EXTRA ORAL RADIOGRAPHIC TECHNIQUES

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INTRODUCTION

These techniques imply that film is placed outside the oral cavity, against the side of the face to be radiographed & x-ray beam is directed towards it.

INDICATIONS

- Trismus
- Large lesions
- Trauma
- Jaws and orofacial bones
- Impacted teeth
- TMJ Area
- Skeletal Growth And Development

DRAWBACKS

1. Magnification occurs due to greater object to film distance used.
2. Details are not well defined due to use of cassettes & intensifying screens.
3. Contrast is reduced as the secondary radiation produced by the soft tissues is more.

An important aspect of the extra-oral radiographic technique is the immobilization of the patient’s head.
**EXTRAORAL LANDMARKS USED FOR PATIENT POSITIONING**

- **Median plane of the head**: (Mid Sagittal plane): A vertical plane passing through the mid sagittal suture, dividing the skull into two halves.
- **Frankfort horizontal line**: This line passes from the lower most border of the boney orbit to the upper border of the external acoustic meatus.

**IMPORTANT PARAMETERS**

- The film focus distance is of paramount importance.
- An increase in the focus film distance will improve the image sharpness, but adequate collimation must be used to prevent scattered radiation.
- Longer the film focus distance, the image is produced by more of the central rays, which in turn give minimum alteration in true anatomical size.

**The centering point**: The direction & angle of the central ray of the x-ray beam play an important & fundamental part in the clarity of the resultant shadow & the presence of distortion.

It is useful to bear in mind the definite relationship to prominent & recognizable anatomical features & the central beam should be directed as to pass or project away from the dense structures which would overshadow the required details.

**Orbito mental line (Canthomeatal line)**: Imaginary line from the outer canthus of the eye to the tragus of ear. This is also known as radiographic base line.

**EQUIPMENT REQUIRED**

A. **X-RAY UNIT**
   i. Intraoral x-ray machine
   ii. Extraoral x-ray machine
   iii. Panoramic x-ray unit
   iv. Cephalometry x-ray unit
High speed rare-earth screen combination
• Lateral oblique views of the mandible use a 5 ×7 inch film and cassette.
• Skull radiography requires at least an 8 ×10 inch film.
• Grids used to reduce the amount of scatter radiation reaching an x-ray film.

**Procedure**

**A. Equipment Preparation**

1. Load the extraoral cassette in the dark room under safelight conditions. Place one extraoral film between two intensifying screens & securely close the cassette.

2. Set the exposure factors (kilovoltage, milliamperage, time) according to the manufacturer’s recommendations.

3. Load the cassette into the cassette carrier.

4. Print in the date, patient’s name, age, sex & the case number.

**B. Patient Preparation**

1. Explain to the patient the radiographic procedure about to be performed.

2. Place a lead apron without a lead collar over the patient & secure it.

• The apron must be placed low around the back of the neck so that it does not block the x-ray beam.

• A thyroid collar is not recommended for extra oral radiography because it blocks part of the beam & obscures important diagnostic information.

• Remove all objects from head & neck that may interfere with the film exposure.

• The patient must remove earrings, eyeglasses, necklaces, napkin chains, hearing aids, hairpins & complete or partial removable dentures or any other removable appliance in the oral cavity.

**Extra Oral Radiographic Projections**

**A. Radiography of Paranasal Sinuses**

1. Posteroanterior projection (also known as occipitofrontal projection of Nasal sinuses)

There are 2 methods for obtaining this projection.

a. Posterior Anterior (Granger projection)

b. Modified method, Inclined Posterior Anterior (Caldwell Projection)
B. Radiography Of The Maxillary Sinuses

1. Standard Occipitomental Projection (0°OM)
2. Modified method (30° OM)
3. Bregma Menton view
4. PA Water’s view

C. Radiography Of The Mandible

1. PA Mandible
2. Rotated PA Mandible
3. Lateral oblique
   A. Anterior body of mandible
   B. Posterior body of mandible
   C. Ramus of mandible

D. Radiography Of Base Of The Skull
1. Submento Vertex projection

E. Radiography Of The Zygomatic Arches
1. Jug handle view (a modification of submentovertex view)

F. Radiography Of The Temporomandibular Joint
1. Trans cranial Projection
2. Trans Pharyngeal Projection
3. Trans Orbital Projection
4. Reverse Towne’s Projection

G. Radiography of the Skull

- 1. Lateral cephalogram
- 2. True lateral
- 3. PA Cephalogram
- 4. PA Skull
- 5. Towne’s Projection

Radiography of the Paranasal Sinuses

- This is used to study the relationship of the sinuses to each other & to the surrounding structures.
- Lateral/anteroposterior view may be taken.
- Routinely the paranasal sinuses are radiographed with the patient in the erect position, so as to demonstrate the presence or absence of fluid & in order to differentiate between the shadows caused by the fluids & those caused by other pathology.
1. Postero anterior Projection (also known as the Occipitofrontal Projection of the Nasal Sinuses)

- There are 2 methods for obtaining this projection:
  
  **A. Posteroanterior (Granger Projection)**

  **Structures shown**
  This view is excellent for evaluating the inner & middle ear because the petrous pyramid can be viewed through the orbits.
  Frontal sinuses lying each on the side of the nasal fossa, sphenoidal sinuses projected through the nasal fossa just below or between the shadows of the ethmoids.
  The upper part of the antrum is superimposed by dense shadows of the petrosae.

**Central Ray**

Is directed to the midline of the skull so that the x-ray beam passes through the canthomeatal plane perpendicular to the film plane.

**Exposure Parameters**
Using Extra Oral Machine
- **kvp**: 70-80
- **mA**: 60-50
- **Seconds**: 1.6

**Film Placement**

- The cassette is placed perpendicular to the floor in a cassette holding device. The long axis of the cassette is positioned vertically.

**Position of Patient**

- The mid sagittal plane should be vertical & perpendicular to the cassette.

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- **B. Modified Method, Inclined Posteroanterior (Caldwell) Projection**

  **Structures Shown**
  The angulation will cause the petrous ridges to be superimposed on the maxillary sinuses, thus allowing more accurate examination of the orbits & ethmoidal air cells.

  **Film Placement**
  - The cassette is perpendicular to the floor in a cassette holding device.
  - The long axis of the cassette is positioned vertically.

**Position of Patient**

- The mid sagittal plane is vertical & perpendicular to the cassette.
- Only the forehead & nose touch the cassette, so that the canthomeatal line is perpendicular to the cassette.
- On the resultant radiograph the superior border of the petrous ridge is projected in the lower third of the orbit.
Radiography of the Maxillary Sinuses

**Indications**
1. Investigation of the maxillary antra
2. Fracture of middle third of the face
   a) Le fort i
   b) Le fort ii
   c) Le fort iii
   d) Zygomatic complex
   e) Nasoethmoidal complex
   f) Orbital blow out fractures
   g) Coronoid process fracture
3. Investigation of Frontal and Ethmoidal sinuses
4. Sphenoidal sinuses

**Central Ray**
- Is directed 23° to the canthomeatal line, entering the skull about 3 cm above the external auditory meatus, passing through the antrum and exiting at the glabella.

**Exposure Parameters**
- Using Extra Oral Machine
  - kvp- 70-80
  - mA-60-50
  - Seconds-1.6

**RADIOGRAPHY OF THE MAXILLARY SINUSES**

1. Standard Occipitomental Projection (0’OM)

**Structures Shown**
This projection shows the facial skeleton & the maxillary antra & avoids superimposition of the dense bones of the base of the skull.

**Film placement**
The cassette is placed perpendicular to the floor in a cassette holding device. The long axis of the cassette is positioned vertically.

**Patient position:**
- Mid sagittal plane is perpendicular to the plane of film.
- Nose and chin should touch the cassette.
- Head is tipped back so that canthomeatal line is 45° to the film.

**Projection of Central ray**
- Horizontally through the occiput
**Exposure Parameters**

**Kvp- 70-80 mA- 60-50 Seconds- 1.6**

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**2. Modified Method (30° OM)**

**Structures Shown**
- This structure shows the facial skeleton, from a different angle enabling certain bony displacements to be detected.

- It is useful in detecting middle one-third fractures (LeFort I,II,III) & coronoid process fractures.

**Film Placement**
- The cassette is placed perpendicular to the floor in a cassette holding device. The long axis of the cassette is positioned vertically.

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**Position of Patient**
- The mid sagittal plane is vertical & perpendicular to the cassette.
- The head is centered so that nasion is the center of the cassette.
- Only the nose and chin touch the cassette. The head is tipped back so that radiographic baseline is 45° to the film.

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**Central Ray**
- Is directed 30° to the horizontal, centered through the lower border of the orbit.

**Exposure Parameters**
Using Extra Oral Machine

**Kvp- 70-80 mA- 60-50 Seconds- 1.6**

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**Bregma Menton**

**Structures Shown**
- This projection is primarily used to demonstrate the walls of the maxillary sinus (especially in the posterior areas), the orbits, the zygomatic arches & the nasal septum.

- It also demonstrates medial or lateral deviations of any part of the mandible.

**Film Placement**
- The cassette is placed parallel to the floor in a cassette holding device or table.

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**Position of Patient**
- The mid sagittal plane should be vertical & perpendicular to the plane of the film.

- The patient’s chin is extended as far as comfortable, to make lower the lower border of the mandible as parallel to the cassette as possible. Only the chin touches the cassette.

- The cantho mental line is approximately parallel to the plane of the film.
**Central Ray**

- The central ray enters the bragma & exits the menton.

**Exposure Parameters**

- Using Extra Oral Machine
- Kvp: 70-80 mA: 60-50
- Seconds: 1.6

**Film Placement**

- The cassette is placed perpendicular to the floor in a cassette holding device. The long axis of the cassette is positioned vertically.

**Position of Patient**

- The mid-sagittal plane should be vertical & perpendicular to the plane of the film. The patient's head is extended so that only the chin touches the cassette.

- When the head is extended too little, the petrosal shadows are projected onto lower part of antrum.

- When the head is extended too much the antral shadows are foreshortened & results in failure to show the antral floor.

- Water’s specified that the tip of the nose should be .5 to 1.5 cm away from the cassette.

**PA Water's View**

- Structures seen:
  - Maxillary sinus
  - Ethmoidal sinus,
  - Sphenoidal sinus (openmouth).
  - Orbit
  - Frontozygomatic suture,
  - Nasal cavity
  - Coronoid process

- The cassette is centered around the acanthion (anterior nasal spine).

- The canthomeatal line should be at 37° to 45° to the plane of the film & line from the external auditory meatus to the mental protuberance should be perpendicular to the film.

**Central Ray** is directed perpendicular & to the mid point of the film. It enters vertex & exists from acanthion.

**Exposure Parameters Using Extra Oral Machine**

- Kvp: 70-80
- mA: 60-50
- Seconds: 1.6
1. **PA Mandible**  
**Structures Shown**  
- The posterioanterior projection of the mandibular body & the ramus.  
- The symphsis region is not well seen because of the superimposition of the spine.

**Indications**  
- Fracture of posterior third of mandible  
- Fracture of the angle  
- Fracture of the lower condylar necks  
- Mediolateral expansion of the posterior third of body  
- Maxillofacial deformities  
  a) Mandibular hypoplasia  
  b) Mandibular hyperplasia

**Film Placement**  
The cassette is placed perpendicular to the floor in a cassette holding device. The long axis of the cassette is positioned vertically.

**Position of Patient**  
- The sagittal plane should be vertical & perpendicular to the film.  
- The head is tipped downwards so that the forehead & nose touch the film.  
- The radiographic base line is horizontal & perpendicular to the film.  
- The film is adjusted so that the lips are centered to the film.

**Central Ray**  
- Is directed at right angles to the film through the mid sagittal plane through the cervical spine, at the level of the mandible.

**Exposure Parameters**  
Using Extra Oral Machine  
- Kvp=80-80 mA= 60-80 Seconds=1.6

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**ROTATED PA MANDIBLE**

**Structure Shown**  
This projection is used to show the tissues of one side of the face & used to investigate the parotid gland & the ramus of the mandible.
Indications

- It is mainly used to demonstrate stones or calculi in the parotid.
- To note the medio lateral expansion of the lesions in the ramus & submasseteric infections.

Film Placement

The cassette is placed perpendicular to the floor in a cassette holding device. The long axis of the cassette is positioned vertically.

Position of Patient

- The patient is positioned facing the film, with the occlusal plane horizontal & tip of the nose touching the film. The head is rotated 10° to the side of interest. This rotates the bones of the back of the skull away from the side of the face under investigation.

Central Ray

- Is directed at right angles to the film, aimed down the side of the face which is of interest.

Exposure Parameters

- Using Extra Oral Machine
- Kvp- 65-80
- mA- 60-80
- Seconds- 1.6

3. Lateral Oblique

A. Anterior Body of the Mandible

Structures Shown

- Anterior body of the mandible, position of the teeth in the same area.
- Helps to evaluate impacted teeth, fractures & lesions located in the anterior portion of the mandible.

Film Placement

The cassette is placed flat against the patient’s cheek & is centered over the body of mandible, overlying the canine teeth. The patient must hold the cassette & the palm against the outer surface of the cassette.

Position of Patient

- The patient’s head is so adjusted, that the ala tragus line is parallel to the floor.
- The mandible is protruded slightly to separate it from vertebral column.
- The cassette is placed against the patient’s cheek & centered over the area of the interest.
The inferior border of the cassette should be parallel to the lower border of the mandible & below it.

The sagittal plane is tilted so that it is 5° to the vertical & rotated 30° from the true lateral position.

For the bicuspid & incisor region, the patient’s head should be turned slightly away from the tube so that the nose & chin approximate the cassette.

Central Ray

- Is directed 2 cm below the angle of the mandible opposite to the side of the interest.
- The beam is directed upward (~10° to ~15°) and centered on the anterior body of the mandible.
- The beam is directed perpendicular to the horizontal plane of the film.

Exposure Parameters

Using Intra Oral X-ray Machine
- Kvp-65-70  mA-7-10  Seconds -.8

Using Extra Oral X-ray Machine
- Kvp-40  mA-40 seconds-1

Film Placement

- The cassette is placed flat against the patients cheek & is centered over the body of the mandible.
- The cassette also should be positioned parallel to the body of the mandible.
- The patient must hold the cassette in position with the thumb placed under the edge of the cassette and the palm against outer surface of the cassette.

Position of Patient

- The patient’s head is so adjusted, that the ala tragus line is parallel to the floor.
- The mandible is protruded slightly to separate it from vertebral column.
- The cassette is placed flat over the patient’s cheek and is centered over the area of interest.
- The inferior border of the cassette should be parallel to the lower body of mandible below it.

B. Posterior Body of the Mandible

Structures Shown

Body of the mandible, position of the teeth in the same area, ramus of the mandible, angle of the mandible. Helps to evaluate impacted teeth, fractures and lesions located in the posterior border of the mandible.
The sagittal plane is tilted so that it is 5° to the vertical & head is rotated 15° from the true lateral position.

For the molar and ramus region, the head should not be turned away from the tube as this will place the ramus behind the vertebral column.

Central Ray
- Is directed from 2 cm below the angle of the mandible opposite to the side of interest.
- The beam is directed upward (-10° to -15°) and centered on the body of the mandible.

 Exposure Parameters

Using Intra Oral X-ray Machine
- kvp-65-70 mA-7-10 Seconds-0.8

Using Extra Oral X-ray Machine
- kvp-40 mA-40 Seconds-1

C. Ramus of Mandible

Structures Shown
The purpose of this view is to evaluate impacted third molars, large lesions, fractures that extend into the ramus of the mandible. This projection demonstrates a view of the ramus from the angle of the mandible to the condyles.

Film Placement
- Cassette is placed flat against cheek
- Cassette is positioned parallel to ramus
- Centered over the ramus of the mandible
- Patient must hold the cassette.

Position of Patient
- The patient's head is so adjusted, that the ala tragal line is parallel to the floor.
- The mandible is protruded slightly to separate it from vertebral column.
- The cassette is placed flat against the patient's cheek & is centered over the area of interest.
- The inferior border of the cassette should be parallel to the lower border of the mandible & below it.
- The sagittal plane is tilted so that it is 10° to the vertical and head is rotated 5° from the true lateral position.

Central Ray
- Is directed from 2 cm below the angle of the mandible opposite to the side of interest, to a point posterior to third molar region on the side opposite the cassette.
- The beam must be directed perpendicular to the plane of the film.

 Exposure Parameters

Using Intra Oral X-ray Machine
- kvp-65-70 mA-7-10 Seconds-0.8

Using Extra Oral Machine
- kvp-40 mA-40 Seconds-1
EXTRA ORAL RADIOGRAPHIC TECHNIQUES

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PART I

RADIOGRAPHY OF BASE OF THE SKULL

1. Submentovertex Projection

Structures Shown

Full axial view of the base of the skull, Sphenoidal Sinuses, facial skeleton from below.
**Indications**
- Destructive or expansive lesions affecting palate, pterygoid region, base of the skull, Sphenoidal sinus.
- **Warning**: Rule out cervical spine fracture or subluxation on trauma patient before attempting this projection.

**Film Placement**
The cassette is placed perpendicular to the floor in a cassette holding device. The long axis of the cassette is placed vertically.

**Position of Patient**
The head is centered on the cassette, with patient's head and neck tipped back as far as possible, the vertex (top) of the skull touches the cassette. The mid sagittal plane should be perpendicular to the plane of the film and radiographic base line should be parallel to the film.

**Central Ray**
Is directed perpendicular to the film and through the mid sagittal plane, at -5° to the horizontal.

**Exposure Parameters**
kvp - 50   mA - 20-30   Seconds - .4

**Radiography Of The Zygomatic Arches**

**Structures seen**
A symmetrical axial view of the zygomatic arches.

**Indications**
- Fracture of the zygomatic arch.
Film Position
Same as that in Submentovertex.

Position of Patient
Same as that of Submentovertex

Exposure Parameters
Kvp - less than 50  mAs -20-30  Seconds .4

• The exposure time for the zygomatic arch is reduced to approximately one-third of the normal exposure time for a submentovertex projection.

Radiography Of The Temporomandibular Joint

1. Transcranial View

Structures seen
Lateral aspect of: glenoid fossa, articular eminence, joint space & condylar head

Indication
• TMJ pain dysfunction syndrome and internal derangements of the joint.
• To investigate the size and position of the disc.
• To investigate the range of movement in the joints.

Film Position
The cassette is placed flat against the patient’s ear and centered over the TM Joint of interest, against the facial skin parallel to the sagittal plane

Position of Patient
• The patient’s head is adjusted so that sagittal plane is vertical.
• The ala- tragal line is parallel to the floor

This view is taken with the patient’s mouth in following positions:
1. Open Mouth
2. Closed Mouth

Central x-ray
The point of entry is different according to the technique used.

A. Post auricular or Lindblom technique
Point of entry of the central ray is ½” posterior & 2” above the auditory meatus.
According to this technique the central ray should be directed from posteriorly so that it passes along the long axis of the condyle. (The medial pole of condyle is more posterior to lateral pole.)

**Grewcock approach**  
The central ray enters through a point 2” above the external auditory meatus.

**Gill’s approach**  
The central ray enters through a point 1/2” anterior & 2” above the external auditory meatus.

In all the 3 techniques the central ray is directed caudally at an angle of +20’ to +25’.  
The point of exit is through the TM Joint of interest.

**Exposure Parameters**  
Intra Oral X-ray Machine  
Kvp-70  mA- 0.7  Seconds-1.5

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**2. Transpharyngeal View**  
*(Infracranial or McQueen Dell Technique)*

**Structures Shown**  
This view is a lateral projection showing medial surface of the condylar head & neck.
Film Placement

The cassette is placed flat against the patient's ear and is centered to a point 1/2" anterior to the external auditory meatus, over the TM Joint of interest, against the facial skin parallel to the sagittal plane.

Position of patient

• The patient is positioned so that the sagittal plane is vertical and parallel to the film with TM joint of interest, against the facial skin parallel to the sagittal plane.

• The film is centered to a point ½" anterior to external auditory meatus.

Central Ray

The X-ray tubehead is positioned in front of the opposite condyle and beneath the zygomatic arch.

It is aimed through the sigmoid notch, slightly posteriorly, across the pharynx at the condyle under investigation.

Exposure Parameters

Using Intra Oral Machine

- Kvp: 65-70
- mA: 7-10

Using Extra Oral X-ray Machine

- Kvp: 40
- mA: 40
- Seconds: 1

Parma Modification

The lead lined open ended cone is removed and the tube head is brought close to the skin surface, producing magnification of the tube side structures and thereby reducing superimposition.

3. Trans Orbital (Zimmer Projection)

• This is the conventional frontal TM joint projection which is most successful in delineating the joint with minimal superimpositions.

Structures Shown

• The anterior view of the temporomandibular joint and the medial displacement of the fractured condyle and fracture of neck of condyle are clearly seen in this view.
Central Ray

- The tube head is placed in front of the patient’s face.
- The central ray is directed to the joint of interest, at an angle of +20°, to strike the cassette at right angles.
- The point of entry may be taken at:
  - A. Pupil of the same eye, asking the patient to look straight ahead.
  - B. Medial canthus of the same eye.
  - C. Medial canthus of the opposite eye.

Film Position

- The film is positioned behind the patient’s head at an angle of 45° to the sagittal plane.

Position of Patient

- The patient is positioned so that the sagittal plane is vertical.
- The canthomeatal line should be 10° to the horizontal, with the head tipped downwards. The mouth should be wide open.

Exposure Parameters

Using Intra Oral X-ray Machine
- kvp-65-70 mA-7-10 Seconds-8

Using Extra Oral X-ray Machine
- kvp-40 mA-40 Seconds-1

4. Reverse Towne’s

Structures Shown

- This view is primarily meant for viewing the condylar neck and head. Fractures of the condylar necks, intra capsular fractures of the TMJ, quality of articular forces, condylar hypoplasia or hypertrophy.
Film Position
The cassette is placed perpendicular to the floor in a cassette holding device. The long axis of the cassette is placed vertically.

• Position of Patient
  • The sagittal plane should be vertical and perpendicular to the film.
  • The film is so adjusted so that lips are centered to the film.
  • Only the patient's forehead should touch the film.

Central Ray
Is directed upwards from below the occiput, with central ray at 30° to the horizontal, centred through the condyles.

Exposure Parameters
Using Extra Oral Machine
• kvp-70-80  mA- 60-50  Seconds -1.6

Skull Projections

Cephalometric Skull Projections
Standardized and reproducible form of skull radiography, to access relationship of the teeth to jaws and jaws to the rest of the skeleton.

Cephalometric means measurements of the head

Indications
Orthodontics
Orthognathic surgeries
A) Orthodontics
1. Initial diagnosis
2. Treatment planning
3. Monitoring treatment progress
4. Appraisal of the treatment

B) Orthognathic surgery
1. Pre operative evaluation
2. Assist in treatment planning
3. Post operative appraisal of the results of surgery
4. Follow up studies

1. Lateral Cephalogram

**Structures Shown**
- This view is used to evaluate the facial growth and development, trauma, disease and developmental anomalies.
- This projection demonstrates the bones of the face, skull as well as soft tissue profile of the face.

**Film Position**
- The cassette is placed perpendicular to the floor with the long axis of the cassette placed vertically.

**Position of patient**
- The right side of the patient’s head is positioned against the cassette.
- The mid sagittal plane is perpendicular to the floor and parallel to the film / cassette.
- The patient’s head is stabilized with the help of ear rods, nasion pointer and the orbital rod.
- The patient is asked to keep teeth in occlusion.

**Central Ray**
The central ray is directed perpendicular to the cassette through the portion. The distance between the x-ray source and the mid sagittal plane of the patient is 60 inches.

**Exposure Parameters**
Using Cephalometric X-ray Machine
- Kvp: 84 mAs: 13 Seconds: 1.6

- The soft tissue outline of the face is more readily seen on the resulting radiograph when a filter is used.
- A filter is placed at the x-ray source, or between the patient and the film, and serves to remove some of the x-rays that pass through soft tissue of the face, thus enhancing the image of the soft tissue profile.
- In oral surgery, orthodontics & prosthetics it is used to establish pretreatment and post treatment records.
2. True Lateral Skull

**Structures Shown**
- Is used to survey the skull and facial bones for evidence of trauma, disease or developmental abnormality. This reveals the nasopharyngeal soft tissues, paranasal sinuses and hard palate.
- Condition affecting the sella turcica, such as tumors of the pituitary gland in acromegaly.

**Film Position**
The film is held vertically against the patient's cheek and centered so that the entire skull is along with the facial skeleton, is seen on the resultant radiograph.

**Position Of Patient**
- The sagittal plane should be vertical and parallel to the film.
- The film is adjusted so that the upper circumference of the skull is 1/2 inch below the upper border of the cassette.

**Central Ray**
- The central ray is directed perpendicular to the cassette and the midsagittal plane is towards the external auditory meatus.
- Distance between the x-ray source and midsagittal plane of the patient is 36 to 40 inches.

3. PA Cephalogram

**Structures seen**
- Entire skull in posteroanterior plane.

**Indication**
- Fracture of skull vault
- Investigation of frontal sinus
- Conditions affecting cranium
  - Paget's disease
  - Multiple myeloma
  - Hyperparathyroidism
  - Intra cranial calcifications

**Exposure Parameters**
Using Extra Oral Machine
- kvp-70-80 mA- 60-50 Seconds -1.6
**Film Position**
The film is held vertically against the patient’s cheek and centered so that the entire skull is along with the facial skeleton, is seen on the resultant radiograph.

**Position of Patient**
The sagittal plane should be vertical & perpendicular to the film.

The head is tipped downwards so that only the nose touches the film. The radiographic base line is 10° with the film.

**Central Ray**
Is directed at right angles to the film through the mid sagittal plane, centered at the level of the bridge of the nose.

**Exposure Parameters**
Using Cephalometric X-ray Machine
- kvp- 84  
- mA- 13  
- Seconds -1.5

**3. PA Skull**

**Structures Shown**
- Is used to survey the skull vault and primarily the facial bones for evidence of trauma, disease or developmental abnormality.
- Fractures of the skull vault, investigation of frontal sinuses, conditions affecting the cranial (e.g. Paget’s disease, multiple myeloma, hyperparathyroidism) intracranial calcifications.

**Upper portion of PA View**

**Postero-Anterior (PA) Skull Projection**
A= Orbital plate of frontal bone
•B= Frontal spine
•C= Sup. border of orbit
•D= Sphenoid sinus

A= Lesser wing of sphenoid
•B= Ethmoid sinus
•C= Middle nasal meatus
•D= Oblique orbital line (innominate line)
•E= Floor of posterior cranial fossa

A= Lacrimal canal
•B= Middle nasal concha
•C= Vomer
•D= Mastoid air cells
•E= Atlas-occipital-condyle articulation

•Lower portion of PA View

A= Zygomatic process of maxilla
•B= Anterior border of ascending ramus
•C= Coronoid process
•D= Odontoid process of axis
•E= Maxillary tuberosity

A= Inferior nasal concha
•B= Inferior nasal meatus
•C= Occipital condyle
•D= Maxillary sinus
Film Position
The cassette is placed perpendicular to the floor in a cassette holding device. The long axis of the cassette is positioned vertically.

Position of Patient
• The sagittal plane should be vertical and perpendicular to the film.
• The head is tipped downwards so that the forehead and nose touch the film.

Exposure Parameters
Using Extra Oral Machine
• kvp- 70-80  mA-60-50
• Seconds-1.6

5. Towne’s Projection

Structures Shown
It is primarily used to observe the occipital area of the skull.

Film Position
• The cassette is placed perpendicular to the floor in a cassette holding device. The long axis of cassette is positioned vertically.
Central Ray
- Is directed at 30° to the cantho mental line and passes through it at a point between the external auditory meatus.

Exposure Parameters
- Using Extra Oral Machine
- Kvp-70-80 mA-60-50
- Seconds- 1.6

Thank you
Radiation in Dental Practice: Awareness, Protection and Recommendations.

Presented by:
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Reader
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BN Praveen, AR Shubhasini, R Bhanushree, PS Sumsum, CN Sushma

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Reason for choosing the article

- There is lack of awareness in dental professionals regarding radiation protection. This article emphasizes on protection based on a survey which was conducted.
- We are surrounded by radiations all around us, hence the need to know about radiation protection.
- For the diagnosis of various pathologies and diseases, various radiological investigations need to be performed, hence, the need for awareness.
- We as radiologists not only need to protect our patients but also ourselves from the harmful effect of radiations so that we are well aware of the various protective measures.

INTRODUCTION

- Radiation has become a part of modern living, reaching every segment of our society. All individuals are exposed to ionizing radiation, both from natural and man-made radiation sources.
- Radiation is the energy that comes from a source and travels through some material or through space. Light, heat and sound are types of radiation.
- Radiation may be ionizing or nonionizing. Ionizing radiation is radiation with sufficient energy to remove an electron from an atom or molecule. This ionization produces free radicals, i.e., atoms or molecules containing unpaired electrons, which tend to be especially chemically reactive.

Radiation hazards

- Scientists learnt that radiation is not only a source of energy and medicine, but it could also be a potential threat to human health, if not handled properly.
- The early pioneers in radiation research died from radiation-induced illnesses due to excessive exposure.
- In March 1896, Edison reported eye irritation associated with the use of X-rays, and cautioned against their continuing use.
- By the end of 1896, numerous reports on X-ray dermatitis and serious injuries had been published in the scientific literature.
- By 1910, it was understood that radioactive materials could cause "burns."
By the 1920s, sufficient direct evidence and indirect evidence had been accumulated to persuade the scientific community that an official body should be established to make recommendations concerning human protection against exposure to X-rays and radium.  

The International Commission of Radiation Protection (ICRP) is the international regulatory body, formed in 1928 to lay down norms for protection against radiation and recommend dose limits for radiation workers and general public.

The Indian regulatory board for protection against radiation is AERB, Atomic Energy Regulatory Board which was constituted on November 15, 1983. The mission of the boards is to ensure that the use of ionizing radiation and nuclear energy in India does not cause undue risk to health and surroundings.

**Sources of radiation**

<table>
<thead>
<tr>
<th>Natural</th>
<th>Artificial</th>
</tr>
</thead>
<tbody>
<tr>
<td>External sources</td>
<td>Radionuclides taken by ingestion and inhalation (radon)</td>
</tr>
<tr>
<td>Cosmic radiations</td>
<td></td>
</tr>
<tr>
<td>Terrestrial radiations</td>
<td></td>
</tr>
</tbody>
</table>

**Exposure and dose reduction**

1. Dose reduction in patients
2. Personal protection
3. Exposure & dose reduction
   - Distance
   - Shielding
   - Dosimetry
4. Patient protection

**Decision making**

- Radiographic examination shall be performed only when indicated by patient's history and physical examination and when radiological investigation can affect the diagnosis and treatment based on the professional judgment keeping in mind the benefit of the total health of the patient.

**Optimizing radiological procedures**

- It is the best way to minimize patient and operator exposure.
- Can be achieved by taking action at 3 levels of radiologic process:
  - at source,
  - at the exposure pathway and
  - modifying characteristics or location of exposed individuals.

- Source:
  - Drifting of dental X-ray tube should be avoided during positioning for exposures. This movement can cause blurred image or cone-cutting.
  - The use of closed end and pointed cones are contraindicated, because of increased scattered radiation.
  - A well-calibrated dental X-ray machine will have an output of 0.7 to 1 R/sec. This calibration must be done in every 3 years.
  - kVp and mA should be adjusted according to the contrast and density of image needed.
  - High contrast image with low kVp are used for visualizing large differences in the density within an object, e.g., caries and soft tissue calcification.
  - Increased kVp, allows visualization of small differences in density, e.g., bone level in periodontitis, but reduces the effective dose delivered per exposure.
  - Image density is controlled by quantity of X-rays produced, which in turn controlled by mA and second.
Collimation:
- Use of rectangular open ended PID (3.5 × 4.4 cm) reduces the skin exposure by 60% than that of round (7 cm) PID. (13)
- Focal spot film distance (FSFD) when X-ray machine is operated above 50 kVp, source skin distance must be greater than 7 inches. (9)
- Studies shows that 16 inch FSFD decreases 38% of thyroid dose, at 90 kVp and 45% decrease in 70 kVp, compared to 8 inch FSFD. (13)
- This is because of the greater distance X-ray beam is less divergent and there will be 32% reduction in exposed tissue volume. (13)
- The use of longer FSFD also results in a smaller apparent focal spot size and thereby increases the resolution of radiograph. (12)

Technique:
- Paralleling technique gives more accurate image and lowers the exposure dose to thyroid gland and lens of eye. (10)
- In bisecting technique X-ray beam has steep vertical angulations that may put the thyroid gland and lens in the path primary as well as secondary radiation. (8)
- Increasing FSFD and rectangular collimation may result in 70 to 80% decrease in exposure. (14)

Receptor selection:
- It is advised to use maximum sensitive film (speed) consistent with image quality. (15)
- E (Ektaspeed) speed film is almost twice as fast as D speed films. (15)
- In 1994 improved E speed film (Ektaspeed Plus) was introduced, which was found to be faster, less sensitive to processing and less grainy than E speed film and the image contrast similar to D speed film. (14)
- Dose reduction of 60% compared with E speed film can be achieved by using digital intraoral radiography. When compared with film, resolution was significantly lower in RVG whereas exposure reduction was to approximately half of Ektaspeed Plus. (15)
- Similarly digital panoramic imaging has been reported to result in dose reduction of 70%. (1)

Film holders avoid unnecessary exposure to patient’s fingers. Patient’s exposure history must be maintained and updated after every exposure. (8)

Patient Protection
- Stabilization of patient head before the exposure decrease blurring and cone-cutting of the image.
- All radiation exposure must be based on the principle ALARA (as low as reasonably achievable).
- Mean exposure of skin entrance for single periapical film is 217 mR and gonad dose will be 1/10,000 of skin dose exposure (0.02 mR). (14)
- Lead aprons reduce 98% of scattered radiation and attenuation dose to a 0.04 µR. (19) This quantity is 60 times less than the dose equivalent resulting from one airline flight. (1)
- Thyroid collar attenuate 92% of scattered radiation. (20) So it should be made mandatory to use thyroid collar and lead aprons before any exposure.
Protection of personnel

- From the occupational perspective there are two sources of radiation, X-ray tube is the true primary source of radiation but in practice only very few situations in which personnel will directly exposed to the primary beam.
- This leaves the secondary source, which is the patient.
- Interaction of the primary beam with the part of the patient’s body being imaged produces scattered radiation, which emits from the patient in all directions. So any procedure that reduces the exposure to patient also reduces the possibility of operator exposure.
- In most cases, the main determinant for occupational exposure is proximity of personnel to the patient when exposures are being made.
- Increasing the distance from the source and shielding from radiation source have proven to be greater importance in protecting operator and public from potential risk of radiation.

- Distance:
  - Exposure decrease inversely on the square of the distance (inverse square law).
  - According to position distance rule operator should stand at least 4 feet from patient at an angle of 130° to the central ray of X-ray beam.
  - This rule take the advantage of inverse square law to reduce X-ray intensity but also consider that in this position most scattered radiation is absorbed by patient’s head.

- Shielding:
  - Shielding implies that certain material (concrete, lead) will attenuate radiation when they are placed between source and operator. Shielding include X-ray tube shielding, room shielding, and personnel shielding. According to AERB guidelines maximum allowable leakage from tube housing not greater than 1mGy/hr/100 cm2.

  - Room and personnel shielding: according to AERB guidelines:
    1. Room housing X-ray unit for dental/OPG should not be less than 12 m2.
    2. X-ray tube room which primary beam falls is not less than 35 cm thick brick and walls of scattered X-ray falls is not less than 23 cm thick brick.
    3. 1.5 mm lead in front of the doors and windows of X-ray room.
    4. Unshielding openings in an X-ray room should located above a height of 2 m from finished level outside the X-ray room.
    5. Rooms should provide with direct viewing and oral communication facilities between operator and the patient.
    6. Protective barrier between the operator and should have a minimum lead equivalence of 1.5 mm, protective apron and gloves should have minimum lead equivalence of 0.25 mm. One millimeter of lead thickness attenuates 99% beam at 75 kVp.

- Radiation detection and dosimetry

  - Instruments used to detect and measure radiation are called radiation dosimeters.
  - The purpose of radiation monitoring is to ensure that the dose limits were not exceeded and protection measures are doing well.
  - There are several methods of detecting radiation which are ionization, photographic effect, luminescence and scintillation.

  - Thermoluminescent monitoring badges (TLD) are commonly used in India. Thermoluminescence is the property of certain materials to emit light when they are stimulated by heat. The amount of light emitted is proportional to the radiation dose.

  - Materials such as lithium fluoride, lithium borate, calcium fluoride and calcium sulfate have been used to make TLDs.

  - During radiography the dosimeter is worn at one of 2 regions—on the trunk of the body or at the level of the waist on the anterior side of the individual or on the upper chest region of the level of the collar area on the anterior surface of the individual.

A questionnaire survey has been conducted in 100 dental clinics in and around Bengaluru.

- The aim of the survey was to understand the level of knowledge of radiation protection among dentist population in and around Bengaluru.
- Clinics with X-ray facilities were selected for the survey. Among 100 dentist 47% of dentists were using short cone and 60% of the dentist's position were near the patient while exposing.
- Survey shows only 20% were using lead barrier and more than 60% dentist were disposing the radiation waste into gutter.
- The result shows that radiation protection among dentist is unsatisfactory in Bengaluru.
- Hence, awareness of radiation protection and safety measures should be followed in order to have hazard free profession.

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**Recommended dose limits**

<table>
<thead>
<tr>
<th>Dose quantity</th>
<th>Occupational dose limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective dose</td>
<td>20 mSv/yr averaged over 5 consecutive years (100 mSv in 5 yrs)</td>
</tr>
<tr>
<td>Equivalent dose in:</td>
<td></td>
</tr>
<tr>
<td>Lens of the eye</td>
<td>150 mSv/yr</td>
</tr>
<tr>
<td>Skin</td>
<td>500 mSv/yr</td>
</tr>
<tr>
<td>Hands and feet</td>
<td>500 mSv/yr</td>
</tr>
</tbody>
</table>

**CONCLUSION**

- Though exposure to radiation in dentistry is minimal, it is very important to follow the guidelines to minimize the radiation exposure.
- Following the AERB guidelines while constructing the radiological unit and monitoring the individual exposure and quality of instruments is very useful in radiation protection.
- Knowledge on the type of radiologic equipment and the calibration of the machine during purchase and later should be made mandatory.
- The simple steps during the establishment of the radiological units and compliance for the AERB guidelines will help the individual for dose reduction in dental practice.

**PROS**

- The article tells us adequately about various safety protocols that can help us to protect ourselves as well as the patient from radiation exposures.

**CONS**

- The article does not describe to us about the potential effects of radiation on pregnant women and their means of protection.
- It also does not discuss about the dose limitation of various types of x-ray exposures.

**Radiation Units**

- **ROENTGEN (R):** It is measurement of energy produced by Gamma or x-rays radiation in a cubic cm of air.
- **RAD:** Radiation Absorbed Dose. Original measuring unit for expressing the absorption of all types of ionizing radiation (alpha, beta, gamma, neutrons, etc.) into any medium.
- **REM:** Roentgen Equivalent Man is a measurement that correlates the dose of any radiation to the biological effect of that radiation. Since not all radiation has the same biological effect, the dosage is multiplied by a "quality factor" (Q).
- The difference between the rad and rem is that the rad is a measurement of the radiation absorbed by the material or tissue. The rem is a measurement of the biological effect of that absorbed radiation.
- **System International (SI) Units:** The System International (SI) units for radiation measurements are "gray" (Gy) and "sievert" (Sv) for absorbed dose and equivalent dose respectively.
Effective dose from radiographic examinations and equivalent background exposures (White & Pharoah)

<table>
<thead>
<tr>
<th>Examination</th>
<th>Effective dose (mSv)</th>
<th>Equivalent background exposure (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectangular collimation</td>
<td>6</td>
<td>3.6</td>
</tr>
<tr>
<td>Posterior following PSP or F</td>
<td>35</td>
<td>4</td>
</tr>
<tr>
<td>Full mouth: PSP or F speed</td>
<td>35</td>
<td>4</td>
</tr>
<tr>
<td>Full mouth: CCD sensor</td>
<td>37</td>
<td>2</td>
</tr>
<tr>
<td>Round collimation: Full mouth D speed</td>
<td>388</td>
<td>46</td>
</tr>
<tr>
<td>Full mouth: PSP or F speed</td>
<td>171</td>
<td>20</td>
</tr>
<tr>
<td>Full mouth: CCD sensor</td>
<td>85</td>
<td>10</td>
</tr>
</tbody>
</table>

Mission:
- Review emergency preparedness plans for nuclear & radiation facilities
- Review of training program, syllabus for training, qualification and license for personnel of radiation facilities

ACR practice guideline for imaging pregnant or potentially pregnant adolescents and women with ionizing radiation

- Goals of the guideline
  - Reoutline the body of knowledge about the risks to the conceptus from ionizing radiation, taking into account the gestation age at time of exposure.
  - Provide guidance as to when and how to screen for pregnancy prior to imaging examinations using ionizing radiation, including evaluation of the adolescent and adult version.
  - Recommend means to control, manage and practically minimize radiation dose to pregnant or potentially pregnant patients.
  - Manage dose assessment, risk assessment and communication issues following exposure of pregnant patients.

Potential effects are:
- Increasing dose that increase with likelihood as dose increases:
  - Mental retardation: IQ deficit of permanent nature
  - Malformations: increases likelihood as dose increases

Radiation exposure:
- Conception to 2 weeks (0-14 days)
- 3-4 weeks (15-28 days)
- 5-10 weeks (29-70 days)
- 11-17 weeks (71-119 days)
- 18-27 weeks (120-189 days)
- >27 weeks (>189 days)

Atomic energy regulatory board (AERB)

- Constitution: 14th November 1983 by the president of India
- Mission: To ensure use of ionizing radiation & nuclear energy in India does not cause undue risk to health and environment
- Functions:
  - Develop safety policies in both radiation and industrial safety areas
  - Develop safety codes, guides and standards for siting, design, construction, operation and granting consents of different types of nuclear and radiation facilities
  - Review emergency preparedness plans for nuclear & radiation facilities
  - Review & provide training program, syllabus for training, qualification and license for personnel of radiation facilities
  - Public informed on radiological safety significance
  - Promote research & development effort in areas of safety
  - Maintain liaison with statutory bodies in the own country as well as abroad regarding safety matters.

Guidelines of AERB

1. Decide a suitable room for housing an X-ray unit to facilitate the easy movement of staff and patient positioning.
2. Room should have preferably one entrance door and window if present. Should be about 2 m from the finished floor level outside the x-ray room.
3. Door should have a hydraulic mechanism to ensure that door is closed during examination.
4. Decide the material and thickness of walls and doors.
5. Measure the distances of all the walls, doors, windows from the external finished floor of x-ray room
6. The required shielding of any material shall be provided at least up to the height of 2 m from the finished floor of x-ray room.
The thickness of wall control room options in shielding materials

- The brick is considered as 1.6 g/cc.
- 45 cm size and
- Room size

Positioning of equipment should be as far as possible from the door and the control console.

- The patient entrance door.
- Entrance door to the gantry room from the control console shall have similar requirements as
- that the patient is completely visible from the control console, during the scanning
- Couch, Separate control console room, viewing window,
- During the scanning

8) Position the location of the equipment for each modality as follows:

- Control panel should be kept behind the mobile protective barrier (MBP) of thickness 2
- • Control panel should be kept behind the mobile protective barrier (MBP) of thickness 2
- • Lead glass of suitable dimensions are provided as viewing windows with 1.5 mm thick lead
- • In such a case, the control should be behind a mobile protective barrier of adequate
- • Couch, Control console and chest stand placed in such a way that chest stand is
- • On the opposite wall of the entrance door and the control console.

- Mobile protective barrier with lead equivalent glass viewing window should be
- positioned in such a manner that the operator is completely shielded during the
- exposure.
- • Control console should be positioned as far away as possible from the x-ray tube.

- 4. The ceiling must have a thickness of concrete (density 2.35 g/cc), not less than 6
- • If the x-ray equipment is installed in a residential complex, it shall be ensured that:

- 3. There is a shielding equivalent to at least 23 cm or 9 inch thick brick or equivalent.
- • The adequacy of shielding depends on the material and thickness used for this

- 2. Walls of the x-ray room on which primary x-ray beam falls are not less than 35
- • Walls of the x-ray room on which primary x-ray beam fall are not less than 35
- • Couch, Control console and chest stand placed in such a way that chest stand is
- • Also, Lead poses a serious environmental hazard and the use of it is being

- 1. Walls of the x-ray room on which primary x-ray beam falls are not less than 35
- • Walls that are irradiated directly by the x-ray equipment must be installed in adequately shielded rooms to ensure that

- • The adequacy of shielding depends on the material and thickness used for this

- • Provisions are made to observe and communicate with the patient on the table.

- • AERB would like to promote use of these materials, on demonstration of shielding

- • The adequacy of shielding depends on the material and thickness used for this

- • Also, not more than one unit of any type shall be installed in the same room, and no

- • The room housing an x-ray unit shall be not less than 18 m2 for general purpose

- • The X-ray installation is located in a residential complex, it shall be ensured that:

- • AERB would like to promote use of these materials, on demonstration of shielding

- • For equipment operating at 125 kV or above, should have a separate control room, and

- • The adequacy of shielding depends on the material and thickness used for this

- • In such a case, the control should be behind a mobile protective barrier of adequate

- • Doors are lined with 2 mm thick lead sheet with proper overlapping at the joint

- • General radiography installation

- • These x-ray units are operated in the range of 50–150 kVp.

- • Walls that are irradiated directly by the x-ray beam are primary barriers.

- • Hence, additional shielding must be provided for the wall behind the chest stand.

- • Provisions are made to observe and communicate with the patient on the table.

- • The mobile protective barrier with lead shield must be a permanent/mobile one with

- • The viewing window of the mobile protective barrier must be 45 × 45 cm size and centered.
AERB GUIDELINES FOR DOSE LIMITS

The limits on effective dose apply to the sum of effective doses from external as well as internal sources. The limits exclude the exposures due to natural background radiation and medical exposures.

Calendar year shall be used for all prescribed dose limits.

Occupational exposures

1. An effective dose of 20 mSv/year averaged over five consecutive years (calculated on a sliding scale of five years);
2. An effective dose of 30 mSv in any year;
3. An equivalent dose to the lens of the eye of 150 mSv in a year;
4. An equivalent dose to the extremities (hands and feet) of 150 mSv in a year and
5. An equivalent dose to the skin of 500 mSv in a year.

Dose limits given above apply to female workers also. However, once pregnancy is declared the equivalent dose limit to embryo/fetus shall be 1 mSv for the remainder of the pregnancy.

Dose limits for Members of the Public

1. An effective dose of 1 mSv in a year;
2. An equivalent dose to the lens of the eye of 15 mSv in a year; and
3. An equivalent dose to the skin of 50 mSv in a year.

REFERENCES


Dose limits for Members of the Public

1. An effective dose of 1 mSv in a year;
2. An equivalent dose to the lens of the eye of 15 mSv in a year; and
3. An equivalent dose to the skin of 50 mSv in a year.

Apprentices and Trainees

The occupational exposure of apprentices and trainees between 16 and 18 years of age shall be so controlled that the following limits are not exceeded:

1. An effective dose of 5 mSv in a year;
2. An equivalent dose to the lens of the eye of 50 mSv in a year;
3. An equivalent dose to the extremities (hands and feet) of 150 mSv in a year and
4. An equivalent dose to the skin of 150 mSv in a year.

REFERENCES


INTRODUCTION

- Nuclear medicine imaging uses small amounts of radioactive materials called radiotracers that are typically injected into the bloodstream, inhaled or swallowed.
- The radiotracer travels through the area being examined and gives off energy in the form of gamma rays which are detected by a special camera and a computer to create images of the inside of your body.
- Nuclear medicine imaging provides unique information that often cannot be obtained using other imaging procedures and offers the potential to identify disease in its earliest stages.

ATOM

- SMALLEST UNIT OF AN ELEMENT
- RUTHERFORD: GOLD FOIL EXPERIMENT – NUCLEUS IN THE CENTER
- NEILS BOHR: ELECTRONS REVOLVE AROUND THE NUCLEUS IN SPECIFIC ORBITS WITH SOME ENERGY

NUCLEUS

- Nucleus contains protons and neutrons which are called nucleons and the nucleus containing protons and neutrons is called a nuclide.
- NUCLEAR BINDING ENERGY

SUB ATOMIC PARTICLES

- ELECTRON: -VE CHARGE, NO MASS
- PROTON: +VE CHARGE, 1 UNIT OF MASS
- NEUTRON: NO CHARGE, 1 UNIT OF MASS
- IONIZED ATOM
- NON-IONIZED ATOM
- ELECTRON BINDING ENERGY
• **Isomer**: Nucleus with different arrangements
• **Ground states**: The most stable energy states
• **Excited states**: Arrangements are so unstable that there is only a short transient time (less than 10^{-12} sec) becoming ground states.
• **Metastable states**: Arrangements are unstable, but relatively long-lived (sometimes up to several hours) before becoming ground states.

**Radioisotopes**

• Elements containing atoms with the same atomic number and a different number of neutrons.
• A radionuclide is a radioactive form of an isotope that behaves chemically in a similar manner to the nonradioactive counterpart.
• The nuclear BE is not capable of holding the nucleus together and undergoes disintegration releasing particulate or ionizing radiation.

**Radioactive Transformation**

• **Isobaric Transitions**
  - Beta Emission
  - Positron Emission
  - Electron Capture

• **Isomeric Transitions**
  - Gamma Emission
  - Internal Conversion
  - Excited state transitions
  - Metastable state transitions

• **Alpha transition**

**Positron Emission**

• A positron is a particle similar to an electron except that it has a positive electric charge.
• The behavior of a positron in tissue is very similar to a particle with one important difference – once the positron has been slowed down by the atomic collisions, it is annihilated by the interaction with an electron from a nearby atom.
• The combined mass of the proton & electron is converted into two annihilation photons each with energy 511 keV.
• The two photons are emitted at 180° to each other – this property is exploited by PET.

The result of the decay modes is a better balance between the forces acting on the nucleus.
**GAMMA EMISSION**

- In most isomeric transitions, a nucleus will emit its excess energy in the form of a gamma photon.
- A gamma photon is a small unit of energy that travels with the speed of light and has no mass; its most significant characteristic is its energy.
- The photon energies useful for diagnostic procedures are generally in the range of 100 keV to 500 keV.

**ALPHA EMISSION**

- An alpha particle consists of two neutrons and two protons.
- α particles interact strongly with matter – very short range of 1mm or less.
- Within this range α particles strongly collide with atoms – disrupting their chemistry – extremely damaging to the tissues.
- α particles have a potential to deliver a lethal radiation dose to small metastatic cell clusters, while mostly sparing the surrounding tissues.

**SPONTANEOUS FISSION**

- This is a very destructive process which occurs in some heavy nuclei which split into 2 or 3 fragments plus some neutrons.
- These fragments form new nuclei which are usually radioactive.
- Nuclear reactors exploit this phenomenon for the production of radioisotopes.
- It’s also used for nuclear power generation and in nuclear weaponry.

**RADIOACTIVE DECAY** is the process whereby the number of radioactive atoms of an element within a population is reduced through disintegration.

**RADIOACTIVE PHYSICAL HALF LIFE** is the time required for one half of the original number of atom in the radioactive sample to decay.

**BIOLOGICAL HALF LIFE** is the time required body to eliminate one half of an administered radio nuclide by a process of regular elimination.

**EFFECTIVE HALF-LIFE**

Time required for the radioactivity from an administered radio nuclide to be reduced to 50% of its initial value as a result of the combined effects of the physical and biologic half-lives.

**DECAY RATE**

- It is the number of nuclear disintegrations occurring per unit time –measuring unit - curie
- The energy level of particulate or electromagnetic radiation is expressed in Kev or meV
- The radiation a patient receives is measured in “rads”.

"The number of electron-volts emitted by the radiation is expressed in "rads.""
Nuclear medicine

- Nuclear Medicine (e.g., PET, SPECT) is based on emission data from radioactive materials injected into the body.
- Nuclear signals penetrated through the body are detected and reconstructed to form images.

NUCLEAR MEDICINE VS DIAGNOSTIC RADIOLOGY

- Nuclear medicine and diagnostic radiology both utilize ionizing radiation to obtain clinical information.
- Information with nuclear medicine is related to organ function while diagnostic radiology information is related to anatomical structures.

Indications for nuclear imaging

- Tumor staging to assess metastasis.
- Investigation of salivary gland function.
- Evaluation of bone grafts.
- Assessment of growth in condylar hyperplasia.
- Investigation of thyroid and brain scans.

INDICATION OF NUCLEAR MEDICINE IN DENTISTRY

- For the detection of active alveolar bone loss.
- For detection of viability of bone grafts.
- For detection of osseointegration around dental implants.
- For detection of salivary gland disorders.
- For detection of function of lymph nodes.
• For staging and grading of orofacial malignancies, colorectal cancer, non-small cell Lung cancer, Melanoma, Lymphomas, Head and Neck cancers.
• For determining the prognosis after treatment
• For evaluating the effect of Hyperbaric oxygen therapy in treatment of Bisphosphonate Induced osteoradionecrosis of the Jaws.

Advantages
• NM imaging has an advantage of providing anatomical details and information that helps in accurate diagnosis
• NM imaging is based on the principle of tracers and show functional images of metabolism, physiology or biochemistry by studying the dynamic behavior of tissues and organs at various stages.
• It can help in early diagnosis of the disease and evaluates the outcome during the initial posttreatment phase.

Disadvantages
• Poor image resolution
• Radiation dose to the whole body can be high
• Images are not disease specific
• Difficult to localize exact anatomical site
• Some investigations take several hours
• Facilities are not widely available.

Branches of Nuclear Medicine

<table>
<thead>
<tr>
<th>Radiotracer</th>
<th>Halflife</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technetium-99m</td>
<td>6 hrs</td>
<td>Skeletal and heart muscle imaging, brain, thyroid, lungs (perfusion and ventilation), liver, spleen, kidney (structure and function), gall bladder, bone marrow, salivary and lacrimal glands, heart blood pool, infection</td>
</tr>
<tr>
<td>Xenon-133</td>
<td>5 days</td>
<td>Used in pulmonary (lung) ventilation studies.</td>
</tr>
<tr>
<td>Krypton-81</td>
<td>32 days</td>
<td>Used in nuclear medicine studies.</td>
</tr>
<tr>
<td>Carbon-11</td>
<td>8 hrs</td>
<td>Used in nuclear medicine studies.</td>
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<tr>
<td>Nitrogen-13</td>
<td>8 hrs</td>
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<tr>
<td>Oxygen-15</td>
<td>2.8 days</td>
<td>Used in nuclear medicine studies.</td>
</tr>
<tr>
<td>Iodine-131</td>
<td>78 hrs</td>
<td>Used in nuclear medicine studies.</td>
</tr>
<tr>
<td>Gallium-67</td>
<td>78 hrs</td>
<td>Used in nuclear medicine studies.</td>
</tr>
<tr>
<td>Indium-111</td>
<td>2.8 days</td>
<td>Used in nuclear medicine studies.</td>
</tr>
<tr>
<td>Rubidium-82</td>
<td>65 hrs</td>
<td>Used in nuclear medicine studies.</td>
</tr>
<tr>
<td>Thallium-201</td>
<td>78 hrs</td>
<td>Used in nuclear medicine studies.</td>
</tr>
</tbody>
</table>
Radioisotopes used in conventional nuclear medicine

**Technetium (99mTc):** The most commonly used isotope for the following reasons:
- **Gamma emission:** Single 141 KeV gamma emissions which are ideal for imaging purposes.
- **Short half-life:** A short half-life of 6 ½ hours that ensures a minimal radiation dose.
- **Ready attached to different substances:** It can be readily attached to a variety of different substances that get concentrated in different organs. E.g., 99mTc + MPD (Methylene diphosphonate) in bone, 99mTc + RBC in blood, 99mTc + Sulphur colloid in the liver and spleen.
- **Ionic form:** It can be used on its own in its ionic form (pertechnetate 99m TcO₄⁻), since the thyroid and salivary glands take this up selectively.
- **Easily producible:** as and when required.

**Technetium production**

- FROM MOLYBDENUM by radioactive decay

**RADIOPHARMACEUTICALS**

Substances which tend to localize in the tissue of interest is tagged with gamma ray emitting radionuclide.
**ROUTES OF ADMINISTRATION**

- Injected into a vein
- Swallowed
- Inhaled as gas.

**THE PROCEDURE**

**Pre-examination procedures:**
- **Patient preparation:**
  - Explanation about the test

**Pre-injection:**
- Relevant history
- Current symptoms, physical findings.
- Results of previous radionuclide imaging
- Results of other imaging studies such as conventional radiographs, CT, MRI
- Relevant laboratory results

**Radiopharmaceutical administration:** The radiopharmaceutical should be administered by the intravenous route.

**Post injection:**
- Unless contraindicated, patients should be well-hydrated and instructed to drink one or more liters of water (4-8 glasses) between the time of injection and the time of imaging as well as during the 24 hours after administration.
- void frequently during the interval between injection and imaging.

**Image acquisition:**
- Between 2 and 5 hours after injection.
- Later (6-24 hour) delayed images (higher target-to-background ratio and may permit better evaluation)

**Image Processing:**
- No processing procedure is needed for planar images.
- In case of SPECT and PET one should consider the different types of gamma camera and software available: careful choice of imaging processing parameters should be adopted in order to optimize the imaging quality.

**GAMMA IMAGING**

**The Device:**

**Components of a gamma camera**
- Collimator
- Detector/ Scintillator
- Photomultiplier

**COLLIMATOR**
- This is a device made of a highly absorbing material such as lead, which selects gamma rays along a particular direction.
- They serve to suppress scatter and select a ray orientation.
- The simplest collimators contain parallel holes.
DETECTOR / SCINTILLATOR

- Made up of sodium iodide crystals.
- It produces multi-photon flashes of light when an impinging gamma ray, X-ray or charged particle interacts with the single sodium iodide crystal of which it is comprised.

Photomultiplier tube (PMT)

- This is an extremely sensitive photocell used to convert light signals of a few hundred photons into a usable current pulse.

PULSE HEIGHT ANALYZER (PHA):

- It lets through only those pulses which lay within the window of ±10 % of the photopeak energy.
- The pulses so selected – ‘Counts’.
- The X Y Z pulses are next applied directly to a monitor for visual interpretation as in older machines or in newer systems via analogue-digital converters into a computer.
- This enables dynamic gated studies to be undertaken as well as range of image processing.
Various radionuclide imaging procedures

- Planar scintigraphy
- SPECT
- PET
- Hybrid scanning techniques

Planar Scintigraphy:

Planar imaging produces a 2D image with no depth information and structures at different depths are superimposed. The result is loss of contrast in the plane of interest.

Single photon emission computed tomography (SPECT)

- SPECT was developed as an enhancement of planar imaging.
- It detects the emitted gamma photons (one at a time) in multiple directions.
- Uses one or more rotating cameras to obtain projection data from multiple angles.
- SPECT displays traces of radioactivity in only the selected plane.
  - Axial, coronal and sagittal.
- Computer manipulation of the detector radiation is also possible.

SPECT is a method of acquiring tomographic slices through a patient.
- Most gamma cameras have SPECT capability.
- In this technique either a single or multiple (single, dual or triple headed system) gamma camera is rotated 360° about the patient
- Image acquisition takes about 30-45 minutes.
- The acquired data are processed by filtered back projection & most recently iterative reconstruction algorithms to form several contiguous axial slices like CT by X-ray.
- After every 6° camera halts for 20-30 seconds & acquires the view of the patient
  - 60 views are taken from different directions.
- These data can then be used to construct multiplanar images of the study area.
- SPECT studies can be presented either as a series of slices or 3D displays.
  - By changing contrast & localization, SPECT imaging increases sensitivity & specificity of disease detection.
- Tomography enhances contrast & removes superimposed activity.
- SPECT images have been fused recently with CT images to improve identifying of the location of the radionuclide.

SPECT bone scintigrams show increased uptake in the right mandible (arrows) in the region of a sequestrum.

Positron emission tomography (PET)

- Positron emission tomography (PET) is a nuclear medicine imaging technique which produces a three-dimensional image or picture of functional processes in the body.
- The system detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (tracer).
Positron Emission
- In this, a proton in the nucleus is transformed into a neutron & a positron.
- Positron emission is favored in low atomic number elements.

Positron Annihilation:
- The positron has short life in solids & liquids.
- Interactions with atomic electrons
- Rapidly loses kinetic energy
- Reaches the thermal energy of the electron
- Combines with the electron
- Undergoes annihilation
- Their mass converts into energy in the form of gamma rays.
- The energy released in annihilation is 1022 KeV.
- To simultaneously conserve both momentum & energy, annihilation produces 2 gamma rays with 511 keV of energy that are emitted 180 degree to each other.
- The detection of the two 511 keV gamma rays forms the basis for imaging with PET.

Coincidence detection
- Coincidence detection- simultaneous detection of the 2 gamma rays on opposite sides of the body. (bismuth germinates)
- If both gamma rays can subsequently be detected, the line along which annihilation must have occurred can be defined.

- By having a ring of detectors surrounding the patient, it is possible to build a map of the distribution of the positron emitting isotope in the body.
- PET employs electronic collimation.
- 3 types of coincidence detection

- Sensitivity in PET
  - Measures capability of system to detect ‘true’ & reject ‘randoms’

Radionuclides used in PET scanning are typically isotopes with short half lives:
- Carbon-11 (~20 min).
- Nitrogen-13 (~10 min).
- Oxygen-15 (~2 min), and
- Fluorine-18 (~110 min).

These radionuclides are incorporated either into compounds normally used by the body such as glucose (or glucose analogues), water or ammonia, or into molecules that bind to receptors or other sites of drug action.
ADVANTAGES:

- Sensitive method for imaging.
- Can investigate disease at a molecular level even in the absence of anatomical abnormalities.
- It is possible to quantify the amount of tracer within a region of interest in the patient’s body; possible to monitor the amount of tracer in mg/100ml of tissues.

DISADVANTAGES:

- High cost of PET setup.
- Requires more space, electricity, and air conditioning than conventional nuclear medicine.
- Requires an on-site cyclotron due to the short half-life of the positron emitting.
- CT data better identifies the invasion of the oral carcinomas into the jaws than FDG PET.
- Major image quality degradation is due to the metallic dental implants therefore all removable artificial dentures & metal parts to be removed during scanning.
- PET & PET/CT like any other imaging technique is not able to identify micro metastasis ie; metastasis up to 2mm.

Hybrid scanning techniques:

- PET scans are increasingly read alongside CT or magnetic resonance imaging (MRI) scans, the combination ("co-registration") giving both anatomic and metabolic information.
- Clinically it has been used in the management of patients with epilepsy, cerebrovascular disease and cardiovascular disease, dementia and malignant tumors including identification of recurrent head and neck cancers.

Overview of the imaging modalities:

- Planar Scintigraphy
- SPECT
- PET
- PET/CT

APPLICATIONS
Maxillofacial scintigraphy

Bone scanning is used to detect:
- Metastatic neoplasia when the primary tumor originated in lungs, prostate, breast, head & neck
- Paget's disease
- Hyperparathyroidism
- Premature cranio synostosis
- Ameloblastoma
- Fibrous dysplasia.

Bone scintigraphy

- A bone scan or bone scintigraphy is a nuclear scanning test to find certain abnormalities in bone which are triggering the bone's attempts to heal.
- Bone scintigraphy is an highly sensitive method for demonstrating disease in bone, often providing earlier diagnosis or demonstrating more lesions than are found by conventional radiological methods.

**Technique:**
- The patient is injected with a small amount of radioactive material such as 600 MBq of technetium-99m-MDP.

- Methylene Diphosphonate (MDP) has affinity for calcium rich hydroxyapatite crystals of bone.
- The technetium (Tc) 99m-MDP undergoes ‘chemisorption’ and gets bound to bone matrix.

  - Increased radioactivity
  - Reduced radioactivity can result from:
    - Replacement of bone by destructive lesion (lytic lesion) - primary or metastatic.
    - Disruption of normal blood flow consequent to radiation.
  - Reduced radioactivity is visualized as ‘cold spot’ or photopenic bone lesion.

Clinical indications

The oncological indications are:
- Primary tumors (e.g. Ewing's sarcoma, osteosarcoma):
  - Staging, evaluation of response to therapy and follow-up of primary bone tumors
- Secondary tumor's (metastases)

- Non neoplastic diseases such as:
  - Osteomyelitis
  - Avascular necrosis
  - Metabolic disorders (Paget, osteoporosis)
  - Assessment of chondro-synostosis in intracranial hypoplasia
  - Arthropathies
  - Fibrous Dysplasia
  - Stress fractures, shin splints, bone grafts
  - Loose or infected joint prosthesis
  - Low back pain
  - Reflex sympathetic dystrophy

Interpretation

- Symmetry of right and left sides of the skeleton and homogeneity of tracer uptake within bone structures - normal features.
- Both increase and decrease of tracer uptake have to be assessed; abnormalities can be either focal or diffuse.
- Increased tracer activity - indicates increased osteoblastic activity.
- Compared to a previous study:
  - Increase in intensity of tracer uptake and in the number of abnormalities
  - Progression of disease
  - Reduction in intensity of tracer uptake and in the number of abnormalities
• Focal decrease in radioactivity:
  – Benign conditions
  – Attenuation
  – Artifact
  – Absence of bone e.g. surgical resection.

• When compared to a previous study:
  Decrease in intensity of tracer uptake and in number of abnormalities
  Improvement or may be secondary to focal therapy (e.g. radiation therapy).

Bone scintigram in a patient with bisphosphonate-related ONJ

Bone scintigram shows uptake in the right masseter.

Bone scintigram obtained approximately 17 months later shows progression of the uptake.

METASTATIC CARCINOMA OF PROSTATE 99mTc scintigram

• It is difficult to differentiate an abnormality in the head or neck of condyle or articular tubercle or articular fossa because of close approximation of structures.

Condylar hyperplasia

• A lack of unusual bone activity demonstrated in a technetium bone scan is a useful indication of arrested condylar growth.

Temporomandibular joint

Ameloblastoma 67Ga scan
In periapical abscess there will be increased uptake of radionuclide due to osteoblastic activity.

Anatomic localization of abnormalities of maxillofacial region detected by radionuclide imaging is done by multiple properly positioned views:
- Posteroanterior view
- Lateral view
- Oblique view
- Water’s view

Frontal and lateral (right and left) radionuclide images of the skull showing intense activity in the left temporomandibular joint in a 41-year-old woman with an MRI-confirmed temporomandibular joint meniscus dysfunction.

TUMOR DETECTION

- Most malignant neoplasm that spread to or arise in the bone evoke an osteoblastic response, which accounts for localization of bone seeking radio pharmaceuticals in this area. However a purely destructive lesion may not have an associated reparative component.

Some nonspecific physiological changes occurring with neoplasm that causes tumor seeking radio pharmaceuticals to accumulate are:
1. Localized increased blood volume
2. Abnormal tumor circulation with increased microvascular permeability
3. Increased affinity for radio tracer-labeled proteins in the metabolically active neoplastic site
4. Prolonged extra vascular presence of radio nuclide that may be secondary to impaired lymphatic drainage from the tumor region

Salivary gland imaging

- Imaged following administration of 99m Tc pertechnetate or radioactive iodine.
- 99m Tc is preferred owing to its low radiation dose and the desirability of its photon emission (which is highly suitable for scintillation camera imaging).
Salivary gland imaging is made possible by the glandular ability to concentrate radionuclide before excretion into the saliva.

Salivary gland imaging is both functional and morphological test.

**Technique**

- **Technique**
  - $^{99m}$Tc pertechnetate administered intravenously in dose range 0.5 to 10 mCi.
  - A vascular blush outlining the parotid gland is seen immediately following pertechnetate administration.

- The concentration phase begins within first 10 minutes and represents the active accumulation of radionuclide by the ductal epithelium.
  - This phase may be enhanced by administration of pilocarpine nitrate 20 mgs subcutaneously.

- The excretory phase begins 10 to 40 minutes following administration and represents tracer being transported into the saliva and excreted into the oral cavity.
  - This phase may be enhanced by oral administration of lemon juice or potassium perchlorate 1gm/70 kgs.

- Salivary excretion is blocked by intramuscular administration of 0.8 to 1mg atropine 30 minutes prior to scanning.

- Primary glandular malignancies as well as metastatic tumor of the gland, abscess cyst fails to accumulate pertechnetate and appears as region devoid of radionuclide; this focus is called “cold focus.”
**HOT FOCUS**

- Benign neoplasm like warthin's tumor actively accumulate radionuclide to a greater depth than surrounding normal glandular tissue due to the ductal inclusion from which the tumor is thought to arise retaining their ability to concentrate pertechnetate.

**WARM FOCUS**

- Mixed tumor like pleomorphic adenoma accumulates radionuclide's nearly equal to surrounding normal gland.

Regions of interest on dynamic scintigraphy:
- RP, right parotid; LP, left parotid; RSm, right submandibular gland; LSm, left submandibular gland; B, background.

- Bilateral intraglandular lesions appears as cold defects on scintigraphic images.
- Dynamic images (1 sec per frame) following intravenous injection of $^{99m}$Tc $p$-ertechnetate show normal uptake and response to secretion stimulation in the upper poles of the parotid glands (arrows). Neither submandibular gland showed significant uptake (arrowheads). Note physiological uptake in the thyroid gland.
CLINICAL USES OF RADIONUCLIDE IN SALIVARY GLAND IMAGING

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Scintigraphic appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warthins tumor</td>
<td>Hot Focus</td>
</tr>
<tr>
<td>Oxyphilic adenoma</td>
<td>Hot focus or cold focus</td>
</tr>
<tr>
<td>Mixed tumors</td>
<td>Cold or warm focus</td>
</tr>
<tr>
<td>Malignant tumors</td>
<td>Cold focus</td>
</tr>
<tr>
<td>Cysts</td>
<td>Cold focus</td>
</tr>
<tr>
<td>Abscesses</td>
<td>Cold focus</td>
</tr>
</tbody>
</table>

**Conclusion**

- Nuclear imaging had got its various applications not only in diagnosis but also in therapeutics of various disorders which also covers a wide spectrum of maxillofacial disorders.
- Several research and advances are going in increasing the specificity of these imaging modalities which may even widen the scope of nuclear imaging.

**REFERENCES**

- Oral radiology - White & Pharoh
- Essentials of dental radiography & radiology-Eric Whaites
- Goss & White radiology

**THANK YOU**
INTRODUCTION

• Oral cancer is a broad term that includes various malignant diagnoses that present in the oral tissues.

• It is traditionally defined as a squamous cell carcinoma (OSCC), because 90% of cancers are histologically originated in the squamous cells.

• It has different levels of differentiation and a propensity for lymph node metastasis.

EPIDEMIOLOGY

• Cancer of the oral cavity and pharynx affects 10.8 of every 100,000 individuals in the United States, based on the National Cancer Institute data, and 7.2 of every 100,000 individuals will have cancer in oral cancer.

• Based on the data from Surveillance, Epidemiology, and End Results program for 2003 to 2009 the 5-year survival in the United States was 62.2%.

• In India, the incidence of oral cancer for males and females was highest in the central region of India.

• For males, it was 64.8% and for females it was 37.2% at 70 years of age.

• The next highest magnitude was observed in the west and northeast regions (58.4%) at 60 years of age.

ORAL CANCER CLASSIFICATION

WHO Classification of Oral Cancer

<table>
<thead>
<tr>
<th>Epithelial cancer</th>
<th>Hemato lymphoid cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>Vermiform carcinoma</td>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td>Basaloid squamous cell carcinoma</td>
<td>Follicular lymphoma</td>
</tr>
<tr>
<td>Papillary squamous cell carcinoma</td>
<td>Extramedullary plasmodyoma</td>
</tr>
<tr>
<td>Spindle cell carcinoma (sarcomatoid SCC)</td>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td>Acantholytic squamous cell carcinoma</td>
<td>Extramedullary plasmodyoma</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td>Carcinoma cuniculatum</td>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td>Lymphoepithelial carcinoma</td>
<td>Burkitt lymphoma</td>
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</tbody>
</table>

Salivary gland cancer

<table>
<thead>
<tr>
<th>Salivary gland carcinoma</th>
<th>Salivary gland adenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinic cell carcinoma</td>
<td>Pleomorphic adenoma</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>Myoepithelioma</td>
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<tr>
<td>Adenoid cystic carcinoma</td>
<td>Basal cell adenoma</td>
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<tr>
<td>Polymorphous low-grade adenocarcinoma</td>
<td>Warthin’s tumor</td>
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<tr>
<td>Basal cell adenocarcinoma</td>
<td>Warthin’s tumor</td>
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<tr>
<td>Epithelial-myoepithelial carcinoma</td>
<td>Warthin’s tumor</td>
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<td>Clear cell carcinoma</td>
<td>Warthin’s tumor</td>
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<td>Cystadenocarcinoma</td>
<td>Warthin’s tumor</td>
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<tr>
<td>Muscious adenocarcinoma</td>
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<tr>
<td>Oncocytic carcinoma</td>
<td>Warthin’s tumor</td>
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<tr>
<td>Salivary duct carcinoma</td>
<td>Warthin’s tumor</td>
</tr>
<tr>
<td>Myoepithelial carcinoma</td>
<td>Warthin’s tumor</td>
</tr>
<tr>
<td>Carcinoma ex pleomorphic adenoma</td>
<td>Warthin’s tumor</td>
</tr>
</tbody>
</table>

1) Burkit Textbook of oral medicine 12th edition
Etiology and Risk Factors

- The two main factors which influence the development of oral cancer are genetic and epigenetic factors.
- The main risk factors identified globally are tobacco and alcohol use.
- Other risk factors include:
  - Diet and nutrition
  - Viruses
  - Radiation
  - Ethnicity
  - Familial and genetic predisposition
  - Oral thrush
  - Immunosuppression
  - Use of mouthwash
  - Syphilis
  - Dental factors
  - Occupational risks

Tobacco

<table>
<thead>
<tr>
<th>Form of Tobacco</th>
<th>Constituents</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tobacco (Smokeless)</strong></td>
<td>Nitrosamines, Polycyclic aromatic hydrocarbons Nitrosodeterhalomine Nitrosoprine Polonium</td>
<td>Short term - Benign hyperkeratosis and epithelial dysplasia Chronic use - Risk of malignant lesions</td>
</tr>
<tr>
<td><strong>Tobacco (Smoke)</strong></td>
<td>Carbon monoxide Thiocyanate Hydrogen cyanide Nicotine</td>
<td>80% - primary oral cancer Risk of recurrent and second primary oral cancer</td>
</tr>
</tbody>
</table>

Alcohol

- Beer and wine are associated with greater risk than hard liquor.
- The combined effects of tobacco and alcohol result in a synergistic effect on the development of oral cancer.
- **Mechanism**: Alcohol 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.
- Smoking and alcohol interaction may influence central nervous system activity.

Betel (Areca) Nut

- People with a betel quid chewing habit, with or without added tobacco, are at a higher risk to develop oral cancer.
- In parts of Asia where the use of betel nut mixed with lime to form a quid is widespread (e.g., India, Taiwan), the incidence of oral cancer is high and more commonly involves the buccal mucosa.
- Substitutes for betel quid, such as guthka and pan masala, are potential carcinogenic as well.
Nutritional Factors

- Consumption of fruits and vegetables is associated with a reduced risk for oral cancer.
- Diets high in eggs and butter and meats-Elevated but inconsistent risk of oral cancer
- Vitamins A, C and E; carotenoids (β-carotene); potassium, selenium - decrease the risk of oral cancer development
- Vitamin D deficiency - associated with oral cancer

Maté

- Maté, which is a tea-like beverage consumed in South America and in parts of Europe has been shown to be an independent cause for development of oral and pharyngeal cancers.
- The exact pathogenesis of maté predisposing to oral cancer is still unknown.
- Many reasons that have proposed for maté’s carcinogenicity are:
  1) Thermal injury
  2) Solvent for other chemical carcinogens
  3) Presence of tannins and N-nitroso compounds.

ENVIRONMENTAL FACTORS
Viral Infections

- Viruses have been strongly implicated in the development of malignant tumors of the squamous epithelium including the oral squamous epithelium.
- Viral infections of latent or chronic nature are usually responsible for inducing malignant transformation by interfering with the host’s cell cycle machinery.
- The viral genes and gene products may affect cell growth and proliferation.
- Certain viral genes such as regulatory oncogenes which become oncogenes when inserted into the host’s DNA and ultimately resulting in malignant transformation.
- Virus involved - human herpes virus (mainly Epstein–Barr virus (EBV)), human papillomavirus (HPV), and herpes simplex virus.

HPV are the most common viruses implicated in oral carcinogenesis.

- High-risk HPV types - 16, 18, 31, 33, 35, and 39 associated with OSCC and oral premalignant lesions.
- HPV encodes two major oncoproteins - E6 and E7.
- The E6 and E7 proteins bind and destroy p53 and Rb, respectively, thereby disrupting the cell cycle with loss of control on DNA replication, DNA repair, and apoptosis.
- HPV-16 and -18 are considered high-risk subtypes due to their association with malignant tumors.
- HPV-16 alone is associated with about 85% to 95% of HPV-positive OPCs

HSV has not been proven to be the direct cause of oral cancer

- Several studies show that oral cancer patients have high serum antibody titers to HSV.
- The available evidences are circumstantial and are rationalized that reactivation of HSV infection is due to immunosuppression, specifically of natural killer lymphocyte activity.
- Based on the evidence of in vitro studies, the possible role of HSV in carcinogenesis has been proposed or the enhancement of activation, amplification, and overexpression of pre-existing oncogenes such as c-myc and c-erb-B-1.

Fungal Infections

- Fungal infections caused by Candida species such as Candida albicans has been implicated in the pathogenesis of oral premalignant lesions.
- Superficial fungal hyphae of Candida albicans have been found superimposed on leukoplakia, especially nodular leukoplakia, many of which have undergone malignant transformation.
- Besides immunocompromised individuals, Candida infection can coexist or be associated with other risk factors like iron deficiency and in chronic smokers which may prove synergistic in the development of oral cancer.
- There is evidence that Candida possesses necessary enzymes from dietary substances to produce nitrosamines and chemicals that have been implicated in carcinogenesis.
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.

Immunosuppression

- Immunosuppressed individuals are more prone to develop oral cancers.
- Human immunodeficiency virus (HIV)-infected patients are predisposed to developing Kaposi’s sarcoma and lymphomas.
- Immunosuppressed organ transplant patients have been shown to develop lip cancers and the possible reason was attributed to increased exposure to solar radiation and other risk factors such as smoking.
- The direct role of immunosuppression with lip cancer development was not proven in the studies.

Occupational Risks

- Occupational risks, namely exposure to excessive solar radiation/ultraviolet (UV) light is known to cause lip cancers.
- UV rays also cause actinic cheilitis which may transform to OSCCs.
- 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 woodworking in an automobile industry.

Dental Factors

- Poor oral hygiene, poor dental status (sharp/fractured teeth due to caries/trauma), and chronic ulceration from an ill-fitting denture has been suggested to promote neoplasm in the presence of other risk factors.
- There has been difficulty in obtaining the evidence whether dental factors influence oral cancer development.
- This is due to the presence of coexisting risk factors like smoking and alcohol consumption.
- In a study, mechanical irritation by scratching with a pulp cleaner has been shown to significantly increase the incidence of a chemical carcinogen-induced tongue carcinoma.
- Therefore, it is prudent to closely monitor patients with known risk factors for signs and symptoms of irritation from teeth and appliances.

Pathogenesis of cancer

- Oral carcinogenesis is a highly complex multifocal process that takes place when squamous epithelium is affected by several genetic alterations.

Theories of carcinogenesis

- Molecular pathogenesis of cancer
- Chemical carcinogens and chemical carcinogenesis
- Physical carcinogens and radiation carcinogenesis
- Biologic carcinogens and viral carcinogenesis

MOLECULAR PATHOGENESIS OF CANCER

- Genetic theory: This is the most popular theory, which suggests that cells become neoplastic because of alterations in the DNA.
- The mutated cells transmit their characters to the next progeny of cells.
- Evidence in support of genetic theory comes from all types of etiologic agents in carcinogenesis.
- Epigenetic theory: This theory is less well supported than the genetic theory.
- According to the epigenetic theory, the carcinogenic agents act on activators or suppressors of genes and not on the genes themselves and result in the abnormal expression of genes.
**Field theory of cancer**

➢ In an organ developing cancer, in the backdrop of normal cells, limited no. of cells only grow in to cancer after undergoing sequence of changes under the influence of etiological agents.

➢ This is termed as field effect concept called field theory of cancer

**Multistep process of cancer growth and progression**

- Carcinogenesis is gradual multistep process involving many generation of cells.
- Ultimately so formed genetically and phenotypically transformed cells having phenotypic features of malignancy.
  ➢ Shows excessive growth.
  ➢ Invasiveness.
  ➢ Distant metastasis

---

**Immune-surveillance theory**:

- In 1909, Paul Ehrlich formulated the hypothesis that host defense may prevent neoplastic cells from developing into tumors

- Lewis Thomas suggested that the immune system recognizes newly arising tumors through the expression of tumor specific neo-antigens on tumor cells and eliminate them.

- Sir Frank MacFarlane Burnet hypothesized that tumor cell neo-antigens induce an immunological reaction against cancer and subsequently formulated the immune surveillance theory.


**Monoclonal hypothesis**

- It is proposed by Nowell in 1976

- Cancer cell develop strategies to survive a hostile host environment and use host resources to grow and proliferate.

- According to this theory: cancer arise from single clone of transformed cells

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**Genetic regulators of normal and abnormal mitosis**

<table>
<thead>
<tr>
<th>Normal cell growth</th>
<th>Cancer cell growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proto oncogenes - growth promoting agents, they encode for cell proliferation pathway.</td>
<td>Proto oncogenes - activation of growth promoting oncogenes causing transformation of cells.</td>
</tr>
<tr>
<td>Anti oncogenes - growth inhibiting or growth inhibitors are present.</td>
<td>Inactivation of Anti oncogenes-suppressor genes permitting the cellular proliferation of transformed cells.</td>
</tr>
<tr>
<td>Apoptosis regulatory genes - control the programmed cell death.</td>
<td>Abnormal apoptosis regulatory genes - these act as oncogenes.</td>
</tr>
<tr>
<td>DNA repair genes - regulate the repair of DNA damage Occurred during mitosis and also control the damage to proto-oncogenes and antioncogenes.</td>
<td>Failure of DNA repair genes - inability to repair DNA damage resulting in mitosis.</td>
</tr>
</tbody>
</table>

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**Chemical carcinogens and chemical carcinogenesis**

- Chemicals which initiate carcinogenesis is called chemical carcinogens.

- Chemicals which increase the effectiveness of carcinogens is called co-carcinogens.

- Stages in chemical carcinogenesis

  - Initiation
  - Promotion
  - progression

---

**Chemicals**

- Chemicals which initiate carcinogenesis

- Chemicals which increase the effectiveness of carcinogens

- Initiation

- Promotion

- progression

---

**Chemical Carcinogens**

- Chemicals which initiate carcinogenesis

- Chemicals which increase the effectiveness of carcinogens

- Initiation

- Promotion

- progression

---

**Chemical Carcinogens**

- Chemicals which initiate carcinogenesis

- Chemicals which increase the effectiveness of carcinogens

- Initiation

- Promotion

- progression

---
Tests for chemical carcinogenicity

Experimental induction

• The traditional method is to administer the chemical compound under test to a batch of experimental animals like mice.
• E.g. painting on skin, giving orally or parenterally, or by inhalation.
• Repeated administration, dose varied, after many months the animal is autopsied and results obtained.

Test for mutagenicity (Ames test)

• Ames test evaluate the ability of a chemical to induce mutation in the mutant strain of salmonella typhimurium that cannot synthesize histidine.
• Strains are incubated with the potential carcinogen to which liver homogenate is added to supply enzymes required to convert procarcinogen to ultimate carcinogen.
• If the chemical is mutagenic, induce mutant strains of s typhimurium
• S typhimurium in the form of functional histidine gene, which will be reflected by the no. of bacterial colonies growing on histidine-free culture medium.

Physical carcinogens and radiation carcinogenesis

• UV light and ionizing radiation are two main forms of radiation carcinogenesis.

UV light

• UV light penetrates into the skin for few millimeters only so that its effect is limited to epidermis.
• The efficiency of UV light as carcinogen depends upon extent of light absorbing protective melanin pigmentation of skin.
• If exposure is more it will cause scc, bcc, malignant melanoma.
• Incidence is high in fair skinned Europeans.

Ionizing radiation

• X rays, α, β, γ rays and radioactive isotopes, photons, neutrons can cause cancers in animals and man.
• Risk of cancer increases by dose with high LET such as neutrons, α rays.
• Low LET such as x rays and γ rays.
• High incidence of radiation dermatitis & malignant tumors of skin common in x ray workers, radiotherapists.
• High incidence of osteosarcoma-young American watch working girls engaged in painting the dials with luminous radium.

Mechanism

• It may directly alter the cellular DNA.
• Formation of high reactive free radicals-damage.
Biologic carcinogens and viral carcinogenesis

• Many DNA & RNA viruses are proved to be carcinogenic.

**Oncogenic RNA viruses**

• Oncogenic retrovirus, human T cell lymphotropic virus -1, (HTLV-1) has demonstrated to cause cancer in humans.

**Pathogenesis**

• Induced T cell leukemia lymphoma.

• HTLV-1 infects many T cells and initially caused polyclonal proliferation by autocrine and paracrine pathways triggered by the TAX gene.

• TAX neutralizes growth inhibitory signals by affecting TP53 & CDKN2A/p16 genes.

• Ultimately a monoclonal T cell leukemia /lymphoma results when one proliferating T cell suffers additional mutations.

**Oncogenic DNA viruses**

• Four DNA viruses HPV, EBV, HBV associated with cancers.

  **HPV**

  • Oncogenic potential HPV related to products of 2 viral genes E6 & E7

  • E7 protein binds to retinoblastoma proteins & release the E2F transcription factors that normally are sequestered by Rb, promoting progression through the cell cycle.

  • High risk stimulates loss of tumor suppressor genes, activate cyclins, inhibits apoptosis, and combats cellular senescence.

  • Low risk HPV’s give rise to benign warts.

  **HBV**

  • Contribute oncogenesis by B cell proliferation, leads to development of lymphoma and occurrence of additional mutations such leading to activation of the MYC gene.

  • E.g. -lymphomas in immunocompromised patients, Hodgkin's lymphoma, nasopharyngeal carcinoma.

**HALLMARKS OF CANCER**

• 1) Excessive and autonomous growth: Growth-promoting oncogenes.

• 2) Refractoriness to growth inhibition: Growth suppressing anti-oncogenes.

• 3) Escaping cell death by apoptosis: Genes regulating apoptosis and cancer

• 4) Avoiding cellular aging: Telomeres and telomerase in cancer

• 5) Continued perfusion of cancer: Cancer angiogenesis

• 6) Invasion and distant metastasis: Cancer dissemination.

• 7) DNA damage and repair system: Mutator genes and cancer.

• 8) Cancer progression and tumour heterogeneity: Clonal aggressiveness.

• 9) Cancer a sequential multistep molecular phenomenon: Multistep theory.

• 10) MicroRNAs in cancer: OncomiRs

**EXCESSIVE AND AUTONOMOUS GROWTH: GROWTH PROMOTING ONCOGENES**

• Mutated form of normal protooncogenes in cancer is called oncogenes.

• Protooncogenes become activated oncogenes by mechanisms

  ➢ By mutation in the protooncogene which alters its structure and function.

  ➢ By retroviral insertion in the host cell.

  ➢ By damage to the DNA sequence that normally regulates growth-promoting signals of protooncogenes resulting in its abnormal activation.

  ➢ By erroneous formation of extra copies of protooncogene causing gene amplification and hence its overexpression or overproduction that promotes autonomous and excessive cellular proliferation.
<table>
<thead>
<tr>
<th>REFRACTORYNESS TO GROWTH INHIBITION: GROWTH SUPPRESSING ANTI-Oncogenes</th>
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</thead>
<tbody>
<tr>
<td>• The mutation of normal growth suppressor anti-oncogenes results in removal of the brakes for growth; thus the inhibitory effect to cell growth is removed and the abnormal growth continues unchecked.</td>
</tr>
<tr>
<td>• Mutated antioncogenes behave like growth-promoting oncogenes.</td>
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<tr>
<th>ESCAPING CELL DEATH BY APOPTOSIS: GENES REGULATING APOPTOSIS AND CANCER</th>
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<tbody>
<tr>
<td>• Besides the role of mutant forms of growth-promoting oncogenes and growth-suppressing anti-oncogenes, another mechanism of tumour growth is by escaping cell death by apoptosis.</td>
</tr>
<tr>
<td>• Apoptosis in normal cell is guided by cell death receptor, CD95, resulting in DNA damage.</td>
</tr>
<tr>
<td>• Besides, there is role of some other pro-apoptotic factors (BAD, BAX, BID and p53) and apoptosis inhibitors (BCL2, BCL-X).</td>
</tr>
<tr>
<td>• In cancer cells, the function of apoptosis is interfered due to mutations in the above genes which regulate apoptosis in the normal cell.</td>
</tr>
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<tr>
<th>AVOIDING CELLULAR AGING: TELOMERES AND TELOMERASE IN CANCER</th>
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<tbody>
<tr>
<td>• After each mitosis (cell doubling) there is progressive shortening of telomeres which are the terminal tips of chromosomes.</td>
</tr>
<tr>
<td>• Telomerase is the RNA enzyme that helps in repair of such damage to DNA and maintains normal telomere length in successive cell divisions.</td>
</tr>
<tr>
<td>• However, it has been seen that after repetitive mitosis for a maximum of 60 to 70 times, telomeres are lost in normal cells and the cells cease to undergo mitosis.</td>
</tr>
<tr>
<td>• Telomerase is active in normal stem cells but not in normal somatic cells.</td>
</tr>
<tr>
<td>• Cancer cells in most malignancies have markedly upregulated telomerase enzyme, and hence telomere length is maintained.</td>
</tr>
<tr>
<td>• Thus, cancer cells avoid aging, mitosis does not slow down or cease, thereby immortalising the cancer cells.</td>
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<tr>
<th>CONTINUED PERFUSION OF CANCER: TUMOUR ANGIOGENESIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cancers can only survive and thrive if the cancer cells are adequately nourished and perfused, as otherwise they cannot grow further.</td>
</tr>
<tr>
<td>• Neovascularisation in the cancers not only supplies the tumour with oxygen and nutrients, but the newly formed endothelial cells also elaborate a few growth factors for progression of primary as well as metastatic cancer.</td>
</tr>
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<thead>
<tr>
<th>INVASION AND DISTANT METASTASIS: CANCER DISSEMINATION</th>
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<tr>
<td>• One of the most important characteristic of cancers is invasiveness and metastasis.</td>
</tr>
<tr>
<td>• As the tumor progression advances, the cells lose their adherence property, detach from the tumor mass and invade the neighboring tissues.</td>
</tr>
<tr>
<td>• The detached cells also enter the circulating blood and lymph and are transported to other organs/tissues away from the site of the primary growth and develop into secondary tumors at the new sites.</td>
</tr>
<tr>
<td>• These form the distant metastases, resulting in widely spread cancers.</td>
</tr>
</tbody>
</table>
DNA DAMAGE AND REPAIR SYSTEM: MUTATOR GENES AND CANCER

- Normal cells during complex mitosis suffer from minor damage to the DNA which is detected and repaired before mitosis is completed so that integrity of the genome is maintained.
- p53 gene is held responsible for detection and repair of DNA damage.
- If this system of DNA repair is defective as happens in some inherited mutations (mutator genes), the defect in unrepaired DNA is passed to the next progeny of cells and cancer results.

CANCER PROGRESSION AND HETEROGENEITY: CLONAL AGGRESSIVENESS

- As time passes, cancers become more aggressive; this property is termed tumour progression.
- Clinical parameters of cancer progression are: increasing size of the tumour, higher histologic grade (as seen by poorer differentiation and greater anaplasia), areas of tumour necrosis (i.e. tumour outgrows its blood supply), invasiveness and distant metastasis.
- This means that though cancer cells remain monoclonal in origin, they acquire more and more mutations which, in turn, produce multiple-mutated subpopulations of more aggressive clones of cancer cells in the growth which have tendency to invade, metastasise and be refractory to hormonal influences.
- Some of these mutations in fact may kill the tumour cells as well.

CANCER A SEQUENTIAL MULTISTEP MOLECULAR PHENOMENON: MULTISTEP THEORY

- Cancer occurs following several sequential steps of abnormalities in the target cell.
- Initiation, promotion and progression in proper sequence.
- Multiple steps are involved at genetic level by which cell proliferation of cancer cells is activated: by activation of growth promoters, loss of growth suppressors, inactivation of intrinsic apoptotic mechanisms and escaping cellular aging.

MICRORNA AS IN CANCER: ONCOMIRS

- MicroRNAs (miRNAs) are evolutionally conserved, endogenous, noncoding single stranded RNA molecules with a length of 22 nucleotides only.
- Normally, miRNAs function as the posttranslational gene regulators of cell proliferation, differentiation and survival.
- Recent evidence indicates that miRNAs have an oncogenic role in initiation and progression of cancer and are termed as oncogenic microRNAs, abbreviated as oncomiRs.
- In combination with other tumour associated genes, oncomiRs can perform various functions: as tumour suppressor, as tumour promoter, and as pro-apoptotic.

CLINICAL SIGNS AND SYMPTOMS

- Discomfort is the most common symptom that leads a patient to seek care and may be present at the time of diagnosis in up to 85% of patients.
- Individuals presents with mass in the mouth or neck.
- Dysphagia, odynophagia, otalgia, limited movement, oral bleeding, neck masses, and weight loss may occur with advanced disease.
- Loss of sensory function – unilateral - indicate neural involvement
- Loss of function involving the tongue can affect speech, swallowing, and diet.

Tissue changes

- 1) Red, white, or mixed red-and-white lesion
- 2) A change in the surface texture producing a smooth, granular, rough, or crusted lesion
- 3) Presence of a mass or ulceration
- 4) The lesion may be flat or elevated and may be minimally palpable or indurated
- High-risk sites - lower lip, the anterior floor of the mouth, and the lateral borders of the tongue.
Lymphatic spread - submandibular and digastric nodes, and the upper cervical nodes and also remaining nodes of the cervical chain.

Lymph nodes - enlarged and firm to hard in texture, and with progression may become fixed and not mobile.

The nodes are not tender unless they are associated with secondary infection or an inflammatory response is present, which may occur after a biopsy.

The fixation of nodes to adjacent tissue due to invasion of cells through the capsule is a late occurrence and is evidence of aggressive disease.

Spread of tumor is critical for prognosis and for selection of treatment.

The understaging of nodes by cursory assessment or the overstaging of nodes following a biopsy, when an inflammatory component may be present, impacts the selection of treatment.

Therefore, accurate node examination is needed before biopsy.

Staging of Oral Squamous Cell Carcinoma

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor 2 cm or less in greatest dimension
- T2: Tumor more than 2 cm but not more than 4 cm in greatest dimension
- T3: Tumor more than 4 cm in greatest dimension
- T4a: Moderately advanced local disease
- T4b: Very advanced local disease

Node category

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
- N2: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
- N2a: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
- N2b: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
- N2c: Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
- N3: Metastasis in a lymph node more than 6 cm in greatest dimension
- N4: Distant metastasis

Stage grouping

- Stage 0: Tis N0 M0
- Stage I: T1 N0 M0
- Stage II: T2 N0 M0
- Stage III: T3 N0 M0
- Stage IVA: T4a N0 M0
- Stage IVB: Any T N3 M0
- Stage IVC: Any T Any N M1

M0: No distant metastasis
M1: Distant metastasis

Additional markers based on blood of saliva samples are also under investigation.

Several aids to the oral examination have been suggested:

1) Light technologies
2) Vital tissue staining using toluidine blue (TB)
3) Computer-assisted cytology of oral brush biopsy specimens.

Diagnostic aids
CONVENTIONAL ORAL EXAMINATION

- Conventional oral examination has various disadvantages like false positive findings, including psychological trauma, over-diagnosis, increased human and financial resources, recognition of varied clinical presentations of premalignant lesion.

- Only a minor fraction of leukoplakias become canceorous and there is impossibility of distinction amongst cancerous lesions and their equivalents that do not convert into malignancy.

BRUSH BIOPSY

- In 1999, the OralCDx Brush Test System (Brush Biopsy) was presented as a probable oral malignancy detection method.

- The examination of clinical lesions that would typically not be subjected to biopsy because the index of suspicion for malignancy was low established upon clinical features were the primary target areas for brush biopsy.

- There is typically collection of an epithelial sample (including the superficial, intermediate and parabasal/basal layers) of cells from a mucosal lesion.

- When an atypical or positive outcome is conveyed, the practitioner should supplement with a biopsy (scalpel) of the suspicious condition, since the usage of oral CDx (brush biopsy) does not specifies conclusive finding.

VITAL TISSUE STAINING

- Toluidine blue (tolonium chloride) stains mitochondrial DNA, dysplastic cells which have increased DNA content or modified DNA in cancerous cells.

- The local application of toluidine blue (a metachromatic dye) facilitates in recognizing malignant alterations and potential areas of high-grade dysplasia.

- Lugol’s solution is used for delimitation of the cancerous alteration that generates a brownish black stain when glycogen reacts with iodine.

- The usage of combination of Lugol’s iodine and toluidine blue provides a valuable addition for diagnosis of patients who are at an increased risk and for selecting the site for biopsy with wide field cancers prior to management.

CHEMILUMINESCENCE

- Chemiluminescence [commercially available as ViziLite (Zila, Batesville, AR, United States)] is an intraoral examination diagnostic tool to increase recognition, assessment and scrutinizing of oral mucosal aberrations in patients with increased possibility of malignant transformation.

- Disposable chemiluminescent light packet is used in ViziLite plus.

- The usage of acetic acid (1%) wash is done to eliminate superficial residues and to improve the conspicuousness of nuclei of the epithelial cells, perhaps as an outcome of slight dehydration of the cells.

- The MicroLux unit utilizes a light source which is battery-powered and reusable.

- Normal epithelium appears lightly bluish under blue-white illumination whereas aberrant epithelium looks noticeably white in appearance (acetowhite).

NARROW-EMISSION TISSUE FLUORESCENCE

- When tissues are exposed to a light of particular wavelength, there is auto fluorescence of cellular fluorophores after excitation (Fluorescence imaging).

- A visual examination of variation in colours is observed due to cellular changes that modulate fluorophores’ concentrations affecting the absorption of light in the cells.

- Visually Enhanced Lesion Scope (VELscope system; LED Dental Inc., White Rock, B.C.) comprises of light-source (wave length: 400-460 nm) and a component (manual) to assist in detailed examination or inspection.

- Typically oral mucosal tissues emanate a auto-fluorescence light of green colour but anomalous oral mucosal lesions absorbs the auto-fluorescent light and emerge as darker areas.
**CONFOCAL IN-VIVO MICROSCOPY**
- Confocal reflectance microscopy is an optical technology that delivers comprehensive descriptions of tissue structure and morphological characteristics of cell trans-epithelium in real time.
- Confocal in vivo microscopy assists the compilation of pathological level high resolution imaging from the tissue for disease recognition in cell biology with an advantage of optical sectioning.
- In vivo confocal images from the oral cavity show the distinctive characteristics like variability in nucleus findings that can recognize malignancy from normal oral mucosa.

**COLPOSCOPY**
- Colposcopy (direct microscopy) is a recognized medical diagnostic technique used to inspect the tissues of the vagina, vulva, and cervix, carried out under illuminated light with a magnified view of the area of interest.
- Colposcopy provides three-dimensional images of the tissue surfaces examined with portable video cameras attached and viewed on a television monitor screen.
- The colposcope is mounted with a green/blue filter to enable the inspection of alterations in vascularity and color quality as unfiltered white or yellow light diminishes the dissimilarity concerning the adjoining tissue and the arterioles.
- An optimum working distance of 200 mm for the focal length of the microscope is required.
- The accurateness of colposcopy was 70%-98% for the recognition of oral mucosal alterations with a study showing that colposcopy of oral premalignant lesions had benefits in choosing a representative area of biopsy.

**TISSUE FLUORESCENCE SPECTROSCOPY**
- The illumination of oral cavity tissue with UV-Visible light region results in the absorption of photons by fluorophores.
- It results in the excitation of fluorophores that causes emission of lower energy photons which are perceived as fluorescence from the mucosal surface.
- The auto fluorescence spectroscopy system contains an optical fibre which is small and similarly generates wavelengths of variable excitations and consists of a spectrograph that collects the continuums of reflected fluorescence from the cellular structures and analyses the received information on a computer.

**SALIVARY BIOMARKERS**
- Salivary proteins like α-amylase, interleukin 8, tumor necrosis factor-α, which are evaluated before and after malignancy from normal oral mucosa.
- The auto fluorescence spectroscopy contains an optical fibre which is small and similarly generates wavelengths of variable excitations and consists of a spectrograph that collects the continuums of reflected fluorescence from the cellular structures and analyses the received information on a computer.

**CELL AND TISSUE MARKERS**
- Tumour growth markers like epithelial growth factor (EGF), Cyclins, AgNOR, bcl2 and telomerase have been used.
- Three angiogenic biomarkers CD105 and Eph receptor tyrosine kinases (Ephs), vascular EGF and four hypoxia biomarkers (GLUT-1, carbonic anhydrase IX, hypoxia inducible factor 1a, and erythropoietin receptor) were identified as biomarkers.
- Retinoblastoma protein, p53 and Cyclin-dependent kinase inhibitors are the examples of tumour suppression markers and anti-tumor response.
- The matrix metallo proteins are proteases typically expressed by invasive cancers and the contiguous stroma and their expression has often been reviewed in various studies.
- Cathepsins, Integrins and desmoplakin have also been found as markers of tumor invasion.
- Cytokeratins, filaggrins, involucrin and glutathione S-transferase have all been investigated.

**ELASTOGRAPHY**
- Lymph node hardness (elasticity) is a major criterion to differentiate between an inflammatory enlargement and a malignant enlargement.
- Elastography assesses the behaviours of compliance of cellular structure.
- The compression to tissues generates displacement or strain in the tissue structure and hence by measuring tissue strain, hardness of the tissue can be estimated.
- The images obtained by elastography are evaluated before and after compression of cervical lymph nodes.
SURFACE ENHANCED RAMAN SPECTROSCOPY

- Raman spectroscopy delivers a factual, great - exactitude and sensitive procurement of the molecular tissue structure due to the particular interaction of cellular molecules with photons.

- The spectral characters of lipids, nucleic acids and proteins functions as precise Raman biomarkers to differentiate between malignant and normal oral mucosal area.

- Disadvantages are that it is random and nonimaging, requires expensive equipment, extensive process, lack of spatial information and multifaceted algorithms to discern various categories of tissues.

OPTICAL COHERENCE TOMOGRAPHY

- The recording of subsurface images to develop an overall cross-sectional tissue structural representation is optical coherence tomography.

- The multimodal distribution of polyethylene glycol linked gold nanoparticles that are antibody-conjugated augments the distinction in in-vivo images of cancerous lesions in oral cavity in a hamster model.

- The practicality of managing optical coherence tomography to detect structural modifications in cancerous molecules was observed in a recent pilot research in 27 cancerous patients.

ROSE BENGAL STAINING

- Rose Bengal stain (RB), the 4, 5, 6, 7-tetrachloro-2', 4', 5', 7'-tetrachlorodervative of fluorescein, can be utilized as a screening tool to detect oral precancerous lesions.

- Du et al concluded in a study that RB staining may be better than toluidine blue staining.

- Future research can ascertain the RB stain as an effective diagnostic tool in the recognition of oral precancerous lesions.

BIO-NANOCHIP

- A novel bio-nanochip (BNC) sensor which is a fast oral-cytology test that amalgamates the power of cytological morphometric examination with quantification of neoplastic biomarkers was documented.

- Generally, microfluidics technology (lab-on-a-chip) is the adjustment, miniaturization, amalgamation, and automation of analytical laboratory procedures into a solitary chip.

- The conducted study on quantitative BNC method to oral cytology effectively revealed cancerous and pre-cancerous conditions in a short time duration (<45 min).

- The recognition of cancerous cells in the BNC sensor utilized membrane-related cell proteins that are especially present on the cellular membrane structure of neoplastic cells.

DNA PLOIDY ANALYSIS

- Recent research has described the probable use of DNA ploidy analysis to predict the character of premalignant lesions in oral cavity.

- Aneuploidy (chromosomal imbalance) in dysplastic cells seen in premalignant lesions, as found by high resolution flow cytometry is suggestive of high possibility of oral malignancy.

- DNA ploidy analysis helps in compensating for intra- and inter-observer irregularity in the grading of dysplasia observed in premalignant lesions and might potentially aid in directing the management of the lesion, and probably suggest more aggressive treatment.

IMAGING MODALITIES

- The most commonly used modalities used for both diagnosis and the planning of treatment

- 1) Magnetic resonance imaging (MRI)

- 2) Computed tomography (CT)

- 3) Positron emission tomography (PET).


**Other modalities**

- 1) Plain radiography
- 2) Orthopantomography (OPG)
- 3) Cone beam computed tomography (CBCT)
- 4) Multidetector computed tomography (MDCT)
- 5) Computed tomography perfusion (CTP)
- 6) Diffusion-weighted MRI (DW-MRI)
- 7) Dynamic contrast-enhanced MRI (DCE-MRI)
- 8) Whole body MRI (WB-MRI)
- 9) Ultrasoundography (USG)
- 10) Single-photon emission computed tomography (SPECT)
- 11) Hybrid techniques such as SPECT/CT, CT/MRI, PET/CT, PET/MRI with radiopharmaceuticals – (^18F-FDG), (^18F-FAMT), (C-TYR)

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**Plain radiography**

- Oral SCC can initially develop in the bones as the primary squamous cell carcinoma (PIOSCC), which is a very rare type of cancer originating from the remnants of the dental epithelium (epithelial cell rests of Malassez and enamel epithelium).
- The diagnosis of PIOSCC is based on the following three criteria:
  1. no contact with mucous membrane or skin
  2. exclusion of distant metastasis in a 6-month follow-up
  3. Histopathological confirmation of squamous cell carcinoma
- The characteristic features of malignant lesions in plain radiographs include:
  - atrophy of cortical lamina, osteolytic defects – both single and multilocular with an initial osteoclastotic capsule.
  - In later stages, the ridges of bone defects become sharp and the teeth lose their bony support at the site of infiltration

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**Computed tomography**

- Computed tomography is a standard tool for detecting the primary tumors as well as their local bone infiltration.
- Contrast-enhanced CT can accurately determine lymph node metastases, which can initially look normal despite the presence of micrometastases detected in microscopic studies.

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**Perfusion computed tomography**

- By assessing perfusion of the tumor site, it is possible to better evaluate the involvement of the surrounding tissues.
  - The tumor is characterized by an increased blood volume (BV) and blood flow (BF) in comparison to healthy tissues.
  - This results from neoangiogenesis in the tumor.
  - It is suggested that perfusion CT is superior to CT as regards the assessment of muscle involvement.
  - The sensitivity of CTP in detecting local lymph node metastases is 67% (specificity 53%).
**Cone beam computed tomography (CBCT)**
- Isovolumetric tomography is an intensely developed diagnostic tool.
- The usefulness of CBCT in detecting osteolysis has been confirmed (sensitivity 89–93%, specificity 60–96.5%).
- CBCT is more accurate than panoramic radiography and comparable to MRI, CT and bone scintigraphy.
- CBCT is increasingly used by dentists in everyday practice which can result in an improved detection of oral cancers.
- CBCT is limited by a poor assessment of soft tissues.

**Magnetic resonance imaging (MRI)**
- MRI enables the detection of very small lesions, assessment of local spread of the tumor, planning surgery, evaluation of complications that can occur during and after surgery.
- MRI can determine the involvement of local soft tissues, bone marrow and bones (sensitivity 82%, specificity 66.7%) as well as vessels and nerves.
- MRI is a better modality in comparison to plain radiography and comparable to CBCT and CT – with similar sensitivity and specificity.
- MRI has a higher sensitivity with respect to the assessment of soft tissues.

**Single-photon emission computed tomography (SPECT)**
- SPECT allows for mapping metabolic activity of the tumor with the use of gamma radiation.
- The sources of radiation are isotopes such as 3-D 99mTc-DPD (technetium-dicarboxy propan SPECT) or 99mTc-Tehesks-2-methoxyisobutyl isonitrile (MIBI).
- In the early stages of oral cancer, sentinel lymph node biopsy (SLNB) is of high importance.
- The most commonly used techniques for the detection of sentinel nodes includes 1) lymphoscintigraphy before surgery, 2) SPECT/CT, and 3) Injection of the patent blue dye.

**CT fluoroscopy-guided biopsy**
- CT fluoroscopy is a minimally invasive imaging technique that enables a real-time assessment.
- It can be used for taking biopsies of oral cancers.
- However, it has not been described so far in a clinical setting in the available literature.

**Cone beam computed tomography (CBCT)**
- MRI effectively detect both local lymph node metastases and distant metastases of oral cancers (features N and M).
- MRI can differentiate between metastases and can assess the size of lymph node clusters (sensitivity 51–74%, specificity 95–100%).
- After diagnosing oral cancer, MRI should be used in order to assess a possible involvement of the neck and chest.
- MRI can assist in planning the scope of resection and further reconstruction, graft implantation, and differentiation between disease recurrence and scars after surgery.
- In patients with ferromagnetic prostheses in the facial skeleton, such as amalgamate fillings, dental crowns, tooth bridges, steel screws after osteosynthesis, MRI can be disturbed by numerous artifacts.

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**Single-photon emission computed tomography (SPECT)**
- FBhand SPECT (freehandSPECT) is a more accurate method which is used for planning biopsy.
- It is based on an intraoperative 3D imaging with the use of 3 gamma cameras - two cameras are placed above the patient and the third one is held by the surgeon who can move it freely around the patient.
- Freehand SPECT can determine the location of the sentinel node, its distance from the skin and relation to the surrounding structures.
- It also evaluates the flow of lymph into the sentinel node so that the physician can change the scope of resection by selectively removing metastatic lymph nodes.
- The assessment of the involvement of the mandible with 99mTc SPECT has almost 100% sensitivity and 14.3% specificity.
- Leitha et al. reported a combined use of 99mTc-DPD SPECT and 99mTc-tehesks-2-methoxyisobutyl isonitrile (MIBI) SPECT that had 100% sensitivity and 17% specificity.
**Positron emission tomography (PET)**

- PET with $^{18}$F-FDG evaluates tissue metabolic activity.
- It is used when planning adjuvant treatment and predicting survival without recurrence.
- It can be used for the detection of metastatic lymph nodes (sensitivity 83%, specificity 88%).
- It allows for an estimation of the risk of recurrence.

**Other methods that can be used to evaluate local infiltration**

1. PET/MRI
2. SPECT/CT
3. CT/MRI

**Radiopharmaceuticals**

1. $^{18}$F-FDG
2. $^{18}$F-fluorothymidine (FLT)
3. L-3-$^{18}$F-fluoro-alpha-methyltyrosine ($^{18}$F-FAMT)
4. L-1-[${}^{11}$C]thyrosine (C-Tyr)

- PET/MRI has a higher sensitivity in assessing soft tissue infiltration in comparison to MRI.
- $^{18}$F-FAMT can be used to assess bone marrow involvement.

**Ultrasonography**

- Ultrasonography is used to evaluate superficial lesions, lymph nodes and to guide needle aspiration biopsies (NAB).
- NAB is used in order to confirm metastatic lymph nodes.
- Chanak et al. reported that ultrasonography is insufficient as a stand-alone method for evaluating cervical lymph nodes (sensitivity 79%, specificity 69%).
- In oral cancer, intrasial USG with color-Doppler can also be used in order to assess the involvement of lymph nodes.
- It can show an increased vascularity within the tumor (blood flow), microvascular changes, size of the lesion and its thickness and the distance between mucous membrane and the front of the tumor.

- Ultrasound imaging can be helpful in assessing lymph nodes following a radical surgical resection with or without adjuvant radiation therapy.
- According to Wu-Chia et al., ultrasound-guided fine needle aspiration (USFNA) results in an improved assessment of disease recurrence in lymph nodes.
- Moreover, they showed that secondary lesions not exposed to radiation therapy had a lower frequency of calcification than lymph nodes treated with radiation.
- Radiotherapy has an effect on image of the classical ultrasound, however, it does not limit USFNA.
• **Hypertrophy** is an increase in the size of cells resulting in increase in the size of the organ.

• **Hyperplasia** is characterized by an increase in cell number because of proliferation of differentiated cells and replacement by tissue stem cells.

• **Atrophy** - Shrinkage in the size of the cell by the loss of cell substance

• **Cancer** is a genetic disorder caused by DNA mutations that are (for the most part) acquired spontaneously or induced by environmental insults.

• Malignant tumors are collectively referred to as cancers, derived from the Latin word for “crab”—that is, they adhere to any part that they seize in an obstinate manner, similar to a crab’s behavior.

• **Malignant**, as applied to a neoplasm, implies that the lesion can invade and destroy adjacent structures and spread to distant sites (metastasize) to cause death.

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**TUMOUR MARKERS**

- Tumor markers are substances produced by tumor cells or by other cells within the body in response to cancer or certain benign conditions.

- It includes a variety of substances like cell surface antigens, cytoplasmic proteins, enzymes, hormones, oncofetal antigens, receptors, oncogenes and their products.

---

<table>
<thead>
<tr>
<th>Circulating body fluids</th>
<th>Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF/VEGF-R</td>
<td>Epithelial markers</td>
</tr>
<tr>
<td>(Vascular endothelial growth factor/receptor)</td>
<td>➢ Cell surface markers – Histocompatibility</td>
</tr>
<tr>
<td></td>
<td>➢ Intracellular markers – Cytokeratins</td>
</tr>
<tr>
<td></td>
<td>➢ Basement membrane markers – Type 4 collagen</td>
</tr>
<tr>
<td></td>
<td>➢ Matrix markers – Tenascin</td>
</tr>
<tr>
<td></td>
<td>➢ Membrane antigen – Blood group antigens</td>
</tr>
<tr>
<td>PD-ECGF</td>
<td>Connective tissue markers</td>
</tr>
<tr>
<td>(Platelet derived endothelial cell growth factor)</td>
<td>➢ Intermediate filament proteins – Desmin</td>
</tr>
<tr>
<td></td>
<td>➢ Other filament proteins – Laminin</td>
</tr>
<tr>
<td>FGF, BCL2</td>
<td>Cellular enzymes – Amylase, lysozyme, Cathepsin-D, CD44, CD80, CD105, CEA, CA-19-9, CA-125, SCC-Ag</td>
</tr>
<tr>
<td></td>
<td>Cytoplasmic non-filamentous non-enzymatic proteins – Myoglobin, S100 protein</td>
</tr>
<tr>
<td>Endoglin, Cytokeratins, Calretinin, Cerb2, Cyclin, MIB and p53</td>
<td>Membrane antigen – Leukocyte specific antigen</td>
</tr>
</tbody>
</table>
IDEAL TUMOUR MARKERS

1) They should be highly sensitive and should have low false negative.
2) They should be highly specific and should have low false positive.
3) They should have high positive and negative predictive value.
4) It should be accurate in differentiating between healthy individuals and tumor patients.
5) They should be able to differentiate between neoplastic and non-neoplastic disease and show positive correlation with tumor volume and extent.

CLASSIFICATION

According to Schliephake H

Tumor growth markers
- Epithelial growth (EGF)
- Cyclins
- Nuclear cell proliferation antigens
- AgNORs (Agryophilic nucleolar organizer region)
- Skp 2 (S-phase kinase interacting, protein 2)
- HSP 27 and 70 (Heat shock protein)
- Telomerase

Markers of tumor suppression and antitumor response
- Retinoblastoma protein (pRb)
- Cyclin dependent kinase
- Inhibitors p53
- Bax
- Fas/FasL

Angiogenesis markers
- VEGF/VEGF-R
- PD-EGF
- FGFs

Markers of tumor invasion and metastatic potential
- MMPs (matrixmetallo proteases)
- Cathepsins
- Cadherins
- catemins
- Desmoplakin

Cell surface markers
- Carbohydrates
- Histocompatibility antigen
- CD57 antigen

Intracellular markers
- Cytokeratins

Markers of anomalous keratinisation
- Filaggrins
- Involutin
- Desmosomal proteins
- Intercellular substances
- Antigen Nuclear analysis.

Arachidonic acid products
- Prostaglandin E2
- Hydroxyeicosatetraenoic acid
- Leukotriene B4

Enzymes
- Glutathione S-transferase


## TUMOUR MARKERS IN RELATION TO SCC

<table>
<thead>
<tr>
<th>Marker</th>
<th>Expression</th>
<th>Presence of cancer</th>
<th>Prognostic/therapeutic value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD44(v3, v6 &amp; v10 isoforms)</td>
<td>Strong expression</td>
<td>Metastatic lymphnode</td>
<td>Expression of CD44 (with v3 &amp; v6) in advanced T stage, regional (v3) and distant (v10) metastasis, peri-neural invasion (v6), and radiation failure (v10)</td>
</tr>
<tr>
<td>CD46, CD55, CD59.</td>
<td>highly expressed.</td>
<td>HNSCC cells including T1/T2N0M0 stages</td>
<td>Expression - much lower or absent in non-neoplastic squamous epithelia or in the submucosa of both normal and tumour tissue.</td>
</tr>
<tr>
<td>Cytokeratin markers</td>
<td>CK 13, CK 20 (less frequently)</td>
<td>Act as markers for poorly differentiated</td>
<td>prognostic markers help in tumour progression and metastasis formation</td>
</tr>
</tbody>
</table>


---

### Salivary biomarkers

- Inhibitors of apoptosis (IAP)
- Squamous cell carcinoma associated antigen (scc-ag)
- Carcinooembryonic antigen (CEA)
- Carcino-antigen (CA19-9), CA128
- Serum tumor marker (CA125)
- Intermediate filament protein (cyfra 21-1)
- Tissue polypeptide specific antigen (TPS)
- Reactive nitrogen species (RNS)
- 8-ohdg DNA damage marker
- Lactate dehydrogenase (LDH)
- Immunoglobulin (IgG), s-IgA
- Insulin growth factor (IGF)
- Metalloproteinases MMP-2 and MMP-11


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### MANAGEMENT OF ORAL CANCER

The principal objective of treatment is to balance long term disease control with good quality of life.

---

### TUMOUR FACTORS

<table>
<thead>
<tr>
<th>Site &amp; location of primary tumour</th>
<th>Age</th>
<th>Surgical skills</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size and depth of the invasion</td>
<td>General medical condition</td>
<td>Radiotherapy skills</td>
</tr>
<tr>
<td>Cell type and degree of differentiation</td>
<td>tolerance</td>
<td>Chemotherapy expertise</td>
</tr>
<tr>
<td>Lymph node status</td>
<td>occupation</td>
<td>Dental &amp; prosthetic services</td>
</tr>
<tr>
<td>The presence or absence of metastases</td>
<td>Acceptance and compliance</td>
<td>Rehabilitation services</td>
</tr>
<tr>
<td>The ability to achieve adequate surgical margins</td>
<td>Lifestyle/smoking/drinking status</td>
<td>Access to minimally invasive surgical technology</td>
</tr>
<tr>
<td>The presence of local bone involvement</td>
<td>Socioeconomic &amp; geographic considerations</td>
<td>Support services</td>
</tr>
</tbody>
</table>

Surgery

Indications for Surgery

- (1) Early or localized oral cancer
- (2) Tumors involving bone, and when the side effects of surgery are expected to be less significant than those associated with radiation
- (3) Tumors that lack sensitivity to radiation
- (4) Recurrent tumor in areas that have previously received radiotherapy.

Factors that influence the choice of a particular surgical approach

1) Size of the primary tumor
2) Its depth of infiltration
3) The site of the primary tumor (that is anterior versus posterior location)
4) Proximity of the tumor to mandible or maxilla.


It is used in palliative cases to reduce the bulk of the tumor and to promote drainage from a blocked cavity.

- Adequate surgical margins are required but may not be attainable due to the size and the location of the tumor and limited information on the molecular status of the margins


Most commonly employed surgical approaches

1) Peroral
2) Mandibulotomy
3) Visor flap approach
4) Sublabial degloving approach
5) Weber-Ferguson incision


Surgical excision of dysplastic and malignant lesions can be accomplished with laser therapy.

- Laser therapy has the disadvantage of limiting the assessment of the margins for histopathologic confirmation.
- In respect to OPC and tongue base cancer, *transoral robotic surgery* has become a common practice with the potential advantage of application in less accessible sites.


Reconstructive surgery

- 1) Split thickness skin graft- Superficial surgical defects.
- 2) Radial forearm free flap - larger defects
- 3) Fibula free flap - Segmental mandibulectomy in any part of the mandible
- 4) Iliac crest, scapula, and the radial forearm osteocutaneous flap- mandible reconstruction.
- 5) Descending circumflex iliac artery flap (DCIA) - provides bone as well as soft tissue and skin for reconstruction of composite defects of the mandible.
- 6) Rectus abdominus or anterolateral thigh flap- edentulous patient, repair of the large surgical defect of the upper gum and hard palate
- Reconstruction with the use of osseointegrated implants offers the ability to provide stable prostheses and enhanced esthetic and functional results.
- The ability to place implants in irradiated bone has increased options for rehabilitation.

Radiation Therapy

- Radiation therapy may be administered with intent to cure, as a single modality, as part of a combined radiation surgery and/or chemotherapy management, or for palliation.

- Radiation may provide symptomatic relief from pain, bleeding, ulceration, and oropharyngeal obstruction.

- Radiation kills cells by interaction with water molecules in the cells, producing charged molecules that interact with biochemical processes in the cells and by causing direct damage to DNA.

- The affected cells may die or remain incapable of division.

- Due to a greater potential for cell repair in normal tissue than in malignant cells and a greater susceptibility to radiation due to the higher growth fraction of cancer cells, a differential effect is achieved.

Three-dimensional (3D) conformal radiotherapy

- Three-dimensional (3D) conformal radiation therapy uses reconstructed matched computed tomograms (CT) and Magnetic Resonance images (MRI) during treatment plan reduces the risk of geographic miss.

- The distribution of the beam can be conformed to the tumor size and shape using customized dense block or by multileaf collimators which has 40 pairs of tungsten measuring 1 cm in width.

- These can be adjusted to define the x ray beam thus reducing the dose of radiation up to 50% to normal tissues and this in turn reduces late damage.

Intensity-modulated radiotherapy (IMRT)

- Intensity-modulated radiation therapy (IMRT) is an improved mode of high-precision radiotherapy that utilizes computer controlled linear accelerators to deliver precise radiation doses to a malignant tumor or to specific areas within the tumor.

- In this technique, the equipment can be rotated around the patient where the beam moves multiple times that may vary with intensity, resulting in three dimensionally sculpted radiation.

- It allows for the radiation dose to conform to the three-dimensional shape of the tumor, by modulating or regulating the intensity of the radiation beam in multiple trivial volumes.

- This permits increased radiation doses to be focused to regions within the tumor, while decreasing the dose to surrounding normal critical structures.
Volumated Intensity modulated Arc Therapy (VMAT)

- Volumated intensity modulated arc therapy (VMAT) is a newer technique of delivering IMRT.
- VMAT delivers IMRT-like distributions in a single rotation of the gantry, varying the gantry speed and dose rate during delivery in contrast to standard IMRT, which uses fixed gantry beams.
- This technique has been implemented in the Eclipse treatment planning software under the name Rapid Arc (RA) Planning.
- Studies using RA demonstrate shorter planning and treatment time, lesser monitor units for treatment delivery, better dose homogeneity and normal tissue sparing.

Image Guided Radiotherapy (IGRT)

- It is often used in conjunction with intensity-modulated radiation therapy (IMRT), proton beam therapy, or stereotactic body radiotherapy (SBRT).
- The most basic and historical form of IGRT comprises of 2 dimensional portal images acquired in perpendicular/orthogonal planes to confirm the position of the isocenter, as well as the distinct fields.
- In most cases, these images are produced by the megavoltage (MV) beam of the treatment machine or less often by a devoted ancillary kilovoltage unit.
- These images are obtained prior to treatment.
- IGRT is used to treat Head and Neck cancers and tumors in areas of the body that are prone to movement, such as the lungs, as well as tumors located close to critical organs and tissues.

Particle Radiation therapy

- Charged particle beams consisting of protons and carbon ions have the Bragg peak and allow highly localised deposition of energy that can be used for increasing radiation doses to target while minimising irradiation to adjacent normal tissues.
- Intensity modulated proton (IMPT) allows modulation of the fluence and position of Bragg peak, permitting three dimensional dose distributions.
- Combination of photon and proton therapy for advanced malignant sinonasal tumours demonstrated good results when used IMRT alone.

- Image guidance can be used for improved tumor delineation and to correct intra and inter fraction movement during radiotherapy.
- Computerized tomograms with image guidance provide three dimensional views of tumor and normal anatomy.
- This consists of a compact CT scanner that is combined into the linear accelerator unit.
- This scan is usually of lower resolution than a diagnostic CT scan but provides adequate bony and soft tissue resolution for anatomic alignment.

- IGRT can be a useful tool that can detect and correct the geographic miss that can occur in treatment delivery.
- This technique can be fused with Positron emission tomography, which aids in delineation of gross tumor volume by using radioactive tracer namely Fluorine 18 labelled fluoromisonidazole have been shown to highlight the hypoxic areas of tumors.

- The present role of proton therapy lies in the treatment of tumor close to the skull base or spinal cord and in pediatric patients.
- Proton therapy provides maximum benefit in terms of normal tissue sparing.
Thermo radiotherapy

- It involves the application of localized high temperature at the tumor site which is said to improve the radiation treatment outcome.

- Currently scientific research has been conducted on this treatment modality.

Radioimmunotherapy (Targeted Radiotherapy)

- Radioimmunotherapy is a form of radiotherapy where cytotoxic radionuclides such as Iridium 90, Iodine 131 are linked to antibodies in order to deliver toxins directly to the tumor targets.

- The efficiency of their radioisotopes is that it has longer path length and thus large tumors may receive a higher dose of radiation to a greater depth.

- Radioimmunotherapy has proved to be effective for treatment of lymphomas, whereas its application in oral cancer has been reported to be under clinical trials using monoclonal antibodies.

Stereotactic radiotherapy

- Stereotactic radiation uses a single high dose of radiation sent into cancerous tissue with very narrow beam of radiation.

- It is a radical type of surgery that uses highly targeted radiation to treat brain abnormalities which is proven safe and effective, with good outcomes.

Carbon ion Therapy

- Carbon ion radiotherapy can offer better dose conformitory to a target volume than other modalities.

- In addition high linear energy transfer (LET) radiation such as carbon ion beams, as greater biological effectiveness than low LET radiation, such as X rays and proton beams.

- Because of its better dose distribution and cell killing potency, carbon ion radiotherapy is a promising modality in the treatment of patient with malignancy.

Boron Neutron Capture Therapy (BNCT)

- A new form of radiation therapy for cancer that is based upon the selective uptake of non-radioactive boron compounds.

- The boron compound is injected in the patient and when the required amount of boron reached the tumor site, the area could be irradiated with a neutron beam causing boron B10 to be transformed into B11, which would disintegrate releasing an α particle and 7Li, which have high linear energy transfer (LET), thus killing the cancer cells with almost no damage to the surrounding normal tissues.

- The BNCT delivery agents currently used in clinical trials are sodium borocaptate (BSH) and boronophenylalanine or BPA.

- The merits of BNCT include distribution of high radiation dose only to the tumor cells while sparing the surrounding normal cells.

Sanctuary Therapy

- Sanctuary therapy is a form of treatment with radiation that offers promise of effectively treating a high risk site of metastasis which could escape the attention of the oncologists.

- The therapy consists of prophylactic treatment with radiation at a level of 2000 to 3000 rads to the area of site of interest.

- The term “sanctuaries” refers to the belief that these organs are sanctuaries for tumour cells, since many chemotherapeutic agents do not cross the lipid barriers.
Intraoperative Electron Radiation Therapy (IOERT)

- IOERT excludes the irradiation of normal tissues and the critical structures in and around the target volume, hence called precision radiotherapy as the clinician views the tumour directly.
- As the dose falls off rapidly below the target site sparing the underlying healthy tissue, electron radiation can be applied directly on the tumour, which is vulnerable for destruction during intraoperative procedures.
- IOERT has proven to be beneficial when used in conjunction with endovascular brachytherapy which in turn reduces integral dose and treatment time.

Brachytherapy

- Interstitial and intracavitary implants are used to treat primary cancers in the head and neck.
- Brachytherapy is the primary treatment modality for localized tumors in the anterior two-thirds of the oral cavity, for boosted doses of radiation to a specific site, or for treatment following recurrence.
- Isotopes - cesium, iridium, and gold.
- The frequency of tissue necrosis is related to the treated volume, fraction size and total dose of radiation therapy, the proximity of the radioactive implant to bone, and the presence of comorbid risk factors including dental status.

Chemotherapy

Cytotoxic Chemotherapy

- Chemotherapy is largely palliative in patients with recurrent or metastatic disease.
- Chemotherapy is combined with radiotherapy &/or surgery to increase local/regional control, decrease distant metastasis and improve survival.
- Chemotherapy may be used as induction therapy prior to local therapies, concurrent chemoradiotherapy (CCRT), and adjuvant chemotherapy after local treatment.

Induction chemotherapy

- Induction, or neoadjuvant, therapy, refers to a modality used before definitive therapy with the goal of maximizing the success of the definitive therapy.
- The objective of induction chemotherapy is to promote initial tumor reduction and to provide early treatment of micrometastases due to the recognition that local control has improved with aggressive combined therapy, but distant failure due to metastatic disease has increased.

CONCURRENT CHEMORADIATION THERAPY

- Chemotherapy, particularly in combination with radiation therapy, is associated with potential local toxicities, such as mucositis, nausea, vomiting, and bone marrow suppression.
- The initial tumor response to chemotherapy prior to radiotherapy may predict tumor responsiveness to radiation.
- CCRT protocols are now the standard of care for stage 3 and 4 as primary therapy and for disease with poor prognostic findings following surgery including close margin and vascular invasion by tumor.
- As CCRT has become more widely used, the morbidities associated with these therapies have become more pronounced.
DRUGS USED FOR CHEMOTHERAPY

➢ Methotrexate
➢ Bleomycin
➢ Cisplatin & its analogue carboplatin
➢ 5-fluorouracil
➢ Taxanes (Paclitaxel, docetaxel)
➢ Gemcitabine
➢ Topotecan

Current Chemotherapy Regimens for Locally Advanced Oral Cancer (Stages III–IVB)

For primary systemic therapy with concurrent radiation
Cisplatin 100 mg/m² IV on days 1, 22, and 43
Cisplatin 40–50 mg/m² IV weekly for 6–7 wk
Cetuximab 400 mg/m² IV loading dose 1 wk before the start of RT, then 250 mg/m² weekly
Paclitaxel 30 mg/m² IV on day 1 weekly for up to 7 wk
Cisplatin 20 mg/m² IV on day 2 weekly for up to 7 wk
Paclitaxel 30 mg/m² IV on day 1 weekly for up to 7 wk
Cisplatin 40–50 mg/m² IV weekly for 6–7 wk
Cetuximab 400 mg/m² IV loading dose 1 wk before the start of RT, then 250 mg/m² weekly
Paclitaxel 30 mg/m² IV on day 1 weekly for up to 7 wk
Cisplatin 20 mg/m²/d IV on days 1–4 and 22–25
5-FU 1000 mg/m²/d by continuous IV infusion on days 1–4 and 22–25
5-FU 800 mg/m² by continuous IV infusion on days 1–5 given on the days of radiation plus Hydroxyurea 1 g PO q12h (11 doses per cycle)
Carboplatin 70 mg/m²/d IV on days 1–4, 22–25, and 43–46
5-FU 600 mg/m²/d by continuous IV infusion on days 1–4, 22–25, 43–46
Carboplatin AUC 1.5 IV on day 1 weekly
Paclitaxel 45 mg/m² IV on day 1 weekly

For patients receiving postoperative concurrent chemoradiation
Cisplatin 100 mg/m² IV on days 1, 22, and 43 or 40–50 mg/m² IV weekly for 6–7 wk

For induction chemotherapy
Docetaxel 75 mg/m² IV on day 1
Cisplatin 100 mg/m² IV on day 1
5-FU 100 mg/m²/d by continuous IV infusion on days 1–4 every 3 wk for three cycles; then 3–8 wk later, carboplatin AUC 1.5 IV weekly for up to 7 wk during radiation therapy; then 6–12 wk later, pursue surgery if applicable
Docetaxel 75 mg/m² IV on day 1
Cisplatin 75 mg/m² IV on day 1
5-FU 750 mg/m²/d by continuous IV infusion on days 1–4 every 3 wk for four cycles; then 4–7 wk later, radiation
Paclitaxel 175 mg/m² IV on day 1
Cisplatin 100 mg/m² IV on day 2
5-FU 500 mg/m²/d by continuous IV infusion on days 2–6 every 3 wk for three cycles; then radiation with cisplatin 100 mg/m² IV on days 1,22 & 43

Targeted Therapy

Mechanism of action Molecular targeted therapy
EGFR monoclonal antibodies Cetuximab, panitumumab, zalutumumab and nimotuzumab
EGFR tyrosine kinase inhibitors Gefitinib, erlotinib, lapatinib, afatinib and dacomitinib
VEGF inhibitors Bevacizumab
VEGFR inhibitors Sorafenib, sunitinib and vandetanib
PI3K/AKT/mTOR pathway inhibitors Rapamycin, temsirolimus, everolimus, torin1, PP242 and PP30
Anti-PD-1 antibodies Pembrolizumab and nivolumab


Photodynamic Therapy

- Photodynamic therapy applies light over a tissue that initially absorbed exogenous sensitizer.
- The sensitizing agent may be delivered systemically or topically and then after it selectively accumulates in target tissue.
- The subsequent light delivery to the target tissue results in cellular destruction.
- Due to the focused cellular destruction, the complications and disfigurement associated with this treatment are relatively small.

Gene Therapy

- It is a technique to deliver small DNA or RNA sequences to cells or tissues to correct a genetic defect or treat a disease.
- This may be accomplished by various strategies:
  1. Addition of a tumour suppressor gene (gene addition therapy) e.g. p53 in cancer cells
  2. Deletion of a defective tumour gene (gene excision therapy),
  3. Down regulation of expression of genes that control tumour growth,
  4. Enhancement of immune surveillance
  5. Activation of pro drugs that have a chemotherapeutic effect and cause toxicity only to the tumour cells (‘suicide gene’ therapy)
  6. Antiangiogenic therapy to inhibit tumour angiogenesis
  7. "Cancer vaccination” with genes for tumour antigens
VECTORS USED IN GENE THERAPY

A vector is a vehicle that is used to deliver the gene of interest to the target tissue.

<table>
<thead>
<tr>
<th>Viral vectors</th>
<th>Nonviral vectors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td>Lipid complex</td>
</tr>
<tr>
<td>Retrovirus</td>
<td>Liposomes</td>
</tr>
<tr>
<td>Adenovirus-associated virus (AAV)</td>
<td>Peptide/protein</td>
</tr>
<tr>
<td>Lentivirus</td>
<td>Polymers</td>
</tr>
<tr>
<td>Vaccinia virus</td>
<td>Mechanical</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Electroporation</td>
</tr>
<tr>
<td></td>
<td>Gene gun</td>
</tr>
</tbody>
</table>

Gene addition therapy

Gene addition therapy is another strategy to inhibit the growth of cancer cells.

In this technique, the defective oncogenes are removed, as a result of which, there is an inhibition in the growth of the tumour cells.

Down-regulation of oncogene expression:

- Oncogene expression can be down regulated by the delivery of short chains of antisense-RNA complimentary to oncogenic DNA nucleotides.

- The resultant DNA/RNA complex is identified as a foreign message and is cleaved out enzymatically reducing the expression of genes such as the oncogenes of the bcl-family, myc, fos, and ras.

- This ‘antisense RNA’ strategy can be used not only to affect tumour growth but also the oncogenic viruses such as human papilloma virus, human t-lymphotropic virus and cytomegalovirus.

Gene excision therapy:

- Gene excision therapy is another strategy to inhibit the growth of cancer cells.

- In this technique, the defective oncogenes are removed, as a result of which, there is an inhibition in the growth of the tumour cells.

Immunotherapy:

- This strategy involves administering antigens or adjuvants to the body’s own immune system or modifying the immunogenicity of cancer cells to increase their detection and destruction.

- Patients with carcinomas often present with numerous deficits in the functioning of immune cells such as NK cells, T-lymphocytes and dendritic cells.

- These deficits may involve generalized host immune deficits or they may be the result of localized cancer tumour evasion.

- General passive immune activation, by administering cytokines such as Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), alpha-Interferon (α-IFN), gamma-Interferon (γ-IFN), Interleukin 2 (IL-2) and Interleukin 12 (IL-12) act by increasing the anti-tumour response.

- General active immunity can also be stimulated by co-administering either whole replication defective cancer cells, or, purified tumour antigens as isolates or mixtures, with cytokines, or lab grown antigen presenting cells, along with cytokines as adjuvants.
Tumour evasion happens when cancer cells express surface proteins that inactivate activated T-cells on binding.

By developing monoclonal antibodies targeting the binding sites of activated T-cells such as anti-PD-1 (anti-Programmed cell Death Receptor-1) and anti-CTLA-4 (anti-Cytotoxic T-Lymphocyte-Associated protein-4), these immune checkpoints are inhibited from being turned off by the cancer cells, permitting destructive immunity to clear the neoplastic cells.

Checkpoint blockers such as ipilimumab, pembrolizumab, nivolumab have been approved for human use and another antibody MPDL3280A is currently undergoing clinical trials.

Suicide gene therapy

The addition of suicide genes by viral vectors is another strategy for treating carcinomas where genes coding for a pro-drug are transfected to cells, via herpes virus or adenovirus.

When these enzymes are synthesized intracellularly, they metabolize drugs which trigger cell death.

The Herpes Simplex Virus Thymidine Kinase (HSV-TK) triggers metabolism of ganciclovir to ultimately terminate DNA-synthesis.

THE DELIVERY OF DRUG RESISTANCE GENE(S) TO NORMAL TISSUES FOR PROTECTION FROM CHEMOTHERAPY

The drug resistance genes protect the normal tissues which are vulnerable to destruction. The drug resistance gene in humans is the Multidrug Resistance-1 (MDR-1) gene, MRP1 (Multidrug Related Protein).

The other drug resistance genes include the bacterial nitroreductase gene and the DHFR(dihydrofolate reductase) mutants which protect against methotrexate.

Gene therapy has three main objectives
1) Action at tumour angiogenesis level
2) Protection of normal tissue, especially medulla, from toxic effects of chemotherapy; and
3) Enhancement of the immune system.

INTRODUCTION OF GENES TO INHIBIT TUMOUR ANGIOGENESIS

The technique consists of the release of therapeutic proteins to encapsulate recombinant cells.

Microcapsules are designed to be permeable to recombinant products and nutrients but not to host immune mediators, due to their large size.

These cells are capable of secreting angiostatin, an important angiogenic inhibitor.

CANCER VACCINES

Cancer vaccines are made from patients’ tumor cells, which strengthen defense mechanism.

These educate T cells to recognize and kill the cancer cells in the tumor.

Cancer vaccine is designed in such way that it contains a desired antigen, may be single antigen such as RNA, DNA, or peptides, or multiple antigens such as pulsed dendritic cells or whole cells.

Advantages: Vaccines can generate long-lived immunity with minimal toxicity and also can be combined with other immunotherapy techniques.

Disadvantages: Expensive, cannot be used for fast-growing tumors, and take long time to get immune response.

Cancer vaccine types

Antigen vaccines: They are made up of specific antigens from patients’ tumor, which in turn can destroy cancer cells.

Dendritic cell vaccines: The role of dendritic cell to recognize and attack tumor cells and this vaccine has a great potential in tumor regression.

DNA or RNA vaccines: These vaccines made of either DNA or RNA material proved to be excellent candidates for tumor regression.

Whole cell vaccines: Instead of specific antigens, DNA, or RNA, these vaccines are developed from entire cancer cells.
REFERENCES

- Burkit Textbook of oral medicine 12th edition
INTRODUCTION

- Healthy oral soft tissues present a typical pink to red hue with slight topographical variations of color.
- This chromatic range is due to the interaction of a number of tissues that compose the mucosal lining:
  1. Presence or absence of keratin on the surface epithelium
  2. Quantity, superficial or deep location of blood vessels in the subjacent stroma
  3. Existence of lobules of adipocytes, and
  4. Absence of melanin pigmentation in the basal cell layer of the epithelium

The oral cavity is lined by a mucous membrane (the oral mucosa) consisting of a stratified squamous epithelium, which may or may not be keratinized, and an underlying connective tissue layer, the lamina propria.

Oral pigmentation

Pigmentation is defined as the process of deposition of pigments in tissues. Various diseases can lead to varied colorations in the mucosa. Pigmented lesions of oral cavity are due to:

- Augmentation of melanin production
- Increased number of melanocytes (melanocytosis)
- Deposition of accidentally introduced exogenous materials

There are four pigments which contribute to the normal color of the skin and mucosa.

- Melanin
- Carotenoids
- Reduced HB
- Oxygenated HB

Melanin is found universally in nature, the pigment derivative of tyrosine and is synthesized by melanocytes, which typically reside in the basal cell layer of the epithelium. Melanin is synthesized within specialized structures known as melanosomes. Becker in 1927 first identified melanocytes in the oral epithelium. During early stages of intrauterine life, precursors of melanocytes, i.e., melanoblasts, differentiate into the dendritic cells and migrate to the epidermis from the neural crest. Keratinocytes actually control melanocytic growth. Their presence in the skin is thought to protect against the damaging effects of actinic irradiation. They also act as scavengers in protecting against various cytotoxic intermediates.

Types of melanin
- Eumelanin- brown-black
- Pheomelanin- red-yellow
- Mixed type melanin
- Neuromelanin
- Oxymelanin

Overproduction of melanin may be caused by a variety of mechanisms, the most common of which is related to increased sun exposure. Intraorally hyperpigmentation is more commonly a consequence of physiologic or idiopathic sources, neoplasia, medication or oral contraceptive use, high serum concentrations of pituitary adrenocorticotropic hormone, postinflammatory changes, genetic factors, and autoimmune disease.

The function of oral melanocytes
- Melanin determines the color of skin, hair and eyes
- Protection from stressors such as UV radiation, reactive oxygen species (ROS) and free radicals in the environment
- Melanin can sequester metal ions and bind certain drugs and organic molecules
- Neutralise bacteria-derived enzymes and toxins
- Act as antigen presenting cells, can stimulate T-cell proliferation, and can phagocytose microorganisms

The keratinocyte-melanocyte unit
- Mature melanocytes contain all the proteins required for melanin biosynthesis and for the structural maturation of melanosomes, including tyrosinase (TYR), tyrosinase-related proteins-1 (TYRP-1) and TYRP-2, gp 100, and melanoma antigen recognizable by T lymphocytes.

Production of melanin by melanosomes
Melanosomes are packed in globules enclosed by the melanocyte plasma membrane, released into the extracellular space from various areas of the melanocyte dendrites, phagocytosed by keratinocytes, and are then dispersed around the perinuclear area.


**MISCELLANEOUS LESIONS THAT MAY BE ASSOCIATED WITH ORAL MUCOSAL DISCOLORATION**

Investigations
- Biopsy
- Dacyscopy
- Radiography
- Blood tests
- Dermoscopy/epiluminiscence microscopy
- Binocular stereomicroscopes

**Primary lesions**
**ENDOGENOUS PIGMENTATION**

- Hemoglobin, hemosiderin, and melanin represent the most common endogenous sources of mucosal color change.
- A submucosal collection of hemoglobin or hemosiderin, produced by extravasation and lysis of red blood cells, may impart a red, blue, or brown ephemeral appearance to the oral mucosa.
- Melanin, which is synthesized by melanocytes and nevus cells, may appear brown, blue, or black, depending on the amount of melanin and its spatial location within the tissue (i.e., superficial vs. deep).

**Common Causes of Endogenous Oral and Perioral Discoloration**

**FOCAL MELANOCYTIC PIGMENTATION**

- Freckle/Ephelis
- Melanotic macule
- Oral melanocanthoma
- Melanocytic nevus
- Malignant melanoma

**Freckle/Ephelis**
- Common, asymptomatic, small (1–3 mm), well-circumscribed, tan- or brown-colored macule
- Seen on the sun-exposed regions of the facial and perioral skin
- Commonly observed in light-skinned individuals and are quite prevalent in red- or light-blonde-haired individuals
- Developmental in origin
- Polymorphisms in the *MC1R* gene are strongly associated with the development of childhood freckles
- More abundant in number and darker in intensity during childhood and adolescence
- Become darker during periods of prolonged sun exposure (spring, summer) and less intense during the autumn and winter months
- With increasing age, the number of freckles and color intensity tends to diminish
- No therapeutic intervention is required.
Oral/Labial Melanotic Macule

- The melanotic macule is a unique, benign, pigmented lesion that has no known dermal counterpart.
- Melanotic macules are the most common oral lesions of melanocytic origin.
- Although the etiology remains elusive, trauma has been postulated to play a role.
- Sun exposure is not a precipitating factor.

Clinical Features

- More frequently in females, usually in the lower lip (labial melanotic macule) and gingiva.
- Any mucosal site may be affected.
- Congenital melanotic macules occur primarily in the tongue.
- Small (<1 cm), well circumscribed, oval or irregular in outline, and often uniformly pigmented.
- Unlike an ephelis, a melanotic macule does not become darker with continued sun exposure.
- Differential diagnosis: melanocytic nevus, malignant melanoma, amalgum tattoo, focal ecchymosis.

Oral Melanoacanthoma

- Unusual, benign, melanocytic lesion that is unique to the mucosal tissues.
- Innocuous melanocytic lesion that may spontaneously resolve, with or without surgical intervention.
- Rapid onset; and acute trauma or a history of chronic irritation usually precedes the development of the lesion.
- The biopsy procedure itself may lead to spontaneous regression of the lesion.
- The underlying source of the irritation should be eliminated to minimize recurrence.

Clinical Features

- Oral melanoacanthoma usually presents as a rapidly enlarging, ill-defined, darkly pigmented macular or plaque-like lesion.
- Generally asymptomatic; may be associated with pain.
- Although any mucosal surface may be involved, close to 50% of melanoacanthomas arise on the buccal mucosa.
- The size of the lesion is variable, ranging from small and localized to large, diffuse areas of involvement, measuring several centimeters in diameter.
- The borders are typically irregular in appearance, and the pigmentation may or may not be uniform.

Melanoacanthoma

- Because oral melanoacanthoma may resemble other melanocytic lesions, such as pigmented nevus, melanotic macule, and melanoma, a biopsy is warranted to obtain a definitive diagnosis.

Diagnosis

- Oral/Labial Melanotic Macule
- Oral Melanoacanthoma
- Melanoacanthoma
Oral Nevi (Oral melanocytic nevus, nevocellular nevus, mole, mucosal melanocytic nevi)

- Categorized as hamartomas, developmental malformations, the nevi are benign proliferations of nevus cells in either epithelium or connective tissue.
- In 1943, Ackerman and Field have reported the first case of an oral nevus.
- King et al. adopted the less anatomically specific term, intramucosal nevus.
- Adult whites harbor this lesion rather commonly but intraoral lesions are much less common.

- Clinically, a pigmented nevus is an asymptomatic, well-circumscribed, round or oval, flat or slightly elevated spot or plaque, and of size usually ranging between 0.1 cm and 3 cm. The color varies from brown to blue, blue-gray to black.
- The hard palate, buccal mucosa, and gingiva are the most commonly affected intraoral sites.
- They can be seen in persons of all ages, with the mean age group affected being 3rd-4th decade. Women are affected more commonly than men.

Nevus cells

- Nevus cells are a variant of melanocytes
- They are larger than typical melanocytes, do not have dendrites, and have more abundant cytoplasm with coarse granules. Multinucleated cell variants are also seen.
- They are usually located at the dermoeipidermal junction or in the dermis of the skin.
- Most nevic cells tend to be round, oval, or spindle shaped.
- Nevus cells have tendency to closely approximate one another in a rosette or polygonal fashion, and have ability to migrate into and/or within the submucosal tissues.

Etiology and Pathogenesis

- Unlike ephelides and melanotic macules, which result from an increase in melanin pigment synthesis, nevi arise as a consequence of melanocytic growth and proliferation.
- Genetic and environmental factors, sun exposure, play a role in nevogenesis.
- Familial atypical multiple mole melanoma syndrome.
- Epithelioid blue nevus may be associated with the Carney complex.
- Turner’s syndrome and Noonan’s syndrome, and congenital nevi are typical of neurocutaneous melanosis.
- A recent study by Pollock et al. demonstrated that up to 90% of dermal melanocytic nevi exhibit somatic, activating mutations in the BRAF oncogene. Mutations in the HRAS and NRAS oncogenes have also been identified. This lends further credence to the notion that melanocytic nevi are neoplastic.
Pathology

In the evolutionary stages of an intramucosal (or intradermal) nevus, the melanocytic lesion may further mature to become flat, ending at the junction of the epithelium and the basement membrane.

In the nevus further matures, the nevus cells completely lose their association with the epithelial layer and become confined to the submucosal tissue, decrease in the amount of pigmentation - intramucosal nevus - brown or tan or even resemble the color of the surrounding mucosa.

Clustered melanocytes are thought to proliferate down into the connective tissue, and some nevus cells can be seen at the epithelial–connective tissue interface - compound nevi.

Clinical Features

• Cutaneous nevi are a common occurrence.
• The average Caucasian adult patient may have several nevi; some individuals may have dozens.
• Higher in males than females.
• Oral melanocytic nevi are rare, typically present as solitary lesions, and may be more common in females.
• Lesions are usually asymptomatic and often present as a small (≤1 cm), solitary, brown or blue, well-circumscribed nodule or macule.
• Once the lesion reaches a given size, its growth tends to cease and may remain stable indefinitely. In rare cases, multifocal lesions have been described.

Blue nevus

• The common blue nevus is the second most common type found in the oral cavity, the blue nevus is common in the mouth than in the skin; which account for 25–36% of all oral nevi, according to different studies.
• Junctional and compound nevi account for only 3–6% of all oral nevi.
• Rare reports of congenital nevus, Spitz nevus, balloon cell nevus, and the cellular, epithelioid, and plaque-type variants of blue nevus have also been described.
• The blue nevus is described as such because the melanocytes may reside deep in the connective tissue and the overlying blood vessels often dampen the brown coloration of melanin, which may yield a blue tint.

Blue nevi are characterized by a variety of microscopic appearances.
• "Common" blue nevus - intramucosal proliferation of pigment-laden, spindle-shaped melanocytes, most common.
• Cellular blue nevus - submucosal proliferation of both spindle-shaped and larger, round or oval-shaped melanocytes, less frequently occurring, more aggressive, and has a greater rate of recurrence. Rare reports of malignant transformation have also been associated with the cellular cutaneous variant.

Malignant Melanoma

• Oral melanomas are uncommon, and, similar to their cutaneous counterparts, they are thought to arise primarily from melanocytes in the basal layer of the squamous mucosa. Melanocytic density has a regional variation. Least common but most deadly of all primary skin cancers.

Etiology and Pathogenesis

• A history of multiple episodes of acute sun exposure, especially at a young age; immunosuppression; the presence of multiple cutaneous nevi; and a family history of melanoma are all known risk factors for the development of cutaneous melanomas.

• Melanoma-prone families have a high incidence of germline mutations in the tumor suppressor genes, CDKN2A/p16INK4a or, less commonly, CDK4.
• Similar to melanocytic nevi, melanomas also frequently exhibit mutations in the BRAF, HRAS, and NRAS proto-oncogenes.

• Other recurrent molecular findings, including NRAS polymorphisms and alterations or loss of PTEN function, have also been described.
Clinical Features

- Cutaneous melanoma is most common among white populations that live in the sunbelt regions of the world.
- Males older than 45 years.
- Has a male predilection, but melanoma is one of the most commonly occurring cancers in women of child-bearing age.
- Melanomas may develop either de novo or, much less commonly, arise from an existing melanocytic nevus.
- On the facial skin, the malar region is a common site.
- In general, the clinical characteristics of cutaneous melanoma are best described by the ABCDE criteria.
- These criteria are very useful (although not absolute) in differentiating cutaneous melanoma from other locally pigmented melanocytic lesions.

Criteria for clinical diagnosis of melanoma - ABCDE-rule

- Symmetry - is when one half of the lesion does not match the other half of lesion.
- Border irregularity - is when the edges are notched, ragged or blurred.
- Color irregularity - colored pigmentation is seen ranging from black, brown, tan, red, blue and white.
- Diameter - more than 6 mm
- Elevation - a rise in the surface is also sign.

Types of melanoma

- Superficial spreading
- Nodular melanoma
- Lentigo maligna melanoma
- Acral lentiginous melanoma
- Mucosal lentiginous melanoma
- Amelanotic malignant melanoma

The Clark Scale has five levels:
- Level 1: Melanoma is confined to the epidermis (the outer layer of the skin).
- Level 2: Melanoma has invaded the papillary dermis (the outermost layer of the dermis, the next layer of skin).
- Level 3: Melanoma has invaded throughout the papillary dermis and is touching on the next, deeper layer of the dermis.
- Level 4: Melanoma has invaded this next deeper layer, the reticular dermis.
- Level 5: Melanoma has now invaded the fat under the dermis.

Diagnosis

One of the main clinical and microscopic challenges in diagnosing oral melanoma is determining whether the lesion is a primary neoplasm or a metastasis from a distant site.

This is not a semantic distinction since confirming the primary site will dictate the patient’s clinical stage and the type of therapy he or she will undergo.

A history of a previous melanoma, sparing of the palate and gingiva, amelanosis, and microscopic features, such as a lack of junctional activity and pagetoid spread, are findings that may be more suggestive of a metastatic tumor.
Management

• For primary oral melanomas, ablative surgery with wide margins remains the treatment of choice.
• Adjuvant radiation therapy may also be necessary.
• A variety of chemotherapeutic and immunotherapeutic strategies are often used if metastases are identified or for palliation.

MULTIFOCAL/DIFFUSE PIGMENTATION

Physiologic Pigmentation

• most common multifocal or diffuse mucosal pigmentation
• Dark-complexioned individuals, including blacks, Asians, and Latinos, frequently show patchy to generalized hyperpigmentation of the oral mucosal tissues.
• Although in many patients, the pigment is restricted to the physiologic pigmentation of the mucosal surfaces, melanosis associated with systemic diseases is not uncommon.
• The pigment is typically first observed during childhood and does not develop de novo in the adult.
• The sudden or gradual onset of diffuse mucosal pigmentation should alert the clinician to consider a pathological etiology.

Differential diagnosis

• idioptic
• drug-induced
• smoking-induced melanosis
• Hyperpigmentation associated with endocrinopathic and other systemic conditions.
Microscopically, physiologic pigmentation is characterized by the presence of increased amounts of melanin pigment within the basal cell layer. This pigmentation is considered a variation of normal. Gingivectomy and laser therapy have been used to remove pigmented oral mucosa. Cryosurgery has also been reported to effectively remove oral pigmentation. **Etiology and Pathogenesis**

Medications may induce a variety of different forms of mucocutaneous pigmentation, including melanosis. The chief drugs implicated in drug-induced melanosis are the antimalarials, including chloroquine, hydroxychloroquine, and quinacrine. In the Western world, these medications are typically used in the treatment of autoimmune diseases. Other common classes of medications that induce melanosis include the phenothiazines, oral contraceptives, and cytotoxic medications such as cyclophosphamide and busulfan.

**Drug-Induced Melanosis**

**Clinical Features**

It has been estimated that 10%-20% of all cases of acquired melanocytic pigmentation may be drug induced. Intraorally, the pigment can be diffuse yet localized to one mucosal surface, often the hard palate, or it can be multifocal and involve multiple surfaces. Some drugs may even be associated with a specific pattern of pigmentation. Much like other forms of diffuse pigmentation, the lesions are flat and without any evidence of nodularity or swelling. Sun exposure may exacerbate cutaneous drug-induced pigmentation.

**Drugs causing oral perioral pigmentation**

- Amiodarone
- Amodiaquine
- Azidothymidine
- Bleomycin
- Chloroquine
- Chlorpromazine
- Clofazamine
- Gold
- Hydralazine
- Imipramine
- Ketoconazole
- Mepacrin

**Pathology**

Microscopically, there is usually evidence of basilar hyperpigmentation and melanin incontinence without a concomitant increase in the number of melanocytes. Although the mechanisms by which melanin synthesis is increased remain unknown, one theory is that the drugs or drug metabolites stimulate melanogenesis. Alternatively, some drugs, including chloroquine and chlorpromazine, have been shown to physically bind melanin. This complexation of melanosomes and drugs within melanocytes may contribute to the adverse mucocutaneous effects.

Drug-induced pigmentation of the palate in a patient who was taking quinacrine for the treatment of discoid lupus erythematosus.
Diagnosis

If the onset of the melanosis can be chronologically and accurately associated with the use of a specific medication (frequently within several weeks or months before development of the pigmentation), then no further intervention is warranted. In most cases, the discoloration tends to fade within a few months after the drug is discontinued. However, pigmentation associated with hormone therapy may tend to persist for longer periods of time, despite discontinuation of the medications. A differential diagnosis includes other causes of diffuse mucosal pigmentation. Laboratory tests may be necessary to rule out an underlying endocrinopathy.

Smoker’s Melanosis

- Diffuse melanosis of the anterior vestibular maxillary and mandibular gingivae, buccal mucosa, lateral tongue, palate, and floor of the mouth is occasionally seen among cigarette smokers.
- Most smokers (including heavy smokers) usually fail to show such changes. However, in certain individuals, melanin synthesis may be stimulated by tobacco smoke products.
- Indeed, among dark-skinned individuals who normally exhibit physiologic pigmentation, smoking stimulates a further increase in oral pigmentation.
- The pigmented areas are brown, flat, and irregular; some are even geographic or map-like in configuration.
- Smokeless tobacco (snuff) does not appear to be associated with an increase in oral melanosis.

Postinflammatory (Inflammatory) Hyperpigmentation

- More commonly in dark-complexioned individuals.
- Most cases present as diffuse or diffuse pigmentation areas that were subjected to prior insult or inflammatory.
- In rare cases, the mucosal overlying a nonmelanocytic malignancy may become pigmented.
- Certain medications (i.e., phenothiazines) have been described in patients with melanin pigmentation.

Melasma (Chloasma)

- Melasma is a relatively common, acquired asymmetrical melanosis that typically develops on sun-exposed areas of the face and frequently on the chest.
- The forehead, cheeks, upper lips, and chin are the most commonly affected areas.
- There is a distinct female predilection, and most cases arise in darker-skinned individuals less commonly in males.
- Evolves rather rapidly over a period of a few weeks.
- Pigmentary changes associated with sun exposure and hormonal factors, including pregnancy and contraceptive hormones.
In various thyroid abnormalities, including hypothyroidism, monogyma may also play a role in the pathogenesis of pregnancy- and nonpregnancy-associated melasma.

A biopsy typically reveals basilar melanosis with no increase in the number of melanocytes. However, the melanocytes that are present may be larger than those in the adjacent normally pigmented areas.

Spontaneous resolution after parturition, cessation of the exogenous hormones, or regulation of endogenous sex hormone levels.

A successful therapeutic approach for the treatment of melasma consists in the topical administration of a triple combination product (4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone).

**Hypoadrenocorticism (Adrenal Insufficiency or Addison’s Disease)**

**Etiology and Pathogenesis**

- In adults, autoimmune disease represents one of the most common causes where the majority of patients show the presence of circulating autoantibodies to steroidogenic enzyme 21-hydroxylase.
- However, infectious agents, neoplasia, trauma, certain medications, and iatrogenic causes may lead to adrenal destruction or impairment of endogenous steroid production. In rare cases, adrenal insufficiency may also be a consequence of genetic disease.
- As a result, decrease in endogenous corticosteroid levels occurs.
- As steroid levels decrease, there is a compensatory activation of ACTH secretion from the anterior pituitary gland. ACTH then acts on the adrenal cortex to stimulate steroid production, and ACTH secretion stops.
- If low steroid levels persist, there is a loss of feedback inhibition, resulting in persistent secretion of ACTH into the serum.
- Concurrently, the serum levels of α-melanocyte-stimulating hormone (α-MSH) also increase.
- At the molecular level, this is explained by the fact that the precursor proopiomelanocortin gene contains the sequences of both the ACTH and α-MSH genes.
- During processing of the progenitor hormone, the ACTH and α-MSH genes may be cleaved independently of one another, thus creating two distinct hormones.
- Apart from the wide array of tissues and organs that these hormones act upon, both α-MSH and ACTH are also thought to have stimulatory effects on melanocytes. However, the exact mechanism by which melanin synthesis increases remains unclear.

**Clinical Features**

- Weakness, poorly defined fatigue, and depression are some of the hypoparathyroid presenting signs of the illness.
- The first sign of disease may be mucocutaneous hyperpigmentation.
- Generalized bronzing of the skin and diffuse but patchy melanosis of the oral mucosa are hallmarks of hypoadrenocorticism.
- Any oral surface may be affected. In some patients, oral manifestations may be the first manifestations of their disease.
- Diffuse hyperpigmentation is more commonly associated with chronic rather than acute-onset disease.

**Diagnosis**

- Endocrinopathic disease should be suspected whenever oral melanosis is accompanied by cutaneous bronzing.
- An oral biopsy typically shows increased melanin in the basal cell layer with melanin incontinence.
- **Differential diagnosis** - phytophagic and drug-induced pigmentation.
- **Laboratory tests** - serum cortisol and electrolyte levels. Serum cortisol levels of less than 100 nmol/L, or 500 nmol/L if measured on a 9:00 a.m. sample, is diagnostic of adrenocortical hyperfunction.
- Hyponatremia and hyperkalemia are frequently associated with adrenal insufficiency.
- Treatment - exogenous steroid replacement therapy with glucocorticoids and mineralocorticoids. There is evidence supporting the use of adrenal androgens such as dehydroepiandrosterone to improve the quality of life of patients with Addison’s disease.
Etiology and Pathogenesis

• Cushing's syndrome develops as a consequence of prolonged exposure to relatively high concentrations of endogenous or exogenous corticosteroids.
• Most cases are iatrogenic in origin and associated with poorly controlled or unmonitored use of topical or systemic steroids.
• Pituitary tumor
• Hyperadrenocorticism
• Ectopic secretion of corticosteroids, ACTH, or corticotropin-releasing hormone by various neoplasms, including small cell carcinoma of the lung.
• Germ line mutations in ACTH receptor

Clinical Features

• more prevalent in female patients.
• prepubertal onset is more commonly seen in boys.
• Apart from the wide array of systemic complications, including weight gain and the characteristic “moon facies,” diffuse mucocutaneous pigmentation may also be seen in a subset of patients, specifically those whose pathology is associated with increased ACTH secretion.

Diagnosis and management

Three main tests are used for the diagnosis of Cushing’s syndrome:
- low dose dexamethasone suppression test
- midnight plasma cortisol
- 24-hour urinary free cortisol.

The pigmentation often resolves following appropriate surgical, radiation, or drug therapy for the specific cause of the endocrinopathy.

Pasireotide (a somatostatin analog) has been approved for the treatment of Cushing’s syndrome.

Hyperthyroidism (Graves’ Disease)

Melanosis is a common consequence of hyperthyroidism (Graves’ disease), especially in dark-skinned individuals. Studies suggest that at least 40% of black patients with thyroiditis may present with mucocutaneous hyperpigmentation.

In contrast, melanosis is very rarely observed in Caucasian patients with the disease. The pigmentation tends to resolve following treatment of the thyroid abnormality.

The mechanism by which excessive thyroid activity stimulates melanin synthesis remains unclear.

Primary Biliary Cirrhosis

Diffuse mucocutaneous hyperpigmentation may be one of the earliest manifestations of primary biliary cirrhosis.

Up to 47% of patients with this condition develop diffuse melanosis.

This uncommon disease is of unknown etiology, although it is thought to be autoimmune in nature as evidenced by the presence of antimitochondrial antibodies. Primary biliary cirrhosis develops mainly in middle-aged women; the disease results from damage to small intrahepatic bile ducts. The mechanism by which melanosis develops is unknown.

Clinical appearance of the upper and lower teeth presenting green discoloration in patient with persistent conjugated hyperbilirubinemia

Green Teeth in the Primary and Permanent Dentition

J Pediatr 2017;191:275
**Vitamin B12 (Cobalamin) Deficiency**

- Diffuse mucocutaneous hyperpigmentation is a rare, and poorly recognized, complication of vitamin B12 deficiency.
- This hyperpigmentation is reminiscent of Addison’s disease.
- The pigmentation resolves following restoration of vitamin B12 levels.
- The predominant mechanism of hyperpigmentation in vitamin B12 deficiency is hypothesized as:
  1. Deficiency of vitamin B12 decreases the level of reduced glutathione, which activates tyrosinase and thus leads to transfer to melanosomes.
  2. Defect in the melanin transfer between melanocytes and keratinocytes, resulting in pigmentary incontinence.

Peutz-Jeghers Syndrome

- An autosomal dominant disease that is associated with mutations in the STK11/LKB1 tumor suppressor gene.
- Clinical manifestations include intestinal polyposis, cancer susceptibility, and multiple, small, pigmented macules of the lips, perioral skin, hands, and feet.
- The macules may resemble ephelides, usually measuring <0.5 cm in diameter. However, the intensity of the macular pigment is not influenced by sun exposure.
- Although uncommon, similar-appearing lesions may also develop on the anterior tongue and buccal and labial mucosa.

**Typical pattern of pigmentation representative of Peutz Jeghers syndrome**

- Histologically, these lesions show increased basilar melanin without an increase in the number of melanocytes.
- The medical management for Peutz-Jeghers syndrome consists of surveillance and treatment of hamartomatous polyps.
- Other genetic diseases associated with a triad of gastrointestinal disease, cancer susceptibility, and mucocutaneous pigmented macules among other findings include Cowden syndrome (and the allelic Bannayan-Riley-Ruvalcaba and Cowden-Canada syndromes) and Cronkhite-Canada syndrome.

**Café au Lait Pigmentation**

- Café au lait spots ("coffee with milk") spots are occasionally observed in the general population, but multiple café au lait spots are often indicative of an underlying genetic disorder.
- Tan- or brown-colored, irregularly shaped macules of variable size.
- They may occur anywhere on the skin.
- Café au lait pigmentation may be identified in a number of different genetic disorders, including neurofibromatosis type 1, McCune-Albright syndrome, and von Recklinghausen syndrome.
Diseases Commonly Associated With Café au Lait Pigmentation

Neurofibromatosis type I

- Neurofibromatosis type I is an autosomal dominant disease caused by a mutation or a deletion of the NF1 gene localized in chromosome 17.
- Neurofibromatosis type I is associated with the development of multiple neurofibromas of various histologic subtypes.
- In addition, the size, number, and age of 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

- It is an extremely rare disorder that classically affects the bones, skin, and endocrine system.
- McCune–Albright syndrome is characterized by fibrous dysplasia of bone, patches of abnormal skin, and multiple endocrine dysfunctions.
- The café au lait spots in McCune–Albright syndrome appear distinct from those associated with neurofibromatosis.
- The borders of the pigmented macules are irregularly outlined, whereas in neurofibromatosis, the borders are typically smooth.

HIV/AIDS-Associated Melanosis

- Diffuse or multifocal mucocutaneous pigmentation has been frequently described in HIV seropositive patients.
- The pigmentation may be related to intake of various medications, including antifungal and antiretroviral drugs, or as a result of adrenocortical destruction by virulent infectious organisms.
- Recent studies suggest that melanosis may be an actual, potentially late-stage, clinical manifestation of HIV/AIDS.
- Goldstein et al. demonstrated a significant correlation between mucocutaneous pigment and CD4 counts in HIV/AIDS patients.
- Studies have also shown that the immune dysregulation associated with HIV/AIDS leads to increased secretion of oxytocin from the anterior pituitary gland, which may also stimulate increased melanin synthesis.
IDIOPATHIC PIGMENTATION

Laugier–Hunziker Pigmentation

Etiology and Pathogenesis

- Laugier–Hunziker pigmentation (also known as Laugier–Hunziker syndrome) was initially described as an acquired, idiopathic, macular hyperpigmentation of the oral mucosal tissues, specifically involving the lips and buccal mucosae.
- Pigmentation of the esophageal, genital, and conjunctival mucosae and the acral surfaces is seen.
- Up to 60% of affected patients also may have nail involvement, usually in the form of longitudinal melanotic streaks and without any evidence of dystrophic change. The fingernails are more commonly affected than the toenails.
- Rare condition, in adult patients with equal sex predilection.
- Caucasian or light-skinned individuals.
- Possible genetic predisposition.

Clinical and Microscopic Features

- Patients typically present with multiple, discrete, irregularly shaped brown or dark brown macules.
- Individual macules are usually no more than 5 mm in diameter.
- In rare instances, the lesions may coalesce to produce a diffuse area of involvement.
- Increased melanin pigmentation in the basal cell layer without an increase in the number of melanocytes and melanin incontinence in the superficial lamina propria are characteristic of this syndrome.

Differential Diagnosis

- Physiologic pigmentation
- Drug- or heavy metal-induced pigmentation
- Endocrinopathic disease
- Peutz–Jeghers syndrome.

Management

- Generally not indicated
- Laser and cryotherapy
Vitiligo

- Vitiligo is a relatively common, acquired, autoimmune disease that is associated with hypomelanosis.
- Vitiligo affects 0.5%–2.0% of the world population with no gender or racial preference.

**Etiology and Pathogenesis**

- Autoimmunity, cytotoxicity, genetics, and alterations from metabolic or oxidative stress have been implicated in this condition where the end result is a destruction of the melanocytes.
- The pathogenesis of vitiligo is multifactorial, with both genetic and environmental factors playing a role in the development of the disease.

**Clinical Features**

- Classification - non-segmental vitiligo, segmental vitiligo, and unclassified/undetermined vitiligo.
- Multiple aching patches with remitting-relapsing course are seen in nonsegmental vitiligo.
- Segmental vitiligo shows a characteristic dermatomal distribution of the aching patches with a rapid onset that is usually not progressive.
- The onset of vitiligo may vary among patients but mostly second and third decade of life.
- The depigmentation is more apparent in patients who have a darker skin tone. Yet the disease actually occurs in all races.
- Vitiligo may also arise in patients undergoing immunotherapy for the treatment of malignant melanomas.
- Vitiligo rarely affects the intraoral mucosal tissues. However, hypomelanosis of the inner and outer surfaces of the lips and perioral skin may be seen in up to 20% of patients.

**Management**

- Objective is to stimulate repigmentation.
- Topical corticosteroids, topical calcineurin inhibitors, ultraviolet B narrow band, and psoralen and ultraviolet A exposure.
- From the standpoint of therapy, topical vitiligo is more resistant to the typical treatments used for cutaneous vitiligo. Consequently, phototherapy and topical corticosteroids are the preferred treatments for repigmentation in vitiligo.
- Surgical intervention may be the only option to achieve an aesthetic result. Autologous epithelial grafts have been used successfully, with patients often reporting a more acceptable cosmetic appearance.
- Split-thickness skin grafts have been reported as having the highest repigmentation success rate.
- Punch grafting and micropigmentation (whereby an exogenous brown pigment is injected into the site, much like a tattoo)
- In rare instances, surgical intervention may stimulate spontaneous repigmentation of vitiligenous lesions elsewhere on the body.

HEMOGLOBIN AND IRONASSOCIATED PIGMENTATION

**Ecchymosis**

- Ecchymosis is common on the lips and face post-traumatic in nature, and trauma to the lips need not involve forceful trauma but can arise from trivial trauma to the lips.
- Immediately following a traumatic event, a red macule or small swelling may appear. The lesion will resolve within a few days, after the hemoglobin is degraded to hemosiderin.

**Purpura/Petechiae**

- Capillary hemorrhages will appear initially as red spots that turn brown and persist for a few days once the extravasated cells have been degraded into hemosiderin.
- The distinction between purpura and petechiae is essentially semantic and based solely on the size of the focal hemorrhages.
- Petechiae are typically characterized as being pinpoint or slightly larger than pinpoint and purpura as multiple, small (2–4 mm) collections of extravasated blood. The same precipitating events can elicit either clinical presentation.
- Oral purpura/petechiae may develop as a consequence of traumatic, viral, or systemic disease.
Viral disease is more commonly associated with oral rather than cutaneous petechiae. In most cases, the petechiae are identified on the soft palate, although any mucosal site may be affected.

Within two weeks, the lesions should resolve. Failure to do so should arouse suspicion of a hemorrhagic diathesis, a persistent infectious disease, or other systemic disease, and appropriate laboratory investigations must be undertaken.

**Causes of Oral Purpura/Petechiae**

- Amyloidosis
- Aplastic anemia
- Bulimia
- Chronic renal failure
- Forceful coughing
- Hemophilia
- Henoch–Schönlein purpura
- Hemochromatosis
- Infections
- Infectious mononucleosis
- Liver disease
- Non-specific trauma
- Oral intubation
- Oral submucous fibrosis
- Overexertion
- Papular–purpuric “gloves and socks” syndrome
- Protein loss in nutrition
- Systemic lupus erythematosus
- Thrombocytopenia
- von Willebrand’s disease

**Hemochromatosis**

- Hemochromatosis is a chronic, progressive disease that is characterized by excessive iron deposition (usually in the form of hemosiderin) in the liver and other organs and tissues.
- Idiopathic, neonatal, blood transfusion, and heritable forms of this disease are recognized.
- Complications of hemochromatosis may include liver cirrhosis, diabetes, anemia, heart failure, hypertension, and bronzing of the skin.
- Studies also suggest an increased incidence of cancer in patients with hemochromatosis. The cutaneous pigmentation is seen in over 90% of affected patients, regardless of the etiology of the disease.

- The primary oral manifestation of hemochromatosis is a blue-gray to brown pigmentation affecting mainly the palate and gingiva.
- Early on in the course of disease, the pigmentation may be more commonly a result of basilar melanosis rather than iron-associated pigment.
- Iron deposition within the adrenal cortex may lead to hypoadrenocorticism and ACTH hypersecretion, with the associated Addisonian type changes. In the later stages of hemochromatosis, the pigmentation is usually a result of hemosiderosis and melanosis.
- A lower labial gland biopsy has been shown to be an easy and effective method for the diagnosis of hemochromatosis.

**Sources of Exogenous Oral and Perioral Pigmentation**
Amalgam Tattoo

**Etiology and Pathogenesis**
- The most common pigmented lesion in the oral mucosa is amalgam tattoo.
- By definition, these are iatrogenic in origin and typically a consequence of the inadvertent deposition of amalgam restorative material into the submucosal tissue.

**Clinical Features**
- Found in 1%-3% of the general population.
- Small, asymptomatic, macular, and bluish gray or even black lesions.
- The gingiva, alveolar mucosa, buccal mucosa, and floor of the mouth represent the most common sites.
- The lesions are often found in the vicinity of teeth with large amalgam restorations or cemented teeth that probably had amalgam, around the apical region of endodontically treated teeth with retrograde restorations or obliterated with silver points, or in areas in and around healed extraction sites.
- Amalgam tattoos of the head and neck skin may occur in dentists and represents an occupational hazard resulting from failure to use facial protective barriers.

Graphite Tattoos

- Graphite tattoos are an unusual source of focal exogenous pigmentation.
- They are most commonly seen on the palate and gingiva and represent traumatic implantation of graphite particles from a pencil.
- Solitary gray or black macules.
- When the graphite tattoo involves areas of cosmetic concern, removal of the lesion and a subsequent autogenous connective tissue graft provide a highly aesthetic outcome.

Ornamental Tattoos

- Mucosal tattoos in the form of lettering or intricate artwork are becoming increasingly common phenomena.
- Amateur tattoo inks are permanent and consist of simple, carbon particles originating from a variety of sources, including burnt wood, plastic, or paper, and from a variety of inks, such as India ink, pen ink, and plant-derived matter.
- Q-Switched laser therapy has been used successfully to remove tattoos of the oral mucosa.
- In certain tribal cultures, esthetically pleasing pigment is plant derived. An unusual South African female tribal custom includes brushing the teeth and gums with a chewed root of the tree Euclea natalensis, with the belief that it promotes oral health. This plant root contains naphthoquinones and other organic substances that have putative antibacterial properties. Naphthoquinones are pigmented, and the mouths of root users are typically bright orange. Unlike ornamental tattoos, this form of pigmentation is usually transient and reversible.

Medicinal Metal-Induced Pigmentation

- Gold therapy.
- Colloidal silver - complementary and alternative medicine therapies.
- Gold and colloidal silver have both been associated with diffuse cutaneous pigmentation.
- Silver may cause a generalized blue-gray discoloration (argyria), whereas gold-induced pigment may appear blue-gray or purple (Chrysiasis).
- Chrysiasis does not involve the oral mucosal tissues since it is thought that exposure to ultraviolet light or other high-intensity light sources precipitate the pigmentation.
- Generalized black pigmentation of the tongue has been attributed to the chewing of medicinal substances containing zinc, which are commonly used herbal.

Heavy Metal Pigmentation

- Diffuse oral pigmentation may be associated with ingestion of heavy metals.
- Occupational and health hazard for some individuals who work in certain industrial plants and for those who live in the environment in and around these types of facilities.
- Other environmental sources - paints, old plumbing, and seafood.
- 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.
- These ingested metal salts tend to extravasate from vessels in areas of chronic inflammation.
The pigmentation is usually found along the free marginal gingiva, where it often dramatically outlines the gingival cuff. This metallic line usually has a gray to black appearance. In some patients, the oral pigmentation may be the first sign of heavy metal toxicity. Additional systemic signs and symptoms of heavy metal poisoning may include behavioral changes, neurologic disorders, intestinal pain, and sialorrhea.

Diffuse mucocutaneous melanosis may also be observed in some affected individuals.

**Drug-Induced Pigmentation**

- Minocycline, which is a tetracycline derivative and frequently used in the treatment of acne, is a relatively common cause of drug-induced nonmelanin-associated oral pigmentation.
- Minocycline when taken chronically, minocycline metabolites may become incorporated into the normal bone. Thus, although the teeth may appear normal in appearance, the surrounding bone may appear green, blue, or even black.
- As a result, the palatal and alveolar mucosa may develop a bluish or bluish-black discoloration. In addition, roots show a green color, whereas developing roots tend to be bluish.
- Methacycline, imatinib cause mucosal pigmentation.

**Vascular Lesions**

- **Infantile hemangioma**: Flat, bright red, or deep blue, or normal skin color.
- **Congenital hemangioma**: Red, purple, or bluish plaques with coarse telangiectasia, or flat, violaceous lesions, or a grayish tumor surrounded by a pale halo with multiple telangiectasia.
- **Kaposiform hemangioendothelioma**: Tiny purple or red spots and a bruise-like discoloration near or around the lesion.
- **Pyogenic granuloma**: Red, pedunculated nodules.

**Sturge-Weber Syndrome**

- It is a congenital, non-hereditary, condition of unknown etiology. The disease shows facial port wine stain, cutaneous abnormalities, glaucoma and choroidal hemangiomas, and leptomeningeal angiomatosis.
- Most common manifestation is the angiomatous lesion of gingiva that varies from slight vascular hyperplasia to massive hemangiomatous proliferation.
- There is an increase in the vascular component and gingival hemorrhage at mental trauma.

**Hairy Tongue**

- The change in oral flora associated with chronic antibiotic therapy may be causative in some patients.
- Various foods, drinks, and confectionaries can contribute to the diffuse discoloration. Smoking of tobacco or crack cocaine has been associated with black hairy tongue.
- Black hairy tongue has also been associated with other pharmacologic treatments.
OTHER SYNDROMES ASSOCIATED WITH HYPERPIGMENTATION

- Cowden syndrome
- Cronkhite–Canada syndrome
- Dowling–Degos syndrome
- Naegeli–Franceschetti–Jadassohn syndrome
- LEOPARD syndrome
- Nelson’s syndrome

TREATMENT OF MUCOCUTANEOUS MELANOSIS

- Perioral and facial pigmentation are more challenging to treat since the skin type may dictate the occurrence of postoperative complications, including post-inflammatory hyperpigmentation.

- Experimental forms of phototherapy have also been employed, including intense pulsed light and fractional photothermolysis.

- First-line therapy remains the application of topical medications—bleaching creams.

- Although single agents such as azelaic acid or hydroquinone have been used, more commonly, dual- or triple-combination therapy is recommended.

- A combination of 4% hydroquinone (0.05%), retinoic acid (0.01%), fluocinolone acetonide, has proven to be effective in greater than 90% of patients.

- However, the majority of patients undergoing such therapy may experience immunologic sensitivity or other treatment-related adverse events, including the development of exogenous ochronosis.

Conclusion

- Pigmented lesions within the oral cavity may present a diagnostic dilemma for the clinician.

- A differential diagnosis for a pigmented lesion may include traumatic, reactive, neoplastic, and systemic pathologies.

- A clinico-pathologic correlation is often required to ensure accurate diagnosis of systemic causes of diffuse pigmentation.
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THANKYOU
INTRODUCTION

- Mouth is directly or symbolically related to major human instincts and passion.
- The oral mucosa is highly reactive to psychological influences.
- Psychosomatic disorders are defined as disorders characterized by physiological changes that originate partially from emotional factors.
- A psychosomatic disorder involves both body and mind.
- These diseases have physical symptoms originating from mental or emotional causes. Most common ones are stress, anxiety and depression.
- A wide spectrum of psychiatric disorders affects oral and para oral structures which have a definite psychosomatic cause, but unfortunately they remain unrecognized because of the common and limited nature of their presenting features.

CLASSIFICATION

<table>
<thead>
<tr>
<th>Pain Related Disorders</th>
<th>Disorders Related to Altered Oral Sensation</th>
<th>Autoimmune Disorders</th>
<th>Miscellaneous Disorders</th>
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<tbody>
<tr>
<td>5. Glossopyrosis</td>
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<td>5. Erythema multiforme</td>
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MPDS

- Myofascial Pain Dysfunction Syndrome is a heterogeneous group of signs and symptoms that affect the jaw joint and/or the chewing musculature.

- Myofascial pain syndrome (MPS) is defined as pain that originates from myofascial trigger points in skeletal muscle.

- In 1940, Travell reported that skeletal muscle in spasm could be a source of pain.

- In 1959, Schwartz was first to implicate the physiologic makeup of the patient as a predisposing factor in pain dysfunction and hypothesized that stress was the significant cause of clenching and grinding habits which results in spasm.

- In 1969, the MPDS term was given by Laskin, he proposed PSYCHOPHYSIOLOGIC THEORY that MPDS is a result of emotional rather than occlusal and mechanical factors.

- The pain pathway that culminates in muscle spasm and pain in MPDS according to theory begins with stress.

- Theory suggests that stress could cause clenching and grinding which in turn lead to muscle fatigue and finally spasm.

EPIDEMIOLOGY

- Very common
- Exact incidence unknown
- May occur as a primary disease
- May occur in conjunction with other painful conditions
- Psychological and behavioral co-morbidities also present

The diagnosis was made based on the signs and symptoms of MPDS, as outlined by Laskin that is, unilateral, dull pain in the ear or preauricular region that is commonly worse on awakening. Tenderness of one or more muscles on palpation. Limited or deviation of mandible on opening.

Treatment

- A number of successful treatment outcomes have been reported, including occlusal splints, physiotherapy, muscle-relaxing appliances, and pharmacological interventions.

- Based on Wall & Melzack's Gate Control Theory, TENS has been used very commonly for pain relief in the last 30 years.

- The tricyclic antidepressants such as amitriptyline and nortriptyline and cognitive behavioral therapy are often generally helpful.

Atypical Facial Pain (AFP)

- According to the International Association for the Study of Pain (IASP), chronic facial pain refers to symptoms which have been present for at least 6 months.

- 'Atypical' pain is a diagnosis of exclusion after other conditions have been considered and eliminated (i.e. it is idiopathic) and is characterized by chronic, constant pain in the absence of any apparent cause in the face or brain.
Many information sources suggest that all ‘unexplained’ facial pains are termed Atypical Facial Pain but this is not the case.

Categories of idiopathic facial pain conditions include Neuropathic Pain due to sensory nerve damage, Chronic Regional Pain Syndrome (CRPS) from sympathetic nerve damage and Atypical Facial Pain.

Facial pain, often described as burning, aching or cramping, occurs on one side of the face, often in the region of the trigeminal nerve and can extend into the upper neck or back of the scalp.

The pain is called “atypical” because it is a different type of pain than that of a typical toothache.

The pain is poorly localized and does not conform to the anatomical boundaries of sensory nerve supply.

The areas affected may be one or more of those supplied by the fifth or ninth cranial nerves, or the second and third cervical nerves.

Sometimes the pain is bilateral.

Treatment

- The patients with chronic pain including facial pain need to be screened for depression.
- Pharmacological treatment with antidepressants, antiepileptic or other drugs can also be tried.
- Cognitive-behavioural therapy may be indicated.
- Patients with AFP may be helped by a technique termed ‘reattribution’ which involves demonstrating and understanding of the complaints by taking a history of related physical, mood and social factors.
- It may help explain that depression/tiredness lowers the pain threshold and that muscle overactivity and spasms (being ‘uptight’) create pain.

Atypical Odontalgia

- Atypical odontogenic (AO) pain implies toothache of unknown origin.
- Exact etiology of this condition is unknown.
- It is considered to be deafferentation neuralgia (causalgia) arising when a dental extraction or pulp extirpation produces either an amputation neuroma or a central degenerative change in the trigeminal nucleus.
- Some consider AO as vascular/neurovascular in origin.
- Recently, psychogenic etiology was considered.
- AO affects 10% of adults and 50% of elderly population. It is more common in women than in men in the age of fourth to fifth decade of life.
- Trauma and psychological factors are implicated factors.

Treatment

- The tricyclic antidepressants such as amitriptyline and nortriptyline are often generally helpful.
- Some consider AO as vascular/neurovascular in origin.
- Recently, psychogenic etiology was considered.

BURNING MOUTH SYNDROME

- BMS is any form of burning or stinging sensation in the mouth in association with a normal mucosa in the absence of local or systemic disease.
- It is a multifactorial disorder associated with psychological components such as anxiety, depression and cancerophobia.
- The term “syndrome” is justified because of the simultaneous presence of several subjective symptoms, including feeling of dryness (subjective xerostomia), altered taste, and burning sensation of the oral tissues and tingling, or numb feeling in the oral cavity.

Treatment

- The tricyclic antidepressants such as amitriptyline and nortriptyline are often generally helpful.
Burning is almost always bilateral and symmetrical and does not follow anatomical distribution of a peripheral sensory nerve.

The onset of pain is spontaneous, bilateral with no identifiable precipitating factors. Pain may be felt deep within the mucosa, continuous for at least 6 months, with moderate to severe intensity that may vary during the day.

BMS is most commonly found in adults over the age of 60. It is estimated to be about five times more frequent in women than in men.

There is no specific test for BMS, which makes it hard to diagnose. No specific treatment works for everyone. However, one can prescribe medications to help in managing the pain, dry mouth, or other symptoms.

**Treatment**

- Cognitive-behavioural therapy or a specialist referral may be indicated.
- ‘Reattribution’ helps manage these patients.
- Topical application of capsaicin (0.025% cream) has been used.
- Topical application of 0.5 ml Aloe vera gel at 70%, 3 times a day combined with tongue protector is found to be effective.
- The topical application of ibuprofen: by sucking a tablet of 2 mg, 3 times a day for 14 days found some success in some.
- Gabapentin, an anticonvulsant drug, is advised 300-1,600 mg/day; 100 mg at bedtime.

**Recurrent Aphthous Stomatitis**

- Recurrent aphthous stomatitis (RAS) is the most common type of ulcerative disease of the oral mucosa, and it affects approximately 20% of the general population.
- The classic presentation of RAS is recurrent, self-limiting ulcers that mainly affect non-keratinized oral mucosa.
- Previous studies have suggested that psychological disturbances such as stress and anxiety could play a role in the onset and recurrence of RAS lesions.

**Idiopathic Xerostomia**

- Xerostomia is a subjective sensation of dry mouth; hyposalivation is defined as an objective assessment of reduced salivary flow rate.
- Depressive symptoms are usually evident in individuals with idiopathic subjective dry mouth.
- Mason and Glen (1967) have noted that at the secretion of saliva is regulated by ANS and is subjected to reflex stimulation from physical and psychic causes, thus xerostomia may result from 4 basic causes in which factor affecting salivary centre are primary cause which include:
  1. Emotions, fear, excitement, stress
  2. Depression
  3. Organic diseases e.g. brain tumor, Parkinson's disease
  4. Drugs: A number of reports have shown that salivary cortisol is associated with depression and anxiety, and hence, salivary cortisol can be used as an important non-invasive biological indicator of stress.
Treatment

- Salivary substitutes and lubricants with moistening properties are designed to provide prolonged mucosal wetting.
- Products include “artificial” saliva, rinses, gels, and sprays, which may contain carboxymethyl cellulose (CMC), a mucopolysaccharide, glycerate polymer gel base, or natural mucins, singly or in combination.
- Pilocarpine increases salivary flow and alleviates subjective dryness as well.
- The selective serotonin reuptake inhibitors like sertraline are often generally helpful.

DYSGEUSIA

- Dysgeusia is defined as a distorted gustatory perception or persistent gustatory sensation in the absence of gustatory stimulants.
- These are often perceived as bitter, sour, or metallic.
- Association between stress and taste might have a possible central mechanism.
- Enhanced activation of multiple neurobiological pathways is involved in stress and appetite regulation.

Treatment

- Zinc supplementation is believed to aid in treating taste disorders by promoting proliferation of normal taste bud cells, even in patients without zinc deficiency.
- The tricyclic antidepressants such as amitriptyline and nortriptyline are often generally helpful.

CHRONIC BITING OF THE ORAL MUCOSA

- It is a form of factitial/unintentional injury that is observed commonly on the buccal and labial mucosa and lateral surface of tongue.
- Habitual lip or cheek biting usually occurs as an unconscious psychogenic habit caused by a wide range of emotions.
- This mild form of self-mutilation may sometimes emerge as a response to oral stimuli or as an attempt to gain attention from family members or caretakers.

RECURRENT HERPES LABIALIS

- RHL occurs due to other physical trauma or emotional stress leading to lesions of skin and labial mucosa.
- Emotional stress apparently serves to prevent the antibodies from acting at the local mucosal site.
- Trigger may include sun exposure, psychological stress, onset of illness, illness and physical trauma.
- Infection with herpes simplex virus 1 (HSV1), which manifests as primary gingivostomatitis, usually occurs in preschool or kindergarten children, adolescents and young adults, and does not recur in the same form.
Treatment

• Antiviral compounds for the treatment of HSL infection have been advocated.
• The tricyclic antidepressants such as amitriptyline and nortriptyline are often generally helpful.

CANCEROPHOBIA

• Fear is an unpleasant emotion and the pervasiveness of cancer fear in the population may have implications for quality of life.
• In addition, cancer fear has been shown to be associated with screening uptake and presentation of suspicious symptoms, although both motivating and deterrent associations have been found.
• This disorder falls under hypochondriasis (It is a persistent fear in the patient's mind that they have contracted cancer).
• Cancerophobia has been noted to be associated with depression but exact pathogenesis is unclear.

Periodontal Diseases

• The etiology of inflammatory periodontal disease is complex. The etiological significance of biological and behavioral risk factors, including systemic conditions, smoking, oral hygiene, and age has been demonstrated.
• However, a significant proportion of the variation in disease severity cannot be explained by taking only these factors into consideration. A psychosomatic disorder affects periodontium by two ways:
  1) Self-inflicted injuries seen in these patients
  2) Via disturbance in autonomic nervous system altering tissue response

Necrotizing Ulcerative Gingivitis

• Necrotizing ulcerative gingivitis (NUG) is a fusospirochetal infection caused by local and systemic predisposing factors.
• Among these, emotional stress appears to be the most common, although debilitating diseases, nutritional deficiencies, and neurologic diseases also play important roles.
• Emotional stress may lead to NUG indirectly by an expression of cortisol and catecholamine levels.

Management of Psychosomatic Disorders

Various treatment modalities tried out are:
1. Psychotherapy or the remedial influence of mind
   a. Cognitive-behavioral therapy
   b. Self-observation
   c. Relaxation training
   d. Hypnotherapy
   e. Biofeedback
CONCLUSION

To conclude, we can say that many diseases manifesting in the oral cavity have a psychological component in their etiology or have some effect of psychologic factors. Further, many psychiatric disorders have an influence upon health of oral tissue. Because stress is increasing in everyday life due to cut-throat competition in every field, there are more chances of dental practitioners encountering patients with such disorders. Hence, one should be familiar with such manifestations, and if accounted, should try to manage them with psychiatrists, whenever needed.

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Thank you
ORAL RED AND WHITE LESIONS

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WHITE LESIONS

- A white appearance of oral mucosa may be caused by a variety of factors.
- Oral epithelium may be
  ✓ Stimulated to an increased production of keratin: Hyperkeratosis
  ✓ An abnormal but benign thickening of stratum spinosum: Acanthosis
  ✓ Intra and extracellular accumulation of fluid in the epithelium
- Microbes particularly fungi, can produce whitish pseudomembranes consisting of sloughed epithelial cells, fungal mycelium and neutrophils which are loosely attached to oral mucosa
  ✓ Juxtaepithelial hyalinization
  ✓ Hypopigmentation

RED LESIONS

- May develop as a result of
  ✓ Atrophic epithelium
  ✓ Reduction in number of epithelial cells
  ✓ Increased vascularization that is dilatation of vessels and/or proliferation of vessels
- Red lesions if persistent can be:
  ✓ FOCAL
  ✓ MULTIFOCAL
  ✓ DISCOID
  ✓ DIFFUSE
  ✓ LINEAR

CLASSIFICATION

- INFECTIOUS DISEASES: Oral candidiasis, hairy leukoplakia
- PREMALIGNANT LESIONS: Oral leukoplakia and erythroplakia, OSMF
- IMMUNOPATHOLOGIC DISEASES: OLP, Drug induced LRs, GVHD, SLE
- ALLERGIC REACTIONS: LCR, Reactions to CHX and dentrifice
- TOXIC REACTIONS: Reactions to smokeless tobacco, Smokers palate
- REACTIONS TO MECHANICAL TRAUMA: Morsiacatio
- OTHER RED AND WHITE LESIONS: BMG, Leukoodema, White sponge nevus, Hairy tongue

CANDIDIASIS

- Most prevalent opportunistic infection
- Vast majority of cases caused by candida albicans
- Affects very young, very sick and very old
- Divided into primary and secondary infections

ETIOLOGY AND PATHOGENESIS

- C. albicans, C. tropicalis, C. glabrata comprise 80% of species isolated from candidial infections
- Factors causing its infection:
  ✓ Adhesion
  ✓ Lipase production
- Various predisposing factors:
  ✓ Local factors
  ✓ General factors
CLASSIFICATION OF ORAL CANDIDIASIS

EPIDEMIOLOGY

- 35% overall prevalence

CLINICAL PRESENTATIONS OF ORAL CANDIDIASIS: PSEUDOMEMBRANOUS

- Also called as thrush
- Most common type affects patients taking antibiotics, immunosuppressive drugs or having disease that suppress immune system
- Clinically presents as white wipable plaques resembling curdled milk and is usually asymptomatic

ERYTHEMATOUS CANDIDIASIS

- Previously referred as atrophic oral candidiasis
- Lesion usually has a diffuse border
- Predominantly seen on palate and dorsum of tongue
- Also referred as antibiotic sore mouth

CLINICAL PRESENTATIONS OF ORAL CANDIDIASIS

CHRONIC PLAQUE TYPE AND NODULAR CANDIDIASIS

- Replaces old term candidal leukoplakia
- White irremovable plaque which may be indistinguishable from oral leukoplakia
- Commonly occurs on anterior buccal mucosa and usually well demarcated
- Associated with higher degree of dysplasia and malignancy than leukoplakia
DENTURE STOMATITIS
- Referred to as chronic atrophic candidiasis
- Most prevalent site is denture bearing palatal mucosa
- Classified into 3 different types:
  Type 1: minor erythematous sites caused by trauma from denture
  Type 2: affects major part of denture covered mucosa
  Type 3: above features plus granular mucosa

ANGULAR CHEILITIS
- Presents as infected fissures of corners of the mouth often surrounded by erythema
- Lesions frequently coinfected with C. albicans and Staphylococcus aureus
- Often symptomatic and bilateral
- Vit B12 deficiency, iron deficiency and loss of VD are associated

MEDIAN RHOMBOID GLOSSITIS
- Clinically characterized by an erythematous lesion in center of posterior part of dorsum of tongue
- Has oval configuration
- Area represents atrophy of filiform papillae and surface may be lobulated
- Biopsy reveals candidal hyphae in 85% of lesions
- Is asymptomatic
- Do not have any increased risk of malignant transformation
- Kissing lesion may be seen

HIV ASSOCIATED CANDIDIASIS
- More than 90% of AIDS patients have had oral candidiasis during the course of their HIV infection
- May presents as pseudomembranous, erythematous or hyperplastic candidiasis or angular cheilitis

DIAGNOSTIC AND LABORATORY FINDINGS
INTRODUCTION

- **Respiration**: It is the process by which oxygen is taken in and carbon dioxide is given out.
- The first breath takes place only after birth.
- Fetal lungs are non-functional. So, during intrauterine life, the exchange of gases between fetal blood and mother’s blood occurs through placenta.

**Normal Respiratory Rate:**
- Newborn: 30 to 60/minute
- Early childhood: 20 to 40/minute
- Late childhood: 15 to 25/minute
- Adult: 12 to 16/minute.

**Types of respiration:**
1. External respiration
2. Internal respiration

**Phases of respiration:**
1. Inspiration
2. Expiration

**FUNCTIONAL ANATOMY OF RESPIRATORY TRACT:**
- Respiratory tract is the anatomical ducts through which air moves in and out. It includes Nose, Pharynx, Larynx, Trachea, Bronchi, and Lungs.
  i) Pleura
  ii) Tracheobronchial Tree:
  - Trachea and bronchi are together called tracheobronchial tree. It forms a part of air passage.

**Components:**
1. Trachea
2. Secondary bronchi
3. Tertiary bronchi
4. Bronchioles
5. Terminal bronchiole
6. Respiratory bronchioles

**Upper and lower respiratory tracts:**
- **Respiratory unit:**
  - Parenchyma of lungs is formed by respiratory unit that forms the terminal portion of respiratory tract.
  - Respiratory unit is defined as the structural and functional unit of lung. Exchange of gases occurs only in this part of the respiratory tract.

**Structure of respiratory unit:**
1. Respiratory bronchioles
2. Alveolar ducts
3. Alveolar sacs
4. Alveoli
5. Alveolus
• Alveolar Cells or Pneumocytes:
• Type I alveolar cells:
  Type I alveolar cells are the squamous epithelial cells forming about 95% of the total number of cells. These cells form the site of gaseous exchange between the alveoli and blood.

• Type II alveolar cells:
  Type II alveolar cells are cuboidal in nature and form about 5% of alveolar cells. These cells are also called Granular pneumocytes. Type II alveolar cells secrete alveolar fluid and surfactant.

• Non-respiratory functions of respiratory tract:
  1. Olfaction
  2. Vocalization
  3. Prevention of dust particles
  4. Defense mechanism
  These cells are lymphocytes, macrophages, mast cells, natural killer cells and dendritic cells.
  5. Maintenance of water balance
  6. Regulation of body temperature
  7. Regulation of acid-base balance
  8. Anticoagulant function
  9. Secretion of angiotensin - converting enzyme
  10. Synthesis of hormonal substances

• Respiratory protective reflexes:
  a) Cough reflex
  b) Sneezing reflex
  c) Swallowing (deglutition) reflex

DISEASES OF THE RESPIRATORY TRACT

Viral upper respiratory tract infections
• Cause: Virus (Rhinovirus)
• Age: Children
• These are the RNA viruses which infect the respiratory tree.
• They are closely transmitted by close person to person contact and by respiratory droplets.
• Shedding can occur from nasopharyngeal secretions for up to 3 wks but seven days or less is typical.

Upper airway Diseases
1) Acute Rhinitis
2) Viral Upper Respiratory infections
3) Allergic Rhinitis and Conjunctivitis
4) Sinusitis
5) Laryngitis
6) Pharyngitis

Lower airway Diseases
1) Acute Bronchitis
2) Pneumonia
3) Bronchiolitis
4) Asthma
5) Tuberculosis
6) COPD
7) Cystic Fibrosis
8) Pulmonary embolism
9) Pulmonary Neoplasms
**Pathophysiology:**

- Viral particles can lodge in either the upper or lower respiratory tract.
  - Invade the respiratory epithelium
- Incubation period for rhinovirus - 2 to 5 days.
- During this time, active and specific immune responses are triggered, and mechanisms for viral clearance are enhanced.

**Clinical and laboratory findings:**

- **Symptoms:**
  - i) Rhinorrhea
  - ii) Nasal congestion
  - iii) Oropharyngeal irritation
- Other symptoms include Cough, Fever, Malaise, Fatigue, Headache and myalgia.
- Complete Blood count (CBC) with differential may demonstrate an increase in:
  - i) Mononuclear cells
  - ii) Lymphocytes
  - iii) Monocytes. (Right shift).

**Diagnosis:**

- Basis of medical history as well as confirmatory physical findings.
- Diagnoses that should be excluded include:
  - i) Acute bacterial rhinosinusitis,
  - ii) Allergic rhinitis
  - iii) Group A streptococcal pharyngitis.

**Management:**

- Analgesics - sore throat and myalgia.
- Antipyretics - febrile patients.
- Antihistamine agents - Reducing rhinorrhea.
- Oral or topical decongestants such as the sympathomimetic amines, are an effective means of decreasing nasal congestion.

**Prognosis:**

- Excellent.

**Oral health considerations:**

- Presence of small round erythematous macular lesions on the soft palate.
- These lesions may be caused directly by the viral infection, or they may represent a response of lymphoid tissue.
- Individuals with excessive lingual tonsillar tissue - enlargement of foci of lymphoid tissue, particularly at the lateral borders at the base of the tongue.
- Oral dryness.

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**Allergic Rhinitis and Conjunctivitis**

- Allergic rhinitis is a chronic recurrent inflammatory disorder of the nasal mucosa.
- Allergic conjunctivitis is an inflammatory disorder involving the conjunctiva.
- When both conditions occur, the term Allergic Rhinoconjunctivitis is used.
- The basis of the inflammation is an allergic hypersensitivity (type I hypersensitivity) to environmental triggers.
- Typical seasonal triggers include grass, tree, and weed pollens.
- Common perennial triggers include dust mites, animal dander, and mold spores.
- Allergic rhinitis is the most prevalent chronic medical disorder.

**Pathophysiology:**
Clinical and Laboratory Findings:

Conjunctival symptoms:
- i) Pruritus
- ii) Lacrimation
- iii) Crusting, and burning

Nasal symptoms may include sneezing, pruritus, clear rhinorrhea, and nasal congestion.

Other symptoms such as postnasal drainage with throat irritation, pruritus of the palate and ear canals, and fatigue.

Direct examination of the nasal mucosa reveals significant edema and a pale blue coloration of the turbinates.

The clinical signs of allergic Rhinoconjunctivitis include:
- Postnasal drainage or oropharyngeal cobblestoning might be identified upon examination of the oropharynx.
- A High-arched palate, protrusion of the tongue and overbite may be seen.

- Injection of the conjunctiva with or without cobblestoning
- Prolonged infraorbital creases (Dennie-Morgan folds/plaits)
- Swelling, and darkening (allergic shiners)
- A transverse nasal crease; and frequent upward rubbing of the tip of the nose (allergic salute).

Patients with allergic rhinitis might have elevated levels of serum IgE and total eosinophil count.

Microscopic examination of nasal secretions often demonstrates significant numbers of eosinophils.

The Radioallergosorbent test (RAST) is a method of testing for specific allergic sensitivities that is based on circulating levels of specific IgE.

Specific IgE levels are determined by using serum samples and are quantified by using radioactive markers.

Classification:

Diagnosis:
- Patients present with a history suggestive of allergic sensitivity and recurrent symptoms with specific exposures.

- Symptoms that have recurred for 2 or more years during the same season are suggestive of seasonal allergic disease.

- Perennial - Indoor allergens (eg, house dust mites, cockroaches, pets)
- Seasonal illness – Outdoor allergens (eg, trees, grasses, weeds).

Management:

General treatment modalities are used in the treatment of allergic Rhinoconjunctivitis:
- i) Allergen avoidance
- ii) Pharmacotherapy (medication) and
- iii) Immunotherapy (allergy injections)

- The best treatment is avoidance of the offending allergen.
- Immunotherapy is an effective means of treatment for patients with allergic Rhinoconjunctivitis.
- Immunotherapy is available for a variety of airborne allergens, including grass, tree, mold, animal dander, and mold spores.
Prominent sneezing, pruritus, or rhinorrhea – antihistamines.
Second-generation antihistamines – Cetirizine, Loratadine and Fexofenadine.
Oral decongestants can be added to oral antihistamines to relieve nasal congestion and obstruction.
Therapy with a cysLT1-receptor antagonist plus antihistamine may have a greater effect.
Topical anti-inflammatory agents – Cromolyn sodium and topical corticosteroid sprays.

Otitis Media
• Otitis media is inflammation of the middle-ear space and tissues.
• Age: children under 8 years of age or younger.
• Otitis media can be subdivided into:
  i) Acute otitis media
  ii) Recurrent otitis media
  iii) Otitis media with effusion and
  iv) Chronic suppurative otitis media.
• The underlying problem in all types of otitis media is dysfunction of the eustachian tube.
The most common infectious causes are viruses, Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis.

Clinical and Laboratory Findings:
• Acute otitis media - Fever and otalgia.
• Other symptoms - Irritability, anorexia, and vomiting.
• On physical examination, the tympanic membrane may appear erythematous and bulging, suggesting inflammation of the middle ear.
• Otoscopic findings include: i) A loss of landmarks and
ii) Decreased mobility of the tympanic membrane as seen by pneumatic otoscopy.
• Otitis media with effusion - Clogged ears and popping.
• Otoscopic examination – Presence of Serous middle-ear fluid and air-fluid levels.
• Clinical and Laboratory otitis media - Otoscopy.

Pathophysiology:
Aspiration of Nasopharyngeal pathogens
Impairs normal eustachian tube function
Negative pressure in the middle ear space

Investigations:
• Tympanometry and
• Myringotomy with aspiration

Otitis Media

Oral Health Considerations:
• Oral dryness.
• Oral candidiasis.
• Allergic respiratory hypersensitivity from exposure to dental materials such as methacrylates and natural rubber latex.

Prognosis:
Excellent.

• **Classification:**  
  - Acute otitis media is defined as middle-ear inflammation with an infectious etiology and a rapid onset of signs and symptoms.
  - Otitis media with effusion is defined as a middle ear effusion (often asymptomatic) that can be either residual (3 to 16 weeks following acute otitis media) or persistent (lasting more than 16 weeks).
  - Recurrent otitis media is defined as three new episodes of acute otitis media in 6 months time or four new episodes in a 12-month period.
  - Chronic suppurative otitis media is defined as persistent otorrhea lasting longer than 6 weeks.

• **Diagnosis:**  
  - Pneumatic otoscopy - Clinician not only to visualize the tympanic membrane but also to assess its mobility.

• **Management:**  
  - Antibiotics  
    - Common choices include amoxicillin, azithromycin, and trimethoprim-sulfamethoxazole.
    - The duration of therapy varies from 3 to 14 days.
  - Surgical modalities:  
    - Myringotomy with or without tympanostomy tube insertion,
    - Tympanocentesis,
    - Adenoidectomy.
  - Chronic suppurative otitis media - Parenteral antibiotics to cover infection by Pseudomonas species and anaerobic bacteria.

• **Prognosis:**  
  - Acute otitis media - Excellent. The most common complication is conductive hearing loss related to persistent effusions.
  - Sinusitis is defined as an inflammation of the epithelial lining of the paranasal sinuses.  
    - The inflammation of these tissues causes mucosal edema and an increase in mucosal secretions.
    - Common trigger factor - Acute upper respiratory infection.
    - If blockage of sinus drainage occurs, retained secretions can promote bacterial growth and subsequent acute bacterial sinusitis.
  - Types:  
    - Acute sinusitis
    - Chronic sinusitis

• **Oral Health Considerations:**  
  - Many children with recurrent otitis media are treated frequently with various antibiotics.
  - It has been demonstrated that antibiotic regimens used for the treatment of otitis media promote the emergence of antibiotic-resistant bacteria.

• **Pathophysiology:**
  - **Rhythmic ciliary movement and clearance of secretions**
    - Foreign bodies and deviated nasal septum
    - Cause obstruction
    - Blockage of the sinus ostia
    - Status of sinus secretions
    - Facilitates bacterial growth.
**Classification:**
- Sinusitis is classified as:
  1. Acute
  2. Subacute
  3. Chronic

- Acute sinusitis is defined as inflammation of less than 4 weeks, subacute as 4 to 12 weeks, and chronic as longer than 12 weeks in duration.

**Diagnosis:**
- Other predisposing factors: Tobacco smoke exposure, immunodeficiency, and septal deviation.
- Evaluation of the osteomeatal complex is crucial in the management of these patients.
  - Rhinoscopy - Direct visualization of sinus ostia.

**Management:**
- First-line antibiotics - Amoxicillin, second-generation cephalosporins, azithromycin, and amoxicillin-clavulanate.
- Comprehensive treatment - Adequate hydration, steam inhalation, and pharmacologic measures to restore ostial patency.
- Nasal glucocorticosteroids.
- Acute frontal or sphenoid sinusitis is very serious because of the potential for intracranial complications.
- Topical corticosteroids - Reduce the swelling and obstruction of the osteomeatal complex.
- Intravenous antibiotics and surgical intervention.
- Functional endoscopic sinus surgery involves the removal of the osteomeatal obstruction through an intranasal approach.

**Prognosis:**
- Ethmoid and maxillary sinusitis - Periorbital or orbital cellulitis.
- Periorbital - Broad-spectrum antibiotics.
- Orbital cellulitis - Hospital admission with broad-spectrum intravenous antibiotics.
- Frontal sinusitis can extend through the anterior wall and present as Font's puffy name.
- Sinusitis can also spread intracranially and result in abscess or meningitis.
- Chronic medication - Rhinitis medicamentosa from prolonged use of topical decongestants.
- Surgical intervention will often reverse the chronic process.

**Laryngitis and Laryngotracheobronchitis**
- Laryngitis is defined as an inflammation of the larynx, usually because of a viral infection.
- Laryngotracheobronchitis is an inflammation involving the larynx, trachea, and large bronchi.
- Laryngitis - adult population.
- Laryngotracheobronchitis - young children and second and third years of life.
- The viruses most commonly implicated in laryngitis are parainfluenza virus, respiratory syncytial virus, adenovirus, and herpes simplex virus.
- The viruses most commonly associated with laryngotracheobronchitis are parainfluenza virus, RSV, influenza virus, and adenovirus.

**Pathophysiology:**
- Infection of the respiratory epithelium
  - Inflammatory response
  - Mononuclear cells and polymorphonuclear leukocytes
  - Vascular congestion and edema.
- Denudation of areas of respiratory epithelium can result.

**Oral Health Considerations:**
- Patients with sinus infections - Toothache.
- The oral health care professional must be able to differentiate between an odontogenic infection and sinus pain.
- Sinus infections usually present with pain involving more than one tooth in the same maxillary quadrant, whereas a toothache usually involves only a single tooth.
- Chronic sinus infections - Mouth breathing.
- Oral dryness and gingivitis.

**Laryngitis:**
- Laryngitis is defined as an inflammation of the larynx, usually because of a viral infection.

**Laryngotracheobronchitis:**
- Laryngotracheobronchitis is an inflammation involving the larynx, trachea, and large bronchi.
Clinical and Laboratory Findings:
- Laryngitis - antecedent viral upper respiratory infection.
- Complaints of fever, sore throat and hoarseness, with weak or faint speech.
- Cough - lower respiratory tract is involved.
- Children presenting with viral croup - Fever, barking cough and intermittent stridor develop.
- Stridor at rest, retractions, and cyanosis can occur in children with severe inflammation.
- Neck radiography will demonstrate subglottic narrowing (steeple sign) on an anteroposterior view.

Diagnosis:
- Presence of hoarseness.
- Differential diagnosis – laryngeal edema, obstruction of venous or lymphatic drainage from masses, decreased plasma oncotic pressure from protein loss or malnutrition, increased capillary permeability, myxedema of hypothyroidism.
- Carcinoma of the larynx can also present with hoarseness.
- Children - Stridor, foreign body aspiration, acute bacterial epiglottitis, and retropharyngeal abscess.

Management:
- Oral corticosteroids.
- Management of laryngotracheobronchitis is airway maintenance.
- The standard therapy includes mist therapy, corticosteroids, and racemic epinephrine.
- Less frequently - Hospitalization and intubation or tracheotomy

Prognosis:
- Most cases of laryngitis and laryngotracheobronchitis are self-limited and require minimal medical intervention.
- Recovery within a few days to a week.

Pharyngitis and Tonsillitis
- Inflammation of the tonsils and pharynx. (viral and Bacterial)
- These infections can be associated with fever, Rhinorrhea, and cough.
- Viral etiologies : Epstein-Barr virus, coxsackievirus A, Adenovirus, Rhinovirus, and Measles virus.
- Bacterial : Group A B-hemolytic Streptococcus (GABHS) infection, specifically Streptococcus pyogenes infection.
- Causes : Chronic mouth breathing, chronic postnasal drainage, and inflammation due to irritant exposure.

Pathophysiology:
- Streptococcal infections are spread through direct contact with respiratory secretions.
- The incubation period is 2 to 5 days.
• Physical examination can reveal hepatosplenomegaly.
• Common laboratory findings include leukocytosis.
• Blood chemistries may reveal elevated liver enzymes.
• Coxsackievirus - distinct illnesses, tonsillopharyngitis.
• Hand-foot-and-mouth disease is characterized by ulcers on the tongue and oral mucosa, in association with vesicles found on the palms and soles.
• Lymphonodular pharyngitis can characterize Small yellow-white nodules on the anterior tonsillar pillars and these nodules do not ulcerate.

• Diagnosis:
  • Diagnosis is based on a history of sore throat.
  • Rapid antigen detection test - Diagnosis of streptococcal pharyngitis.
  • Antistreptococcal antibody titers reflect past and are of no value in the diagnosis of acute GABHS pharyngitis.
  • They are valuable for confirmation of prior GABHS infections in patients suspected of having Acute Rheumatic fever or Poststreptococcal Acute Glomerulonephritis.

• Management:
  • The viral causes of tonsillopharyngitis are treated symptomatically.
  • Gargle solutions, analgesics, and antipyretics.
  • Acute streptococcal pharyngitis is treated with oral penicillin V, cephalosporins, macrolides, clindamycin, or an intramuscular injection of benzathine penicillin G.

• Prognosis:
  • Viral tonsillopharyngitis - very good.
  • Other complications due to streptococcal tonsillitis include cervical adenitis, peritonsillar abscesses, otitis media, cellulitis, and septicemia.

• Oral Health Considerations:
  • The association between GABHS infection and Rheumatic fever is well known.
  • When toothbrushes were rinsed with sterile water, organisms could not be cultured beyond 3 days, where as nonrinsed toothbrushes harbored GABHS for up to 15 days.
  • Thus, patients with GABHS infections should be instructed to thoroughly clean their toothbrushes and removable acrylic appliances daily.
  • It is also advisable to change to a new toothbrush after the acute stage of any oropharyngeal infection.

• Lower Airway diseases

  • Acute Bronchitis:
    • Acute bronchitis is an acute respiratory infection involving the large airways (Trachea and Bronch) that is manifested predominantly by cough with or without phlegm production that lasts up to 3 weeks.
    • Viruses : Influenza B, Influenza A, Parainfluenza, and RSV.
    • Bacteria : Mycoplasma pneumoniae, Chlamydia pneumoniae, Bordetella pertussis, and Bordetella parapertussis.
• Pathophysiology:
  • Infection of the mucosal cells and congestion of the respiratory mucosa
    • Inflammation causes an increase in secretory activity.
    • Increased sputum production.
    • Polymorphonuclear leukocytes infiltrate the bronchial walls and lumen.
    • Desquamation of the ciliated epithelium.
    • Spasm of bronchial smooth muscle.

• Clinical and Laboratory Findings:
  • Acute viral bronchitis - Sudden onset of cough, with or without sputum expectoration, common cold, acute asthma, or an acute exacerbation of chronic bronchitis.
  • Chest discomfort.
  • Other symptoms: Dyspnea and respiratory distress.
  • Physical examination may reveal wheezing.
  • Symptoms gradually resolve over a period of 1 to 2 weeks.

• Diagnosis:
  • Diagnosis of acute bronchitis is based on a suggestive history and a physical examination.
  • Chest radiography may be helpful in distinguishing bacterial bronchitis from pneumonia.
  • Patients with recurrent bouts of acute bronchitis should be evaluated for possible asthma.
  • This evaluation would include pulmonary function testing.
  • Sputum cultures.

• Management:
  • Viral bronchitis - Supportive care.
  • Airway obstruction or hyperreactivity - Inhaled bronchodilators, such as albuterol.
  • Cough suppressants - Codeine.
  • Bacterial bronchitis - Amoxicillin, amoxicillin-clavulanic acid, macrolides, and cephalosporins.
  • Pertussis infection - Macrolide or trimethoprim-sulfamethoxazole is appropriate.
  • Inhaled B2-agonist bronchodilators.

• Prognosis:
  • Acute bronchitis - Excellent prognosis.
  • Chronic lung disease and respiratory compromise - Hospitalization and respiratory failure.
  • High-risk individuals such as Human immunodeficiency virus (HIV) infection acute bronchitis may lead to the development of bronchiectasis.

• Oral Health Considerations:
  • Resistance to antibiotics may develop rapidly and last for 10 to 14 days.
  • Amoxicillin for acute bronchitis should be prescribed with another type of antibiotic (such as clindamycin or a cephalosporin) when an antibiotic is needed for an odontogenic infection.

• Pneumonia
  • Pneumonia is defined pathologically as an infection and a subsequent inflammation involving the lung parenchyma.
  • Pneumonias can be broadly classified as either community-acquired or nosocomial.
  • Nosocomial infections are infections that are acquired in a hospital or health care facility and often affect debilitating or chronically ill individuals.
  • Community-acquired infections can affect all persons but are more commonly seen in healthy individuals.
  • The most common bacterial cause of community acquired pneumonia is S. pneumoniae, followed by H. influenzae.
- Nosocomial pneumonia: Aerobic gram-negative bacilli, such as P. aeruginosa, Escherichia coli, Klebsiella pneumoniae.
- Aspiration pneumonia: Dysphagia, depressed consciousness, aspiration of oral contents into the lung.
- Atypical organisms commonly associated with pneumonia include M. pneumoniae, Legionella, and Chlamydia.
- Pneumonia can also be caused by viruses (such as influenza, parainfluenza, adenovirus); fungi such as Candida, Histoplasma, Cryptococcus, and Aspergillus; and by protozoa such as Pneumocystis carinii, Nocardia, and Mycobacterium tuberculosis.

**Pathophysiology:**
- Bacteria first enter the alveolar spaces after inhalation:
  - Edema develops.
  - Cause a vigorous inflammatory response
  - Influx of polymorphonuclear leukocytes and capillary leakage
  - Deposition of fibrin ensues and the inflammatory response resolves.

- Atypical infections of the lung (i.e., viral, mycoplasmal),
- Inhaled into the alveolar spaces.
  - Type I pneumocytes
  - Type II pneumocytes
  - Interstitial inflammatory response
  - Mononuclear leukocytes.
  - Progress to interstitial fibrosis.

**Clinical and Laboratory Findings:**
- Community-acquired bacterial infection: Common symptoms include fever, pleuritic chest pain, and coughing that produces purulent sputum. Chills and rigors.
- Nosocomial pneumonia with Staphylococcus secondary to aspiration: Fever, dyspnea, cough, and purulent sputum.
- Physical examination demonstrates crackles (rales) in the affected lung fields.
- Decreased breath sounds and dullness to percussion and signs of respiratory distress.
- Symptoms usually develop over 3 to 4 days and initially consist of low-grade fever, malaise, a nonproductive cough, and headache.

**Diagnosis:**
- When a patient with probable pneumonia is being evaluated, the possible causative organism will be suggested by:
  1. The clinical presentation and course of the illness.
  2. The degree of immunocompromis of the patient.
  3. The presence or absence of underlying lung disease, and
  4. The place of acquisition (hospital or community).
- The goal is rapid diagnosis to institute an antimicrobial therapy.
- Sputum analysis.
- Chest radiography.

- A pattern of lobar consolidation and air bronchograms - pneumococcal pneumonia.
  The lower lobes and right middle lobe are most commonly involved.

- A pattern of patchy nonhomogeneous infiltrates, pleural effusion, and cavitary lesions - staphylococcal pneumonia.
- Interstitial infiltrative pattern or patchy segmental infiltrates - Viral or atypical organisms.
- Rapid accumulation of pleural fluid or empyema - bacterial infection.
- Presence of cold agglutinins - Mycoplasma pneumonia.
- Cold agglutinins are antibodies (produced in response to Mycoplasma infection) that agglutinate red blood cells upon cold exposure.
Management:
- Empiric treatment.
- Community-acquired pneumonia include B-lactams (e.g., Amoxicillin-clavulanate), macrolides, and fluoroquinolones.
- Nosocomial pneumonia - Empiric therapy such as a third-generation cephalosporin or fluoroquinolones.
- Nonspecific treatment - Aggressive hydration to aid in sputum clearance.
- Chest physiotherapy.
- Active immunization - Pneumococcal vaccine.

Prognosis:
- Mortality due to community-acquired pneumonia is low.
- Mortality - Higher for older patients, patients with underlying pulmonary disease, patients with immunodeficiency (i.e., asplenia), and patients with positive blood cultures.
- Most deaths occur within 5 days of the onset of disease.
- Mortality due to staphylococcal pneumonia - high.
- Mortality due to atypical pneumonia - low.

Oral Health Considerations:
- Provision of effective oral care is an important strategy in reducing nosocomial pneumonia.
- Systematic clinical assessment of the oral cavity using standardised methods.
- The use of soft bristled brush can remove debris and subsequent plaque.
- Mouth swabs should be used where there is a contraindication to brushing (e.g., Bleeding gums associated with thrombocytopenia).
- Tap water should not be used for oral hygiene in the critically ill.

Bronchiolitis:
- Bronchiolitis is a disease that is characterized by infection of the lower respiratory tract with the bronchioles that affects children under the age of 2 years.
- The inflammatory response can be caused by various pathogens, including RSV, human metapneumovirus, parainfluenza virus, influenza virus, adenovirus, and M. pneumoniae.

Subglottic suctioning in mechanically ventilated patients to limit aspiration of contaminated secretions.
- Although the optimal frequency for oral hygiene has never been evaluated, brushing at least twice a day was suggested.
- Although the optimal duration for oral hygiene has never been evaluated, oral cleansing for 3-4 min using a brush that allows access to all areas of the mouth was suggested.
- While there is no evidence available to support the use of individual, clean storage devices for oral hygiene tools, guideline committee recommends the use of designated containers.
- Other measures: Implanted patients may include removal of all dental appliances and repositioning of the tracheal tube or tracheostomy cuff.
Clinical and Laboratory Findings:
- Infants with infection of URT: Low-grade fever, profuse clear rhinorrhea, and cough.
- Infection in the LRT: Tachypnea, retractions, wheezing, and cyanosis.
- Crackles can be audible, and thoracic hyperresonance can be noted on percussion.
- Associated findings can include conjunctivitis, otitis media, and pharyngitis.
- Chest radiography: Peribronchial cuffing, flattening of the diaphragms, hyperinflation, and increased lung markings.
- Laboratory studies: Mild leukocytosis with a prominence of polymorphonuclear leukocytes (left shift).

Diagnosis:
- The diagnosis is clinical, based on the history and physical examination.
- The etiology can be determined by performing a nasopharyngeal culture for RSV and other respiratory viruses.
- Rapid viral diagnostic assays.
- Differential diagnosis: Asthma, congenital heart disease, and cystic fibrosis (CF).

Management:
- Infants may be placed in cool-mist oxygen tents, where continuous oxygen administration can be given.
- Antiviral therapy: Ribavirin (delivered by aerosol on a semicontinuous basis for up to 1 week).
- Mechanical ventilation.
- An intramuscular monoclonal antibody to the RSV F protein, palivizumab, is effective in preventing severe RSV disease in high-risk infants.
- This prophylaxis is currently recommended only for high-risk patient populations such as those with chronic lung disease, a history of prematurity, or congenital heart disease.

Prognosis:
- Most patients recover without sequelae.
- Epidemiologic studies with a several-year follow-up show a higher incidence of wheezing and asthma in children.

Asthma
- Asthma is a chronic inflammatory disorder of the airways characterized by recurrent and often reversible airflow limitation due to an underlying inflammatory process.
- Multiple risk factors: Family history of asthma, atopy, respiratory infections, inhaled pollutants, allergens, food sensitivities.
- Early childhood.

Pathophysiology:
- Infiltration of airway by inflammatory cells
  - Denudation of epithelium
  - Mast cells and Alveolar macrophages secrete proinflammatory mediators
  - Increase the capillary permeability
  - Mucosal edema.
Clinical and Laboratory Findings:
- Recurrent reversible airflow limitation and airway hyper-responsiveness.
- Signs and symptoms: Intermittent wheezing, coughing, dyspnea, and chest tightness.
- Triggers include allergens, exercise, cold air, respiratory irritants, and viral infections.
- Severe disease: Increased anteroposterior chest diameter, a prolonged expiratory phase, wheezing, and diminished breath sounds.
- Allergic rhinitis.
- Signs of respiratory distress, with tachypnea, intercostal retractions, nasal flaring, and cyanosis.
- Pulmonary function testing or spirometry.
  - The technique involves a maximal forced expiration following a maximal inspiration.
  - The key measurements are:
    i) The forced vital capacity (FVC) - which is the amount of air expired during the forced expiration.
    ii) The forced expiratory volume in 1 second (FEV1) - which is the volume of air expired during the first second of expiration and FEV1 is a measure of the rate at which air can be exhaled.
  - Reversibility can be demonstrated after administration of a short-acting bronchodilator (such as albuterol) and a repeat spirometric measurement.
- Subsequent measurements of peak expiratory flow rate (PEFR) can be helpful for the diagnosis and management of asthma.
- Allergy skin testing.
  - This testing allows the accurate identification of allergic triggers, which can translate into more specific therapies, such as allergen avoidance and immunotherapy.
- Chest radiography.
- Classification:
  - National Asthma Education and Prevention Program (NAEPP) are the most widely used in the United States.
  - Asthma patients are classified as:
    i) Mild-intermittent
    ii) Mild-persistent
    iii) Moderate-persistent or
    iv) Severe-persistent disease.
  - The categories are defined by both subjective (historical) and objective (spirometric) points.
- Diagnosis:
  - Spirometry or PEFR determinations
  - Differential diagnosis: Chronic coughing and wheezing, chronic rhinitis or sinusitis, CF, gastroesophageal reflux disease and COPD (chronic bronchitis).
  - Factors: Intermittent symptoms with asymptomatic periods, complete or nearly complete reversibility with bronchodilators, the absence of digital clubbing, and a history of atopy.
- Management:
  - Regular monitoring: spirometry, PEFR measurement, exhaled nitric oxide levels, and questionnaires may be useful tools for this purpose.
  - Pharmacotherapy of asthma is based on the severity of disease.
    - Mild-intermittent disease: Short-acting bronchodilators (such as albuterol).
    - Mild-persistent asthma: Inhaled corticosteroids
    - Leukotriene receptor antagonists – Montelukast and Zafirlukast.
    - Moderate and Severe persistent disease – Inhaled corticosteroid therapy and long acting β2-agonists such as salmeterol.
• Prognosis:
  • Early diagnosis and a comprehensive management plan; patients with asthma can experience a normal life expectancy with good quality of life.

• Oral Health Considerations:
  1. Fluoride supplements should be instituted for all asthmatic patients, particularly those taking R2-agonists.
  2. The patient should be instructed to rinse his or her mouth with water after using inhalers.
  3. Oral hygiene should be reinforced to reduce the incidence of gingivitis and periodontitis.
  4. Antifungal medications should be administered particularly in patients who are taking inhaled corticosteroids.
  5. Steroid prophylaxis needs to be used with patients who are taking long-term systemic corticosteroids.
  6. Use stress-reducing techniques.
    • Conscious sedation - Hydroxyzine.
    • Barbiturates and narcotics should be avoided.
    • Nitrous oxide can be used for all but patients with severe asthma as it may irritate the airways.
  7. Avoid dental materials that may precipitate an attack. Dental materials without methylmethacrylate should be considered.
  8. Schedule these patients’ appointments for late morning or later in the day to minimize the risk of an asthmatic attack.
  9. Have oxygen and bronchodilators available in case of an exacerbation of asthma.
  10. There are no contraindications to the use of local anesthetics containing epinephrine, but preservatives such as sodium metabisulfite may contribute to asthma exacerbation in susceptible patients.
  11. Judicious use of rubber dams will prevent reduced breathing capability.
  12. Care should be used in the positioning of suction tips as they may elicit a cough reflex.
  13. Up to 10% of adult asthmatic patients have an allergy to aspirin and other nonsteroidal anti-inflammatory agents.
  14. Macrolide antibiotics may increase the level of theophylline, whereas phenobarbitals may reduce the level.
  15. If no improvement is noted, administer epinephrine subcutaneously (1:1,000 concentration, 0.01 mg/kg of body weight, up to a maximum of 0.3 mg) and alert emergency medical assistance.

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12. Care should be used in the positioning of suction tips as they may elicit a cough reflex.
13. Up to 10% of adult asthmatic patients have an allergy to aspirin and other nonsteroidal anti-inflammatory agents.
14. Macrolide antibiotics may increase the level of theophylline, whereas phenobarbitals may reduce the level.
15. If no improvement is noted, administer epinephrine subcutaneously (1:1,000 concentration, 0.01 mg/kg of body weight, up to a maximum of 0.3 mg) and alert emergency medical assistance.

**Tuberculosis**

• TB is an airborne bacterial infection caused by M. Tuberculosis which can occur in any part of the body and most commonly the lungs.

• M. Tuberculosis is exposed to the air as droplet nuclei from coughing, sneezing, speaking with pulmonary or laryngeal TB.

• Transmission occurs through inhalation of these droplet nuclei which pass through the mouth or nasal cavities, upper respiratory tract, bronchi and finally reaches the alveoli of the lungs.

• Pathogenesis:
Spread of TB:
1. Local spread
2. Lymphatic spread
3. Haematogenous spread
4. By the natural passages:
   - Lung lesions into pleura
   - Transbronchial spread into adjacent lung segments.
   - Infected sputum into larynx
   - Swallowing of infected sputum
   - Renal lesions into ureter & down to bladder

Classification:

• i) Pulmonary TB
  a) Primary
  b) Secondary
  c) Miliary
 ii) Extra pulmonary TB

Clinical findings:

• Primary pulmonary TB: febrile illness and cough, which may be dry or productive.
• Post-primary TB or secondary TB - fever, cough, chest pain, and hemoptysis.
• Miliary TB - acute febrile illness (children) and it is more insidious with gradual development of ill health, anorexia, loss of weight, and fever (adults)
• Bilateral crackles on auscultation, hepatosplenomegaly and lymphadenopathy may be present
• Choroid tubercles – children
• Tuberculous infection of submandibular and cervical lymph nodes – Scrofula
• Primary tuberculosis of the skin - Lupus vulgaris

Oral manifestations:

• Primary oral tuberculosis - Gingiva and is present as diffuse, hyperemic, nodular, or papillary proliferation of the gingival tissues.
• Secondary tuberculosis - Tongue is most commonly affected, followed by the palate, lips, buccal mucosa, gingiva, and frenula.
• The usual presentation is an irregular, superficial or deep painful ulcer which tends to increase slowly in size.
• It is frequently found in areas of trauma.
• Occasional mucosal lesions show swelling, granular, nodular or fissured lesions, but no obvious clinical ulceration.

Diagnosis:

• 1) Skin or blood tests

  Mantoux tuberculin test: Injecting a standard dose of tuberculin fluid into the skin of the lower portion of the arm subcutaneously.
  The results depend on the diameter in millimetres of a skin reaction characterised by an induration (a palpable raised hardened area free from erythema) after 48 to 72 hours of testing.
  A diameter of 0 to 4 mm represents a negative skin test reaction a diameter of 5 to 9 mm is a doubtful result while 10 mm or more represents a positive reaction.

Interferon-Gamma Release Array (IGRA): It measures the extent to which the immune system reacts to the tubercle bacilli.
• The United States Food and Drug Administration (FDA) has approved the use of two IGRA.
  i) QuantiFERON-TB Gold In-Tube test (QFT-GIT) and
  ii) T-SPOT TB test.
• Positive response - Presence of tubercle bacilli.
• Negative response - Absence of TB infection.

Drug susceptibility testing (DST): It is performed on the isolated tubercle bacilli according to test for resistance to any of the first-line anti-tuberculosis drugs.
2) Chest radiography
3) Computerized tomography (CT) scan
4) Bacteriologic examination of clinical specimens.
5) Specific purified protein derivative (PPD)

- Newer methods of diagnosis of tuberculosis include radioimmunoassays (RIAs), soluble antigen fluorescent antibody (SAFA) test and enzyme linked immunosorbent assay (ELISA), polymerase chain reaction (PCR)

- Prevention:
  - Bacilli calmette –Guerin (BCG vaccine) - Used preventive measure to control tuberculosis worldwide.
  - Administered to newborns in a single dose, it prevents severe disease and reduces mortality among children from miliary and meningeal disease.

- Management:
  - Isoniazid is cornerstone drug and include in all regimens.
  - DOTS: Directly Observed treatment short course is also followed in TB cases.
  - INH + R- 9 months/ INH+R+ P- 2 months followed by INH+R- 4 months.

Chronic Obstructive Pulmonary Disease

- COPD is a disease state characterized by airflow limitation.
- COPD:
  - A) Emphysema: an anatomically defined condition characterized by destruction and enlargement of the lung alveoli.
  - B) Chronic bronchitis: a clinically defined condition with chronic cough and phlegm, and small airways disease. A condition in which small bronchioles are narrowed.

- Diagnosis: Symptoms of cough, sputum production or dyspnea.
- Risk factors: Environmental exposures and host factors (hereditary deficiency in the enzyme A1-antitrypsin).

- This enzyme is responsible for inhibiting the activity of trypsin and other proteases in the serum and tissues. The characteristic panlobular emphysematous changes that are seen in a1-antitrypsin deficiency are related to the loss of alveolar wall.

- Pathophysiology:
  - 1) Chronic inflammation throughout the airways, parenchyma, and pulmonary vasculature
     - a) Oxidative stress
     - b) Imbalance of proteases and antiproteases in the lung.
  - These pathologic changes lead to mucus hypersecretion, ciliary dysfunction, airflow limitation, pulmonary hyperinflation, gas exchange abnormalities, pulmonary hypertension and cor pulmonale.

- Chronic exposure to tobacco smoke results in an increase in the number of goblet cells because of hyperplasia and metaplasia.
- Acrolein.
- Nitrogen dioxide.
- Hydrogen cyanide.
- Carbon monoxide.
- Polycyclic hydrocarbons have been implicated as carcinogens.
Clinical and Laboratory Findings:

Symptoms: Dyspnea, cough, and sputum production. An increase in the production of purulent sputum is a sign of exacerbation due to respiratory infection.

Physical findings: Diffuse wheezing, respiratory distress, including the use of accessory muscles of respiration (retractions) and tachypnea.

Liver enlargement due to congestion, ascites, and peripheral edema can develop as the disease progresses to pulmonary hypertension and cor pulmonale. This leads to the characteristic clinical patient presentation termed the Blue bloater.

Patients can be adequately oxygenated in the early stages of the disease and thus can have fewer signs of hypoxia (pink puffer).

Classification:

COPD is classified into five stages: at risk, mild, moderate, severe, and very severe.

The at-risk stage is defined by normal spirometry, but patients have chronic symptoms of cough and sputum production.

Mild, moderate, and severe COPD has evidence of increasing airway obstruction on spirometry in each progressive stage.

Very severe COPD is defined by severe airway obstruction with chronic respiratory failure.

At this stage, quality of life is significantly impaired and exacerbations may be life-threatening.

Diagnosis:

Patients often have cough, dyspnea, and sputum production.

Complete pulmonary function tests are a valuable means of assessing airflow limitation and the reversibility of airway obstruction.

Pulse oximetry.

Chest radiography.

A determination of arterial blood gases is important for the management of hospitalized patients.

Management:

Maintenance therapy: Trials of inhaled bronchodilators such as Albuterol and ipratropium bromide.

Long-acting bronchodilators: Formoterol or salmeterol (Global Initiative for Obstructive Lung Disease).

A partial pressure of arterial oxygen of 55-60 mm Hg - Reduce hypoxemia while maintaining respiratory drive.

Typical treatment includes 7-10 days of second generation cephalosporin.

Oral Health Considerations:

The association between oral disease and lung disease was analyzed by the National Health and Nutrition Examination Survey I (NHANES I).

Individuals with a confirmed chronic respiratory disease had a significantly greater oral hygiene index than subjects without a respiratory disease.

Cystic Fibrosis

CF is a multisystem genetic disorder that is characterized chiefly by chronic airways obstruction and infection and by exocrine pancreatic insufficiency, with its effects on gastrointestinal function, nutrition, growth, and maturation.

Disorder: Transmembrane conductance regulator (CFTR).

The disease is characterized by hyperviscous secretions in multiple organ systems.

Pathophysiology:
Clinical and Laboratory Findings:
- Infancy - extrapulmonary manifestations such as meconium ileus or failure to thrive.
- Pulmonary manifestations - cough, recurrent infections of the lower respiratory tract, refractory lung infiltrates, and bronchiectasis.
- Physical examination - Tachypnea and crackles.
- As the disease progresses, digital clubbing and bronchiectasis may become apparent.
- Spirometry and pulmonary function testing.
- CT analysis of the remarkable lung structural changes may be another potential outcome measure to monitor disease progression.

Diagnosis:
- A sweat test can be performed to confirm the diagnosis.
- The procedure involves the collection of sweat after stimulation with pilocarpine.
- Samples containing > 60 mEq/L chloride are considered positive.

Management:
- Conventional treatment: Antibiotics, bronchodilators, anti-inflammatory agents, chest physiotherapy with postural drainage, and macrolide agents.
- Inhaled antibiotics – Tobramycin.
- Long-term macrolide antibiotics - Diffuse panbronchiolitis.
- Recombinant enzyme deoxyribonuclease therapy - Purulent airway secretions.
- Exercise.

Oral Health Considerations:
- The tongue, boccal inososa, dental plaque, and saliva serve as a reservoir of colonization by both mucoid and nonmucoid strains of P. aeruginosa, an important bacterial pathogen for CF patients.
- This suggests that oral hygiene strategies may help reduce the level of these pathogens in the mouth and thus reduce potential lung infection.

Pulmonary Embolism
- Pulmonary embolism (PE) is a result of an exogenous or endogenous material travelling to the lung and causing blockage of a pulmonary arterial vessel.
- Substances: Neoplastic cells, air bubbles, carbon dioxide, intravenous catheters and fat droplets.
- Risk factors: Prolonged immobilization, lower extremity trauma, a history of deep venous thromboses, and the use of estrogen-containing oral contraceptives.

Pathophysiology:
- Occlusion of pulmonary arterial vessels
  - Ventilation-perfusion mismatch.
  - Right-sided heart failure.
  - Local bronchoconstriction.
  - Platelets and mast cells.
  - Pulmonary hypertension and arterial vasoconstriction.
- Clinical and Laboratory Findings:
  - Dyspnea.
  - Other features: Chest pain, fever, diaphoresis, cough, hemoptysis, and syncope.
  - Physical findings: Evidence of a lower extremity deep venous thrombosis, tachypnea, crackles or rub on lung auscultation, and heart murmur.
  - Hypoxemia.
  - Measurements of arterial blood gases are helpful as patients may demonstrate a decrease in partial pressure of arterial oxygen (PaO2) and partial pressure of arterial carbon dioxide (PaCO2) with an increase in hydrogen ion concentration (pH).
Classification:
- Massive PE
- PE with pulmonary infarction
- PE without infarction or cor pulmonale
- Organized emboli in central arteries.

Diagnosis:
- Negative d-dimer - venous thromboembolism is absent.
- Chest radiography - Elevated hemi-diaphragm, pleural effusions, and pulmonary artery dilatation.
- Troponin levels may be elevated, the echocardiogram may be abnormal with increased right ventricular volume.
- Ventilation-perfusion scan - PE is suspected.
- Spiral (helical) CT scanning.
- Pulmonary arteriography is the gold standard study.
- Pulmonary angiography.

Management:
- Heparin (both unfractionated and low molecular weight).
- Systemic thrombolytic therapy (such as streptokinase, urokinase, and tissue-type plasminogen activator).
- Pulmonary embolectomy - patients who are unable to receive thrombolytic therapy.
- Oxygen administration.
- Mechanical ventilation.

Oral Health Considerations:
- Provision of dental care - Managed with oral anticoagulants.
- Dental care (including simple extractions) can safely be provided for patients with prothrombin times of up to 20 seconds or an international normalized ratio of 2.5.

Pulmonary Neoplasm
- Lung cancer is the leading cause of cancer deaths in both men and women.
- Squamous cell carcinomas account for one-third of all lung cancers. The neoplasm derives from bronchial epithelial cells that have undergone squamous metaplasia. This is a slow-growing neoplasm that invades the bronchi and leads to airway obstruction.
- Small cell carcinomas account for approximately one-fourth of all lung cancers. This type of lung cancer has the highest association with smoking. These derive from neuroendocrine cells in the airways and metastasize rapidly.
- Adenocarcinomas account for approximately one-third of all lung cancers. These neoplasms are of glandular origin and develop in a peripheral distribution. They grow more rapidly than squamous cell carcinomas and tend to invade the pleura. The bronchoalveolar tumor is derived from bronchiolar or alveolar epithelium. This cancer is not associated with exposure to tobacco smoke.
- Large cell carcinomas include anaplastic and giant cell tumors. They are poorly differentiated tumors that resemble neither squamous cell carcinomas nor adenocarcinomas.

Pathophysiology:
- Metaplasia of the respiratory epithelium occurs in response to injury, such as that induced by tobacco smoking.
- With continued injury, the cells become dysplastic, with the loss of differentiating features.
- Neoplastic change first occurs locally, invasive carcinoma usually follows shortly.
• **Clinical and Laboratory Findings:**
  - Chronic nonproductive cough.
  - Sputum production, Hemoptysis, Dyspnea.
  - Superior vena cava syndrome - Facial edema, cyanosis, and orthopnea caused by compression of the superior vena cava by tumor. The acute onset of hoarseness may signal tumor compression of the recurrent laryngeal nerve.
  - Shoulder and forearm pain might suggest the presence of Pancoast’s tumor, which is found in the apical region of the lungs below the pleura.
  - The bones, the brain, and the liver are common sites of metastasis.
  - Paraneoplastic effects - Endocrine abnormalities that are due to tumors that secrete hormones such as antidiuretic hormone, adrenocorticotropic hormone, and parathyroid hormone-related peptides.

• **Classification:**
  - The World Health Organization has differentiated pulmonary neoplasms into 12 distinct histologic types:
    i) Squamous cell carcinoma
    ii) Small cell carcinoma
    iii) Adenocarcinoma
    iv) Large cell carcinoma

• **Diagnosis:**
  - CT scanning.
  - Other diagnostic modalities:
    i) Sputum or pleural fluid cytology.
    ii) Excisional biopsy.
    iii) Transthoracic needle aspiration.
    iv) Bronchoscopy.

• **Management:**
  - Complete surgical resection.
  - Treatment is based on the stage of the disease and the patient’s clinical status.
    - Early-stage disease – surgical.
    - Locally advanced disease - chemotherapy and radiotherapy.
    - Advanced disease – chemotherapy with supportive care.
    - Radiation therapy is an important palliative measure, especially for patients with superior vena cava syndrome, brain metastases, or bone lesions.

• **Prognosis:**
  - Patients with lung cancer has remained poor.
  - Most pulmonary cancers are found too late for a cure only about 20% of patients undergo a radical surgical procedure, which is the only curative treatment.

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CORONAVIRUS (COVID-19): A PANDEMIC DISEASE

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INTRODUCTION

The emerging coronavirus disease (COVID-19) swept across the world, affecting more than 200 countries and territories. Genomic analysis suggests that the COVID-19 virus originated in bats and transmitted to humans through unknown intermediate hosts in the Wuhan seafood market, China, in December 2019.

This virus belongs to the Betacoronavirus group, the same group of the 2003 severe acute respiratory syndrome coronavirus (SARS-CoV), and for the similarity, it was named SARS-CoV-2.

1st case in world: In December 2019, 55 yr old individual from Hubei Huanan seafood market, China.

1st case in India: In January 27, 2020, 20 yr old female presented to the emergency department in general hospital Thrisur, Kerela.

CORONA DIVERSITY??

-CoV members belong to the subfamily Coronavirinae within the family Coronaviridae and the order Nidovirales. Based on their protein sequences and phylogenetic relationships, members of the Coronavirus subfamily can be classified into four groups, Alphacoronavirus, Betacoronavirus, Gamacoronavirus, and Deltacoronavirus. Gamacoronavirus and Deltacoronavirus infect birds and might infect mammals, but never reported to cause any illnesses in humans.

On the other hand, Alphacoronavirus and Betacoronavirus are capable of causing respiratory illnesses in humans and gastrointestinal illnesses in animals.

-SARS-CoV and MERS-CoV belong to the Betacoronavirus group.

SEVER STRAINS OF COROHA VIRUS:

Dangerous strains are:
1. SARS-CoV was 1st reported in Asia in Feb 2003 and quickly spread to 26 countries in 4 months more than 8000 people fell ill and 774 died.
2. MERS-CoV is a middle east respiratory syndrome. Corona virus first reported in Sep 2012 in Saudi Arabia and 2,259 people fell ill and 866 died.
3. SARS-CoV-2(2019 acute respiratory syndrome) a morotic, with Chinese horseshoe bats and pangolins are intermediate host.

Harmless strains are:
1. serotype 229e
2. serotype OC43

Saliva as potential diagnosis

Impact of corona virus infectious disease on oral health

Infection control in dental setting

Diagnosis

1. Introduction
2. Types of corona virus
3. Structure
4. Pathogenesis
5. Epidemiologic characteristic
6. Clinical manifestation
7. Diagnosis
8. Treatment
9. Complication
10. Infection control in dental setting
11. Impact of corona virus infectious disease on oral health
12. Saliva as potential diagnosis

EPIDEMIOLOGY

1. 31-DECEMBER-2019, WHO alerted by Chinese authorities of a string of pneumonia cases in Wuhan.
2. 1-JANUARY-2020, Huanan seafood market identified as source of pneumonia.
3. 6-JANUARY-2020, 1st death from COVID-19 occurs in Wuhan.
4. 10-JANUARY-2020, Gene sequencing data of COVID-19 established and shared globally.
5. 13-JANUARY-2020, 1st infection occur in Thailand outside of China.
6. 16-JANUARY-2020, 1st infection occur in Japan.
7. 19-JANUARY-2020, sudden spike in reporting of another 136 cases in Wuhan.
8. 20-JANUARY-2020, 1st infection occurs in South Korea.
9. 21-JANUARY-2020, Taiwan and the United States reports there 1st infection.
10. 27-JANUARY-2020, first infections occur in India.
11. 22-JANUARY-2020, 1st infection occurs in Macau and Hong Kong.

12. February 26/2020: COVID 19 has been recognised in 34 countries with a total of 80,239 laboratory confirmed cases and 2,700 deaths.
13. July 22/2020: Over 14.9 million confirmed cases and more than 610,000 deaths related to covid 19 has been reported worldwide.
14. 2/JAN/2021: In Asia, Africa, Europe, North America, South America, 83,963,941 Confirmed cases are found and 1,827,544 Deaths occur.
PATHOGENESIS

Following viral transmission, SARS-CoV-2 attaches to the surface of the epithelial membrane of the oral cavity, the mucosal membranes of the conjunctiva or the otic canal.

ACE2 protein, which is highly expressed on multiple human cells including type II alveolar cells (AT2), oral, esophageal, ileal epithelial cells, myocardial cells, proximal tubule cells of the kidneys as well as urothelial cells of the bladder is believed to mediate the internalization of SARS-CoV2.

The spike (S) protein of SARS-CoV2 is cleaved by a cellular enzyme named furin at the S1/S2 site. This cleavage is essential for viral entry to the lung cells.

The activated S protein is primed by the TMPRSS2 and finally attaches ACE2 receptors to enter the host cells.

SARS-CoV-2 binds ACE2 receptors with tenfold higher affinity.

Severe COVID-19 patients demonstrate a remarkable reduction of lymphocytic T Cells (CD4+ and CD8+) and natural killer (NK) cells.
EPIDEMIOLOGIC CHARACTERISTIC

MODE OF TRANSMISSION: Interpersonal transmission occurs mainly via respiratory droplets and contact transmission. In addition, there may be risk of fecal-oral transmission and by coughing and sneezing.

SOURCE OF TRANSMISSION: Asymptomatic patients and patients in their incubation period are also carriers of SARS-CoV-2. Patients in the recovering phase are a potential source of transmission.

INCUBATION PERIOD: The incubation period of COVID-19 has been estimated at 5 to 6 days on average, but there is evidence that it could be as long as 14 days, which is now the commonly adopted duration for medical observation and quarantine of (potentially) exposed persons.

SURVIVAL TIME OF CORONA VIRUS

CLINICAL MANIFESTATION

Early Symptoms:
- Cough
- Shortness of breath
- Fatigue
- Fever

Late symptoms:
- Chills
- Repeated shaking with chills
- Headache
- Loss of taste or smell
- Muscle aches and pains
- Sore throat
- Runny or stuffy nose
- Nausea
- Diarrhea

One-third developed serious complications, such as acute respiratory distress syndrome, arrhythmia, and shock, metabolic acidosis, Coagulation dysfunction and were therefore transferred to the intensive care unit.

People at high risk of infection: Those who are in close contact with patients with symptomatic and asymptomatic COVID-19, including health care workers and other patients in the hospital.
- Older adults (more than 60 years of age)
- People with chronic medical conditions like kidney disease, sickle cell disease, heart disease, Type II diabetes and lung disease including chronic obstructive pulmonary disease
- Those living in a nursing home or long term care facility
- Obesity (BMI > 30)
- Those who have weakened immune system

SYMPTOMS OF CORONA
ONSET OF SYMPTOMS WITHIN 14 DAYS AFTER EXPOSURE

DIFFERENCE BETWEEN CORONA VIRUS, SEASONAL VIRUS, AND COMMON COLD

DIAGNOSIS

• The diagnosis of COVID-19 can be based on a combination of epidemiologic information (e.g., a history of travel to or residence in affected region 14 d prior to symptom onset), clinical symptoms, CT imaging findings, and laboratory tests (e.g., reverse transcriptase polymerase chain reaction [RT-PCR] tests on respiratory tract specimens, antigen test and antibody test).

• Chest computed tomography (CT), most showed bilateral pneumonia, with ground-glass opacity and bilateral patchy shadows being the most common patterns.

• RT-PCR Test:

TREATMENT

According to National Institute of Health, drugs which are very useful are:

1. REMEDESIVIR:
   • Antiviral medication.
   • Disrupts viruses ability to replicate and spread within the body.
   • Recommended for patient who have been Hospitalized and require oxygen.
   • Not for patient on mechanical ventilation.
   • Globally in short supply.

2. DEXAMETHASOME:
   • Corticosteroid
   • Makes adjustment to how immune system regulates itself
   • Can be used in patients who needs oxygen, mechanical ventilation.
   • Patients who don't need oxygen this drug is not recommended.
   • As side-effect of drug may worsen their condition.

3. ENOXAPARIN:
   • Anticoagulant
   • Patient with covid-19 are at high risk of developing venous thromboembolism.

4. HYDROCHLOROQUINE:
   • Antimalarial drug it affects the virus entry and exit from the host cell
   • It is given with combination to other antibiotic and antiviral drug.

5. AZITHROMYCIN:
   • Antibiotic drug
   • Treats bacterial infection such as bronchitis and pneumonia.

6. DOXYCYCLINE:
   • Antibiotic
   • Use to treat infection
   • It chelate metalloproteinas.

7. FAVIPRAVIR:
   • Antiviral drug
   • Inhibit enzyme called RNA Polymerase of SARS-COV2

4. HYDROCHLOROQUINE:
   • Antimalarial drug it affects the virus entry and exit from the host cell
   • It is given with combination to other antibiotic and antiviral drug.
8. FAMCICLOVIR:
   - Antiviral drug
   - Preventing viruses from multiplying
   - Reduces the severity of infection.

9. zinc:
   - Keeps immune system healthy.
   - Maintain ability to taste and smell.

10. b-fORMOTEROL/BUSESONIDE:
    - Relieves symptoms of asthma and copd.
    - Makes breathing easier.
    - Inhibits release of certain chemical,
    - That causes inflammation and swelling.
    - Reduces the muscle in airway.

11. IVERMECTIN:
    - Anti-parasite drug.
    - Inhibit SARS-CoV-2 replication in vitro.

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**TREATMENT**
(for Home isolated Asymptomatic patient)

**TREATMENT IN MILD CASES**

1. People who develop severe symptoms are need to be hospitalized.
2. Treatment focused on supporting individual so that their body fights against infection.
3. And to reduce patient symptoms.
4. People who have troubled in breathing may be given supplemental oxygen.

**SUPPORTIVE TREATMENT OF CORONAVIRUS**

**OXYGEN THERAPY IN MODERATE AND SEVERE CASES**

1. People who develop severe symptoms are need to be hospitalized.
2. Treatment focused on supporting individual so that their body fights against infection.
3. And to reduce patient symptoms.
4. People who have troubled in breathing may be given supplemental oxygen.
5. If oxygen alone is insufficient to help the patient condition then mechanical ventilation is given.

6. And in some cases intubation and oxygenate the patient by conventional ventilators.

5. CORONA VACCINE:
- COVAX IN, India indigenous covid-19 vaccine by Bharat biotech is developed in collaboration with Indian council of medical research.
- National regulatory authorities approved six vaccine:
  - Two RNA vaccine TOZINAMERAN and PEPFIZER BIONTECH MRNA-1273 from moderna.
  - 2 conventional inactivated vaccine BIBP CORV from sinopharm and CORONA VAC from sinovac and 2viral vector vaccine GAM COVID -VAC from gamaliya research institute and AZD1222 from university of Oxford.

COMPLICATION
- Respiratory system involvement:
  The predominant manifestation of COVID-19 is the interstitial and alveolar pneumonia.
  The CT scan of COVID-19 patients demonstrates a various pattern, ranging from single ground-glass opacity (GGO) to bilateral diffuse heterogeneous consolidation with air bronchogram and bronchiectasis, the 'white lung.'
- Cardiovascular involvement:
- Kidney involvement:
- Ocular involvement:
  SARS-CoV has been detected from the tear samples in the previous reports. Evidence suggests possible conjunctivitis related to SARS-CoV via inoculation of droplets to the eyes, lacrimal infection and virus migration from the nasolacrimal duct.
- Hematologic involvement:
  Thrombocytopenia, damage to the spleen and lymph nodes (congestion, hemorrhage, atrophy, depletion of lymphoid follicles) has also been observed. And venous thromboembolism.
- Coagulopathy:
  Thrombosis in pulmonary vessels in severe COVID-19.
- Electrolyte imbalance:
  Urinary potassium loss, severe diarrhea and/or vomiting, extrarenal hypokalemia.
- Liver involvement:
  Elevation of liver enzymes is frequently transient in mild cases of the disease, significant elevation of liver enzymes is observed in severe COVID-19.
- Endocrine involvement:
  Diabetic ketoacidosis, hyperglycemia.
- Obstetric & gynecologic complications:
  Limited evidence suggests that vertical transmission of COVID-19 during late pregnancy is possible. Increased oxygen demand and physiologic anemia during pregnancy are the potential factors that could exacerbate the severity of COVID-19. COVID-19 probably increases the risk of miscarriage and intrauterine growth restriction.
- GI-tract involvement:
  Diarrhea, abdominal pain and vomiting.
- Neuromuscular involvement:
  Diastatic headache, impaired consciousness, cerebrovascular disease, ataxia and epilepsy. Guillain Barre syndrome is another neurologic complication proceed by COVID-19. Progressive weakness of extremities, paraesthesia, facial diplegia, ataxia, and bulbar weakness occurred 5-14 days after the infection.
- Central nervous system involvement:
  Acute cerebrovascular diseases and encephalopathy.
- Skin involvement:
  Several skin conditions, including erythema, papules, maceration and scaling accompanied with symptoms of burning, itching and oozing.
COMPLICATION OF CORONA VIRUS

INFECTION CONTROL IN DENTAL SETTING

Risk of Nosocomial Infection in Dental Settings

Dental patients who cough, sneeze, or receive dental treatment including the use of a high-speed handpiece or ultrasonic instruments make their secretions, saliva, or blood aerosolize to the surrounding and spreads the infection especially when patients are in the incubation period, are unaware they are infected, or choose to conceal their infection.

Effective Infection Control Protocols

Hand hygiene has been considered the most critical measure for reducing the risk of transmitting microorganisms to patients. The use of personal protective equipment, including masks, gloves, gowns, and goggles or face shields, is recommended to protect skin and mucosa from (potentially) infected blood or secretions.

PPE KIT (PERSONAL PROTECTIVE EQUIPMENT)
**AEROASYMPTOMATIC TRANSMISSION**

_Risk factors:_
- Household contacts
- Person to person
- Healthcare workers
- Public setting
- Air vehicle

**CONTROL MEASURES**

- **Hygiene:**
  - Standard precautions
  - Personal protective equipment
  - Decontamination
  - Disinfection

- **Disinfectant:**
  - Alcohol-based hand sanitizers
  - Disinfectant wipes
  - Disinfectant sprays

- **Infection control procedures:**

- **Universal precautions:**
  - Standard precautions
  - Personal protective equipment

- **High-risk practices:**
  - Isolation of patients
  - Contact precautions
  - Airborne precautions

- **Other measures:**
  - Regular handwashing
  - Social distancing
  - Vaccine development
COVID-19 PATIENT PRESENTING A WHITE PLAQUE ON TONGUE DORSUM, A NODULE LOCATED IN LOWER LIP AND UNCLEANED MUCOSA SUGGESTING A REACTIVE LESION (FIBROMA).

PATIENT PRESENTING ATROPHIC AREAS SUGGESTING GEOGRAPHIC TONGUE ASSOCIATED WITH FISSURED TONGUE.

PATIENT SHOWING ATROPHIC AREAS MODERATE GEOGRAPHIC TONGUE, SLIGHTLY ERYTHEMATOUS AREA IN RIGHT PAUTINE TONGUE REGION.

SALIVA AS POTENTIAL DIAGNOSIS IN CORONA VIRUS- RECENT

• Some virus strains have been detected in saliva as long as 29 days after infection, indicating that non-invasive platforms to rapidly differentiate the biomarkers using saliva could enhance disease detection.

• There is a minimum of three different pathways for COVID-19 to present in saliva: firstly, from COVID-19 in the lower and upper respiratory tract that enters the oral cavity together with the liquid droplets frequently exchanged by these organs.

• Secondly, COVID-19 present in the blood can access the mouth via crevicular fluid, an oral cavity-specific exudate that contains local proteins derived from extracellular matrix and serum-derived proteins.

• Finally, another way for COVID-19 to occur in the oral cavity is by major and minor salivary gland infection, with subsequent release of particles in saliva via salivary duct.

• Further studies are needed to investigate the potential diagnostic of COVID-19 in saliva.

THANK YOU