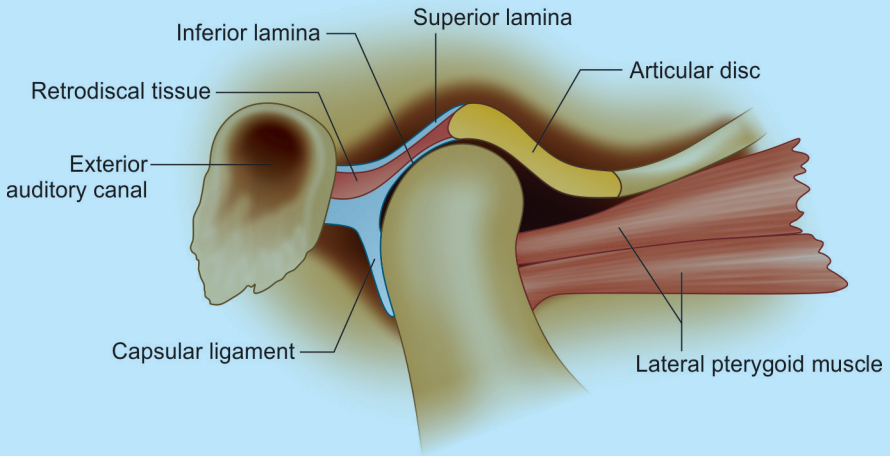
The S-shaped form of the fossa and eminence develops at about 6 years of age and continues into the second decade. During wide mouth opening, the condyle rotates around a hinge axis and glides, causing it to move beyond the anterior border of the fossa, which is identified as the articular eminence.

TABLE 11.1: Anatomy of TMJ

Bony component of TMJ Fibrous capsule	⁎ The capsule is lined with synovium, joint cavity is filled with synovial fluid. The synovium is a vascular connective tissue lining the fibrous joint capsule extending to the boundaries of the articulating surfaces covering upper and lower joint cavities. ⁎ The synovial membrane consists of macrophage-like type A cells and fibroblast-like type B cells. ⁎ Synovial fluid is a filtrate of plasma with added mucins and proteins. Its main constituent is hyaluronic acid. Fluid forms on the articulating surfaces decrease friction during joint compression and motion. ⁎ Joint lubrication is achieved by weeping lubrication and boundary lubrication. Weeping lubrication occurs as fluid is forced laterally during compression and expressed through the unloaded fibrocartilage. Boundary lubrication is function of water that is physically bound to the cartilaginous surface by a glycoprotein.

Contd.

TABLE 11.1: Anatomy of TMJ *(Contd.)*

Articular disc	▪ A fibrocartilage is made up of dense collagen and referred to as a disc which occupies the space between the fibrocartilage coverings of each of condyle and mandibular fossa. ▪ The disc consists of collagen fibers, cartilage like proteoglycans, and elastic fibers and number of cells that resemble fibrocytes and fibrochondrocytes. ▪ The disc is primarily avascular and has sensory nerve penetration. It is attached by ligaments to the lateral and medial poles of the condyle. The ligaments consist of both collagen and elastic fibers. These ligaments permit rotational movement of the disc on the condyle during mouth opening and closing. ▪ The disc and its attachments divide the joint into upper and lower compartments which do not communicate. The passive volume of the upper compartment is estimated to be 1.2 ml and that of the lower compartment is estimated to be 0.9 ml. The roof of the superior compartment is the mandibular fossa, and floor is the superior surface of the disc. The roof of the inferior compartment is the inferior surface of the disc and the floor is the articulating surface of the mandibular condyle. At its margins, the disc blends with the fibrous capsule. ▪ Fibers of the posterior one-third of the temporalis muscle and the deep masseter muscle attach on the anterolateral aspect, and fibers of the superior head of the lateral pterygoid insert into the anteromedial two-thirds of the disc.  **Fig. 11.1**
Retrodiscal tissue	 **Fig. 11.2**

Contd.

TABLE 11.1: Anatomy of TMJ *(Contd.)*

	▪ A mass of soft tissue occupies the space behind the disc and condyle. It is referred to as the posterior attachment; a loosely organized system of collagen fibers, branching elastic fibers, fat, blood and lymph vessels, and nerves. Synovium covers the superior and inferior surfaces with a loose areolar, highly vascular, and well-innervated tissue. ▪ The superior lamina arises from the posterior band of the disc and attaches to the squamotympanic fissure and tympanic part of the temporal bone consists of elastin. The inferior lamina arises from the posterior band of the disc and inserts into the inferior margin of the posterior articular slope of the condyle composed of collagen fibers.
Temporomandibular ligaments	
Capsular ligament	The capsular ligament is a thin inelastic fibrous connective tissue envelope that attaches to the margins of the articular surfaces and neck of the condyle.
Lateral temporomandibular ligament	The lateral temporomandibular ligament is the main ligament of the joint. Its fibers pass obliquely from bone lateral to the articular tubercle in a posterior and inferior direction and insert in a narrower area below and behind the lateral pole of the condyle.
Sphenomandibular ligament	The sphenomandibular ligament arises from the sphenoid bone and inserts on the medial aspect of the mandible at the lingula.
Stylomandibular ligament	The stylomandibular ligament extends from the styloid process to the deep fascia of the medial pterygoid muscle. It is thought to become tense during protrusive movement of the mandible and limits protrusive movement.

TABLE 11.2: Muscles of mastication

Muscle of mastication	*Origin*	*Insertion*	*Function*
Masseter	▪ From maxillary process of zygomatic bone. ▪ Superficial part of maxillary process of zygomatic bone and the anterior two-thirds of the inferior part.	▪ Lateral aspect of ramus	▪ Masseter and medial pterygoid join together to form a sling that cradles the ramus of the mandible and produces the powerful forces required for chewing.
Medial pterygoid	▪ Medial surface of lateral pterygoid plate	▪ Medial aspect of ramus.	▪ Closing of mandible.
Temporalis	▪ Temporal fascia	▪ Coronoid process and mandibular ramus.	▪ Fan-shaped opening and retrusion of mandible.
Lateral pterygoid	▪ Inferior part: Lateral surface of lateral pterygoid plate. ▪ Superior part: Greater wing of sphenoid.	▪ Anteromedial aspect of condylar neck and disc.	▪ Main protrusive and opening muscle.

Contd.

TABLE 11.2: Muscles of mastication *(Contd.)*

Muscle of mastication	*Origin*	*Insertion*	*Function*
Digastric (accessory muscle)	⋆ Anterior belly from digastric fossa of mandible. ⋆ Posterior belly from mastoid notch of temporalis.	⋆ Together they insert on the hyoid bone.	⋆ Depression and retrusion of mandible.
Buccinator (accessory muscle)	⋆ From the alveolar processes of maxilla and mandible, and pterygo-mandibular raphae.	⋆ Orbicularis oris	⋆ Compresses cheek into the teeth for chewing.

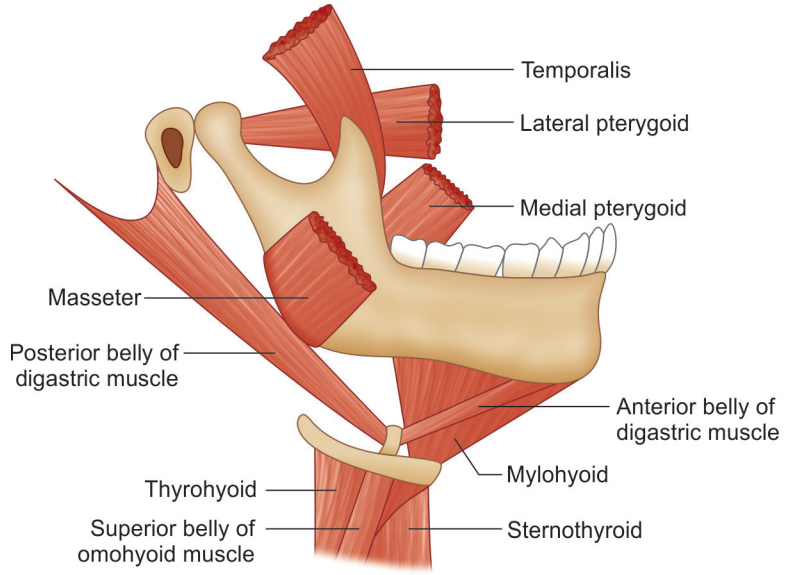


Fig. 11.3

Flowchart 11.1

Diagnostic classification of temporomandibular disorders

Cranial bones
Congenital and developmental disorders:
- Aplasia
- Hypoplasia
- Hyperplasia
- Dysplasia (e.g. first and second branchial arch anomalies, hemifacial microsomia, Pierre Robin syndrome, Treacher Collins syndrome, condylar hyperplasia, prognathism)

Acquired disorders:
- Neoplasia
- Fracture

Temporomandibular joint
- Deviation in form
- Disc displacement (with reduction, without reduction)
- Dislocation
- Inflammatory conditions (synovitis, capsulitis)
- Arthritides (osteoarthritis, osteoarthrosis, polyarthritides)
- Ankylosis (fibrous, bony)
- Neoplasia

Masticatory muscle
- Myofacial pain
- Myositis spasm
- Protective splinting
- Contracture

(*Adapted from* McNeill C.127) (*Courtesy:* Classification from Burett, 12th ed)

CLASSIFICATION

TABLE 11.3: Taxonomic classification for temporomandibular disorders

Temporomandibular joint disorders

1. **Joint pain**
   - A. Arthralgia
   - B. Arthritis

2. **Joint disorders**
   - A. Disc disorders
     1. Disc displacement with reduction
     2. Disc displacement with reduction with intermittent locking
     3. Disc displacement without reduction with limited opening
     4. Disc displacement without reduction without limited opening
   - B. Other hypomobility disorders
     1. Adhesions/adherence
     2. Ankylosis
        - a. Fibrous
        - b. Osseous
   - C. Hypermobility disorders
     1. Dislocations
        - a. Subluxation
        - b. Luxation

3. **Joint diseases**
   - A. Degenerative joint disease
     1. Osteoarthrosis
     2. Osteoarthritis
   - B. Systemic arthritides
   - C. Condylysis/idiopathic condylar resorption
   - D. Osteochondritis dissecans
   - E. Ostronecrosis
   - F. Neoplasm

Vascular supply of masticatory system structures: The external carotid artery is the main blood supply for the masticatory system structures. The artery sends two important branches, the lingual and facial arteries to the region. At the level of the condylar neck, the external carotid bifurcates into the superficial temporal artery and the internal maxillary artery. These two arteries supply the muscles of mastication and the TMJ.

Nerve supply of masticatory system structures: The masticatory structures are innervated primarily by the trigeminal nerve, but cranial nerves VII, IX, X, and XI and cervical nerves 2 and 3 also contribute. The mandibular division of the trigeminal nerve supplies motor innervation to the muscles of mastication and the anterior belly of the digastric muscle. Branches of the auriculotemporal nerve supply the sensory innervation of the TMJ; this nerve arises from the mandibular division in the infratemporal fossa and sends branches to the capsule of the joint.

The deep temporal and masseteric nerves supply the anterior portion of the joint. The auriculotemporal nerve, a branch of the mandibular portion (V3) of the trigeminal nerve, provides innervation of the TMJ.

ANATOMIC CORRELATION WITH FUNCTIONAL MOVEMENTS

Jaw jerk reflex: The jaw jerk reflex, analogous to the knee jerk reflex, is a stretch reflex that occurs by applying a downward tap on the chin. The tap produces a monosynaptic reflex contraction of the jaw closing muscles. This reflex is thought to relate to the fine control of jaw movements required to masticate different consistencies of food.

Jaw-opening reflex: Stimulating mechanoreceptors or nociceptors in the mouth triggers the jaw-opening reflex. The pathway is polysynaptic; the first synapse is in either the trigeminal sensory nuclei or the adjacent reticular formation and the final synapse is in the trigeminal motor nucleus. The reflex results in an inhibition of the activity of the jaw-closing muscles. This reflex is thought to help in preventing injury while biting or chewing objects.

Rest position: When the mandible is not functionally active, it adopts rest position in which the condyle occupies a relatively neutral position in the glenoid fossa with the teeth separated. The rest position is

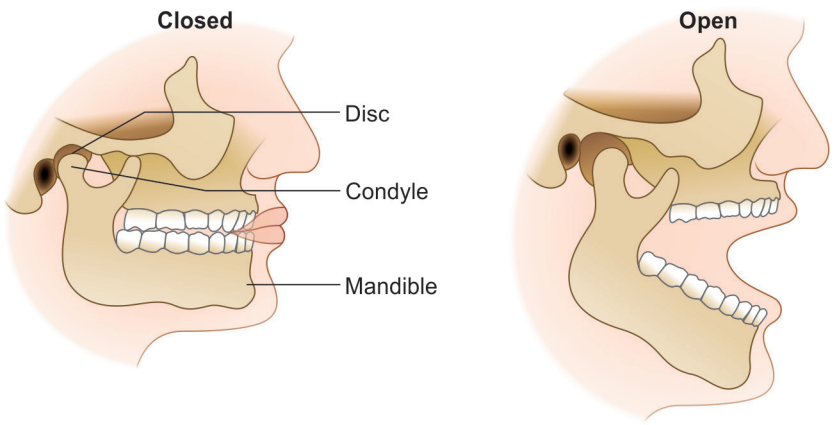


Fig. 11.4: Disc in close and open mouth position

considered to be associated with minimum muscular activity and with the articulating surfaces of the mandibular teeth a few millimeters from the occlusal contact position with the opposing teeth.

Mandibular range of motion: Mandibular motion during normal function is composed of rotation and translation of the condyles. During translation, the disc and condyle move downward and forward along the posterior slope of the articular eminence. The articular disc translates with the condyle, and simultaneously it rotates posteriorly as the condyle moves anteriorly; consequently, the movement of the disc across the fossa is limited to a range of 5–9 mm. The temporomandibular, sphenomandibular, and stylomandibular ligaments, together with the articular eminence, have been suggested as the main constraints of jaw opening.

CASE HISTORY TAKING FOR TMDs

Pain is subjective measure provided by the patient. It is measured in several ways like VAS using 10 cm line scale (left side of scale: No pain, right side: Worst pain). Other means of assessment of pain can be through pain diaries or pain diagram which can be drawn to locate and define the extent of pain.

Symptoms to be asked while examining the Patient

1. Do you feel dizziness or nausea?
2. Do you experience ringing in ears?
3. Any earache, headache, cheek pain?
4. Restricted mouth opening or deviation or does your jaw get lock or stuck often?
5. Do you experience any tingling or burning sensation, etc?
6. Do you experience any jaw misalignment or altered occlusion while opening or closing?
7. Check for mandibular movements: Lateral/protrusive.
8. Do you have any pain in the joint while clenching?

Physical Examination

1. Any facial asymmetry, swelling, mouth deviation while closing and opening mouth.
2. Range of mandibular movements: Any discomfort while opening or lateral and protrusive movements.
3. Palpate masticatory, TMJ, lymph nodes, neck muscles to rule out other causes.
4. Pain in the joint or muscle while clenching the teeth or chewing wax and sugarless gum.
5. Any parafunctional habits, tooth mobility, all the hard and soft tissues to be examined in particular.

EXAMINATION OF MUSCLES OF MASTICATION

The primary finding of masticatory muscle palpation is pain.

The TMD guidelines recommend to apply 1 lb pressure for joint and 2 lb for muscles.

Other things like site of pain, whether referred pain to distant site, etc. should be ruled out while taking case history.

A. **Temporalis:** Palpated in 3 areas:
   1. *Anterior region:* Palpated above zygomatic arch and anterior to TMJ
   2. *Middle region:* Palpated above the TMJ and superior to zygomatic arch
   3. *Posterior region:* Above and behind the ear

B. **Masseter:** Palpated bilaterally
   1. *Superior attachment:* The fingers are placed on each zygomatic arch and dropped down to the portion of the masseter attached to zygomatic arch.
   2. *Deep attachment:* Fingers dropped down from zygomatic arch .

Palpation of TMJ:

a. Any pain or irregularities during condylar movements like crepitus or clicking?
b. Any joint noises or pain?

Diagnostic imaging: TMJ imaging should be done when clinical presentations suggest pathological condition of TMJ. Any recent injury, sensory or motor abnormality, altered occlusion; degenerative changes are to be examined.

Usually examination of TMJ is carried by plain film radiography, tomography, arthrography, CT, MRI, single photon emission computed tomography and radioisotope scanning.

Other factors of TMD should also be considered like psychological factors, musculoskeletal problems, incidence of trauma, etc:

Dawson's criteria: Six ways to verify that the TMJs are healthy:

1. Screening history
2. Load test
3. **Range and path of movements:** Normal protrusive range 10–14 mm.
   - Lateral movement: 10 mm
   - Max. mouth opening: 40–60 mm
4. **Doppler analysis:** Intact healthy joint is quiet on rotation and translation
5. **Radiography/imaging:** Not necessary, if other tests are negative.
6. **Anterior bite plane for muscle deprogramming:** If flat, permissive anterior bite plane does not relieve pain, suspect intracapsular disorder.

MYOFACIAL PAIN DYSFUNCTION SYNDROME

The temporomandibular joints (TMJ) are complex joints that need to work in concert, essential for mastication, and probably the most used joints in the body.

The temporomandibular joint pain dysfunction syndrome (TMPD; myofascial pain dysfunction (MFD), facial arthromyalgia (FAM), mandibular dysfunction, or mandibular stress syndrome) refers to the common joint symptoms which together comprise the Laskin's criteria:

1. Facial pain in the region of TMJ.
2. Limitation or deviation in mandibular movements.
3. Hyperalgesia of musculoskeletal structures.
4. TMJ sounds during jaw function and movement.

Incidence: The prevalence is at least 12% of the general population, but these symptoms have been reported at some time by up to 88%—with as many as 25% reporting severe symptoms.

Age: This disorder afflicts young adults mainly, typically teenagers and up to 20–30 years of age.

Gender: Most of the patients are females compared to males.

Etiology: The etiology of the most common TMDs is unknown. The literature has been dominated by several hypothesized

causes like occlusal disharmony, muscle hyperactivity, central pain mechanisms, psychological distress and trauma. Premature contacts such as faulty restorative dentistry are traditionally believed to initiate sleep bruxism.

Given the available evidence, the factors that have supporting evidence and at least some biological plausibility, from local to systemic causes are as follows:

The occlusal condition: It is an etiology of temporomandibular disorder, a contributing factor to TMD that has been strongly debated for many years is the occlusal condition. If occlusal factors are related to TMD, the dentist is responsible for providing proper therapy, since dentists are the only health care professionals trained to change the occlusion. On the other hand, if occlusal factors are not related to TMD, the dentist should refrain from treating TMD with occlusal changes.

Trauma: Road accidents, sports injuries, fights and dental treatment or extractions is common and can occasionally be followed by TMJ dysfunction. Trauma can result in muscle spasm or hyperactivity.

Muscle hyperactivity: Psychological stress can also cause muscle hyperactivity. 50–70% of patients (twice as common as controls) have experienced stressful life events in the 6 months before onset. These problems concerning work, money, health loss and interpersonal relationships probably have a causative role by inducing anxiety, which then produces increased jaw muscle activity.

Other risk factors for TMPDs are:

1. TMJ hypermobility
2. Parafunctional behaviors (e.g. sleep bruxism, tooth clenching, jaw guarding, lip or cheek biting)
3. Sleep disturbance
4. Comorbidity in the form of other rheumatic, musculoskeletal, or pain disorders
5. Emotional distress
6. Poor general health and an unhealthy lifestyle

Depression and shortage of sleep are also considered as important risk indicators.

Clinical Features

Symptoms are highly variable, but dysfunction is usually unilateral and characterized by one or more of the following features:

1. **Recurrent clicking in the TMJ:** Clicking occurs either on attempted mouth opening or closing. Often the click allows the completion of that phase of mandibular movement. Clicks are not diagnostic, since they are common in normal TM joints. A grating noise (crepitus) may signify intra-articular arthritic change, there may be crepitus at any point of jaw movement, especially with lateral movements.
2. **Jaw locking or limitation of movement:** Limitation of opening may be intermittent, with jaw 'locking'. There may be deviation of the jaw to the affected side on attempted opening with variable jaw deviation or locking. If there is reduced mouth opening, this often suggests bilateral disease. Limitation may be more obvious on awakening, especially after nocturnal grinding. In some the limitation increases throughout the day.
3. **Pain in the joint and/or surrounding muscles and elsewhere ipsilaterally:** The main site is usually preauricular, but can radiate to back of the mouth, down the neck, up to the temple or behind the ear.

Pain may occur at an early stage or sometimes after the onset of clicking or stiffness of the jaw. It may range from a vague dull ache to an acute pain. The symptoms of individuals who clench or grind during working hours tend to worsen towards evening, and sometimes have a psychogenic basis.

The pain may be aggravated by chewing or other jaw movements. Muscles like masseter, temporalis and pterygoid muscles may be tender to palpation. Sometimes pain is more clearly sited in a single jaw muscle, and sometimes trigger points can be located. Some patients may also complain of headaches, neck aches, and lower back pain

Flowchart 11.2

Treatment of myofacial pain

↓

Patient education explanation and reassurance about diagnosis

↓

Self care–eliminating oral habits like clenching, jaw exercises

↓

Physical therapy–education regarding biomechanics of jaw, neck and head posture

↓

Passive modalities like heat and cold therapy, ultrasound, laser and TENS

↓

Intraoral appliances–such that it covers all the teeth on the arch the appliance is seated on

↓

Pharmacotherapy–NSAIDs, muscle relaxants and tricyclic anti-depressants

↓

Behavioral/relaxation techniques—relaxation, hypnosis, biofeedback cognitive-behavioural therapy

Flowchart 11.3

Intra-articular disc disorders

- With reduction
- Without reduction

Etiological factors of disc displacements

1. Chronic low grade microtrauma from long-term bruxism or clenching of teeth
2. Generalized laxity of joints
3. Craniofacial morphological alterations
4. Indirect trauma from cervical flexion extension injuries
5. Chronic loading of joint increases susceptibility of certain individuals to restraining of ligaments and displacement of disc
6. Pain is severe when it is accompanied by capsulitis and synovitis

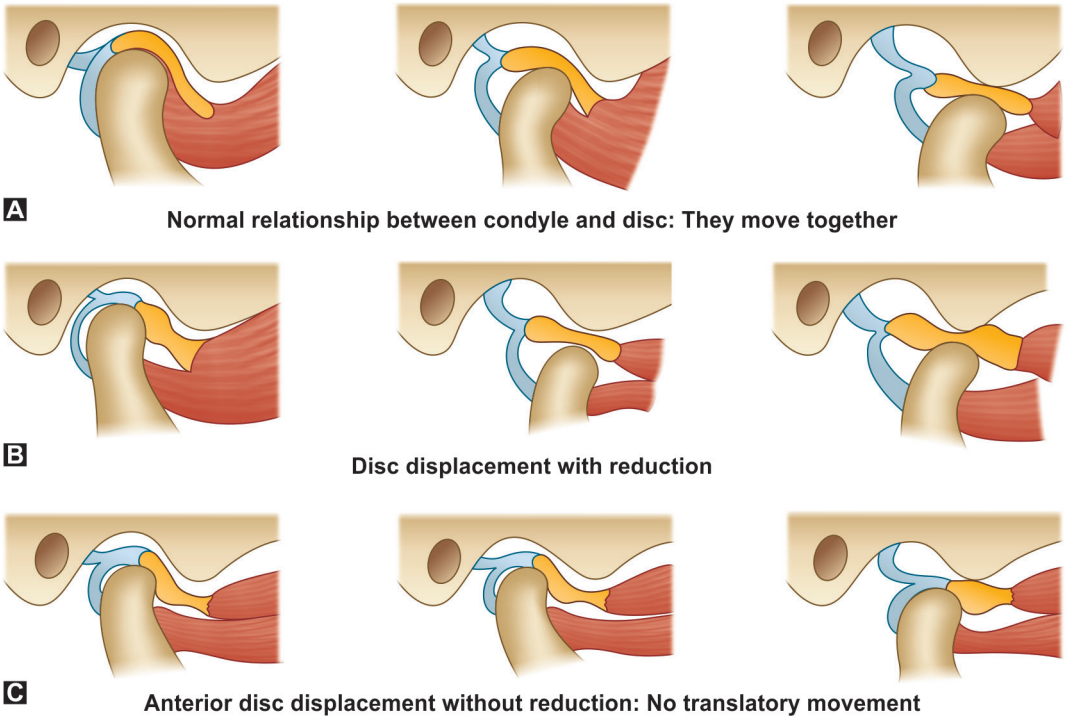


Fig. 11.5: Disc displacement with and without reduction

1. Disc Displacement with Reduction

Clinical features: An intracapsular biomechanical disorder involving the condyle—disc complex. In the closed mouth position, the disc is in anterior position relative to the condylar head, and the disc reduces upon opening of the mouth. Medial and lateral displacement of the disc may also be present. Clicking, popping or snapping noises may occur with disc reduction. A history of prior locking in the closed position coupled with interference in mastication precludes this diagnosis.

2. Disc Displacement With Reduction With Intermittent Locking

Clinical features: An intracapsular biomechanical disorder involving the condyle—disc complex. In the closed mouth position, the disc is in an anterior position relative to the condylar head, and the disc intermittently reduces with opening of the mouth. When the disc does not reduce with opening of the mouth, intermittent limited mandibular opening occurs. When limited opening occurs, a maneuver may be needed to unlock the TMJ. Medial and lateral displacement of the disc may also be present.

Clicking, popping, or snapping noises may occur with disc reduction.

3. Disc Displacement Without Reduction With Limited Opening

An intracapsular biomechanical disorder involving the condyle-disc complex. In the closed mouth position, the disc is in an anterior position relative to the condylar head, and the disc does not reduce with opening of the mouth. Medial and lateral displacement of the disc may also be present. This disorder is associated with persistent limited mandibular opening that does not resolve with the clinician or patient performing a specific manipulative maneuver. This is also referred to as **"closed lock."**

Clinical Features

1. Jaw lock or catch so that the mouth would not open all the way; and
2. Limitation in jaw opening which is severe enough to limit jaw opening and it also interferes with ability of eating.

Maximum assisted opening (passive stretch) <40 mm including vertical incisal overlap.

4. Disc Displacement without Reduction without Limited Opening

An intracapsular biomechanical disorder involving the condyle–disc complex. In the closed mouth position, the disc is in an anterior position relative to the condylar head and the disc does not reduce with opening of the mouth. Medial and lateral displacement of the disc may also be present. This disorder is not associated with limited mandibular opening.

Clinical features: Same as specified for disc displacement without reduction with limited opening.

Maximum assisted opening (passive stretch) >40 mm including vertical incisal overlap.

5. Subluxation

It is a hypermobility disorder involving the disc-condyle complex and the articular eminence.

In the open mouth position, the disc–condyle complex is positioned anterior to the articular eminence and is unable to return to a normal closed mouth position without a specific manipulative maneuver. The duration of dislocation may be momentary or prolonged. When prolonged, the patient may need the assistance of the clinician to reduce the dislocation and normalize jaw movement; this is referred to as "Open lock".

Clinical Features

1. In the last 30 days, a jaw locking or catching in a wide open mouth position,

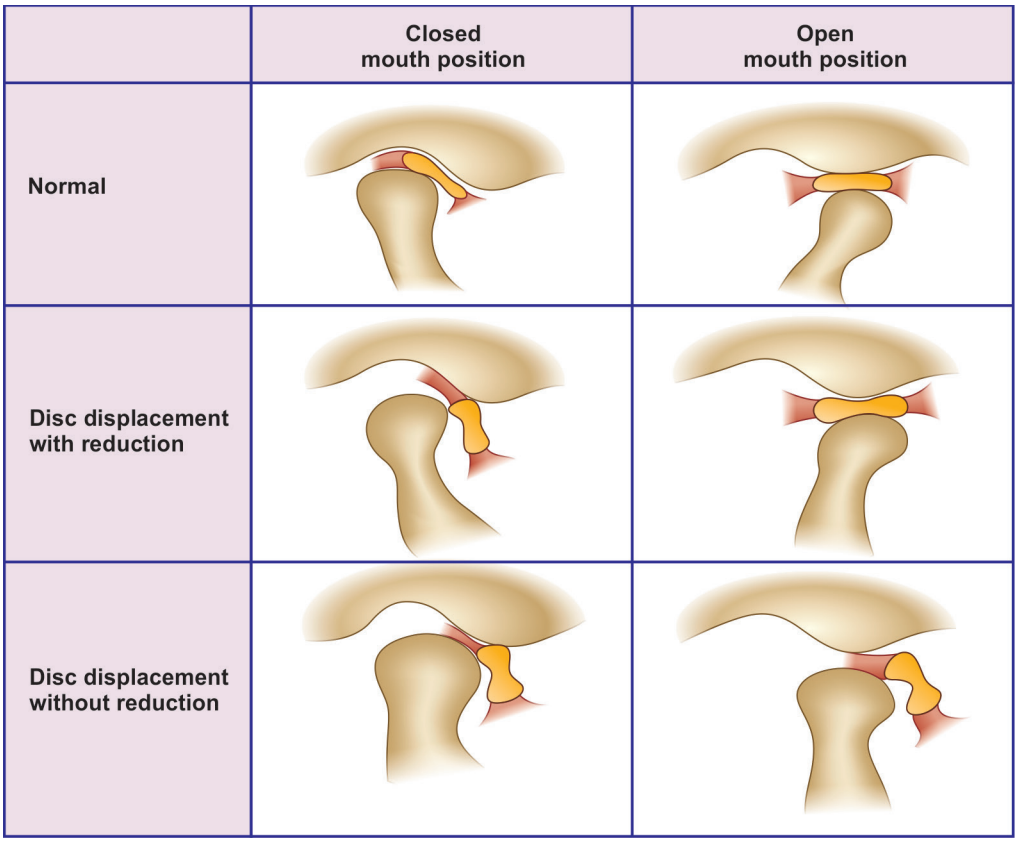


Fig. 11.6: Disc derangements in closed and open mouth position

even for a moment, so that the mouth cannot be closed from the wide open position.

2. Inability to close the mouth without a specific manipulative maneuver.

Although no findings are required, when this disorder is present clinically, examination is positive for inability to return to a normal closed mouth position without the patient performing a specific manipulative maneuver.

6. Dislocation

In dislocation of the mandible, the condyle is positioned anterior to the articular eminence and cannot return to its normal position without assistance. This disorder contrasts with subluxation, in which the condyle moves anterior to the eminence during wide opening but it is able to return to the resting position without manipulation. It has been demonstrated that subluxation is a variation of normal function and that the normal ROM of the condyle is not limited to the fossa.

1. Dislocations of the mandible usually result from muscular incoordination in wide opening during eating or yawning and less commonly from trauma;
2. They may be unilateral or bilateral.
3. The typical complaints of the patient with dislocation are an inability to close the jaws and pain related to muscle spasm.
4. On clinical examination, a deep depression may be observed in the preauricular region corresponding to the condyle being positioned anterior to the eminence.
5. The condyle can usually be repositioned without the use of muscle relaxants or general anesthetics. If muscle spasms are

severe and reduction is difficult, the use of intravenous diazepam (approximately 10 mg) can be beneficial.

Treatment: The practitioner who is repositioning the mandible should stand in front of the seated patient and place his or her thumbs lateral to the mandibular molars on the buccal shelf of bone; the remaining fingers of each hand should be placed under the chin.

The condyle is repositioned by a downward and backward movement. This is achieved by simultaneously pressing down on the posterior part of the mandible while raising the chin. As the condyle reaches the height of the eminence, it can usually be guided posteriorly to its normal position.

POSTREDUCTION RECOMMENDATIONS

1. Consist of limiting mandibular movement and the use of NSAIDs to lessen inflammation.
2. The patient should be cautioned not to open wide when eating or yawning because recurrence is common, especially during the period initially after repositioning.
3. Chronic recurring dislocations have been treated with surgical and nonsurgical approaches.
4. Injections of sclerosing solutions have been used but they are not used as often now because of difficulty in controlling the extent of fibrosis and condylar limitation.
5. Various surgical procedures have been advocated for treating recurrent dislocations of the mandible; these include bone grafting to the eminence, lateral pterygoid myotomy, eminence reduction, eminence augmentation with implants, shortening the temporalis tendon by intraoral scarification, plication of the joint capsule, and repositioning of the zygomatic arch.

Treatment of Disc Displacements and Disorders

1. Anterior positioning appliances
2. NSAIDs
3. Application of moist heat or ice depending on symptoms

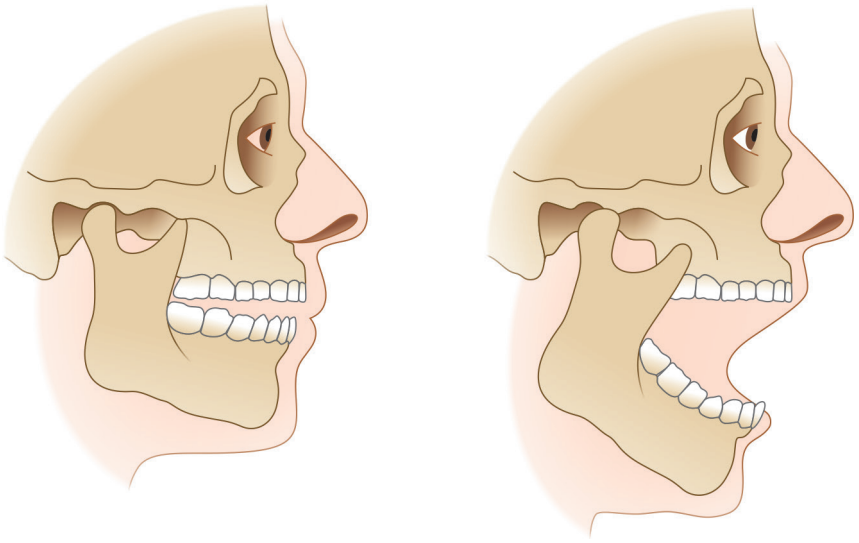


Fig. 11.7: TMJ dislocation

4. Physiotherapy
5. Surgical procedures
6. Prosthesis
7. Orthodontics for facial deformity
8. Soft diet during acute exacerbation

Fractures

Fractures of the condylar head and neck often result from a blow to the chin. The patient with a condylar fracture usually presents with pain and edema over the joint area and limitation and deviation of the mandible to the injured side on opening.

Bilateral condylar fractures may result in an anterior open bite. The diagnosis of a condylar fracture is confirmed by diagnostic imaging. Intracapsular nondisplaced fractures of the condylar head are usually not treated surgically. Early mobilization of the mandible is emphasized to prevent bony or fibrous ankylosis.

Ankylosis

Ankylosis can be defined as *a pathological fusion between two articulating surfaces.* TMJ ankylosis involves fusion between condylar head and temporal bone. Trauma to the chin is the most common cause of TMJ ankylosis, although infections also may be involved. Children are more prone to ankylosis because of greater osteogenic potential and an incompletely formed disc. Ankylosis frequently results from prolonged immobilization following condylar fracture.

Classification

A. **True or intra-articular ankylosis**
   - Fibrous
   - Bony

B. **False or extra-articular ankylosis**
   - Fusion of coronoid process with zygomatic arch
   - OSMF
   - Muscle fibrosis
   - Myositis ossificans

Clinical Features

Mouth opening is gradually decreased, limited mandibular movement, deviation of the chin to the affected side, fullness of the face on the affected side are some of the common clinical features seen in TMJ ankylosis. The inability to open the mouth may also lead to poor oral hygiene. Characteristic *bird face deformity* is seen in cases of bilateral ankylosis.

Radiographic Features

- **Fibrous ankylosis**
  - The articulating surfaces are usually irregular due to erosions.
  - The joint space is usually very narrow and the two irregular surfaces may appear to fit into one another like jigsaw puzzle.
- **Bony ankylosis**
  - The joint space may be completely or partially obliterated by the osseous bridge.
  - Secondary degenerative changes of the joint components are common.
  - Compensatory elongation of the coronoid processes is seen.
  - Deepening of the antegonial notch in the mandibular ramus of the affected side as a result of muscle function during attempted mandibular opening.

Treatment: Ankylosis has been treated by several surgical procedures. Gap arthroplasty using interpositional materials between the cut segments is the technique most commonly performed.

Treatment modalities

- Brisement force
- Condylectomy
- Gap arthroplasty
- Interpositional arthroplasty with reconstruction of the joint

Sleep Bruxism

Sleep bruxism is thought to aggravate or contribute to the persistence of pain symptoms associated with TMD.

1. The etiology is not understood, but the evidence suggests that occlusal abnormalities are not the cause. Occlusal appliances may protect the teeth from the effects of bruxism but cannot be expected to prevent or decrease the bruxism activity.
2. When bruxism is considered to be the cause or a factor of TMD symptoms, oral appliance therapy is effective.
3. Symptoms of bruxing is resolved when the dosage is decreased or when buspirone is added. Buspirone has a postsynaptic dopaminergic effect and may act to partially restore suppressed dopamine levels associated with the use of SSRIs.
4. Severe bruxers in the masseter muscles with botulinum toxin in an open-label prospective trial have reported significant improvement in symptoms and minimal adverse effects. Botulinum toxin exerts a paralytic effect on the muscle by inhibiting the release of acetylcholine at the neuromuscular junction.

TEMPOROMANDIBULAR JOINT ARTHRITIS OSTEOARTHRITIS (DEGENERATIVE JOINT DISEASE)

Degenerative Joint Disease (DJD) also referred to as osteoarthrosis, osteoarthritis, and degenerative arthritis. It is primarily a disorder of articular cartilage and subchondral bone, with secondary inflammation of the synovial membrane.

1. It is a localized joint disease without systemic manifestations. The process begins in loaded articular cartilage that thins, clefts (fibrillation), and then fragments leading to sclerosis of underlying bone, subchondral cysts, and osteophyte formation.
2. The articular changes are essentially a response of the joint to chronic microtrauma or pressure. Microtrauma may be in the form of continuous abrasion of the articular surfaces as in natural wear associated with age or due to increased loading possibly related to chronic parafunctional activity.

Etiology: DJD may be categorized as primary or secondary.

Etiology of degenerative joint diseases

- Primary DJD is of unknown origin, but genetic factors play an important role.
- Secondary DJD results from a known underlying cause, such as trauma, congenital dysplasia or metabolic disease.
- The possibility that a diet of excessively hard or chewy foods might cause increased loads on the joints and lead to degenerative changes.
- Psychological stress leading to parafunctional activities such as tooth clenching or bruxing has been proposed as one of the factors.
- Biologic, biochemical, and hormonal changes that might contribute to changes in the joints, leading to osteoarthritis.

Pathogenesis: The present model suggests that excessive mechanical loading on the joints produces a cascade of events leading to the failure of the lubrication system and destruction of the articular surfaces. These events include the generation of free radicals, the release of proinflammatory neuropeptides, signaling by cytokines, and the activation of enzymes capable of matrix degradation.

Clinical manifestations: DJD of the TMJ begins early and has been observed in over 20% of joints in individuals older than 20 years.

1. The incidence of degenerative changes increases with age.
2. Many patients with mild to moderate DJD of the TMJ have no symptoms, although arthritic changes are observed on radiographs.
3. Degenerative changes of the TMJ detected on radiographic examination may be incidental and may not be responsible for facial pain symptoms or TMJ dysfunction; however, some degenerative changes may be underdiagnosed by conventional

radiography because the defects are confined to the articular soft tissue. These soft tissue changes are better visualized with MR.

4. Patients with symptomatic DJD of the TMJ experience pain directly over the affected condyle, limitation of mandibular opening, crepitus, and a feeling of stiffness after a period of inactivity. Examination reveals tenderness and crepitus on intra-auricular and pre-auricular palpation. Deviation of the mandible to the painful side may be present.
5. Radiographic signs of DJD include signs of previous remodeling, such as flattening and subchondral sclerosis or degenerative changes can be observed.
   - DJD may have a spectrum of appearance ranging from substantial subchondral sclerosis and osteophyte formation (proliferative component) to extensive erosions (degenerative component).
   - The osteophytes may break and lie free within the joint space (joint mice).
   - In maximal intercuspation position, the joint space may appear narrow or absent, which correlates with internal derangement. Perforation of the disk or posterior attachment, resulting in bone to bone contact of the joint components is common.
   - The enlargement of the fossa and reduced size of the condylar head allows the latter to move forward and superiorly into an abnormal anterior position that may result in an anterior open bite.
   - Sometimes small, round radiolucent areas with irregular margins surrounded by a varying increased density are visible deep to the articulating surfaces, these are called Ely's cysts.

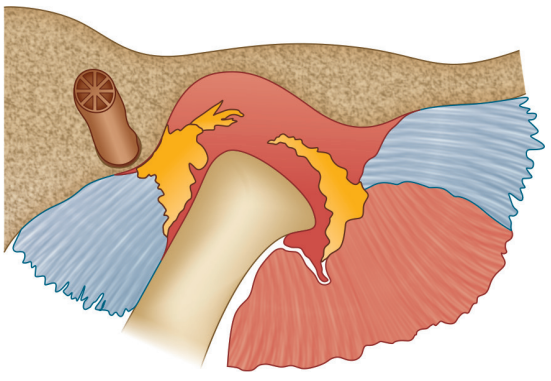


Fig. 11.8: Degenerative lesions in TMJ with disc perforation

Rheumatoid Arthritis (RA)

RA is an inflammatory disease primarily affecting periarticular tissue and secondarily bone. The percentage of RA patients with TMJ involvement ranges from 40% to 80%, depending on the group studied and the imaging technique used.

The disease process starts as a vasculitis of the synovial membrane. It progresses to chronic inflammation marked by an intense round cell infiltrate and subsequent formation of granulation tissue. The cellular infiltrate spreads from the articular surfaces eventually to cause an erosion of the underlying bone.

Clinical manifestations: The TMJs in RA are usually involved bilaterally.

Pain is usually associated with the early acute phase of the disease. Other symptoms often noted include morning stiffness, joint sounds, tenderness and swelling over the joint area.

The symptoms are usually transient in nature, the most consistent clinical findings include pain on joint palpation, limited mouth opening, and crepitus, micrognathia.

Radiographic changes

- The initial changes are seen as generalized osteopenia (decreased density) of the condyle and the temporal component.
- Diminished joint space due to destruction of the disk by the pannus.
- The pannus also causes bone erosions of the articular eminence and the anterior aspect of the condylar head, which permits antero-superior positioning of the condyle when the teeth are in maximal intercuspation, this results in an anterior open bite.

- There is a little evidence of marginal proliferation in RA in contrast to the radiographic changes often observed in DJD.
- High resolution CT of the TMJs in RA patients shows erosions of the condyle and glenoid fossa that are not detected on conventional radiography.
- There may be sharpened pencil appearance of the condylar head due to erosion of the anterior and posterior condylar surfaces at the attachment of the synovial lining.

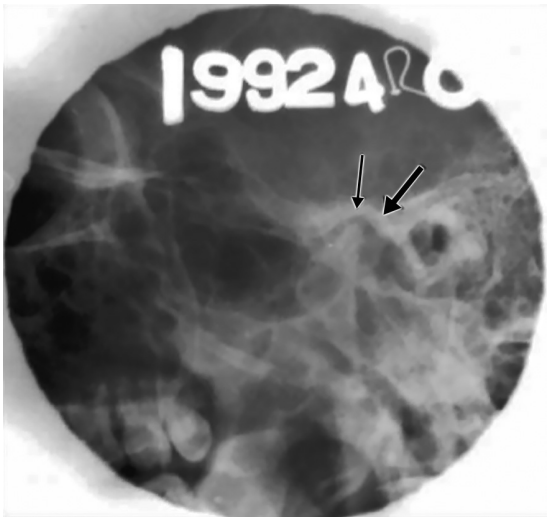


Fig. 11.9: Erosion of condylar surfaces

Connective Tissue Disease

Connective tissue diseases that affect the TMJ include systemic lupus, systemic sclerosis (scleroderma), undifferentiated connective tissue disease and mixed connective tissue disease. When the TMJ is involved, the clinical presentation is similar to other disorders causing inflammation and subsequent degenerative changes.

Clinical Features

A clinical examination supplemented with diagnostic imaging is usually adequate to confirm involvement of the TMJ.

1. Diseases associated with crystal deposits in joints; Gout is a disease that includes hyperuricemia, recurrent arthritides, renal disease and urolithiaisis, effecting men.
2. Acute pain in a single joint is the characteristic clinical presentation. The TMJ is not commonly involved. Calcium pyrophosphate deposition is also known as pseudogout. Deposits of microcrystals in affected joints are responsible for the clinical manifestations.
3. Examination of aspirated synovial fluid from the involved joint by polarized light and detection of monosodium urate crystals confirm the diagnosis.

Treatment: It includes colchicine, NSAIDs, and intra-articular steroid injection. Pseudogout affecting the TMJ has been treated with colchicine and arthrocentesis. Treatment is directed toward the systemic disease with supportive local therapy consisting of jaw self-care, physiotherapy, oral appliance therapy, topical NSAID, and intra-articular corticosteroid injection.

Nonsurgical management may consist of jaw self-management, including behavior modification, heat application, soft diet, physical therapy including jaw exercises, NSAID, and oral appliance therapy.

Arthroscopy, arthroplasty, and arthrotomy are surgical procedures that may be indicated depending on the response to more conservative treatment and the severity of pain and disability. Surgical treatment of the joints, including placement of prosthetic joints is indicated in patients who have severe functional impairment or intractable pain not successfully managed by other means. Orthognathic surgery and orthodontics are required for correction of facial deformity resulting from arthritis during growth.

ARTHROSCOPY

Seronegative Spondyloarthropathies

Several arthropathies that are distinct from RA are not associated with positive serology (rheumatoid factor).

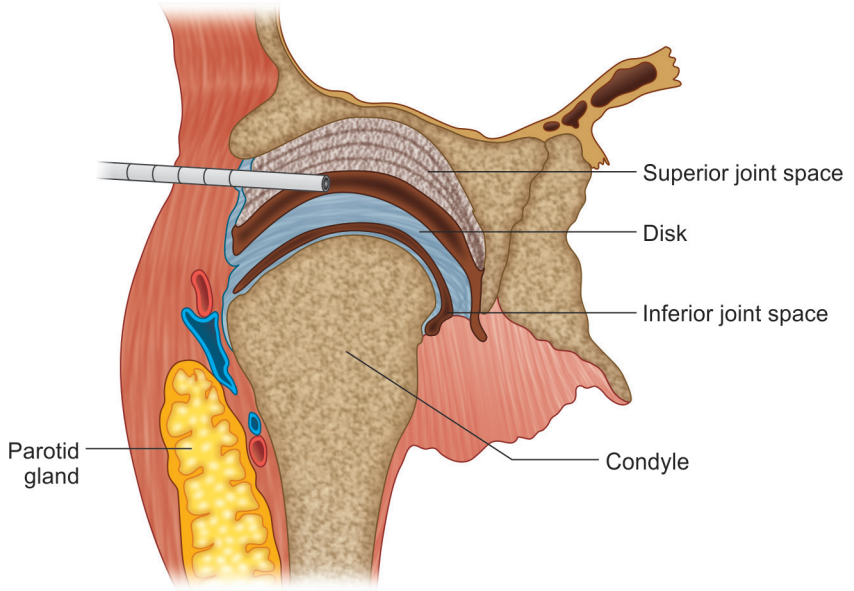


Fig. 11.10: Seronegative spondyloarthropathies

These disorders, characterized by arthritis, are known as the seronegatives spondyloarthropathies and include ankylosing spondylitis (AS), psoriatic arthritis (PA), and Reiter's syndrome. The TMJs can be involved in these arthropathies.

Clinical Features

The clinical manifestations are joint pain with function, limited mouth opening, and erosion of the superior surface of the condyle on radiography. There are no specific findings that are pathognomonic of involvement of the TMJs. It causes inflammation that can lead to new bone formation, causing the spine to fuse, reducing mobility, and producing a forward, stooped posture. The disease usually involves the sacroiliac joints where the spine joins the pelvis.

1. PA is a chronic disease characterized by psoriasis and inflammation of the joints. Approximately 10% of patients who have psoriasis develop joint inflammation. The skin lesions may precede the joint involvement by several years. PA commonly involves the fingers and spine, pitting of the nails is common. The cause is unknown, and the disease presents in a variety of forms.
2. Reiter's syndrome includes polyarthritis, urethritis, and conjunctivitis. It is thought to be triggered by infection, but the arthritis is not septic. It occurs more frequently in males in the third decade. The syndrome usually follows venereal infection most often involving Chlamydia, Mycoplasma, or Yersinia. Approximately 25% of male patients with Reiter's syndrome reported recurrent pain, swelling, and/or stiffness of the TMJ.

Synovial Chondromatosis (SC)

It is an uncommon benign disorder characterized by the presence of multiple cartilaginous nodules of the synovial membrane that break off resulting in clusters of free floating loose calcified bodies in the joint.

It is theorized that SC originates from embryonic mesenchymal remnants of the subintimal layer of the synovium that becomes metaplastic, calcify, and break off into the joint space; most commonly involves

one joint, but cases of multiarticular SC have been reported.

Clinical Features

It includes slow progressive swelling in the preauricular region, pain and limitations of mandibular movement which are the most common presenting features. TMJ clicking, locking, crepitus and occlusal changes may also be present.

Radiographic features: Conventional radiography may not lead to the diagnosis due to superimposition of cranial bones that may obscure the calcified loose bodies.

Diagnosis: In a CT scan the lesion may appear as a single mass or as many small loose bodies. Arthroscopy may be necessary for accurate diagnosis, particularly when the loose bodies are not calcified and cannot be visualized by conventional radiology or CT.

Treatment: It should be conservative and consists of removal of the mass of loose bodies. This may be done arthroscopically when only a small lesion is present, but arthrotomy is required for larger lesions.

Septic Arthritis

Septic arthritis of the TMJ most commonly occurs in patients with previously existing joint disease such as RA or underlying medical disorders (particularly diabetes). Patients receiving immunosuppressive drugs or long-term corticosteroids also have increased incidence of septic arthritis. The infection of the TMJ may result from blood-borne bacterial infection or by extension of infection from adjacent sites such as the middle ear, maxillary molars and parotid gland. *Gonococci* are the primary blood-borne agents causing septic arthritis in a previously normal TMJ, whereas *Staphylococcus aureus* is the most common organism involved in previously diagnosed arthritic joints.

Clinical Features

Symptoms of septic arthritis of the TMJ include trismus, deviation of the mandible to the affected side, severe pain on movement, and inability to occlude the teeth, owing to the presence of inflammation in the joint space. Signs and symptoms of gonorrhea such as purulent urethral discharge or dysuria. The affected TMJ should be aspirated and the fluid obtained must be tested by Gram's stain and cultured for *Neisseria gonorrhoeae*.

Treatment of septic arthritis of the TMJ consists of surgical drainage, joint irrigation, and four to six weeks of antibiotics.

Oral Dyskinesia and Dystonia

Oral dyskinesias are abnormal, involuntary movements of the tongue, lips, and jaw.

Etiology: Oral dyskinesias may be a factor contributing to muscle stiffness, TMJ degenerative changes, mucosal lesions, damage to teeth and dental prostheses. Complete loss of teeth is considered to be one cause of oral dyskinesia. Ill-fitting dentures or the lack of replacements may initiate dyskinesia.

Clinical Features

Dyskinesias are characterized clinically by the observation of involuntary mouth movements and the effects of these movements on the jaw muscles, TMJs, oral mucosa, and teeth.

Emphasis on management is prevention because none of the treatment is predictably effective and safe.

A dentist observing dyskinesia in a patient taking conventional antipsychotics should inform the physician managing the medication. Palliative treatment using tetrabenazine, a central monoamine depleter, clonazepam, and baclofen has been tried.

Oromandibular dystonia produces involuntary and excessive contractions of tongue, lip, and jaw muscles. The etiology and pathophysiology are unknown.

The proposed mechanism is related to defective inhibitory control of the basal ganglia of the forebrain, thalamus and brainstem. Injection of botulinum toxin

has been used in cases of oromandibular dystonia.

Radiographic Features of TMJ Disorders

1. Condylar Hyperplasia

- The condyle may appear relatively normal but symmetrically enlarged.
- Sometimes an altered shape: Conical, spherical, elongated, lobulated or irregular in outline.
- There may be an elongation of the condylar head and neck with a compensating forward bend, forming an inverted L.
- The cortical thickness and trabecular pattern of the enlarged condyle is normal.
- The affected ramus may have an increased vertical height and may be thicker in the anteroposterior dimension. This prevents the occlusion of the posterior teeth.

2. Condylar Hypoplasia

The condyle appears normal, slightly diminished in size and the mandibular fossa is also proportionately smaller.

The condylar neck and coronoid process are very slender and in some cases shortened or elongated.

- The posterior portion of the ramus and condylar neck may have a dorsal (posterior) inclination.
- The ramus and the mandibular body on the affected side may also be small,



Fig. 11.11: Condylar hyperplasia

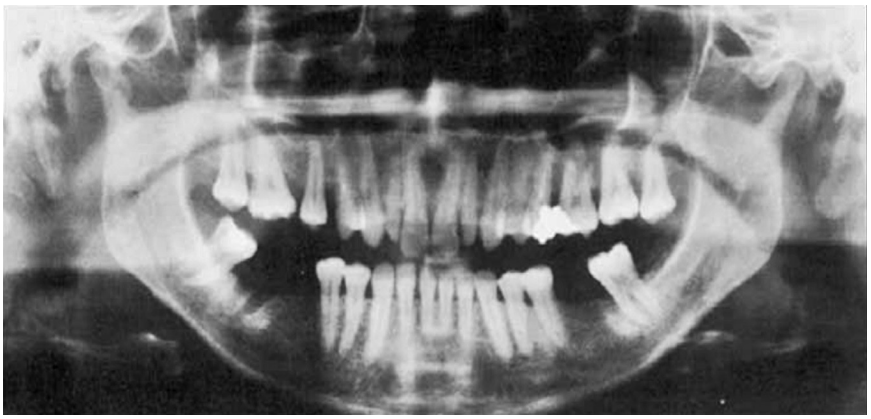


Fig. 11.12: Condylar hypoplasia

resulting in a mandibular asymmetry and dental crowding.The antegonial notch is deepened.

3. Agenesis of the Condyle

Absence of the condyle: The condyle is not seen.

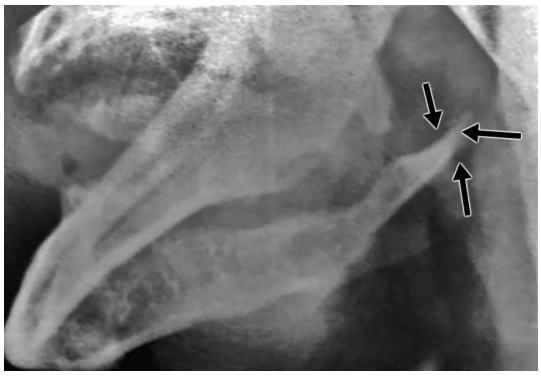


Fig. 11.13: Condylar hypoplasia

4. Juvenile Arthrosis

The condylar head has a typical toad stool appearance, with marked flattening and apparent elongation of the articulating condylar surface and dorsal (posterior) inclination of the condyle and neck.

5. Coronoid Hyperplasia

This is best seen on the panoramic, Water's and lateral tomographic views and CT scan.The coronoid appears elongated and may have a large but normal shape or may curve anteriorly and may appear very radio-opaque.

6. Remodeling and Arthritic Conditions

The radiographic appearance may include one or a combination of the following:

- Flattening
- Cortical thickening of articulating surfaces
- Subchondral sclerosis

TMJ Radiography

The diagnosis and management of temporomandibular disorders (TMD) require both clinical and imaging examinations of the temporomandibular joint (TMJ). A variety of modalities can be used to image the TMJ.

Because of the anatomic complexity of the TMJ imaging can be difficult. Choosing the proper imaging technique is essential. Conventional radiography nowadays is of limited interest. The use of flat plane films for TMJ pathology is not sufficient, because this joint requires three-dimensional imaging views.

Temporomandibular joint is bounded laterally by zygomatic arch and medially by petrous ridge of temporal bone. In TMJ radiography, we should be able to identify:

- The external auditory meatus of the ear.
- Articular eminence.
- Articular fossa.
- The neck of condyle.
- Mandibular condyle.

The articular disk (soft tissue) appears radiolucent so it needs specialized imaging techniques.

Radiography for TMJ can be classified into:

A. **Non-invasive radiography**
   1. Conventional radiography
      a. Orthopantomogram and sectional view
      b. Transcranial radiography
      c. Transpharyngeal radiography
      d. Transorbital radiography
   2. Specialized radiography
      a. Computed tomography
      b. Magnetic resonance imaging
      c. Cone beam computed tomography
      d. Ultrasonography

B. **Invasive radiography**
   1. Arthrography

Conventional Radiography

Conventional radiographs have a limited role in evaluation of the TMJ. The shortcomings are:

a. They can be used to evaluate only the bony elements of the TMJ.
b. They also do not give useful information concerning joint effusions, which are

commonly associated with pain and disc displacements.

c. Another disadvantage concerning conventional radiographs is the problem of superimposition of adjacent structures.

◈ Orthopantomogram

It permits visualization of both the joints in one film and can be used to assess only lateral part of condyle.

Sectional view of TMJ helps to visualize condyles laterally. This view is best utilized in cases of hypermobility as it shows position of condyles in relation to fossae in open and closed mouth position. In case of hypermobility, condyle moves beyond articular eminence in open mouth position.

◈ Trans Pharyngeal View
(Infracranial/McQueen Dell)

Indications

- Osteoarthritis and rheumatoid arthritis, cysts and tumors
- Cyst and tumor
- Fracture of neck and condyle

Area of joint seen

Lateral view: Condylar head and neck articular surface

Film placement: Patient holds the cassette flat against patient's ear centered over TM joint of interest against facial skin parallel to sagittal plane/2 inch anterior to EAM.

Position of patient: Occlusal plane parallel to transverse axis of film—soft parts are in a line with nasopharynx and joint.

- Patient instructed to inhale slowly through nose
- Open mouth—condyles move away from base of skull and mandibular notch is enlarged on opposite side.
- Central ray—directed from opposite side cranially at angle (–5 to –10 degrees)
- Beneath the zygomatic arch, through sigmoid notch posteriorly across pharynx at the condyle.

◈ Transorbital View (Zimmer)

Indication

- Trauma
- Fracture cases

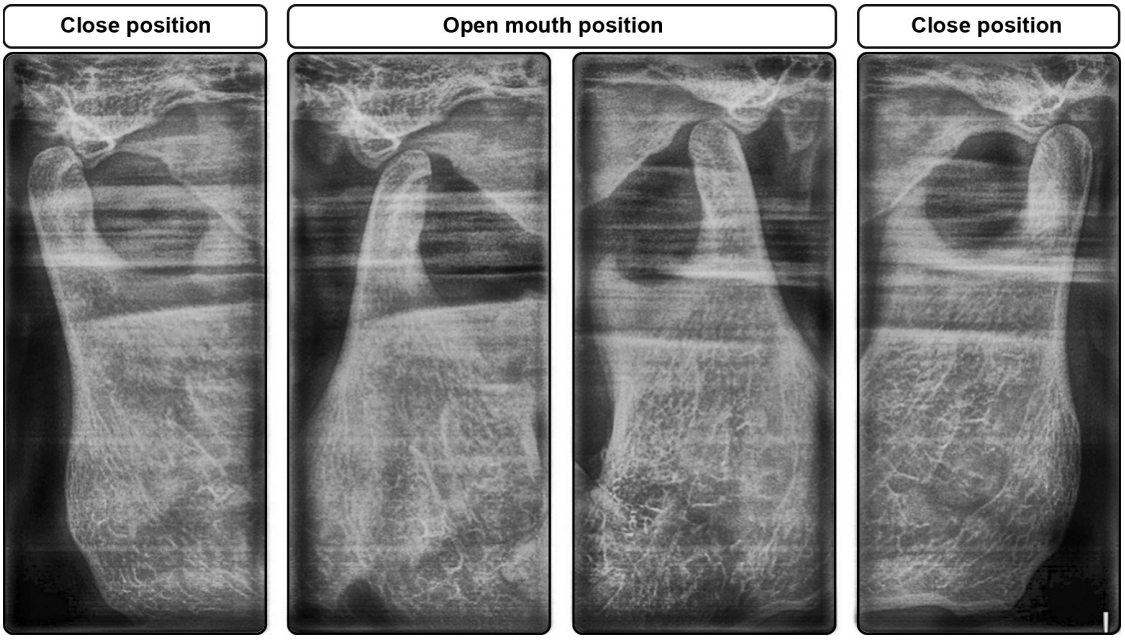


Fig. 11.14: Sectional view showing open and closed joint positions in a single tomogram

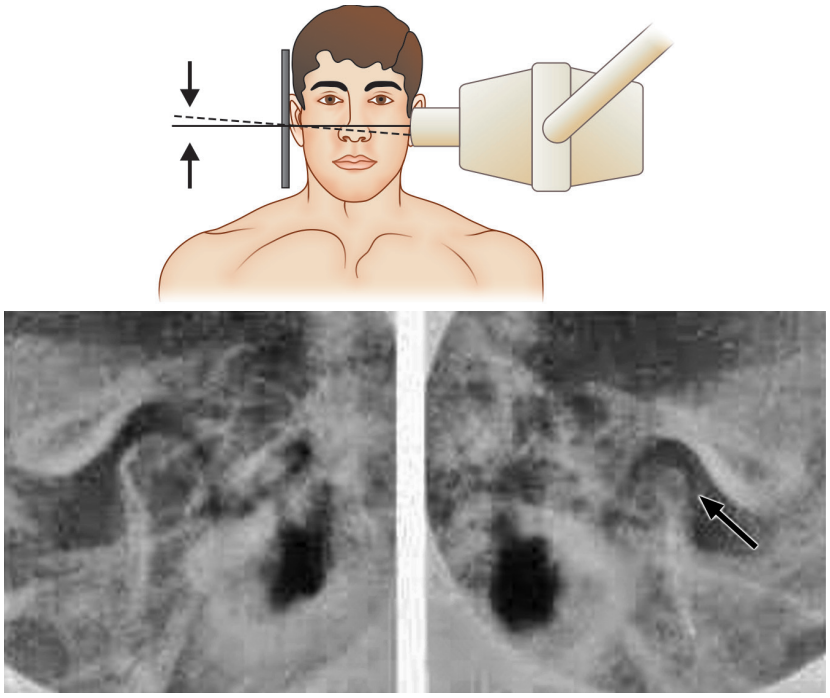


Fig. 11.15: Transpharyngeal view showing medial pole of condyle

Area of joint seen

- Anterior view of TMJ
- Mediolateral displacement of condyle
- **Film position:** Behind patients head at an angle of 45 degree to sagittal plane
- **Position of patient:** Sagittal plane vertical canthomeatal line should be 10 degree to the horizontal with head tipped downwards
- Central ray—tube head—front of patient's face directed to joint of interest at an angle of +20 degrees to strike cassette at right angles

Point of entry may be taken as pupil of the indicated side eye by asking patient to look straight ahead.

Disadvantage: If the patient cannot open wide, areas of the joint articulating surfaces will be obscured because of mutual superimposition (Fig. 11.16).

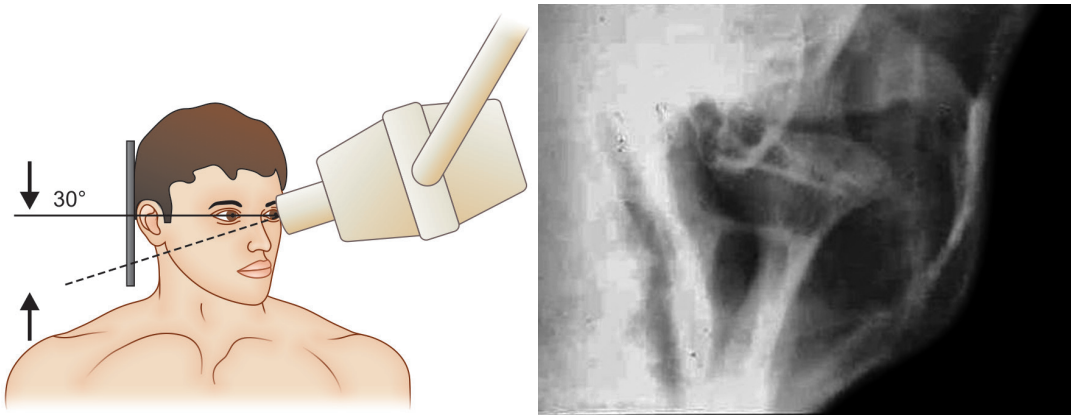


Fig. 11.16: Transorbital view showing mediolateral positioning of condyle

◈ Transcranial View

Indication

1. TMJ dysfunction syndrome
2. Internal derangement

Area of joint seen

1. Lateral aspect of glenoid fossa
2. Articular eminence
3. Joint space
4. Condylar head

Film position: Flat against patient's ear; against facial skin parallel to sagittal plane.

Patient position: Head is adjusted such that sagittal plane is vertical to the floor and ala-tragus line is parallel to the floor.

Central ray 0.5 inch behind and 2 inch above auditory meatus. It should be directed posteriorly so that it passes along the long axis of condyle. This is postauricular/ Lindblom technique.

Grewcock approach: Central ray passes through a point 2 inches above external auditory meatus.

Gill's approach: 0.5 inch anterior and 2 inches above external auditory meatus.

Central ray aimed downwards at 25° to the horizontal, across the cranium, centering through the area of interest.

Disadvantages

1. Superimposition of ipsilateral petrous ridge over the condylar neck.

SPECIALIZED RADIOGRAPHY

Ultrasound

- Ultrasound is a less expensive and easily performed imaging modality that can be used to evaluate the TMJ.
- This is simple way to look for the presence of a joint effusion.

It is used to evaluate:

1. Cartilage and disk.
2. It is used for image-guided injections for both diagnostic and therapeutic purposes.

Computed Tomography and Cone Beam Computed Tomography (CBCT)

It is considered to be the best method for assessing osseous pathologic conditions of TMJ. It allows a multi-planar reconstruction (sagittal, axial, coronal) of TMJ structures, obtaining 3D images in closed and opened-mouth positions.

Magnetic Resonance Imaging

MRI is currently considered the reference method for imaging the soft tissue structures of the TMJ (articular disc, synovial membrane, muscles). It has been pointed out as the best imaging modality in diagnosing disc displacements.

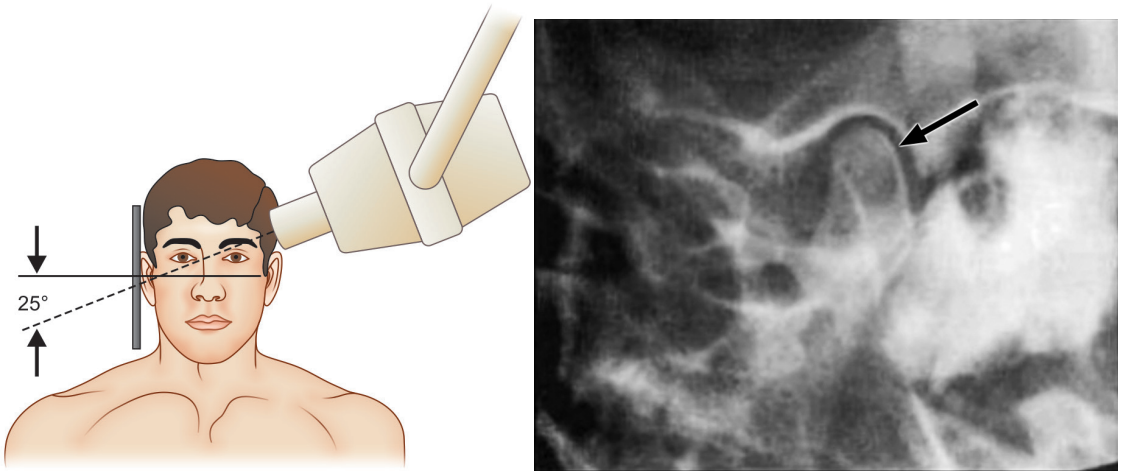


Fig. 11.17: Transcranial view showing lateral pole of condyle

MRI can detect the early signs of TMJ dysfunction, like thickening of anterior or posterior band, rupture of retrodiscal tissue, changes in shape of the disc and joint effusion.

Invasive Radiography

Arthrography is an invasive imaging technique to evaluate the TMJ. This imaging modality requires injection of radiopaque contrast into the TMJ under fluoroscopic guidance. Once the contrast is injected, the joint can be evaluated for adhesions, disk dysfunction, as well as disk perforation based on how contrast flows in the joint. This modality is rarely used today because MRI can be used to evaluate the TMJ without being invasive, exposing the patient to a possibility of allergic reaction from the contrast, possibility of infection.

Treatment Modalities for TMJ Disorders

Instructions to Patients for Self-Care as Part of Initial Therapy

1. Be aware and control oral parafunctional behaviors.
2. Teeth should only contact during chewing and swallowing.
3. Monitor jaw at regular intervals through the day for any clenching, grinding, touching, or tapping of teeth or any tensing or rigid holding of the jaw muscles.
4. Monitor jaw for parafunctional behaviors during specific situations such as while driving, studying, using computer, reading, engaging in athletic activities, when at work, or in social situations, and when experiencing overwork, fatigue, or stress.
5. Practice neutral jaw posture: Place the tip of the tongue behind the top teeth or in the floor of the mouth, separate the teeth slightly, and allow the jaw to "hang" in this position; maintain this position when the jaw is not being used for functions such as speaking and chewing.
6. Modify the food texture in your diet.
7. Choose softer foods and only those foods that can be chewed without pain.
8. Cut foods into smaller pieces; avoid foods that require wide mouth opening and biting off with the front teeth or foods that are chewy and sticky and that require excessive mouth movements.
9. Do not chew gum. Avoid certain postures or movements.
10. Do not lean on or cup the chin when performing desk work or at the dining table.
11. Do not test the jaw by opening wide or moving the jaw around excessively to assess pain or motion.
12. Avoid habitually maneuvering the jaw into positions to assess its comfort or range.
13. Avoid habitually clicking the jaw if a click is present.
14. Do not sleep on the stomach or in postures that place stress on the jaw.
15. Avoid elective dental treatment while symptoms of pain and limited opening are present.
16. During yawning, support the jaw by providing mild counter-pressure underneath the chin with the thumb and index finger or with the back of the hand.
17. Use thermal agents to control pain.
18. Apply moist hot compresses to the sides of the face and to the temple areas for 10–20 min twice daily.
19. Apply ice packs to targeted areas for 10 min; can alternate with heat.

Managing TMD Patients with Necessary Dental Procedures:

Prior to the procedure:

1. Use hot compresses to masseter and temporalis areas 10–20 min two to three times daily for 2 days.
2. Use a minor tranquilizer or skeletal muscle relaxant (e.g. lorazepam, 1 mg;

cyclobenzaprine, 10 mg) on the night and day of the procedure.
3. Start a nonsteroidal anti-inflammatory analgesic the day of the procedure.

During the procedure:

1. Use a child-sized surgical rubber mouth prop to support the patient's comfortable opening; remove periodically to reduce joint stiffness. Alternatively, an extra oral device that supports the jaw can be used.
2. Consider intravenous sedation and/or inhalation analgesia.
3. Provide frequent rest periods to avoid prolonged opening.
4. Apply moist heat to masticatory muscles during rest breaks.
5. Gently massage masticatory muscles during rest breaks.
6. Perform the procedure in the morning, when reserve is likely to be greatest.

After the procedure

1. Extend the use of muscle relaxant and NSAID medication as necessary.
2. Apply cold compresses to the TMJ and muscle areas during 24 hrs after the procedure.

FREQUENTLY ASKED QUESTIONS

1. Classify TMJ disorders. Write in detail about MPDS.
2. Osteoarthritis
3. Ankylosis
4. Disc derangement

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Chapter 12

Orofacial Pain

Pain can be defined as 'an **unpleasant emotional experience** usually initiated by noxious stimulus and transmitted over a specialized neural network to the CNS where it is interpreted as such'.

Tissue damage and the activation of nociceptors

↓

Transmission of a noxious stimulus to the brain.

However, due to the rich innervation of the head, face and oral structures, orofacial pain entities are often very complex and can be difficult to diagnose.

Orofacial pain interferes with daily life activities, impacting negatively on quality of life.

The most important aspect in orofacial pain is in understanding the problem and arriving at a proper diagnosis. It is only by proper diagnosis that an appropriate treatment can be selected.

The objective of diagnosis is to accurately identify the what, where, how and why of the patients complaints.

There can be different reasons of having orofacial pain which can be classified as follows:

NEURALGIAS

1. Primary trigeminal neuralgia (tic douloureux)
2. Secondary trigeminal neuralgia (CNS lesion or facial trauma)
3. Herpes zoster
4. Post-herpetic neuralgia
5. Geniculate neuralgia (cranial nerve VII)
6. Glossopharyngeal neuralgia (cranial nerve IX)
7. Superior laryngeal neuralgia (cranial nerve X)
8. Occipital neuralgia

Pain of Musculoskeletal Origin

1. Cervical osteoarthritis
2. Temporomandibular joint disorders
3. TMJ rheumatoid arthritis
4. TMJ osteoarthritis
5. Myofascial pain dysfunction
6. Fibromyalgia
7. Cervical sprain or hyperextension
8. Stylohyoid (Eagle's) syndrome

Primary Vascular Disorders

1. Migraine with aura
2. Migraine without aura
3. Cluster headache
4. Tension-type headache
5. Hypertensive vascular changes (aneurysm, emboli)
6. Cranial arteritis
7. Carotidynia
8. Thrombophlebitis

Psychogenic Pains

1. Delusional/hallucinatory
2. Hysterical/hypochondriac

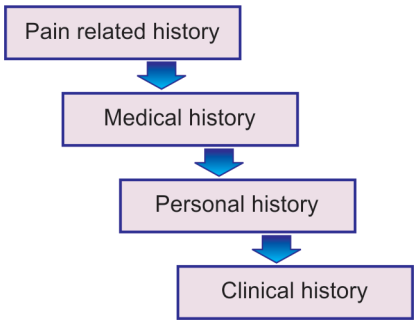
Generalized Pain Syndromes

1. Post-traumatic pains
2. Sympathetically maintained pain (causalgia)
3. Phantom pain
4. Central pain

Lesions of the Ear, Nose, and Oral Cavity

1. Maxillary sinusitis
2. Otitis media
3. Dentin defects
4. Pulpitis
5. Periapical pathology/abscess
6. Cracked tooth/restoration
7. Atypical odontalgia
8. Periodontal pathology
9. Occlusal trauma
10. Dental impaction
11. Cysts and tumors
12. Osteitis
13. Mucocutaneous diseases
14. Salivary gland diseases
15. Atypical facial pain
16. Glossodynia
17. Malignancy associated pain

Steps in diagnosing a pain complaint, consists of:



A. **Thorough history of pain:** Questions to facilitate the history taking for pain:
   i. Onset
   ii. Frequency
   iii. Duration
   iv. Provoking factors
   v. Site of initiation of pain
   vi. Radiation and referral of pain
   vii. Is the pain deep or superficial
   viii. Aggravating or exacerbating factors
   ix. Relieving factors
   x. Characteristics of the pain
   xi. Severity
   xii. Other associated features, for example, lacrimation or other autonomic signs and symptoms
   xiii. Previous management strategies attempted
   xiv. Patient's perceived cause(s) of pain

B. **Medical history**
   i. History of systemic disease
   ii. History of medications
   iii. History of major surgery
   iv. History of trauma

C. **Personal history**
   i. History of any deleterious habits
   ii. History of mood imbalances
   iii. History of any psychological illness

D. **Clinical examination**
   i. Accurately identifying the location from which the pain originates
   ii. Imaging can be used to confirm a suspected abnormality. It is the best method to evaluate a suspected tumor, infection, or inflammation.
   iii. *Diagnostic anesthetic blocking:* Skilful anesthetic blocking of muscles of masticatory system, maxillofacial region and TMJ are especially useful in the diagnosis of masticatory pain and non-masticatory myofascial pain disorders. Nerve block injections are especially helpful in identifying whether the painful structure is a site or source of pain.
   iv. *Utilization of diagnostic drugs/Trial therapy:* A short period of trial therapy is a good means of confirming a diagnosis. Oxcarbazepine can be used to confirm a doubtful diagnosis of paroxysmal neurologic conditions.

For proper identification of the pain disorders on occasion, pain problems require medical, otolaryngologic, orthopedic, neurologist, rheumatologic, or psychological consultation.

In the assessment of pain intensity, rating scales often used are:

Different scales can be used depending on cause and site of pain

- Numerical rating scale
- Visual analogue scale (VAS)
- McGill pain questionnaire
- Behavioral rating scale

Amongst these scales the VAS has been shown to be more sensitive to change and is therefore more widely used. It consists of a 10 cm line with anchor points at each end.

The pain management generally covers following factors:

- Elimination of causative noxious stimuli
- Interception of nociceptive circuits
- Enhancement of neural mechanism of pain inhibition.

Physical therapy modalities which are generally included in pain management are sensory stimulations, massage, vapo-coolant therapy, mechanical vibration, hydrotherapy, transcutaneous stimulation (TENS), electroaccupuncture, cryotherapy, ultrasound, diathermy, electrogalvanic stimulation, deep heat and other methods.

Management of Specific Orofacial Pain Disorders

Trigeminal Neuralgia (TN)

The term 'neuralgia' means pain in the nerve. Trigeminal neuralgia also known as "*ticdouloureux*".

Trigeminal neuralgia is a sudden, unilateral, brief, stabbing, recurrent pain in the distribution of one or more branches of the fifth cranial nerve. It is localized most often to the second and third distributions of the trigeminal nerve (V2 and V3) intraorally and extraorally.

The diagnosis is made using the history alone, based on characteristic features of the pain.

- Pain occurs in paroxysms, which can last from a few seconds to several minutes. The frequency of the paroxysms ranges from a few to hundreds of attacks per day.
- Periods of remission can last for months to years, but tend to get shorter over time.
- The condition can impair activities of daily living and lead to depression. Symptoms may worsen also over time and become less responsive to medication, despite dose increases and adding further agents.

Pain usually elicited by momentary stimulation of "Trigger Zones".

Etiology

- Peripheral causes
  - Nerve compression
  - Nerve trauma
  - Nerve back talk
  - Aneurysm around the nerve
  - Demyelination of the nerve
  - Herpes zoster infection
- Central causes
  - Microaneurysm around the nerve root
  - Cerebro-pontine angle tumors
  - Multiple sclerosis
  - Demyelination of the nerve
  - Pulsation of basilar artery
  - High petrous ridge

The etiology of TN is often related to vascular compression that may result in focal demyelination. The superior cerebellar artery compression on the trigeminal root has been shown to be responsible for attacks of TN pain; however, nonvascular compression by a cerebellopontine angle neoplasm, such as acoustic neuromas, meningiomas, cholesteatomas, and neurofibromas, have also been shown to result in TN attacks. A cranial nerve exam can demonstrate other neural deficits that may be present due to a mass pressing on the trigeminal root. Therefore, magnetic resonance imaging (MRI) and computed tomography (CT) imaging of the brain should be requested in

order to rule out any intracranial pathology. Furthermore, myelin loss due to multiple sclerosis has been shown to be a causative disorder related to the paroxysmal pain firing of TN attacks.

Clinical Features

There is gender variability in the incidence of TN with a female to male ratio of 1.74:1 with majority cases occurring after 50 years of age. Clinical history, examination, investigations, and imaging are necessary to make a correct diagnosis.

TN is characterized by an abrupt onset and short-lived unilateral shock-like pain, in the distribution of the trigeminal nerve. Usual triggers for classical TN (CTN) include mastication, touch, tooth brushing, eating, talking, and cold wind on the face. Trigger zones are present in more than 90% of the patients, with touch and vibrations being the most common stimuli in provoking pain. Pain is usually distributed along the V2 and V3 branches. Right side of the face is often associated with pain and rarely it is bilateral.

Diagnostic criteria for TN from The International Classification of Headache Disorders (ICHD-3) are summarized below.

TN is orofacial pain restricted to one or more divisions of the trigeminal nerve. It is abrupt in onset and typically lasts only a few seconds (2 min at maximum). Patients may report their pain as arising spontaneously, but these pain paroxysms can always be triggered by innocuous mechanical stimuli or movements. Patients usually do not experience pain between paroxysms. If they do report additional continuous pain, in the same distribution and in the same periods as the paroxysmal pain, they are considered to have TN with continuous pain.

- **Classical TN:** Caused by vascular compression of the trigeminal nerve root resulting in morphological changes of the root.
- **Secondary TN:** Caused by major neurological disease, e.g. a tumor of the cerebello-pontine angle or MS idiopathic
- **TN:** No apparent cause

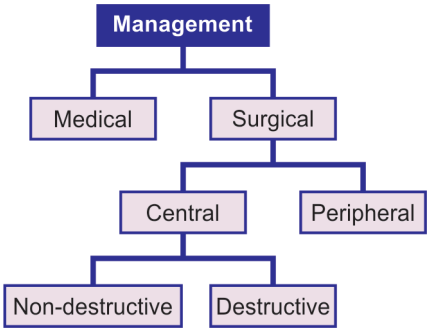
A. At least three attacks of unilateral facial pain fulfilling criteria B and C
B. Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution
C. Pain has at least three of the following four characteristics:
   1. Recurring in paroxysmal attacks lasting from a fraction of a second to 2 min
   2. Severe intensity
   3. Electric shock-like, shooting, stabbing or sharp in quality
   4. Precipitated by innocuous stimuli to the affected side of the face
D. No clinically evident neurological deficit.
E. Not better accounted for by another ICHD-3 diagnosis

13.1.1.1 Classical TN (classical TN, purely paroxysmal; classical TN with concomitant continuous pain)
13.1.1.2 Secondary TN (TN attributed to MS; TN attributed to space-occupying lesion; TN attributed to other cause
13.1.1.3 Idiopathic TN (idiopathic TN, purely paroxysmal; idiopathic TN with concomitant continuous pain).

(IASP—International Association for the Study of Pain; ICHD—International Classification of Headache Disorders; MS—Multiple Sclerosis, TN—Trigeminal Neuralgia)

Management

- Medical
- Surgical
  - Peripheral: Injections, neurectomies, cryosurgery
  - Central



A. **Non-destructive**
- Microvascular decompression (MVD)

B. **Destructive**
- Percutaneous balloon compression
- Glycerol rhizotomy
- Radiofrequency thermocoagulation
- Gamma knife radiosurgery

Medical Management

Antiepileptic medications are the drugs of choice for the management of trigeminal neuralgia.

First line drugs
- Carbamazepine: 100 to 1200 mg, two weeks followed by review
- Oxycarbazepine: 600–1800 mg, two weeks followed by review
- Gabapentine: 900–1200 mg, two weeks followed by review

Carbamazepine, the first-line agent provides pain relief in 72% of patients. Suggested dose is 100 mg twice daily; increase if necessary by 50–100 mg every 3–4 days; target range 400–1200 mg/day.

If these medications are not effective or if the therapeutic range cannot be achieved due to side effects, then doses should be lowered and second-line drugs, such as baclofen and lamotrigine, may be added to reduce the pain attacks.

Second-line drugs
- Lamotrigine: 50–100 mg
- Baclofen: 8 mg
- Pregabalin: 50–100 mg

Side Effects of Medicinal Drugs

- Dizziness
- Confusion
- Drowsiness
- Vision problems
- Nausea
- Gingival hypertrophy
- Neutropenia

If medications are no longer effective or if unmanageable side effects develop, then neurosurgical options, such as microvascular decompression or gamma knife radio surgery may be considered.

Peripheral Management

Alcoholic injections: 95% Absolute alcohol in small quantities 0.5 to 2 ml is given in peripheral branches of trigeminal nerve.

Neurolytic agents
- Long acting local anesthesia
- Ropivacaine with gabapentin
- Absolute alcohol 0.5–2 ml
- Botox type A (25–75 U)

Side effects

Repeated injections may cause:
- Local tissue toxicity
- Inflammation
- Fibrosis
- Burning alcohol neuritis

Peripheral Neurectomies
(Nerve Avulsion)

Indicated in patients in whom craniotomy is contraindicated due to age, debility, limited life expectancy and no respond to medication.

It can be done under local anesthesia in which partial avulsion of offending nerve is done. After avulsion of nerve from bone and soft tissue nerve end is cauterized or suture into viable muscle, periosteum or bone and later foramen is plugged with non-absorbable material.

Cryotherapy for Peripheral Nerve

In this method direct application of cryotherapy probe, i.e. nitrous oxide probe is done. Temperature colder than –60°C, for 2–3 minutes and procedure is repeated for three times. It produces Wallerian degeneration without destroying the nerve sheath.

GLOSSOPHARYNGEAL NEURALGIA

Definition: Glossopharyngeal neuralgia is a rare condition associated with pain in the area supplied by the glossopharyngeal nerve.

Painful sites may include the nasopharynx, posterior part of the tongue, throat, tonsil, larynx, and ear.

Signs: This disorder presents shooting paroxysms of pain that can occur multiple times a day with stimulation of the oropharyngeal region. Common triggers may include mechanical stimulation of the trigger zone as well as activities including chewing, swallowing, coughing, talking, and head movement. The painful episodes may continue for months and then spontaneously go into remission.

Associated pain: Due to the proximity of the vagal sensory nerves, glossopharyngeal neuralgia may coincide with a cardiac dysrhythmia such as bradycardia, asystole, and syncope.

Diagnosis: Diagnosis may be confirmed by blocking the tonsillar and pharyngeal region with topical or local anesthetics. Imaging with a CT scan of the head and a brain MRI should be conducted to rule out pathology related to the nerve compression and possible oropharyngeal carcinoma.

Treatment: Pharmacologic treatment of glossopharyngeal neuralgia is similar to that for TN and may include the use of antiepileptic medications. If medical management fails, then surgical procedures may be considered, such as a microvascular decompression to remove pressure from the glossopharyngeal nerve, radiofrequency thermocoagulation, gamma knife radiosurgery, or rhizotomy.

Atypical Odontalgia (AO)

Atypical Odontalgia is a centralized trigeminal neuropathy often localized in a tooth or tooth area that is frequently misdiagnosed, leading to unnecessary dental treatments in attempts to relieve the pain.

Atypical odontalgia is described as a persistent idiopathic pain that does not fulfill the diagnostic criteria for cranial neuralgias and which is not attributed to another disorder, and can be throbbing and burning in nature.

Management

The pharmacological management of AO may include topical and systemic medications. If the pain is localized to a peripheral origin and the diagnostic block gives an equivocal response but a decrease in pain, a topical medication can be used and a neurosensory stent can be fabricated.

Systemic approaches, such as tricyclic antidepressants, calcium channel blockers (pregabalin and gabapentin), sodium channel blockers (carbamazepine), and antiepileptics such as topiramate, can be used for the management of this condition.

The management of AO is very challenging, and a multidisciplinary approach is necessary, which should include orofacial pain specialists and neurologists in addition to psychiatric and psychological evaluations in order to identify comorbidities with depression and anxiety.

Burning Mouth Syndrome

BMS is defined as a burning painful sensation in the mouth (oral dysesthesia) with normal clinical examination and no obvious organic cause.

BMS is therefore a diagnosis of exclusion.

Evidence suggests that this disorder has a multifactorial cause, with neurologic, psychogenic, and hormonal factors all contributing to the disease.

Prevalence and epidemiology: The prevalence of BMS reported for the general population varies between 0.7% and 15% and seems to depend on the diagnostic criteria used. BMS seems most prevalent in postmenopausal women, although younger women as well as men can also be affected. Most reports suggest a female-to-male ratio of 1:5 to 1:7. Prevalence does seem to increase with age in both male and female subjects.

Etiology: Although the etiology remains mostly unknown, the ICHD-3 beta suggests BMS is a neuropathy. It is commonly accepted

that the etiology of BMS is multifactorial and involves the interaction between local and systemic entities.

Local factors: Local factors, such as odontogenic or mucosal disease; mechanical or chemical irritation; hypersensitivity reactions; viral, fungal, or bacterial infection; and xerostomia, can produce oral burning by direct irritation of the tongue and other oral mucosal surfaces.

Systemic factors: Several systemic factors have been suggested as least partially responsible for BMS. Systemic factors to be considered include nutritional and vitamin deficiencies, such as vitamin B_{12}, folic acid, iron, and zinc. Autoimmune, gastrointestinal, and endocrine disorders, such as diabetes and thyroid dysfunction, have been suggested as well. Pharmacotherapeutic agents like angiotensin-converting enzyme inhibitors, including captopril, enalapril, and lisinopril, also deserve consideration.

Clinical features: The clinical presentations of BMS are typically not consistent and vary from patient to patient. The onset of pain may be gradual or sudden, typically with no identifiable precipitating factors. In some cases, however, it can be traced to a precipitating event, such as a dental procedure, trauma, and introduction of a new medication, illness, or stressful life event. At presentation, patients usually complain of chronic pain of 4 months to 6 months duration and describe it as annoying, burning or scalding, tingling, or sometimes itchy or numb.

The pain can be continuous or intermittent and is typically localized to the tongue (67.9%), usually the anterior two-thirds, but may involve other mucosal surfaces, such as the palate, lip, buccal mucosa, and floor of the mouth. The pain tends to present bilaterally and symmetrically more so than unilaterally.

Associated features: In addition to the burning sensation, many patients also complain of dry mouth (xerostomia) and taste alterations. Alterations, such as sour and bitter taste perceived as stronger, sweet tastes perceived as weaker, and salty tastes perceived as weaker or stronger are commonly reported.

Diagnosis: A diagnosis of BMS is considered to be one of exclusion of all secondary factors. A comprehensive medical and dental history, including a complete review of current medications, along with an exhaustive review of systems is essential for establishing a definitive diagnosis. Patients should be queried as to any history of previous upper respiratory tract infections, middle ear disease, or surgery that may have damaged the chorda tympani nerve.

Management strategies: It must be determined if the presentation is primary or secondary. If the complaint seems secondary to an identifiable etiologic factor, treatment of the underlying condition most often alleviates the BMS complaint.

Behavioral Therapies

BMS patients should be educated as to the potentially detrimental effects of parafunctional habits, such as clenching, bruxism, and tongue habits. The use of oral care products should be scrutinized and amended to avoid the use of products that contain alcohol and those that contain flavoring agents or other known oral irritants.

Self-regulatory approaches, such as regular exercise, diaphragmatic breathing, maintaining a proper diet and adequate hydration, and intentional relaxation, have been shown beneficial in reducing chronic pain complaints.

Cognitive behavioral therapy provided by trained clinicians has also proved beneficial in some instances.

Topical Therapies

Several topical therapies have been recommended and used in the management for BMS.

- 1 mg tablet of clonazepam for 3 minutes and then expectorate reduces the pain significantly.
- 0.15% Benzydamine hydrochloride 3 times per day
- Salivary substitutes
- Topical antifungals
- Topical capsaicin (0.025% cream) or rinsing with Tabasco sauce and water (1:2–4 solution).

Systemic Therapies

Systemic agents to consider include:

- α-Lipoic acid, 600 mg per day for 2 months
- Clonazepam, 0.5 mg per day at bedtime
- Gabapentin, 100 mg to 300 mg up to 3 times per day
- Pregabalin, 25 mg to 75 mg up to 3 times per day
- Serotonin/norepinephrine reuptake inhibitor: Sertraline, 50 mg per day; paroxetine, 20 mg per day; or duloxetine 30 mg to 60 mg per day. P. salivary stimulant: Pilocarpine, 5 mg to 10 mg 3 times per day, or cevimeline, 30 mg 3 times per day.
- Tricyclic antidepressant (TCA): Amitriptyline, 25 mg to 100 mg per day at bedtime, or nortriptyline, 10 to 75 mg per day at bedtime.
- Botulinum toxin A injected intradermally (16 total units) into the tongue and lower lip gives relief for 20 weeks.

HEADACHE

Headache affects most people at least occasionally. Headache denotes pain or discomfort from the level of the brows back to the suboccipital region.

Classification of Headache

Primary headache

- It is a condition in which headache is a primary manifestation with no underlying disease.
- It is usually benign and recurrent.

Secondary headache

- It is a condition in which headache is a secondary manifestation of an underlying disease process. It is usually sudden and progressive.

Primary headache disorders can be categorized in three types.

- **Cluster headache:** Pain is in and around one eye.
- **Tension headache:** Pain is like a band squeezing the head.
- **Migraine headache:** Pain, nausea and visual changes are of typical classic form.

Migraine

Prevalence in western countries—10 to 12% in adults.

Migraine is a common primary headache with an additional number of rarer related syndromes. The 2 most common types of migraine headaches are migraine without aura (MWA) and migraine with aura (MA).

MWA is an inherited disorder affecting the young, with an onset before the age of 20 years in about half of the cases. There is up to a twofold increase of MWA among first-degree relatives of patients with MWA and a fourfold increase in MA.

Migraine presentation may be divided into phases and each may occur alone or in combination with each other. The headache phase is identical in MA and MWA.

Phases of Migraine

Prodrome: Premonitory signs and symptoms occurring days or hours before some or all headaches. Nonspecific neurologic/autonomic signs and constitutional symptoms. Tiredness, difficulty in concentration, and stiff neck.

Aura (in MA): Focal neurologic signs or symptoms:

- Visual (flashing lights), sensory (pins and needles), and motor (speech) symptoms.
- Develop over 5 to 20 minutes and last for less than 60 minutes.
- Followed in about 10 minutes by a typical headache.

Headache Phase

Postdrome phase: Depressed, irritable, and tired.

TABLE 12.1: Differential diagnosis of headaches

Condition	*Signs and symptoms*
Migraine	Prodromal symptoms—euphoria, depression, irritability, food cravings, constipation, neck stiffness, increased yawning • Aura—visual, sensory, verbal, and/or motor disturbances • Throbbing and pulsatile • Photophobia and phonophobia • Long duration
Cluster headache (subclassification of TAC)	• Orbital and temporal regions • Short-lived • Unilateral • Autonomic symptoms—ptosis, miosis, lacrimation, rhinorrhea • Nasal congestion
Tension-type	Diffuse, dull aching pain • Bilateral • Precipitated by stress and mental tension
Paroxysmal hemicrania (subclassification of TAC)	Unilateral • Shorter-lived than cluster headaches (lasts 2–30 minutes) • Most often in V1 distribution • Orbital, temporal, and frontal regions • Abrupt onset and cessation • Similar autonomic symptoms as cluster headaches
Temporal arteritis	Age >50 years • Localized headache of new onset • Tenderness or decreased pulse of the temporal artery • Erythrocyte sedimentation rate >50
Other TACs	• SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) • SUNA (short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms)

Migraine Triggers

- Several factors have been reported as initiators of individual attacks in migraineurs, termed triggers or precipitating factors.
- Anxiety and stress.
- Fatigue, sleeping difficulties.
- Foods and drinks.
- Menstruation.
- Weather changes.
- Smells, smoke, and light.

Differential Diagnosis

- Tension-type headache (TTH)
- Oral/dental pain
- Sinusitis
- Vascular disorders
- Transient ischemic attacks, thromboembolic stroke, intracranial hematoma, subarachnoid hemorrhage, and arterial hypertension may cause migraine-like headaches.
- Intracranial tumors, infections and regional trauma may induce migraine-like headaches.
- Some are sudden-onset headaches or are accompanied by atypical neurologic signs and symptoms.

Management

- Non-pharmacologic
- Pharmacologic

Non-pharmacologic treatment

- Sleep
- Diet
- Lifestyle modification

Pharmacologic treatment

Abortive (acute, symptomatic)

- Aim to rapidly relieve headache with no recurrence or side effects.
- Used when fewer than 4 to 8 attacks per month or to supplement prophylactic regimens.

TABLE 12.2: Some of the common abortive treatments for migraine

Class	*Drugs*	*Initial oral dose mg*
Analgesics	Aspirin	500–1000
Combinations	Aspirin and	500–600
	Paracetamol and	200–400
	Caffeine	50–200
	Paracetamol and	400
	Codeine	25
Ergot alkaloids	Dihydroergotamine NS	2
NSAIDs: Selective COX-2 inhibitors	Nonspecific Naproxen sodium	550–825
	Ibuprofen	400–800
	Diclofenac	50–100
	Rofecoxib	25–50
Triptans (5-HT agonist)	Sumatriptan	50–100
	Sumatriptan NS	20 (1 NS metered dose)
	Sumatriptan SC	6
	Naratriptan	2.5
	Eletriptan	40
	Rizatriptan	10
	Zolmitriptan	2.5
	Zolmitriptan NS	2.5 (1 NS metered dose)
	Frovatriptan	2.5
Opioids	Butorphanol NS	1–2 metered doses

Nonspecific medication (Table 12.1).

- Triptans
  - Triptans of choice
    - Rizatriptan 10 mg consistently provides rapid relief.
    - Almotriptan (12.5 mg) has good efficacy and tolerability.
    - Eletriptan will provide high efficacy with low recurrence but low tolerability.
    - Frovatriptan for the prevention of menstrually related migraine.
- Preventive (chronic, prophylactic Table 12.2): Aims to reduce attack frequency, severity, and duration.

FREQUENTLY ASKED QUESTIONS

1. Define and classify orofacial pain. Write in detail about trigeminal neuralgia.
2. Cluster headache.
3. Migraine

TABLE 12.3 : Choice of migraine preventive treatment

Drug	*Dose mg*	*Adverse effects*	*Contraindication*	*Relative indications*
Propranolol (SR)	80–240	Bradycardia, hypotension fatigue, sleep disturbances dyspepsia, depression	Asthma, depression, cardiac failure, Raynaud disease, diabetes	Hypertension angina
Amitriptyline	10–50	Sedation, weight gain, dry mouth, blurred vision, constipation, urinary retention, postural hypotension	Mania, urinary retention Heart block	Insomnia, anxiety depression, other chronic pains
Sodium valproate	500–1000	Nausea, vomiting, alopecia, tremor, weight gain/loss	Liver disease, bleeding disorder	Mania, epilepsy, anxiety
Topiramate	25–200	Dizziness, confusion, language problems, paresthesias, nausea, anorexia, diplopia	Renal disease, respiratory disorders, glaucoma	Overweight

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Chapter 13

Diseases of Tongue

INTRODUCTION

Tongue is a complex muscular internal organ well encased within the oral cavity and protected from the environment, with dorsal and ventral surfaces.

The tongue is situated in the floor of mouth having oral and pharyngeal part separated by V-shaped sulcus terminalis which end at foramen cecum. It is composed of a tip, body and root. It has dorsal (superior) and ventral (inferior) surface, the dorsal surface is divided by a groove into symmetrical halves by the median sulcus. The dorsal surface has projections/papillae of the mucous membrane which carries taste buds and also imparts characteristic roughness to the anterior two-thirds of the tongue. The tongue mucosa is very thin and highly vascular on the ventral surface of the oral cavity which allows the rapid delivery of medication into the cardiovascular system bypassing the gastrointestinal tract. On the ventral surface of the tongue is a fold of mucous membrane called lingual frenum that binds the tongue to the floor of the mouth at midline. On either sides of the frenum are small prominences on the floor of mouth called sublingual caruncles in which the submandibular and sublingual glands drain into. The bulk of the tongue consists of several extrinsic and intrinsic muscles which perform the several functions of tongue.

The tongue begins to develop in the fourth week of embryogenesis. The anterior two-thirds of the tongue develop from first brachial arch from the fusion of two lateral swellings and a midline swelling tuberculum impar while posterior one-third develops from 3rd and 4th brachial arches. The failure in the normal course of tongue development may lead to various developmental anomalies of tongue.

FUNCTIONS OF TONGUE

- Ingestion
- Suckling
- Swallowing
- Perception—taste, temperature, pain and general sensation
- Phonation
- Respiration
- Jaw development
- Symbolic function, tongue plays a role in physical intimacy and sexuality in human and mammals.

TONGUE EXAMINATION

One should inspect the tongue when it is at rest. The tongue is stabilized and can be gently guided right and left by holding the tongue tip with the gauze to inspect all the surfaces or its right and left lateral borders. The tongue should be examined for variation

in size, color, texture, coating, mucosal eruptions, ulcer, and swelling. The papillae, margins of tongue, taste perception, frenal attachment and the movement of the tongue also should be examined.

DISEASES OF TONGUE

Epidemiology

Tongue lesions are quite prevalent; the prevalence of 12.07 to 13.75% was noted in Indian population. The most common tongue conditions are coated tongue, geographic tongue, fissured tongue and depapillated tongue. Tongue lesions are more common in persons who are denture wearers, tobacco users, diabetic, hypertensive and anemic. The diseases of tongue can be congenital or acquired, and can be manifested as depapillation, discoloration, soreness, pain, redness and swelling.

I. *Diseases of tongue can be categorized as follows:*

- **Injury**
  - Physical, chemical and thermal
- **Infections**
  - *Bacterial:* Tuberculosis and scarlet fever
  - *Viral:* Human immunodeficiency virus (HIV) and hairy leukoplakia
  - *Fungal:* Candidiasis
- **Developmental disturbances**
  - Aglossia
  - Ankyloglossia
  - Macroglossia
  - Geographic tongue
  - Fissured tongue
  - Median rhomboid glossitis
  - Hairy tongue
- **Nutritional deficiency**
  - Iron deficiency anemia
  - Pernicious anemia
  - Vitamin deficiency
- **Premalignant**
  - Leukoplakia
  - Oral submucous fibrosis
- **Tumors**
  - Squamous cell carcinoma
- **Immunological**
  - Recurrent aphthous
  - Pemphigus
  - Lichen planus
- **Miscellaneous**
  - Lichenoid reaction
  - Pyogenic granuloma

II. **International Classification of Diseases (10th Revision)**
ICD-10 Category K14

	K14: Diseases of tongue
Erythroplakia (K13.29)	ICD-10K14.0: Glossitis
Focal epithelial hyperplasia (K13.29)	ICD-10K14.1: Geographic tongue
Hairy leukoplakia (K13.3)	ICD-10K14.2: Median rhomboid glossitis
Submucous fibrosis of tongue (K13.5)	ICD-10K14.3: Hypertrophy of tongue papillae
Leukoedema of tongue (K13.29)	ICD-10K14.4: Atrophy of tongue papillae
Leukoplakia of tongue (K13.21)	ICD-10K14.5: Plicated tongue
Macroglossia (congenital) (Q38.2)	ICD-10K14.6: Glossodynia
	ICD-10K14.8: Other diseases of tongue
	ICD-10K14.9: Disease of tongue, unspecified

Aglossia

It is the complete absence of the tongue at birth.

Ankyloglossia (Tongue Tie)

Ankyloglossia (tongue tie) where the lingual frenum attaches the tongue to the floor of the mouth due to the congenital shortness of lingual frenum, it can be partial or complete. It interferes with oral hygiene, speech, feeding, in addition, it may lead to midline mandibular diastema and lingual periodontal defects, hence frenectomy may be indicated.



Fig. 13.1: Tongue tie

Hypoglossia/Microglossia

Hypoglossia/microglossia congenitally short or small tongue.

The incomplete development of the tongue is associated with hypoglossia. This rare disease may occur as an isolated disorder or may be one of the manifestations of syndromic condition, e.g. Pierre Robin syndrome, cleft lip and palate. The patient has difficulties in eating and talking.

Macroglossia

Macroglossia an abnormally large tongue. It is characterized by an increase in the size of the tongue. It may be congenital or acquired. The congenital macroglossia is due to overdevelopment of the musculature. It also occurs as a result of a tumor in the tongue such as lymphangioma, hemangioma, inflammatory/allergic processes or as a part of syndrome, e.g. Down syndrome.

Glossoptosis

It is a medical condition and abnormality which involves the downward displacement or retraction of the tongue. It may cause non-fusion of the hard palate leading to cleft palate. It is one of the features of Pierre Robin syndrome and Down syndrome.

Patent Thyroglossal Ducts, Thyroglossal Duct Cyst and Lingual Thyroid

Thyroid gland develops from analage of endothelial cells in the midline of the floor of the pharynx between the first and second branchial arches. The foramen cecum on the dorsum of tongue is the point of attachment of the thyroglossal duct and is formed during the descent of the thyroid diverticulum in embryonic development. Lingual thyroid is mass of the thyroid on the dorsum at foramen cecum which may lead to enlarged tongue and dysphagia.

Cleft, Lobed, Bifurcated and Tetrafurcated Tongues

It is caused by a failure of the lateral lingual swellings to merge partially or completely, the complete cleft tongue is a rare condition. It is the separation of anterior two-thirds of the tongue by deep midline or clefts which may occur in isolation or as a manifestation of syndrome.

Fissured Tongue/Scrotal Tongue

It is presented as numerous small furrow/grooves on the dorsal surface radiating out from a central groove or may form various patterns on the tongue. It is usually painless except in some cases food debris tends to collect in the grooves and produce irritation so patients are advised to keep it clean. It is associated with extrinsic factors such as chronic trauma and vitamin B deficiency, candidiasis, salivary hypofunction. It is commonly associated with Melkersson-Rosenthal syndrome and Down's syndrome. Recently, the various fissure patterns as a tongue print are being studied greatly as a biometric tool for personal identification.

Tongue Coating

The food debris, desquamated epithelial cells and bacteria often form a visible tongue coating. This coating has been identified as a major contributing factor in bad breath which can be managed by brushing the tongue gently with a toothbrush or using special oral hygiene instruments such as tongue scrapers.

Geographic Tongue/Benign Migratory Glossitis

This disease is characterized by red areas in a map-like pattern on the tongue, the irregular patches of depapillation form on the tongue giving the map-like appearance. The classic lesions show the red areas with atrophic filiform papillae and white circinate borders. They are usually seen on the dorsum of the tongue and on the sides of the tongue, but it might also spread to other areas of the mouth. Patients with this condition may also develop burning, soreness or tenderness. Patients with this condition need to avoid eating acidic or spicy foods. There may be an association between certain types of psoriasis (especially pustular psoriasis) and geographic tongue and leukocyte antigen: HLA-Cw6 and HLA-DR5.

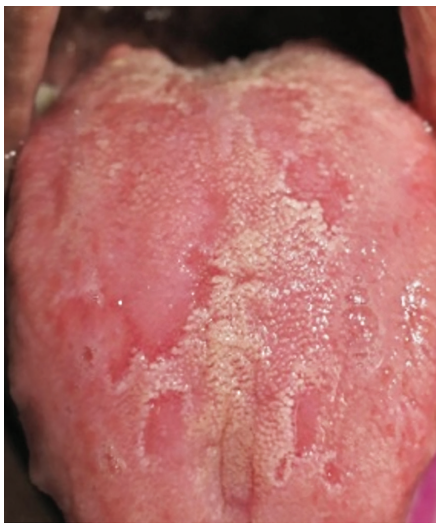


Fig. 13.2: Geographic tongue

Median Rhomboid Glossitis

It appears as a well-demarcated rounded or rhomboid-shaped, raised area in the midline of the tongue dorsum just anterior to the vallate papillae. It is said to be a developmental anomaly resulting from persistence of tuberculum impar due to its failure to retract before the fusion of the lateral halves of the tongue, so that the structure devoid of papillae is interposed between them. The area is devoid of filiform or other papillae. The texture may vary from a reddish, smooth or granular surface to a more lobulated and indurated. It is also linked to the fungal infection due to the demonstration of *Candida* in 90% of cases.

Histologically, it shows the hypoplastic, acanthotic epithelium with elongated rete pegs, subepithelial inflammatory infiltrate, vascular dilatation and fibrosis, and hyalinization of underlying muscle. If symptomatic, it may be treated by surgical excision, cautery and topical and systemic antifungal therapy.



Fig. 13.3: Median rhomboid glossitis

Black Hairy Tongue

It is a condition characterized by hypertrophy or excessive overgrowth of filiform papillae associated with growth of black pigment producing microorganism on the dorsum of tongue. These papillae may continually grow or get worn down over time by daily activities such as eating, brushing, etc. The growing papillae provide favorable environment for the bacteria to grow and lead to darkened or blackened appearance on the tongue. This disease is usually seen in individuals who have poor oral hygiene, heavy smoking habit, antibiotics, psychotropic agents and systemic

disturbance, e.g. anemia, hyperacidity, peptic ulcer. It may be asymptomatic or may cause gagging and tickling sensation.

Pigmentations

The extrinsic or intrinsic pigmentations may occur on the tongue.

Exogenous Pigmentation

The exogenous pigmentation involves filiform papillae, the pigmentation of filiform papillae results from microbial growth and metabolic products, food debris, and dyes from candy, beverages and mouth rinses. In addition, the tattooing of lateral margins and ventral surface of tongue result from deposits of amalgam and other metals from lacerations during dental treatment. The medications such as tricyclic antidepressants, zidovudine, doxorubicin, and alpha-methyl dopa are also responsible for exogenous pigmentation.

Endogenous Pigmentation

The endogenous pigmentation of tongue occurs in the following conditions:

- Racial melanin pigmentations, jaundice
- Primary adrenal deficiency (Addison's disease), Peutz-Jeghers syndrome
- Albright's syndrome, acanthosis nigricans
- Neurofibromatosis, hemochromatosis
- For such patients, the tongue evaluation should be done simultaneously.

Oral Hairy Leukoplakia

Oral hairy leukoplakia is a corrugated white lesion that usually occurs on the lateral or ventral surfaces of the tongue in patients with severe immunodeficiency. Epstein-Barr virus (EBV) is implicated as the causative agent in oral hairy leukoplakia. The most common disease associated with oral hairy leukoplakia is HIV infection. Oral hairy leukoplakia is reported in approximately 25% of adults with HIV infection, its prevalence may be higher in patients with acquired immunodeficiency syndrome (AIDS). Oral hairy leukoplakia most commonly involves the lateral borders of the tongue but may extend to the ventral or dorsal surfaces and is usually bilateral. Lesions on the tongue are usually corrugated or frayed appearance or may manifest as a plaque-like lesion.

Histopathologic examination of the epithelium reveals severe hyperparakeratosis with an irregular surface, acanthosis with superficial edema, and numerous virally affected "balloon" cells/koilocytic cells in the spinous layer. The characteristic microscopic feature is the presence of homogeneous viral nuclear inclusions with a residual rim of normal chromatin. The definitive diagnosis can be established by demonstrating the presence of EBV through *in situ* hybridization, electron microscopy, or polymerase chain reaction.

Glossitis

Glossitis is a general term for tongue inflammation which can have various etiologies. It is associated with smoothing of the tongue, discoloration and swelling. It may be transient and chronic. The surface of tongue may appear smooth, red/pale or tongue may swell. There may be tenderness, burning, taste disturbances and difficulty in chewing, speaking and swallowing. This disease can be attributed to various conditions or infections, allergic reaction, genetic predisposition, malnutrition, deficiency of vitamin B or iron, tongue piercing, mechanical irritants, and poor hydration. Some types of glossitis are caused by infections, e.g. median rhomboid glossitis (*Candida* species), "strawberry tongue" (seen in scarlet fever), and syphilitic glossitis (seen in tertiary syphilis). Oral candidiasis can affect the tongue. Risk factors for oral candidiasis include antibiotic and corticosteroid use and immunodeficiency or diabetes mellitus.

The treatment involves elimination of the cause of inflammation, topical medications, e.g. corticosteroids may reduce redness or swelling.

Depapillation of Tongue

Bald tongue of Sandwith is named after scientist Fleming MantSandwith.

It is characterized by a smooth glossy tongue that is often tender, painful caused by complete atrophy of lingual papillae leaving behind an erythematous surface.

The main characteristic features include glossitis, associated with painful, fiery red and enlarged tongue, profused salivation and raw beefy tongue caused mainly by deficiency of niacin/vitamin B_3. The dorsal surface of tongue may be affected completely or in patches associated with pain and erythema.

Bald tongue can be diagnosed by differentiating it from atrophic glossitis, median rhomboidal glossitis, benign migratory glossitis, strawberry tongue.

Causes

Main cause of bald tongue is niacin deficiency which is caused due to alcoholism and digestive system disorder and due to prolonged treatment with isoniazid. Other causes of glossitis include:

1. Iron deficiency anemia mainly caused by blood loss, during gastrointestinal hemorrhage often results in depapillated, atrophic glossitis, giving the tongue bald and shiny appearance, along with pallor lips and tendency towards oral ulceration and cheilosis.
2. Pernicious anemia is usually caused by autoimmune destruction of gastric parietal cells. Parietal cells secrete intrinsic factor, which is required for the absorption of vitamin B_{12}. Vitamin B_{12} deficiency results in megaloblastic anemia and may present as glossitis. The appearance of the tongue in vitamin B_{12} deficiency is described as 'beefy' or 'fiery red and sore'. There may be linear or patchy red lesions.
3. Vitamin B_1 deficiency (thiamine deficiency) can cause glossitis. Vitamin B_2 deficiency can cause glossitis, along with angular cheilitis, cheilosis, peripheral neuropathy and other signs and symptoms. Vitamin B_3 deficiency (pellagra) can cause glossitis. Vitamin B_6 deficiency (pyridoxine deficiency) can cause glossitis, along with angular cheilitis, cheilosis, peripheral neuropathy and seborrheic dermatitis. Folate deficiency (vitamin B_9 deficiency) can cause glossitis, along with macrocytic anemia, thrombocytopenia, leukopenia, diarrhea, fatigue and possibly neurological signs.
4. Bacterial, viral or fungal infections can cause glossitis. *Candida* species are involved in median rhomboid glossitis. *Candida* species also may be involved in creating a more generalized glossitis with erythema, burning, and atrophy, e.g. erythematous candidiasis (e.g. as may occur in HIV/AIDS) may involve the tongue giving glossitis with depapillation.
5. Syphilis is now relatively rare, but the tertiary stage can cause diffuse glossitis and atrophy of lingual papillae, termed "syphilitic glossitis", "luetic glossitis" or "atrophic glossitis of tertiary syphilis". It is caused by *Treponema pallidum* and is a sexually transmitted infection.

Treatment: The goal of treatment is to reduce inflammation. Maintaining good oral hygiene is necessary, including thorough tooth brushing at least twice a day, and flossing at least daily. Corticosteroids such as prednisone may be given to reduce the inflammation of glossitis. For mild cases, topical applications such as a prednisone mouth rinse may be recommended. Antibiotics, antifungal medications, or other antimicrobials may be prescribed if the cause of glossitis is due to infection. Anemia and nutritional deficiencies such as a deficiency in niacin, riboflavin, iron, or vitamin E must be treated, often by dietary changes or other supplements. Avoidance of hot or spicy foods, alcohol, and tobacco is advised to minimize the discomfort.

NUTRITIONAL DEFICIENCIES AND HEMATOLOGIC ABNORMALITIES

The term atrophic glossitis (loss of papillae, redness and painful swelling of the tongue) is used to describe the appearance of the tongue that results from various nutritional deficiencies and hematologic abnormalities. The hunter's glossitis is the term for atrophic glossitis associated with raw, beefy, magenta, bright red tongue.

The redness, loss of papillae, and painful swelling of the tongue are characteristically found in deficiencies of several B vitamins as niacin, riboflavin, pyridoxine, folic acid, and vitamin B_{12}. Similar changes also are associated with iron deficiency. The Plummer-Vinson syndrome/sideropenic anemia manifests as atrophic glossitis, angular cheilitis, generalized atrophic oral mucosa, oral ulcerations, secondary candidiasis, dysphagia and oropharyngeal carcinoma. In many cases, the depapillation of the tongue and atrophic glossitis resolve completely following administration of the appropriate nutritional factor or correction of malabsorption problem.

The medications such as antibiotics, cancer chemotherapeutic agents and anticholinergic agents may also lead to depapillation to cause smooth or bald tongue. Decreased nutritional status of the lingual papillae as a result of vascular changes, chronic xerostomia, chronic candidiasis, diabetes or fibrosis of the submucosal tissues secondary to obliteration of small vessels by an autoimmune process as seen in oral submucous fibrosis, scleroderma, mixed connective tissue disease, and lupus erythematosus may lead to depapillation.

Burning Mouth Syndrome/Glossodynia/ Burning Tongue Syndrome

It is characterized by chronic burning sensation of the tongue and other oral mucous membranes in the absence of any identifiable signs or causes. This condition causes burning sensation, loss of taste, and swelling or the feeling of swelling of the tongue. It commonly affects women before or after menopause, the 10 to 20% of the females may be affected. The main cause is not known but it has been commonly associated with medical conditions, e.g. nutritional deficiency.

Traumatic Injuries, Ulcers and Infectious Diseases

Tongue being the central organ in oral cavity is vulnerable for injury from trauma; there can be various reasons for the occurrence of ulcer on tongue. The ulcerations of the tongue result from variety of physical agents and infectious agents. Any jagged, broken cusps or rough surfaces on restorations, biting trauma, oral parafunction/chronic tongue thrusting or sudden blow to jaw may cause ulcerations of the tongue. More chronic ulcers may be seen in patients with uncontrolled grinding and chewing movements as result of *Morsicatio linguarum* or brain damage.

The trauma may be of iatrogenic origin, it may occur while any dental procedures, the fimbriated folds on either side of lingual frenum may get aspirated during dental procedure. The ulcers of the lingual frenum in neonates are due to abrasion of the tongue by lower incisors during suckling, known as Riga's ulcers or Riga-Fede disease.

The vesiculobullous disorders and infectious diseases commonly lead to ulcerations on tongue. Lateral margins and tip of the tongue are frequently involved in severe episodes of recurrent aphthous ulcers and Behçet's syndrome, also the shallow persistent tongue ulcer especially on the posterior ventral surfaces are common in patients with lichen planus. In primary herpes simplex gingivostomatitis, the dorsum, ventral surface and lateral margins of tongue may be ulcerated. Herpes zoster produces a series of ulcers along the anterior third of the tongue unilaterally.

In addition, the ulcerative and proliferative lesions of the tongue occur in a number of chronic granulomatous infections such as

tuberculosis, histoplasmosis, blastomycosis, cryptococosis, sporotrichosis, mucormycosis, primary and secondary syphilis, and lymphogranuloma venerum. The multiple pseudomembranous ulcerations of the tongue and palate have been noted with septicemia caused by *Capnocytophaga* species in granulocytopenic patients. The tongue involvement is common in acute necrotizing ulcerative gingivitis; chronic low grade fevers such as scarlet fever, typhoid fever, and *Haemophilus influenzae* B infections. In tertiary syphilis, the characteristic lesion forms on the tongue known as gumma. The soft tissue infections of the tongue frequently reveal *Streptococci* and anaerobes, the Ludwig's angina is characterized by an indurated swelling of the whole floor of the mouth and base of the tongue, which pushes the tongue upward and prevents the patient from closing the mouth. Dysphagia and upper airway obstruction are common complications. Lingual mucosal glands are affected in Sjögren's syndrome and pan sialadenitis. Large cysts of the sublingual glands that often distend the overlying floor of the mouth and displace the tongue are referred to as ranula.

The various nutritional deficiencies, hematological problems and patients with xerostomia frequently show ulcerations on tongue. The solitary eosinophilic ulcer or traumatic granuloma of the tongue sometimes



Fig. 13.4: Traumatic ulcer



Fig. 13.5: Aphthous ulcers on tongue

mistakenly diagnosed as carcinoma, though it is rapidly developing histologically reveals no evidence of carcinoma and that contains numerous eosinophils. Such ulcers heal spontaneously in 2 to 3 weeks.

Diseases Affecting the Body of the Tongue

In amyloidosis, the amyloid gets deposited in the tongue. The tongue may be diffusely enlarged or is the site of nodular deposits or is unaffected, the enlarged tongue can affect the dentition, chewing, swallowing and speaking. The various neuromuscular disorders of central, peripheral or muscular origin, e.g. hypoglossal nerve weakness, parkinsonism, tardive dyskinesia, various muscular dystrophies and athetosis may produce symptoms of dysphagia, speech chewing problems due to the involvement of tongue. Angioneurotic edema is an acute anaphylactic reaction representing an immediate hypersensitivity response to antigenic stimuli. It manifests as a swelling of the tongue, glottis and laryngeal structures with rapid occlusion of the airway.

The tongue is a frequent site for the oral cancer and many red and white lesions that are considered to have malignant potential. The tongue is common site of oral cavity for

the involvement by squamous cell carcinoma (SCC); more than 90% malignant tumors of the tongue are SCC. On the tongue, SCC predominantly occurs on lateral borders and ventral surface of tongue. It is manifested in middle and later decades of life (median age 60 years) with male predilection, although now it is apparent in younger age group also. It commonly presents as an exophytic growth and an ulcer, the local infiltration and lymphadenopathy are the common features. The etiology is the tobacco consumption, alcohol, chronic dental trauma, it is also been related to syphilis, infection with *C. albicans*, iron deficiency, virus infection. The thorough clinical evaluation is essential for the involvement of oral cavity, base, pharynx and floor and lymph nodes. Chronic ulcer should be biopsied if it does not regress promptly following removal of a suspected irritant.

Treatment depends on TNM staging, the smaller size or early carcinomas are mostly treated by surgical excision or radiation with predictive 5-year survival rate of more than 50%. The advanced carcinoma of the tongue (T3 category) is treated by combined surgical and radiation therapy with 5-year survival rate is 10 to 30%. The advanced stages of node involvement are usually treated by mandibulectomy and radical neck dissection. The prognosis and survival depend upon the degree of local infiltration involving base and the floor, metastasis to submandibular, jugulodigastric and cervical lymph nodes.

The benign tumors of the tongue such as irritation fibromas, tongue papillomas, granular cell myoblastoma, viral-induced keratoacanthoma. These hyperplasias may resemble carcinomas, the presence or absence of cellular atypia separates these hyperplasias from carcinomas.

The tongue lesions occur in the population with significant prevalence. Hence, oral health professionals should be trained enough to evaluate and diagnose the etiology of tongue lesions so that proper treatment can be instilled.



Fig. 13.6: Malignant ulcer involving lateral border of tongue

FREQUENTLY ASKED QUESTIONS

1. Median rhomboid glossitis
2. Depapillation of tongue
3. Geographic tongue

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Chapter 14

Cardiovascular Diseases—Oral Manifestations and Dental Considerations

INTRODUCTION

Cardiovascular diseases (CVD) have now become the most leading cause for mortality worldwide, as well as in India. More than 80% of cardiovascular deaths are predominantly seen in ischemic heart disease and stroke. The age-standardized CVD death rate in India is higher (i.e. 272 per 100,000 population) in comparison to the global burden (i.e. 235 per 100,000 population). Because of the high prevalence of the CVDs and its impact on the overall health of the patient's, the dentist should have a thorough knowledge on oral manifestations and dental considerations for efficient management.

Eliciting History and Clinical Manifestations Amongst Cardiovascular Patients

Cardiovascular history is fundamental for accurate diagnosis and management of the patients. Table 14.1 illustrates assessment criteria for cardiovascular diseases.

CARDIOVASCULAR DISORDERS

Hypertension

Definition: Hypertension is defined as having systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or as having to use antihypertensive medications.

Etiology and Classification (*refer* to Tables 14.2 and 14.3).

TABLE 14.1: Assessment criteria for cardiovascular diseases

Past and family history
Risk factors
Chest pain
Shortness of the breath (dyspnea)
Palpitations
Dizziness and unsteadiness
Syncope
Fatigue
Bilateral ankle edema
Discomfort and pain in lower limb
Cyanosis

TABLE 14.2: Causes of hypertension

Primary hypertension (Idiopathic or essential): Cause unknown in ninety-five percent cases
Secondary hypertension occurs due to secondary causes such as: • Renal disorders (renal parenchymal disease, renovascular disease, renin-producing tumors, primary sodium retention). • Endocrine abnormalities (Cushing's syndrome, thyroid disease, primary aldosteronism, pheochromocytoma) • Aortic coarctation

Contd.

TABLE 14.2: Causes of hypertension *(Contd.)*

- Complications of pregnancy (pre-eclampsia)
- Neurologic diseases
- Stress
- Alcoholism
- Drug-induced (cyclosporine, tacrolimus, sympathomimetics, steroid hormone, COX-1 and COX-2 inhibitors)

Malignant hypertension

- Systolic BP ≥240 mmHg and diastolic BP ≥ 120 mmHg
- It is associated with organ damage (eyes, kidneys, brain, lungs are affected).

White coat hypertension: Elevated BP in clinical setting/ hospital but not when ambulatory/ home.

TABLE 14.3:

Blood pressure classification	*Systolic BP (mmHg)*	*Diastolic BP (mmHg)*
Optimal	<120	<80
Normal	<130	<85
Prehypertension	120–139	80–89
Hypertension		
Stage 1 (mild)	140–159	90–99
Stage 2 (moderate)	160–179	100–109
Stage 3 (severe)	≥180	≥110
Isolated systolic hypertension	≥140	<90

Clinical Manifestations

Generally asymptomatic for many years

Type	*Clinical manifestation*
Early symptoms	Occipital headache, vision changes, ringing ears, dizziness, weakness, nose bleeding, odontalgia
Signs	Visual changes, enlarged left side of heart, deteriorated renal function are complications of arteriosclerosis
Chronic hypertension	Encephalopathy, a cerebrovascular accident, coronary artery disease, angina pectoris, myocardial infarction, congestive heart failure, aortic aneurysms, hematuria and proteinuria.
Malignant hypertension	Severe kidney damage.

Oral Manifestations

Oral manifestations are a result of antihypertensive medications or occur when target organ disease is present.

TABLE 14.4: Oral adverse effects of antihypertensive medications

Side effects	*Drugs*
Dry mouth	Diuretics, ACE inhibitors, central acting adrenergic inhibitors.
Lichenoid reaction	Furosemide, labetalol, methyldopa, propranolol and thiazides.
Loss of taste, dry mouth, angioedema	ACE inhibitors
Gingival enlargement, dry mouth, altered taste	Calcium channel blockers
Dry mouth, taste changes, parotid pain	Central acting drugs
Dry mouth, angioedema, sinusitis, taste loss	Angiotensin II antagonists
Lupus-like facial rash	Hydralazine, nifedipine, verapamil, diltiazem.

- Excessive bleeding after surgical procedure may be a complication of severe hypertension.

Diagnosis

Periodic measurement of blood pressure (BP) can be recorded using sphygmomanometer. The patient should be at rest and relaxed.

Measurement of Blood Pressure (BP)

The direct intra-arterial measurement with a catheter is considered a standard measurement tool of BP. Since its an invasive procedure, some indirect methods have been commonly used to assess BP like palpatory and auscultatory methods. The pressure cuff of a sphygmomanometer is wrapped around the arm of the patient an inch above the ante-cubital fossa.

- **Palpatory method:** Palpate for the radial pulse with three fingers (index, middle

and ring finger) on the radial artery. Now, inflate the cuff slowly (10 mmHg/sec) in increments, until no longer the radial pulse felt. The cuff inflated further until the pressure is 30 mmHg higher. Deflate the cuff slowly (5 mmHg/sec), the first pulsatile trill appears will be systolic pressure and, the disappearance of the trill is the diastolic BP.

- **Auscultatory method:** Brachial pulse is palpated at the anticubital fossa, followed by placement of the diaphragm of the stethoscope over the artery. In this method the cuff is inflated to a level 30 mmHg above systolic pressure as determined by palpatory method. The cuff is gradually deflated 5 mmHg; arterial pulse (Korotkoff sounds) appears which is the systolic BP, then the sounds totally disappear. The total disappearance of sounds is diastolic BP.

At least two or three separate readings provide the most accurate assessment of BP.

Management

- Treatment depends on stage of disease
- Patients with mild and moderate hypertension should be managed non-pharmacologically:
  - They are advised to restrict salt intake, fatty foods
  - Weight control
  - Avoid smoking
  - Restricting alcohol and caffeine
  - Regular exercise
- Antihypertensive medications advised for other stages of hypertension
- In patients with secondary hypertension, treat the primary cause.

Antihypertensive Medications

TABLE 14.5: Antihypertensive medications

Direct-acting vasodilators: Nitroglycerin, hydralazine, minoxidil, sodium nitroprusside, diazoxide.
Angiotensin II receptor blocker: Losartan, candesartan, valsartan, irbesartan
Diuretics - Thiazides: Hydrochlorothiazide, chlorthalidone - High ceiling: Furosemide - K+ sparing: Spironolactone, amiloride
ACE inhibitors: Captopril, enalopril, lisinopril, perindopril, ramipril, fosinopril
Calcium channel blockers: Verapamil, dlltiazem, nifedipine, felodipine, amlodipine, nitrendipine, lacipine
β-adrenergic blockers: Propranolol, metoprolol, atenolol
β + α-adrenergic blockers: Labetolol, carvedilol
α-adrenergic blockers: Prazosin, terazosin, doxazosin, phentalamine, phenoxybenzamine
Central sympatholytics: Clonidine, methyldopa

Dental Considerations

- Patient assessment is important prior dental treatment in terms of medical history, drug history, controlled or uncontrolled hypertension.
- Elicit history for presence of end organ disease or on antihypertensive medication.
- Schedule short appointments for patients who receive dental treatment.
- Ensure adequate anesthesia to reduce anxiety and pain as it may induce dysrhythmias.
- Prior anesthesia ensure syringe aspiration to prevent the entry of epinephrine into blood vessels.
- Epinephrine in local anesthesia (LA) not contraindicated unless systolic BP is above 200 mmHg and/or diastolic BP 115 mmHg.
- LA with epinephrine in large doses should be avoided in patients with non-selective beta blockers.
- Gingival retraction cords containing epinephrine should be avoided.
- Concentrations of epinephrine greater than 1:100,000 are avoided as it carries a higher risk, and New York Heart Association recommends not more than 0.04 mg of epinephrine with heart disease.
- A substitution to epinephrine is levonordefrin at concentration of 1:20,000.

- Patients with history of combined multiple antihypertensive medications are more difficult to manage than on patients with one or two medications.
- Record blood pressure prior initiating any dental treatment.

The guidelines for BP monitoring:

- Recheck every two years for patients with BP <120/80 mmHg
- Every year for patients with BP 120–139/80–89 mmHg
- Every visit for patients with BP >140–90 mmHg
- Every visit for patients with underlying systemic disease with BP >135–85 mmHg
- Every visit with established hypertension

Modifications of dental treatment in patients with elevated BP

- *Asymptomatic:* If no history of target organ disease and BP <159/99 mmHg, patient can be treated without any modifications in a dental outpatient setting.
- *Asymptomatic:* If BP 160–179/100–109 mmHg and no history of target organ disease, dental treatment depends on risk assessment of an individual.
- If BP >180/110 mmHg, no history of target organ damage, then no elective dental care should be performed.
- Medically compromised patients with end organ disease and uncontrolled diabetes mellitus, no elective treatment until BP is controlled.
- Dentist should be aware of drug interactions with antihypertensive medication and their side effects, i.e. orthostatic hypotension is a major side effect in patients taking antihypertensive medications.

Ischemic or Coronary Heart Disease

The decreased oxygen supply to heart for long-term leads to ischemic heart disease.

Causes

Atherosclerosis	Aortic stenosis
Hypertension	Congenital heart disease
Aneurysm	Thrombus formation

Angina Pectoris

Angina pectoris is an ischemic heart disease that occurs secondary to atherosclerosis in the walls of the arteries, leading to stenosis and reduced blood flow to heart. It is characterized by paroxysmal thoracic pain due to deprivation in oxygen to the myocardium. The pain occurs when cardiac work and oxygen demand exceed the supply of oxygen. It is precipitated by increased physical exercise, emotional stress, cold weather, smoking.

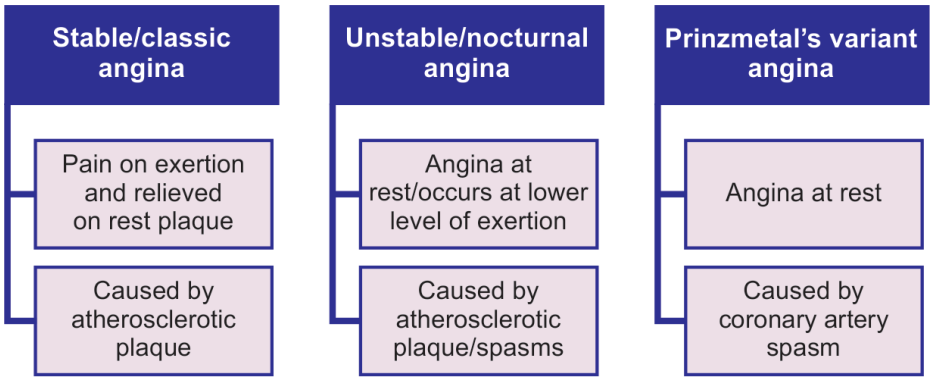
Clinical Features

Age	Occur in older individuals
Chest pain	Classically described as a sense of choking, tightness, heaviness, compression of the chest
Levine's sign	Patients make a fist over the location of pain on chest
Radiation of pain	Shoulders, arm, fingers, neck, mandible and sometimes teeth

Management

1. Control risk factors such as smoking, hypertension, fatty foods and strenuous exercise.
2. Pharmacologic mode of management
   a. *Nitrates:* These are first line of drugs—it has a vasodilation property, can be administered sublingually at the dose of 0.3–0.6 mg.
   b. *Beta-adrenergic blockers:* These are second line therapy when nitrates fail to respond. It improves myocardial oxygen consumption by inhibiting the sympathetic nervous system.
   c. *Calcium channel blockers:* These medications prevent calcium entry to the myocardium, thereby preventing contraction, and also relax smooth vessels of blood vessels, thereby dilating the coronary artery and thus increases oxygen supply.

Flowchart 14.1: Variants of angina



3. Other modalities when pharmacotherapy fails:
   a. Coronary angiography
   b. Coronary artery bypass grafting (CABG)
   c. Percutaneous transluminal coronary angioplasty (PTCA)

Anticoagulants such as aspirin are commonly prescribed following CABG and PTCA.

Oral Manifestations

- Pain in jaws and teeth
- Occasionally burning sensation in the tongue and hard palate
- Concurrent chest pain and orofacial pain
- Orofacial manifestations secondary to antianginal medications are as follows:
  - Nitroglycerin administration has a side effect of burning sensation at the site of placement and headache due to rapid vasodilatation property.
  - Calcium channel blockers cause gingival enlargement.

Dental Considerations

- Schedule short mid-morning appointments to reduce stress
- Employ good sedation techniques that are not cardio depressing
- Use of epinephrine at the dose of 0.04 mg
- Avoid epinephrine impregnated gingival cord
- Encourage use of alternative vasoconstrictors such as phenylephrine (1:2,500); levonordefrin (1:20,000).
- Availability of nitroglycerine, oxygen and emergency equipment readily available. Antibiotic prophylaxis prior dental treatment in patients with coronary bypass operation.

Management of angina attack on the dental chair:

- Dentist should discontinue the dental treatment immediately.
- Place patient in the supine position and ensure good airway.
- Administer sublingual nitroglycerin
- Monitor vital signs
- If clinical signs of cyanosis is evident, supplement oxygen therapy, followed by 2nd tablet of sublingual nitrates, if ineffective an amylnitrite ampule is broken and held under patients nose to enhance vasodilatation. No relief even after 10 minutes, a third tablet of nitroglycerin is administered. Even after 3 tablets, symptoms are unresolved, suspect myocardial infarction that warrants medical emergency.

◈ Myocardial Infarction (MI)

It is the severe form of coronary artery disease; it occurs if an angina attack persists longer than 30 minutes. Acute MI is an irreversible ischemic event that produces an area of myocardial necrosis.

TABLE 14.6: Myocardial infarction: Causes and clinical features

Causes	*Clinical features of MI*
• Coronary atherosclerosis • Thrombosis • Vasospasm • Increased myocardial demand • Coronary artery occlusion	• Substernal pain • Palpitations, dizziness, vomiting • Shortness of breath, cough • Patient becomes pale, vital signs are unstable, increased BP, weak thready/ absent pulse

Oral Manifestations and Dental Considerations

- The oral manifestations are similar to angina pectoris but with greater severity in pain.
- Physician consent is mandatory prior to any dental treatment as these patients are on anticoagulants in order to prevent thromboembolic event.
- Defer dental treatment with recent MI within 6 months
- Provide effective local anesthesia
- Premedication with antianxiety drugs
- Schedule appointments either in late mornings or early noon.
- Elective procedures, especially that require general anesthesia should be avoided at least for the first 4 weeks following MI, as there is increased risk of re-infarction.

Management of MI in Dental Office

- Monitor vital signs every 5 minutes
- Provide oxygen therapy
- Give analgesic nitrous oxide at the rate of 5 L/min to calm the patient and limit the release of catecholamines, which might trigger arrhythmias
- Perform resuscitative procedure
- Administer 2 mg of intravenous morphine for pain relief
- Availability of emergency drugs such as atropine, lidocaine, phenylephrine readily available.

Infective Endocarditis and Associated Disease

◈ Rheumatic Fever (RF)

- RF is an autoimmune inflammatory condition that follows infection caused by group A beta-hemolytic streptococci.
- RF precedes with pharyngitis and sore throat.

Clinical Features

Major manifestations	*Minor manifestations*
Carditis	Arthralgia
Chorea	Fever
Erythema marginatum	Abnormal C reactive protein
Polyarthritis	Previous RF of rheumatic heart disease
Subcutaneous nodules	Characteristic ECG recording

Oral Manifestations

- Oropharyngitis
- Increased oral temperature
- Edematous and erythematous soft palate
- Tonsillar ulcerations
- Skin rashes (erythema marginatum)
- Gingiva is usually spared

Dental Considerations

- Physician consent prior any dental treatment
- Risk of developing infective endocarditis (IE), hence treatment and precautions similar to IE.
- Avoid general anesthesia

◈ Rheumatic Heart Disease

It is an autoimmune, non-suppurative disease of the heart that occurs subsequent to acute rheumatic fever.

Clinical findings: Heart murmur, tachycardia, arrhythmias may be present.

Oral manifestations and dental considerations:

- Oropharyngitis and increased oral temperature
- Progressive disease leads to congestive heart disease produces distended neck veins and bluish color over skin.
- Prescribe antibiotic prophylaxis prior dental treatment.

◈ Infective Endocarditis (IE) (Table 14.7)

Etiopathogenesis

Flowchart 14.2

IE is a cardiac infection preceded by bacteremia and fungemia

↓

Microbes enter circulation from mouth, GIT, genitourinary tract

↓

These microorganisms adhere to damaged heart valves, indwelling catheter, shunts

↓

This produces turbulent blood flow and provide suitable environment for colonization of microorganisms and cardiac damage

↓

Cardiac damage is through microbial proliferation and cardiac tissue destruction, microbial vegetations into circulation and production of immune complexes

TABLE 14.7: Infective endocarditis

IE based on clinical presentation	*Organisms*
Sub-acute IE	Alpha-hemolytic Streptococcus: *Streptococcus viridians*
Acute IE	*Staphylococcus aureus*
Chronic IE	*Streptococcus faecalis*

Clinical Findings

Age	Affects older individuals
Symptoms	Low-grade fever, malaise, lethargy, weight loss, joint pains, dyspnea, orthopnea, hematuria, café-au-lait pigmentation on skin.
Signs	Anemia, heart murmur, vasculitis, evidence of sublingual hemorrhages, petechial hemorrhages, Osler's nodes, Roth's spots, Janeway's lesions, Splenomegaly

Oral Manifestations and Dental Considerations (Table 14.8)

- Pallor mucous membrane and facial skin
- Mucosal petechiae that do not blanch under pressure
- Followed by purpuric lesions

TABLE 14.8: Oral manifestations and dental considerations

Dental procedures, which require antibiotic prophylaxis	*Procedures, which do not require antibiotic coverage*
Periodontal probing and sub-gingival procedures, which elicits bleeding	Exfoliation of primary teeth
Extractions	Making of impressions
Surgical procedures	Non-surgical procedures that do not induce bleeding
Operative procedure requiring manipulation beyond the apex	Taking radiographs
Raising mucogingival flaps/ periodontal surgeries	Removal of orthodontic bands and brackets
Implant placement	Adjustment and placement orthodontic brackets
Administering LA	
Sialography	
Wedge placement, rubber dam and matrix band placement	

TABLE 14.9: Therapeutic regimens for a dental procedure

Situation	*Agent*	*Adult*	*Children*
Oral	Amoxicillin	2 gm	50 mg/kg
Unable to take oral medication	Ampicillin or cephazolin or ceftriaxone	2 gm IM* or IV# 1 gm IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin$^{\Phi\delta}$ or clindamycin or azithromycin or clarithromycin	2 gm 600 mg 500 mg	50 mg/kg 20 mg/kg 15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cephazolin or ceftriaxone$^{\delta}$ or clindamycin	1 gm IM or IV 600 mg IM or IV	50 mg/kg IM or IV 20 mg/kg IM or IV

*IM: Intramuscular; #IV: Intravenous
$^{\Phi}$ or other first or second-generation oral cephalosporins in equivalent adult or pediatric dosage
$^{\delta}$ Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins and ampicillin.

Cardiac diseases that require antibiotic prophylaxis for dental treatment

- Prosthetic heart valve
- History of IE
- Congenital heart disease
- Heart transplantation

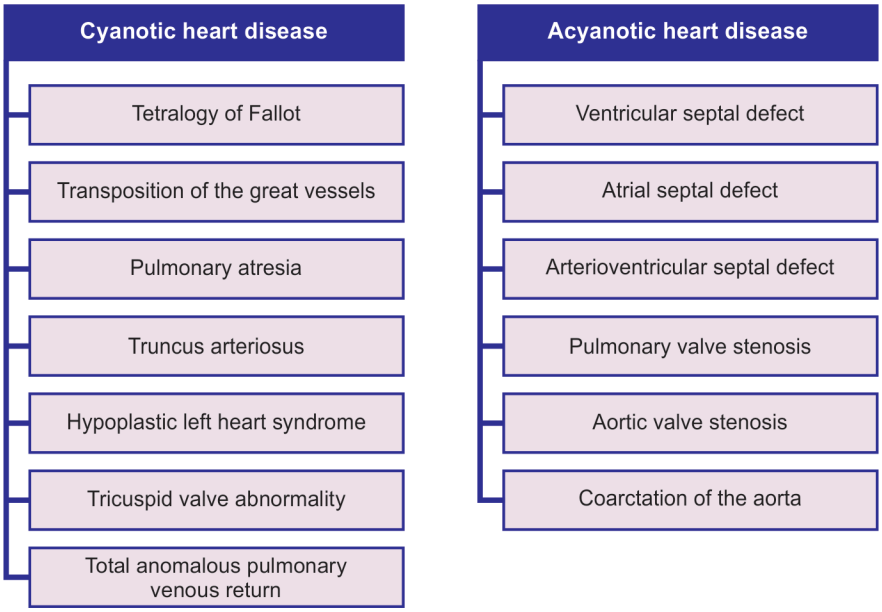
Congenital Heart Disease

It is the most common heart disease amongst children.

Classification

Flowchart 14.3 describes classification of congenital heart disease.

Flowchart 14.3: Classification of congenital heart disease



Oral Manifestations and Dental Considerations

- Cyanosis of mucosa, lips and auricles of ear
- Cleft palate
- Midline abnormalities
- Growth anomalies of primary teeth
- Delayed eruption of both primary and permanent teeth
- Hypoplastic enamel
- Increased incidence of dental decay
- Antibiotic prophylaxis to prevent infective endocarditis prior dental treatment.
- Bleeding tendencies due to platelet dysfunction and excessive fibrinolytic activity.

Heart Failure (Congestive Heart Failure)

Heart failure is a clinical syndrome where the heart muscle fails to contract adequately resulting in inadequate cardiac output and reduced oxygenated blood supply to end organs. Failure of heart can be either left-sided or right-sided.

Causes

Flowchart 14.4 describes causes of heart failure.

Clinical Findings

Manifestations in left-sided heart failure	*Manifestations in right-sided heart failure*
Symptoms are related to pulmonary edema	Symptoms are related to congestion of blood both systemically and in the portal hypertension
Tachycardia	Hepatomegaly
Fatigue on exertion	Distended neck veins
Dyspnea	Fullness in abdomen
Cough	

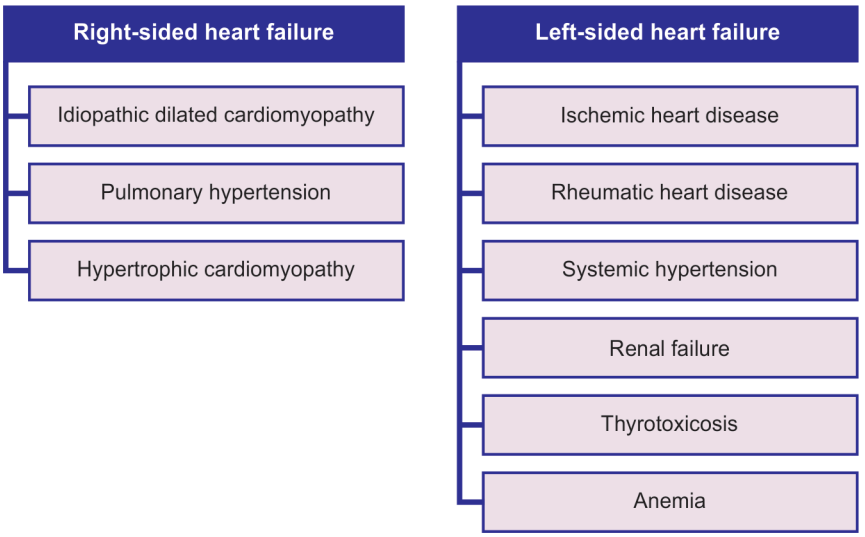
Oral Manifestations

- Infections
- *Bleeding tendencies:* Petechiae, ecchymosis
- Drug-related xerostomia
- Lichenoid mucosal lesions
- Distension of neck veins (external jugular vein)

Dental Considerations

- Obtain medical consultation prior initiating dental treatment
- Administration of prophylactic antibiotics

Flowchart 14.4: Causes of heart failure



- Defer dental care for 6 months of recent MI
- Monitor blood levels of digitalis for evaluation of digitalis toxicity and may cause vomiting and nausea
- Monitor vital signs
- Prefer upright dental chair position as supine position of patient may precipitate pulmonary complications and cause dyspnea
- Avoid respiratory depressant medication during treatment
- Advise complete blood count prior any surgical procedures
- Elective surgery with patients under general anesthesia is relatively contraindicated because of cardiac–depressant effect of volatile anesthesia
- NSAIDs other than aspirin should be avoided in patients with ACE inhibitors, as there is risk of kidney damage.
- Schedule appointment in late morning as there is peak endogenous epinephrine at early morning
- Use of electromechanical toothbrushes for effective cleaning of teeth
- Use of hemostatic agents over the extraction sites.

FREQUENTLY ASKED QUESTIONS

1. Oral manifestations/dental considerations of cardiovascular diseases.
2. Angina pectoris
3. Discuss the prophylactic regimen for SABE.

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Chapter 15

Respiratory Disorder—Oral Manifestations and Dental Considerations

INTRODUCTION

Patients with respiratory disorders have an increased risk of morbidity on a dental chair due to reduced pulmonary function, medications that they take, drug interactions and risk of disease transmission. Thus, there is a need for understanding clinical manifestations, diagnosis, oral manifestations, oral health considerations and management.

Functions of the Lung

Ventilatory function	*Non-ventilatory function*
Gaseous exchange: It involves exchange of carbon dioxide and oxygen gases between the circulating blood and air in the alveolus	Defense against noxious atmospheric substance
Oxygen supply to end organs	Conversion of angiotensin I to angiotensin II, which is the potent vasoconstrictor by endothelial cells of the lung.
	Metabolism of bradykinin, serotonin and some prostaglandins

Medical History and System Review

- Breathing difficulties
- Frequent upper respiratory infections
- Cough (productive or nonproductive)
- Hoarseness, dyspnea, production of sputum, hemoptysis, wheeze, chest pain.
- Abnormalities in size and shape of the lung
  - Barrel-shaped chest—find in asthma and emphysema
  - Pigeon chest find in asthma of early childhood
  - Flattening of upper anterior chest in fibrosis of lung
  - Distended veins on chest and jugular veins—superior vene cava obstruction and portal hypertension.

CLASSIFICATION OF RESPIRATORY DISEASES

Table 15.1 provides classification of respiratory diseases.

TABLE 15.1: Classification of respiratory diseases

Upper respiratory infections
• The common cold
• Sinusitis
• Pharyngitis and tonsillitis
• Laryngitis

Contd.

TABLE 15.1: Classification of respiratory diseases (*Contd.*)

Lower respiratory disorders
- Asthma
- Chronic obstructive pulmonary disease
  - Chronic bronchitis
  - Emphysema
- Pulmonary foreign bodies
- Pneumonitis
- Granulomatous lung disease
  - Tuberculosis
  - Sarcoidosis

Occupational lung disease
- Pneumoconiosis

Other diseases affecting the respiratory tract
- Histoplasmosis
- Wegener's granulomatosis
- Midline granuloma
- Cystic fibrosis

Upper Respiratory Infections

The Common Cold (Acute Rhinitis, Coryza)

Description

- It is the most common infection of upper respiratory tract caused by group of viruses
- Common cold lasts for 5–7 days.

Etiology

- Rhinovirus, coxsackie virus A21, respiratory syncytial virus, parainfluenza virus
- The mode of spread is through aerosol droplets, hand to hand and body to body contact.

Clinical Features

- Rhinorrhea (nasal discharge)
- Nasal congestion
- Often precedes sore throat
- Associated with other symptoms such as headache, cough, fever, myalgia.

Treatment

- **Antihistamines:** These medications reduce nasal secretion
- **Sympathomimetic amines (phenyl propanolamine):** These medications relieve nasal congestion
- **Symptomatic therapy:** These medications include analgesics, antipyretics and fluid intake to treat myalgias, fever and dehydration respectively.
- **Antibiotics:** These medications have no role in treating common cold until secondarily infected with bacterias.

Sinusitis

Description

- It is the inflammation of sinus secondary to bacteria or viral infections.
- It could be a sequelae of common cold
- Infective organisms causing sinusitis: *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Haemophilus influenzae* are the most common organism among children.

Clinical Features

- Severe pain localized to the region of sinus involved
- This can be accompanied with headache, fever, malaise
- Edema and erythematous areas over the malar eminence
- Referred pain in the maxillary teeth (especially in premolars and molars) may seek for dental treatment
- Morning headache is the common symptom that disappears gradually during day because of the upright position
- Postnasal discharge.

Diagnosis

- It is based on history
- Transillumination test: It usually appears dull
- Increased pain on firm pressure over the sinus
- Radiographic evaluation (intraoral periapical radiographs, occlusal films and paranasal view)
- Computed tomography

Treatment

- Sinusitis cannot be differentiated as viral of bacterial, therefore, first line of medication irrespective of causative organism would be antibiotics along with sympathomimetic medication.
- If found no relief on medication, surgical drainage can be performed.

◈ Pharyngitis and Tonsillitis

Description

Inflammation of mucosa and lymphoid tissue in pharynx is termed pharyngitis and tonsillitis respectively.

Etiology

Infection from herpes simplex virus, infectious mononucleosis, group A beta hemolytic streptococci and rarely diphtheria.

Clinical Features

- Sore throat, dysphagia, may be associated with common cold
- Extreme pain, swelling, dysphagia in case of peritonsillar abscess, which is the serious illness because of possible extension of infection to the deeper structures.

Diagnosis

- Throat culture to differentiate viral and bacterial pharyngitis
- Differential white cell count and mononucleosis antibody tests.

Treatment

- If it is due to viral etiology, treat symptomatically such as analgesics, decongestants and antihistamines
- If it is because of bacterial origin, it should be treated with beta-lactam antibiotics
- Among children, amoxicillin is the choice of drug if *H. influenzae* is the etiologic agent.

Oral Manifestations and Dental Considerations in Upper Respiratory Diseases

- Multiple oral ulcerations are the most common feature of respiratory diseases. Erythema multiforme and acute ulcerative gingivitis are noted as late manifestation.
- **Herpangina:** Multiple painful ulcers often preceded by vesicles involving posterior pharynx. The gingiva remains unaffected.
- The anatomic relation of maxillary premolars and molars are in close relation with maxillary sinus, maxillary sinusitis can cause pain resembling the tooth pain. The associated teeth may be tender on percussion and feel elongated.
- Radiographs of the sinuses (panoramic and water's view) show a cloudy antrum, generalized thickening of mucosal lining, a fluid level and often polyps.
- Periapical abscess of maxillary premolars and molars occasionally open into the maxillary sinus. The infected tooth may produce foul smelling, nasal discharge and halitosis, whereas sinusitis produces headache-like pain without bad odor. Pain aggravation on bending head forward suggests sinusitis.
- The paresthesia of the sinus region may indicate malignant growth in the sinus.
- During extraction the root stump can be forced into the maxillary sinus, this event should be reported to the patient and an oral surgeon should attempt to remove the root piece.
- Following the removal of the root piece near the maxillary sinus, there is impaired healing and results in an exophytic tissue growth, which tends to bleed.
- Radicular cyst of maxillary premolars and molars when secondarily infected encroached on sinus; it is been misdiagnosed as acute sinusitis and treated inappropriately. Suitable investigations are required for correct management.

Lower Respiratory Tract Infections

◈ Asthma

Description

- It is a respiratory disorder associated with hyperactivity of airway that produces recurrent bronchial smooth muscle contraction, inflammation and swelling of bronchial smooth muscle resulting in narrowing of airways.
- There is hypersecretion of thick mucosa results in sputum plugging with subsequent increased airway resistance to expiration, and the lungs become hyperinflated.

Etiology

- Allergens, upper respiratory tract infections, exercise, cold air
- Medications such as salicylates, NSAIDs, cholinergic medication and beta-adrenergic blocking agents
- Chemicals, tobacco smoke, anxiety, stress and nervousness, atopy
- It can have a significant hereditary contribution.

Classification

Table 15.2 provides classification of asthma.

Clinical Features

Asthma can be acute, intermittent or chronic

Clinical type	*Clinical features*
Acute	• The asthmatic attacks last for a few minutes and resolve spontaneously with drugs • The symptoms include wheezing, cough, chest tightness, dyspnea and flushy
Intermittent	• If the individuals present with symptoms for less than 5 days/month is considered as intermittent
Chronic	• Individuals with symptoms for more than 5 days/month
Status asthmaticus/ acute severe asthma	• Is an medical emergency • The condition persists despite the therapy and individuals fail to respond

TABLE 15.2: Classification of asthma

Category	*Etiology*	*Mechanism*
Extrinsic asthma	Caused due to allergens such as pollens, dust, house mites and animal danders	• When IgE combines with mast cells, there is release of vasoactive substances (histamine, leukotriene, prostaglandins, bradykinins, platelet-activating factor (PAF). ✦ IgE + mast cells → vasoactive substances ✦ Histamine → causes bronchoconstriction and increased vascular permeability ✦ Leukotrienes → increased migration of leukocytes to airway space and cause increased tissue edema ✦ PAF → it increases plasma leakage into airway space
Intrinsic asthma	Non-allergic stimuli	• Vagal mediated bronchospasm
Exercise-induced asthma	Bronchoconstriction due to increased physical activity	• Thermal changes produce mucosal irritation and trigger symptoms
Drug-induced (aspirin-induced or triad asthmatics)	Medications-induced asthma. For example: Ibuprofen, aspirin, beta adrenoreceptor blockers, tartrazine sulfites in food preservatives and local anesthesia	• The blockage of cyclo-oxygenase pathway by medications causes accumulation of leukotrienes through lipoxygenase pathway that causes bronchial spasm.
Infectious asthma	Bacteria, virus, Mycoplasma	• Infectious agents cause bronchial inflammation.

Diagnosis

- It is based on history
- Symptom of asthma tends to worsen at night and in early morning hours
- Allergens can trigger attacks
- Radiographic evaluation reveals increased anteroposterior chest diameter
- Spirometry shows reduced forced expiratory volume
- Allergen skin test can help determine the substances that cause allergic reaction in an individual
- Sputum smears are performed to evaluate for eosinophilia.

Management

Medication	Description
Bronchodilators (albuterol, terbutaline, epinephrine, metaproterenol)	• It causes bronchodilation and smooth muscle relaxation, thereby reducing the resistance to airway • Epinephrine is the drug of choice for severe asthma attack
Methylxanthines (theophylline, aminophylline)	• Chronic asthma can be managed by this group of medications • Bronchial smooth muscle relaxation by blocking adenosine receptors and inhibition of forms of cyclic AMP.
Corticosteroids (prednisone, beclomethasone)	• Advised in refractory cases of asthmatics • It reduces inflammatory response and prevents formation of mast cell mediators
Inhibitory of mast cell release (cromolyn sodium)	• Prophylactic medication that protects against allergic/exercise-induced asthma
Anticholinergics (ipratropium bromide)	• It inhibits the vagal reflex, thus preventing bronchoconstriction and mucous secretion

Oral Manifestations and Dental Considerations

- Pseudomembranous candidiasis in chronic asthmatic patients on steroid inhalers. Lozenge or liquid form of nystatin can be used for 2 weeks to treat these patients.
- Dental products such as toothpaste, fissure sealants, tooth enamel dust, methyl methacrylate can exacerbate asthma.
- Chronic asthmatics with severe airway obstruction can cause mouth breathing and dolichocephalic face form.
- Decreased salivary flow due to prolonged use of beta-2 agonists, this increases the incidence of dental caries, calculus deposition, gingivitis, periodontitis, change in oral microflora.
- Fluoride supplements can be used as a preventive and prophylactic measure
- Regular oral rinse following the use of inhalers
- Administer prophylactic steroids for individuals who are on long-term systemic steroids to avoid adrenal suppression
- Avoid anxiety, supplement with anxiolytics to reduce anxious patients
- Barbiturates and narcotics should be avoided in asthmatics as it may cause bronchoconstriction
- Schedule appointments late morning to reduce the risk of asthmatic attack
- Accessibility for oxygen and bronchodilators during exacerbations of asthma
- Sulfite in local anesthesia can exacerbate the asthma in susceptible cases
- Recommend and prescribe acetaminophen instead of aspirin
- Discontinue dental procedure during acute asthma attack, position the patient in a comfortable position, accessibility to beta-2 agonists and oxygen therapy. If no improvement noted, administer 1:1000 epinephrine subcutaneously.

◈ Chronic Obstructive Pulmonary Disease (COPD)

Description

It is a chronic inflammatory disease of lungs that causes limitation or obstruction of airflow.

Two major diseases include:

- Chronic bronchitis
- Emphysema

☛ *Chronic Bronchitis*

Description

- It is a chronic inflammatory condition affecting the bronchoalveolar epithelium for at least 3 months for more than two years.

Pathogenesis

- There is increased mucin secretion associated with ciliary dysfunction
- Airway limitation, diminished gaseous exchange
- Chronic hypercarbia (increased levels of carbon dioxide in blood due to diminished gaseous exchange)
- Hypoxemia
- Secondary bacterial infection (particularly *Streptococcus pneumoniae, Haemophilus influenzae*)
- As a sequence the condition may lead to pulmonary hypertension, respiratory failure and eventually cor pulmonale (i.e. right heart failure secondary to chronic pulmonary obstruction)
- Constituents in tobacco cause several changes in the morphology and function of respiratory system (Table 15.3):

TABLE 15.3: Tobacco product and its effects

Tobacco product	*Effects*
Tobacco smoke	Increase in number of goblet cells because of hyperplasia and metaplasia
Acrolein	Impaired ciliary and macrophage function
Nitrogen dioxide	Toxic damage to respiratory epithelium
Hydrogen cyanide	Functional impairment of respiratory enzymes that are required for respiratory metabolism
Carbon monoxide	Reduction in oxygen carrying capacity of red blood cells by combining with hemoglobin to form carboxy-hemoglobin
Polycyclic hydrocarbons	These are the known carcinogens

Clinical Features

- Productive cough, wheezing, shortness of breath, exertional dyspnea
- Reduced forced expiratory rate
- Liver enlargement due to congestion
- Ascitis and peripheral edema, pulmonary hypertension, cor pulmonale
- Chronic bronchitis patient shows characteristic presentation termed blue bloaters (patient appears blue and overweight).

Treatment

- There is no cure for chronic bronchitis
- Patients advised to stop smoking
- Expectorants (guaifenesin) prescribed in patients with excessive sputum production
- Bronchodilators (theophylline and selective beta-2 agonists) to relax smooth muscles of bronchioles
- Corticosteroids in refractory cases
- Antibiotics to treat the secondary lung infections
- Diuretics in patients with severe bronchitis and right-sided heart failure.

Oral manifestation and dental considerations

- Patients with habit of smoking may show tobacco-associated oral lesions and oral potentially malignant disorders (e.g. smokers melanosis, nicotina stomatitis, leukoplakia, erythroplakia, non-healing ulcer or malignancy)
- Patients with poor oral hygiene present with gingival and periodontal diseases
- Patient is seated in an upright position while peforming dental treatment to prevent breathing difficulties caused in supine position.

- Anticholinergics and antihistamines are avoided as they dry the respiratory mucosa and increase mucous thickness.
- Respiratory depressants such as barbiturates and narcotics should be avoided.
- Patients on long-term steroid therapy may require additional dosage to prevent adrenal suppression.

☛ *Emphysema (means air in tissues)*

Description: It is an obstructive lung disease that causes damage to the alveolar sac.

Etiopathogenesis

- Tobacco smoke and environmental pollutants are the major contributing factors for emphysema
- It can also be preceded by chronic bronchitis
- It may be due to hereditary deficiency of alpha-1 antitrypsin
- Smokers have increase number of neutrophils and macrophages in their alveoli
- Smoking stimulates release of elastase and enhances its activity in macrophages.
- Smoking inhibits alpha-1 antitrypsin.
- Tobacco smoke contains reactive oxygen species with inactivation of anti-proteases.
- This results in enlargement and dilatation of acini, collapse of terminal bronchioles and loss of elastic recoil, causing alveolar destruction and diminished gaseous exchange due to the collapsed alveoli, finally overinflated lung tissue and poorly oxygenated blood.

Clinical Features

- Barrel chest, dyspnea
- Patients are described as pink puffers (because they find difficulty in catching breath and their skin appears pink)
- Easy fatigability, exertional dyspnea, weight loss, non-productive cough, tachypnea, increased use of accessory respiratory muscles (i.e. intercostal and supraclavicular muscles)
- Expiratory wheeze, respiratory acidosis, hypoxemia, pulmonary hypertension, peripheral edema, cor pulmonale and congestive heart failure.

Diagnosis

- Diagnosed by clinical features, laboratory diagnosis and radiologic investigation
- Hyperinflation of lungs
- Increased retrosternal air space, flat diaphragm, lung parenchymal damage
- Decreased pO_2 and relatively normal pCO_2
- Biopsy confirms disease

Oral manifestations and dental considerations

- Tobacco-induced oral lesions as discussed in chronic bronchitis
- These patients have mouth breathing, results in xerostomia that results in increased incidence of dental caries, gingival and periodontal diseases and change in oral microflora.
- Avoid respiratory depressants, general anesthesia, bilateral inferior alveolar nerve block, anticholinergics and rubber dam placement.
- Position patient in upright position to improve patients ability to ventilate.

Occupational Lung Disorders

◈ Pneumoconiosis

Description

It is a chronic pulmonary disease caused due to occupational hazard, due to inhalation of mineral or organic dusts such as asbestos, coal dust and silica.

Pathogenesis

The alveolar macrophages engulf the foreign particles and expire, thereby releasing lysosomal enzymes that destroy lung parenchyme, that eventually leads to fibrosis.

Clinical Features

- Initially patient presents with non-productive cough, dyspnea and progress to productive cough and right-sided heart failure.
- **Silicosis:** Produced by inhalation of crystalline silica particles or silicon dioxide. It occurs due to exposure to mining,

quarrying, sandblasting, grinding and polishing ceramics.
- **Asbestosis:** Caused due to inhalation of asbestos fibers and dusts, the use of production of asbestos is in insulation, floor tile and friction and fire proofing materials.
- **Coal miners lung (black lung):** Caused due to long-term inhalation of coal dust.

Oral Manifestations and Dental Considerations

- Deposition of silica gritty particles in the oral cavity.
- Teeth abrasion
- A bite guard can be provided as preventive measure.

Other Diseases Affecting the Respiratory Tract

◈ Cystic Fibrosis

Description

- It is an inherited life-threatening disorder damaging lungs and digestive system, characterized by numerous mutations in gene that encodes the cystic fibrosis transmembrane conductance regulator.
- The body produces thick and sticky mucous that blocks the lungs and obstruct pancreas.

Clinical Features

- Affects young children.
- Pulmonary manifestation—cough, recurrent infections of lower respiratory tract, bronchospasm, tachypnea, clubbing and bronchiectasis
- Digestive malfunction—meconium ileus, fatty tools, the digestive problems result in malnutrition and affect growth.
- There is an increased risk of diabetes and osteoporosis.

Oral Health Manifestations and Considerations

- Patients have history of mouth breathing, change in morphology of face, increased incidence of dental caries, missing teeth, increased deposition of teeth, gingivitis and periodontal diseases.
- Patients advised meticulous oral hygiene.

Tuberculosis is discussed in infectious diseases.

FREQUENTLY ASKED QUESTIONS

1. Oral manifestations/dental considerations of respiratory disorders.
2. Describe sinusitis.

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Chapter 16

Gastrointestinal Diseases—Oral Manifestations and Dental Considerations

INTRODUCTION

The gastrointestinal (GI) system encompasses oral cavity, pharynx, esophagus, stomach, small and large intestine, rectum. In addition, liver, biliary system and pancreas play an important role in performing various physiologic functions. The oral health practitioners should be aware of oral manifestations and dental considerations in GI diseases.

Classification

1. **Oral-related GI disorders**
   - Eating disorder: Anorexia and bulimia
   - Xerostomia
   - Ptyalism
2. **Upper GI disease**
   - Gastroesophageal reflux disease (GERD)
   - Hiatal hernia
3. **Diseases of the lower GIT**
   - Disorders of stomach
   - Disorders of intestines
   - Inflammatory bowel disease
     - Crohn's disease
     - Ulcerative colitis
   - Peptic ulcer (hypersecretion disorder)
   - Antibiotic-induced diarrhea and pseudomembranous enterocolitis
4. **Disease of hepatobiliary system**
   - Jaundice
   - Hepatitis
   - Liver cirrhosis
   - Drug-induced hepatotoxicity
5. **GI syndromes**
   - Gardener's syndrome
   - Plummer-Vinson syndrome
   - Cowden's syndrome

Eating Disorders

A. **Anorexia:** It is a condition, in which individuals have extreme loss of appetite, probably because of fear of becoming fat. In spite of being underweight, individuals consume less food and are thin and malnourished.

B. **Bulimia:** Bulimia means OX-hunger. In this condition individuals eat abnormally. It occurs when one eats considerably large quantity of food (binge) over a short period of time, then induces oneself to vomit (purge); or uses excessively laxatives or diuretics to avoid weight gain. These individuals cannot resist eating, they engage in bingeing and purging at least twice a week for 3 months. They have excessive concern with the body shape and weight.

Clinical Features

Anorexia develops in young adolescence between 14–18 years of age and bulimia in early twenties. Both conditions are psychiatric disorders with physical complication.

Anorexic patients have no body fat, have protruding bones, bradycardia, leukopenia, and absence of menstruation (amenorrhea) among women.

Bulimic patients have hypokalemia and metabolic alkalosis due to vomiting and use of excessive laxatives.

Oral Manifestations and Dental Considerations

- Erosion of enamel on lingual surfaces of maxillary anteriors
- Mandibular incisors are usually spared by tongue
- Dentinal hypersensitivity due to erosion—prescription of desensitizing agents and restoring the teeth depending on the severity of the lesions
- Parotid gland enlargement because of starving
- Erythematous pharyngeal mucosa due to starving
- Psychological counselling and good nutritional food intake

Xerostomia and ptyalism are discussed in detail in salivary gland disorders.

UPPER GI DISEASES

1. Gastroesophageal Reflux Disease (GERD)

- It is the most common disease of the upper GIT
- It is the condition with regurgitation of gastric contents (chyme) from stomach into the esophagus.

Clinical Features

- In early onset, patients may be asymptomatic, as disease progresses endoscopic examination shows surface abnormalities.
- Heartburn, chest pain, esophageal ulcerations, esophagitis, stricture, dysphagia and dysplasia may be noted.
- *Barrett's esophagus:* It is a variant of GERD, wherein the squamous lining of esophagus is replaced with the columnar epithelium. These patients have reported to have an increase in incidence of adenocarcinoma.

Management

◈ Medical Management

- *Weight loss:* It will reduce the pressure difference between the abdomen and the thorax, thereby reduces reflux
- Cessation of smoking
- Reducing fatty meal, this reduces the gastric emptying time and speeds up the digestion process
- Frequent small meals
- Avoid sleeping immediately after meals
- Elevation of head on bed that will empty the esophagus and prevents the symptoms
- H2 blocker antagonists to reduce the heart burn and regurgitation
- Proton pump inhibitors heal erosive and ulcerative esophagus
- *Promotility drugs (Cisapride):* These drugs increase the lower esophageal sphincter that reduces the acid reflux, decrease heart burn at night.

◈ Surgical

- Indicated when all therapies in medical management fails
- Antireflux operations are performed to correct the functional and anatomical abnormalities of GERD.

Oral Manifestations and Dental Considerations

- Dysguesia, dental erosion/pulpitis, dentinal hypersensitivity, atrophy and erythematous oral mucosa due to chronic exposure of acid
- Dysguesia can be managed with mild baking soda mouth rinse
- Depending on severity of dental erosions—mild erosive cases can be treated with topical fluoride application, advanced erosive areas involving dentin can be restored, involving pulp can be endodontically treated.

- Individuals on H2 blockers (cimetidine) will experience toxic reactions to intravascular injections of lidocaine
- Cimetidine interacts with antifungal agent (ketoconazole) and prevents its absorption.
- H2 blockers in elderly individuals have shown CNS side effects such as confusion, delirium, and seizures.

2. Hiatal Hernia

- The hiatus is a narrow opening in the gastroesophageal junction, which permits esophagus through the diaphragm to the stomach.

Normal

- When the hiatus is weakened or enlarged due to various factors such as hereditary, obesity, exercising (weightlifting), or chronic straining while passing stools.
- The stomach herniates into the chest cavity through the enlarged or weakened hole resulting in hiatal hernia.

Types

1. *Sliding hiatal hernia:* The most common type, the gastroesophageal junction and superior portion of the stomach slide above the diaphragm.
2. *Rolling hiatal hernia:* The gastroesophageal junction is at normal location but the superior portion of the stomach herniates above the diaphragm.
3. *Complicated hiatal hernia:* Almost the entire stomach moves into the chest.

Clinical Features

- Infants with hiatal hernia regurgitate blood stained food and have difficulty in breathing and swallowing
- Adults have acid reflux into the esophagus, causes esophageal erosions, bleeding, and inflammation of esophageal lining producing scarring resulting in narrowing. This causes dysphagia, bloating, heartburn on bending forward or lying down
- The pain spreads to jaw and down to the arms similar to the angina attack

Diagnosis

Diagnosis is by barium meal, endoscopy.

Management

In Infants

The defect may be self-corrected, but precautionary measures such as head raised position while sleeping and administering of thicker consistency foods.

In Adults

A. **Conservative management**
- Avoid activity that increases abdominal pressure such as abdominal exercises, tight belts
- Sleeping in head elevated position, which will reduce the symptom
- H2 blockers reduce the production of gastric acids from the parietal cells
- Frequent small meals
- Light supper with nothing consumed 2–3 hours before bedtime
- Foods that increase the reflux of acids should be avoided that include alcohol, nicotine, caffeine, chocolate, fatty foods, peppermint, etc.

B. **Surgical management**
- Indicated only when medical management fails
- Laparoscopic surgical corrections can be made.

Oral Health Considerations

- It is similar to GERD
- If the patients are treated with anticholinergic medications that cause xerostomia, then prescribe artificial saliva, alcohol-free mouthwashes and advise increased fluid intake
- Tooth cavities as a sequelae of xerostomia can be restored

DISEASES OF LOWER GIT

1. Disorders of Stomach

Cells in stomach and its function:

Cell type in stomach	*Secretion*	*Function*
Parietal cell	• Hydrochloric acid • Intrinsic factor	• Digestion of food • Killing of swallowed bacteria • Required for absorption of vitamin B_{12}
Chief cells	Pepsinogen	Digestion of proteins
G cells	Gastrin	Potent stimulator of HCl, pepsin, casein
Mucous cells	Mucous	Coat and lubricate the stomach to propel the chyme

The disorders that affect the secretion or production of cells in the stomach impairs the physiological functions.

2. Peptic Ulcer Disease

◈ Gastric Ulcers

- It is the benign ulcerative condition of the epithelial lining of the stomach
- It can be a gastric ulcer in stomach and duodenal ulcer in duodenum

Pathogenesis

- Ulcers are due to imbalance in defense mechanism such as mucous production and HCl production, bicarbonate secretion and mucosal resistance.
- *Helicobacter pylori* (*H. pylori*) plays an important role in development of an ulcer
- *H. pylori* causes hyperacidity, gastritis and reduced mucosal resistance that lead to ulcer formation.
- Incidence of duodenal ulcers increases in cigarette smokers, patients with chronic renal disease and in alcoholics.

Clinical Features

- Burning epigastric pain that radiates to back especially during the empty stomach or 2–3 hours after a meal, and during middle of the night
- 3–8% of gastric ulcers represent malignant ulceration.

Management

- **Antacids:** H2 blockers and proton pump inhibitors can be prescribed.

◈ Duodenal Ulcers

Causes

- *H. pylori* infection, NSAIDs, stress, glucocorticoids, parathyroid disease, malignant carcinoid, cirrhosis, Zollinger- Ellison disease, polycythemia vera, and chronic lung disease.

Clinical Features

- Epigastric pain, burning and gnawing sensation associated with nausea and vomiting when the stomach is empty
- Blood loss in stool and vomit, may lead to iron deficiency anemia
- Patients with duodenal ulcer awaken at night and have intense urge to eat because indigestion of food rapidly provides relief
- Life-threatening complication such as hemorrhage, perforation and obstruction can occur.

◈ Zollinger-Ellison Syndrome

- Caused by gastrinoma of pancreas, causes multiple ulcers and diarrhea
- There is elevated levels of serum gastrin, and HCl.

Lab Diagnosis

- Anemia, leukocytosis, examination of stool, serum calcium test due to associated hyperparathyroidism.

Management

- Drugs that eradicate *H. pylori* (if the organism is evidenced)
- Antacids: H2 blockers, proton pump inhibitors
- Anticholinergic medication to reduce the production of acid from gastric mucosa.

Oral Health Considerations

- Oral manifestations of peptic ulcers are rare
- The manifestations may be due to anemia from GI bleeding or persistent regurgitation of gastric acid that leads to dental erosion
- Vascular malformations on the lip
- Avoid medications that exacerbate ulcerations such as aspirin and other NSAIDs
- Intake of antibiotics such as erythromycin and tetracycline may decrease their absorption.
- Xerostomic patients having denture should be advised denture adhesives and artificial saliva that aid in retention of denture
- Increased risk of dental caries due to hyposalivation
- Cimetidine and ranitidine prescribed in duodenal ulcers may be associated with thrombocytopenia and compete with antibiotics or antifungal medications.

3. Inflammatory Bowel Disease

As the name suggests it is the inflammation of large and small intestines.

It comprises

- Ulcerative colitis
- Crohn's disease

◈ Ulcerative Colitis

It is the ulceration affecting entire large intestine.

The etiology for the disease is not established, possible has bacterial, viral, immunologic or psychological role, or it could be due to autoimmune reaction with sensitization and destruction of the colonic mucosa.

Clinical Features

- Rectal bleeding
- Severe nocturnal diarrhea
- Erythema nodosum, i.e. red swollen nodules on thighs and legs
- Episcleritis, uveitis, corneal ulcers and retinitis cause pain and photophobia
- Liver disease and underlying anemia (hypochromic anemia) due to blood loss
- Electrolytic imbalance, hypoalbuminemia, low magnesium and potassium occur because of diarrhea.

Management

- Sulfasalazine is commonly used in ulcerative colitis
- Corticosteroids and corticotropin are used in patients who do not respond to sulfasalazine
- Other immunosuppressive medication such as azathioprine, cyclosporine and mercaptopurine can be used
- Surgical intervention when traditional medical therapy fails.

Oral Manifestations and Oral Health Considerations

- Delayed healing and increased risk of infection are sequelae of anemia
- Minor or major type aphthous ulcers
- **Pyoderma gangrenosum:** Occur as deep ulcer that may involve tonsillar pillar
- **Pyostomatitis vegetans:** Purulent inflammation of oral cavity characterized by deep tissue vegetations or proliferative lesions that may ulcerate and suppurates. These lesions are due to circulating immunocomplexes induced by antigens that are derived from gut lumen or damages colonic mucosa.
- **Hairy leukoplakia:** The presence of this lesion may be the marker of immunosuppression, the reason may be the use of immunosuppressive medication by these individuals.
- These patients are on regular glucocorticoids, consider the side effects of medication, such as hypertension,

hyperglycemia, osteoporosis, adrenal suppression, bone fracture. Careful seating of patients during dental treatment to avoid vertebral compression.
- Corticosteroids undergo metabolism in liver, liver function tests are required to elicit any changes in functions of liver that may affect the treatment.
- Because of impaired vitamin B_{12} absorption investigate for complete blood count
- Because of malabsorption of vitamin K, there may be defective synthesis of vitamin K dependent clotting factors (II, VII, IX, X), investigate for bleeding time, international normalized ratio.

◈ Crohn's Disease (Regional Enteritis)

- It is a chronic granulomatous disease of unknown origin and produces inflammation of small and large intestine
- Ileum is the most common site

Types

- *Non-perforating form:* The disease that tends to recur slowly
- *Perforating form:* The disease that tends to recur rapidly

Clinical Features

- It involves both genders, middle aged women are most commonly affected
- Disease shows familial tendency
- Diffuse ulceration of intestinal mucosa
- Hyperplasia of lymphoid tissue
- Fibrosis and muscular hypertrophy leading to constrictures
- Fever, abdominal pain accompanied with loose stools
- Reduced absorption of nutrients such as calcium, iron, folate, vitamin B_{12}, bile salts, fat, protein, etc.
- Patients have electrolytic imbalance, anemia, leukocytosis

Features that differentiate Crohn's disease from ulcerative colitis

Crohn's disease has following characteristics:
1. Involvement of small intestine
2. Rectum is spared
3. Appearance of fissures or sinus tract
4. Formation of sarcoid-like granuloma

Oral Manifestations

- Recurrent aphthous ulcerations
- Chronic stomatitis
- Anemia (pallor, glossitis, angular cheilitis)
- Lip swelling
- Pyostomatitis vegetans
- Cobblestone mucosal architecture
- Granulomatous changes of salivary glands, which is the hallmark of Crohn's disease
- Inflammation of salivary gland duct
- Oral epithelial tags and folds
- Gingivitis
- Candidiasis
- Lichenoid mucosal reactions
- Biopsy of ulcers shows granulomatous inflammations.

Oral Health Considerations

- Anti-inflammatory and sulfa medications used to manage Crohn's disease are associated with risk of lichenoid reaction
- Increased incidence of infections such as dental caries, bacterial and fungal infections
- Topical steroids can be administered for infections, inflammations or granulomatous lesions
- Any surgical intervention requires following lab investigations:
  - CBC, hematocrit values, hemoglobin level, platelet count, prothrombin time/INR/partial thromboplastin time and other liver function test and estimation of blood glucose level.

4. Antibiotic-induced Diarrhea and Psueodomembranous Enterocolitis

- Antibiotics-induced diarrhea occurs due to alteration in colonic microflora because of chronic use of antibiotics, which result in diarrhea, e.g. clindamycin, ampicillin, cephalosporins.
- Pseudomembranous enterocolitis is formation of thick mucosal exudate that

has appearance of membrane induced by antibiotics. *Clostridium difficile* that produces cytopathic toxins is involved in pathogenesis of pseudomembranous enterocolitis.

DISEASES OF HEPATOBILIARY SYSTEM

- Hepatobiliary system comprises liver, biliary tract and pancreas that aid in digestion
- Liver is the major organ that contributes for many catabolic and detoxifying actions.
- Following are the functions of liver:
  - Heme excretion
  - Store glycogen
  - On depletion of glycogen storage, liver gluconeogenesis form amino acids
  - Lipids are metabolized in the liver to form cholesterol
  - Synthesis of clotting factors I, II, V, VII, IX, X of which II, VII, IX, X are vitamin K dependent clotting factors
  - Metabolism of drugs by cytochrome P-450 occurs in hepatocyte
  - First pass metabolism of oral medication occurs in liver
  - Liver inactivates action of insulin, aldosterone, antidiuretic hormone, oestrogen and androgen.

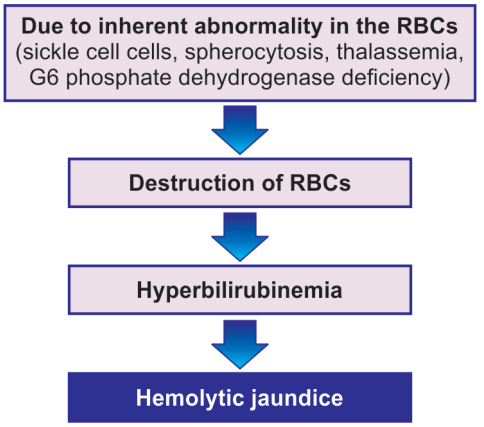
Liver dysfunction can cause multiple systemic diseases, one of which is jaundice that can lead to liver failure and cirrhosis.

Jaundice

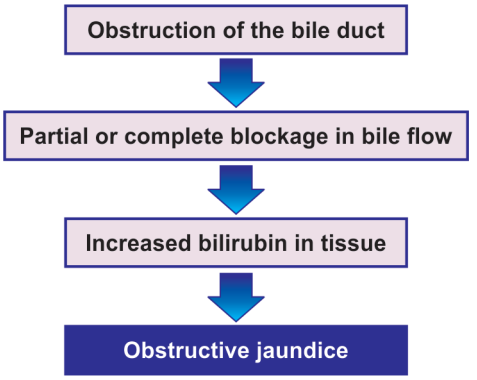
- It is accumulation and circulation of excess bilirubin in the tissue. There is yellowish discoloration of skin and mucous membrane and in sclera of the eye.
- Jaundice occur when total bilirubin level >3 mg/dl.

Type	*Description*
Hemolytic jaundice	Excessive production of bilirubin due to hemolysis of RBCs
Obstructive jaundice	Obstruction of biliary tree therefore prevention of excretion of bilirubin
Hepatocellular jaundice	Occurs due to liver parenchymal disease

◈ Hemolytic Jaundice



◈ Obstructive Jaundice (Cholestasis)



◈ Hepatocellular Jaundice

Caused by hepatitis and cirrhosis

Oral Manifestations

- Petechiae
- Ecchymosis
- Yellowish discoloration of mucosa
- Manifestations of anemia such as angular cheilitis, pallor, glossitis
- Sweet ketone breath (it is indicative of liver gluconeogenesis)

Oral Health Considerations

- Risk of bleeding due to defective synthesis of clotting factors and vitamin malabsorption
- Secondary infections due to anemia
- Investigate for liver function test

Hepatitis

It is the inflammation of hepatocytes in liver

Etiology: Physical, chemical, parasitic, bacterial, viral agents are the cause for hepatitis

◈ Viral Hepatitis

Hepatitis A, hepatits B, hepatitis non-A, non-B, hepatitis C, delta hepatitis, hepatitis E.

◈ Alcoholic Hepatitis

- It is a toxin-induced liver disease, that causes cirrhosis and fulminant hepatic failure
- This condition is caused by excessive use of alcohol, which causes direct cellular toxicity of acetaldehyde.

Oral Health Considerations

- Jaundice
- Intraoral petechiae and ecchymosis
- Gingival bleeding
- Manifestations of malnutrition such as vitamin deficiency and anemia (angular cheilitis, pallor, glossitis)
- Sweet ketone breath
- Elective dental treatment is deferred in patients who have ingested large amount of alcohol
- Investigate for liver function tests to provide necessary dental treatment.

Cirrhosis

- It is a condition characterized by fatty infiltration, necrosis, fibrosis that reduce hepatocytes, thus the metabolic, synthesis and excretory functions are impaired.

Etiology: Alcohol abuse, biliary obstruction, viral infection, toxins, congestive cardiac failure, hemochromatosis, immune mediated injury.

Oral manifestations: Poor oral hygiene, calculus, dental caries, periodontal disease, xerostomia, fungal infections, bilateral sialadenosis, precancerous lesions such as erythroplakia and ulcerations of oral mucosa, gingival and mucosal bleeding, anemia.

Oral health considerations

- Evaluate for bleeding disorders
- Investigate for liver function tests.
- Obtain CBC, PT<APTT, AST, aspartate transaminase (APT) and alanine amino-transferase (ALT)
- Hemorrhagic procedures should be deferred until physician consent
- Avoid general anesthesia halothane that potentiates liver damage
- Avoid hepatotoxic medication (aceta-minophen)

FREQUENTLY ASKED QUESTIONS

1. Discuss the oral manifestations and dental considerations of inflammatory bowel disease.
2. Oral manifestations and dental considerations of GI diseases.

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Chapter 17

Renal Diseases—Oral Manifestations and Dental Considerations

INTRODUCTION

Kidneys are the vital organs situated in the peritoneum that maintains internal homeostasis by regulating fluid electrolyte, acid–base balance and purifies blood by removing toxic substances. Nephrons are the functional unit of kidneys. Kidneys remove toxic and waste products from blood and excrete approximately 1.5 to 2.5 L of urine in a day.

Functions of Kidney

- **Regulatory function:** Acid–base and fluid electrolyte balance
- **Excretory function:** Removes metabolic waste products such as urea, creatinine, uric acids, excretion of urine, and removes drug metabolites from blood
- **Non-excretory/endocrine function:** Secretes renin (has an important role in regulation of BP), synthesis active form of vitamin D (promotes hydroxylation of 25 (OH) D to 1,25(OH)$_2$D, which is an active form) and erythropoietin (production of red blood cells).

Classification of Renal Diseases

1. **Based on onset**
   - Acute
   - Chronic
2. **Based on location of nephron destruction**
   - Acute
     - Pre-renal failure
     - Renal/intrinsic failure
     - Post-renal failure
   - Chronic
     - Pre-renal failure
     - Renal/intrinsic failure
     - Post-renal failure
3. **Based on disorders of hydrogen ion concentration and electrolytes**

Diagnosis in Renal Disease

1. **Serum chemistry:** Changes in internal body homeostasis are reflected in serum chemistry. Serum creatinine and blood urea nitrogen (BUN) are important markers of GFR.

Parameter	*Normal range*
GFR	100–150 ml
Creatinine clearance	85–125 ml/min
Serum creatinine	0.6–1.2 mg/dl
Blood urea nitrogen	8–18 mg/dl
Serum calcium	8.5–10.5 mg/dl
Serum phosphate	2.5–4.5 mg/dl
Serum potassium	3.8–5 mEq/l

2. **Urine analysis:** Urine analysis includes detection of protein (proteinuria), blood (hematuria) in urine, specific gravity

or osmolality of urine and microscopic examination. Proteinuria and hematuria are the important markers for kidney disease.

3. **Creatinine clearance test:** This test helps to determine whether the kidneys are functioning normally. Specifically, the creatinine clearance test gauges the rate at which a creatinine is "cleared" from the blood by the kidneys. It is done on urine sample collected for 24 hours.
4. **IV pyelography:** Radiologic examination of kidney with IV contrast medium injection, this test cannot be used for low GFR that prevents the excretion of dye.
5. **Renal ultrasonography:** It distinguishes solid tumors from fluid-filled cysts.
6. **CT and MRI:** The application of CT is limited for imaging in kidneys, but both imaging modalities are helpful in detection of retroperitoneal masses.
7. **Biopsy:** Nephrologists usually perform percutaneous needle biopsy guided by USG.

Renal Failure

Acute Renal Failure (ARF)

- Decline in kidney function over a period of days to weeks that leads to severe azotemia (abnormal accumulation of nitrogenous products in blood).
- It mainly occurs in hospital admitted patients due to medications, surgery, pregnancy related complications, and trauma can result in ARF.

The causes for ARF can be categorized into three categories as given in Table 17.1.

Chronic Renal Failure (CRF)

National Kidney Foundation—kidney disease has termed CRF as either of the following:

1. The presence of kidney damage for >3 months with structural and functional abnormalities of kidneys associated with or without reduction in GFR, which manifests as pathological abnormalities or other markers of kidney damage such as abnormalities in the composition of blood or urine.

TABLE 17.1: Causes for ARF

Condition	*Pre-renal failure*	*Renal/intrinsic*	*Post-renal failure*
Description	Compromised renal function without injury to kidney	Damage within kidneys	The conditions that obstruct the flow of urine at any level of urinary tract and subsequent reduction in glomerular filtration rate (GFR)
Cause	• Volume depletion • Cardiovascular diseases that result in decreased cardiac output • Changes in fluid volume distribution such as in burns and sepsis	1. Glomerular disease: Glomerulonephritis is immune mediated damage to kidneys 2. Vascular disease: Obstruction of renal artery by thrombus 3. Tubulointerstitial disease: It includes interstitial nephritis, acute tubular necrosis	Prostatic enlargement (could be benign or malignant neoplasm) Cervical malignancy
Clinical presentation	Azotemia	• Hypertension, proteinuria, hematuria • Red blood cells, sudden severe lower back pain, oliguria	Total anuria or polyuria

2. The GFR is <600 cc/min/1.73 m^2 for >3 months with or without signs of kidney damage

Clinical staging of chronic kidney disease

Stage	*GFR cc/min*	*Manifestation*
1	>90	Normal kidney function, may have proteinuria, hematuria
2	60–90	Reduced kidney function, may have proteinuria, hematuria
3	30–60	Anemia
4	15–30	Patient should be medically prepared for dialysis
5	<15	Long-term chronic dialysis

Etiology of CRF: The most common causes of CRF or end stage renal disease (ESRD)/uremic syndrome are (Table 17.2):

- Glomerulonephritis
- Nephrotic syndrome
- Pyelonephritis
- Hypertensive nephrosclerosis
- Connective tissue disorders
- Polycystic kidney disease
- Metabolic disorders
- Interstitial nephritis
- Obstructive uropathy

Clinical manifestations of CRF/uremic syndrome/ESRD: Renal disease affects various multi-organ systems with the following manifestations (Table 17.3):

TABLE 17.2: Causes of CRF

S. no	*Diseases that cause CRF*	*Characteristics*
1.	Glomerulo-nephritis (GN)	• GN is immunologic in origin • Often associated with infectious agents such as Streptococcus, Staphylococcus, Pneumococcus • Sudden in onset, patients have hypertension, proteinuria

2.	Nephrotic Syndrome	• It is a clinical state characterized by increased glomerular membrane permeability resulting in:
		  ◆ Proteinuria
		  ◆ Edema
		  ◆ Hypoalbuminemia
		  ◆ Hypercholestremia
		• Clinically patients present with edema of lower extremities and in periorbital region, lethargy, tiredness, muscle wastage
		• Hypertension, nitrogen imbalance, hypercoagulation, loss of proteins (albumin binding proteins, and immunoglobulins).
		• Urine may appear frothy
		• Muerke's lines: These are transverse white bands on fingernails in chronic hypoalbuminemia patients

3.	Pyelo-nephritis	• Caused by pyogenic infection in kidney with *E. coli* • Patients have generalized sepsis, bacterial endocarditis, and staphylococcal septicemia
4.	Hypertensive nephro-sclerosis	• Vascular or glomerulus lesion that causes hypertension without renal failure is referred to as hypertensive nephrosclerosis. • Hypertension is the leading cause of CRF—the heart; brain, eyes and kidneys are the target organs of hypertension.

Contd.

TABLE 17.2: Causes of CRF *(Contd.)*

S. no	*Diseases that cause CRF*	*Characteristics*
5.	Connective tissue disorders	✦ Systemic lupus erythematosis, rheumatic arthritis, progressive systemic sclerosis have shown clinical evidence of renal involvement. There may be progressive sclerosis of vasculature of kidney
6.	Polycystic renal disease	Is an autosomal dominant inheritance Associated with hematuria, abdominal pain, recurrent urinary tract infection, and hypertension.
7.	Metabolic disorders	Diabetes mellitus (DM), amyloidosis, gout primary hyperparathyroidism are the most common causes of CRF Diabetic nephropathy refers to various changes that affect the structure and function of kidneys in presence of DM. The disease progresses stagewise beginning with early functional changes, followed by structural changes, and progresses to nephropathy, advances to progressive renal failure and finally azotemia resulting in ESRD.
8.	Toxic nephropathy	The kidney is the route of excretion of many foreign substances, and medications when exposed to the nephrotoxic medications and chemicals, they damage kidney.

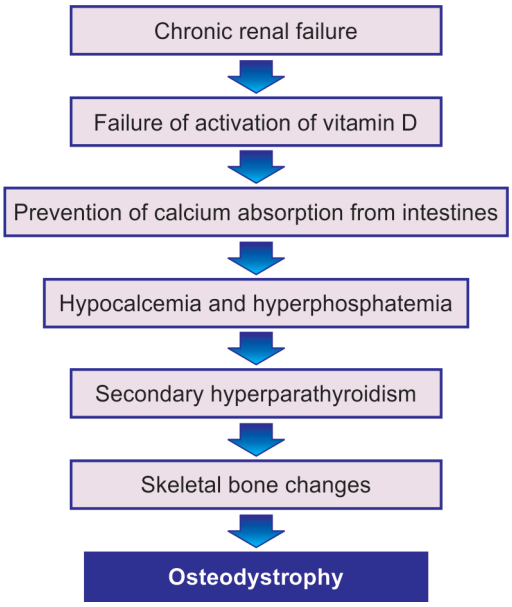
TABLE 17.3: Renal disease and its manifestations

System	*Manifestations*
Gastrointestinal	Nausea, vomiting, anorexia, ammoniacal taste and smell, stomatitis, parotitis, esophagitis, gastritis
Neuromuscular	Headache, peripheral neuropathy, paralysis, myoclonic jerks, seizures
Hematologic immunologic	Normocytic and normochromic anemia, coagulation defect, increased susceptibility to infection, decreased erythropoiesis
Cardiovascular	Hypertension, congestive heart failure, arrhythmias
Endocrine-metabolic	Renal osteodystrophy, secondary hyperparathyroidism, impaired growth and development
Dermatologic	Pallor, hyperpigmentation, ecchymosis, uremic frost, pruritis
Biochemical disturbance	Metabolic acidosis results in anorexia, lethargy, nausea, Kussmaul's breathing

Renal Osteodystrophy (Renal Rickets)

It is skeletal changes as a result of chronic kidney disease.

Pathogenesis



Radiographic Features

- Generalized loss of bone density
- Thinning of bony cortices
- Brown's tumor secondary to hyperparathyroidism

- Increased jaw size in dialysis patients due to widened marrow spaces
- Hypoplasia and hypocalcification of teeth
- Loss of lamina dura
- Osteoporosis circumscripta (well-defined radiolucency in skull)
- Ground glass appearance
- Central giant cell lesion
- Socket sclerosis (calcified healing in extraction socket)
- Metastatic calcifications of falx cerebri

Oral Manifestations

Dry mouth	Hyposalivation
Enlarged salivary glands	Retrograde parotitis
Uremic stomatitis	Uremic odor
Poor taste sensation, ammonia like taste and smell	Metallic taste
Enamel hypoplasia	Extrinsic and intrinsic stains on teeth
Malocclusion	Pale mucosa
Petechie and ecchymosis	Prolonged bleeding
Gingival bleeding	Candida infections
Dysesthesia of lips and tongue area as consequence of neuritis secondary to metabolic acidosis	Low caries rate, calculi formation
Peripheral giant cell lesion	

Uremic Stomatitis

- It is a rare lesion affecting oral cavity in undiagnosed CRF patients.
- It is sequelae of formation of ammonia due to hydrolysis of urea in saliva by the urease enzyme. The ammonium compounds cause chemical injury and irritation to mucosa. It occurs when concentration of urea exceeds 30 mmol/l.

Clinically there are two types of uremic stomatitis:

- **Type I:** Localized or generalized erythema of oral mucosa with thick pseudomembranous exudate, which does not leave ulcerated base on its removal.
- **Type II:** Leaves ulceration on pseudomembrane removal.

Both types are associated with pain, halitosis, xerostomia, gingival bleeding, dysgeusia, secondary candida infection, and anemia due to underlying kidney disease.

Management of CRF

Management of CRF can be divided in two categories:

- Conservative therapy
- Renal replacement therapy

Conservative Therapy

- **Regulation of dietary proteins:** Patients are restricted for protein intake
- Limiting phosphate containing foods to prevent hyperphosphatemia
- Maintain blood pressure
- Maintain adequate hemoglobin level by substituting erythropoietin stimulating factor
- Cessation of smoking
- **Administering statins:** Lipid lowering medications
- Access for dialysis when blood creatinine level increases (> 4 mg/dl or GFR- <20 ml/min)

Renal Replacement Therapy

- **Dialysis:** It removes the nitrogenous and toxic products from blood by means of a hemodialyzer system (artificial kidney) in end stage renal disease when GFR is <20 ml/min.
- The two methods of dialysis are:
  - *Hemodialysis:* Vascular access in arms or legs is used for hemodialysis, performed 3 times per week
  - *Peritoneal dialysis:* Access to the body is achieved through catheter placed in peritoneal cavity of the abdomen, performed every 8–12 hours, 5 to 7 days a week.
- **Kidney transplantation:** It indicated for irreversible kidney damage. Patients are usually on immunosuppressive medication, hence more prone for secondary infections and exposed to the side effects of medications.

Dental Considerations

Oral health management in patients with kidney disease can be considered in two groups:

- In patients with acute renal failure
- In patients with chronic renal failure/end stage renal disease

In patients with acute renal failure:

- Elective dental care in individuals with ARF is deferred as individuals have accumulated toxic products.

In patients with chronic renal failure

- Individuals with CRF are unable to perform the normal kidney functions, therefore, oral health practitioners should be aware of various complications during dental treatment
- Excessive bleeding and anemia should be suspected in individuals with CRF
  - Local hemostatic agent such as DDAVP (1-Deamino-8-D arginine vasopressin) should be considered to stop bleeding, which is effective for shorter duration
  - Longer hemostasis can be attained with DDAVP conjugated with estrogen
  - Tranexamic acid (an antifibrinolytic agent) can be used to control post-operative bleeding
  - Local hemostatic aids such as microfibrillar collagen and oxidized regenerated cellulose can be used
- Obtain platelet count and complete blood count to manage bleeding and assess anemic conditions
- Patient undergoing dialysis will be heparinized, therefore, elective dental and oral surgical procedures should be scheduled on non-dialysis days, as this is the time where blood is free of toxins.
- Avoid tying cuff to the arm of vascular access for dialysis to measure blood pressure, avoid both intramuscular and intravenous injections to the arm; do not use the access site as an injection site
- Avoid longer sitting in patients with access site in the leg
- Patients with CRF are more prone for infections; therefore, meticulous oral hygiene, maintenance of good oral hygiene, use of antifungal and antimicrobial oral rinse may reduce dental infections.
- Prophylactic antibiotic regimen can be administered as these individuals are more prone for bacterial endocarditis.
- Hemodialysis patients receive blood transfusion, these patients are more prone for blood borne diseases such as hepatitis B, HIV and even tuberculosis
- Avoid excessive stress to prevent elevation of blood pressure, as these individuals are known hypertensive
- Avoid nephrotoxic medications such as phenacetin, ketorolac, aspirin, NSAIDs, tetracycline, carbenicillin, cephalosporins, aminoglycosides, steroids, etc. Instead alternative medications such as acetaminophen, barbiturates, penicillin, and narcotics can be used with caution.

FREQUENTLY ASKED QUESTIONS

1. Oral manifestations/dental considerations of renal diseases.

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Chapter 18

Diabetes Mellitus and Endocrine Disorders—Oral Manifestations and Dental Considerations

INTRODUCTION

Endocrine system is the collection of various glands that produce hormones, which are released directly into the blood stream. The hormones are specific chemical messengers as they transfer information from one group of cells to another, or act on specific tissue or organ. The hormones are proteins, polypeptides, steroids or derivatives of amino acids. These hormones play a key role in metabolism and regulation of all physiologic functions of the body. The overactivity of hormones is prevented by negative feedback mechanism.The various endocrine glands in our body are pituitary, thyroid, parathyroid, thymus, pancreas, adrenal, pineal, ovaries and testes.

TABLE 18.1: Terminologies with description

Terminology	*Description*
Endocrine glands	These are ductless glands that release their secretion directly into blood that act on target cells located at distant sites
Exocrine glands	These glands have ducts that secrete on epithelial surface
Neuro-endocrine	Hormones secreted by neurons into circulation that act on distant sites
Paracrine	Hormones secreted by cells into extracellular fluid that affect neighboring/ different cells
Autocrine	Hormones secreted by cells into extracellular fluid that affect same cells

Endocrine Glands, Hormones and Functions (Table 18.2)

Endocrine disorders can be due to

- Hypofunction (under production of hormone)
- Hyperfunction (excessive production of hormones)
- Hormone resistance (target organs are resistant to the hormonal effects in spite of optimal production of hormones)

Diabetes Mellitus (DM)

DM is a chronic metabolic or genetic disorder characterized by relative or absolute lack of insulin that results in elevated glucose levels and produces disturbances in carbohydrate, lipid and protein metabolism.

TABLE 18.2: Endocrine glands, hormones and functions

Endocrine glands	*Hormone secreted*	*Major function*
Hypothalamus	Thyrotropin-releasing hormone (TRH)	Stimulates secretion of TSH and prolactin
	Corticotropin-releasing hormone (CRH)	Release of ACTH
	Growth hormone–releasing hormone (GHRH)	Causes release of growth hormone peptide
	Growth hormone inhibitory hormone (GHIH) (somatostatin)	Inhibits release of growth hormone peptide
	Gonadotropin-releasing hormone (GnRH)	Causes release of luteinizing hormone and follicle stimulating hormone
	Dopamine or prolactin-inhibiting factor (PIF)	Inhibits release of prolactin
Pituitary gland		
Anterior lobe hormones (adeno-hypophysis)	Adrenocorticotropic hormone (ACTH)	Secretion of cortisol Regulation of androgen production
	Thyroid stimulating hormone (TSH)	T3 and T4 are associated with metabolism of all parts of the body (carbohydrate and protein metabolism, synthesis and degradation of triglycerides and cholesterol) Stimulate contraction of heart and heart rate Maturation of central nervous system
	Prolactin	Regulates lactation
	Luteinizing hormone (LH)	Ovulation in female Estrogen and progesterone synthesis in ovaries Testosterone formation in male
	Follicle stimulating hormone (FSH)	Development of ovaries Maturation of testes
	Growth hormone (GH)	Skeletal development, growth and protein synthesis
	Melanocyte stimulating hormone	Melanin pigmentation
	Beta-endorphin	Endogenous opiates released after exposure to painful stimulus
Posterior lobe hormones (Neurohypophysis)	Antidiuretic hormone (ADH)/ Vasopressin	Regulates plasma osmolality Conserves water by reabsorption of water by kidneys Decreases urinary output by acting on distal renal tubule Causes vasoconstriction and increases blood pressure
	Oxytocin	Stimulates the contraction of the uterus during pregnancy Promote milk secretion and ejection from the lactating breast

Contd.

TABLE 18.2: Endocrine glands, hormones and functions (*Contd.*)

Endocrine glands	*Hormone secreted*	*Major function*
Thyroid gland	▪ Thyroxine (T4) and triiodothyronine (T3) ▪ Calcitonin	▪ Increases body metabolic rate ▪ Increases bone calcium absorption and reduces extracellular calcium levels
Parathyroid gland	▪ Parathyroid hormone (PTH)	▪ Regulates serum calcium levels by absorbing calcium from gut, kidneys and release of calcium from bones
Adrenal cortex	▪ Cortisol ▪ Aldosterone	▪ Controls various metabolic functions involving proteins, carbohydrates and fat ▪ Anti-inflammatory effects ▪ Increases sodium absorption, potassium secretion, hydrogen ion secretion
Adrenal medulla	▪ Epinephrine and nor-epinephrine	▪ Sympathetic stimulation
Pancreas	▪ Insulin from β cells ▪ Glucagon from α cells	▪ Controls carbohydrate metabolism by promoting entry of glucose into cells and reduces blood glucose levels ▪ Increases blood sugar level by promoting synthesis and release of glucose from liver
Testes	▪ Testosterone	▪ Develops male reproductive system and secondary male sexual characteristics
Ovaries	▪ Estrogens ▪ Progesterone	▪ Promotes development of females reproductive system, female breasts, secondary sexual characteristics of female ▪ Promotes uterine secretion
Pineal gland	▪ Melatonin	▪ Regulates biological rhythm that controls sleep and wake cycle.
Thymus	▪ Thymosin	▪ Development of immune system
Kidney	▪ Renin ▪ 1,25- dihydroxy-cholecalciferol ▪ Erythropoietin	▪ Converts angiotensinogen to angiotensin I ▪ Increases intestinal absorption of calcium and bone mineralization ▪ Increases erythrocyte production
Heart	▪ Atrial natriuretic peptide (ANP)	▪ Reduces blood pressure and increases sodium excretion from kidneys
Stomach	▪ Gastrin	▪ Secretion of hydrochloric acid from parietal cells
Small intestine	▪ Secretin ▪ Cholecystokinin (CCK)	▪ Stimulates pancreatic acinar cells to release of bicarbonate and water ▪ Stimulates gallbladder cells and release of pancreatic enzymes release
Adipocytes	▪ Leptin	▪ Inhibits appetite and promotes thermogenesis

Classification

I. Formerly DM was classified based on:
   a. Age at onset
   b. Type of therapy
II. According to American Diabetes Association (Table 18.3).

Blood Glucose Regulation

Flowchart 18.1 provides blood glucose regulation.

Pathophysiology

Type 1 Diabetes Mellitus (Fig. 18.2)

- In response to stress, cortisol secretion is increased in Type 1 diabetic patients that cause breakdown of proteins and loss of nitrogen in the urine.
- Fat breakdown into fatty acids and glycerol. The glycerol is converted to glucose for cellular use.
- Fatty acids are further reduced to ketone bodies (acetone and beta hydroxyl butyric acid), its accumulation in blood results diabetic ketoacidosis.
- Ultimately results in coma and death

Type 2 Diabetes Mellitus

- Most common type (85%)
- Etiology is multifactorial with environmental and lifestyle factors (obesity) superimposed on genetic predilection
- Type 2 DM is a result of:
  - Peripheral resistance of insulin
  - Increased production of glucose by liver
  - Impaired insulin secretion from beta cells of pancreas
- In response to high glucose levels, there is increased secretion of insulin (hyperinsulinemia) from pancreas
- Unlike the patients with Type 1, Type 2 DM patients are generally resistant to diabetic ketoacidosis because of sufficient production of pancreatic insulin, which prevents ketone formation.
- Ketoacidosis in Type 2 DM is usually due to physiologic stress.

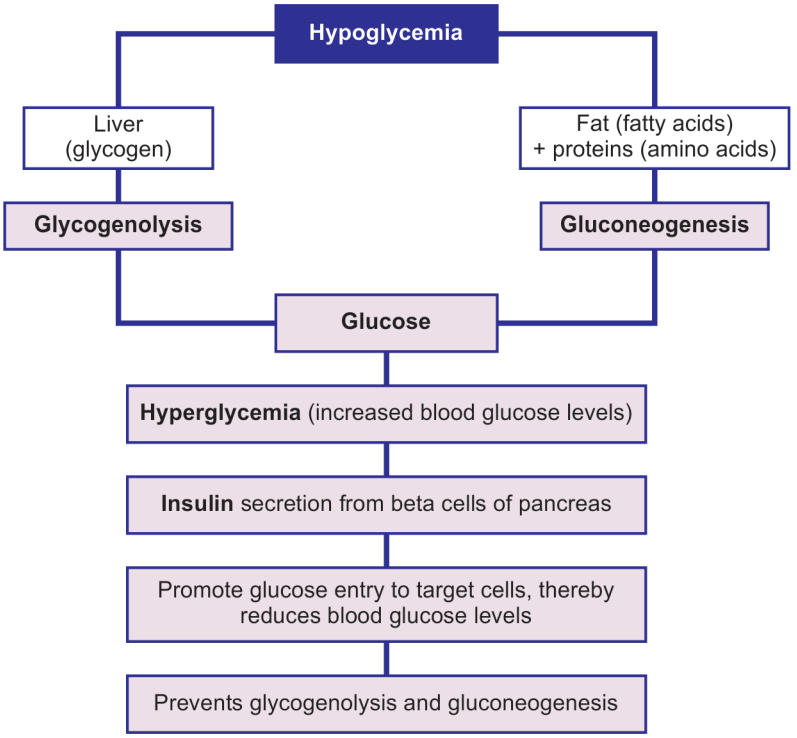
Gestational DM

- DM occur during pregnancy is gestational DM
- Pregnant women develop either Type 1 or 2 DM

TABLE 18.3: Classification of diabetes mellitus according to American Diabetes Association

Type	*Former nomenclature*	*Etiology*
Type 1	• Juvenile diabetes • Insulin dependent diabetes mellitus (IDDM) • Type I	• Autoimmune destruction of beta cells • Immune mediated • Idiopathic cause
Type 2	• Adult onset diabetes • Non-insulin dependent diabetes mellitus (NIDDM)	• Insulin resistance in peripheral tissue • Relative insulin deficiency
Other specific types of DM	• Genetic defects of beta cell function • Genetic defects in insulin action • Disease of exocrine pancrease • Endocrinopathies such as hyperthyroidism • Drugs or chemical induced • Exogenous steroids • Infections • Chronic alcohol intake • Immune mediated diabetes • Genetic syndromes (Down's syndrome, Klinefelter syndrome, etc)	
Gestational diabetes	• Glucose intolerance amongst pregnant women	

Flowchart 18.1: Blood glucose regulation



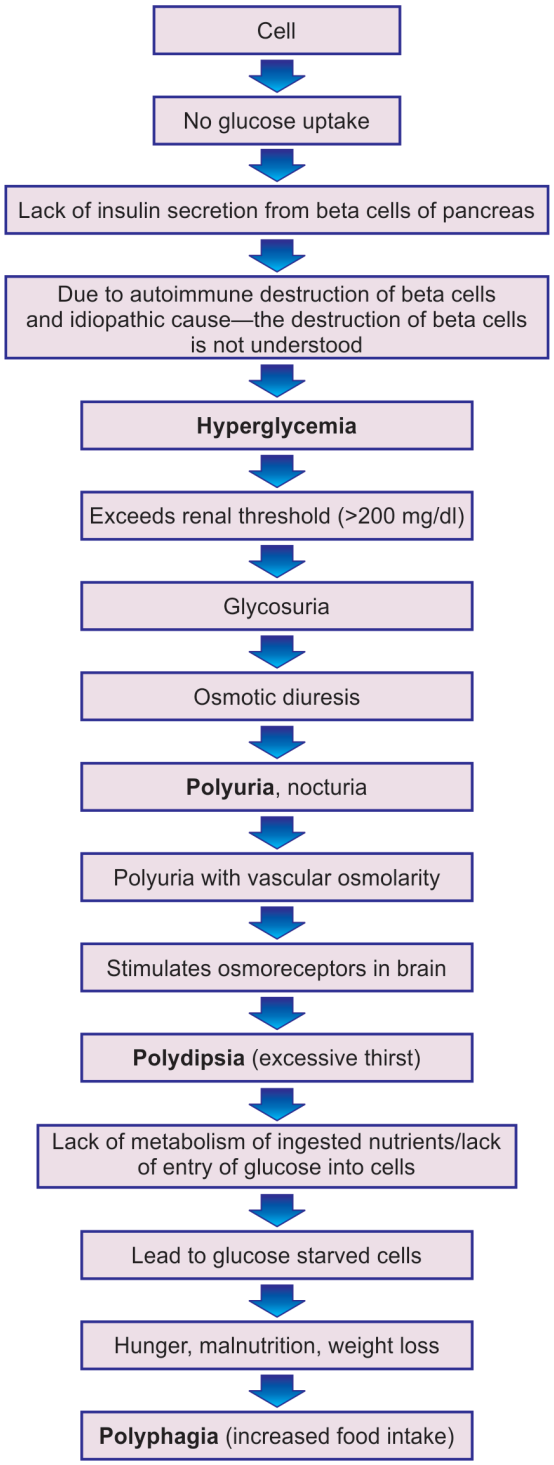
- It is usually associated with increased insulin resistance
- It is seen in older women, overweight women, women of minority ethnic group
- Hormones that increase blood sugar levels—glucagon, growth hormone, epinephrine, thyroid hormone, and corticosteroids. Only hormone that reduces blood glucose levels is insulin.

General characteristics of Type 1 and Type 2 DM are shown in Table 18.4.

TABLE 18.4: General characteristics of Type 1 and Type 2 DM

Characteristics	*Type 1*	*Type 2*
Incidence	5%	85%
Clinical	Abrupt onset	Gradual in onset
Age	Less than 20 years of age	More than 40 years of age
Weight	Thin/loss of weight	Obese
Endogenous insulin	Absent	Low, normal, or high levels
Islet cell antibodies	Present	Absent
Ketoacidosis	Common	Less common
Genetic susceptibility	HLA-D linked	No HLA association
Pathogenesis	Autoimmunity/immune mediated destruction of pancreatic beta cells	Insulin resistance by peripheral tissues

Flowchart 18.2: Type 1 diabetes mellitus



Clinical Features

TABLE 18.5: Clinical features of type 1 DM and type 2 DM

Type 1 DM	*Type 2 DM*
Polydipsia	Visual changes
Polyuria	Weight loss/gain
Polyphagia	Postural hypotension
Weight loss	Nocturnal urination
Visual impairment	Loss of sensation
Bed wetting	Paresthesia
Thirst/dry mouth	Pruritis
Headache	Impotence
Irritability	
Ketoacidosis	
Chronic skin infections	
Periodontal diseases	

Oral Manifestations

TABLE 18.6

Oral dysesthesia	Dental caries, increased dental plaque, gingivitis, periodontitis, periodontal abscess
Burning mouth	Increased glucose level in gingival crevicular fluid
Delayed wound healing	Sialadenitis (especially of parotid gland)
Increased susceptibility for infection	Neuropathy
Candida infection (acute pseudomembranous candidiasis of tongue, buccal mucosa and gingiva)	Antral mucormycosis is a serious complication amongst immunocompromized individuals with diabetes.
Xerostomia, antidiabetic medication induced salivary hypofunction	Dental caries, increased dental plaque, gingivitis, periodontitis, periodontal abscess
Mucosal ulcerations	Increased glucose level in gingival crevicular fluid
Sialadenitis (especially of parotid gland)	

Diagnosis (Table 18.7)

- Glycosylated hemoglobin assay will determine blood glucose status over 30–90 days, there are two different glycosylated hemoglobin A1 (HbA1) test and hemoglobin A1c (HbA1c).

Normal HbA1 value	8%
Normal HbA1c value	6–6.5%
Glycosylated hemoglobin level HbA1c	Clinical interpretation
4–6%	Normal
Less than 7.5%	Good diabetes control
7–9%	Moderate diabetes control
>9%	Poor diabetes control

- Glycosylated hemoglobin assay is used to monitor glycemic control in patients already diagnosed as having diabetes.
- HbA1c value of more than 8% suggests change in management protocol
- *Fructosamine test* is used to determine long-term glucose control analysis. The normal range is 2–2.8 mmol/1
- *Glucometers* are self-screening tools regularly used at home and even used as chair side investigation for measurement of blood glucose levels.

Complications

DM affects multiple organ systems affecting micro and macro vasculature (Table 18.8).

Management

- The overall goal of medical management is prevention of diabetic complications and achieving blood glucose levels

TABLE 18.8

Organ involved	*Associated complication*
Cardio-vascular system	• Atherosclerotic plaque in major and minor vessels leading to peripheral vascular disease • Coronary artery disease • Cerebrovascular disease • Gangrenous foot • Ischemic ulcers
Kidneys	• Nephropathy • Renal failure
Nervous system	• Peripheral neuropathy • Cranial neuropathy • Changes in cardiac rate, rhythm, dysfunction • Postural hypotension • Gastrointestinal neuropathy • Impotence
Skin and oral mucosa	• Unusual infections and delayed wound healing
Eyes	• Retinopathy, cataracts, blindness
Teeth and surrounding structures	• Gingivitis and periodontal diseases

- Proper diet, lifestyle modification, weight reduction, prevention of smoking and alcoholism and adequate exercise are important in management of DM.

Oral Hypoglycemic Agents

Medication	*Generic name*
Sulfonylureas	
First generation	Chlorpropamide Tolbutamide Tolazamide Acetohexamide

Contd.

TABLE 18.7: Diagnostic criteria for diabetes mellitus

	Normal	*Impaired fasting glucose*	*Diabetes mellitus*
Fasting glucose	<110 mg/dl	110–126 mg/dl	≥126 mg/dl
2 hours post-prandial plasma glucose	<140 mg/dl	140–200 mg/dl	≥200 mg/dl
Oral glucose tolerance test			Plasma glucose at 2 hours ≥200 mg/dl

Medication	*Generic name*
Second generation	Glyburide Glipizide Glimepiride
Biguanides	Metformin
Thiazolidinediones	Rosiglitazone Pioglitazone
Alpha-glucosidase inhibitors	Acarbose
Meglitinide	Repaglinide Nateglinide

Insulin Preparations

Insulin type	*Time of onset (hour)*	*Duration (hour)*
Fast-acting insulins		
• Lispro	15 min	<5
• Insulin injection (regular)	30–60 min	6–8
• Prompt insulin zinc suspension	1–2	12–16
Intermediate-acting insulins		
• Isophane insulin suspension	1–2	18–28
• Insulin zinc suspension	1–3	18–28
Long-acting insulin		
• Protamine zinc insulin suspension	4–8	36
• Extended insulin zinc suspension	4–8	20–36

Dental Management

Dental management of patients can be performed under three categories:

A. Diagnosis of unsuspected diabetes
B. Management of oral condition in diabetic patients
C. Managing dental emergencies in diabetic patients

A. **Diagnosis of unsuspected diabetes**
- Recognize signs and symptoms of diabetes as mentioned earlier
- Elicit proper medical history, concomitant systemic disease, drug history
- Use of glucometer as a chair side screening tool to assess blood glucose levels

B. **Management of oral condition in diabetic patients**
- Monitor blood glucose level with glucometer in dental office
- Antibiotic prophylaxis is mandatory for patients with high HbA1c level (>11–12%)
- Carbohydrates (candies, table sugar, juice or soda) should be kept readily available to prevent hypoglycemic event
- Determine the type of diabetes, treatment, level of control and presence of diabetes-associated complications (e.g. hypertension, cardiovascular diseases, renal insufficiency require BP monitoring and modification of anticoagulant drugs such as aspirin, NSAIDs).
- Obtain medical consultation prior any dental procedure if blood glucose levels is below 60 mg/dl
- Schedule dental appointments either before or after periods of insulin activity, this reduces the risk of hypoglycemia
- Ensure patient has consumed regular meal before and after periods of insulin activity, this reduces the risk of hypoglycemia.
- Ensure adequate pain control and stress reduction as this may cause endogenous production of epinephrine and cortisol secretion, epinephrine is not contraindicated in these individuals as this will provide adequate dental anesthesia
- Candidiasis is the most prevalent oral infection in DM patients, sugar-free topical antifungal agents are advised for 7–10 days, if treatment is unsuccessful, then switch to systemic antifungal agents.
- Avoid nephrotoxic antiviral medications such as acyclovir, famicyclovir, valacyclovir in patients with renal insufficiency having herpes simplex viral infection.

- Burning mouth in diabetic individuals can be managed by amitriptyline.
- Well-controlled DM patient may not require antibiotic prophylaxis during surgical procedures, whereas prophylactic antibiotics to be considered in poorly controlled DM.
- Corticosteroids used for treating various oral lesions should be used cautiously with patient's physician consultation especially with systemic steroids, which require dose modifications of DM drugs.

C. **Managing dental emergencies in diabetic patients:** Diabetic emergency in dental office may be
- Hypoglycemic (most common)
- Hyperglycemic (less likely to occur in dental office)

Management of hypoglycemia in dental office
- Recognize the signs and symptoms of hypoglycemia, this includes:
  - Confusion, irritability, sweating, tremor, anxiety, dizziness, tingling or numbness, tachycardia, severe hypoglycemia result in seizure or loss of consciousness
- Monitor blood glucose level with a glucometer
- If glucometers are unavailable, the condition should be treated as a hypoglycemic episode

Management of hyperglycemia in dental office
- The symptoms are similar to hypoglycemia
- Monitor blood glucose levels with glucometer
- If glucometer is unavailable, treat the episode as a hypoglycemic event as individuals are more prone for severe adverse effects of hypoglycemia and manage as stated earlier, even in doubt a little sugar may not be detrimental even if the patient is hyperglycemic.
- Opening airway, administering oxygen, monitor the vital signs and transport patients to hospital for further medical management.

TABLE 18.9: Management of hypoglycemia in the dental office

Patient condition	*Management*
Conscious patient and able to take food by mouth	• Give 15 g oral carbohydrate • 125–175 ml fruit juice or soda • 3–4 tablespoon of sugar • Hard candy
Patient is unable to consume food by mouth and intravenous line is available	• Give 50% dextrose solution or • 1 mg glucagon
Patient is neither able to take food by mouth nor intravenous line available	• Give 1 mg glucagon subcutaneously or intramuscularly at almost any body site

Pituitary Gland Disorders

Hypersecretion of growth hormone (GH)	Gigantism	Excessive production of growth hormone occurs before epiphyseal closure
	Acromegaly	Excessive production of growth hormone occurs after epiphyseal closure
Hyposecretion of GH	Dwarfism	

Gigantism and Acromegaly

GH affects the entire body that results in enhanced growth of connective tissue, cartilage and bone. The new growth enlarges craniofacial skeleton, increased metabolic effects cause increased protein synthesis, lipolysis, gluconeogenesis, glycogenolysis.

Etiology

Pituitary adenomas

Clinical Features

- Well-proportionate individual who is usually tall, but physically weak

- The liver, spleen, kidneys and other internal organs are enlarged
- Diabetes mellitus, hypertension, cardiomegaly, congestive heart failure, abnormal electrolyte filtration, osteoporosis, visual disturbances are associated systemic diseases
- Enlargement of nose and frontal bossing
- Soft tissue edema leads to increase in shoe, hat, glove and ring sizes
- Headache, muscle pain, muscle weakness
- Coarsening of skin as the subcutaneous tissues increase in size

Oral Manifestations

- Thick lips, macrocephaly, macrognathia, disproportionate mandibular growth with prognathic mandible, generalized spacing, anterior open bite, malocclusion, tooth migration
- Macroglossia, hypertrophy of pharyngeal and laryngeal tissues producing hoarseness in voice, stridor, dyspnea, patient susceptible for sleep apnea.

Radiographic Features

- Enlarged sella turcica
- Enlarged paranasal sinuses
- Widened carpel joint spaces
- Thickened cranium with exaggerated muscle and ridge attachments
- Enlargement of the mandible, excessive condylar growth and height of ascending ramus
- Hypercementosis
- Enlarged pulp chambers

Dental Management

- Patients with hyperpituitarism may have underlying systemic disease (hypertension, cardiomegaly, heart failure, insulin resistance, diabetes mellitus Type 2, hepatomegaly, goiter), dentist should be aware of underlying systemic disease
- General practitioners should be aware of complications and dental treatment should be performed with physician consultation.

Dwarfism (Hypopituitarism)

Hypofunction of pituitary gland to secrete GH results in dwarfism.

Etiology

Craniopharyngioma, trauma, infarction, infection, radiotherapy and idiopathic disorders.

Clinical Features

- Large head, short muscular arms
- Low levels of ACTH lead to hypoadrenalism with complaints of weakness and signs of hypertension
- Lack of secretion of thyroid results in secondary hypothyroidism that produces weakness, hypotension, cold intolerance, mental illness, bradycardia, delayed sexual development, amenorrhea, hypogonadism.
- Reduced mandibular size
- Microdontia
- Small dental arch that contributes to crowding and malocclusion
- Hypofunction of salivary glands results in salivary hypofunction, that contributes to increased oral infection.

Radiographic Features

- Delayed exfoliation of primary teeth
- Delayed eruption of permanent teeth
- Absent third molars
- Small mandible which results in crowding and malocclusion

Dental Consideration

- Fluoride treatment for early management of dental caries
- Early orthodontic evaluation to correct malocclusion
- Hypopituitarism with hypoadrenalism require supplemental corticosteroids.

Disorders of Posterior Pituitary (ADH)

Disorder	*Description*	*Signs and symptoms*
Diabetes insipidus	Decreased production of ADH	▪ Kidneys are unable to retain water ▪ Symptoms include polyuria (>3 L/d), polydipsia, hypernatremia ▪ Water deprivation test is used for diagnosis
Syndrome of inappropriate ADH (SIADH)	Excessive production of ADH	▪ Hyponatremia, altered mental status that lead to seizures and death if undetected, stroke, infection, trauma and hemorrhage

Adrenal Gland Disorders—Cushing's Syndrome (Hyperadrenocortism)

Cushing's syndrome is caused by excessive production of cortisol by adrenal cortex.

Clinical Features

- Fluid retention, hypertension
- Glycosuria, hyperglycemia, increased tendency for diabetes
- Hypokalemia, hypernatremia
- Central obesity, moon face, buffalo hump, purple striae over the abdomen
- Skeletal muscle weakness, thin skin, thin limbs and fingers
- Osteoporosis, back pain
- Hirsutism, virilism
- Thromboembolism, amenorrhea
- Psychological disturbances.

Oral Manifestations

- Enlarged and swollen gingiva that bleeds readily
- More prone for bacterial and fungal infections such as periodontal and candida infections.

Dental Considerations

- Individuals on long-term use of glucocorticoids have tendency to bleed and bruise easily
- Impaired wound healing and delayed scar formation
- Individuals are more prone for infection as they are immunocompromised, therefore, these individuals should be on prophylactic antibiotics
- Individuals are more prone for candida infection as oral microflora is altered.

Addison's Disease (Adrenal insufficiency/ Hypoadrenocorticism)

Glucocorticoids and mineralocorticoids secretion is reduced due to hypofunction of adrenal glands.

Clinical Features

- Muscle weakness, lethargy and fatigue
- Nausea, vomiting, loss of appetite and weight
- Hypoglycemia, dehydration and postural dizziness
- Hypotension, cardiac arrhythmias and cardiovascular collapse from electrolyte imbalance
- Irregular menstrual cycle amongst women
- Loss of body hair because of decreased androgens
- The feedback loop from adrenal gland to pituitary gland fails in response to decreased production of cortisol and increased secretion of ACTH in blood, this in turn stimulates melanocytic stimulating hormone, which causes increased melanin pigmentation of skin and mucosa.

Oral Manifestations and Dental Considerations

- Diffuse melanin pigmentation involving buccal mucosa, tongue and gingiva
- Acute adrenal insufficiency as a sequela of steroid deficiency causes increased risk of infection and stress induced complication

- There is significant risk amongst individuals who regularly take steroids for 2 weeks continuously, individuals are at moderate risk of adrenal suppression who receive steroid on alternate days
- Patients on topical steroids have found no significant risk for adrenal suppression.
- The individuals with adrenal suppression have reduced ability to withstand stress of dental treatment and thus requires increased steroid dosage prior dental treatment for extensive surgical procedure
- These individuals should be managed with reduced stress with short morning appointments, use of anxiolytic agents such as nitrous oxide, oxygen, postponement of extensive procedure and deferral of oral surgical procedure.
- In case of dental emergency in patients with adrenal insufficiency should be administered 100 mg hydrocortisone intramuscularly prior the dental procedure. The following day, twice the normal equivalent dose should be prescribed if pain or infection persists. Dose is tapered by halving the dose daily once for next 5 days.

Disorder of Adrenal Medulla
(Pheochromocytoma)

The condition occurs due to excessive secretion of catecholamine's (epinephrine and norepinephrine) by adrenal medulla.

Clinical Features

- Hypertension, tachycardia, palpitations
- Headache, sweating, tremor, hyperglycemia

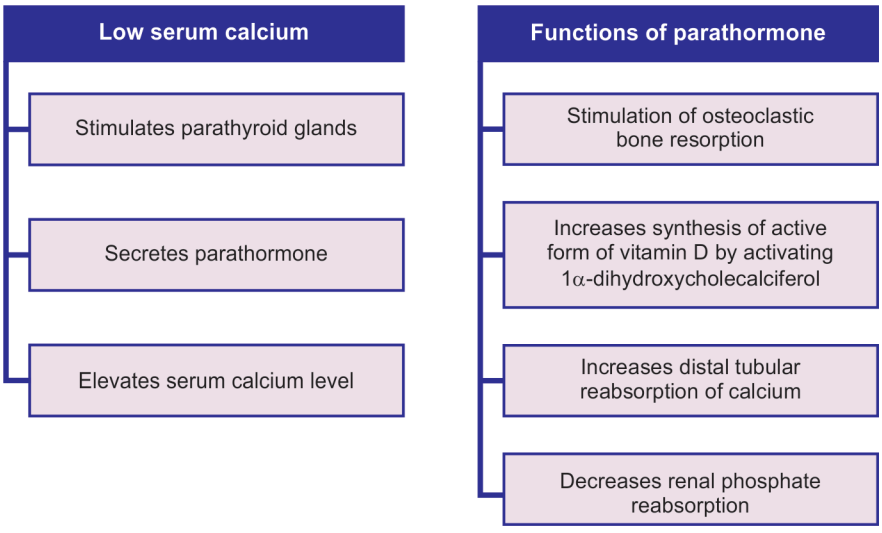
Oral Manifestations and Dental Considerations

- Individuals with persistent headache should be evaluated by dentists to rule out myofacial pain dysfunction syndrome
- Pheochromocytoma with multiple endocrine neoplasia IIb, there may be multiple neuromas in oral cavity (tongue, buccal mucosa), high narrow arched palate and maxillary anterior protrusion.

Parathyroid Gland Disorders

Parathyroid glands are situated in pairs posterior to thyroid gland. It secretes parathormone (PTH) that maintains plasma concentration of ionized calcium (Flowchart 18.3).

Flowchart 18.3: Type 1 diabetes mellitus



Functions of ionized calcium:

- It is essential for neuromuscular excitability
- Bone and tooth development
- Maintain membrane integrity
- Cell communication
- Cell adhesion
- Play an important role in blood clotting

Calcitonin, a hormone secreted by thyroid gland, reduces serum calcium level and the functions are exactly opposite to PTH.

Disorders of Parathyroid Hormone

Hyperparathyroidism (hypersecretion of parathormone)

Type	*Etiology*
Primary hyperparathyroidism	• Caused by neoplasia of parathyroid glands
Secondary hyperparathyroidism	• Caused secondary to chronic renal disease • In individuals undergoing chronic renal dialysis • Vitamin D deficiency (osteomalacia, rickets)
Ectopic (psuedohyperparathyroidism)	• Caused due to ectopic malignant tumors of lungs, breast, liver, pancreas, kidneys)

Clinical Features

Women of age 30–60 years are most commonly affected.

System	*Symptom and sign*
Cardiovascular problems	Cardiac arrhythmias, excitability, hypertension
Gastrointestinal disorders	Pain in abdomen, peptic ulcerations, pancreatitis, constipation
Neuromuscular disorders	Mental confusion, lethargy, drowsiness, stupor
Disorders of eye	Deposition of calcium in cornea, calcinosis
Genitourinary disorders	Polyurea, polydipsia, kidney stones, kidney damage
Bone	Bone pain, pathologic fractures, hypercalcemia, osteopenia

Oral Manifestations

- Vague jaw pain
- Loosen teeth and drifting of teeth
- Pulp stones, root resorption
- Soft tissue calcifications of salivary glands (sialolithiasis)
- Skeletal muscle weakness.

Radiographic Features

General radiographic manifestations

- Subtle erosions in the sub-periosteal surface of phalanges of hands
- Generalized demineralization of skeletal tissues
- **Osteitis fibrosa cystica:** Localized demineralization of bone due to osteoclastic activity
- **Brown's tumors:** These are radiolucent lesions that occur in the late stage of the disease, could be central or peripheral
- Pathological calcifications in soft tissues
- Thinning of cortex of the calvarium and loss of central (diploic) trabeculation.

Radiographic Appearance in Jaws

- Cortical thinning of inferior border of mandible, mandibular canal and maxillary sinuses
- **Osteoporosis of jaws:** Overall reduction in bone density in jaws
- Ground glass appearance
- **Brown's tumor:** Commonly observed in jaws and facial bones. It usually resembles central giant cell granuloma radiographically and histologically. The basal metabolic tests and serum biochemistry for calcium, phosphorus and alkaline phosphatase should be evaluated along with biopsy of the lesion. If the calcium, alkaline phosphatase levels are increased and reduction in phosphor is noted, Brown's tumor secondary to hyperparathyroidism should be considered.
- *Loss of lamina dura:* It may be localized or generalized depending on the severity of disease or may show partial or complete loss around the teeth.

- Presence of lytic bone cysts in jaws
- Pulp calcifications

Hypoparathyroidism

Hyposecretion of parathormone from parathyroid glands resulting in decreased serum calcium (hypocalcemia) and increased phosphor (hyperphosphatemia).

Etiology

- Accidental removal/damage to parathyroid gland during thyroidectomy
- DiGeorge syndrome (congenital absence of parathyroid glands)
- Hypomagnesaemia
- Radiation therapy.

Clinical Features

- Increased neuromuscular excitability (tetany), therefore, spasmic muscular contraction
- Numbness and tingling in the extremities
- **Chvostek's sign:** Spasm of the facial muscle particularly the lips and alae of the nose on tapping the facial nerve at the point of origin (anterior to tragus of the ear)
- **Trousseau's sign:** Carpal spasm (spasm in hand) after inflating cuff during measurement of blood pressure
- Memory loss, seizures, nail deformities
- Candidiasis, cataract development

Oral Manifestations and Dental Considerations

- Mucocutaneous candidiasis
- Circumoral paresthesia is the first symptom of hypoparathyroidism.

If the hypoparathyroidism occurs before tooth development, following changes are noted:

- Abnormal eruption pattern during tooth development
- Enamel hypoplasia and poorly mineralized dentin
- Malformed teeth, anodontia, short blunt root apices, elongated pulp chambers, pulp stones in primary and permanent teeth, impacted teeth, mandibular tori

If the hypoparathyroidism occurs after tooth development, there are no abnormalities noticed.

Thyroid Gland Disorders

Table 18.10 provides thyroid gland disorders.

Regulation of Thyroid Hormone

Refer to Flowchart 18.4.

Disorders of Thyroid Gland

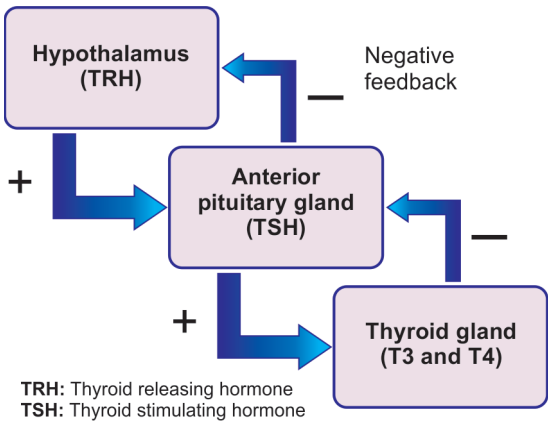
Table 18.11 provides disorders of thyroid gland.

TABLE 18.10: Thyroid gland disorders

Thyroid gland	*Hormone*	*Function*
Follicular cells	Triiodothyronine (T3) Tetraiodothyronine, (Thyroxine T4)	• Increases metabolic rate • Enhances oxygen consumption • Lowers cholesterol level • Increases epinephrine secretion • Stimulates growth • Promotes protein, carbohydrate and lipid metabolism
Parafollicular C cells	Calcitonin	• Reduces plasma calcium levels by affecting bone and kidney

T3 (10%) and T4 (90%) are the hormones secreted by follicular cells of thyroid gland, T3 is the active hormone that binds to the thyroid hormone receptor, which bring about physiologic changes, on requirement T4, is converted to T3. These hormones exist either in free or bound with protein (thyroglobulin).

Flowchart 18.4: Regulation of thyroid hormone



Hyperthyroidism

Clinical Features

- The thyroid gland is enlarged, palpable, overlying skin is warm, systolic bruit on palpation
- Patients are thin, nervous, emotionally instable, irritable
- Weight loss in spite of increased appetite
- Heat intolerance, sweating
- Tremors, muscle weakness
- Palpitations, tachycardia
- Menstrual changes
- Exophthalmos
- Clubbing of fingers and toes

Oral Manifestations

- Premature loss of primary teeth
- Early eruption of secondary teeth
- Enlarged tongue
- Lingual thyroid tissue
- Difficulty in swallowing
- Increased susceptibility of patients for dental caries and periodontal disease

Dental Considerations

- Agranulocytosis and leukopenia are the side effects of antithyroid medications (propylthiouracil), thus these patients are more prone for infections, increased incidence of sialolith formation and increased anticoagulant effects of warfarin

TABLE 18.11: Disorders of thyroid gland

Disease	*Characteristics*	*Causes*
Goiter	Hypersecretion of thyroid hormones	• Graves disease (diffuse toxic goiter) • Toxic multinodular goiter • Toxic uninodular goiter • Hashimoto's thyroiditis (hypothyroid state) • Endemic goiter (caused due to dietary deficiency of iodine)
Hyperthyroidism (thyrotoxicosis) Graves disease	Increased secretion of T3 and T4	• Hyperactive thyroid nodule • Toxic adenoma • Toxic multinodular goiter • Jod-Basedow disease
Hypothyroidism	Deficiency of circulating thyroid hormone	• Destruction of thyroid gland • Dysfunction of hypothalamus pituitary axis • Hashimoto's thyroiditis (autoimmune disorder involving lymphocytic infiltration of the gland)
Cretinism	Reduction/ deficiency of thyroid hormone in children and infants	• Congenital absence of gland, hypoplasia, thyroid dysplasia, fibrous replacement
Myxedema	Reduction/ deficiency of thyroid hormone in adults	• Surgical excision of the thyroid gland • Radiation therapy • Atrophy of anterior pituitary gland • Hashimoto's disease

- Practitioners should be cautious while prescribing aspirin, as this may increase the circulating T4 leading to thyrotoxicosis
- NSAIDs can decrease effect of blockers
- The use of epinephrine and other sympathomimetics needs special precaution in patients with non-selective blockers
- Hyperthyroid patients are more susceptible for CVS diseases, which include atrial dysarrhythmias, tachycardia, hypertension
- Local hemostatic measures required to control bleeding during dental treatment
- Epinephrine is contraindicated in patients with thyroid storm and elective dental procedures can be deferred.

Radiographic features: Generalized loss of bone density in some areas of edentulous alveolar bone.

Diagnosis: Suppressed or reduced TSH level is the most sensitive test for hyperthyroidism

Treatment

- β-blockers for tachycardia
- Antithyroid medications
- Radioactive ^{131}I
- Surgery

Hypothyroidism

The conditions associated with hypothyroidism are cretinism (in infants and children) and myxedema (in adults)

Cretinism	*Myxedema*
Clinical features	
Mental retardation	Puffy face
Hypothermia	Dull facial expression
Feeding difficulties in infants	Non-pitting edema
Retarded physical growth	Weight gain
Hypertelorism	Queen Anne's sign (non-pitting edema of eyelids with loss of eyebrows on lateral third)
Broad face	Bradycardia
Delayed fontanelle closure	Cold intolerance
Stout neck	Cold skin
Protruded abdomen	Constipation
Constipation	
Bradycardia	
Oral manifestations	
Enlarged tongue and gingiva	Rampant caries
Open mouth with mouth breathing	Delay in eruption of primary and secondary teeth, therefore, malocclusion
Gingivitis	Slurred speech
Radiographic Features	
Delayed closure of epiphyses and skull sutures	Thinning of lamina dura
Delayed eruption	Relatively small jaws
Short roots	In adults: Periodontal disease, loss of teeth, spacing between teeth due to enlarged tongue, external root resorption.
Dental considerations	
Hypothyroid patients are lethargic and have diminished respiratory rate therefore increased risk of aspiration of dental materials	
Hypothyroid patients on anticoagulants will have a risk of bleeding, hence estimation of PT, PTT and INR is recommended prior any dental treatment	
Prophylactic antibiotics for compromised cardiac patients	
Narcotic analgesics should be limited as it may cause CNS depression	
These individuals have deposition of mucopolysaccharides which prevent constriction of small vessels	

Contd.

Contd.

Cretinism	*Myxedema*
✦ Excessive bleeding following trauma, which can be prevented by local pressure application and hemostyptics	
✦ Delayed wound healing due to decreased metabolic activity in fibroblasts and stressful situation such as surgery or trauma may precipitate the condition	
Treatment	
✦ Thyroid hormone replacement therapy (levothyroxine sodium)	

FREQUENTLY ASKED QUESTIONS

1. Describe the etiopathogenesis, clinical features, diagnosis and oral manifestations of diabetes mellitus.
2. Explain radiographic features of hyperparathyroidism.
3. Oral manifestations of endocrine disorders.
4. Write a short note on oral hypoglycemics.
5. Explain blood glucose regulation.
6. Explain pituitary gland disorders.
7. Discuss adrenal gland disorders.
8. Describe hyperthyroidism.

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Chapter 19

Red Blood Cell Disorders—Oral Manifestations and Dental Considerations

INTRODUCTION

Blood is the fluid connective tissue that predominantly contains water containing both the cellular elements (red blood cells, white blood cells, and platelets), and extracellular elements (plasma—a mixture of water and proteins). The plasma proteins are albumin, globulin, and fibrinogen, and other dissolved solutes such as glucose, lipids, electrolytes, and dissolved gases.

The primary function of blood is to deliver oxygen and nutrients to and remove wastes from body cells, in addition, includes defense, distribution of heat, and maintenance of homeostasis. Blood constitutes approximately 8 percent of adult body weight. In an adult male the average blood is about 5 to 6 liters of blood; average of 4–5 liters in females. The pH of the blood is 7.4, it is also slightly alkaline, and its temperature is slightly higher than normal body temperature. There is wide array of hematological disorders that show various oral manifestations that can be identified by an oral physician.

Hemopoiesis

Schematic representation of hemopoiesis: The primitive stem cells in the bone marrow is pluripotent in nature, they differentiate as lymphopoietic and hematopoietic series. The hemopoiesis is self-regulatory process and there is a constant check system for formation/elimination from the system. Blood cells are formed on demand and eliminated whenever required. The demand for production of cells is infection, immune challenges, hemorrhage, hypoxia (Flowchart 19.1).

The lifespan of various types of blood cells is as follows:

Cells	*Life span*	*Site of destruction*
Erythrocytes	120 days	Reticuloendothelial system (more than 50% are destructed in spleen, and remaining is destroyed in liver, bone marrow, mononuclear phagocyte system).
Neutrophils	6 hours to 3 days	Apoptosis
Platelets	5–10 days	Spleen and phagocytosis by macrophages.

Before understanding the disorders of RBC, we should understand the normal blood parameters (Table 19.1).

Flowchart 19.1: Hemopoiesis

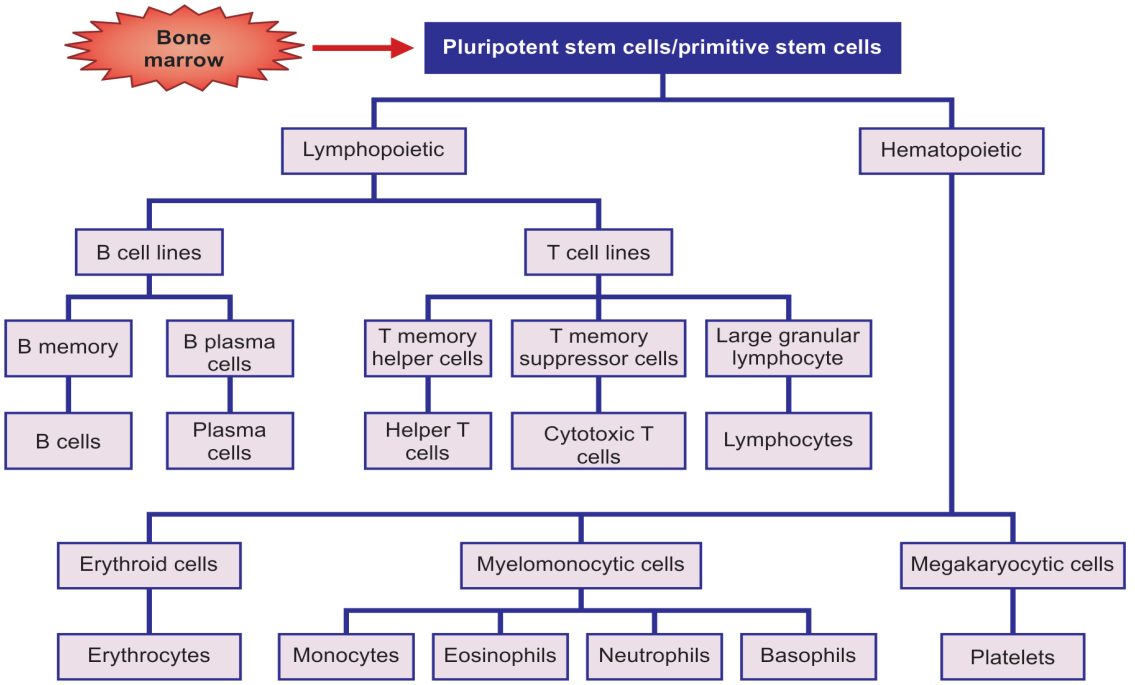


TABLE 19.1: Red cell indices

Parameter	*Men*	*Women*	*Increased*	*Decreased*
RBC count ($\times 10^{12}$/litre)	4.4–6.1	4.2–5.4	▪ Erythrocytosis ▪ Polycythemia	▪ Anemia
RBC indices			▪ Macrocytosis	▪ Microcytosis
Hemoglobin (g/dl)	13–18	11.5–16.5	▪ Erythrocytosis ▪ Polycythemia	▪ Anemia
Hematocrit (packed cell volume)	0.40–0.54	0.37–0.47	▪ Erythrocytosis ▪ Polycythemia	▪ Anemia
Mean corpuscular volume (MCV) (fl)	75–99	75–99	▪ Vitamin B_{12} and folate deficiency	▪ Iron deficiency anemia ▪ Thalassemia
Mean corpuscular hemoglobin (MCH) (pg)	27–31	27–31	▪ Hyperchromia	▪ Hypochromic anemia
Mean corpuscular hemoglobin concentration (MCHC) (g/dl)	32–36	32–36	▪ Hyperchromia	▪ Hypochromic anemia

TABLE 19.2: Conditions affecting RBC counts

Increased levels of red blood cell	*Decreased levels of red blood cell*
Erythrocytosis	Anemia (Classification described in Table 19.3)
Polycythemia vera	
Fluid loss due to dehydration, diuretics, diarrhea, burns	

Red Blood Cell Disorders (Table 19.2)

Erythrocytosis

Definition: It is a condition that describes an increase in circulating RBCs and raised hematocrit in blood.

Causes: Tissue hypoxia, congenital heart disease, high altitude, post-renal transplantation.

Types

- Relative erythrocytosis
- Absolute erythrocytosis
- Idiopathic erythrocytosis

Polycythemia Vera

Polycythemia means "too many cells in blood". First described by Vasquez in 1892.

Description: It is a chronic myeloproliferative disease, with an abnormal increase in the number of red blood cells in the peripheral blood, usually with an increased hemoglobin level.

Types

- Primary polycythemia or polycythemia rubra vera
- Secondary polycythemia
- Relative polycythemia

Clinical Manifestations

- More common in men
- Occurs in middle age or later
- Present as diffusely reddened or flushed skin
- Pruritis
- Tender splenomegaly, gastrointestinal pain
- Mucosal cyanoses, acrocyanosis
- Bleeding tendencies
- Headache, dizziness, weakness, lassitude, tinnitus, visual disturbances
- Mental confusion, slurring of speech, inability to concentrate
- Gas pains, belching, peptic ulcers, hemorrhage from varices
- Plethoric color of the skin in polycythemia

Oral Manifestations

- Deep purplish red hue of oral mucosa
- Tongue and gingiva are most commonly affected
- Swollen and engorged gingivae that bleed upon slightest provocation
- Submucosal petechiae, ecchymosis and hematomas
- Glossitis
- Gingival bleeding

Diagnosis: Elevated RBC mass, normal oxygen saturation, palpable splenomegaly

Treatment

- Phlebotomy (to remove RBCs) and myelosuppressive chemotherapy are the cornerstones of therapy
- The goal of phlebotomy is to maintain normal red cell mass and blood volume, with a target hematocrit of less than 45% for men, and less than 42% for women.
- Hydroxyurea is a principal myelo-suppressive agent in high-risk patients
- Current recommendations for treatment of young patients primarily rely on phlebotomy because the thrombosis is far less likely to occur in children and the long-term risks of leukemia over a longer life span are increased.
- *Secondary polycythemia:* Phlebotomy is used for symptomatic hyperviscosity. The goal is to treat the underlying cause of polycythemia.

Dental Considerations

- Control of hemorrhage after oral surgical procedures
- Significant bleeding requires platelet transfusion, ε-aminocaproic acid, and tranexamic acid
- Control blood counts by phlebotomy or drug therapy.

Anemia (Table 19.3)

Iron Deficiency Anemia

Definition: It is defined as a reduction in total body iron, that is required for hemoglobin synthesis.

TABLE 19.3: Classification of anemia

A. **Pathophysiologic**
I. Anemia due to blood loss
- Acute post-hemorrhagic anemia
- Chronic blood loss

II. Anemia due to impaired red cell production
a. Cytoplasmic maturation defect
- Deficient haem synthesis
- Iron deficiency anemia
- Deficient globin synthesis
- Thalassaemic syndromes

b. Nuclear maturation defects
- Vitamin B_{12} and/or folic acid deficiency
- Megaloblastic anemia

c. Defect in stem cell proliferation and differentiation
- Aplastic anemia
- Pure red cell aplasia

d. Anemia of chronic disorders
e. Bone marrow infiltration
f. Congenital anemia

III. Anemia due to increased red cell destruction
- Hemolytic anemia

A. Extrinsic (extracorpuscular) red cell abnormalities
B. Intrinsic (intracorpuscular) red cell abnormalities

B. **Morphologic**
I. Microcytic hypochromic, e.g. iron deficiency anemia, thalassaemia, sideroblastic anemia and anemia of chronic disease
II. Normocytic normochromic, e.g. anemia due to acute blood loss, anemia of chronic disease
III. Macrocytic normochromic, e.g. megaloblastic/pernicious anemia
IV. Spherocytosis: Hereditary spherocytosis, autoimmune hemolytic anemia

C. **Hematopoietic stem cell proliferation and differentiation abnormality**
- Aplastic anemia
- Pure red cell aplasia

D. **Bone marrow failure due to systemic diseases (anemia of chronic disorders)**
- Anemia of inflammation/infection, disseminated malignancy
- Anemia in renal disease
- Anemia due to endocrine and nutritional deficiency
- Anemia in liver disease

Contd.

TABLE 19.3: Classification of anemia (*Contd.*)

E. **Bone marrow infiltration**
- Leukemia
- Lymphoma
- Myelosclerosis
- Multiple myeloma

F. **Congenital anemia**
- Sideroblatic anemia
- Congenital dyserythropoietic anemia

Causes

- Inadequate intake and increased demand during gestation/pregnancy/and lactating mother.
- Reduced absorption due to gastrectomy, malabsorption, excessive use of antacids
- Most common in women due to blood loss during menstruation.

Clinical Manifestations

- Weakness, fatigue, lemon-tinted pallor of the skin, lips, mucous membranes and sclera, dyspnea on exertion, palpitations, numbness and tingling in fingers and toes, bone pain.
- Older patients may develop angina and congestive cardiac failure
- Brittle nails with spooning (koilonychia) and cracking and splitting of nail beds, palmar crease rubor.

Oral Manifestations

- Plummer-Vinson syndrome/Paterson-Brown Kelly syndrome/sideropenic dysphagia

Atrophic glossitis/ bald tongue	Stomatitis
Mucosal pallor	*Angular stomatitis* (painful fissures at the corners of the mouth) and *cheilosis* (dry scaling of the lips and corners of the mouth)
Migratory glossitis	Oral candidiasis
Recurrent aphthous stomatitis	Glossodynia
Recurrent oral ulcers	Burning mouth

- First described by Plummer in 1914 and Vinson in 1922.

The main features include

- The classic triad of esophageal web, iron deficiency anemia, and dysphagia
- Other features are migratory glossitis, koilonychia, and growth in postcricoid area
- Plummer-Vinson syndrome is associated with increased risk of squamous cell carcinoma of pharynx and oesophagus.

Diagnosis

- The peripheral smear shows microcytic hypochromic anemia
- Low serum iron, low transferrin saturation, and low ferritin
- The low serum ferritin <25 mcg/L level is the diagnostic feature of iron deficiency anemia

Treatment

- **Oral iron supplementation:** Ferrous sulphate 325 mg orally for three times daily for 3 months
- Failure of oral therapy or hemoglobin less than 6 gm% than parenteral iron dextran/ iron gluconate/ iron sucrose is given

Dental considerations

- If the hemoglobin is less than 8 g/dl, avoid general anesthesia
- Poor wound healing in anemic patients
- Narcotics should be limited in severe anemic individuals
- Dentists should be aware of increased risk for ischemic heart diseases.

Pernicious Anemia/Megaloblastic Anemia

Description: Pernicious anemia is the form of megaloblastic anemia caused due to deficiency of vitamin B_{12}, which is an extrinsic factor. This is due to atrophy of gastric mucosa and subsequent lack of intrinsic factor. Vitamin B_{12} and folic acid are needed for the maturation of RBCs in the bone marrow; and intrinsic factor is required for absorption of vitamin B_{12}.

Causes

- Reduced intake or absorption of vitamin B_{12} or folic acid
- Deficiency due to gastrectomy, tropical sprue, alcoholism, scleroderma and drugs such as colchicine.
- Autoimmunity causes self-destruction of intrinsic factor/ gastric parietal cells
- Folic acid deficiency is seen in chronic alcoholics, drug users and vegetarians with reduced intake of leafy vegetables.

Clinical Manifestations

- Generalized weakness, anorexia, abdominal pain, weight loss, shortness of breath, yellowish pigmentation
- Neurological abnormalities in vitamin B_{12} deficiency, tingling of the extremities is presented even before appreciating features of anemia, cerebral disturbances due to memory loss, irritability, depression

(There are no neurological abnormalities in folic acid deficiency as in pernicious)

Oral Manifestations

- Hunter's glossitis or Moller's glossitis
- **Glossodynia:** Painful tongue
- **Glossopyrosis:** Burning sensation of lingual mucosa
- **Disguesia:** Distortion of the sense of taste.
- Persistent or recurrent stomatitis
- Oral mucosa becomes intolerant to dentures
- **Hunter's glossitis:** Inflamed tongue, 'Beefy red' in color, small and shallow ulcers may develop, gradual atrophy of papillae, ultimately results in smooth or 'bald' tongue.

Diagnosis

- **Schilling test:** Demonstrates vitamin B_{12} deficiency
- Achlorhydria
- Antibodies to intrinsic factor/parietal cells
- Peripheral smear shows macrocytic normochromic anemia
- Mean corpuscular volume is increased
- Decreased folic acid

Treatment

- High dose of oral supplementation of 1000–2000 mcg daily for 2 weeks, followed by 1000 mcg for maintenance
- Parenteral vitamin B_{12} injections once in a month

Dental considerations

- Patients with pernicious anemia should be given diphenhydramine elixir for symptomatic relief, so that individuals can take food by mouth
- Surgical procedures should be deferred until the anemia and thrombocytopenia are medically controlled, otherwise, bleeding could be a problem.
- Folate deficiency due to alcoholism leads to bleeding problems because of inhibition of liver coagulant precursors, therefore, obtain bleeding profiles prior any dental procedure.

Hemolytic Anemia

Description: Hemolytic anemia results from excessive destruction of red blood cells

Causes

- **Extracorpuscular defect**
  - Autoimmune hemolytic disease
  - Overwhelming infections or toxins
  - Rh factor incompatibility
- **Intracorpuscular defects**
  - Hereditary spherocytosis
  - Glucose-6 phosphate deficiency
  - Sickle cell anemia
  - Thalassemia
- **Congenital hemolytic anemia**
  - Membrane defects (hereditary spherocytosis)
  - Enzyme deficiency (G-6-PD deficiency and pyruvate kinase deficiency)
  - Disorders of hemoglobin (sickle cell anemia and thalassemia)

Clinical Manifestations

- Acute back pain
- Free hemoglobin in plasma and urine
- Renal failure
- Fatigue, loss of stamina
- Breathlessness, tachycardia, jaundice and hemoglobinuria
- Splenomegaly

Oral Manifestations

- Pallor/yellowish discoloration of oral mucosa
- Paresthesia of mucosa
- Hyperplastic marrow spaces in mandible, maxilla and facial bone

Hemoglobinopathies

Description

- Hemoglobinopathies occur due to point mutations and deletions in globin genes that cause changes in amino acid that causes defective synthesis of globin protein, resulting in abnormal hemoglobin
- Sickle cell anemia and thalassemia are considered as hemoglobinopathies. The qualitative defect in globin chain synthesis occurs in sickle cell anemia, whereas thalassemia is due to quantitative defect.

Sickle Cell Anemia

Description

- It occurs due to qualitative defect in globin chain, i.e. glutamic acid is replaced by valine
- It is an autosomal recessive disorder
- Due to structural variation in globin chain synthesis, hemoglobin is susceptible for low oxygen tension, low temperature or decreased pH; this leads to sickling of cell that leads to stasis, vascular obstruction, and hemolysis of the red cells.

Types

- Sickle cell trait (heterozygous)—one of the beta chains is abnormal
- Sickle cell trait (homozygous)—both the beta chains are abnormal

Clinical Manifestations

- Impaired growth and development

- Most susceptible for infections
- Delayed sexual maturity
- End organ damage due to vascular obstruction
- Splenic fibrosis
- Jaundice

Oral Manifestations

- Pallor
- Osteomyelitis due to compromised blood supply
- Impaired healing
- Delayed eruption
- Step ladder trabeculae on radiographs
- Hyperplasia and widening of marrow spaces
- Thickening of diploe with hair on end appearance on lateral skull radiographs

Diagnosis

- Peripheral smear shows normocytic normochromic cells
- Decreased hemoglobin and abnormal hemoglobin on electrophoresis

Treatment

- Children born with sickle cell disease will undergo close observation by the pediatrician and will require management by a hematologist to assure they remain healthy.
- 1 mg folic acid supplement daily for life.
- Penicillin for first 5 years of age in children as they are more prone for infections due to immature immune system.
- Blood transfusion in severe anemia and bone marrow transplantation.

Thalassemia

Description: Congenital hemoglobinopathies due to reduced rate of production of one more of globin chains (either alpha or beta) in hemoglobin molecule.

Types

- **Alpha thalassemia:** Alpha chain is deficient in hemoglobin molecule
- **Beta thalassemia:** Beta chain is deficient in hemoglobin molecule
  - *Beta thalassemia minor:* The individuals are heterozygous for beta chains
  - *Beta thalassemia major/Cooley's anemia:* The individuals are homozygous for beta chains.

Clinical Manifestations

- Clinical features are similar to sickle cell anemia
- Retarded growth and development
- Ashen grey skin color due to pallor and jaundice
- Cardiomegaly, splenomegaly, hepatomegaly.

Oral Manifestations

- Malocclusion, spacing, and occlusal abnormalities
- Sialadenitis of parotid gland due to deposition of iron
- Discolored primary and permanent teeth
- Chipmunk facies—prominent premaxilla
- Short roots with thin lamina dura
- Generalized rarefaction of alveolar bone, enlarged marrow spaces and coarse trabeculation
- Hair on end appearance on skull
- Thickened diploe
- Rib—within-a-rib appearance: A long linear density within or overlapping the medullary space of the rib and running parallel to its long axis.
- Poorly defined cortices of skull

Diagnosis

- Peripheral smear shows normocytic normochromic cells
- Similar to sickle cell anemia

Treatment

- Multiple blood transfusion for amongst thalassemia major individuals
- Folic acid supplements
- Splenectomy

Dental Considerations

- Prophylactic antibiotic prior dental treatment
- Risk of hepatitis due to blood transfusion
- Poor wound healing
- Surgical correction for facial deformities

Aplastic Anemia

Description: It is a rare but life-threatening blood dyscrasia associated with pancytopenia and bone marrow aplasia.

Types

- Acquired (drugs, viruses, chemicals, toxins and radiation)
- Inherited
- Idiopathic

Clinical Manifestations

- Sudden onset of bleeding due to thrombocytopenia—increased bruising, purpura and petechiae , epistaxis, gingival bleeding
- Fever and more prone for infection—particularly neutropenia
- Fatigue, malaise, chest pain, shortness of breath.

Oral Manifestations

- Oral bleeding
- Prone for infections especially candidiasis and viral infection
- Gingival hyperplasia and spontaneous gingival bleeding
- Herpetic lesions

Treatment

- Blood transfusion
- Immunosuppressive medication is effective in restoring blood cell production
- Prophylactic antibiotics—broad spectrum antibiotics, antifungal therapy.

FREQUENTLY ASKED QUESTIONS

1. Discuss the etiology, clinical features, oral manifestations, diagnosis and management of iron deficiency anemia.
2. Write a short note on Plummer-Vinson syndrome.
3. Oral manifestations and dental considerations of anemia.
4. Discuss hemoglobinopathies.
5. Discuss the etiology, clinical features, oral manifestations, diagnosis and management of pernicious anemia.

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Chapter 20

White Blood Cell Disorders—Oral Manifestations and Dental Considerations

INTRODUCTION

White blood cells (WBCs) are nucleated cells classified as granulocytes (neutrophils, eosinophils, and basophils) and agranulocytes (B and T lymphocytes, monocytes and macrophages), or either by their cell lineage (myeloid and lymphoid cells). Their normal range of WBCs in blood is between 4000 and 11,000 per microliter. The WBCs originate from pluripotent stem cells, and colony-forming unit. The most abundant granulocyte is the neutrophil.

The functions of the WBCs are shown in Table 20.1.

Classification of WBC Disorder

Can be broadly classified as quantitative and qualitative disorders:

- **Quantitative disorder:** In this disorder, the cells appear normal, but present in abnormal quantities either in excess or deficient.
- **Qualitative disorder:** In this disorder, abnormal cells appear in circulation due to extrinsic or intrinsic abnormalities (Table 20.2).

TABLE 20.1: Functions of WBCs

WBC type	*Normal range*	*Function*
Neutrophils	41–78%	Phagocytosis of the bacteria
Basophils	0–2%	They contain heparin that prevents blood from clotting, also contains vasodilator histamine that promotes blood flow to tissues.
Eosinophil's	0–4%	Defense against multicellular parasites and anti-inflammatory
T and B lymphocytes	23–44%	Cellular and humoral immunity
Monocytes	0–7%	Phagocytosis, antigen presentation, and cytokine production

QUANTITATIVE LEUKOCYTIC DISORDERS

Granulocytosis

It can be either neutrophilia, eosinophilia, basophilia.

- **Definition:** Abnormally increased number of cells (>11,000/μL) and absolute neutrophil count >7,700/μL.
- **Abnormal increase** in number of neutrophils (neutrophilia), increase in eosinophils (eosinophilia), increase in basophils (basophilia).
- **Causes:** Bacterial infection, stress, smoking, pregnancy, burns, acute myocardial infarction, acute gout, acute glomerulonephritis, rheumatic fever,

TABLE 20.2: WBC disorders

Quantitative disorders	Granulocytosis Agranulocytosis
Qualitative disorders	*Defects in adhesion* • Leukocyte adhesion deficiency (Type 1, 2, and 3) *Defects in phagocyte activation* • Hyperimmunoglobulin E (Job's syndrome) • Chronic granulomatous disease • Chédiak-Higashi syndrome *Granulocyte disorder* • Myeloperoxidase deficiency • Chédiak-Higashi syndrome • Chronic granulomatous disease
Neoplastic disorders	• Leukemia • Lymphoma • Multiple myeloma

strenuous exercises and myeloproliferative disorders.

Agranulocytosis (Neutropenia and Granulocytopenia)

Definition: Agranulocytosis is reduced quantity of granulocytes.

Causes

- Impaired production is the main cause
  - It is due to severe vitamin B_{12} deficiency / bone marrow replacement resulting from malignant infiltration
  - Increased utilization due to the acute phase of infections / autoimmune diseases
- Mild (1000–2000 cells / μL) to moderate neutropenia (500–1000 cells / μL)
  - Is due to Epstein-Barr virus infection or respiratory syncytial virus
  - Drug-induced such as antineoplastics alkylating agents, antimetabolites antibiotics (chloramphenicol, sulfonamides, penicillins), anticonvulsants (carbamazepine), antithyroid agents, mercurial diuretics, and phenothiazines.
  - Autoimmune disorders such as rheumatoid arthritis, Felty's syndrome, lupus erythematosis, Wegener's granulomatosis.
- Severe form (less than 500 cells / μL)

Oral Health Considerations

- Ulcerations and necrotizing lesions on gingiva, floor of the mouth, buccal mucosa, pharynx
- The ulcers lack the surrounding inflammation and are characterized by foul smell and necrosis

The distinct form of agranulocytosis is the cyclic neutropenia.

Cyclic Neutropenia

- It is autosomal dominant disorder due to mutations in the gene for neutrophil elastase
- It is a rare disorder characterized by periodic failure of stem cells in bone marrow, resulting in repetitive episodes of fever, mouth ulcers, and infections due to neutropenia.
- The individuals present with cyclical episodes of neutropenia, with a regular 21 days interval, neutropenia persists for 3–5 days characterized by infections.

Clinical Features

- Fever, stomatitis, pharyngitis, skin abscess, lymphadenopathy
- History of repeated infections of ear and respiratory infections
- The severe consequences of neutropenia are gangrene, bacteremia, septic shock.

Oral Manifestations

- Recurrent aphthous ulcers, recurrent gingivitis and periodontitis
- Ulcers lack surrounding inflammation / red inflammatory border and are characterized by necrosis.

Treatment

- Administration of hematopoietic growth factors such as granulocyte colony stimulating factor.

Chronic Neutropenia

Definition: A low absolute neutrophil count for more than 6 months.

Classification

- Congenital neutropenia (also called Kostmann's syndrome)
- Acquired
- Idiopathic (it is the predominant type)

Etiology: Kostmann's syndrome is caused due to mutations in variety of genes (ELANE, HAX1, and GF11 genes).

Clinical Features

- Deep tissue infections, lung and liver abscesses, severe skin infections
- Infants are chronically ill after birth with anemia, thrombocytopenia
- The bone marrow shows promyelocytic maturation arrest.

Oral Manifestations

- Recurrent gingivitis and periodontitis in early childhood
- Premature primary tooth loss

Treatment: Administration of granulocyte colony stimulating factor

Diseases of Agranulocytes

Agranulocytes include T and B lymphocytes, monocytes that constitute of about 20–40% of WBCs.

Lymphocytes facilitate cellular and humoral immunity.

The diseases of agranulocytes are shown in Table 20.3.

QUALITATIVE DISORDERS

Lazy Leukocyte Syndrome

Definition: It is caused by loss of chemotactic function of neutrophils.

Description: Marrow contains normal number of matured neutrophils, but patients have severe neutropenia because the cells are unable to migrate from the marrow to peripheral blood.

Clinical Features and Oral Manifestations

- Individuals are more prone for infections as neutrophils fail to migrate at the site of inflammation.
- Becomes apparent at the age of 1–2 years when infectious complications begin.
- Gingivitis, stomatitis, otitis media and bronchitis
- Total leukocyte count <100–200 mm

Treatment

- The management of patients with the lazy leukocyte syndrome does not present major difficulties since appropriate antibiotic therapy is generally effective although less promptly than in hematologically normal subjects.

TABLE 20.3: Lymphocyte disorders

	Lymphocytopenia	*Lymphocytosis*
Definition	• A decrease in number of lymphocytes <1,000 cells µL in blood	• An increase in number of lymphocytes
Causes	• Iatrogenic • Infections (bacterial, viral, fungal, parasitic) • Systemic diseases (systemic lupus erythematosis, rheumatoid arthritis, Sjögren's syndrome), lymphoma, sarcoidosis, renal failure, aplastic anemia, Cushing's syndrome) • Others (malnutritions, stress)	• *Viral infections* (Epstein-Barr virus, cytomegalovirus, HIV, pertussis) • *Lymphoproliferative disorders* (acute and chronic lymphocytic leukemia)
Treatment	• Treat the underlying disease	

- The treatment of major infectious episodes as well as the prevention of recurrences include the well-known measures common to other granulocyte function disorders.
- Oral prophylaxis
- Oral rinses for stomatitis—chlorhexidine.

Chédiak-Higashi Syndrome

Description

- Chédiak-Higashi syndrome (CHS) was described by Beguez Cesar in 1943, Steinbrinck in 1948, Chédiak in 1952, and Higashi in 1954.
- It is a rare childhood autosomal recessive disorder that affects multiple systems of the body.

Clinical Features

- Individuals exhibit hypo-pigmentation of the skin, eyes, and hair
- Prolonged bleeding times; easy bruisability
- Recurrent infections
- Abnormal natural killer cell function
- Peripheral neuropathy
- Most patients who do not undergo bone marrow transplantation die of a lymphoproliferative syndrome, although some patients with Chédiak-Higashi syndrome have a relatively milder clinical course of the disease.

Leukemia

Definition: It is the disordered differentiation and malignant proliferation of hematopoietic tissue that displaces normal blood forming elements of the bone marrow.

Classification

- Based on cell type
  - Lymphoid
  - Myeloid
- Based on degree of maturity
  - Mature cells
  - Immature cells
- Based on clinical course
  - Acute
  - Chronic

Broadly classified as:

1. Acute lymphoblastic/lymphoid leukemia
2. Chronic lymphoblastic/lymphoid leukemia
3. Acute myelocytic/myeloid leukemia
4. Chronic myelocytic/myeloid leukemia

Characteristics of acute and chronic lymphoid leukemia shown in Table 20.4.

Clinical Features

These are shown in Table 20.5.

TABLE 20.4: Features of leukoplakia

Features	*Acute lymphoid leukemia*	*Chronic lymphoid leukemia*
Age of occurrence	• Most common amongst children • Can involve about 15% adults	• 15–39 years of age
Gender predilection	• Male predominance	• Male predominance
Male to female ratio	3:2	2:1
Classification	• L1—has small lymphoblast cells predominantly affect children • L2: Mixed blast cells and occur in adults • L3: Uniform large blast cells which resemble Burkitt's lymphoma and are associated with worst prognosis	• M1, M2, M3: Predominantly has granulocytes • M4, M5—proliferation of monocytes • M6—presence of erythrocytes components • M7—presence of megakaryocytes components
Prognosis	• Favorable prognosis of all leukemias	• Most aggressive disease amongst men

TABLE 20.5: Different features of leukoplakia

Acute leukemia	*Chronic leukemia*
✦ Due to replacement of normal cells by leukemic cells the following manifestations are noted- ✦ Anemia ✦ Neutropenia ✦ Thrombocytopenia ✦ Hepatosplenomegaly ✦ Back pain and pain in abdomen, bone and joint ✦ CNS abnormalities.	✦ The symptoms are generally milder than acute leukemia ✦ Due to leukemic cell infiltrates- ✦ Anemia ✦ Skin pallor ✦ Shortness in breadth ✦ Petechiae and ecchymosis on skin due to thrombocytopenia
✦ Night sweats, fever, weight loss, lethargy, weakness, individuals are more prone for infections	✦ Night sweats, fever, weight loss, lethargy, weakness, anorexia, individuals are more prone for infections
✦ Cervical lymphadenopathy and enlargement of Waldeyer's ring are due to lymphoid expansion	✦ Chronic myeloid leukemic (CML) patients always have abdominal full due to splenomegaly, hepatomegaly
✦ Life-threatening bacterial, fungal and viral infections due to splenomegaly and granulocytopenia	✦ CML patients have increased serum vitamin B_{12} due to overproduction of transcobalamin by granulocytes
✦ CNS manifestations such as palsies, vomiting and headache. These manifestations are more severe with acute lymphocytic leukemia	✦ Individuals are more prone for infections due to reduced immunoglobulins
Chloroma: The localized accumulation of leukemic cells in gingiva, neck, head. The chloroma turns to green on exposure to sunlight.	

Oral Manifestations

- Gingival enlargement is the most common finding in AML
- Chemotherapy induced mucositis is most common finding amongst individuals undergoing treatment
- Infections such as herpes simplex viral infection and candidiasis due to neutropenia
- Odontalgia due to leukemic cell infiltrates
- Ulecration in palate
- Gingivitis and gingival bleeding
- Petechiae and ecchymosis of hard and soft palate, tongue and tonsils
- Graft-versus-host disease when individuals undergo allogenic hematopoietic stem cell transplantation
- Salivary gland enlargement due to leukemic cell infiltrate.

Radiographic Features

- Loss of lamina dura
- Displacement of teeth
- Loss of the crypt outline around the unerupted teeth
- Widened PDL space and abnormal marrow spaces in the bone
- Periodontal destructions
- Increased mobility
- Protrusion of teeth
- Rarefying osteitis
- Chloroma within the jaw bone

Diagnosis

- **For acute leukemia**
  - Increased WBC count of more than 1,00,000 cells / mm^3
  - Decreased platelet count below 1,00,000 cells / mm^3

- **For chronic leukemia**
  - Increased WBC count
  - Bone marrow aspirate shows increased cellularity and Philadelphia chromosome

Treatment

Chemotherapy to reduce the blood count, decrease lymphadenopathy, and splenomegaly

- Chemotherapy is achieved in the following phases:
  - *First phase (induction phase):* Causes initial killing of tumor cells and act as cytotoxic agent
  - *Second phase (consolidation phase):* Killing of remaining cells
  - *Third phase (remission phase):* It is maintenance treatment to prevent leukemic cell proliferation.

Dental Considerations

- In pre-induction phase thorough clinical and radiographic examination should be performed
- Debridement and fluoride application is completed
- In the induction phase patients are neutropenic and are highly susceptible for infections; therefore should maintain meticulous oral hygiene by total elimination of plaque
- Oral care with 0.12% chlorhexidine gluconate and nystatin
- During maintenance phase and remission phase of therapy, routine dental care is provided.
- Use of topical antimicrobials that may reduce the systemic infections
- Topical anesthetic and analgesics can be used to reduce pain
- Cytoprotective agents such as palifermin (keratinocytic growth factor) is used to reduce the severity and duration of mucositis
- Emergency dental care are infrequent, if the granulocyte count is below 2000 cells/ml, antibiotics is must
- Absorbable gelatin sponges with topical thrombin and microfibrillar collagen can be placed to control bleeding.

Lymphoma

Definition

- These are the solid neoplastic growth of lymphoid cells that arise in reticuloendothelial and lymphoid tissue and can spread to distant lymphoid tissues such as liver, spleen, and bone marrow.
- Lymphoma frequently originates in the lymph nodes but can arise extranodularly.
- Extranodular lymphomas have more benign course.

Classification

- Hodgkin's lymphoma
- Non-Hodgkin's lymphoma
- Burkitt's lymphoma

Hodgkin's Lymphoma (HL)

- It is a malignant disorder originating in the lymphoid tissue
- It constitutes of about 10% of lymphomas

WHO classification of Hodgkin's lymphoma (HL)

- The major subtypes of HL are
  - Classic (characterized by presence of Reed-Sternberg cells)
  - Nodular
- The four subtypes are:
  - Nodular sclerosis [60–80%]
  - Mixed cellularity [15–30%]
  - Lymphocyte depletion [<1%], and
  - Lymphocyte-rich [5%]

Clinical Features

- It has bimodal age distribution (first being at age thirty and second being after the age of 55)
- Frequently occurs in men
- Patients complain of pain in chest, cough, dyspnea if mediastinal lymph nodes are involved
- Night sweats, fever, weight loss

- Generalized pruritis, pain in the involve lymph node
- Waldeyer's ring is commonly involved in Hodgkin's lymphoma

Staging System

Ann-Arbor staging classification—the Cotswolds staging system of HL
Stage
I. Involvement of one lymph node region or lymphoid structure (e.g. spleen, thymus, or Waldeyer's ring) II. Involvement of two or more lymph node regions on the same side of the diaphragm III. Involvement of lymph node regions on both sides of the diaphragm 1. Splenic hilar, coeliac, or portal nodes 2. Para-aortic, iliac, or mesenteric nodes IV. Involvement of extranodal sites other than one contiguous or proximal extranodal site
Modifying features
A No symptoms B Fever, drenching night sweats, loss of >10% body weight over 6 months X Bulky disease (mediastinal mass >1/3 of thoracic diameter or any nodal mass >10 cm in diameter) E Involvement of one contiguous or proximal extranodal site
Source: Reproduced from Burket's 12th edition.

Treatment

Treatment is based on the following:

- The histology of the disease
- The anatomical stage
- Presence of prognostic features

Stagewise management of HL

- **Early stage disease:** Combination chemotherapy followed by involved field radiation therapy (IFRT)
- **Advanced stage:** Longer course of chemotherapy often without radiation therapy
- **Refractory cases**
  - High dose chemotherapy followed by stem cell transplant
  - Patients who fail to respond to the above therapy: Brentuximab vedotin, an anti-CD-30 antibody conjugated to an antimicrotubule drug.

Oral Health Considerations

- Chemotherapy-induced oral mucositis, oral ulcerations, candida infections
- Damage to the salivary glands if it is in the field of radiation therapy
- Topical varnish and fluoride application for prevention of caries
- Osteoradionecrosis is rare that is limited to the lower border and angle of mandible.

Non-Hodgkin's Lymphoma (NHL)

- NHL is the malignant disease of lymphoid system highly heterogenous both histologically and clinically.
- It is a lymphoproliferative disorder that is multicentric in cell origin and is usually multifocal when detected.
- NHL is associated with systemic diseases such as Sjögren's syndrome, celiac disease, and rheumatoid arthritis
- Approximately 85% to 90% of NHL cases arise from B cells, e.g.
  - Burkitt lymphoma,
  - Chronic lymphocytic leukemia/small cell lymphoma
  - Diffuse large B-cell lymphoma,
  - Follicular lymphoma,
  - Mantle cell lymphoma
- The remaining arise from T cells, e.g.
  - Mycosis fungoides,
  - Anaplastic large cell lymphoma,
  - Precursor T-lymphoblastic lymphoma

Etiology

- **Infectious agents:** Epstein-Barr virus, human T cell leukemia type I virus, hepatitis C virus, *Helicobacter pylori* infection
- **Environmental factors**
  - Chemicals, e.g. pesticides, herbicides, hair dye, etc.
  - Chemotherapy
  - Radiation exposure
- **Immunodeficiency states:** AIDS, celiac disease

- **Chronic inflammation:** Sjögren's syndrome, Hashimoto thyroiditis

Clinical and Oral Manifestations

- Painless lymphadenopathy that is rubbery in consistency, mobile, and rarely matted
- Abdominal pain, vomiting, gastrointestinal obstruction are the common abdominal complaints
- Rapid nodal growth may impair lymphatic drainage, resulting in lymphedema, pain, paresthesia and skin infiltrations
- Thoracic involvement may cause pleural effusions, ascites, and dyspnea
- Bone marrow infiltrations can cause destructive lesions in bone, pathological fractures, anemia
- Splenomegaly
- Hypogammaglobulinemia and opportunistic infections are frequent
- Oral involvement is rare, it can cause gingival and mucosal swelling
- Destruction of jaw bone, tooth ache
- Nerve invasion can cause paresthesia or anesthesia
- Non-healing mucosal ulceration

Clinical difference between HL and NHL

Clinical differences between Hodgkin's lymphoma and non-Hodgkin's lymphoma are shown in Table 20.6.

Treatment

NHL is a radiosensitive tumor, radiotherapy is of choice for all the subtypes:

NHL type	*Behavior*	*Treatment*
Indolent lymphoma	Grade I or low grade type	Radiotherapy
Aggressive lymphoma	Grade II or high grade lymphoma	Radiotherapy is used after or to consolidate chemotherapy and for palliative treatment

The "staging," or evaluation of extent of disease, for both HL and NHL are similar, discussed in the section of HL.

Burkitt's Lymphoma (BL)

It is the most aggressive and common types of childhood NHL. It starts in the abdomen and spreads to other organs including brain. In African children, it often involves facial bones and associated with Epstein-Barr virus.

Types

- African (endemic) BL
- Sporadic (non-endemic/American) BL
- Subset of aggressive lymphoma (immunodeficiency related)

TABLE 20.6: Lymphomas

	Hodgkin's lymphoma	*Non-Hodgkin's lymphoma*
Age	• Bimodal age distribution • 1st peak: 15–34 years • 2nd peak: Over 50 years	• Increased with advanced age
Appearance	• Localized involvement of lymph node or contiguous lymph node involvement	• Widespread involvement of lymph nodes
Involvement site	• Extranodal involvement uncommon	• Extra nodal involvement common
Spread of disease	• Orderly spread by contiguity	• Non-contiguous spread
Location	• Frequently involves the cervical chain giving the bull-neck appearance	• Frequently involves hard and soft palate—Waldeyer's ring
Fever type	• Pel-Ebstein fever	• Non-specific fever

Clinical and Oral Manifestations

Burkitt's lymphoma is shown in Table 20.7.

Oral Manifestations

- Jaw tumors that are clinically evident that results in tooth mobility and pain, intraoral swelling of the mandible and maxilla, and anterior open bite.

Radiographic Features

- Resorption of alveolar bone
- Loss of lamina dura
- Enlargement of tooth follicles
- Destruction of cortex of the tooth crypts
- Displacement of tooth and tooth buds by enlarging tumor resulting in teeth floating in air appearance
- Sunray appearance

Management

- Aggressive chemotherapy is used to cure BL. The most commonly used chemotherapeutic agents are cytarabine, cyclophosphamide, methotrexate, doxorubicin, vincristine, and etoposide.

Multiple Myeloma

Definition

- It is the malignant neoplasm of plasma cells (derived from B cells)
- It is most common malignancy of bone in adults.

Clinical Features

- Age of occurrence: 35–70 years
- Commonly affects men
- Patient complains of fatigue, bone pain, pathologic fractures, osteopenia, weight loss, anemia, usually complain of low back pain
- Secondary features include amyloidosis, hypercalcemia, Bence Jones proteins in patient's urine, which causes urine to be foamy
- Focal osteolytic bone lesions

Oral Manifestations

- Tooth pain, mobility of teeth, swelling, hemorrhage, paresthesia, dysesthesia
- Macroglossia, gingival and soft tissue enlargement due to amyloid deposition
- Pallor, petechiae, ecchymosis, and increased bleeding tendency.

Radiographic Features

- Mandible is most commonly affected than maxilla, punched-out radiolucency in the bones without corticated margins, asymptomatic osteolytic lesions, sunray appearance.
- Generalized bone rarefactions and osteoporotic changes as disease advances.

TABLE 20.7: Burkitt's lymphoma

Type	*Clinical features*
Endemic BL	• Occurs most commonly in African children age of occurrence 4–7 years • Male to female ratio—2:1 • Caused by Epstein-Barr virus • Primarily involves the facial bone and jaws • Extranodal sites are kidneys, gasterointestinal tract, ovaries, breast • Rarely occurs in the United States
Sporadic BL	• Uncommon form of NHL • Affects older adult patients (age >40 years) • Illeocecal area in the abdomen is the most common site of involvement • Other features are pleural effusion, ascites, involvement of lymph nodes, Waldeyer's ring, ovaries, breast, kidneys.
Immunodeficiency related BL	• Manifestations are secondary to immunosuppressive drugs used to prevent transplant rejection

Treatment

- Chemotherapy with radiation therapy for painful bony lesions
- Combination of cyclophosphamide/melphalan with prednisolone is often used

Dental considerations

- Dental treatment is complicated by anemia, infections, hemorrhagic tendency, renal failure and use of corticosteroids.
- Bleeding tendency due to thrombocytopenia

FREQUENTLY ASKED QUESTIONS

1. Write a short note on cyclic neutropenia, agranulocytopenia.
2. Discuss the classification, clinical features, oral manifestations, diagnosis and management of leukemia.
3. Describe lymphoma.
4. Discuss multiple myeloma.

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Chapter 21

HIV Infection and Acquired Immune Deficiency Syndrome (AIDS)

AIDS or acquired immune deficiency syndrome is caused by human immunodeficiency virus (HIV). HIV is a type of retrovirus with nucleic acid in the form of RNA and during replication this RNA changes into DNA. Its shape is round and 80–100 nm in diameter. It comprises four elements—genome, matrix, capsid, envelope. It is originated between 1960s and 1970s, where humans were infected with it from chimpanzee.

Etiology and Spread

There exist two recognized types of HIV: HIV-1 and HIV-2. Both the types have similar modes of transmission, and can cause immunosuppression or AIDS. This virus attack on the immune system, especially the CD4 T-lymphocytes (CD4 cells). Once infected, the virus gradually and silently suppresses the host's defense mechanisms, resulting in opportunistic infections and even cancers. Differentiated CD4 cells have an essential role in the activation of cell-mediated and humoral immune systems. Various causes and modes of spread for HIV are as follows.

Causes

People transmit HIV in body fluids, including blood, semen, vaginal secretions, anal fluids and breast milk.

Spread

- Anal or vaginal intercourse with a person who has HIV
- Sharing equipment for injectable banned drugs, hormones, and steroids with a person who has HIV
- A pregnant woman with HIV infection who has recently given birth might transfer the disease to her child during pregnancy, childbirth, or breastfeeding.
- Through blood transfusions and during blood donations.

REVISED CLASSIFICATION SYSTEM FOR HIV-1993 BY CDC2

The CDCs proposed classification system for HIV infection: Divides HIV infected patients into three laboratory categories and three clinical categories.

Clinical Category A

Conditions

- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute (primary) HIV infection with accompanying illness or history of acute HIV infection
- Conditions listed in categories B and C must not have occurred.

Clinical Category B

Symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical category C and that meet at least one of the following criteria:

a. The conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity or
b. The conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection.

Examples of, but not limited to, the following conditions:

- Bacillary angiomatosis
- Candidiasis, oropharyngeal (thrush)
- Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/ cervical carcinoma *in situ*
- Constitutional symptoms, such as fever (38.5°C) or diarrhea lasting greater than 1 month
- Oral hairy leukoplakia
- Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
- Peripheral neuropathy

Clinical Category C

Conditions

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV related
- Herpes simplex: Chronic ulcer(s) (greater than 1 month's duration) or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (greater than 1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *M. kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis carinii* pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

Laboratory Categories

Category 1: A CD4+ lymphocyte count of more than 500 cells/mm^3

Category 2: A CD4+ lymphocyte count from 200 through 499 cells/mm^3

Category 3: A CD4+ lymphocyte count below 200 cells/mm^3.

Clinical Features

The early symptoms of HIV infection may include: Fever, chills, joint pain muscle aches, sore throat, sweats particularly at night, enlarged glands, a red rash tiredness, weakness unintentional weight loss, thrush.

Flu-like symptoms {acute retroviral syndrome} can be seen within a month

or two, but not in all patients (when CD4 count falls below 200 cells/mm^3). These symptoms usually disappear within a couple of weeks {2–6 weeks}, and a person may be asymptomatic (CD4 cell count up to or above 500 cells/mm^3)for many years. This period can last for five to seven years or longer in adults and two to five years or longer in children born with HIV. If patient is not on medication, HIV weakens the ability to fight infection which leads to late stage or stage 3 (CD4 cell count <50 cells/mm^3).

Symptoms of late-stage HIV infection may include: Blurred vision, diarrhoea, which are usually persistent, chronic dry cough, a fever of over 100 °F (37 °C) lasting for weeks, night sweats, permanent tiredness, shortness of breath or dyspnea, swollen glands lasting for weeks, unintentional weight loss,white spots on the tongue or mouth.There are many opportunistic infections found in HIV patients (Table 21.1).

Investigation

HIV infection is confirmed by correct laboratory testing. Western blot analysis is standard confirmatory test. This is highly sensitive and specific, with low false-positive rates.

But, many cases of recent HIV infection may be missed because it takes several weeks to develop antibody response. As a concern, other testing methods have been developed and approved by the Food and Drug Administration (FDA). Currently, there are four rapid HIV tests that have been approved by the FDA. Two of these rapid HIV tests (OraQuick and Multispot) are able to screen for both HIV-1 and HIV-2, whereas the other two tests (Reveal and Uni-Gold Recombigen) only screen for HIV-1 (Table 21.1).

Treatment

The initial task is to identify the state of current infection (acute or chronic) and it consists of a complete medical history, physical examination, and laboratory evaluation. Treatment of HIV has now become simpler and cheaper because of availability of fixed dose combinations and low cost generic drugs. There are many classes of antiretroviral drugs with many new additions to manage and prevent drug resistant mutations and it completely depends upon CD4+ count and viral load. Treatment is suggested when count goes below 200 cells/mm^3. It is based on targeting the opportunistic infections associated with immunosuppression and the HIV itself. These are:

1. Fusion inhibitors
2. Nucleoside reverse transcriptase inhibitors (NRTIs)

TABLE 21.1: Investigations for HIV/AIDS

S. no	*Headings*	*Tests*	
1.	Specific	ELISA	
2.	Antibodies based tests	1. Screening: ELISA, Rapid test	2. Supplemental or confirmatory test a. Western Blot . b. Immunofluorescent assay c. Radioimmuno precipitation assay
3.	Other tests	a. P24 Antigen detection b. Polymerase chain reaction test c. Culture d. Plasma /viral load e. Alternative to classical test: Saliva and urine test	

3. Non-nucleoside reverse transcriptase inhibitors (NNRTIs), and
4. Protease inhibitors (PIs).

WHO guidelines for ART initiation have also changed recently based on the evidence of benefits of early ART initiation in terms of providing healthier life to HIV infected patients. Guidelines for ART in paediatric age group have also been revised recently.

Recently wide range of NRTIs drugs which include abacavir (ABC), didanosine (ddI), emtricitabine (FTC), lamivudine (3TC), stavudine (d4T), tenofovir disoproxil fumarate (TDF), zalcitabine (ddC), and zidovudine (AZT, ZDV) are used. It binds near the catalytic site of reverse transcriptase and inhibits a crucial step in the transcription of the RNA genome into a double-stranded retroviral DNA.

The treatment of HIV infection requires combination therapy known as highly active antiretroviral therapy (HAART).

Oral Health Considerations

Each patient must be assessed individually. Initial priorities to treat the patient are:

1. Alleviate pain
2. Restore function
3. Prevent further disease
4. Consider esthetic results

Pain is the most common cause for which patient visits a dentist. Before reaching the diagnosis, detailed history, vital sign and cardiovascular history and other history should be taken. HIV-infected patients will require care either for their routine dental treatment or oral conditions associated with their underlying disease. Prior to initiating therapy, the dental practitioners should check for patient's immune status, medication profile, CD4+ count, neutrophil count, and platelet count.

1. For pulpits dentist should do the needful restoration and if it is not restorable then plan extraction. Before extraction antibiotics should be given to the patients. In case of abscess it is necessary to differentiate its origin between periodontal and periapical and frame the treatment accordingly.
2. Treatment of NUG/NUP involves mechanical debridement to eliminate microbial accumulations with scaling of gross deposits followed by meticulous scaling and root planing, oral hygiene instruction, chemotherapeutic agents and frequent recall visits. In addition to antibiotics and antifungal agents, twice daily home use of a 0.12% chlorhexidine oral rinse is recommended for preventing and controlling plaque formation and to reduce the development of gingivitis.
3. Periodontal lesions that fail to respond to correctional therapy must be evaluated further, usually by biopsy for a definitive diagnosis. Teeth with a poor prognosis may be maintained instead of extracted if a patient is deemed a poor candidate for tooth replacement.
4. "Dry socket" (localized osteitis), is common complication with an extraction which occurs in 3–4% of all extractions among the general population. Studies to date suggest that this complication rate is similar in the HIV positive group. Wisely use of aseptic and atraumatic surgical techniques is essential to minimize the introduction of pathogens into a surgical wound and to reduce postoperative complications. Also use of a prophylactic, intra-alveolar socket medicament after surgery may prevent delayed healing in patients with HIV.
5. Orthodontic treatment is considered in early stages and it is contraindicated in late stage. In some cases, orthodontic treatment may be modified for the HIV patients. Specific modalities can be chosen that avoid stress on teeth. Combination of different appliance therapy are used to reduce length of time and to provide faster results. Combined restorative and orthodontic treatments are another available alternative.
6. Oral lesion like ulcers and opportunistic infections should be treated as an

emergency by routine management. It can be treated either topical or systemic administration of drugs on the basis of severity and extent of infection. Fluconazole 750 mg tablet and gel for 14 days are widely used in treatment of oropharyngeal candidiasis.

For oral candidiasis topical application of clotrimazole used as an oral troche 10 mg. One troche should be dissolved in mouth for 15–20 mins for 5 times a day and dose for systemic clotrimazole drug is 200 mg. Maintenance phase is necessary as the patient's HIV status progresses.

In case of deep mycosis, the role of the dental practitioner is to instruct the patient for regular home care to optimize oral hygiene.

7. For viral infections acyclovir and valaciclovir are used. Acyclovir resistant herpes ulcerations are usually treated with foscarnet. Herpes zoster is treated with acyclovir 800 mg five times daily for 10 days with added symptomatic treatment (3,4).

Precaution for patients: When patients are on ART, chance of major complications is reduced so the goal of the therapy is to improve oral hygiene and function, manage HIV-associated oral lesions and drug-induced oral side effects and improve quality of his or her life. Patients with low platelet counts are at high risk for increased bleeding and should be managed accordingly. Hemoglobin below 7g/dl requires conservative dental treatment.

Precaution for dentist: The most important part in these cases is infection control, it plays a vital role in health safety of both patients and doctors as well as assistants. Proper method of sterilization and use of personal protection measures like immunization, clothing, hand gloves, eyewear, face shield are recommended.

FREQUENTLY ASKED QUESTIONS

1. Oral manifestations/dental considerations of HIV.

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Chapter

22

Neuromuscular Disorders

INTRODUCTION

Neuromuscular disorder literally means caused due to muscle impairment because of pathology in the associated nerves.

These neuromuscular disorders have a collective lifetime prevalence rate of 3% to 5% which makes their encounter common with the dental practitioner.

These disorders affect the dentition, soft tissues and the occlusion and hence we should be aware of their oral manifestations, dental management and treatment.

History Taking for Neuromuscular Disorders

1. While obtaining the medical history, the clinician should attempt to define onset and course of the illness as well as the distribution of symptoms.
2. The course of the disease may be chronic and progressive, monophasic, or relapsing.
3. The patients presenting symptoms are dependent upon the muscle groups that are predominantly affected. Early manifestation of proximal lower extremities weakness is progressive difficulty climbing stairs and in arising from a chair, commode, or the floor.
4. A patient with neck weakness will often complain of difficulty lifting their head off a pillow. Further, sudden braking or accelerating in a car can cause the head to jerk back and forth. Involvement of cranial muscles may result in ptosis, diplopia, dysarthria, or difficulty chewing and swallowing.
5. The examiner should ask about the presence of extreme fluctuations in strength during the day or associated with physical activities. Such fluctuations in strength are more typical of neuromuscular junction disorders.
6. Observant patients may also detect a progressive loss of muscle bulk about various aspects of their body, particularly involving the anterior thigh, shoulder, and occasionally face and small intrinsic hand muscles.
7. Alternatively, some muscle groups may be noted to be enlarged. Some disorders are associated with fasciculations, myalgias, cramps, stiffness or myotonia, periodic paralysis, and myoglobinuria. If these symptoms are not offered by the patient, their presence should be inquired by the clinician.
8. It is important to inquire about sensory symptoms. Patients may complain of feeling "numb," but this word has different meanings for different people. If not offered by the patient, the examiner should specifically ask the patient about the presence or absence of sensory loss or tingling, prickly, or burning pain.

9. The pain associated with these disorders is typically described as a deep, aching discomfort in the muscles and is seldom severe enough to warrant analgesics. Usually the pain is diffuse rather than localized and is not tender.
10. The past medical history of patients should be addressed because various medical diseases are associated with neuromuscular disorders. For example, inflammatory myopathies may be seen in patients with connective tissue disease; concurrent autoimmune disorders may be present in patients with myasthenia gravis.
11. A careful family history is also vitally important in attempting to define the possible mode of inheritance or degree of genetic penetrance. When a hereditary disorder is suspected, it is valuable to examine affected family members.
12. In patients with progressive weakness, a history regarding possible toxin exposures is important. These exposures may come from the work or home environment or from medications. Such toxins can result in damage of the peripheral nerves, neuromuscular junction, or muscle. The severity of the clinical manifestations often depends upon the type of toxin as well as the dose and duration.

Clinical History in Neuromuscular Diseases

- Weakness
  - Anatomic distribution/pattern of weakness and focal wasting or hypertrophy of muscle groups (arms versus legs, proximal versus distal, symmetric versus asymmetric)
  - Myopathies have weakness that is usually proximal greater than distal with rare exception
- *Course of weakness:* Acute onset (days to weak)
  - Chronic (month to year)
  - Episodic
  - Is the weakness getting worse, staying the same, or getting better?
  - Ascertain the rate of progression (days, weeks, months or years)
- Fatigue or lack of indurance
- Muscle cramp or stiffness
- Lack of sensory loss
- *Gait characteristics:* Toe walking, excessive, lordosis, Trendelenburg or gluteus maximus, lurch, etc.
- Functional difficulties
  - Ambulatory distances
  - Frequency of falls
  - Transition from the floor to standing
  - Problems of climbing stairs
  - Problems in dressing
  - Problems in reaching overhead
  - Difficulty lifting
  - Running ability, problems in physical education and recreational or athletics performance
- Onset age (neonatal , childhood, teen, adult (20–60 yrs) or geriatric)
- Identify factors which worsen or help primary symptoms
- History of recent illness (e.g. recent viral illness, respiratory difficulties, pneumonia, pulmonary infection)
- Pain
- Feeding difficulties, dysphagia , nutritional status and body composition
- Cardiac symptoms (dizziness, syncope, chest pain , orthopnia, cardiac complaints with exertion)
- Pulmonary symptoms (breathing difficulties, sleep disturbances, morning headache)
- Anesthetic history (e.g. malignant hyperthermia)
- History regarding child's acquisition of developmental milestones
  - Ascertain when the child was able to control his or her head, sit independently, crawl, stand with or without support, walk with and without support, gain fine motor prehension and acquire bimanual skill (bringing objects to midline, transfer of objects)

- History regarding language acquisition, mental development and school performance
- History regarding pregnancy and neonatal period
  - Quality of fetal movement, pregnancy complication, perinatal complication, evidence of fatal distress, respiratory difficulties in the recovery room, need for resuscitation or ventilation problems in early infancy, infantile hypotonia, weak cry, poor feeding.

This chapter focuses on the most common neuromuscular disorder affecting the orofacial region and their management, pertaining to oral physicians.

- CVD
- Multiple sclerosis
- Parkinsonism
- Huntington's disease
- Seizure disorders
- Bell's palsy
- Myasthenia gravis

1. Cerebrovascular Disease or CVA or Stroke

Refers to disorders that cause damage to cerebral blood vessels due to impaired cerebral circulation.

Etiology

A. It is caused due to sudden impairment in central leading to death or focal neurologic deficit.

B. Strokes result from:
- Hypertension
- Trauma
- Substance abuse
- Aneurysmal rupture

C. 85% strokes result from ischemia due to atherosclerotic disease, thromboembolic event, occlusion of cerebral vessels.

Clinical Features

It depends on the size and location of the affected brain region. Common signs and symptoms are:

- Sensory and motor deficit
- Paresis in eye movements
- Visual defects
- Sudden headache
- Dizziness
- Nausea
- Seizures
- Impaired memory

Diagnosis

1. Stroke should be considered whenever a patient experiences the aforementioned clinical features.
2. Other diagnostic methods are MRI brain, non-contrast CT scan
3. Lab investigations include complete blood count, urinalysis, coagulation profile and when indicated blood culture, ECG and lumbar puncture.

Treatment

1. Management of acute stroke includes medical therapy to reduce bleeding or thromboembolic occlusion.
2. Thrombolysis with intravenous tissue plasminogen activator (TPA) from 3–4.5 hours after stroke onset.

Oral Health Considerations

1. Following stroke patients may experience oral problems like masticatory and facial muscle paralysis, impaired taste sensation, diminished gag reflex and dysphagic which need to be managed according to the presenting complaint.
2. Maintenance of oral hygiene replacement of missing teeth should be done.
3. Blood pressure should be monitored to prevent stroke and history should be taken about previous episode of stroke.
4. Patients with a history of stroke are usually using aspirin and warfarin, hence use of NSAIDs may increase the risk of bleeding and their long-term use may reduce the protective effect of aspirin.
5. Stress reduction during dental visits should be done for which pre-operative inhalation N_2O-O_2 or oral anxiolytic can be used.

6. Local anesthesia containing epinephrine can be used in stroke patients but should be used judiciously.

2. Multiple Sclerosis

It is a relapsing remitting autoimmune inflammatory demyelinating disease of the CNS.

Etiology

1. It can be caused secondary to trauma.
2. Though the exact cause of MS is unknown, genetic susceptibility clearly exists.
3. It is mostly an autoimmune reaction in which major histocompatibility complex (MHC) on chromosome 6p21 has been identified.
4. Infections agents like Epstein-Barr virus and human herpesvirus 6 are also implicated in the pathogenesis of MS.

Clinical Features

1. Age of onset of MS is typically between 20–45 years.
2. It is more common among women than men (2:1 ratio).
3. Clinical features of MS depend upon the area of the CNS involved and frequently affected areas include optic chiasma, brainstem, cerebellum and spinal cord.
4. The sudden onset of optic neuritis without any other CNS signs or symptoms could be the first symptom of MS.
5. Diplopia, blurring, nystagmus are also commonly seen.
6. Limb weakness is characteristic of MS and can be manifest as loss of strength, fatigue or gait problems.
7. Ataxia may affect the head and neck of MS patients and may cause cerebellar dysarthria.
8. These patients often show sensory impairment including paresthesia and hyperesthesia.
9. These patients often show sensory impairement including paresthesia and hyperesthesia.

Diagnosis

1. MS lesions are called 'plaques' which are characterised by perivenular cuffing with inflammatory mononuclear cells, which are seen in the white matter and periventricular area of the CNS.
2. These plaques are visible as hypertense and hypotense areas on T2 and T1 weighted images respectively, suggestive of chronic and active lesions which are diagnostic of MS.
3. Other advanced imaging techniques that are being evaluated for diagnosis of MS are diffusion sensor imaging, magnetization transfer imaging, proton magnetic resonance spectroscopy and functional MRI.

Treatment

1. Glucocorticoids can be used to manage both initial attacks and acute exacerbation of MS.
2. Intravenous methylprednisolone is administered at a dose between 500–1000 mg per day for 3–5 days
3. Disease modifying agents include injectable (interferon) IFN-beta/a, IFN-beta/b, and glatiramer acetate.
4. Nitroxantrone (novantrone) is a chemotherapeutic agent administered intravenously that is effective in reducing neurologic disability.
5. Some other common agents used for management of MS are anticonvulsants, benzodiazepines, tricyclic antidepressants, smooth muscle relaxant, anticholinergic agents and analgesics.

Oral Health Considerations

1. MS patients can present with trigeminal neuralgia (TN) with possible absence of trigger zones and continuous low intensity pain which should be managed similar to typical TN.
2. Patients may present with neuropathy of the maxillary (V2) and mandibular branch (V3) of the trigeminal nerve which may result in burning, tingling or reduced sensation.

3. Neuropathy of the mental nerve can cause numbness of the lower lip and chin.
4. Facial weakness and paralysis may be seen in MS patient.
5. Dysarthria may be seen as scanning speech in these patients.
6. Elective dental treatment should be avoided in MS patients during acute exacerbation.
7. These patients may require dental treatment in operating room under general anesthesia.
8. Patients relatives or nurse should be appraised about the importance of daily home care of oral hygiene.

3. Parkinsonism

It is a neurodegenerative disorder characterized by rigidity, tremors, bradykinesis and impaired postural reflex.

Etiology

1. In idiopathic parkinsonism, there is dopamine depletion due to degeneration of the dopaminergic higrostriatal system in the brainstem.
2. This leads to an imbalance of dopamine and acetylcholine which are neurotransmitters that are normally present in the corpus striatum.
3. Symptoms similar to parkinsonism may also be induced by drugs that cause a reduction of dopamine in the brain, the most common drugs being phenothiazine derivatives.
4. Although, a definite etiology has not been established, the most likely explanation is that the disease results from a combination of accelerated aging, genetic predisposition, exposure to toxins and abnormality in oxidative mechanisms.

Clinical Features

1. It affects people older than 50 years of age.
2. The 4 cardinal motor signs of parkinsonism are resting tremors, rigidity or stiffness, bradykinesia and postural instability or impaired balance and coordination.
3. 50% of patients with this develop dementia, depression, anxiety, apathy and irritability.
4. Anatomic dysfunction can cause orthostatic hypotension, constipation, urinary frequency and urgency and abnormal sweating.

Diagnosis of Parkinsonism

1. The diagnosis is based on the health history, neurologic examination and response to levodopa therapy.
2. Differentiating classic parkinsonism from a variety of parkinsonian syndromes characterized by motor decline and dementia can be challenging.
3. Anatomic and functional brain imaging, CSF evaluation can be useful to exclude other diagnosis.

Treatment

1. Dopamine replacement therapy using levodopa combined with carbidopa remains the initial gold standard.
2. Anticholinergics such as scopolamine may help control tremor and rigidity.
3. Dopamine agonists such as bromocriptine, pergolide, pramipexole alone or in combination with levodopa may control parkinsonism.
4. Rivastigmine, a cholinesterase inhibitor, is effective in treating parkinsonism dementia.
5. Clozapine is effective for treating parkinsonism psychosis.
6. Exercise has demonstrated significant benefit in physical conditioning, gait, balance, leg strength and walking speed.

Oral Health Considerations

1. Patients experience increased salivation and drooling, making maintenance of dry field difficult for some dental procedures.
2. Angular cheilitis is common in these patients.
3. Use of anticholinergic drugs causes xerostomia which leads to damage to teeth

and PDL and also difficulty in retaining dentures, mucosal ulcerations, denture sores, increased chance of bacterial and fungal infections.
4. Patient loses facial expressions and has slow speech that is soft and fading.
5. Tremor of the head, lips and tongue is common.
6. These patients require periodontal recall every 4–6 months owing to poor oral hygiene.
7. Enameloplasty or mouth guard is required to prevent injury to the tongue due to tardive dyskinesis.
8. Salivary substitutes and topical fluoride application are necessary in patients with xerostomia.
9. During dental procedures, chair should be positioned at 45 degree to limit muscle rigidity and breathing difficulties.
10. Appointments should be short and relaxing with nitrous oxide sedation which helps reduce stress and prevalence of tremors.

4. Huntington's Disease

Etiology

It is hereditary degenerative disease of the central nervous system characterized by chorea (involuntary movements) and dementia.

Clinical Features

1. The earliest manifestation of this disease consists of depression and irritability coupled with slowing of cognition.
2. There are subtle changes in coordinated and minor choreiform movements appear.
3. There could be progressive nonsensing of choreic movements that are observed in the face, tongue and head.
4. In advanced cases, the hyperkinesis becomes aggravated and movement can become violent, with difficulty in speech and swallowing.

Diagnosis

1. The diagnosis is based on neurological, neuropsychological and psychiatric evaluation.
2. MRI or contrast enhanced CT scan of brain can be done to reveal structural changes at particular sites in the brain.
3. Genetic testing is a confirmatory test for this disease.

Treatment

1. There is no cure for Huntington's disease, progression cannot be halted and treatment is purely symptomatic.
2. Treatment is usually involving blocking of dopamine receptors such as haloperidol and phenothiazines, which temporarily reduce the hyperkinesis and the behavioural disturbances.

Oral Health Considerations

1. Dysphagia and choreic movements of the face and the tongue will make dental treatment quite challenging.
2. Sedation with diazepam can be considered.
3. Whenever possible, dentures for such patients should be avoided because of the danger of fracture or its accidental swallowing.

5. Seizure Disorders

Seizures are paroxysmal disorders of cerebral function characterized by an attack involving changes in the state of consciousness, motor activity or sensory phenomenon.

Etiology

1. Isolated, nonrecurrent, generalized seizures among adults are caused by metabolic disturbances, toxins, drug effects, hypotension, hypoglycemia, uremia, encephalopathy drug overdoses and drug withdrawal.
2. Cerebrovascular disease may account for approximately 50% of new cases of epilepsy in patients older than 65 years.

3. Other etiologies for epilepsy include degenerative CNS disease, developmental disabilities and familial/genetic factors.

Clinical Features

There are seven types of seizures:

a. **Grand mal**
   1. It is most common type of seizure which can occur alone or with other types.
   2. This seizure begins with aura in which patient experiences epigastric discomfort or hallucinations of heating, vision or smell.
   3. It is followed by the tonic phase in seconds by unconsciousness, cry and tonic muscle spasm.
   4. The tonic phase is followed by the clonic phase composed of convulsive jerky movements, incontinence and tongue biting.
   5. Jaw is clamped shut and there is foaming at the mouth.

b. **Petit mal**
   1. These seizures occur exclusively in children and frequently disappear during second decade of life.
   2. The patient loses his consciousness, but will continue his normal activity immediately after the seizure.

c. **Psychomotor**
   1. During the seizure, the patient exhibits purposeless movements and bizzare behaviour.
   2. Patient may wander about aimlessly or may exhibit violent behaviour during the seizure.

d. **Jacksonian**
   1. The seizure begins with clonic movements of a distal portion of extremities or the face.
   2. The convulsive movements spread to the limbs, become generalized and cause loss of consciousness.

Diagnosis

1. History and physical examination are critical to diagnose a seizure.
2. Complete neurologic examination is essential which includes the testing of cranial nerve function, assessment of mental status and testing of motor function.
3. Blood studies like complete blood count, electrolytes, glucose, magnesium, calcium are done to identify any metabolic cause of seizure.
4. All the patients should undergo MRI and CT scan for detection of any pathology in the brain responsible for seizures.
5. An EEG (electroencephalogram) is an important tool for classifying seizure disorder.

Treatment

A. **Immediate management during seizure**
   1. The patient should be moved away from danger like fire, water or sharp objects.
   2. After convulsion seizes, the patient should be positioned supine with legs slightly elevated.
   3. Basic life support should be given if indicated.
   4. If convulsion continues for more than 5 minutes urgent medical help should be summoned.
   5. Intravenous anticonvulsant like diazepam should be given.

B. **Pharmacologic management**
   1. Lamotrigine, carbamazepine and phenytoin are indicated for the treatment for partial seizures.
   2. Valproic acid is indicated for the treatment of generalized tonic—clonic seizures.

Oral Health Considerations

1. These patients have high rate of physical injuries, including dental and facial trauma.
2. Hence, precipitation of seizures during dental treatment should be avoided by reducing psychologic stress. Inhalation sedation with nitrous oxide (up to 20%) and oxygen is highly recommended.

3. Phenytoin-induced gingival hyperplasia is commonly seen in anterior labial surfaces of the maxillary and mandibular gingiva. Maintenance of oral hygiene by chlorhexidine mouthwash can reduce the inflammation or surgical reduction can be done if recession.
4. Patients taking AEDs (antiepileptic drugs) have marked bone marrow suppression which causes increased chances of infection and prolonged bleeding. Hence, a complete blood count should be done prior to any dental treatment.
5. Aspirin and other NSAIDs should be avoided in patients taking valproic acid and it can possibly cause increased bleeding.

6. Bell's Palsy

It is also called facial paralysis or seventh nerve paralysis.

Etiology

1. The exact etiology is not known but viral infection like herpes simplex affecting the facial nerve causes inflammation and hence paralysis of the nerve.
2. Other causes like trauma during dental extraction, surgical procedures like parotidectomy, tumors of the cranial base, parapharyngeal space and infratemporal fossa can lead to seventh nerve palsy.

Clinical Features

1. Bell's palsy begins with slight pain around one ear, followed by an abrupt paralysis of the muscles on that side of the face.
2. The eye on the affected side stays open, corner of the mouth drops, and there is drooling.
3. As a result of masseter weakens, food is retained in both the upper and lower buccal and labial fold.
4. The face becomes expressionless and the creases of the forehead are flattened.
5. Due to impaired blinking, corneal ulcerations from foreign bodies can occur.
6. Involvement of the chorda tympani nerve leads to loss of taste perception on the anterior two-thirds of the tongue and reduced salivary secretion.

Diagnosis

1. A thorough history taking and physical examination helps in diagnosing Bell's palsy and the extent of the weakness of the facial muscles.
2. Blood tests to detect viral or bacterial infection can diagnose the etiology for Bell's palsy.
3. MRI or CT scan can be advised to rule out any pathology in the brain.

Treatment

1. Spontaneous improvement is generally seen within 6 months in most cases.
2. Combination of acyclovir 400 mg 5 times daily with prednisolone (40–60 mg daily) for a week is believed to be more effective than steroid alone.
3. Supportive measures like protecting the eye with eye patches, artificial tear substitutes should be given.
4. Injection of botulinum toxin has shown to be effective in treating this disease.
5. Physiotherapy can be advised for the muscles of face.

Oral Health Considerations

1. Patient has dropping corner of mouth due to which there is drooling of saliva. Hence dental treatment becomes difficult.
2. There may be for oral hygiene due to retention of food in the upper and lower buccal and labial folds due to weakness of buccinator.
3. Patient experiences difficulty in speech and mastication.

7. Myasthenia Gravis

Etiology

1. It is a chronic neuromuscular disease caused by autoimmune destruction of the skeletal neuromuscular junction

resulting in impaired neurotransmission and muscle weakness
2. In this condition, autoantibodies are produced to the acetylcholine receptors on the motor end plates of muscles, thus binding of acetylcholine is blocked, muscle activation is inhibited.
3. The most common autoantibody is anti-acetylcholine receptor (AChR) and less commonly a muscle specific receptor tyrosine kinase (MUSK).

Clinical Features

1. Patients with ocular symptoms like diplopia and/or ptosis.
2. Oropharyngeal, facial and masticatory muscle weakness is common and results in dysphagia, asymmetry and dysarthria.

TABLE 22.1: Guidelines for oral healthcare of patients with neuromuscular disease

Medical consultation	*Stress reduction/ anxiolytic guidelines*	*Chair position guidelines*	*Analgesia guidelines*
▪ It should be summoned when patient's status, severity and level of control is uncertain.	▪ A rapport should be established to reduce stress and anxiety.	▪ Local anesthesia can be safely used in patients with seizure disorder.	▪ NSAIDs can be used safely in majority of patients with neurologic disease
▪ Patient who has not seen a physician within last year	▪ The type of steroid taken, dose and duration of treatment should be ascertained.	▪ Intraoral anesthetics should be administered slowly following aspiration	▪ Major concern is bleeding tenderness which is most prevalent in patients with cerebrovascular disease who take anticoagulants.
▪ Corticosteroids have been taken within last 12 months	▪ Patient should obtain proper rest the night before treatment and should reduce work on the day of treatment.	▪ In patients with impaired mental capacity, lip biting after LA administration is a common post-operative problem.	▪ Respiratory depressant narcotics should be used with caution in patients with neurologic respiratory difficulties
▪ Medications and dosage are not well known by the patient	▪ Appointment should be in the morning and kept short		
▪ Need for additional medication or change in medication during dental treatment	▪ Benzodiazepines, which have minor CNS depressant activity, are the sedative/anxiolytic drugs of choice.		
▪ There are plans for stressful or complex oral surgical procedures.			
▪ Iatrogenic problem arises from dental treatment, e.g. Bell's palsy that persists more than 6 hours after dental injection.			

TABLE 22.2: Guidelines for oral healthcare of patients with neuromuscular disease

Antibiotic guidelines	*Airway maintenance and gaseous administration*	*Drug effects and interactions guidelines*	*Infection control guidelines*
Culture and sensitivity testing should be done whenever oral infection is present.	Rubber dam is recommended for routine operative procedures in patients with neurologic disease especially in patients with drooling saliva.	Valproic acid inhibits platelet aggregation and can produce palatal petechiae and abnormal bleeding.	Antibiotic prophylaxis and oral antibiotic rinses should be used when the patient is severely immunocompromised.
Oral penicillin can be used safely as long as the patient is not hypertensive to it.	Nitrous oxide therapy is an excellent anxiolytic.	Carbamazepine depresses bone marrow leading to bleeding tenderness and increased incidence of oral infections.	Contact with blood, saliva and aerosol should be minimized.
Broad spectrum antibiotics should be prescribed with caution in epileptic women who use oral contraceptives.		Primidone and phenobarbital cause atexia and drowsiness. Additional sedatives and respiratory depressants should be avoided.	Routine aseptic protocol should be followed.
In patients with myasthenia gravis, aminoglycosides who have a neuromuscular blocking effect, should be avoided.		Patient with history corticosteroid therapy may have adrenal suppression. Consultation with the physician is mandatory	

3. In severe cases, respiratory difficulty arises.
4. Patient's tongue may be supple and flaccid with bilateral groves on the dorsal surface due to atrophy of tongue musculature.
5. Palatal muscles may be affected causing patient to have difficulty in elevating soft palate.

Diagnosis

1. The clinical examination and history are highly suggestive of myasthenia gravis.
2. Diagnosis is confirmed by a variety of bedside, electrophysiological and immunological tests.
3. The most commonly used immunological test to establish a diagnosis of myasthenia gravis quantifies serum anti-AChR, with a reported sensitivity of 85%.

Treatment

1. Anticholinesterase drugs such as neostigmine and pyridostigmine bromide increase acetylcholine availability and receptor binding and provide symptomatic benefit.
2. Plasma exchange and high-dose intravenous immunoglobulin can rapidly and temporarily reduce circulating antibodies.
3. Autoantibody production can be reduced using corticosteroids and non-steroid immune suppressants.

Oral Health Considerations

1. Patient may have difficulty with prolonged mouth opening and swallowing.
2. Aspiration risks can be high and can be reduced by adequate suction, the use

of rubber dam and avoiding bilateral mandibular anaesthetic block.
3. The patient may be at risk for respiratory crisis due to overmedication.
4. Drugs that may affect the neuromuscular junction such as narcotics, tranquilizers and barbiturates should be avoided.
5. Certain antibiotics like tetracycline, streptomycin, sulphonamides and clindamycin can affect neuromuscular activity and should be avoided.

Guidelines for Oral Healthcare of Patients with Neuromuscular Disease

See Table 22.1.

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Chapter

23

Forensic Odontology

Forensic odontology is a specialized field of dentistry that deals with legal aspects. In other words, it is the application of dental science to Law. It is derived from Latin 'Forum' meaning 'Court of Law' where legal matters were debated during the Roman era. FDI defines forensic odontology as that branch of dentistry that in the interest of justice deals with the proper handling and examination of dental evidence and with the proper evaluation and presentation of dental findings.

Though the permanent tooth develops in the first two decades of life, they harbor a lot of information in the hard tissues. Forensic odontologists are highly experienced trained individuals whose job is to extract this information and use it for identification of unknown remains. Apart from its use in identification, teeth are also used as weapons and in some fortunate circumstances leave the information of the biter. Analysis of bite marks is the second major responsibility of a forensic odontologist. Forensic odontologists have also been known to assist archeologists and anthropologists in determining the ethnicity and building up a picture about the lifestyle and diet of a population. In addition, acting as an expert witness in the court of law is a legal duty of a forensic odontologist.

In the latter part of this century forensic odontology has evolved by leaps and bounds by incorporating dental anatomy, histology, radiography, pathology and dental materials

HISTORY OF FORENSIC ODONTOLOGY



Fig. 23.1: Dr. Oscar Amoedo: Father of Forensic Odonotology

Historically some cases of identification have been reported far back as 49AD. It has been said that Nero's mistress was satisfied that the decapitated head was of Nero's wife since she could recognize the anterior tooth.

Folklore attributes the first use of bitemark identification to King William the conqueror in 1066 AD who had a habit of sealing his

envelopes with sealing wax with his teeth marks on them. His mal-aligned anterior teeth allowed the substantiation of the authencity of his documents.

Dr Oscar Amoedo is regarded as the Father of Forensic Odontology. His notes made from observations during mass disasters served as the first textbook of forensic odontology termed 'L'art Dentaire en Medicine Legale'. The techniques used in forensic odontology have evolved with the evolution of mankind. During the American Revolution Paul Revere a young dentist helped identify war causalities by their dental work.

After the first dental identification in a mass disaster during the charity bazaar fire of Paris in 1897, dental identification has been used during various mass fatalities including the Thai Tsunami in 2006 and the terrorist attack of 9/11. DNA extracts from the toothbrushes of the victims were used in identification of some victims during 9/11 and 87% Thai Tsunami victims were identified using their dental records.

Forensic odontology officially entered the Indian subcontinent in 1998, but its presence was felt way before that. Raja Jaichand of Kannuj was identified by his false teeth. In fact the late prime minister Mr. Rajiv Gandhi was assassinated in a terrorist attack in 1991, and was identified by his dentition.

METHODS OF IDENTIFICATION

Reason why identification is required:

1. Legal and humanitarian reasons
2. Settlement of property and insurance
3. Facilitate remarriage of a surviving spouse
4. Last rites according to relevant religious and cultural customs.

Dental Identification

◈ Identification of an Individual

Comparative Identification

When the deceased's identity is suspected scientific methods are employed to confirm the identity by comparison of the antemortem and postmortem records of the individual.

A postmortem dental record is prepared by careful examination, charting and written description of all the dental structures including radiographs and additional supportive records like casts and photographs. Antemortem and postmortem radiographs can be marked using a rubber dam punch to avoid confusion. Once postmortem record is complete, a thorough comparison is made with the antemortem records. Features that are noticed during comparison include tooth morphology, dental restorations, and pathologies. Similarities and discrepancies are noted during comparison. The discrepancies can be explainable or non-explainable. An explainable discrepancy is when the point of discordance can be explained using the time gap between the antemortem and postmortem records.

An example of an explainable discrepancy is the presence of an intact tooth antemortem but a restored or an extraction space postmortem. Similarly extension of a filling from antemortem to postmortem can be explained.

A person with multiple dental restorations and unusal features like a mesiodens or a rotated incisor has a better likelihood of being easily identified as compared to someone who has no dental treatment done. As concluded by Acharya and Taylor unlike 12 points of concordance that fingerprints need, a single point of concordance is sufficient to establish an identity but the uniqueness of the feature has to be considered as well as the circumstances of the case.

Once an identity is established, it has to be legally documented in the form of a detailed report and conclusion is based on facts. The explainable discrepancies and significance of similarities have to be mentioned and either of the following conclusions can be drawn:

a. **Positive identification:** Indicates the antemortem and postmortem dental

data match each other. The identity can be proven "beyond reasonable doubt".

b. **Probable identification:** There is a high level of concordance between the two sets of data but may lack radiographic support. There is a consistency in data but due to the lack of quality, the identity cannot be confirmed.

c. **Possible identification:** The postmortem and antemortem data correspond but the information that is available is insufficient.

d. **Excludes identification:** There is inconsistency in postmortem and antemortem data. The data contains unexplainable differences which indicates a negative result.

e. **Insufficient information:** The available postmortem and antemortem information is minimal or insufficient to draw conclusions on the identity of the deceased.

Dental records : A dental record has subjective and objective record of the patient and the dentist is in possession of it. Whenever possible the original records should be examined. Such records may be in the form of photographs, radiographs, casts or dental charts. Frequently people visits multiple dentists, hence all the chronologically relevant contents should be noted on the composite Interpol antemortem form.

Reconstructive Identification

The purpose of reconstructive identification is to narrow down the search for the deceased individual. It helps to generate a profile of a person whose identity is unknown. Information about the deceased person's race, age, gender, socioeconomic status, occupation, and various other parameters can be determined by reconstructive identification. The skull can help identify the gender and the race to some extent. Skull along with the rest of the bones can aid in determining gender with an accuracy of 98%. Along with the shape and form of skull, other features like cusp of carabelli, shovel-shaped incisors, 3–4 cuspal premolars all aid in determination of race.

For adults age can be estimated by examining the development of teeth and comparing the teeth to an atlas of tooth development proposed by various authors like Schour and Massler, Demirijian and so on. The age can be estimated using the development stages of a tooth uptil their eruption. Gustafson used the regressive changes of the dentition like attrition, secondary dentin formation, cemental apposition, loss of periodontal attachment and transparent dentin to determine age.

Age estimation: Age can be estimated by

a. Histological methods
b. Radiographical methods
c. Eruption

Age estimation is required for an aborted fetus, a homicide victim, severely mutilated mass disaster victim, or living person who requires age estimation. Age estimation of a living person is required if birth certificate is not available or if the records are suspected. Quite a few times a request is made to help determine whether the child has attained an age of criminal responsibility.

Age estimation in Neonates: Histological methods is the more sensitive technique. Early mineralization can be detected up to 12 weeks before it is visible on a radiograph. Although radiographic interpretation has an advantage that it is non-mutilating. The incremental lines can be taken into consideration. The neonatal line is present on the developing deciduous teeth and the first permanent molar. The presence of neonatal line indicates a live birth but the absence is not an indication of a stillbirth since the neonatal line takes 3 weeks to form after birth.

Calcification of deciduous teeth begin at 12–14 weeks IU, whereas calcification of the first molar starts at the age of 6 months.The dry weight of the mineralized tooth cusps can also be measured. Stack mentions that the combined weight of the teeth in a child

at 6 months IU is about 60 mg, 0.5 gm in a newborn and 1.8 gm at 6 months after birth.

Age estimation in juveniles/adolescents: Unless there is enough of evidence and antemortem data to support the findings, age estimation should be used as an important parameter in identification rather than a definitive parameter. While writing the conclusion it should be mentioned that "the findings are consistent with a person of that age." The atlas for age estimation gives an age range for a particular range of development. Atlas has to be customized for different populations since growth variations exist for different population groups due to the difference in genetic and environmental factors. Following are the common dental development atlas.

Schour and Massler's Atlas

It describes 20 chronological stages of tooth development starting from 5 months IU until 21 years of age.

Advantages: Both deciduous and developing dentitions are shown and it includes root development and eruption sequence for deciduous teeth. The figures are to 1:1 scale and hence it becomes easy to directly compare with radiographs.

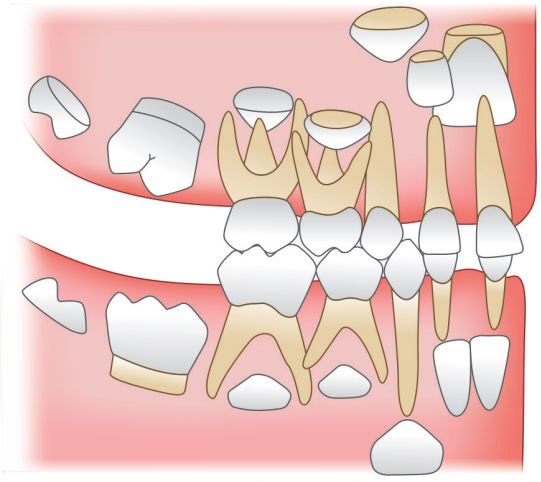


Fig. 23.2: Schour and Massler's pictorial presentation of teeth development

Disadvantages: No separate charts for males and females. The mean ages correspond well to males than to females.

Uberlaker modified the original chart and the modified altas should be used since it is more accurate.

Demirjian's Atlas

Eight stages of dental development are shown on the atlas. Each stage of mineralization is given a score which provides an estimate of dental maturity on the scale of 0 to 10. Data obtained from the regression graph indicate that the differences between males and females are not significant until the age of 5 years. A formula for an Indian population was developed by Acharya which is as follows:

Males: Age = 27.4351 – (0.0097 × S2) + (0.000089 × S3)

Females: Age = 23.7288 – (0.0088 × S2) + (0.000085 × S3)

Advantages: Missing teeth from one side can be substituted by those of the opposite side. There is a detailed description accompanying the atlas and it is simple to use.

Disadvantages: Consider only mandibular teeth and does not include the developing third molar (Fig. 23.3).

Third Molar Development

After 14 years of age once the 2nd molar is erupted, the 3rd molar is the only tooth of significance, even if the third molar has not erupted yet, its calcification should be investigated. The eruption of the third molar definitely places the age of the individual at approximately 18 years of age, though the absence of the third molar is not an indication that the individual is below 18 years of age. In many countries including India 18 years is considered the age where the individual can be tried as an adult and not considered a juvenile anymore. The juvenile justice amendment bill states that a juvenile who has committed a crime cannot be sentenced to death or life imprisonment in prison. Due

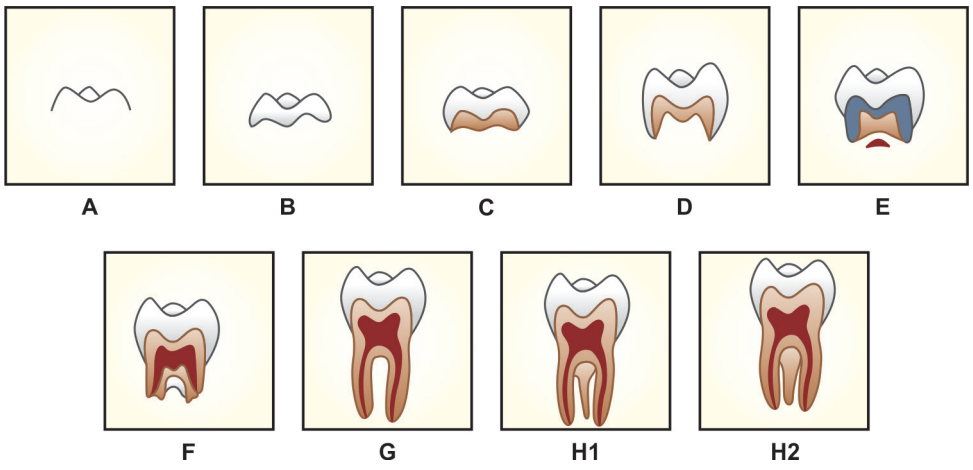


Fig. 23.3: Demirjian's method

to this law the third molar in spite of having an erratic calcification and eruption timing is still considered vital since it is the only tooth undergoing calcification.

Eruption Timing

Eruption is regarded the least accepted method for dental age assessment. This is because eruption of teeth is known to be affected by dietary, climatic, racial and geographical variation. The deciduous teeth help estimate age from 6 to 33 months and permanent teeth help estimate age from 6 to 25 years. The advantage of this method is that it does not require any special equipment, expertise and is very economical.

Age Estimation in Adults

Gustafson's method: Gustafson evaluated ground sections of teeth for 6 parameters. These 6 physiological parameters which included attrition, loss of periodontal attachment, secondary dentin deposition, sclerotic or transparent dentin formation, root resorption and cemental apposition were measured and given a score from 0 to 3. The above parameters were chosen since they showed age related changes. Transparent or sclerotic dentin and secondary dentin formation have the most correlation with age, and the former can be used independently to estimate age as well. The drawback of this method is that it is subjective. Johanson modified it and introduced 6 scores instead of 3 with an interval of 0.5. This decreased the subjectivity of the method.

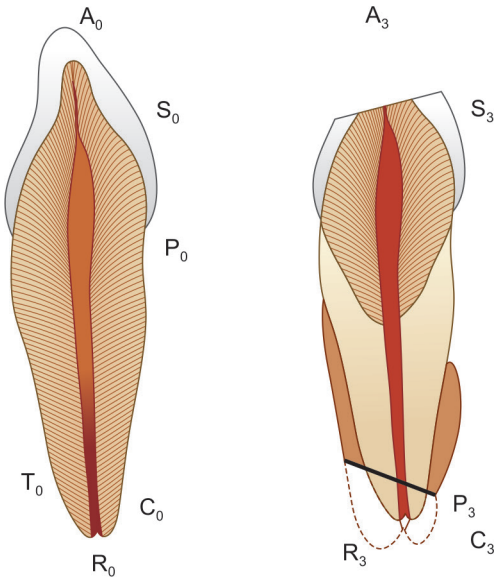


Fig. 23.4: Gustafson's variable and the first and last grades given by Johanson

Bang and Ramm's method: Transparent dentin or sclerotic dentin measurement is a relatively accurate and easy method to estimate age. Root dentin becomes transparent during the third decade of

life starting from the apical region and progressing coronally as age advances. It is least affected by external stimuli and so more accurate. The diameter of the dentinal tubules decreases as a result of intra-tubular calcification. It appears dark in reflected light and light in transmitted light, translucency is measured either on intact extracted teeth or ground sections of teeth although the latter gives a better clarity.



Fig. 23.5: Transparent or sclerotic dentin

Age estimation using tooth–pulp ratio: The area of the pulp chamber and root canal and the tooth area of canine is measured and their ratio is known as pulp to tooth area ratio. As age advances the area of pulp chamber and root canal reduces. A ratio is calculated to compensate for image magnification on radiographs and the angulation between X-ray beam and film. Population-based formulae are better, the formulae based on the Indian population predict age more accurately as compared to the formulae given by Cameriere.

Report writing in age estimation: A report is a formal document. The method used for age estimation should be mentioned in the report as well. More than one age estimation method should be used to arrive at a more accurate result. The validity of the method on the local population should be mentioned. Age should be always been mentioned as an approximate age and it is never a definite number.

Gender determination: Out of the three major parameters in dental profiling determination of gender is second important parameter. Morphology or skull and mandible, tooth measurements and analysis of dental DNA can be used to determine gender.

Morphology of skull and mandible: A number of features of skull and mandible are used to determine gender. Skull along with the rest of the skeleton can help achieve an accuracy of 98%. The reliability increases after puberty. According to William and Rogers, an ensemble of 6 traits, including mastoid process, supra-orbital ridge, size and architecture of skull, extension of the zygomatic arch beyond the external auditory canal, nasal aperature and gonial angle of the mandible can help achieve an accuracy of 94%.

Tooth measurements: The buccolingual and mesiodistal dimensions of teeth can be used to determine gender. This is especially used in children where skeletal secondary sexual characteristics have not yet developed.

Race determination: The diversity of humans is a result of combination of genetic and environmental factors including geographical location. Traditionally the human species around the world are classified into three races, viz Caucasoid, Mongoloid and Negroid. This traditional classification has been disregarded by anthropologists. Scott and Turner divided humans based on geographical origin and this classification is the current accepted classification. This diversity is seen in the human dentition as well as characterized by anthropologist, thus making it convenient to identify an individual's population origin based on the dentition.

The non-mentric morphological trait is one of the means of identifying population origin. Their presence or absence of such traits is evaluated. More than 30 nonmetric traits which include cusp of Carabelli, winging, four cuspal mandibular molars, three cuspal mandibular premolars and shoveling. Both

high and low incidences of these traits should be considered. Due to overlap of these traits in different populations, more than 2–3 non-metric traits should be considered which drawing conclusions about a particular population.

Determination of occupation/habits/socioeconomic status: In addition to the three major parameters, the findings on teeth, such as erosion, stains can help determine the occupation of the individual as well as any habits the individual possesses like drinking excessive carbonated drinks, anorexia. Stains on the teeth indicates if the individual drinks a lot of tea/coffee, chews pan, tobacco. The notching of incisors suggests habitual placement of nails or bobby pins like carpenters and tailors do respectively. The presence or absence of dental treatment as well as the quality and quantity of treatment indicate the financial status of the individual.

Identification in Edentulous Individuals

In edentulous individuals labeled dentures or the uniqueness of the denture material can be used to narrow down the search for the identity of the deceased. Presence of Kevlar fibres in the denture has been used to help establish the identity of the individual. Denture marking or labeling is particularly useful during mass fatality incidents.

DNA in Dental Identification

Dental identification essentially needs dental records, but in the absence of dental records DNA proves vital. Since dental tissues are resilient to environmental changes, teeth are considered to be an excellent source of DNA. Polymerase chain reaction causes amplification of DNA at pre-selected sites, so DNA retrieved from a root canal treated tooth is useful. DNA has been used for identification at mass disaster sites as well. DNA from the deceased is matched with an antemortem sample obtained from toothbrush, hairbrush, blood, or any other personal belongings. Mitochondrial DNA is better cause of its maternal inheritance and high copy number. The maternal inheritance allows the DNA to be matched with the parents and siblings of the deceased.

Cheiloscopy and Palatalscopy

The wrinkles and grooves on the labial mucosa form a characteristic pattern called 'Lip Prints', the study of which is referred to as cheiloscopy. Lip prints were first described by Fisher in 1902 . Edmond Locard, the French criminologist and the pioneer of forensic science, had first suggested the use of lip prints as evidence. Quite a few times lip prints are invisible; these latent lip prints are lifted using aluminium powder and magnetic powder. The oil produced by the sebaceous glands at the edges of the lips are responsible for the latent lip prints. The usefulness of the uniqueness of lip prints in identification is established but their sustainability to age changes and trauma has yet to be determined.

Palatal rugae are irregular asymmetric ridges that run laterally from the incisive papilla and the anterior part of the mid-palatine raphe. The study of palatine rugae is called rugoscopy. Palatal rugoscopy was first proposed in 1932 by Trobo Hermisa and are useful in identifying the edentulous. The rugae pattern on the deceased's maxilla can be compared to the pattern of ridges on old dentures or even to plaster models that may be available with the treating dentist. Subsequent studies on palatal rugae as a method of identification have concluded that it is difficult to formulate a universally accepted classification of palatal rugae and is more valuable as a method of comparative identification rather than determining the predipondence of a certain kind in males or females. The classification suggested by Lysell is the most commonly quoted one.

- Primary rugae (>5 mm)
- Secondary rugae (3–5 mm)
- Fragmentary rugae (2<3 mm)

Rugae less than 2 mm is not taken into consideration.

Thomas and Kotze further catergorized rugae into branched, unified, cross-linked, annular and papillary. They suggested further that as long as the technique used to compare the rugae is accurate, one need not conform to a particular classification. Ohtani et al added that the more complex the rugae pattern, greater is the tendency for non-identification.

Mass Disasters and Mass Fatalities

Webster's dictionary describes a disaster as a sudden calamitous event producing great material damage, loss of life and mental stress. Disasters can be man-made or natural. When a death of 12 or more persons occurs in a single episode, it is accepted as a mass disaster. Natural disasters are even more enormous sometimes because man cannot control nature's fury.

While managing a mass disaster priority should be given to the survivors. All efforts should be carried out to save the life of the injured person first. The area should be cordoned off with rope or tape and no outsiders should be allowed within the perimeter.

Norway was probably the first country to develop a model of investigation procedure in a mass disaster and included a dentist as well in the team.

A mass disaster is of two types:

1. *Open disaster:* Where there is no manifesto of the deceased, e.g. terrorist attack
2. *Closed disaster:* Where there is a manifesto of the deceased, e.g. plane accident

Identification in a mass fatality or a closed disaster is essentially the same as in comparative identification of an individual except the circumstances in which it is carried out is more complex due to the emotional and physical nature of the situation. Lack of standardization of dental records, poor working conditions, psychological stress, decomposition, dismemberment of human remains at the site of disaster all compounds the complexity of the situation and in turn affects the identification process. There could also be political and jurisdictional issues that may have to be addressed.

Forensic odontologists are a part of the identification team that may also include forensic pathologist, fingerprint experts, and biotechnologist as well. In addition to a forensic odontologist, general dentists and dental auxillaries should also be included considering the vast nature of the destruction. Each team member should be aware of the protocol and procedures to be followed. Tasks may vary from taking radiographs to making notes. According to the INTERPOL's disaster victim identification guide, the odontology section should be divided into three subsections, namely antemortem unit, postmortem unit and the comparison and identification unit.

Antemortem Unit

The most important requirement is to obtain a work area specific to the dental team, and the most important purpose is to obtain antemortem records of the individuals missing or believed to be involved in the disaster and dispatch the dental record to the postmortem unit. More than one dentist is required for the antemortem unit. It is the duty of the dentist to provide written records, radiographs and study models to the antemortem unit. Once the dental records are collected, a composite chart is prepared on the INTERPOL antemortem form which is yellow in color. Majority of times, the dentist fails to undertake a full mouth charting when the patient first attends and only indicates work done by one dentist. The aim of the antemortem unit is to obtain as much data as possible about as much victims as possible in as short a time as possible.

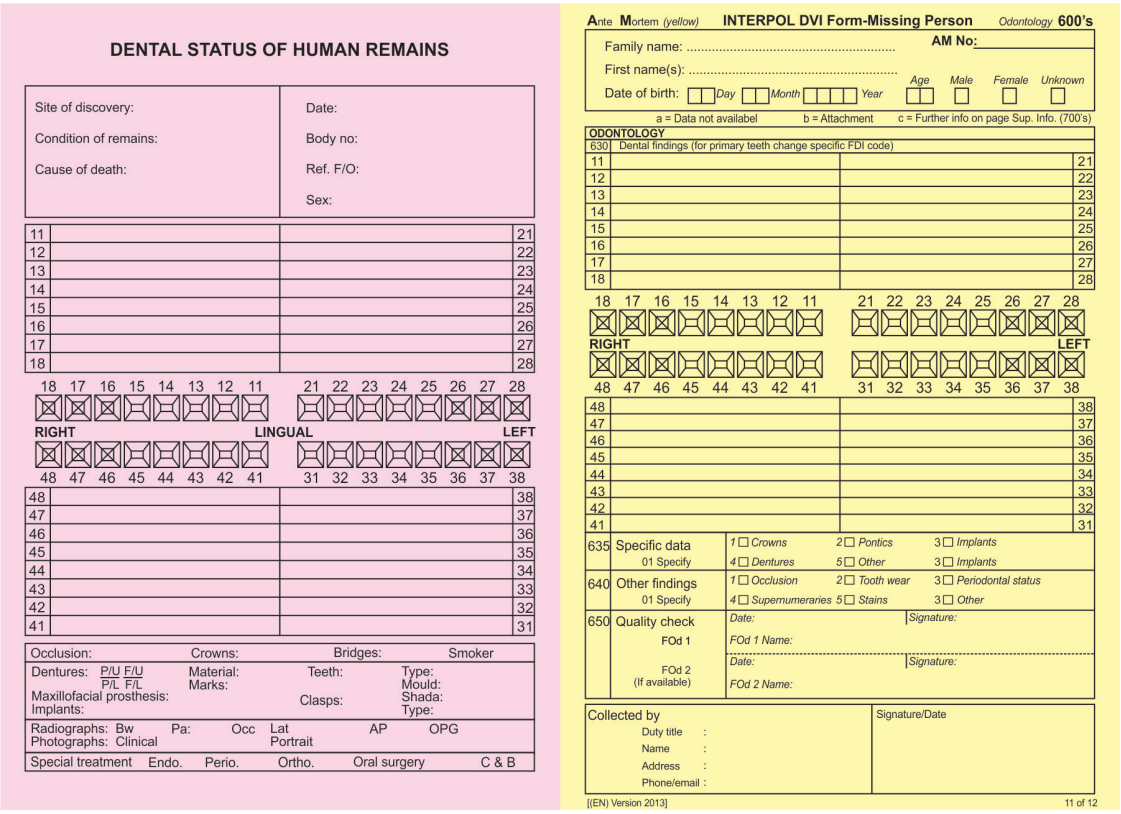
Postmortem Unit

Before postmortem charting, personal effects are removed, fingerprints, radiographs and photographs are taken and then the jaws are resected. A portable dental radiography

apparatus can be installed at the temporary mortuary with proper precaution for radiation hazard. The dentists work in pairs, one of them examining the oral cavity and the other carrying out the charting. The charting is done on an INTERPOL postmortem form which is pink in color. If the jaws are removed they should be immediately tagged with a waterproof label with the body number mentioned, bagged and tagged. In mass disasters there may be maxillofacial injuries and teeth and jaws go missing. In such cases the missing parts should be searched for, recovered and labelled. If the portions are not recovered, then the missing parts should be marked as "lost postmortem". Composite restorations cause a problem because they are not easily detected. After the charting is done the jaws have to be repatriated.

Antemortem and Postmortem Comparison Unit

Each antemortem record is compared to the most likely postmortem file spread out on a table. If the postmortem records do not provide any useful information, we move on to the next most likely record. Computer programmes like CAMPI have been used but a computer never carries out an identification, the final identification is always carried out manually. A computer just reduces the number of records to be compared. Consultation should be carried out with other teams such as DNA, fingerprinting, etc. As a positive identification is established, the antemortem and postmortem records should be stapled together. As time progresses the number of positive dental identification will grow and the supply of incoming



DENTAL STATUS OF HUMAN REMAINS

Site of discovery: | Date:
Condition of remains: | Body no:
Cause of death: | Ref. F/O:
Sex:

11 12 13 14 15 16 17 18 | 21 22 23 24 25 26 27 28

18 17 16 15 14 13 12 11 | 21 22 23 24 25 26 27 28
RIGHT LINGUAL LEFT
48 47 46 45 44 43 42 41 | 31 32 33 34 35 36 37 38

48 47 46 45 44 43 42 41 | 38 37 36 35 34 33 32 31

Occlusion: Crowns: Bridges: Smoker
Dentures: P/U F/U P/L F/L Material: Marks: Teeth: Clasps: Type: Mould: Shada: Type:
Maxillofacial prosthesis:
Implants:
Radiographs: Bw Pa: Occ Lat AP OPG
Photographs: Clinical Portrait
Special treatment Endo. Perio. Ortho. Oral surgery C & B

Ante Mortem (yellow) INTERPOL DVI Form-Missing Person Odontology 600's
AM No:
Family name: .....
First name(s): .....
Date of birth: ☐☐ Day ☐☐ Month ☐☐☐☐ Year Age ☐☐ Male ☐ Female ☐ Unknown ☐
a = Data not availabel b = Attachment c = Further info on page Sup. Info. (700's)

ODONTOLOGY
630 Dental findings (for primary teeth change specific FDI code)

11 12 13 14 15 16 17 18 | 21 22 23 24 25 26 27 28

18 17 16 15 14 13 12 11 | 21 22 23 24 25 26 27 28
RIGHT LEFT
48 47 46 45 44 43 42 41 | 31 32 33 34 35 36 37 38

48 47 46 45 44 43 42 41 | 38 37 36 35 34 33 32 31

635 Specific data 01 Specify: 1 ☐ Crowns 2 ☐ Pontics 3 ☐ Implants 4 ☐ Dentures 5 ☐ Other 3 ☐ Implants
640 Other findings 01 Specify: 1 ☐ Occlusion 2 ☐ Tooth wear 3 ☐ Periodontal status 4 ☐ Supernumeraries 5 ☐ Stains 3 ☐ Other
650 Quality check FOd 1: Date: Signature: FOd 1 Name:
FOd 2 (If available): Date: Signature: FOd 2 Name:

Collected by
Duty title :
Name :
Address :
Phone/email :
Signature/Date

[(EN) Version 2013] 11 of 12

Fig. 23.6: INTERPOL antemortem yellow form and postmortem pink form

antemortem records will reduce. The left over unidentified victims cause problems and take a lot of time. According to the guide provided by INTERPOL, success of a disaster identification depends on the co-operation of different identification teams.

Bitemarks

McDonald has defined bitemarks as "a mark caused by the teeth either alone or in combination with other mouth parts". It can caused by humans or animals and can be made on inanimate objects as well. Biting is considered a primitive weapon.

Classification

McDonald's classification

Tooth pressure marks: Marks produced by direct application of pressure by teeth. It shows indentation of incisal or occlusal surfaces.

Tongue pressure marks: The tongue may press on the rigid areas like the palatal or lingual surfaces of teeth when sufficient amount of tissue is taken into the mouth. This may cause a central area of ecchymosis.

Tooth scrape marks: Marks caused by scrapping of teeth along the object. It exhibits as abrasions or scratches.

Appearance of a Bitemark

A bitemark is actually an injury and can be identified using the following characteristics:

Gross characteristics: Circular or elliptical mark with a central area of ecchymosis. The elliptical mark is due to the upper and lower arches.

Class characteristics: The marks produced by different classes of teeth are different and distinctive. Incisors create rectangular marks, canines triangular and molars spherical or point shaped.

Individual characteristics: Certain teeth may show unique characteristics like rotation and fractures.

Bitemark Investigation

Preliminary questions: Drinnan and Melton as well as Sweet have suggested preliminary questions to aid in the investigation of the bitemark:

1. Is the injury a bitemark?
2. If it is a bitemark, is it human or animal?
3. Is the bitemark by an adult or a child?
4. Are there any unique characteristics that can help analyze the bitemark?
5. Can these characteristics be compared to the teeth of the subject?

Evidence Collection from the Victim

In the event that a bitemark case comes to the dentist directly the law enforcement authority has to be informed. Studies have shown that there is a probability of transmission of HIV, hepatitis B, and syphilis from the bite to the victim, so due care has to be taken especially when there is a break in the dermis. The victim's name, age, gender, date of examination, and name of examiner has to be noted. In case the bite mark is on an area where there is a possibility of self-inflection, then the vicitim can also be considered as a suspect.

According to Brown, visual examination has to be carried out before the autopsy is done. During visual examination the following points have to be noted.

1. Orientation of the bitemark
2. Color, size and shape of the bitemark
3. Type of injury
4. Contour and elasticity of the bite site
5. Differences between upper and lower arches

Photography

Pictures should be taken as soon as the case presents itself to the dentist since the injury changes color because of healing. Both color and black and white pictures are to be taken.

Orientation photograph: It depicts the location of the bitemark on the body.

Close-up photograph: The ABFO scale no. 2 is a rigid reference scale. It is placed on the

bitemark in one plane and a photograph is taken. The scale should not obstruct the view of the bitemark on the photograph. A second close-up photograph can be taken to depict that no part of the bitemark is obstructed by the scale.

The camera is positioned such that its long axis is perpendicular to the bitemark to reduce distortion. If the bitemark is on a curved surface like the forearm and the upper and lower arches of the bitemark are far apart, then separate photographs of each arch should be taken. According to Brown, if the victim is alive then photographs can be repeated every few hours to record the color changes due to healing.

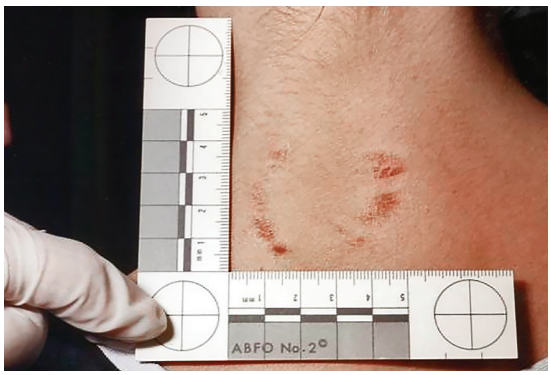


Fig. 23.7: Correct position of ABFO scale no. 2

Saliva Swab

The saliva left behind on a bitemark can be swabbed for DNA. The site of injury should not be washed before swabbing. If the bite mark is made through clothes, then the clothes should be swabbed for salivary DNA. A cotton swab moistened with distill water should be swabbed for DNA. Swabbing should always be done from the centre of the injury to the periphery in circular motions. There are two schools of thought, one which says that the swab should be air dried, bagged labeled and then stored in the fridge and the other which says that the swab should be placed in a plastic bag and labeled and then stored. The former has a disadvantage of contamination and the later of degradation of DNA and bacterial growth.

Impression

Impressions can be made only when tooth indentations exist. Impressions are made using Vinyl Poly siloxane and can be reinforced with dental stone or impression compound to prevent dimension change. In case of suspected self-inflected bites impressions of the victims dentition should also be taken.

Evidence Collection from the Suspect

A warrant (court order), a signed and witness informed consent are needed before collection of evidence. Infection protocol. The following evidence have to be procured from the suspect

1. Photographs of the suspect teeth in occlusion and in open bite.
2. Impressions of the maxillary and mandibular teeth.
3. Saliva swabs

Evidence has to be stored in well-labeled boxes or bags. The labels should include case number date, times, place as well as witness present during evidence collection. A 'chain of custody' should be maintained. Every individual that handles the evidence after collection signs and puts a date/time stamp on it.

Bitemark Analysis and Comparison

Factors to be considered during bitemark analysis include movement on the part of the victim, the elasticity of the area bitten, movement of the perpetrator and distortion during photography. Due to these variables majority of the bitemarks cannot be analyzed. It is erroneous to forcefully analyse and compare such bitemarks. Measurements such as intercanine distance are obtained once the canines are identified. These measurements are then compared to the model of the dentition of the suspect.

Bitemark analysis and comparison are two different concepts. Bitemark analysis is conducted as a part of a medicolegal autopsy. It provides information that when shown to

the criminal justice system can dramatically influence the outcome.

Analysis should be carried out before introducing any suspect to prevent bias. It involves answering basic questions. Answers to these questions produce a large amount of information which along with other non-dental evidence can be valuable to the prosecution or the defense.

Bitemark comparison, on the other hand, is the comparison of a human bitemark to a suspect, dentition using various methods such as dental models and overlays. This is usually done to eliminate the suspect from a pool of perpetrators.

Direct method: Authors such as Ciapparelli and Hughes advocate the direct method of comparison where the suspect's dental models are placed directly over the photograph of the bitemark.

Indirect method: The incisal and occlusal surfaces of the teeth are traced onto clear acetate paper and superimposed onto bitemark photographs that are of 1:1 scale. The lifesize image is taken to minimize distortation. Authors Johansen and Bowers have suggested the use of adobe Photoshop® instead over transparent overlays with the incisal and occlusal edges.

Conclusions in Bitemark Analysis

Definite biter: There is enough of evidence to indicate that the bitemark is produced by the suspect beyond reasonable doubt.

Probable biter: Some degree of specificity is present due to significant number of matching points.

Possible biter: The bitemark and the suspect's dentition are consistent although there are not significant number of matching points to be absolutely certain.

Not the biter: There is no consistency between the bite mark and the suspects teeth.

Due to the confusion between bite mark comparison and bitemark analysis, there is a possibility that the information from bitemark analysis could also be lost if bite mark evidence is disallowed.

Forensic Radiology

The first civil case in which X-rays were accepted in US court took place in Denver. The earliest case of an identification on an unknown decent made through comparisons of sinuses in skull radiographs was published in 1926.

The antemortem radiographs are evaluated for quality, type of radiograph and the time period of when it must have been taken. It is possible to fix sub-optimal radiographs but it would depend on the situation when the comparison is required as in the case of mass disasters fixing the radiograph is not of prime importance. The postmortem specimen is evaluated and it is exposed such that it duplicates the areas of interest seen in the antemortem films. It is difficult to re-create the antemortem film geometry on postmortem films. It may require a number of attempts. Because of the complex nature of exposing radiographs, more postmortem radiographs are taken than the bare minimum necessary. The films are then marked as AM or PM. Points of concordance and disconcordance are noted.

Dental treatment carried out on the ante-mortem and postmortem radiographs is considered for comparison. In the absence of dental intervention, less common but static anatomical features are used as concordant points.

Sometimes despite a number of attempts, it is not possible to duplicate radiographs of the maxilla during postmortem because of the X-ray beam angulation of the antemortem dental films.

Facial bones are difficult to use for radiographical identification because of their anatomical complexity and overlapping structures. Frontal sinuses are used for comparison instead. The radiographic view most commonly used to demonstrate it is Water's view. The first radiographic

comparison of paranasal sinuses was carried out by Culbert and Law.

Bite wing photographs are easily performed as compared to periapical radiographs.

Width and length of the maxillary sinus are measured in computer tomography scans with the application of software.

CONCLUSION

Dental identification is based on unique individual characteristics of the dentition and dental restoration, the resilience of dental tissues, the regressive changes in teeth.

FREQUENTLY ASKED QUESTIONS

1. Write a note on bitemark analysis.
2. Write a note on Demirjian's method.
3. Write a note on age estimation in juveniles.

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Chapter

24

Geriatric and Oral Health

INTRODUCTION

Geriatrics is the branch of medicine that treats all health issues related to the aging patients, including the clinical problems of senescence and senility. This chapter focuses on geriatric changes present in oral cavity which may co-exist all manifested separately.

Physiology of Aging

It is generally believed that the physiological systems deteriorate with advancing age. Theoretically process of aging is simply the death of cells.

Progressive age changes are characterized in the following categories.

- Gradual tissue desiccation.
- Gradual retardation of cell division, capacity of cell growth, and tissue repair including reduced capacity to produce immune bodies.
- Gradual retardation in the rate of tissue oxidation (lowering of the basal metabolic rate).
- Cellular atrophy, degeneration, increased cell pigmentation, and fatty infiltration.
- Gradual decrease in tissue elasticity and degenerative changes in the elastic connective tissue.
- Decreased speed, strength, and endurance of skeletal "neuromuscular reactions".
- Decreased strength of skeletal muscle.
- Progressive degeneration and atrophy of the nervous system.

Following are the different oral changes seen with aging:

1. Tooth attrision
2. Tooth loss
3. Atrophy of alveolar and basal bone
4. Oral mucosal changes
5. Tongue changes
6. Temporomandibular joint changes
7. Changes in amount and composition of saliva
8. Changes in microbiological ecology
9. Increased incidence of malignant changes

Changes in Teeth with Aging

The gradual changes taking place in the dental tissues after teeth are fully formed are referred to as age changes. The teeth change in form and color with age. The tooth form is affected by wear and attrision.

1. Changes in enamel:

- All changes in the enamel are based on ion exchange mechanisms. It

is generally accepted that enamel becomes less permeable and possibly more brittle with age.

- Some acquired properties of surface enamel are slowly built up during life, such as the fluoride content. These changes in the surface content may therefore be considered age changes.

2. Changes in cementum

- Cementum may be resorbed and new cementum may form both locally in resorption defects or more generally over the roots, especially in the apical half, to compensate for tooth wear during function.
- The composition of cementum has also been reported to change with age, for example, the fluoride and magnesium content.
- The most characteristic age change in cementum is the gradual increase in thickness cementum deposition occurs throughout life.
- The total width of cementum almost triples between the age of 10 to 75 years.

3. Changes in dentine: The two age dependent changes take place in dentine:

- Continued growth referred to as physiological secondary dentine formation and gradual obturation of the dentinal tubules, referred to as dentine sclerosis.
- These processes occur concomitantly, but they are independent.
- The formation of secondary dentine reduces the pulp chamber. This reduction in size does not affect the pulp chamber evenly, and it varies for different types of teeth.

4. Changes in pulp

- The dental pulp in teeth from old individuals differ from that in younger teeth by having more fibers and fewer cells.
- The blood supply apparently decreases with age; at least, the number of arteries entering the apical foramen does.
- The number of branches of blood vessels was markedly reduced with age, including the branching in subodontoblastic region.
- Increased number of pulp stones is seen in pulp with increasingly age but it also has been considered as pathological changes.

5. Tooth attrision

- With age, enamel and dentine undergo certain sclerotic changes following increased mineralization and deposition of trace elements.
- In spite of this increased hardness (and brittleness) the every day use of a natural dentition causes progressive tooth attrision.



Fig. 24.1: Severe gingival recession and cervical abrasion

6. Root surface caries

- Root surface caries result from an age-related conditions that develop on cementum following gingival recession.
- These lesions appear as well-defined and discolored defects on cementum or at the cementum-enamel junction
- The prevalence of untreated root surface caries has been reported as 22% in an older population.
- Other factors that predispose elderly individuals to root surface caries are a poor diet (with frequent sugar consumption), salivary gland hypofunction, insufficient fluoride

exposure, gingival recession, oral-facial motor deficits, poor oral hygiene, and decreased access to regular dental treatment.



Fig. 24.2: Root caries

7. Tooth loss

- Successive tooth loss, which can lead to the complete edentulous state, is the most conspicuous change in the stomatognathic system in the elderly of the civilized world.
- The picture of the toothless old individual with hollow cheeks, retracted lips, strongly prominent chin, hanging nose and collapsed bite is classical.
- Caries and periodontitis account for more than 90% of tooth extractions.



Fig. 24.3: Toothless old individual with hollow cheeks, retracted lips, prominent chin.

Changes in Periodontal Tissues with Aging

Decrease in number of fibroblast has been reported with increasing age.

With aging collagen fiber becomes more stable, showing increased thermal stability, insolubility and mechanical strength.

- Gingivitis is much more likely to develop in older patients because of oral and systemic factors.
- Dental plaque, gingival bleeding, and calculus accumulations develop as a result of softer diets, reduced oral motor activity, and salivary gland hypofunction.
- Gingival recession, root caries, tooth furcation involvement, and tooth drifting and mobility increase the likelihood of developing gingivitis.
- Gingival hyperplasia has been associated with the use of phenytoin, cyclosporine, and calcium channel blockers.
- Diabetes, even when well controlled, is associated with rapid periodontal breakdown.



Fig. 24.4: Gingival recession and stains on teeth due to habit

Changes in Bone with Aging

- Compact or cortical bone.
- Spongy or trabecular or cancellous bone.

Effect of Aging

- Thinning of cortical bone
- Increase in porosity
- Loss of trabecular



Fig. 24.5: Generalized alveolar bone loss

- Cellular atrophy
- Sclerosis

With aging, changes in bone composition have also been observed that alter the volumetric proportions of adipose tissue, hematopoietic tissue, trabecular bone and osteoid, the unmineralized newly formed matrix, decreases by 3 fold by age 20, then remains constant.

The volume of hematopoietic tissue is also highest in the young, decreasing by 50 to 60% by age 40. Adipose tissue volume increases throughout life, with the most marked increase occurring between the ages of 40 and 60 years. Bone volume declines by 30% or more after age 60.

Osteopenia is a condition of low bone mass and osteoporosis is a disease in which low bone mass is associated with fractures. Both the conditions are common in old age but difficult to diagnoses. Osteoporosis is regarded as being more frequent and advanced in elderly females than elderly males.

Changes in Oral Mucosa with Aging

As a result of the metabolic changes in the elderly person, including a shift in water balance the oral mucous membranes may become atrophic and friable taking on a shiny wax-like appearance.

The gingivae also show these changes together with a loss of stippling.

The progressive thinning of the epithelial layer occurs in combination with a decrease in the elastic properties of connective tissue. Clinically these effects add up to a reduction in resiliency of those tissues which may be subjected to pressure.

In addition, the decrease in surface capillaries and consequent reduced blood supply delay micronutrition and impairs the capacity to regenerate.

As a result of the above disturbances, the aging mucosa is more sensitive to external influence. It can be easily damaged by coarse food or ill-fitting appliances and its healing capacity is markedly slower than mature mucosa.



Fig. 24.6: Coatings on tongue mucosa

Oral Mucosal Diseases

Oral vesiculobullous diseases in older adults include lichen planus, pemphigus vulgaris, and cicatricial pemphigoid.

Lichenoid mucosal lesions can also be caused by a variety of medications commonly prescribed in older patients (e.g., acyclovir, gold salts, methyl-dopa, and thiazide diuretics).

- Pemphigus vulgaris is a potentially serious autoimmune vesiculobullous disorder that usually affects individuals in their fifth and sixth decades.
- Cicatricial pemphigoid is another immunologically mediated disorder; it affects primarily older women.
- Persistent low-grade irritation by an ill-fitting denture can induce a hyperplastic reaction, leading to the formation of an epulis fissuratum.
- Nutritional and hematologic deficiencies that are common in older adults can predispose to recurrent ulcers.
- Oral cancer is the most significant oral mucosal disease in older adults.
- Incidence rates increase with age; over 95% of all oral cancers occur in individuals aged 45 years.

Nutritional Deficiencies

Nutritional deficiencies are often associated with changes in the mucosa of the aging mouth. Most characteristics are the smooth, atrophic tongue and angular cheilitis. Abnormal taste sensations and burning sensations are also common and probably due to progressing atrophy of taste buds hastened by concomitant dehydration, iron deficiency and frequently through vitamin B complex deficiencies.

Tongue Disorders

Tongue is a most valuable source of diagnostic information. Changes in appearance, sensation and movement are not infrequent in the elderly. The more common complaints are outlined below.

Atropic Glossitis

Essentially it is reflection of nutritional failure originating from reduced intake or malabsorption, and is particularly associated with deficiencies of the vitamin B complex.



Fig. 24.7: Atrophy of tongue mucosa

Furred Tongue

- Fur is formed continuously and is normally removed by food and saliva.
- With reduction of salivary flow and poor oral hygiene the keratin accumulates on the surface of the filiform papillae.
- This then provides a good environment for accumulation of bacteria, debris and coloring substances.

Fissured Tongue

- It is often regarded as a result of long standing glossitis and scarring and is irreversible.
- The fissures are rather deep and tend to collect cellular and food debris and microbiological flora.
- As a result the adjoining areas of the tongue often show inflammation.

Glossopyrosis

- Is a very common symptom amongst elderly people. A variety of causes may be responsible.



Fig. 24.8: Fissured tongue

- Such sensation on mucous membrane could be a result of a minimal cerebral vascular accident (especially if there is a history of hypertension) dizziness or unexplained syncope.
- Where clinical changes in the tongue can be recorded, the symptoms may be associated with local irritation nutritional deficiencies or systemic disease such as diabetes, pernicious anemia or the Plummer-Vinson syndrome.
- In the absence of clinical signs psychological pressures and tensions may be suspected.

Temporomandibular Joint Disorders with Aging

In old people generally the range of mandibular movements is basically undisturbed and usually the temporomandibular joint functions well. This might be due partly to the fact that although they are stress bearing, it is only a limited degree. Those who are edentulous have some change as opposed to the people with some natural teeth.

Joint Dislocation

The danger of subluxation of the temporomandibular joint as a result of even simple dental procedure is increased in the older person. For example, a complaint of altered function and discomfort following pressure on the mandible must be investigated both clinically and radiographically.

Degenerative Joint Disease

Amongst the elderly there is an incidence of up to 27% to 50% of structural changes in the joint. Degenerative joint disease undoubtedly increases in the older age groups. The radiographical changes that are associated with this form of arthritis are marginal erosions, seen as discontinuance in the cortical layer of the joint surfaces.

- Osteophytic depositions especially in the anterior part of the condyle head.
- Osteoporosis.
- Sclerosis of joint surfaces.
- Reduced distance between joint surfaces
- Abrasion of articular fossa and the condylar head.
- Degeneration and partial destruction of the articular disc and exposure of bony structure.
- Adhesions between joint capsule can also be seen. All these changes may be attributed to a combination of aging changes and stress above the physiological limits.
- In severe degenerative joint disease clinical symptoms:
  - Pain and tenderness of the joint
  - Clicking and crepitations on movement
  - Reduced mobility of the joint is not a common presentation.

Rheumatoid Arthritis

Rheumatoid arthritis is a systemic disease with special affinity to collagen and, therefore, to connective tissue and bone. It is justifiable to assume that at least half of such patients have or will have temporomandibular joint disturbances of a progressive type. The changes in the temporomandibular joint resulting from rheumatoid arthritis appear to go parallel with the disease in other parts of the body.

It is not a disorder mainly of old age as the onset usually comes in the age period of 25–50 years. However, with increasing age it becomes more marked with an increased frequency in the elderly.

Salivary Gland Disorders with Aging

Salivary flow reduces due to intake of medications like antihypertensive, antiparkinsonian drugs, antihistaminic drugs, antipsychotic drugs.

Salivary Gland Atrophy

Consequences

- Diminished functions like mastication
- Digestive problems
- Poor retention of dentures
- Interference with patient's ability to wear dentures.
- Susceptibility of mucosa to frictional irritation from denture movement

No reduction in salivary output from the parotid gland, whereas that of submandibular gland is reduced.

Submandibular gland: 45% of total output.

Changes in composition

- Ptyalin—decreased
- Mucin—increases

Physical changes

- Viscous ropy
- Plaque formation and growth of cariogenic bacteria.
- Salivary gland dysfunction

Extraoral manifestations of salivary gland dysfunction include

- Candidiasis in the labial commissures.
- Dry cracked lips.
- Parotid or submandibular gland enlargement
- With associated pain and suppuration may indicate infection or ductal obstructions.

Infectious Diseases with Aging

Due to numerous age and disease-related changes in the oral and systemic immune systems, older adults are more susceptible to developing opportunistic oral infections.

Viral, fungal, and bacterial organisms invade, infect, and become latent in the hard and soft tissues of the oropharyngeal region, predisposing the person to disseminated systemic infections.

Viral Infections

The most common oral viral infections come from the herpes family

- Herpes simplex virus [HSV] and
- Varicella-zoster virus [VZV]

Fungal infection

The most frequent oral fungal infection in older adults is caused by *Candida albicans*.

The predisposing factors are

- Removable dental prostheses poor oral or denture hygiene.
- Endocrine disorders (e.g. diabetes).
- Underlying immunosuppression.
- Nutritional deficiencies.
- Salivary gland hypofunction.
- Medications (e.g., antibiotics, corticosteroids, *immunosuppressants*, and cytotoxic agents) have all been associated with oral fungal infections
- The loss of vertical dimension, as well as drooling problems secondary to cerebrovascular accidents, creates a moist environment in the labial commissures that also favors yeast infection.

Bacterial Infection

The bacteria that cause the most common infections are those associated with:

- *New and recurrent dental caries:* *Streptococcus mutans* and Lactobacillus
- *Periodontal diseases:* *Porphyromonas gingivalis* and *Treponema denticola*
- *Acute and chronic salivary infections:* *Staphylococcus aureus* and *Streptococcus viridans*.

Disorders of Taste Sensation with Aging

Taste sensation tends to be less intensive in the elderly person particularly with regards to sweet and salty foods.

Parageusia may be due to age changes in the papillary structure of the tongue.

In the elderly the circumvallate papillae tend to become more prominent with a result that bitter tastes can become highly disagreeable.

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