Christine E. Niekrash
Elie M. Ferneini
Michael T. Goupil
Editors

Dental Science for the Medical Professional

An Evidence-Based Approach

Springer

Christine E. Niekrash • Elie M. Ferneini
Michael T. Goupil
Editors

Dental Science for the Medical Professional

An Evidence-Based Approach

Springer

Editors
Christine E. Niekrash
Quinnipiac University
Frank H Netter MD School of Medicine
North Haven, CT, USA

Elie M. Ferneini
Division of Oral and Maxillofacial Surgery
University of Connecticut
Farmington, CT, USA

Michael T. Goupil
Surgery
Consultant in Oral and Maxillofacial
Carmel, IN, USA

ISBN 978-3-031-38566-7 ISBN 978-3-031-38567-4 (eBook)
https://doi.org/10.1007/978-3-031-38567-4

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Paper in this product is recyclable.

Foreword

Traditionally, the education and training of physicians and other medical professions have paid little attention to (or even ignored) diseases of the oral cavity and trauma involving this region and the surrounding tissues. Although these issues are the primary concern of the dental profession, it is extremely common for many patients to present first to medical professionals, especially in urgent care settings. This book provides clear and concise information for medical professionals to help them recognize and diagnose these oral and dental issues, to provide initial treatment and stabilization as needed, and to refer patients for definitive care.

As people are living longer and retaining their teeth, the need for better collaboration between dental and medical care providers has increased dramatically to provide optimal healthcare for the whole patient. This book also explores the role of oral health in overall general health and vice versa. Every medical professional will benefit from this book.

Frank H. Netter MD School of Medicine, Quinnipiac University
North Haven, CT, USA

Bruce M. Koeppen

Introduction

The earliest description of the healing arts was all inclusive without a defined separation between dentistry and medicine. One of the oldest works on Medicine, the Ebers Papyrus, describes disease and treatments of the oral cavity. A thousand years later, the historian Herodotus (500–424 BC) described the early specialization of medicine "Thus, Egypt is full of doctors: those for the eyes; those for the head; some for the teeth…" [1]. Over the centuries dentistry evolved away from being a specialty within medicine to become a stand-alone profession.

Fortunately, during the end of the last century more attention has been placed on the important role oral health plays in overall general health. In addition, people are living longer, and this increasingly geriatric population are retaining their teeth. The result is more patients presenting to their dentist with significant polypharmacy and complex medical problems. The resultant need for increased medical knowledge for dental practitioners formed the basis of the establishment of the University of Connecticut Schools of Medicine and Dental Medicine. Similarly, other institutions like Harvard and Columbia Universities with established medical and dental schools developed a combined basic medical science curriculum. Students in both scenarios spend their first 2 years in a shared curriculum learning medicine together.

Dental students receive a variable amount of medical education and in most cases probably still not enough. However, dental oral health education is relatively nonexistent in medical education. The purpose of this book is to help correct this deficiency. In an environment of ever-decreasing healthcare resources, dental and medical providers need to increase their collaboration for the attainment of good health for all.

The majority of this text is written by dentists with a special interest or expertise in their assigned chapter and all have a close relationship with their medical colleagues. Part I focuses on Head and Neck Anatomy with an emphasis on the teeth and their supporting structures. Part II deals with Dental Infections and their potential life-threatening spread. A common question is whether antibiotic prophylaxis is required for dental procedures, and this is addressed in Chap. 15. Dental caries is the most common infection worldwide and this section includes a comprehensive review along with prevention strategies. Part III covers Perioral Pathology with chapters detailing both benign and malignant pathology. Chapter 19 is valuable for both our medical and dental colleagues. Part IV reviews Head and Neck Trauma. This section most likely will be useful to urgent care providers. Chapter 21 is applicable to all medical care providers, particularly those treating pediatric patients. Finally, Part V covers a number of topics that may be useful in initiating or answering consultations between dental care providers and physicians and associated medical health providers. Anxiety Management and Pain Management are issues that clearly concern all healthcare providers. Additionally, the Oral Management of Chemotherapy Patients is a complex problem for all medical and dental providers.

It is the editors' intent that this book augments the dental education of our medical colleagues. The hoped-for end result will be effective and efficient overall healthcare for the patients we serve.

Reference

1. Guerini V. A history of dentistry from the most ancient times until the end of the eighteenth century. Philadelphia: Lea & Febiger; 1909.

Carmel, IN, USA Michael T. Goupil

Contents

Part III Perioral Pathology

Part IV Head and Neck Trauma

Part V Other

Part I

Head and Neck Anatomy

Christine E. Niekrash

Examination of the Head and Neck

1

Keyur Naik and Elie M. Ferneini

Introduction

The head and neck examination is a fundamental part of the standard physical examination. However, unlike other parts of the body, the head and neck region is unique in its complexity and the way in which the examination is performed. A comprehensive head and neck examination requires an understanding of the relevant anatomy and clinical experience in order to be performed correctly. While many medical providers do not perform routine head and neck exams in their practice, a sequential approach can help prevent a missed diagnosis. Dentists and dental specialists frequently complete head and neck exams as a routine part of their practice. While most of the exam is performed either visually or manually, specialized instrumentation is necessary to perform a complete examination and will be reviewed in this chapter. Most clinicians have some but not all of the equipment needed for a complete exam. As such, appropriate referrals may be necessary to perform a complete head and neck examination.

While this chapter will focus on the various components of the head and neck examination, obtaining a history remains vitally important. The head and neck exam when completed in its entirety is lengthy and can be inefficient when attempting to narrow a differential diagnosis. As such, the clinical history provided by the patient will allow the clinician to focus on the individual aspects of the exam that are most pertinent. Pieces of information elicited during the patient interview will guide a focused exam.

Given the complexity of the head and neck region, an individual clinician cannot hope to examine, diagnose, and treat the broad spectrum of what may be encountered during an exam. Each of the systems discussed in this chapter could easily occupy an entire text. However, the goal of this chapter is to give the practitioner a systematic approach to the head and neck exam, an appreciation for basic examination maneuvers that can be completed in most medical or dental offices, and information about how to make the most appropriate referrals in order to ensure the best outcomes for their patient based on their findings.

The Scalp, Face, and Neck

The physical examination demands that clinicians utilize their ability to inspect and palpate parts of the body in order to distinguish normal from abnormal. The head and neck exam is no different. The head and neck examination begins with inspection of the face, scalp, and neck. While humans are not perfectly symmetrical, the head and neck should be grossly symmetric. Significant asymmetries of the head and neck should be noted. Large tumors, infections, traumatic injuries, strokes, and other neurologic disorders may be responsible for such irregularities.

An examination of facial sensation and movement can also help a clinician ascertain asymmetries. The trigeminal nerve provides sensation to the face. The face can be roughly divided into horizontal thirds. Each third is supplied by a different branch of the trigeminal nerve: the ophthalmic branch (V1), the maxillary branch (V2), and the mandibular branch (V3) [1]. Disturbances ~~is~~ in facial sensation can indicate either central or peripheral nervous system conditions, and the pattern of neurosensory loss should be noted during the clinical exam. The facial nerve innervates the muscles of facial expression. Asymmetric movement of the face can be caused by a number of acute or chronic neurologic conditions. The facial nerve has five branches: temporal, zygomatic, buccal, marginal mandibular, and cervical. Asking a patient to raise their eyebrows (temporal), closing their eyes tightly (zygomatic), puffing out their cheeks (buccal), smiling (buccal), and frowning (marginal mandibular) can be

K. Naik (✉)
Department of Oral and Maxillofacial Surgery, New York University/Bellevue Hospital Center, New York, NY, USA
e-mail: keyur.naik@nyulangone.org

E. M. Ferneini
Division of Oral and Maxillofacial Surgery, University of Connecticut, Farmington, CT, USA

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_1

used to assess the different branches [2]. Neurosensory or motor deficits should be characterized as part of the head and neck examination and referrals should be made to the most appropriate specialist based on the most likely etiology.

Next, the quality of the skin of the scalp, face, and neck should be evaluated. The skin is a complex and dynamic organ that serves as a barrier between the body and the surrounding environment. It can be divided into layers: the overlying epidermis, dermis, and subcutaneous tissue. Skin has visible, topographical, and mechanical qualities. Erythema, pigmentation, dullness, and shine are all visible characteristics that can be used to describe facial skin. Topographical features include roughness, and fine and course lines. Mechanical qualities include elasticity, firmness, and thickness [3]. Individual skin lesions are also important to evaluate as part of the head and neck examination. Unlike other parts of the body, the face and neck are typically not covered by clothing and are more commonly exposed to ultraviolet (UV) radiation. Prolonged exposure to UV radiation is a risk factor for all three main types of skin cancer: basal cell carcinoma, squamous cell carcinoma, and melanoma. Premalignant lesions such as actinic keratosis can also appear on the skin [4]. Referral to a clinician trained in head and neck oncologic surgery or a dermatologist is warranted for evaluation, biopsy, and further treatment of any dermatologic lesions of the head and neck.

The neck is a complex structure that connects the head to the rest of the body. Evaluation of the neck requires inspection and palpation of the structures that it houses. The thyroid is a midline gland in the neck that plays multiple roles in homeostasis. The gland can be identified on exam below the cricoid cartilage at the level of the first two tracheal rings. The isthmus of the thyroid overlies these tracheal rings. The lateral lobes of the thyroid lay adjacent to the tracheal rings bilaterally and are connected by the isthmus. In a normal thyroid exam, palpation of the lobes and isthmus should reveal a soft and symmetric gland. Diffuse enlargement, nodes, and tenderness require further investigation. Ultrasound is typically the first line imaging modality used to evaluate the thyroid along with thyroid function labs [5].

The neck also houses a network of lymphatics that drains the head and adjacent neck structures. The lymphatic nodes in the neck are bilaterally divided into six levels based on their location [6]. The neck should be palpated for enlarged nodes. The level, size, and mobility of the neck nodes should be appreciated. Enlarged neck nodes are commonly part of a reaction to inflammatory or infectious processes in the head and neck. However, malignancies can also metastasize to the cervical lymph nodes and should be ruled out. Enlarged lymph nodes can be characterized by ultrasound. If malignancy is known or suspected, a computed tomography (CT) image is frequently obtained in order to characterize the primary lesion as well as to assess the extent of local metastasis in the neck [7]. Referral to a surgeon trained in head and neck oncologic surgery is recommended.

The Intraoral Exam

Dentists and dental specialists routinely perform intraoral exams as part of their daily practice. The intraoral exam requires an evaluation of both the hard and soft tissues found within the oral cavity. The exam requires an evaluation of the dentition (see Chap. 2). The adult dentition consists of 32 teeth, including 2 central incisors, 2 lateral incisors, 2 canines, 4 premolars, and 6 molars on both the maxilla and the mandible. The primary, or deciduous, dentition consists of 20 teeth, including 2 central incisors, 2 lateral incisors, 2 canines, and 4 molars in the maxillary and mandibular arches. Between the ages of 6 and 12 years, the primary dentition is lost, and the permanent dentition begins to erupt. The pattern of visible teeth during this transition period is termed mixed dentition [8]. Disruptions in the eruption of teeth should be assessed by a multidisciplinary dental team. Pediatric dentists frequently evaluate the development of primary teeth and the transition to the adult dentition. Orthodontists treat malocclusion that can be a product of irregular eruption of the permanent dentition as well as the underlying skeletal relationship between the maxilla and mandible. Evaluation of irregularities in the pattern of dental development should be referred to the appropriate dental specialist in order to improve a patient's long-term function.

Along with tooth development, the dentition should also be evaluated for pathology. Caries, or tooth decay, is common and can range in its appearance (see Chap. 6). Caries in the early stage can appear as chalky white spots. These lesions typically do not cause symptoms and may be difficult to evaluate even with the utility of dental imaging. Clinical examination remains the best way to detect early caries. Dental excavators are used to evaluate the enamel surface for evidence of demineralization. As caries progress, the enamel and underlying dentin is destroyed. Eventually a cavitation in the tooth can appear. The caries can reach the dental pulp, which houses the blood supply and nerve endings of the tooth. Reversible pulpitis refers to inflammation of the dental pulp that can be reversed with treatment of the caries. Patients typically experience bursts of cold sensitivity that do not linger. Irreversible pulpitis refers to inflammation that is incapable of healing and requires treatment [9]. Patients will experience spontaneous pain or pain that lingers with exposure to cold. Pulpitis that goes untreated can result in necrosis of the pulpal tissue. Pulpal necrosis can result in the spread of disease and inflammation to the apical tissues and result in abscesses at the apex of the tooth. Apical periodontitis presents as tenderness or percussion on exam [9]. Apical abscesses are an inflammatory reaction to pulpal infection

and necrosis. Such abscesses can be defined as acute or chronic. Acute apical abscesses present as spontaneous pain and exquisite tenderness on exam. Purulent discharge and soft tissue swelling may be identified as well. Chronic apical abscesses are insidious in development and present with little or no symptoms. Purulent discharge from the apical tissues may occur [9]. Pathology of the dental surface such as caries can be evaluated by a general dentist. If there is evidence of inflammation of infection of the pulpal or apical tissues, a referral to an endodontist is appropriate to determine the etiology and correct treatment.

In addition to the dentition, the soft tissue structures of the oral cavity should be evaluated during the intraoral exam (see Chaps. 16–19). Inspection of the oropharynx is performed by placing a tongue depressor on the dorsal tongue and evaluating the posterior pharyngeal wall, the tonsils, tonsillar crypts, and anterior and posterior pillars. Signs of inflammation or infection, asymmetric enlargements, or ulcerations should be noted and further characterized, typically with imaging. There has been a steady increase in the incidence of human papillomavirus (HPV)-related oral cancers, many of which can appear along the pharyngeal walls and tonsils [10]. The soft palate and uvula should also be inspected. The soft palate and uvula should move loosely and symmetrically as a patient phonates. Anteriorly, the hard palate should be both inspected and palpated. The hard palate has a rough, corrugated structure due to the palatal rugae. A typical abnormal finding is the presence of the torus palatinus, which is an exostosis of bone in the midline of the hard palate. This torus can take a range of shapes and sizes but typically becomes a concern only when a patient wears a maxillary dental prosthetic or denture as it can hinder correct seating of the appliance [11].

The buccal and labial mucosa lines the cheek and inner aspect of the lips. The mucosa should be inspected and palpated while being stretched away from the teeth. This allows for proper evaluation of the maxillary and mandibular vestibules. Normal mucosal tissue should appear pink. The parotid gland drains into the oral cavity through Stenson's duct. Stenson's duct is found in the buccal mucosa adjacent to the maxillary second molar. Compression of the parotid gland and cheek extraorally should force drainage of saliva through the duct. The duct should be assessed for patency [12]. Pathology of the intraoral mucosa is diverse. In patients with a significant smoking or drinking history, the rest of the buccal mucosa should be evaluated for evidence of leukoplakic, erythroplakic, and ulcerated lesions that can be evidence of malignant or premalignant lesions. These lesions should be better characterized with biopsy [13].

Like other areas of the mouth, the floor of mouth should be thoroughly inspected and palpated as part of the intraoral examination. Wharton's duct drains salivary fluid from the submandibular glands into the floor of mouth at the sublingual caruncle. The duct should be evaluated for patency as saliva spontaneously exits through the duct. The lingual frenum is a muscle attachment from the floor of mouth to the tongue. The sublingual caruncles are found on either side of the frenum. The floor of mouth should be flat and soft. A firm mass or elevation of the floor of mouth is indicative of pathology. Floor of mouth elevation may also be appreciated as deviation of the tongue [14].

The tongue is a muscular structure in the midline of the oral cavity, which aids with eating, swallowing, taste, and speech. The dorsal surface describes the surface of the tongue facing the palate. The lingual papillae on the dorsal surface of the tongue serve to increase the surface area of the tongue and allow for taste and manipulation of food. The ventral surface describes the side of the tongue adjacent to the floor of mouth. The lateral surfaces of the tongue face toward the cheeks. Description of tongue pathology should include the surface of the tongue that is affected. The tongue should be manipulated in order to evaluate the multiple surfaces of the tongue. Like the buccal mucosa, leukoplakic, erythroplakic, or ulcerated lesions can be evidence of malignant or premalignant lesions. These lesions typically necessitate biopsy [13].

The temporomandibular joint (TMJ) is a diarthrodial joint. It is composed of the mandibular condyle, a glenoid fossa in which the condyle sits while the mandible is at rest, and an articular disk that translates with the condyle when the mandible is in function. The examination of the temporomandibular joint starts with inspection of the preauricular area. Any erythema, swelling, or deformity should be noted. Next, the joint should be palpated while in function. The condylar head should be felt first rotating then translating forward over the articular eminence in a smooth motion. Irregularities in the motion of the condyle such as deviation or limited opening of the mouth can be signs of temporomandibular disorder (TMD). Adults should reach a maximal incisal opening of greater than 35 mm. Signs of crepitus, grinding, clicking, or popping may be both felt and sometimes heard in patients who are experiencing internal derangement of the joint. The Wilkes classification is used to stage joint dysfunction. The classification system relies on clinical features and radiographic and surgical findings to stage disruption within the joint space. Oral and maxillofacial surgeons use the Wilkes classification to aid in nonsurgical or surgical treatment planning in patients with an internal joint disorder [15]. The joint is also affected by the pull of the muscles of mastication, including the masseter, temporalis, and pterygoid muscles. Palpation of the masticatory and cervical muscles may elicit tenderness in those with myofascial pain. The masseter can be felt extending from the zygomatic arch to the angle of the mandible. The temporalis can be assessed both in the temporal fossa and intraorally along the ramus. The lateral pterygoid can be palpated along the

medial aspect of the mandible. Tenderness of these muscles may point toward myofascial causes of TMD [16]. The joint can be assessed with a variety of imaging modalities. A panoramic radiograph can be obtained by most dentists and demonstrates the maxilla and the mandible in a two-dimensional view. Though limited in its utility, bony changes in the mandibular condyle can be appreciated in a panoramic radiograph. Bony and soft tissue pathology associated with the TMJ can be further characterized in CT imaging. However, CT imaging is limited in its rendition of the articular disk and intracapsular tissues. Magnetic resonance imaging (MRI) is the most sensitive imaging for evaluating internal derangement of the TMJ. MRIs can also be obtained while the patient is in function to assess the position of the articular disk and intracapsular tissues while the patient is opening and closing their mandible [17]. Dysfunction of the TMJ is evaluated and treated by orofacial pain specialists and oral and maxillofacial surgeons. Pathologies associated with the joint will be discussed later in this text.

The Eye and Orbit

The eye is an intricate structure that allows for vision. Disturbances to the eye, the orbital walls, and the structures within those walls can be detrimental to our ability to see. Ophthalmologists are the specialists who most frequently evaluate the globe itself and the contents of the orbit. While ophthalmologists utilize specialized equipment to perform a detailed exam, most clinicians can perform examinations that can quickly evaluate the integrity of the eye and orbit in order to make certain diagnoses and provide appropriate referrals when necessary.

Examination of the eyes typically begins with a test of visual acuity. Diagnosis of various ocular pathologies requires special instrumentation including a slit-lamp to examine the iris, cornea, and conjunctiva and tonometry to test intraocular pressures. However, evaluating visual acuity and diagnosing gross visual disturbances can be done with a Snellen chart, which is widely available. Snellen charts come in a variety of sizes, but a standard chart is meant to be used with the patient approximately 20 ft away from the chart. The patient should remove any corrective lenses that they are using before starting the test. The eyes are tested individually. The patient is instructed to read out the smallest line of the letters that they can correctly identify. If the patient is able to identify letters that "most" subjects can identify at a distance of 20 ft, the patient is considered to have 20/20 vision. However, if the patient is only able to identify a line of letters that most subjects can see at 100 ft, they are considered to have 20/100 vision. Decreased visual acuity is most commonly due to myopia, or near-sightedness, which is chronic and progressive in nature [18]. However, acute changes in a patient's exam demand an urgent consultation to an ophthalmologist as some conditions can leave a patient with complete or partial vision loss if not acted on in a time-sensitive manner.

The movement of the eye is controlled by several extraocular muscles. Abnormal movement of the globe most commonly indicates an issue with the nerves that innervate the extraocular muscles or the muscles themselves. The majority of the extraocular muscles are supplied by the oculomotor nerve, but two muscles are unique in their innervation. The lateral rectus is controlled by the abducens, or sixth, cranial nerve and serves to abduct the eye. The superior oblique is innervated by the trochlear, or fourth, cranial nerve and serves to abduct, depress, and internally rotate the eye. Evaluating extraocular movement is simple and requires no special equipment. The examiner should position their finger approximately 3 ft from the patient's face and move their finger slowly in an H-shaped pattern. Doing so will test the integrity of all of the extraocular muscles. Inability to move the eyes may also present as diplopia, or double vision. Asking the patient whether they experienced diplopia at any point during the exam may also clue the examiner to limitations in eye movement. Fractures of the orbital floor can lead to restrictions in upper eye movement and diplopia. The mechanism is typically entrapment of the inferior rectus muscle and is a surgical emergency. The types of diplopia, monocular versus binocular, should be distinguished during the exam if present. Binocular diplopia is present when both eyes are open and resolves when one is closed. It is caused by misalignment of the eyes, or strabismus. Neurological conditions such as multiple sclerosis or myasthenia gravis can cause binocular diplopia. On the other hand, monocular diplopia is double vision experienced when only one eye is open. Refractive error or cataracts are common causes for monocular diplopia [19].

There are a number of reflexes that are associated with protective or regulatory functions of the eye. While many of them require a deeper understanding of ophthalmology and neurology, there are two that should be part of an initial head and neck examination. The Pupillary Light Reflex is an autonomic reflex that constricts the pupil in response to light. The afferent limb is the optic nerve. Signals are transmitted to the Edinger-Westphal nuclei in the midbrain bilaterally. The efferent limb is via sympathetic preganglionic fibers that travel on the oculomotor nerve and cause constriction of the bilateral pupils by their effect on the iris. The reflex can test for relative afferent pupillary defect (RAPD) in which light is shined into the affected eye, but constriction is not seen in either eye. However, when light is shined in the unaffected eye, the pupils constrict bilaterally [20]. The Corneal Reflex is a protective reflex that causes both eyes to blink in response to tactile stimulation of the cornea. The afferent limb is the trigeminal nerve. The afferent fibers connect to the spinal

trigeminal nucleus. Fibers from the trigeminal nucleus communicate with the bilateral facial nuclei. From the facial nuclei, the facial nerve stimulates the orbicularis oculi muscles to close the eyelids. The reflex is useful for testing damage to the ophthalmic branch (V1) of the trigeminal nerve or when examining brainstem reflexes in patients who are obtunded or comatose [21].

The morphology of the orbit can be altered by a number of pathologic processes and can be discerned on clinical examination. For simplicity, the orbit is frequently described as a four-walled pyramid or cone. However, the orbit is made up of seven bones. These include the sphenoid, frontal, zygomatic, ethmoid, lacrimal, maxilla, and palatine bones [22]. The volume of the orbit is approximately 30 mL. Acute changes in the volume of the orbit are typically the result of orbital trauma and prompt diagnosis is crucial. Enophthalmos describes posterior displacement of the eye. Fractures of the orbital walls, typically the orbital floor, are most commonly responsible for enophthalmos in an acute setting. Proptosis, or exophthalmos, describes protrusion of the eye. The differential diagnosis of proptosis is broad. Proptosis should be distinguished as either unilateral or bilateral and the time course should be noted [22].

The Auditory System

For the purposes of the clinical exam, the auditory system can be broken up into three parts: the external, middle, and inner ear. The external ear is made of two principle structures, the auricle and the external auditory canal (EAC). The external ear extends from the pinna to the lateral surface of the tympanic membrane. The purpose of the auricle is to channel sound toward the tympanic membrane and inner portions of the ear. The ears should first be inspected for asymmetry. Then, turning attention to either ear, the auricle should be inspected and palpated for any gross abnormalities. The pinna should be inspected for erythema, edema, masses, surgical or traumatic scars, or malformation. Tenderness of the tragus may indicate otitis externa. The postauricular area should be examined for erythema, tenderness, or edema, which may cause loss of the postauricular sulcus, a potential sign of mastoiditis. The external auditory canal (EAC) should be inspected with an otoscope. The EAC is a part cartilaginous and part osseous structure that leads from the auricle to the tympanic membrane. For the purposes of identifying the two parts of the EAC, the lateral cartilaginous portion is typically hair-bearing and the skin in the area contains sebaceous glands. The medial osseous portion of the EAC is not hair-bearing. The pinna should be retracted in a posterior and superior direction. This motion helps straighten the EAC and facilitate visualization with the otoscope. The EAC should be inspected for edema, purulence, wax, and foreign bodies. The tympanic membrane should be inspected for perforation, retraction, or fluid levels behind the membrane. The mobility of the tympanic membrane can be assessed with pneumatic otoscopy. A bulging tympanic membrane or fluid behind the membrane should raise suspicion of acute otitis media [23].

The middle ear is composed of the internal layer of the tympanic membrane, three ossicles (the malleus, incus, stapes), and the opening to the Eustachian tube. The function of the middle ear is to transmit sound signals from the tympanic membrane to the inner ear via the ossicles. Tympanometry can be used to assess middle ear function; however, it requires instrumentation not found in the offices of most clinicians. Tuning fork tests, specifically the Weber and Rinne tests, help differentiate between conductive hearing loss and sensorineural hearing loss. Conductive hearing loss is typically a product of middle ear disturbances that limit sound conducting from the tympanic membrane to the inner ear [24]. However, the Weber test is performed by striking the tuning fork and placing it on the patient's forehead. In patients with normal hearing or symmetric hearing loss, the sound is heard equally on both sides. In sensorineural hearing loss, the sound is loudest in the normal ear. In conductive hearing loss, the sound is loudest in the damaged ear. The Rinne test is performed by striking the tuning fork and placing it close to the EAC. After a few seconds, the fork should be placed on the mastoid bone. If the tuning fork is louder in the air than on the bone, then hearing is either normal or there is sensorineural hearing loss. If bone conduction is louder, it is a sign of conductive hearing loss [25].

The inner ear is made up of the cochlea and the vestibular system. The cochlea is responsible for converting vibrating sound signals produced by the ossicles into neural signals. The vestibular system is responsible for detecting changes in position of the head in order to help maintain balance. The inner ear cannot be examined clinically, but suspicion of inner ear dysfunction should prompt imaging studies to evaluate for pathology. Sensorineural hearing loss most commonly occurs due to damage to the inner ear or the vestibulocochlear nerve. Vertigo is commonly due to disruptions of the vestibular system [26].

The Nose and Sinuses

The nose and sinuses are unique in that much of the clinical examination cannot be completed without specific instrumentation. However, an understanding of the pertinent anatomy is crucial for clinicians who are examining the head and neck. The external nose is divided into thirds: the bony vault (upper third), the upper cartilaginous vault (middle third), and laginous vault (lower third). Any skin changes can be appreciated through inspection. Like other parts of the face,

the nose is frequently exposed to sunlight and can be a site of skin cancers such as basal cell or squamous cell carcinoma among other malignant and premalignant lesions. Frank deformities or deviation of the nose should be noted as they can indicate either acute or chronic fractures of the nose.

Internally, the nares are divided by the nasal septum. The septum is composed of multiple structures including the septal cartilage, the perpendicular plate of the ethmoid, and the vomer. Inspection of the internal nose can be performed by externally illuminating the nares. Evaluation of the nasal vestibule, nasal septum, and inferior turbinate can be performed with the aid of a nasal speculum. Breathing is directly affected by the morphology of the nasal valves. The nasal valves are the areas of the nares with the greatest airflow resistance. The internal valve is formed between the septum and lateral nasal wall and is typically between 10° and 15°. The Cottle maneuver is used to diagnose disorders of the internal valve. The test is performed by gently pulling the cheek laterally in order to open the internal valve. Subjective improvement in passage of the air is a positive test and indicates obstruction at the level of the internal valve or valve collapse [27].

The blood supply to the nose is provided by branches of the ophthalmic, maxillary, and facial arteries. The nasal septum is supplied by a network of arteries that makes up Kiesselbach's plexus. The arteries that supply the septum are the anterior and posterior ethmoidal arteries, sphenopalatine artery, greater palatine artery, and the superior labial artery. The vast majority of nasal bleeds occur at the plexus. A nasal speculum can be used to evaluate the septum to determine if the plexus is the source of bleeding.

There are four paired paranasal sinuses: the maxillary sinuses, the sphenoid sinuses, ethmoid air cells, and the frontal sinuses. Each is lined with respiratory epithelium and all drain into the nasal cavity at different points. The only two that can be evaluated during the clinical examination are the maxillary and frontal sinuses, though the exam is limited. Dentists and dental specialists are most commonly concerned with the maxillary sinus. The maxillary sinus is lateral to the nasal cavity. The roots of the maxillary posterior dentition can be close to or directly abutting the floor of the maxillary sinus. Complications of maxillary molar extractions include oral–antral communications and sinusitis, which may require operative intervention to resolve. Facial tenderness on palpation over the maxillary sinuses may indicate underlying sinusitis. Endoscopy is necessary to view the maxillary sinuses and to better evaluate sinus pathology. CT imaging is also routinely used to evaluate the maxillary sinuses as clinical examination is challenging and limited [28].

The frontal sinus is located in the frontal bone as its name implies. The sinus is comprised of a thicker anterior table and a thinner posterior table that lies in front of the dura mater and brain. The two frontal sinuses are divided by a septum. The frontal sinus drains via the frontonasal duct that is found in the medial aspect of the sinus floor and opens into the middle meatus. Nasofrontal outflow obstruction can lead to frontal sinusitis and is most commonly caused by inflammatory polyps and synechia in those with previous frontal sinus surgery [29]. When repairing bony injuries to the frontal sinuses, the outflow tract must be carefully evaluated for patency. The clinical exam of the frontal sinuses is limited like the maxillary sinus exam. Palpation can elicit tenderness over the sinuses, but imaging is needed to construct a differential diagnosis if underlying pathology is suspected.

The sphenoid sinuses are located along the anterior cerebral fossa at the skull base. Importantly, the optic canal can be found in the posterior–superior aspect of this sinus. The lateral wall contains the canal of the second branch of the trigeminal nerve and Vidian nerve in the pterygoid canal [30]. The ethmoid sinuses or ethmoid air cells lie superior and lateral to the nasal cavity and lateral to the medial orbital wall. These sinuses are not amenable to clinical examination and imaging is needed to evaluate suspected pathology [31].

Conclusion

The head and neck examination is inherently complex. This chapter presents only the basic exam. An organized approach is crucial in order to avoid missed diagnoses. Conducting a full head and neck exam can be challenging and inefficient. Eliciting a full history of illness can help narrow the parts of the exam that need to be performed. Specialized instrumentation is necessary to perform certain parts of the exam and referrals may be needed to obtain a complete and thorough examination. The remainder of this text will explore the various pathologies associated with the head and neck structures discussed in this chapter.

References

1. Huff T, Daly DT. Neuroanatomy, cranial nerve 5 (trigeminal). In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2021.
2. Dulak D, Naqvi IA. Neuroanatomy, cranial nerve 7 (facial). In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2021.
3. Ambroisine L, Ezzedine K, Elfakir A, Gardinier S, Latreille J, Mauger E, Tenenhaus M, Guinot C. Relationships between visual and tactile features and biophysical parameters in human facial skin. Skin Res Technol. 2007;13(2):176–83. https://doi.org/10.1111/j.1600-0846.2007.00203.x.
4. Badash I, Shauly O, Lui CG, Gould DJ, Patel KM. Nonmelanoma facial skin cancer: a review of diagnostic strategies, surgical treatment, and reconstructive techniques. Clinical Med Insights Ear Nose Throat. 2019;12:1179550619865278. https://doi.org/10.1177/1179550619865278.

5. Indra R, Patil SS, Joshi R, Pai M, Kalantri SP. Accuracy of physical examination in the diagnosis of hypothyroidism: a cross-sectional, double-blind study. J Postgrad Med. 2004;50(1):7–11.
6. Wijers OB, Levendag PC, Tan T, van Dieren EB, van Sörnsen de Koste J, van der Est H, Senan S, Nowak PJ. A simplified CT-based definition of the lymph node levels in the node negative neck. Radiother Oncol. 1999;52(1):35–42. https://doi.org/10.1016/s0167-8140(99)00076-6.
7. Jones AS, Roland NJ, Field JK, Phillips DE. The level of cervical lymph node metastases: their prognostic relevance and relationship with head and neck squamous carcinoma primary sites. Clin Otolaryngol Allied Sci. 1994;19(1):63–9. https://doi.org/10.1111/j.1365-2273.1994.tb01150.x.
8. Hovorakova M, Lesot H, Peterka M, Peterkova R. Early development of the human dentition revisited. J Anat. 2018;233(2):135–45. https://doi.org/10.1111/joa.12825.
9. Levin LG, Law AS, Holland GR, Abbott PV, Roda RS. Identify and define all diagnostic terms for pulpal health and disease states. J Endod. 2009;35(12):1645–57. https://doi.org/10.1016/j.joen.2009.09.032.
10. Brodsky L. Modern assessment of tonsils and adenoids. Pediatr Clin N Am. 1989;36(6):1551–69. https://doi.org/10.1016/s0031-3955(16)36806-7.
11. Vaduganathan M, Marciscano AE, Olson KR. Torus palatinus. Proc (Bayl Univ Med Cent). 2014;27(3):259. https://doi.org/10.1080/08998280.2014.11929131.
12. Brown JE. Salivary gland diseases: presentation and investigation. Prim Dent J. 2018;7(1):48–57. https://doi.org/10.1308/205016818822610280.
13. Villa A, Villa C, Abati S. Oral cancer and oral erythroplakia: an update and implication for clinicians. Aust Dent J. 2011;56(3):253–6. https://doi.org/10.1111/j.1834-7819.2011.01337.x.
14. La'porte SJ, Juttla JK, Lingam RK. Imaging the floor of the mouth and the sublingual space. Radiographics. 2011;31(5):1215–30. https://doi.org/10.1148/rg.315105062.
15. Wilkes CH. Internal derangements of the temporomandibular joint. Pathological variations. Arch Otolaryngol Head Neck Surg. 1989;115(4):469–77. https://doi.org/10.1001/archotol.1989.01860280067019.
16. Moss RA, Garrett JC. Temporomandibular joint disfunction syndrome and myofascial pain dysfunction syndrome: a critical review. J Oral Rehabil. 1984;11(1):3–28. https://doi.org/10.1111/j.1365-2842.1984.tb00548.x.
17. Talmaceanu D, Lenghel LM, Bolog N, Hedesiu M, Buduru S, Rotar H, Baciut M, Baciut G. Imaging modalities for temporomandibular joint disorders: an update. Clujul Med. 2018;91(3):280–7. https://doi.org/10.15386/cjmed-970.
18. Tsui E, Patel P. Calculated decisions: visual acuity testing (Snellen chart). Emerg Med Pract. 2020;22(4):CD1–2.
19. Porter JD, Baker RS, Ragusa RJ, Brueckner JK. Extraocular muscles: basic and clinical aspects of structure and function. Surv Ophthalmol. 1995;39(6):451–84. https://doi.org/10.1016/s0039-6257(05)80055-4.
20. Kardon R. Pupillary light reflex. Curr Opin Ophthalmol. 1995;6(6):20–6. https://doi.org/10.1097/00055735-199512000-00004.
21. Peterson DC, Hamel RN. Corneal reflex. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2021.
22. Baujat B, Krastinova D, Bach CA, Coquille F, Chabolle F. Orbital morphology in exophthalmos and exorbitism. Plast Reconstr Surg. 2006;117(2):542–52. https://doi.org/10.1097/01.prs.0000200773.00268.56.
23. Cole LK. Otoscopic evaluation of the ear canal. Vet Clin North Am Small Anim Pract. 2004;34(2):397–410. https://doi.org/10.1016/j.cvsm.2003.10.004.
24. Margolis CZ, Porter B, Barnoon S, Pilpel D. Reliability of the middle ear examination. Isr J Med Sci. 1979;15(1):23–8.
25. Weber/rinne.
26. Smouha E. Inner ear disorders. NeuroRehabilitation. 2013;32(3):455–62. https://doi.org/10.3233/NRE-130868.
27. Fischer H, Gubisch W. Nasal valves--importance and surgical procedures. Facial Plast Surg. 2006;22(4):266–80. https://doi.org/10.1055/s-2006-954845.
28. Bell GW, Joshi BB, Macleod RI. Maxillary sinus disease: diagnosis and treatment. Br Dent J. 2011;210(3):113–8. https://doi.org/10.1038/sj.bdj.2011.47.
29. Rice DH. Chronic frontal sinus disease. Otolaryngol Clin N Am. 1993;26(4):619–22.
30. Fooanant S, Angkurawaranon S, Angkurawaranon C, Roongrotwattanasiri K, Chaiyasate S. Sphenoid sinus diseases: a review of 1,442 patients. Int J Otolaryngol. 2017;2017:9650910. https://doi.org/10.1155/2017/9650910.
31. Rózyło-Kalinowska I, Jedrzejewski G, Burdan F. Types of ethmoid sinus morphology on the basis of computed tomography examination. Folia Morphol (Warsz). 2003;62(4):407–9.

Primary and Secondary Dentition

2

Steven Chussid, Claudia Perez, Riley Reardon, Ryan Foree, Rachel Cubilla, Carly Galitz, and Neal Patel

Introduction

The American Academy of Pediatric Dentistry (AAPD) recommends an initial oral evaluation of a child within 6 months of their first erupted primary tooth and no later than 12 months of age. Issues may arise during tooth development and eruption, such as number of teeth, shape, discoloration, and enamel or dentin defects.

Primary Tooth Development

The development of primary teeth (Fig. 2.1) begins through a process called odontogenesis while the baby is still in utero. At birth, the baby has a full set of 20 developing primary teeth (10 in the maxilla, 10 in the mandible) that will begin to erupt into the oral cavity over the coming months. Primary teeth are often referred to as deciduous teeth, milk teeth, or baby teeth [2].

S. Chussid · R. Reardon · R. Foree
Department of Pediatric Dentistry, Columbia University, New York, NY, USA
e-mail: sc2023@cumc.columbia.edu; rr3195@cumc.columbia.edu; rf2669@cumc.columbia.edu

C. Perez (✉)
Department of Pediatric Dentistry, Montefiore Medical Center, Bronx, NY, USA
e-mail: clperez@montefiore.org

R. Cubilla
Division of Pediatric Dentistry, Northwell Health, Queens, NY, USA

C. Galitz
Department of Pediatric Dentistry, Nova Southeastern University, Fort Lauderdale, FL, USA

N. Patel
Department of Pediatric Dentistry, St. Barnabas Hospital, Bronx, NY, USA

Initiation The first stage of odontogenesis involves two layers of distinct tissue at around 5 weeks of gestation: the oral epithelium and the ectomesenchyme. These two layers serve as developmental signals for one another, and it is the ectomesenchyme that signals the surrounding oral epithelium to proliferate and thicken into the dental lamina [2].

Bud Stage At around 8 weeks, the dental lamina continues to proliferate and forms a dental placode. The ectomesenchyme surrounding the placode begins to condense [3].

Cap Stage The dental placode indents and begins to differentiate into distinct layers, forming the enamel organ. These layers include the outer enamel epithelium (OEE; the outer cell layer), the inner enamel epithelium (IEE; the inner cell layer), the stellate reticulum (the cells between the OEE and IEE), and the enamel knot (thickenings of the IEE that determine cusp location). The condensed mesenchyme differentiates into the dental papilla that borders the IEE and dental follicle that surrounds the enamel organ and dental papilla [3].

Bell Stage At 11 weeks, the cells of the IEE differentiate into ameloblasts while the cells of the dental papilla differentiate into odontoblasts. Simultaneously, the shape and size of the eventual crown is determined. The enamel organ continues to grow, and the invagination of the cap forms the cervical loop at the tip of the invagination where the OEE and IEE meet [3].

Apposition At 14 weeks, the odontoblasts begin to secrete a dentin matrix made of collagen, which then signals the ameloblasts to secrete an enamel matrix of amelogenin. The cervical loop elongates on each end to form Hertwig's epithelial root sheath (HERS). HERS stimulates odontoblasts to produce radicular dentin and begin formation of root dentin and subsequently the root itself. The stellate reticulum collapses and the OEE and IEE join completely. This combined

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_2

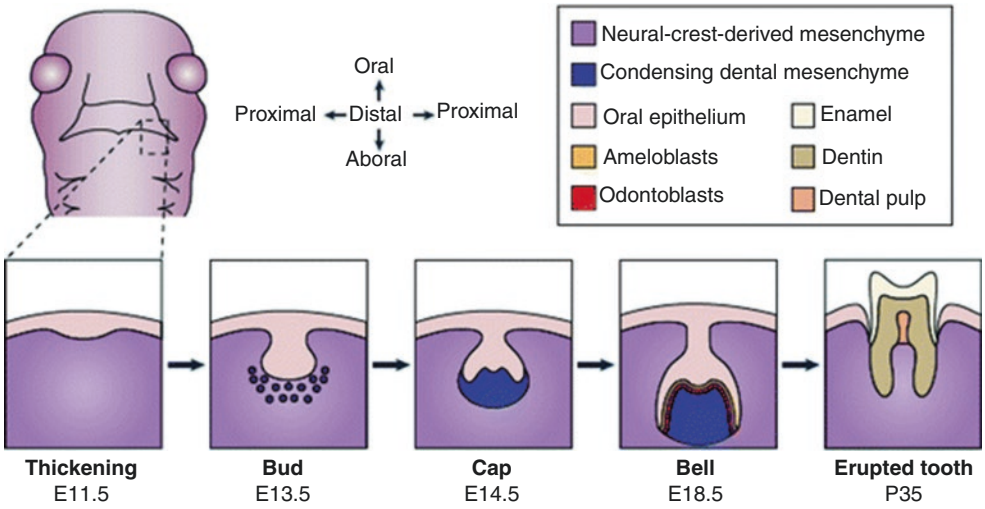


Fig. 2.1 Schematic detailing the stages of tooth development in embryonic days (E) [1]

layer later becomes junctional epithelium. The remnants of the dental papilla begin to form the pulp and the dental lamina disintegrates [1].

Maturation After 14 weeks and up to 2 years for primary teeth, the amelogenin and collagen matrices will start to calcify and form enamel and dentin, respectively. Calcification begins coronally and moves apically [1].

Primary Tooth Eruption

Tooth eruption is the process by which a tooth travels from the pre-eruptive position in the alveolar bone into the oral cavity through the mucosa [4]. This process transpires by means of multiple tissue changes, including apposition and resorption of the alveolar bone along with the development of the root and periodontal ligament [4]. Kjær [4] describes this process as multifactorial, influenced by "cell proliferation, increased vascularity, and increased bone formation around the teeth" in addition to "endocrine influence, vascular changes, and enzymatic degradation." Moreover, the dental follicle, which is a sac encompassing the developing tooth and its odontogenic organ, has demonstrated to have an essential role in tooth eruption as it is a source of cytokines, growth factors, and eicosanoids [5]. Before erupting, the reduced enamel epithelium surrounds the crown of a tooth. The enamel epithelium and the oral epithelium of the gingiva fuse as a tooth erupts and advances through the jaw. Subsequently, the fused epithelium breaks down when the tooth erupts into the oral cavity [5].

There are a total of 20 primary teeth—including 8 incisors, 4 canines, and 8 molars. Although the timing of tooth eruption varies widely, most children get their first deciduous tooth at approximately 6 months of age and their last between 24 and 30 months of age. Typically, the lower central incisors will be the first pair of teeth to erupt and the upper second molars will be the last pair of teeth to erupt (Fig. 2.2). Generally, teeth emerge in pairs, with the mandibular teeth erupting prior to the maxillary teeth. Tooth eruption should be in a symmetrical pattern. Moreover, eruption times tend to be sex specific, with girls' teeth erupting earlier than boys' [4]. Typically, the average number of teeth a child ought to have is their age in months −6 until they are 24 months of age [5].

The American Academy of Pediatric Dentistry (AAPD) recommends an initial oral evaluation of a child within 6 months of their first erupted primary tooth and no later than 12 months of age. Following this initial evaluation, the patient should be seen according to a schedule recommended by the dentist based on the patient's particular needs and susceptibility to disease. If an oral examination by a dentist cannot be achieved, a pediatrician or another qualified health professional, such as a dental hygienist, should complete an oral health risk assessment by the age of 6 months since early intervention and adequate risk assessment are essential com-

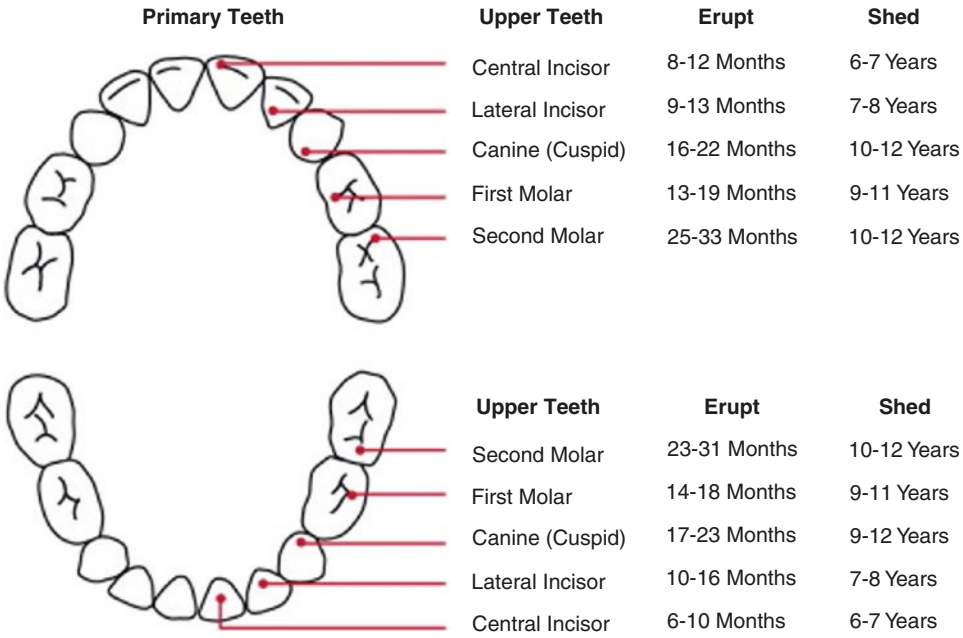


Fig. 2.2 Primary teeth eruption chart. (*Source*: American Dental Association; used with permission)

ponents in assuring that good oral health is an outcome for all children. Early dental intervention is also of value to assess the child's fluoride needs and intake, dietary assessment, and establishing a dental home. The dental home is a concept defined by the continuous relationship between the dentist and the patient comprising all aspects of oral health care, and should be established by the child's first year. A dental home addresses anticipatory guidance (the information provided to the child and family concerning the patient's present oral health and what to anticipate as the child enters the next developmental phase).

Secondary (Permanent) Tooth Development

The tissues of secondary teeth begin to develop in utero. The enamel and crown dentin begin developing in the eighth embryonic week. The root dentin and cementum begin developing 6 years after birth and continue until 25 years of age. The periodontal ligament, alveolar bone, and junctional epithelium develop during tooth eruption.

Similar to the primary dentition, the secondary dentition also develops from the dental lamina. The tooth buds of secondary teeth begin developing around week 8 in utero. At this time, there are ten primary tooth buds in each dental lamina.

During the cap stage of primary tooth development, the process of odontogenesis begins to repeat itself for succedaneous (secondary) tooth development. Another placode forms

Table 2.1 General ages of calcification of maxillary and mandibular secondary teeth

	Initial calcification	Crown completion	Root completion
Central incisors	3–4 months	4–5 years	9–10 years
Lateral incisors	*Maxilla*: 10–12 months	4–5 years	*Maxilla*: 11 years
	Mandible: 3–4 months		*Mandible*: 10 years
Canines	4–5 months	6–7 years	12–15 years
First premolars	18–24 months	5–6 years	12–13 years
Second premolars	24–30 months	6–7 years	12–14 years
First molars	Birth	2.5–3 years	9–10 years
Second molars	2.5–3 years	7–8 years	14–16 years
Third molars	*Maxilla*: 7–9 years		
	Mandible: 8–10 years		

from the dental lamina cells on the lingual side of the developing cap and the steps of odontogenesis—initiation, bud, cap, bell, apposition, and maturation—repeat from there.

Odontogenesis for secondary molars, which are not succedaneous teeth, occurs when the jaws have grown long enough. At this time, the dental lamina grows posteriorly into the ectomesenchyme beneath the epithelial lining. It is here that the tooth germs of the first, second, and third permanent molars form and develop following the same odontogenic process as in the primary dentition. Hence, the development of secondary teeth is extremely similar to that of primary teeth, except for differences in timing. Table 2.1 shows the general ages of calcification of maxillary and mandibular secondary teeth.

Teething

For most infants, the first primary teeth to erupt usually break through the gingiva around 4–7 months of age with all 20 primary teeth present by 30 months of age [5]. However, tooth eruption times can vary greatly in the population. Teeth tend to erupt in pairs with the lower teeth usually erupting prior to the upper teeth. It is important to have the first pediatric dental visit either when the first tooth erupts or by age 1 to monitor development and rule out pathology.

Delays in Tooth Eruption

The following are common causes of delays in tooth eruption: impacted teeth, Down syndrome, cleidocranial dysplasia, congenital hypothyroidism, Gaucher disease, osteopetrosis, and rickets [5].

Natal and Neonatal Teeth

While the presence of teeth in newborns is uncommon, it occurs in 1:2000–1:3000 live births. Natal teeth are those present at the time of birth and neonatal teeth are those that erupt during the first 30 days of life [6, 7]. The majority of natal and neonatal teeth are not supernumerary teeth, but rather primary teeth that have erupted prematurely [8]. Natal and neonatal teeth may be conical or of normal size and shape, of a yellow-brownish color [6, 9]. These teeth are considered mature, with a relatively good prognosis, when fully developed and comparable to primary teeth while those considered immature have a poor prognosis due to incomplete development [6, 10]. Pediatric dentists have a patient-specific approach when deciding if these teeth should be maintained with possible complications including aspiration, sublingual ulceration, and difficulty with breastfeeding [11]. Periodic follow-up is necessary.

Riga-Fede Disease

Riga-Fede disease is a complication associated with neonatal teeth when sublingual ulceration occurs due to repetitive trauma by the tooth during tongue movements [11]. It is important to diagnose this lesion in a timely manner as failure to do so can result in persistent trauma that may cause tongue deformities, dehydration, and inadequate nutrition intake, all of which ultimately result in poor growth and development [11].

Eruption Cyst and Hematoma

The eruption cyst, a soft tissue analogue of the dentigerous cyst, is a benign cyst that accompanies erupting primary or permanent teeth prior to their appearance in the oral cavity [12, 13]. They occur when a tooth is impeded in its eruption within the soft tissues overlying the bone, but the exact etiology is unknown [13, 14]. The cysts are a circumscribed, fluctuant, often translucent swelling of the alveolar ridge over the site of the erupting tooth and when the cavity contains blood it is referred to as an "Eruption hematoma" [13, 15]. Unless they hurt, bleed, or are infected, in which cases surgical treatment may be needed, these cysts disappear on their own and do not require treatment [13, 16].

Systemic Conditions

Teething occurs during a time period in an infant's life when they are exposed to many childhood illnesses and are at risk for contagious illnesses as passive immunity due to maternal antibodies wanes. During this time, teething may be incorrectly blamed for systemic symptoms such as changes in sleep/eating patterns, rhinorrhea, drooling, rash, fussiness, and diarrhea. However, localized symptoms and low-grade fever may be seen [5]. Some children may also have increased drooling, suck on their finger, and rub their gums during this time [17].

Management of Symptoms

Cold teething rings provide relief as the cold temperature causes localized vasoconstriction that decreases inflamma-

tion and biting the object applies pressure to the gums. Teething rings that are liquid-filled should not be subjected to extreme temperatures, such as the freezer or dishwasher, as it can lead to leakage of the fluid. Teethers made of plastic should be carefully checked to see if they are made of diisononyl phthalate, a potentially toxic chemical. The Consumer Product Safety Commission has advised parents to dispose off phthalate-containing products. Acetaminophen and ibuprofen may be used conservatively for teething discomfort with careful consideration to the correct dosage. Over-the-counter teething remedies with benzocaine as the active ingredient are not recommended due to the risk of methemoglobinemia, a condition where hemoglobin is oxidized to its ferric form and is incapable of oxygen transport. Methemoglobinemia can occur with both therapeutic and subtherapeutic doses of benzocaine as it is a known oxidizing agent and young children are susceptible due to immature mechanisms that protect against oxidative stress [5].

Secondary Tooth Eruption

The American Dental Association (ADA) has published standard eruption times for secondary, also referred to as permanent, teeth seen in Table 2.2 [18]. There are bilateral pairs of each tooth listed in the chart, making a total 16 teeth in an arch and 32 teeth in the mouth. This chart serves as a general sequence of when each tooth appears in the oral cavity, rather than a strict timetable that all teeth should adhere to. There are stronger correlations in eruption within tooth groups in a particular arch, for example mandibular canines, compared to correlations between tooth groups [19]. Thus, it is more important to clinically note that the same teeth within the tooth group are bilaterally synchronous in an arch than to track every tooth with set chronological guidelines. In addition, studies have elucidated that girls' teeth erupt sooner than boys' [20, 21]. Any deviation from Table 2.2 may or may not be indicative of pathology, emphasizing the importance of regular dental visits to monitor individual growth and development.

Table 2.2 General eruption times published by the American Dental Association. Note that each tooth listed has a bilateral pair in the arch [18]

Maxillary/upper teeth	Erupt (years)
Central incisor	7–8
Lateral incisor	8–9
Canine	11–12
First premolar	10–11
Second premolar	10–12
First molar	6–7
Second molar	12–13
Third molar	17–21
Mandibular/lower teeth	**Erupt (years)**
Central incisor	6–7
Lateral incisor	7–8
Canine	9–10
First premolar	10–12
Second premolar	11–12
First molar	6–7
Second molar	11–13
Third molar	17–21

Permanent teeth can be expected to erupt when two-thirds to three-quarters of the root is formed [22]. While the exact mechanism of eruption is not fully understood, in general, the eruption of teeth includes preparation of a path through bone and soft tissues and subsequently moving teeth through the path. Path preparation involves resorption of the coronal alveolar bone and primary tooth roots, allowing for primary tooth exfoliation, while bone formation apical to the erupting secondary tooth moves it along the path and into the mouth [23]. It has been established that the dental follicle is essential to facilitating alveolar bone resorption and formation [24]. Other factors such as jaw innervation [19] and periodontal ligament formation and pulpal pressure [25] have also been hypothesized to have roles in the initiation and force of eruption. Further research is required to permit better clinical management of aberrant eruption times and patterns.

Developmental Disturbances of Teeth

Developmental disturbances of the primary and permanent dentition can present as abnormalities in the number of teeth present, as well as variances in the size, shape, color, quality, and quantity of enamel/dentin structures. These anomalies can have an idiopathic etiology; however, the majority arises as a result of environmental or genetic perturbations in tooth development.

Number of Teeth

Hypodontia is defined as the lack of development of one or more teeth in the arch [26]. This is the most common developmental anomaly, which is prevalent among 1.5–10% of the population. Excluding third molars, mandibular second premolars are the most common to be congenitally missing. Maxillary lateral incisors and mandibular second premolars are the second and third most common teeth to be congenitally missing [27].

Oligodontia is defined as the lack of development of multiple teeth (six or more) and typically is associated with systemic disorders such as ectodermal dysplasia. ***Anodontia*** is

the complete absence of teeth in the maxillary and mandibular arches [26].

Associations Ectodermal dysplasia, incontinentia pigmenti, progeria, Down syndrome, Rieger syndrome, Crouzon's syndrome, Albright hereditary osteodystrophy.

Hyperdontia is defined as having an increased number of teeth, or supernumerary teeth, in the arch. The most common supernumerary teeth that erupt palatal to the maxillary incisors are mesiodens. In contrast, multiple supernumerary teeth in an arch are commonly found lingual to the mandibular premolars. The presence of supernumerary teeth can cause crowding, which increases the risk of gingival inflammation and periodontal disease. Therefore, extraction of these teeth is often indicated [28].

Associations Cleidocranial dysplasia, craniometaphyseal dysplasia, Apert syndrome, Gardner syndrome, Sturge-Weber syndrome, Hallermann-Streiff syndrome, angio-osteodystrophy.

Size

Microdontia is the term used to describe teeth that appear smaller than normal, which historically has been subdivided into three types: localized (focal), relative microdontia, and true microdontia [29]. Relative microdontia is due to macrognathia, in which there is a generalized appearance of small teeth due to a large jaw size. In contrast, true microdontia is the generalized appearance of small teeth due to the actual size of the teeth, irrespective of the jaw, and is associated with systemic disorders such as ectodermal dysplasia, Down syndrome, and congenital hypopituitarism [29].

Associations Ectodermal dysplasia, Down syndrome, congenital hypopituitarism, hemifacial microsomia.

Macrodontia is the term used to describe teeth that appear to be larger than normal and can be further subdivided into relative and true macrodontia. Relative macrodontia is due to micrognathia, in which the teeth appear large because the jaw is small. True macrodontia is the appearance of large teeth due to the actual large size of the teeth. True macrodontia is commonly associated with gigantism and congenital hemifacial hypertrophy [29].

Associations Gigantism, congenital hemifacial hypertrophy.

Shape

Fusion occurs when two tooth germs fuse and form one large tooth. As a result, counting the number of teeth in the arch will reveal one less tooth when the double or anomalous tooth is counted as one. This typically involves the primary incisors bilaterally and is confirmed radiographically by the presence of one large crown with separate pulp chambers and canals [30].

Gemination is the result of the division of a single tooth bud, forming a bifid crown with a single pulp chamber. Similar to fusion, this typically presents bilaterally in the primary incisors. To differentiate between fusion and gemination clinically, counting the number of teeth will reveal an accurate number of teeth in the arch when the double or anomalous tooth is counted as one [30].

Concrescence is defined as the union of two adjacent teeth by cementum, which can occur before or after tooth eruption. This is associated with trauma to or crowding of the maxillary posterior teeth, causing the cementum of the teeth to fuse [29].

Dens evaginatus is an extra cusp, also known as a central tubercle, in the central groove of teeth. This typically is found bilaterally on the surface of the permanent mandibular premolars [31]. When the extra cusp is found on the lingual surface of anterior teeth, it is known as a ***talon cusp***. Talon cusps are more common on the lingual surfaces of maxillary lateral incisors [29].

Dens invaginatus, also known as "dens in dente" or a "tooth within a tooth," is a deep invagination of the enamel into the dentin. These invaginations in the enamel are commonly found on the lingual surfaces of lateral incisors, and increase the risk of a communication forming between the oral cavity and pulp chamber [32].

Taurodontism describes the radiographic findings of vertically long pulp chambers, apical displacement of the pulpal floor, and shortened roots [29].

Associations Cleft lip, cleft palate, Down syndrome, Klinefelter syndrome, ectodermal dysplasia, tricho-dento-osseous syndrome.

Dilaceration describes the abnormal angulation of the root, which typically involves the permanent maxillary incisors. As a result of intrusive or displacement trauma of a primary, the underlying developing permanent tooth can be damaged and cause bending or twisting of the tooth [33].

Association Congenital ichthyosis.

Discoloration

Extrinsic and ***intrinsic staining*** of teeth can be caused by both environmental and systemic factors. Metallic and nonmetallic causes of extrinsic staining include bacteria, iron, tobacco, food and tannin-containing beverages, and medications (i.e., amoxicillin, chlorhexidine mouth rinse). Intrinsic staining can be caused by aging, amelogenesis imperfecta, dentinogenesis imperfecta, and excess exposure to tetracycline and fluoride. In addition, intrinsic staining can arise in the setting of systemic diseases such as alkaptonuria, congenital erythropoietic purpura, and congenital hyperbilirubinemia [34].

Enamel

Enamel hypoplasia is a defect of the enamel that occurs during tooth development. Alterations in enamel matrix formation can be caused by localized factors or systemic diseases. Localized factors associated with enamel hypoplasia include trauma, local infection, and irradiation. In the setting of trauma or infection of a singular primary tooth, the enamel formation of the underlying permanent tooth can be disturbed, which can result in ***Turner's hypoplasia***. Systemic factors that are associated with generalized enamel hypoplasia include premature birth, fluorosis, vitamin (A, C, D) deficiency, calcium and phosphorous deficiency, lead poisoning, Sturge-Weber syndrome, cerebral palsy, nephrotic syndrome, rubella, etc. [35].

Associations Turner's hypoplasia, trauma, fluorosis, vitamin (A, C, D) deficiency, calcium deficiency, phosphorus deficiency, Sturge-Weber syndrome, cerebral palsy, cleft lip/cleft palate, radiotherapy/chemotherapy, lead poisoning, nephrotic syndrome, rubella, hypoparathyroidism, vitamin-D resistant rickets, pseudohypoparathyroidism.

In the absence of a systemic disorder, developmental alterations in enamel are known collectively as ***amelogenesis imperfecta***. Amelogenesis imperfecta is a heterogeneous group of hereditary disorders that can be further classified into many subtypes based on patterns of inheritance and the specific features of enamel defects. However, the three major subtypes of amelogenesis imperfecta include the following phenotypes: hypoplastic (type I), hypomaturation (type II), and hypocalcified (type III) [36].

Hypoplastic amelogenesis imperfecta (type I) is a result of the inadequate *formation* of enamel matrix, causing a deficiency in the quantity of enamel. This means that even though there is sufficient mineralization of the enamel, not enough of the matrix is formed and teeth are subsequently abnormally shaped with open contacts. Since there is appropriate mineralization of enamel, type I amelogenesis imperfecta can be distinguished from type II and type III amelogenesis imperfecta by the preserved radiographic contrast between enamel and dentin [37].

Hypomaturation amelogenesis imperfecta (type II) is a result of inadequate *maturation* of the enamel crystalline structure. While the teeth affected are normal in shape, they can appear as pigmented ("mottled") or snow-capped (opaque enamel on incisal/occlusal surface). As a result of poor maturation, the enamel is soft and chips away. In comparison to type I amelogenesis imperfecta, the distinction between enamel and dentin on radiographs is less clear [37].

Hypocalcified amelogenesis imperfecta (type III) is a result of inadequate *mineralization* of the enamel. Like type II amelogenesis imperfecta, these teeth are soft and easily lost, and little distinction can be made between enamel and dentin radiographically. In addition, teeth affected by type III amelogenesis imperfecta can range in color from yellow to brown or black [37].

Dentin

Dentinogenesis imperfecta is a hereditary dentin defect that occurs during the histodifferentiation stage of tooth development. As a result of defective mineralization of the predentin matrix, amorphic, atubular circumpulpal dentin is produced. Both primary and permanent teeth can be affected, and the teeth can appear red/brown or gray/opalescent in color. Radiographically, teeth affected by dentinogenesis imperfecta show bulbous crowns with cervical constriction and obliterated pulp chambers [38]. Dentinogenesis imperfecta is further divided into three subtypes:

Shield type I dentinogenesis imperfecta more severely affects primary teeth, and is associated with osteogenesis imperfecta (blue sclera, fragile bones, hearing loss).

Shield type II dentinogenesis imperfecta, also known as hereditary opalescent dentin, is the most common type that affects both primary and permanent teeth.

Shield type III dentinogenesis imperfecta, also known as brandy wine type dentinogenesis imperfecta, presents as a shell-like appearance and increases the risk of multiple pulp exposures in primary teeth.

Loss of organization of the dentin in primary and permanent teeth is known as ***dentin dysplasia*** [29].

Type I dentin dysplasia, the radicular type, presents as "rootless teeth." While the crown is normal in shape and color, the roots are short and pointed. Radiographic examination will reveal the complete absence of pulp chambers in primary teeth, and crescent-shaped pulp chambers in permanent teeth. In addition, multiple periapical radiolucencies are often associated with this type of dentin dysplasia. Clinical

examination may reveal significant mobility, which increases the risk of periodontal disease and tooth loss [29].

Type II dentin dysplasia, the coronal type, presents as blue-brown translucent teeth with cervical constriction of bulbous crowns. This description is similar to the presentation of dentinogenesis imperfecta; however, primary dentition affected by type II dentin dysplasia has absent pulp chambers (radiographically similar to type I dentin dysplasia). In contrast, permanent teeth affected by type II dentin dysplasia typically have thistle-tube or flame-shaped pulp chambers and pulp stones. Radiographically, these teeth may show enlarged pulp chambers with significant apical extension [29].

Regional odontodysplasia, also known as "ghost teeth," is a non-hereditary developmental abnormality that is associated with an enlarged pulp, short roots, and an open apical foramen. Maxillary teeth have a higher prevalence of regional odontodysplasia, and those that erupt into the oral cavity have small, irregular, yellow-brown crowns [39].

Oral Habits

Oral habits are defined as any repetitive behavior pattern that utilizes the orofacial structures, for example, thumb or finger sucking, pacifier sucking, tongue thrust, nail biting, lip biting, bruxism, and mouth breathing. Oral habits are learned patterns of muscular contraction. While these habits often result from reflex and instinct, they interfere with regular patterns of facial growth. With oral habits, it is important to consider the frequency of the habit, its duration, and its intensity. Certain oral habits may have adverse consequences in the dentoalveolar-skeletal complex, such as: constricted maxillary arch, increased overjet, reduced overbite, anterior open bite, anterior flaring of maxillary incisors, excessive eruption of posteriors, posterior crossbite, long facial height, and Class II molar relationships. Other oral habits may lead to speech problems or malocclusion. When treating oral habits, it is essential to adopt an individualized approach that considers the patient's age, maturity, parental support, and an adequate assessment of the deformity. There are different treatment modalities for oral habits. First, counseling of both the patient and parent in why the habit ought to discontinue. Second, behavior modification techniques may be utilized. These include reminder therapy (i.e., aversive conditioning, adhesive bandage, cotton glove, arm, or finger wrap) and the reward system (i.e., prizes and self-esteem rewards). Third, appliance therapy may be valuable with the adequate patient. Fourth, the provider may refer to other specialists.

Sucking behaviors, commonly seen in utero and in infancy, serve two purposes: the first being nutritive and the second being sensory pleasure. While non-nutritive sucking behaviors are considered age appropriate for infants and young children, as development continues, other neural pathways are established, and the sucking mechanism becomes less important. Thumb or finger sucking may affect the patient's occlusion. The malocclusion is contingent on the position of the digit, the mandibular position during sucking, the associated orofacial muscle contraction force, facial-skeletal genetic pattern, and the amount, frequency, and duration of force applied. Characteristic cues in identifying the offending digit include wrinkled skin, calluses, red coloration, and exceptionally clean skin. Persistent thumb or finger sucking before the age of 3 years will primarily affect the patient's anterior dentition. After the age of 4 years, the habit is more established and the harm will be more significant; however, the worst amount of damage will occur after the eruption of the permanent incisors. Treatment for this habit is dependent on the age of the patient. This habit before the patient reaches the age of 36 months, will consist of patient and parent counseling coupled with behavior modification. After the age of 36 months but before the patient is 6 years of age, the provider should adopt a more aggressive counseling approach and behavior modification. If the behavior persists when the patient is 6 or 7 years of age, appliance therapy is advantageous.

Mouth breathing is associated with a distinctive pattern of effects on the growth of the orofacial complex as this habit affects the position of the tongue and is associated with an open-mouth posture. First, the maxilla is narrower in mouth breathers because the lower tongue position decreases the function of the tongue in widening the maxilla. Second, patients may have a longer lower face height and retrusive mandibles as the open-mouth posture may prompt the over-eruption of the permanent molars causing the mandible to rotate downward and posteriorly while resting. The dentist may refer to a specialist when indicated, if respiratory or anatomic problems predispose the child to mouth breathing.

Summary

This chapter summarizes primary teeth development and issues arising during development and eruption. A comprehensive evaluation is needed to avoid future complications.

References

1. Tucker A, Sharpe P. The cutting-edge of mammalian development; how the embryo makes teeth. Nat Rev Genet. 2004;5(7):499–508.
2. Ooé T. On the early development of human dental lamina. Okajimas Folia Anat Jpn. 1957;30(2–3):197–210.
3. Thesleff I, Nieminen P. Tooth morphogenesis and cell differentiation. Curr Opin Cell Biol. 1996;8(6):844–50. https://doi.org/10.1016/s0955-0674(96)80086-x. PMID: 8939666.
4. Kjær I. Mechanism of human tooth eruption: review article including a new theory for future studies on the eruption process. Scientifica. 2014;2014:1–13. https://doi.org/10.1155/2014/341905.

5. Markman L. Teething: facts and fiction. Pediatr Rev. 2009;30(8):e59–64. https://doi.org/10.1542/pir.30-8-e59. PMID: 19648257.
6. Cunha RF, Boer FA, Torriani DD, Frossard WT. Natal and neonatal teeth: review of the literature. Pediatr Dent. 2001;23(2):158–62. PMID: 11340731.
7. Massler M, Savara BS. Natal and neonatal teeth; a review of 24 cases reported in the literature. J Pediatr. 1950;36(3):349–59. https://doi.org/10.1016/s0022-3476(50)80105-1. PMID: 15405415.
8. Rahul M, Kapur A, Goyal A. Management of prematurely erupted teeth in newborns. BMJ Case Rep. 2018;2018:bcr2018225288. https://doi.org/10.1136/bcr-2018-225288. PMID: 29982188; PMCID: PMC6040504.
9. Rusmah M. Natal and neonatal teeth: a clinical and histological study. J Clin Pediatr Dent. 1991;15(4):251–3. PMID: 1911449.
10. Chow MH. Natal and neonatal teeth. J Am Dent Assoc. 1980;100(2):215–6. https://doi.org/10.14219/jada.archive.1980.0061. PMID: 6928153.
11. Jamani NA, Ardini YD, Harun NA. Neonatal tooth with Riga-Fide disease affecting breastfeeding: a case report. Int Breastfeed J. 2018;13:35. https://doi.org/10.1186/s13006-018-0176-7. PMID: 30065775; PMCID: PMC6062915.
12. Anderson RA. Eruption cyst: a retrograde study. J Dent Child. 1990;57:124–7.
13. Dhawan P, et al. Eruption cysts: a series of two cases. Dent Res J. 2012;9(5):647–50. https://doi.org/10.4103/1735-3327.104889.
14. Neville BW, Damm DD, Allen CM, Bouquot JE. Oral and maxillofacial pathology. 3rd ed. Pennsylvania: Sauders; 2009. p. 682–3.
15. McDonald RE, Avery DR, Dean JA. Dentistry for child and adolescent. 8th ed. St. Louis: Mosby, Elsevier; 2004. p. 160–82.
16. Singh B, Bajaj P, Singh G. Presentation of two simultaneous eruption cysts haemtomas in relation with two adjacent permanent teeth, causing tumor scare. Indian J Dent Sci. 2011;3:16–8.
17. Tsang AKL. Teething, teething pain and teething remedies. Int Dent. 2010;5(4):18.
18. American Dental Association (ADA), Division of Communications. Tooth eruption: the permanent teeth. J Am Dent Assoc. 2006;137:127.
19. Parner ET, Heidmann JM, Kjaer I, et al. Biological interpretation of the correlation of emergence times of permanent teeth. J Dent Res. 2002;81(7):451–4.
20. Helm S, Seidler B. Timing of permanent tooth emergence in Danish children. Community Dent Oral Epidemiol. 1974;2(3):122–9.
21. Svanholt M, Kjaer I. Developmental stages of permanent canines, premolars, and 2nd molars in 244 Danish children. Acta Odontol Scand. 2008;66(6):342–50.
22. Kreiborg S, Jensen BL. Tooth formation and eruption – lessons learnt from cleidocranial dysplasia. Eur J Oral Sci. 2018;126:72–80.
23. Marks SC, Schroder HE. Tooth eruption: theories and facts. Anat Rec. 1996;245(2):374–93.
24. Cahill DR, Marks SC. Tooth eruption: evidence for the central role of the dental follicle. J Oral Pathol. 1980;9:189–200.
25. Avery JK, Steele PF. Essentials of oral histology and embryology: a clinical approach. St. Louis: Mosby-Year Book; 1992. Print.
26. Shahrani A, et al. A review of hypodontia: classification, prevalence, etiology, associated anomalies, clinical implications and treatment options. World J Dent. 2013;4(2):117–25.
27. Fekonja, et al. Hypodontia in orthodontically treated children. Eur J Orthod. 2005;27(5):457–60. https://doi.org/10.1093/ejo/cji027.
28. Fariborz, et al. Prevalence and pattern of accessory teeth (hyperdontia) in permanent dentition of Iranian orthodontic patients. Iran J Public Health. 2013;42(11):1259–65.
29. Poulsen S. Pediatric dentistry: a clinical approach. Weinheim: Wiley; 2013.
30. More CB, Tailor MN. Tooth fusion, a rare dental anomaly: analysis of six. Int J Oral Maxillofac Pathol. 2013;4(1):50–3.
31. Levitan, et al. Dens Evaginatus: literature review, pathophysiology, and comprehensive treatment regimen. J Endod. 2006;32(1):1–9. https://doi.org/10.1016/j.joen.2005.10.009. ISSN 0099-2399.
32. Hülmann, et al. Dens Invaginatus: aetiology, classification, prevalence, diagnosis, and treatment considerations. Int Endod J. 2007;30(2):79–90. https://doi.org/10.1046/j.1365-2591.1997.00065.x.
33. Jafarzadeh, et al. Dilaceration: review of an endodontic challenge. J Endod. 2007;33(9):1025–30. https://doi.org/10.1016/j.joen.2007.04.013. ISSN 0099-2399.
34. Watts, et al. Tooth discolouration and staining: a review of the literature. Br Dent J. 2001;190:309–16. https://doi.org/10.1038/sj.bdj.4800959.
35. Nikiforuk G, et al. The etiology of enamel hypoplasia: a unifying concept. J Pediatr. 1981;98(6):888–93. https://doi.org/10.1016/S0022-3476(81)80580-X. ISSN 0022-3476.
36. Crawford A, et al. Amelogenesis imperfecta. Orphanet J Rare Dis. 2007;2:17. https://doi.org/10.1186/1750-1172-2-17.
37. Gadhia, et al. Amelogenesis imperfecta: an introduction. Br Dent J. 2012;212:377–9. https://doi.org/10.1038/sj.bdj.2012.314.
38. Sapir, et al. Dentinogenesis imperfecta: an early treatment strategy. Am Acad Pediatric Dent. 2006;33(1):232–7.
39. Reddy, et al. Regional odontodysplasia. J Indian Soc Pedod Prev Dent. 2010;28:315–8.

Overview of the Periodontium

3

Navid N. Knight

Introduction

Basic understanding of normal structures of the periodontium and their anatomical relationship is a prerequisite to any discussion about variations caused by a pathophysiological process. The term "periodontium" is a noun when broken down into its components means: (Peri-) surrounding and (-odont) tooth. The literal definition would therefore be "around the tooth," which describes the supporting and surrounding structures of the dentition.

The periodontium is a specialized set of soft and hard tissues that surround and support the teeth in the maxillary and mandibular jaws. The main components of these specialized support structures are the *alveolar bone*, *cementum*, *periodontal ligament*, and *gingiva* (Fig. 3.1).

These structures have been subdivided into two main components: the *gingiva*, which is the overlying tissue protecting the underlying structures, and the *attachment* part of the periodontium, which includes the periodontal ligament, cementum, and the alveolar bone. This chapter will focus on the general structures of these support structures.

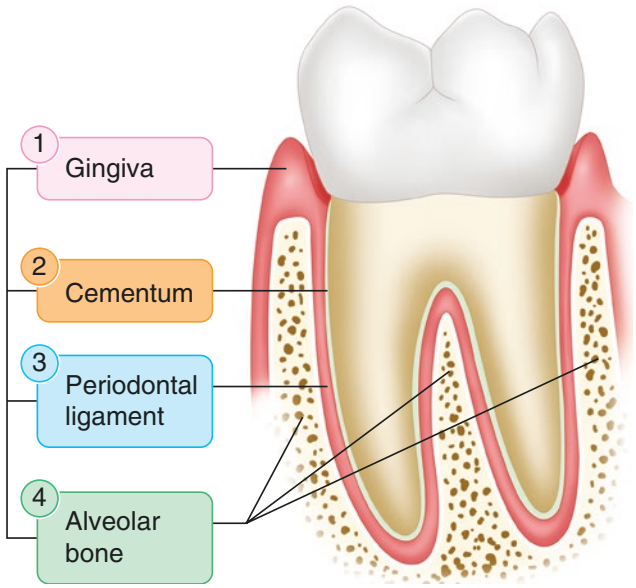


Fig. 3.1 Components of the periodontium: (1) Gingiva, (2) Cementum, (3) Periodontal ligament, (4) Alveolar bone

Gingiva

The gingiva is a part of the oral mucosa. It is the peripheral part of the oral tissues that surround the tooth. It extends from the *mucogingival junction*, which is the demarcation between the non-keratinized oral mucosa, and covers the coronal portion of the alveolar bone. On the palatal portion of the maxillary arch, the mucogingival junction is absent as the gingiva is part of the keratinized firmly attached palatal mucosa.

The gingiva is broken down into three components: (a) the free gingiva, which is also referred to as marginal or unattached gingiva, (b) the attached gingiva that extends down to the mucogingival junction as well as covering the palate, and (c) the interdental gingiva extending between the teeth (Fig. 3.2).

N. N. Knight (✉)
Department of Periodontology, University of the Pacific Arthur A. Dugoni, School of Dentistry, San Francisco, CA, USA
e-mail: Nknight@pacific.edu

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_3

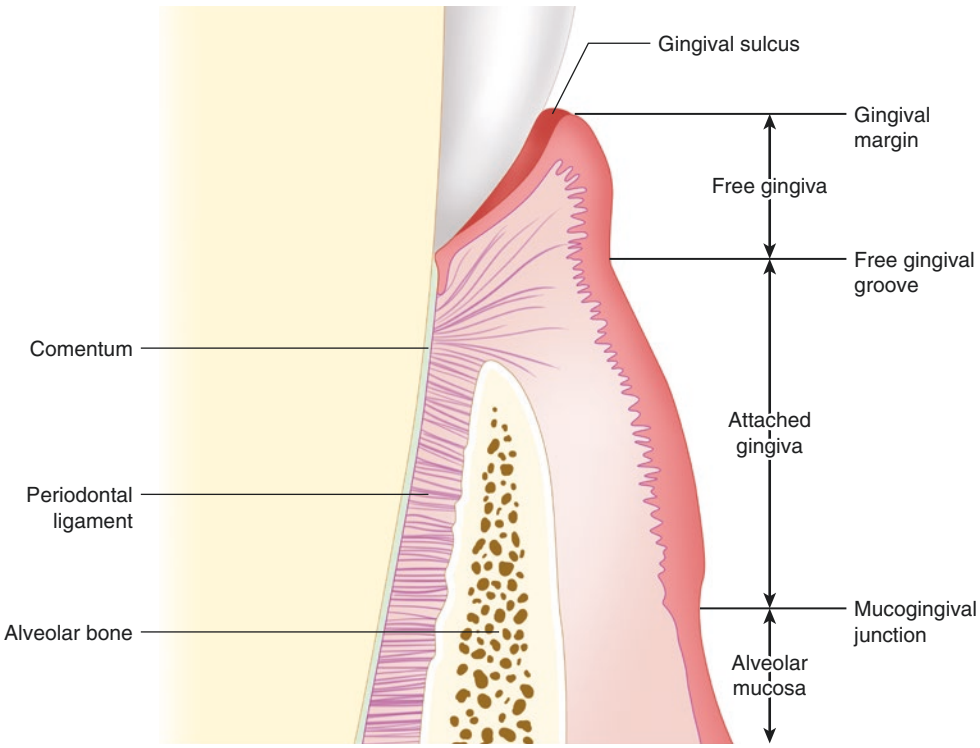


Fig. 3.2 Components of the gingiva

Marginal, Unattached, or Free Gingiva

The marginal, unattached, and free gingiva are terms used interchangeably and it is the border of the gingiva that surrounds the teeth. It is the outer soft tissue component of the gingival sulcus. It can be separated from the tooth surface with a periodontal probe or curette. The gingival sulcus is the shallow space around the tooth that has the surface of the tooth on one side and the inner epithelial lining of the free gingival margin on the other. It is commonly referred to as the gingival sulcus creating a V shape that will barely permit probing in health. The depth of the sulcus as evaluated by histologic sections is about 1.8 mm [1]; other studies have reported 1.5 mm [2] and 0.69 mm [3].

Attached Gingiva

Clinically, the attached gingiva is continuous with the marginal gingiva. It ends coronally at the gingival margin and apically extends to the boundary between the loose alveolar mucosa, which is distinguished by the mucogingival junction (Fig. 3.2). As outlined earlier, the palatal tissues on the maxillary arch is completely attached with no alveolar mucosa and therefore no detectable mucogingival junction.

The width of the *attached gingiva* is an often clinically relevant parameter. It is the distance between the mucogingival junction and the external anatomical surface of the base of the sulcus where attachment to the tooth structure begins (Fig. 3.3). The marginal and attached gingiva are described as *keratinized gingiva*. This is not to be confused with attached gingiva as the keratinized gingiva will include both the marginal and attached gingiva.

The width of the attached gingiva will have variations depending on the different locations in the oral cavity [4]. It is described as being greater in width in the incisor region and narrower in the posterior segments [5]. It is important to note that the position of the mucogingival junction remains in the same location and stationary during adult life [6]. Changes in the width of the attached tissues are due to atrophic changes and modifications throughout life.

Interdental Gingiva

The interdental gingiva as the name implies occupies the space between the teeth from the surface on the outside (facial or buccal) to the inside (lingual or palatal). It is the space beneath the contact area of the teeth and it can have a pyramidal shape based on the presence and location of the contact between the teeth to a valley-shaped appearance known as the "col." The covering epithelium of the interdental gingiva of the col. is non-keratinized.

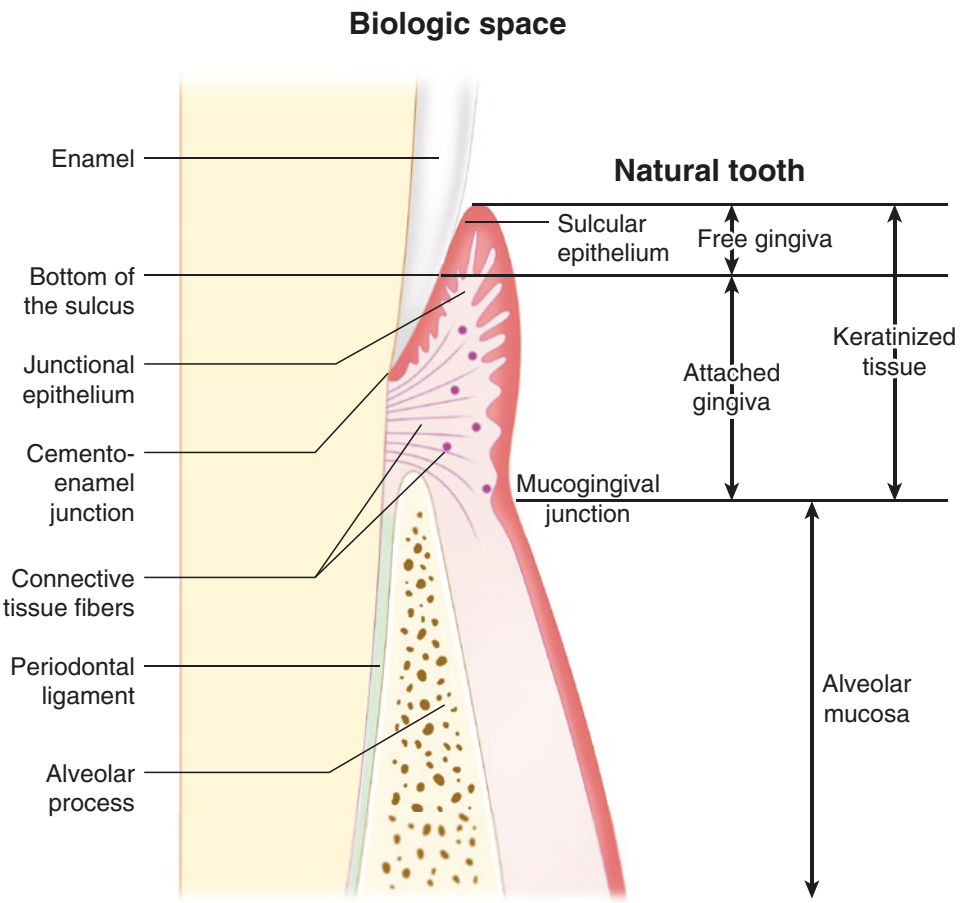


Fig. 3.3 Attached gingiva extends from the base of the sulcus where initial attachment to the tooth begins to the mucogingival junction

Microscopic Features

Microscopic evaluations indicate that gingiva is composed of an overlying *stratified squamous epithelium* and an underlying core of *connective tissue*. Epithelium is mostly cellular in nature whereas the central core of connective tissue is primarily made of collagen fibers arranged in various bundle groups.

Gingival Epithelium

The gingiva is composed of stratified squamous epithelium. It can be divided into three different areas based on their function and morphology: the *oral or outer epithelium*, *sulcular epithelium*, and *junctional epithelium.*

The oral or outer epithelium includes the marginal epithelium to its crest along with the attached gingiva. The oral epithelium is 0.2–0.3 mm in thickness and the surface is keratinized, parakeratinized, or a combination of both [7]. The sulcular epithelium is a thin non-keratinized stratified squamous lining of the gingival sulcus that extends from the coronal portion of the junctional epithelium to the crest of the gingival margin. As previously mentioned, the gingival epithelium in the col is also non-keratinized [8]. The junctional epithelium is the first attachment to the tooth and it is a band of stratified squamous epithelium that is non-keratinized. It is 1–2 cell layers thick at its most apical extent and up to 10–29 cell layers thick at its coronal extent. It is attached to the cementoenamel junction in healthy tissues. Epithelial cells are attached to each other by desmosomes, which act as specialized adhesive protein complexes that help to maintain the integrity of the tissues. The junctional epithelium is attached to the tooth surface via hemidesmosomes. This attachment to the tooth is reinforced by the gingival fibers, which helps to brace marginal gingiva against the tooth surface. The gingival fibers and the junctional epithelium together are called the dentogingival unit [9].

Gingival Connective Tissue

The connective tissue of the gingiva is also known as *lamina propria*. The major components of the gingival connective tissue are the type I collagen fibers that provide the tensile strength to the gingival tissues. They make up about 60% of the lamina propria by volume. Fibroblasts make up 5% and the remaining 35% is made up of nerves, vessels, and matrix.

The gingival connective tissue consists of two layers: the *papillary layer*, which is adjacent to the epithelium that forms papillary projections between the epithelial ridges (Fig. 3.4), and a *reticular layer*, which is contiguous with the overlying layer of alveolar bone, the *periosteum*.

The collagen fibers of the gingival connective tissue are densely packed and in bundles. They are anchored into the acellular cementum starting just below the junctional epithelium forming the connective tissue attachment. This attachment will help to stabilize and limit the apical migration of the junctional epithelium [10]. The marginal gingiva has a predominant system of collagen fibers arranged in bundles called *gingival fibers*. These fibers perform some key functions such as:

1. Bracing the marginal gingiva firmly against the tooth.
2. Providing the resistance and toughness needed to prevent the tissue from being pushed away from the tooth during the forces of mastication.
3. Creating a connection between the marginal gingiva and the adjacent attached gingiva and the cementum.

The gingival fibers are arranged in three different bundle groups: *gingivodental*, *circular*, and *transseptal* groups.

Gingivodental Group

The gingivodental fiber groups are noted on the facial, lingual, and interproximal surfaces. They extend from their attachment into the cementum below the epithelial attachment of the junctional epithelium in a fan-shaped fashion toward the marginal gingiva (a), across to the attached gingiva (b) and over the crest of the bone (c). In the interproximal areas, they extend toward the crest of the interdental gingiva (Fig. 3.5).

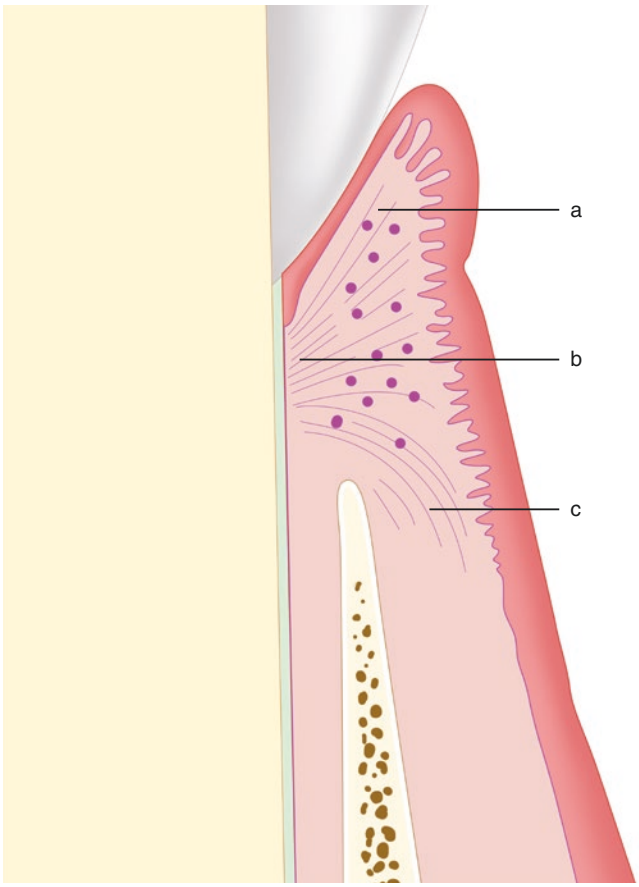


Fig. 3.5 Gingivodental group

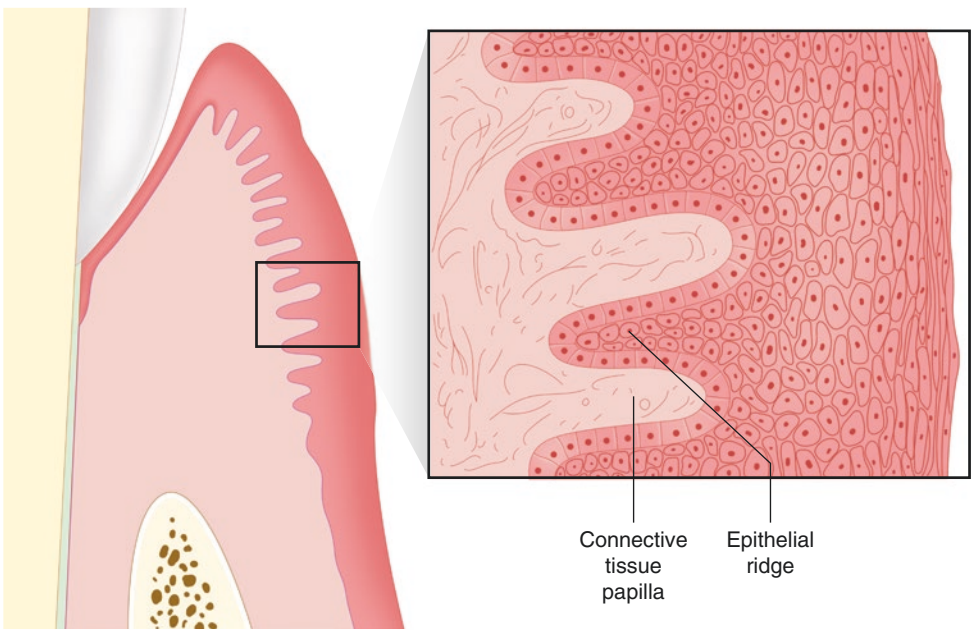


Fig. 3.4 The connective tissue and gingival epithelium interface. Connective tissue papillae and epithelial ridges are noted

Circular Group

The circular bundles of connective tissue fibers create a ring or a band that encircles the tooth in a belt-like fashion in the marginal and interdental gingiva. It functions to keep the gingival tissue closely adapted to the tooth (Fig. 3.6).

Transseptal Group

The transseptal group is positioned in between the teeth with fibers moving interproximally in horizontal bundles connecting into the cementum of the adjacent teeth. They predominantly occupy the space between the apical extent of the junctional epithelial attachment and the crest of the interdental bone (Fig. 3.7).

Other components of the gingival connective tissue include the presence of numerous fibroblasts in the gingival tissues between the collagen fiber bundles. They play an important role in the development, maintenance, and repair of the gingival connective tissue. Other cells noted are plasma cells, lymphocytes, mast cells, and neutrophils. In healthy gingival tissues, these cells are usually noted in smaller amounts. Microcirculatory blood and lymphatic vessels are also noted and play role in the circulation, drainage of tissue fluids, and spread of inflammation. Neural tissues are closely associated with the blood vessels in the gingival connective tissues and are extensively distributed.

We describe the color, consistency, texture, and shape of the gingiva as part of our clinical evaluation. In a healthy gingiva the color is considered to be "coral pink," which is the result of the vascular supply, the thickness of the epithelium, and extent of keratinization and pigmentation. The degree of melanin pigmentation can alter the healthy color of the gingival tissues in health. It is important to note that this pigmentation is not an indication of a disease process (Figs. 3.8 and 3.9).

The consistency would be described as firm in healthy gingival tissues. The surface texture can have an orange peel

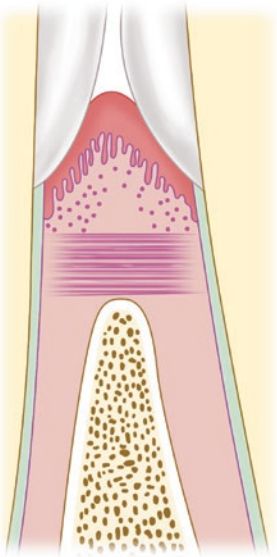


Fig. 3.7 Transseptal group

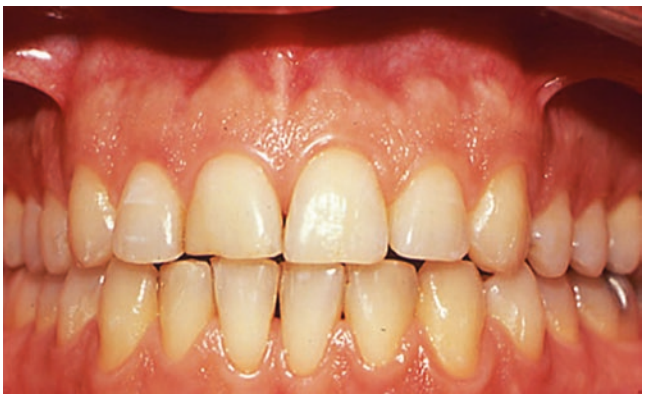
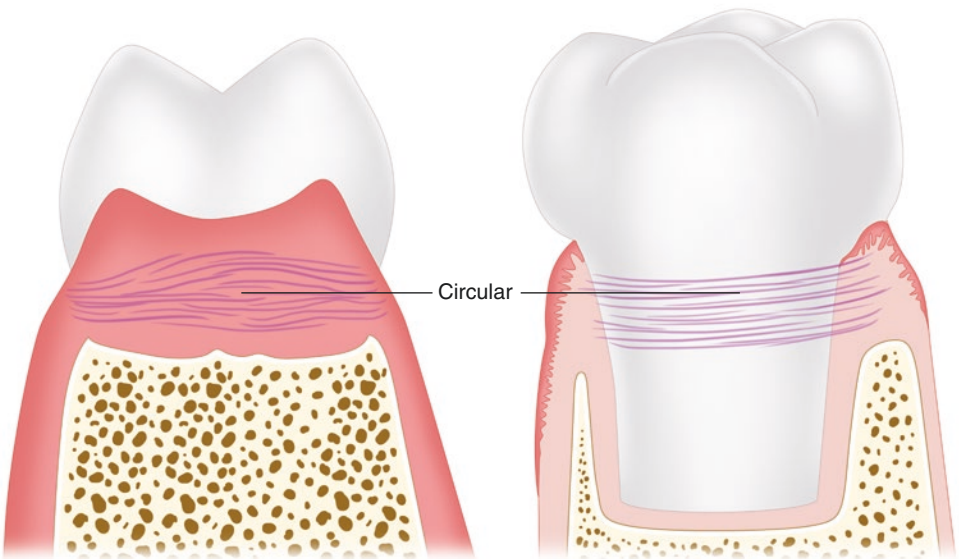


Fig. 3.8 Healthy gingival tissues

Fig. 3.6 Circular group



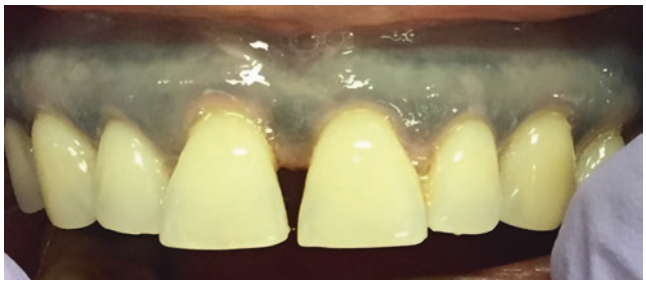


Fig. 3.9 Healthy gingival tissues with melanin pigmentation

appearance known as *stippling*. Although the presence of stippling is not always noted, when present it is a clinical indication of health with cases of heavy stippling noted in thick gingival tissues, "thick gingival phenotype," with lightly stippled tissues noted in thin gingival tissues, "thin gingival phenotype." The papillae tend to be pointed with scalloped knife-edge margins. This is dictated by the contour of the proximal tooth surfaces, the location of the gingival embrasure spaces, and the location of the interproximal contacts.

Periodontal Ligament

Periodontal ligament is one of the three components of the tooth-supporting structures. It is composed predominantly of collagenous principal fibers arranged in bundles that surround the tooth root and connect the cementum to the alveolar bone [11]. The average width of the periodontal ligament space has been noted at 0.2 mm with some variations noted due to lack of or hyper function. There are fibroblasts, osteoblasts, nerves, and vessels noted in the periodontal ligament space as well.

The most important and prominent element of the periodontal ligament are the type I collagen fibers arranged in groups called the *principal fibers*. At their terminal extensions, these principal fibers attach to the cementum and the bone. This terminal attachment portion is termed *Sharpey's fibers*. The principal fibers of the periodontal ligament are arranged in five groups: the *alveolar crest*, *horizontal*, *oblique*, *apical*, and *interradicular* fibers.

Alveolar Crest Group

The alveolar crest fibers extend from the cementum beneath the junctional epithelial attachment and extend to the crest of the alveolar crest (Fig. 3.10). These fibers function in preventing extrusion of the tooth and resist lateral tooth movement [12].

Horizontal Group

The horizontal group extend horizontally in a 90-degree angle to the long axis of the tooth from the cementum to the alveolar bone (Fig. 3.10).

Oblique Group

The largest and most predominant group of periodontal ligament fibers is the oblique group. These fibers extend from the alveolar bone in an apical direction to the cementum. They take the majority of the vertical occlusal and masticatory load and act as shock absorbers (Fig. 3.10).

Apical Group

The apical fibers of the periodontal ligament are noted at the apical portion of the fully formed root socket. They fan out in an irregular pattern to connect the apical cementum to the alveolar bone at the base of the tooth socket (Fig. 3.10).

Interradicular Group

On multi-rooted teeth, the interradicular fibers are noted connecting the cementum to the furcation areas in a fan-like arrangement (Fig. 3.10).

The cellular components of the periodontal ligament are connective tissue cells, immune system cells, and cells associated with neurovascular elements. The connective tissue cells include fibroblasts, cementoblasts, and osteoblasts with the fibroblasts being the most predominant cells in the periodontal ligament. The immune system and defense cells in the periodontal ligament include neutrophils, lymphocytes, macrophages, mast cells, and eosinophils. The same array of defense cells as well as the neurovascular supply are also noted in other connective tissue.

Function of Periodontal Ligament

Although the predominant function of the periodontal ligament is physical in nature, it also has formative, remodeling, nutritional, and sensory functions. The physical functions of the periodontal ligament can be broken down into the following:

1. Creation of a soft tissue compartment protecting the nerves and vessels from injury from masticatory and mechanical forces.

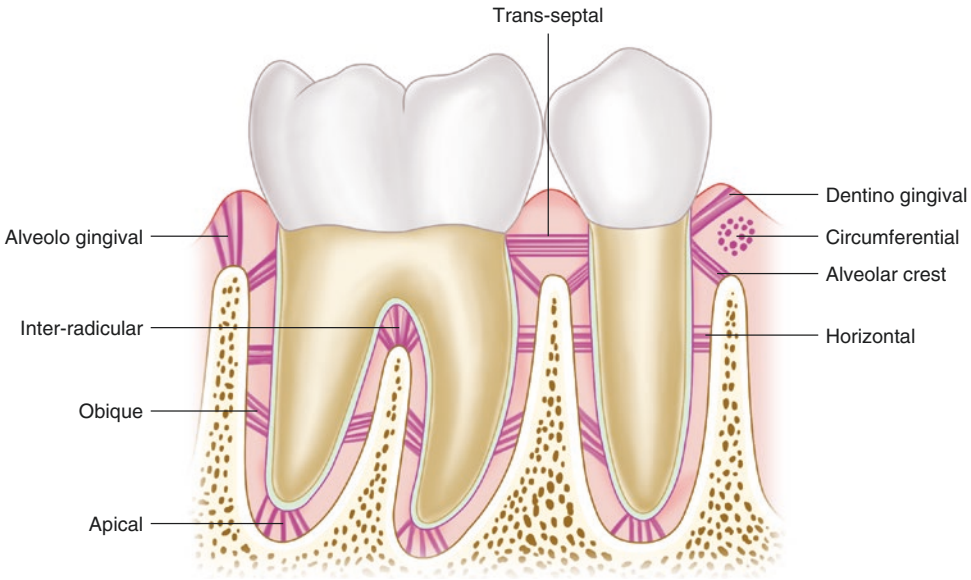


Fig. 3.10 Periodontal ligament fiber groups

2. Allowing for transmission of occlusal loads to the bone.
3. Resistance of the impact from occlusal forces by acting as a shock absorber.
4. Attachment of the teeth to the bone.

The resistance of forces and its shock-absorption mechanism is by support from the principal fiber groups as they flex and recoil under tension as well as the viscoelastic damping by the fluids present in the periodontal ligament space.

When the periodontal ligament is exposed to forces from mastication, traumatic loads, parafunction, or orthodontic tooth movement, the cells in the periodontal ligament are involved in the formation and resorption of collagen fiber, cementum, and bone. The periodontal ligament is undergoing constant remodeling by breaking down old cells and fibers and replacing them with new ones.

The periodontal ligament also supplies nutrients via its vasculature as well as sensory inputs. The highly abundant vasculature supplies nutrients to the cementum, bone, and the gingiva as well as provides lymphatic drainage. The high infiltration of the sensory nerve fibers allows for the transmission of the tactile, pressure, and pain sensations by the trigeminal pathways [13, 14].

Cementum

Cementum is the second component of the tooth-supporting structures of the periodontium. Cementum is a calcified, mineralized specialized tissue covering the root surfaces of the teeth. Although It has some features that are similar with the bone, cementum differs in that it contains no blood or lymph vessels, has no sensory nerves, and does not undergo physiologic resorption and remodeling. Cementum serves to attach the periodontal ligament fibers to the root. The two types of cementum noted are the acellular (primary) and cellular (secondary) cementum [15].

Both acellular and cellular cementum contain calcified matrix and collagen fibers. The collagen fibers in cementum derive from two sources. The first is the *extrinsic* source from the Sharpey's fibers that are the terminal portion of the periodontal ligament and gingival fibers that are embedded into the cementum that help in supporting the tooth. These extrinsic fibers are formed by the fibroblasts. The second are the *intrinsic* fibers that belong to the cementum matrix itself and are produced by the cementoblasts [16]. Both the intrinsic and extrinsic collagen fibers noted in cementum are predominantly type I collagen.

Acellular cementum covers the middle and cervical portion of the roots and is the first cementum formed. It does not contain cells and is formed before the root reaches its occlusal plane. The thickness of acellular cementum has been documented to be between 30 and 230 μm [17]. Sharpey's fibers are the primary component of acellular cementum that functions to support the tooth. These fibers tend to insert deep into the cementum at a right angle. Some intrinsic fibers are also noted in a smaller quantity and they tend to be arranged more in a parallel direction to the surface of the root. Cellular cementum is usually formed after the tooth reaches the occlusal plane and tends to cover the apical portion of the root as well as in the furcation areas (Fig. 3.11). It tends to be more irregular in its pattern and contains cells (cementocytes) and tends to be less calcified than the acellular cementum [18].

The process of cementum deposition is continuous throughout life and it progresses at varying rates. Due to tooth eruption from various events such as attrition, wear,

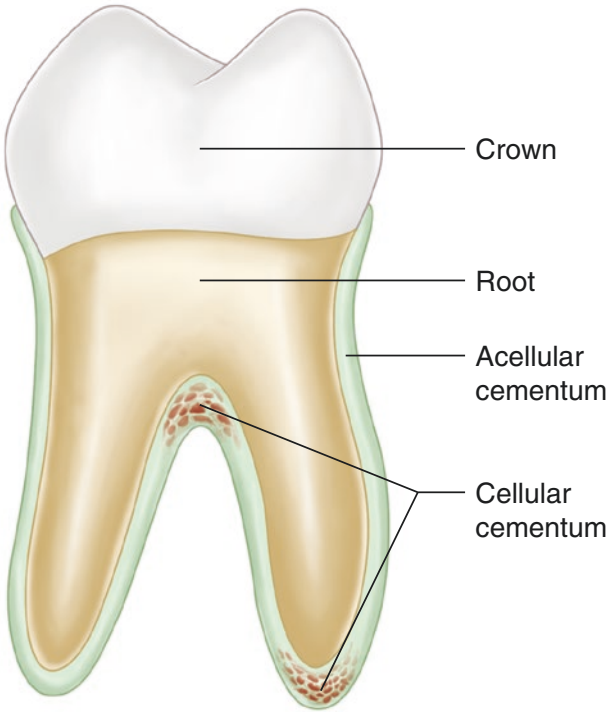


Fig. 3.11 The two types of cementum: the acellular and cellular cementum

tipping, and lack of opposing occlusion, cementum formation tends to occur and seems to be more rapid in the apical regions. It tends to be thinner in the coronal half of the root and at its thickest in the apical third and furcation areas.

Alveolar Bone

The alveolar bone is the third component of the supporting structures of the tooth. The alveolar bone is part of the alveolar process that forms and supports the sockets for the teeth. These tooth sockets are also termed *alveoli.* As the tooth is developing, the alveoli forms to help create the bony component that along with the periodontal ligament and cementum forms the attachment apparatus of the tooth. Once the tooth is lost the alveoli disappears gradually. The alveolar process development and remodeling is dependent on the formation of the tooth. It is therefore a tooth-dependent bony support [19]. The size, function, location, and shape of the teeth will determine the anatomical shape of the alveoli.

The alveolar process consists of three anatomical components (Fig. 3.12):

1. An external cortical plate of compact bone.

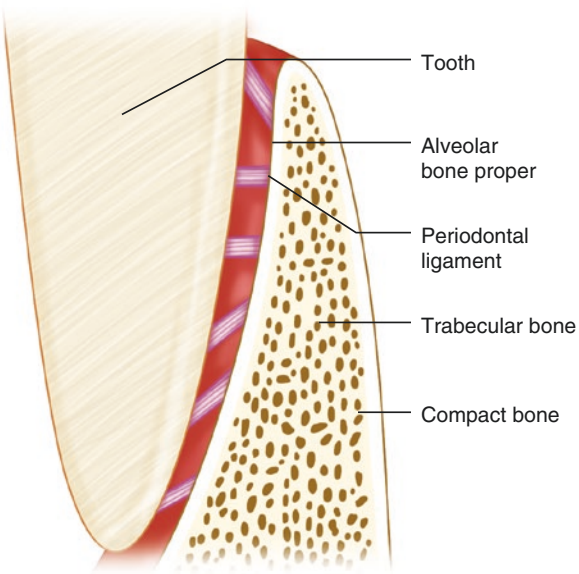


Fig. 3.12 The components of the alveolar process

2. An internal or inner compact or cortical thin lining of the tooth socket. This thin inner wall lining of the socket is called the *alveolar bone proper*. Radiographically, this thin layer of bone is called *lamina dura.*
3. A softer cancellous bone between the two compact layers, which function as the supporting alveolar bone.

In addition to the tooth-supporting portion of the alveolar process, the *basal bone* is that portion of the alveolar jaw bone that is apical to the teeth and is unrelated to the support structures of the dentition. Although we have these anatomical separations of the alveolar process, all parts work together in the support of the teeth. In many cases the facial and lingual portions of the tooth socket are formed by compact bone only, with the apical, interproximal, and interradicular areas having cancellous bone adjacent to the lamina dura.

Bone consists of two-thirds inorganic matter and one-third organic matrix. The main component of the inorganic matter is in the form of calcium and phosphate minerals. Other portions of the inorganic matter noted in small amounts are hydroxyl, carbonate, and citrate with trace amounts of other ions. The organic matrix is predominantly type I collagen with small amounts of non-collagenous proteins [20]. Bone formation and resorption is the major pathway for remodeling noted in the bone as it affects the shape based on resistance to forces applied, repair of wounds, and the hemostasis between the calcium and phosphate ions. This bone remodeling is an interplay between the two major cells, the osteoblasts and osteoclasts, that form and resorb the mineralized connective tissue of the bone, respectively [21].

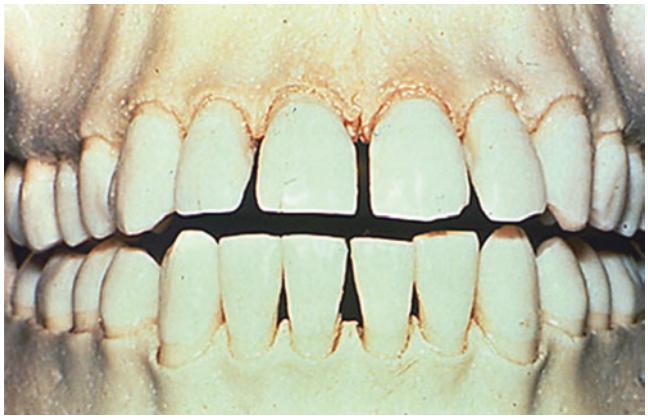


Fig. 3.13 Normal osseous topography

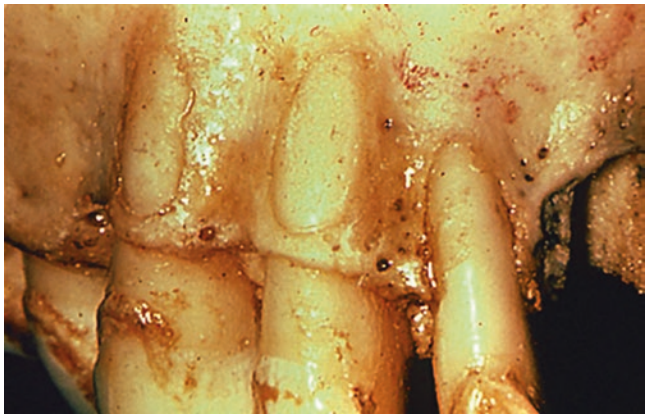


Fig. 3.14 Dehiscence and fenestration

Osseous Topography

The alveolar bone shape varies among the patients and due to its form may have some clinical implications. The shape and contour of the bone tend to follow the shape and prominence of the roots and the interdental spaces. The thickness and height of the bone noted on the facial and lingual surfaces of the teeth are affected by the position of the root in the bone, the angulation, and alignment. Therefore, with teeth that are placed more facially the bone is thinner, exhibits a knife-edge margin, and can be more apically positioned (Fig. 3.13). On teeth with a more lingual position the facial bone is thicker with blunted margins, rounded edges, and exhibits a more horizontal pattern. In normal and healthy tissues, the contour and form of the overlying gingival tissues follow that of the underlying bone.

Fenestration and Dehiscence

The position of the root in the alveolar bone can create areas where the root is denuded of bone. Lack of this alveolar bone on the buccal or lingual surfaces that is continuous with the bony margins is called a *dehiscence.* Lack of alveolar bone on the buccal and lingual surfaces that is not continuous with the bony margins, leaving a small bridge of bone, is called a *fenestration* (Fig. 3.14). Such defects can be seen on approximately 20% of the teeth and are seen more on the facial bone than on the lingual. They tend to be more frequent on the anterior teeth than posteriors and are often seen bilaterally. Although the etiology is not clear but prominent roots, tooth position, and thin bone have been discussed as the possible culprits [22]. The anatomical presence of fenestrations and dehiscence is important to note, as they could impact the outcome of periodontal surgical therapy.

The overall role of the periodontium is to support the teeth. The stimulation of the supporting structure during function helps to maintain this structure and therefore there is a constant balance between the external forces applied and the periodontal support structures. An understanding of the basic structures of the periodontium will help us understand how any deviation from this balance may lead to functional or pathologic changes.

References

1. Orban B, Kohler J. Die physiologische Zahn-fleischtasche, Epithelansatz und Epitheltiefenwucherung. Z Stomatol. 1924;22:353.
2. Weski O. Die chronische marginales enzundungen des alveolar-fortsatzes mit besonderer berücksichtigung der alveolarpyorrhoe. Vierteljahrschr Zahnheilk. 1922;38:1.
3. Gargiulo AV, Wentz FM, Orban B. Dimensions and relations of the dentogingival junction in humans. J Periodontal. 1961;32:261.
4. Bowers GM. A study of the width of the attached gingiva. J Periodontal. 1963;34:210.
5. Ainamo J, Loe H. Anatomical characteristics of gingiva: a clinical and microscopic study of the free and attached gingiva. J Periodontal. 1966;37:5.
6. Ainamo A. Influence of age on the location of the maxillary mucogingival junction. J Periodontal Res. 1978;13:189.
7. Weinmann JP, Meyer J. Types of keratinization in the human gingiva. J Invest Dermatol. 1959;32:87.
8. Biolcati EI, Carranza FA Jr, Cabrini RL. Variaciones y alteraciones de la queratinizacion en encias humanas clinicamente sanas. Rev Asoc Odontol Argent. 1953;41:446.
9. Listgarten MA. Changing concepts about the dentogingival junction. J Can Dent Assoc. 1970;36:70.
10. Cho MI, Garant PR. Development and general structure of the periodontium. Periodontol 2000. 2000;24:9.
11. McCulloch CA, Lekic P, McKee MD. Role of physical forces in regulating the form and function of the periodontal ligament. Periodontol 2000. 2000;24:56.
12. Carranza FA, Carranza FA Jr. The management of the alveolar bone in the treatment of the periodontal pocket. J Periodontal. 1956;27:29.
13. Avery JK, Rapp R. Pain conduction in human dental tissues. Dent Clin North Am. 1959;3:489.

14. Bernick S. Innervation of teeth and periodontium. Dent Clin North Am. 1959;3:503.
15. Gottlieb B. Biology of the cementum. J Periodontol. 1942;13:13.
16. Selvig KA. The fine structure of hyman cementum. Acta Odontol Scand. 1965;23:423.
17. Simpson HE. The degeneration of the rest of Malassez with age as observed by epoxeatic technique. J Periodontol. 1965;36:288.
18. Ishikawa G, Yamamoto H, Ito K. Microradiographic study of cementum and alveolar bone. J Dent Res. 1964;43:936.
19. Schroeder HE. Oral structural biology. New York: Time Medical Publishers; 1991.
20. Eastoe JE. The organic matrix of bone. In: Bourne GH, editor. The biochemistry and physiology of bone. New York: Academic Press; 1956.
21. Sodek J, McKee MD. Molecular and cellular biology of alveolar bone. Periodontol 2000. 2000;24:99.
22. Elliot JR, Bowers GM. Alveolar dehiscence and fenestration. Periodontics. 1963;1:245.

Paranasal Sinuses

4

Derek Groskreutz and Danielle Bottalico

Overview/Introduction

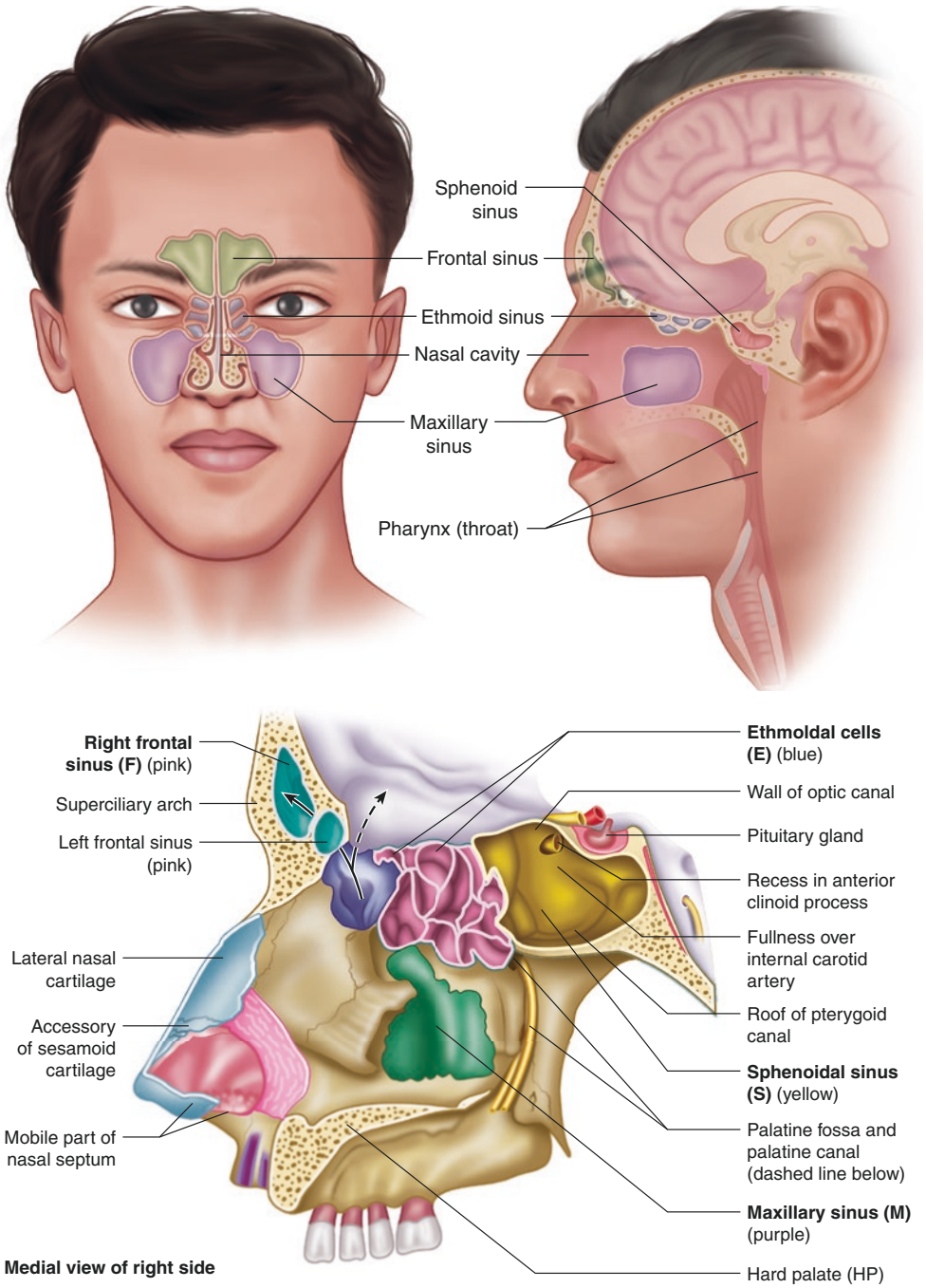
There are four paired paranasal sinuses. They are pneumatized areas of the facial and skull base bones named according to the bone in which they are located. The maxillary sinus is the largest followed by the frontal, sphenoid, and ethmoid sinus, respectively (Fig. 4.1). They communicate with the nasal cavity via small ostia that allows for air exchange and drainage of secreted mucous. The sinus cavities are lined with ciliated pseudostratified epithelium with mucus secreting goblet cells. The cilia beat in a coordinated fashion to transport mucus from the point of secretion toward the natural ostium. Knowledge regarding paranasal sinus embryology and anatomy is essential to understand common pathology associated in this unique region [1, 2].

D. Groskreutz
Frank H. Netter MD School of Medicine at Quinnipiac University, North Haven, CT, USA
e-mail: derek.groskreutz@quinnipiac.edu

D. Bottalico (✉)
Department of Otolaryngology - Head and Neck Surgery, Albert Einstein College of Medicine, Montefiore Medical Center, Medical Arts Pavilion, Bronx, NY, USA
e-mail: Dbottali@montefiore.org

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_4

Fig. 4.1 Paranasal sinus



Paranasal Sinus Embryology

The sinuses form as evaginations within the developing nasal cavity that invade into the surrounding bone. They begin to develop during gestation. However, the maxillary and ethmoid are the only sinuses present at birth. The maxillary sinus begins to develop first during the third week of gestation. In early childhood, the floor of the sinus is located superior to the nasal floor due to unerupted dentition. By age 12, the sinus is level with the floor of the nasal cavity. With continued pneumatization into adulthood and eruption of adult molars, the floor of the sinus descends to approximately 1 cm below the floor of the nasal cavity [3]. The ethmoid sinus begins developing during week 12 of gestation. At birth, the anterior ethmoid cells are aerated while the posterior ethmoid cells are fluid filled. These cells pneumatize

with advancing age and continue to develop until about age 12 [4]. The sphenoid and frontal sinus pneumatize postnatally with the frontal sinus being the last to fully develop at the end of the second decade of life [1].

Paranasal Sinus Anatomy

Maxillary Sinus

The maxillary sinus is shaped like a quadrangular pyramid and is the largest of the four paired paranasal sinus. It is bounded superiorly by the orbital floor, inferiorly by the alveolar and palatine process of the maxilla, laterally by the zygoma, medially by the lateral nasal wall, posteriorly by the pterygopalatine and infratemporal fossa, and anteriorly by the facial surface of the maxilla (Fig. 4.2). The sinus ostium and nasolacrimal duct are located within the medial wall of the maxillary sinus. The ostium is located superomedially and drains into the infundibulum that joins the semilunar hiatus and empties into the middle meatus. It is important to note that some individuals have an accessory ostium with the opening outside the infundibulum and semilunar hiatus. The nasolacrimal duct, which houses the lacrimal apparatus, runs 4–9 mm anterior to the os and empties at the anterior portion of the inferior meatus [5].

Other important structures in close association with the maxillary sinus include the infraorbital foramen and canal, and superior alveolar nerves that are branches of the maxillary nerve. The infraorbital canal runs along the roof of the maxillary sinus and houses the infraorbital nerve, artery, and vein. The anterior superior alveolar nerve arises behind the infraorbital foramen and descends inferiorly in the anterior wall of the maxilla. The middle superior alveolar nerve arises from the infraorbital nerve and courses along the posterolateral or anterior wall of the sinus to supply the premolar teeth. The posterior superior alveolar nerve is a branch off the posterior aspect of the infraorbital nerve. There are usually two branches of this nerve, a smaller superior branch and a larger inferior branch. The inferior branch supplies the molar teeth and joins the anterior and middle superior alveolar nerve to form the alveolar plexus.

The maxillary sinus has a rich blood supply including contributions from the infraorbital, sphenopalatine, posterior lateral nasal, facial, pterygopalatine, greater palatine, and posterior superior alveolar arteries. Venous return occurs anteriorly via the cavernous plexus that drains into the facial vein and posteriorly via the pterygoid plexus ultimately emptying into the internal jugular vein. Innervation to the maxillary sinus comes from the anterior, middle, and posterior superior alveolar nerves [4].

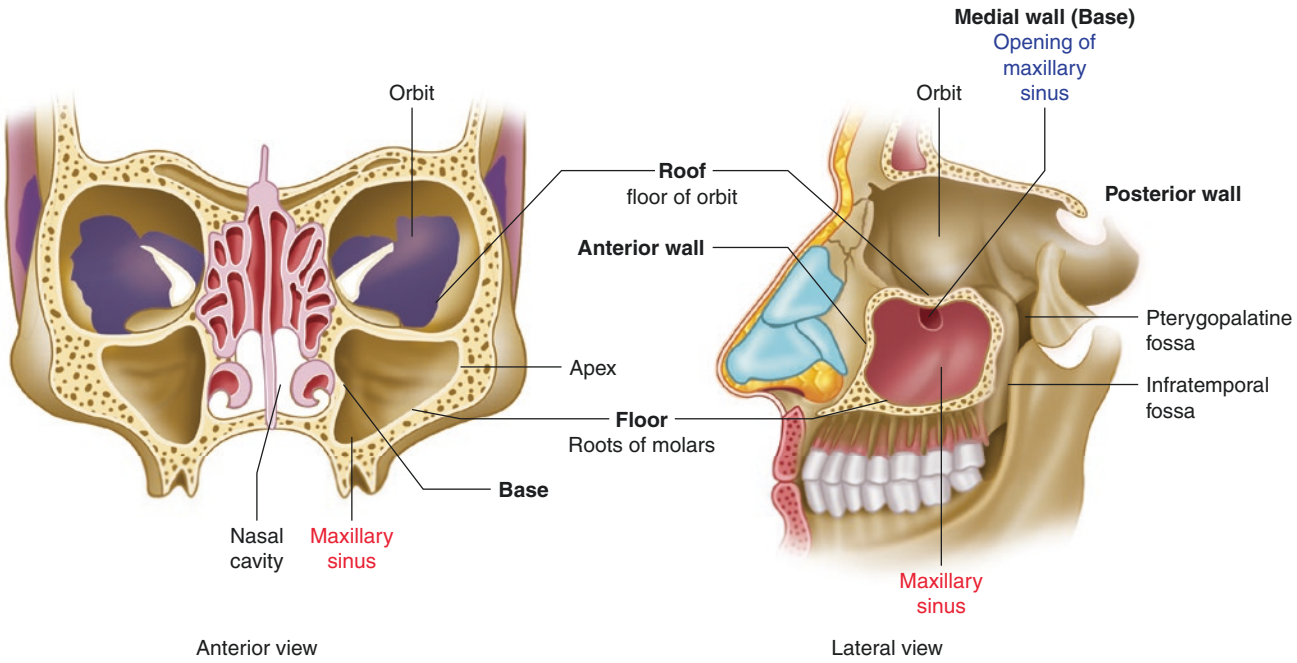


Fig. 4.2 Maxillary sinus

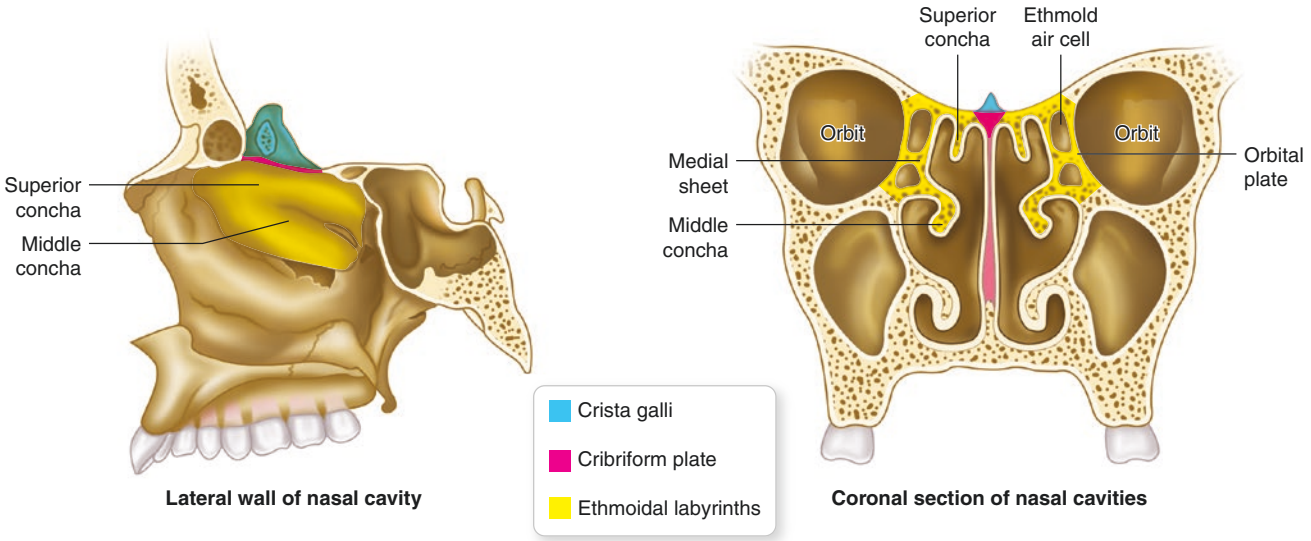


Fig. 4.3 Ethmoid sinus. (© TeachMeAnatomy)

Ethmoid Sinus

The ethmoid sinus is located between the nose and the orbit, and is separated from the latter by the lamina papyracea (Fig. 4.3). It lies inferior to the anterior cranial fossa and the frontal bone and sinus. Along with the maxillary sinus, the ethmoid sinus is present at birth and grows in size as the face develops through puberty. Mucus drainage flows through the ethmoid ostium, which is bound inferiorly and medially by the middle meatus (on or above the ethmoid bulla) and posteriorly by the superior meatus [6]. Anatomically, the ethmoid air cells are grouped into anterior and posterior cells divided by the basal lamella. The posterior ethmoid cells drain into the superior meatus above the middle nasal concha, while the anterior group drains into the middle meatus via the infundibulum [7].

The ethmoid cells are innervated by sensory fibers from the anterior and posterior ethmoidal nerves, both originating from the nasociliary nerve on the medial wall of the orbit. The nasociliary nerve arises from the ophthalmic division of the trigeminal nerve [6]. The anterior ethmoid nerve descends toward the nasal cavity from the anterior cranial fossa. The posterior ethmoid nerve follows a similar route more posteriorly, allowing it to innervate a segment of the sphenoid sinus as well. Postganglionic parasympathetic innervation, responsible for stimulating mucus secretion, is derived from the pterygopalatine ganglion of the facial nerve and enters the nasal cavity through the sphenopalatine foramen [6].

Arterial supply to the ethmoid sinus is predominantly sourced from two branches of the ophthalmic artery. The anterior ethmoid artery travels with the anterior ethmoid nerve through the anterior ethmoidal foramen to supply the anterior ethmoid air cells. The posterior ethmoid artery

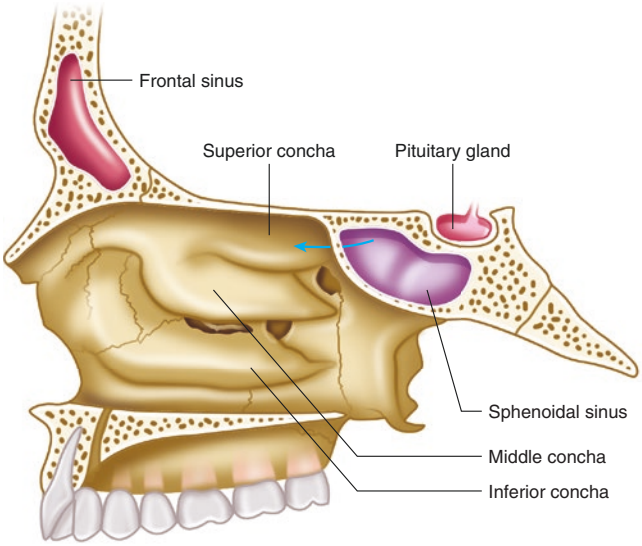


Fig. 4.4 Sphenoid sinus

enters the cavity through the posterior ethmoid foramen and supplies the posterior part of the sinus. It should further be noted that branches of the sphenopalatine artery can anastomose with the ethmoidal arteries.

Sphenoid Sinus

The sphenoid sinus is the most posterior of the paranasal sinuses and consists of two wedge-shaped cavities separated by an irregular septum below the pituitary gland and hypophyseal fossa (Fig. 4.4) [8]. It is bordered inferiorly by the nasopharynx and pterygoid canal, laterally by the infero-

lateral aspects of the cavernous sinus, and anteriorly by the nasal cavity. It drains into the nasal cavity through its ostium, which resides in the sphenoethmoidal recess. The sphenoid sinus is not present at birth, but instead develops with the growth of the skull, completing development with puberty [9].

The sphenoid sinus is innervated by two branches of the trigeminal nerve, the posterior ethmoid nerve from the ophthalmic branch and the orbital branch of the pterygopalatine ganglion from the maxillary division. The posterior ethmoid nerve enters the cavity through the posterior ethmoidal foramen to provide dual innervation to both the sphenoid sinus and the proximal posterior ethmoid air cells. The orbital branch of the pterygopalatine ganglion enters the orbit via the inferior orbital fissure and occasionally provides innervation to the sphenoid sinus.

Blood supply to the sphenoid sinus is provided by the posterior ethmoid artery and posterior lateral nasal artery branches. The former derives from the ophthalmic artery of the internal carotid artery, traveling with the posterior ethmoid nerve through the posterior ethmoidal foramen to supply both the sphenoid sinus and the posterior ethmoid air cells. The latter arises from the sphenopalatine artery of the maxillary artery to anastomose with the ethmoidal arteries [8].

Frontal Sinus

The paired frontal sinuses are located between the outer and inner tables of the frontal bone. The anterior table is a thick bony wall while the posterior table is thinner. The posterior wall of the frontal sinus forms the anterior wall of the anterior cranial fossa. The sinuses are often asymmetric in size and are separated by an intersinus septum located in the midline. They are bordered by the orbit inferolaterally and by the dura, cribriform plate, and frontal lobes of the brain posteriorly.

The anatomic shape of the frontal sinus can be thought of as an hour glass structure with the narrowest point corresponding to the frontal sinus ostium (Fig. 4.4). The frontal ostium opens into the frontal recess, which is described as an inverted, cone-shaped space. The frontal recess merges with the anterior ethmoid cells ultimately draining into the semilunar hiatus of the middle meatus. The frontal sinus is innervated by branches of the supraorbital nerve originating from the ophthalmic nerve (CN V1). The supraorbital and supratrochlear arteries of the ophthalmic artery provide blood supply to the frontal sinus [10].

Conclusion

The paranasal sinuses are complex structures lined by pseudostratified ciliated epithelium with many notable functions. They serve to reduce the weight of the skull, provide resonance for phonation, help regulate humidity and temperature, filter air, and provide immunologic benefits. It is important to understand the embryologic origin and anatomy of the sinuses in order to understand common paranasal sinus pathology. As one can imagine, infection, environmental toxins, impaired ciliary clearance, and immunocompromised states can disrupt normal physiology leading to pathologic states [1, 2].

References

1. Baroody FM. Nasal and paranasal sinus anatomy and physiology. Clin Allergy Immunol. 2007;19:1–21.
2. Stammberger HR, Kennedy DW, Anatomic Terminology Group. Paranasal sinuses: anatomic terminology and nomenclature. Ann Otol Rhinol Laryngol Suppl. 1995;167:7–16.
3. Woo I, Le BT. Maxillary sinus floor elevation: review of anatomy and two techniques. Implant Dent. 2004;13(1):28–32.
4. Ogle OE, Weinstock RJ, Friedman E. Surgical anatomy of the nasal cavity and paranasal sinuses. Oral Maxillofac Surg Clin North Am. 2012;24(2):155–66, vii.
5. van den Bergh JP, ten Bruggenkate CM, Disch FJ, Tuinzing DB. Anatomical aspects of sinus floor elevations. Clin Oral Implants Res. 2000;11(3):256–65.
6. Norton NS, Netter FH, Machado CAG. Ethmoid sinus. In: Netter's Head and neck anatomy for dentistry. Amsterdam: Elsevier; 2017. p. 328.
7. Hechl PS. Endoscopic anatomy of the paranasal sinuses. Berlin: Springer; 2013. p. 9–28.
8. Norton NS, Netter FH, Machado CAG. Sphenoid sinus. In: Netter's Head and neck anatomy for dentistry. Amsterdam: Elsevier; 2017. p. 332.
9. Jacob S. Head and neck. In: Human anatomy: a clinically-orientated approach. Edinburgh: Churchill Livingstone Elsevier; 2007. p. 211.
10. Dassi CS, Demarco FR, Mangussi-Gomes J, Weber R, Balsalobre L, Stamm AC. The frontal sinus and frontal recess: anatomical, radiological and surgical concepts. Int Arch Otorhinolaryngol. 2020;24(3):e364–75. https://doi.org/10.1055/s-0040-1713923.

Skeletal Disharmony

5

Steven Halepas, Soomin Park, and Bridget Ferguson

Introduction

The goal of treating dental malocclusion is to restore functional and esthetic skeletal and dental alignment and promote a proper oral health environment. The proper dental anatomy relationship is critical for preventing other pathological diseases in the mouth and jaws as well as improving the patient's psychosocial well-being [1]. Skeletal disharmony is an umbrella term. Skeletal disharmony is often used to denote the inappropriate relationship between the upper and lower jaws. When discussing skeletal disharmony, one evaluates first the bony positioning of the face, i.e., if the maxilla is excessive or deficient, and then if the mandible is excessive or deficient. The functional relationship between the maxilla and mandible is then evaluated. Steiner was one of the first to relate the cranial base to the maxilla and mandible and by doing that one could pinpoint the offending jaw. When evaluating the dental malocclusion, one evaluates the relationship between the molars and the canines between the upper and lower jaws. Patients can have a skeletal discrepancy, such as a deficient maxilla, or a dental discrepancy, such as the first molars aligning with the wrong teeth, or commonly, a combination of both (see Table 5.1). The goal of this chapter is not to provide the reader with how to diagnose and treatment plan patients with skeletal disharmony, but rather educate the practitioner on these disorders and provide insight into the treatment modality.

Table 5.1 Definitions [2]

Basic terminologies:
1. The maxilla is a term for the upper jaw.
2. The mandible is the lower jaw.
3. Mesial refers to closest to the midline of the mouth or anterior.
4. Distal refers to farther from the midline or posterior.
5. Buccal/facial/labial refers to the side closest to the cheek or lips.
6. Lingual/palatal refers to the side closest to tongue or palate.
7. Teeth crowding takes place when there is not enough space for the teeth to be placed in the dental arch.
8. Diastema is a notable gap between each adjacent tooth.
9. The dental arch form is looking at the overall curvature of individual upper and lower jaw and how anterior and posterior teeth are aligned in the transverse plane.
10. Elliptical arch form is when all teeth are aligned in a nice gradual curvature without much notable indentation in the arch form.
11. The square arch form is when the right and left back teeth are parallel to each other.
12. Tapering arch from is when the right and left line connecting the curvature of the posterior teeth makes a V shape, tapering toward the front teeth.
13. Malocclusion is the improper alignment of biting or chewing surfaces of upper and lower teeth.
14. An occlusal surface is a surface of a posterior tooth or occlusion rim that is intended to make contact with an opposing occlusal surface.
15. Occlusion is any contact between biting or chewing surfaces of maxillary (upper) and mandibular (lower) teeth.
16. Orthognathic is the functional relationship between the maxilla and mandible.

Craniofacial Development

The craniofacial bones continue to grow long after the fetal period. The maxilla grows downward and forward due to the continued growth of the brain and cranial base. The maxilla will descend and increase in vertical height while the zygomas are also repositioned downward and forward. The fron-

S. Halepas (✉)
Division of Oral and Maxillofacial Surgery, NewYork-Presbyterian/Columbia University Irving Medical Center, New York, NY, USA
e-mail: sh3808@cumc.columbia.edu

S. Park
College of Dental Medicine, Columbia University, New York, NY, USA
e-mail: sp3887@cumc.columbia.edu

B. Ferguson
College of Dental Medicine, Columbia University, New York, NY, USA

Oral and Maxillofacial Surgery, Orlando Veterans Administration, Orlando, FL, USA

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_5

tozygomatic, frontonasal, and frontomaxillary sutures grow in a vertical position while the nasomaxillary and temporozygomatic suture grow in a horizontal direction [3]. The midpalatal suture and the zygomaticomaxillary suture provide the transverse growth of the maxilla [3].

The mandible has the most delayed growth, which is why surgical repair of most skeletal disharmony is held until the growth is complete. At birth, the right and left bodies of the mandibles are separate until after a year when the midline symphysis fuses [3]. The mandible grows upward and backward in the rami and the posterior alveolar ridges postnatally, and the rate of growth peaks around 6 months after birth [3]. The continued backward growth of the condylar cartilage serves to increase the ramus height and the growth of alveolar ridge expands the mandibular body height predominantly. During childhood, the condylar growth leads to greater increase in height than length yet the variability of the ratios is well reflected from the general population. The final growth of the mandible is influenced by the downward nasomaxillary growth and dental eruption until the end of adolescence [3].

Skeletal Relationships

Maxillary Hypoplasia

An individual can exhibit maxillary hypoplasia if the upper jaw is small relative to the rest of the face (see Fig. 5.1). Maxillary hypoplasia marks underdevelopment of maxillary and is commonly associated with the following craniofacial differences: Crouzon syndrome, Angelman syndrome, fetal alcohol syndrome, cleft lip, or cleft palate. The maxillary deficiency can lead to dysphagia, nasopharyngeal airway restrictions, as well as sleep apnea.

Maxillary Hyperplasia

An individual can exhibit maxillary hyperplasia if the upper jaw is big relative to the rest of the face. Maxillary hyperplasia presents an abnormally enlarged maxilla in relation to the mandible and leads to the malocclusion and malalignment of the teeth. Patients are typically known to have the "gummy smile."

Mandible Hypoplasia

An individual with mandible hypoplasia can have a relatively smaller lower jaw in relation to the rest of the face (see Fig. 5.2). Mandible hypoplasia exhibits underdevelopment of the mandible, resulting in abnormal teeth alignment as well as upper airway obstruction. The chin is small and displaced backward.

Mandible Hyperplasia

An individual with mandible hyperplasia can have a relatively big lower jaw in relation to the rest of the face. Mandible hyperplasia or mandibular condylar hyperplasia is marked by an excessive growth of the mandible, the most common being the unilateral condylar hyperplasia where one condyle outgrows the other resulting in facial asymmetry.

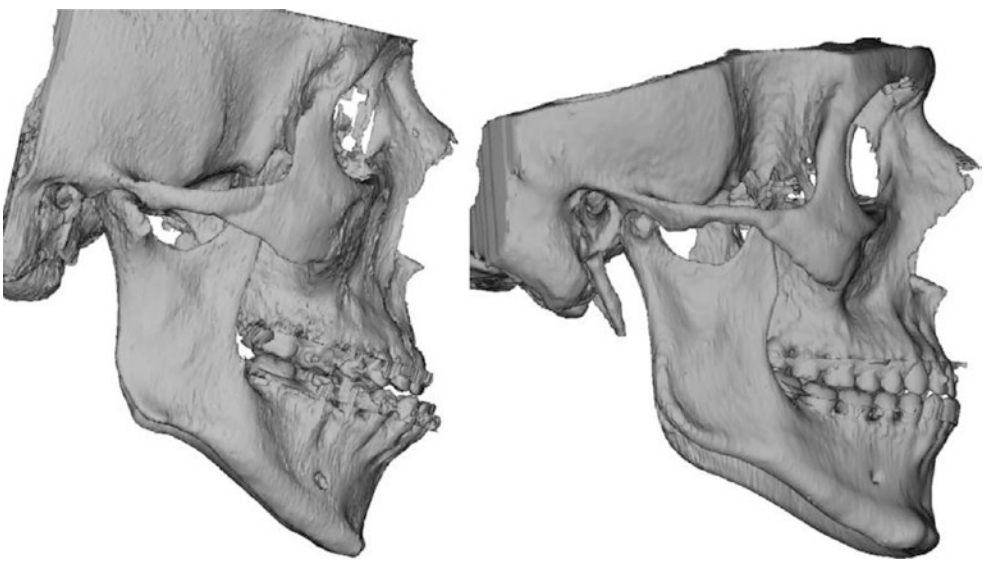


Fig. 5.1 A patient with maxillary hypoplasia (left) and a patient with maxillary hyperplasia (right)

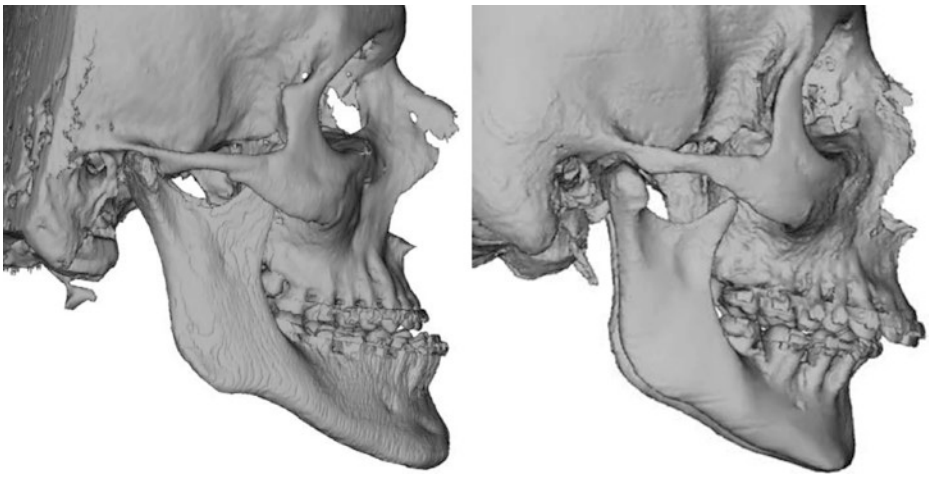


Fig. 5.2 (Left) A patient with mandibular hyperplasia and (right) a patient with mandibular hypoplasia

Dental Relationships

Angle's classification of dental malocclusion is the most used modalities to identify the relationship between the teeth. Angle defines three different classes, Class I, II, and III, and uses the cusp of the upper first molar, and the groove of the lower first molar [4–6] (see Fig. 5.3a, b). Class I is considered the ideal occlusion. The mesiobuccal cusp (the front cusp closest to the cheek) of the upper first molar aligns with the buccal groove (line in the middle of the tooth on the side closest to the cheek) of the lower first molar [7]. The canine relationship is such that the maxillary canine occludes with the distal half of the mandibular canine and the mesial half of the mandibular first premolar [7]. The teeth all fit align with each other with a smooth curve throughout.

Class II is when the mesiobuccal groove of the mandibular first molar is posterior to the mesiobuccal cusp of the upper first molar. The mesial incline of the upper canine occludes anteriorly with the distal incline of the lower canine. Class II is further divided into two sections. Class II has two divisions where division I has the maxillary anterior teeth proclined and an overjet is present, meaning the front teeth stick out and there is a large gap between the top and bottom front teeth [7]. An overjet is when the upper anterior teeth are horizontally inclined, aligning closer to the transverse plane. Division II has the maxillary anterior teeth retroclined and an overbite is present. An overbite is when the upper anterior teeth cover more than one-third of the lower anterior teeth height in a bite position.

Class III is characterized by protrusion of the mandible beyond the maxillary teeth and manifests as an underbite [8]. A patient with severe underbite displays a forward protrusion of the chin and the mandible, and biting using the upper and lower incisors is difficult.

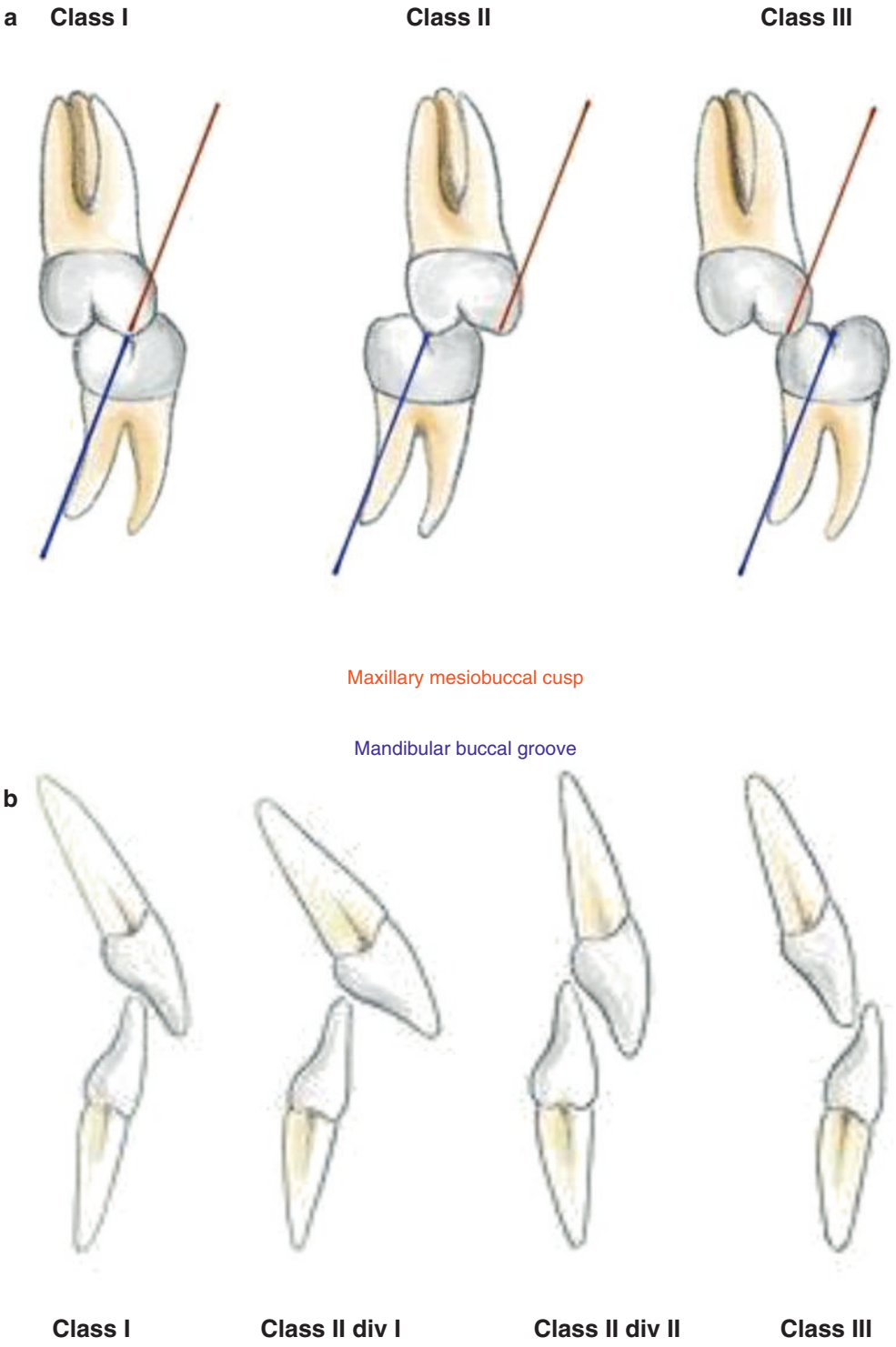


Fig. 5.3 (**a**) Angles Class I, Class II, and Class III dental relationships for molars. (Public domain image. Reproduced without alterations. https://commons.wikimedia.org/wiki/File:Molar_relationship.jpg. Date accessed: 06.05.21). (**b**) Angles Class I, Class II, and Class III dental relationships for incisions. (Public domain image. Reproduced without alterations. https://commons.wikimedia.org/wiki/File:Incisal_class.jpg. Date accessed: 06.05.21)

Relationship Between Malocclusion and Skeletal Disharmony

It is important to acknowledge the difference between dental and skeletal classifications. The dental classifications (Class I, II, and III) can often be manipulated by orthodontics (braces) to achieve the Class I relationship. This however would not help the skeletal discrepancy. In a skeletal Class I relationship, the maxillary and mandibular arch profile is straight and both planes are equally protruded. In skeletal Class II, there are three possible cases where first there is mandibular hypoplasia, resulting in a retruded mandible and

a Class II dental bite. Second, one can have maxillary hyperplasia leading to the relative retrusion of the mandible and protrusion of the maxilla. Lastly, maxillary hyperplasia and mandibular hypoplasia can result in similar Class II malocclusion. Similarly with a skeletal Class III patient, it could be due to maxillary hypoplasia or mandibular hyperplasia. According to the National Health and Nutrition Examination Survey (NHANES) from 2008, about 80–85% of the population were categorized to skeletal Class I, 15% in skeletal Class II, and 1% in skeletal Class III [9].

Medical History

The patient's medical history should be obtained, and any existing medical problems can be further discussed with the appropriate physicians and specialists. Identifying potential complications with general anesthesia or surgical intervention can be noted.

Craniofacial Conditions and Skeletal Disharmony

Currently, 13 craniofacial syndromes are identified to severely affect dental skeletal relations [10]. While surgical options are limited, an interdisciplinary diagnosis and treatment planning between medical and dental specialists can lead to proper function of craniofacial development often in conjunction with orthognathic surgery.

Neurofibromatosis Type I

Neurofibromatosis type I (NF1) is characterized by growth of tumors on skin, nerve, and brain and is very clinically heterogeneous; café-au-lait spots and Lisch nodules are few of the clinical hallmark features. Patients with NF1 commonly present with notable craniofacial differences such as macrocephaly, micrognathia, high arched palate, and Class III molar relationship [11].

Pierre Robins Sequence

Pierre Robins sequence (PRS) is marked by a growth defect of the embryonic mandible along with mutations in cartilaginous structures [12]. PRS is commonly presented with cleft palate and varying degrees of mandibular hypoplasia or micrognathia, with reduced jaw length and size [10]. Patients also display glossoptosis, a relatively enlarged tongue that can easily obstruct the airway [13, 14].

Hemifacial Microsomias

Hemifacial microsomia (HFM) presents with uni- or bilateral ear abnormalities. As of 2005, HFM was the second most common craniofacial condition after cleft palate affecting 4000–5600 live births. Commonly manifested as a sporadic condition, HFM presents with craniofacial asymmetry and mandibular condyle, maxillary, and zygomatic hypoplasia often on the same side as the ear abnormality for unilateral HFM [15].

Treacher Collins Syndrome

Treacher Collins syndrome (TCS) is largely an autosomal dominant condition affecting the ears, eyes, cheekbones, and jaw with variable expressivity. Most TCS patients present with mandibular hypoplasia and cleft palate [16]. Notably, the majority of the TCS patients displayed hypoplasia of the maxilla and a retrognathic mandible [10].

Stickler's Syndrome

Stickler's syndrome is an autosomal dominant disorder affecting the connective tissues and clinically presents with flattened midface or midfacial hypoplasia, micrognathia, cleft palate, and varying degrees of vision, hearing, and articulation difficulties [17, 18].

Beckwith-Wiedemann Syndrome

Beckwith-Wiedemann syndrome (BWS) is characterized by somatic gigantism and macroglossia, and often, glossectomy is performed [19]. Open bite and skeletal Class III manifestations due to enlarged jaw and constricted maxilla are common [20].

Assessment of the Facial Skeleton

The complex positioning and growth of dentofacial structures make it difficult to accurately and correctly discriminate important features that influence dental occlusion. In order to classify various dentofacial disturbances, understanding the different assessment tools and available categories is critical. For clarity, while classes and types are synonymous, classes are often used to describe dental malocclusion and types are used as descriptors of skeletal relationships. A complete diagnosis includes an extensive association between skeletal disharmony and malocclusions.

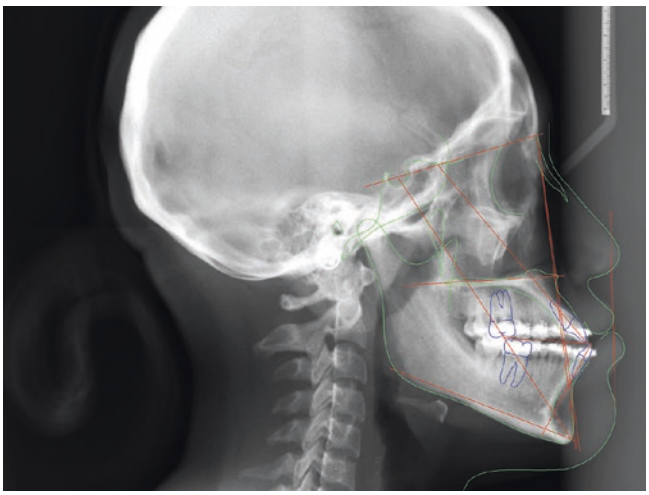


Fig. 5.4 Example of a cephalometric tracing

Cephalometry is the study and measurement of the human head. Dental and skeletal analyses, or cephalometric analyses, are often used by dentists, orthodontists, and oral and maxillofacial surgeons as a clinical diagnosis and treatment tool (see Fig. 5.4). Dental and skeletal analyses are measured in relation to a facial landmark or plane on the lateral cephalogram. Traditionally, these cephalometric analyses were hand traced but nowadays cephalometric software such as QuickCeph® and Dolphin Imaging® are available [21].

Rickett's Cephalometric Analysis

Rickett's analysis identifies five separate measurements: (1) the facial angle, (2) the XY axis angle, (3) the measure of contour, and (4 and 5) the relationship of the upper and lower incisors to the APo plane (A-Pogonion plane) [22]. These measurements provide numerical values for facial depth, facial height, and profile contour, which facilitates communication and comparison to different conditions and cases [22].

Down's Analysis

Down's analysis is one of the most commonly used cephalometric analysis that includes five skeletal and five dental parameters. It is often used to determine the degree of retrognathism and prognathism [21].

Steiner Analysis

Steiner's method was proposed as certain skeletal and dental landmarks such as the orbitale and porion were often difficult to identify and thus Steiner centers its reference to point nasion. While Steiner's method is not applicable to larger skeletal discrepancies, it includes skeletal, dental, and soft tissue analyses [21].

Planar Assessment

Frontal Plane

The frontal plane relationship is used to assess the superior and inferior facial relationship.

Transverse Plane

The transverse plane relationship is used to assess the right and left facial relationship.

Sagittal Plane

The sagittal plane relationship is used to assess the anterior–posterior facial relationship.

Soft Tissues Relationship and Facial Types

An individual with a relatively broader cranial width compared to the lower jaw dimension is assessed to be ***brachiocephalic***. It is often marked by a broad, square head shape.

An individual with a broad square face with a prominent chin, straight facial profile, and low mandibular plane angle is assessed to be ***brachyfacial or hypodivergent***.

An individual with narrower cranial width with long and narrow facial shape and high mandibular plane angle is assessed to be ***dolichocephalic or hyperdivergent***.

An individual with a long narrow face with a high mandibular facial angle, less prominent chin development, and convex facial profile is assessed to be ***dolichofacial***.

An individual with features in between brachycephalic and dolichocephalic with average cranial width is assessed to be ***mesocephalic***.

An individual with balanced facial features is assessed to be ***mesofacial***.

Frontal Facial View

The frontal facial view is used to pick up right and left facial asymmetry, which is often associated with craniofacial syndromes.

Facial Midline

A facial midline is drawn perpendicular to the interpupillary line and the mid-glabella line to the tip of the nose down the philtrum and through the midline of the chin.

Dental Midline (Midsagittal Line)

Each dental arch—maxillary and mandibular—possesses its own midline and the relative position of the different dental midlines can be used to evaluate different occlusal patterns.

Maxillary dental midline is drawn perpendicular to the upper jaw occlusal plane and the line drawn through the proximal contacts of upper central incisors [23].

Mandibular dental midline is drawn perpendicular to the lower jaw occlusal plane and the line drawn through the proximal contacts of lower central incisors [23].

Lip Line

Lip line marks the vertical position of the lower border of the upper lip and evaluates the amount of tooth or gingival tissues exposed at rest.

Smile Line

The smile line assesses the amount of tooth and gingival tissues exposed during a strained smile. The maximum upper lip elevation is studied and categorized in high, average, and low smile. For assessing different lip lines, the relative position of the cervical line, a line drawn through each tooth's mid-cervical point in the esthetic zone, and the upper lip line are compared.

Facial Profile

Evaluating the facial profile is a critical step in identifying and treating occlusal issues. The facial profile is drawn connecting three prominent facial features: ***Glabella*** or the brow ridge, ***subnasale*** or the point of nasal septum emergence, and ***pogonion***, which marks the most anterior point on the chin. The three points are marked and connected to draw the facial profile, and different classifications of convex, concave, or straight can be determined. Straight or the ideal facial profile will display 169°.

Dental Plane

Sagittal Dental Relationship

Angle Classification is one of the first malocclusion classification methods regarding the sagittal dental relationship. It compares the mesiobuccal cusp of the first upper molar and the buccal groove of the first lower molar.

There are three classifications: Class I, II, and III.

Anterior tooth position (overjet, anterior crossbite).

Transverse Dental Relationship

A posterior crossbite can be evaluated via the transverse dental relationship. A posterior crossbite is present when the upper jaw is narrower than the bottom and the top back teeth occlude inside the bottom back teeth.

Vertical Dental Relationship

An overbite and open bite can be assessed through the vertical dental relationship.

An overbite is present when the incisors of the upper jaw overlap over 2 mm of the incisors of the lower jaw.

An open bite is when there is no overlap of the upper and lower jaws leading to no or improper contact between the incisors.

Corrective Surgeries

Many different surgical options exist for the treatment of skeletal disharmony. While this is not an exhaustive list, most treatments include maxillary osteotomies such as a Le Fort 1 osteotomy, and mandibular osteotomies such as bilateral sagittal split osteotomy (BSSO), intraoral vertical ramus osteotomy (IVRO), the inverted "L" osteotomy, and genioplasty. If the skeletal disharmony is corrected earlier, other treatment options exist such as distraction osteogenesis or surgically assisted rapid palatal expansion (SARPE).

The maxillary osteotomies are utilized when patients have maxillary hypoplasia or hyperplasia, or when a vertical or transverse discrepancy exists. If a transverse discrepancy is present, sometimes a two- or three-piece Le Fort 1 osteotomy is preformed where additional cuts are made between the teeth to expand the maxilla (see Fig. 5.5). The incisions for a Le Fort 1 incision are all inside of the mouth. After dis-

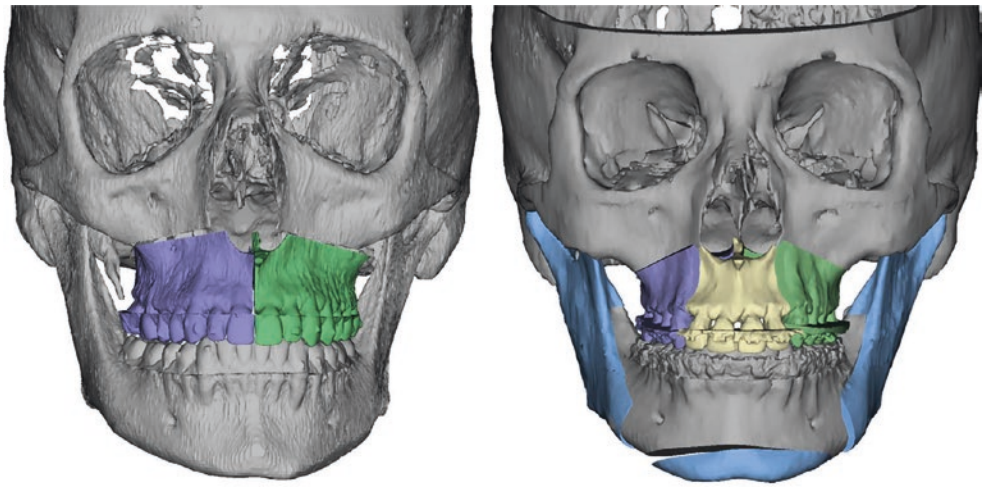


Fig. 5.5 Virtual surgical planning of a two-piece Le Fort 1 osteotomy (left) and a three-piece Le Fort 1 osteotomy (right)

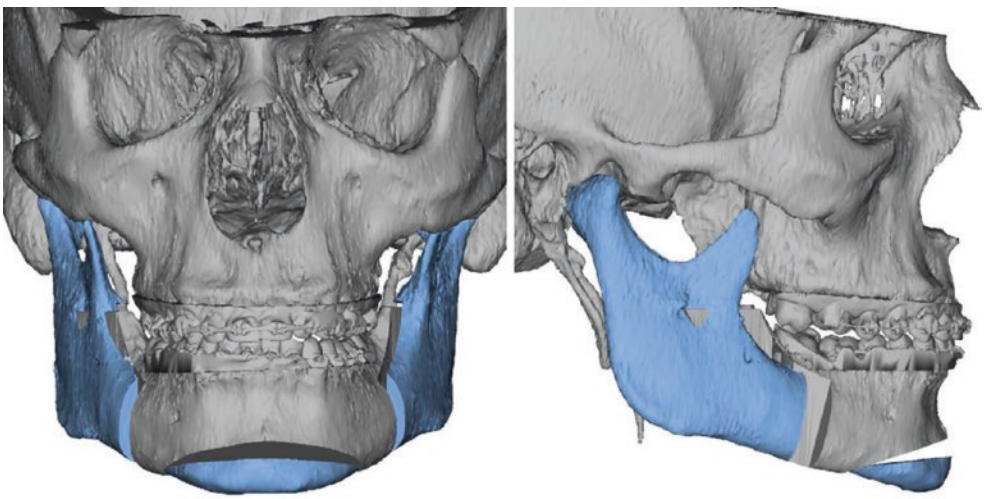


Fig. 5.6 Virtual surgical planning of a bilateral sagittal split osteotomy and genioplasty of a severely Class II patient

section to bone is carried out, the Le Fort 1 osteotomy is completed with bone saws and osteotomes. The maxilla is down fractured and repositioned using the prefabricated surgical splint. The blood supply is maintained via the soft tissue. Four individual plates or a custom titanium plate is used to fixate the maxilla. The oral mucosa is then sutured with dissolvable sutures.

A SARPE (surgically assisted rapid palatal expansion) is a combination of a modified Le Fort 1 osteotomy and distraction osteogenesis. The cuts are all intraoral, similar to the Le Fort 1 osteotomy. The cuts are placed in the anterior maxillary wall and the lateral maxillary wall. A palatal osteotomy is made through the hard palate just posterior to the incisive foramen. A distinct difference between SARPE and the Le Fort 1 osteotomy is that the maxilla is not down fractured. The orthodontist places a device to facilitate expansion of the maxilla in the transverse plane prior to the surgery. The patient will then be able to expand the maxilla at home with a special key until the desired expansion is complete.

Mandibular osteotomy surgical techniques are utilized when patients have mandibular hypoplasia or mandibular hyperplasia and the lower jaw needs to be moved. A BSSO is one of the most common techniques for patients with mandibular discrepancies (see Fig. 5.6). All the incisions for a BSSO and a genioplasty are generally made inside of the mouth. In some instances, a small (2–3 mm) incision will be made on the skin to allow a trocar to be placed for placement of the plates and screws. Since this technique utilizes a split, it provides good bone overlap to allow for proper healing regardless if it is moved forward or backward. Its position allows for the placement of bi-cortical screws or titanium plates at the osteotomies to allow for rigid fixation. Rigid fixation minimizes the need for patients to be wired shut in maxillary–mandibular fixation during the healing process. The drawback, however, is the cut is in the same plane as the inferior alveolar nerve, which is why the final osteotomy is performed by a "split" with osteotomies. A cut is placed just below the cortices above the inferior alveolar

nerve. The fracture is propagated along the plane of the preformed cut and split.

IVROs are another type of mandibular osteotomy where all the incisions are again inside the mouth. Instead of cuts being placed along the ramus in a sagittal direction, the cuts are vertical, behind the lingula to prevent damage to the inferior alveolar nerve (see Fig. 5.7). This technique can only be utilized for mandibular setbacks because plates and screws are not typically used. Instead, bony overlap of the setbacks during the segments allows for proper healing and the patient is wired shut for a period of 4–6 weeks.

Mandibular distraction osteogenesis is another type of surgery used to correct skeletal discrepancies. It can be utilized in many instances but a classic example is in neonates with a retrognathic mandible causing respiratory insufficiency. Mandibular osteotomies are made and a titanium device is placed to stabilize the segments (see Fig. 5.8). The distraction arms extend extraoral just below the ears. Practitioners' protocols vary by institution but typically the devices are turned to advance 0.9 mm twice a day. After the advancement is complete, the extraoral arms are disconnected and the titanium device is left in place for several weeks while the bone heals. The hardware is then removed to allow continued growth of the mandible as the child develops.

Many surgical procedures can be utilized to correct the skeletal discrepancy. While this summary is nowhere exhaustive, it covers the vast majority most patients would likely receive. While these corrective skeletal surgeries can have huge impact on function, it also provides a large esthetic benefit to patients (see Fig. 5.9).

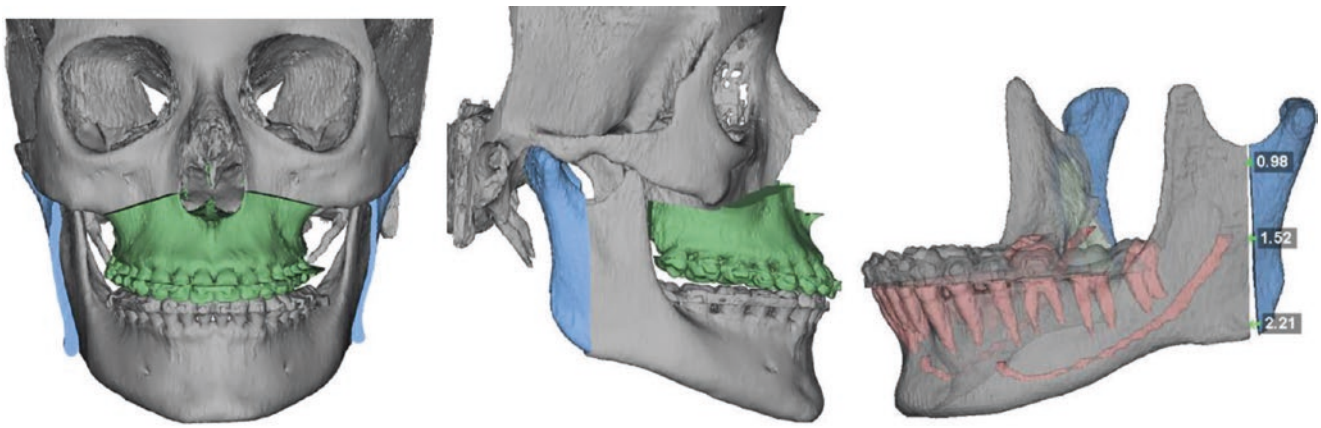


Fig. 5.7 Virtual surgical planning of a Le Fort 1 osteotomy and a intraoral vertical ramus osteotomy (IVRO)

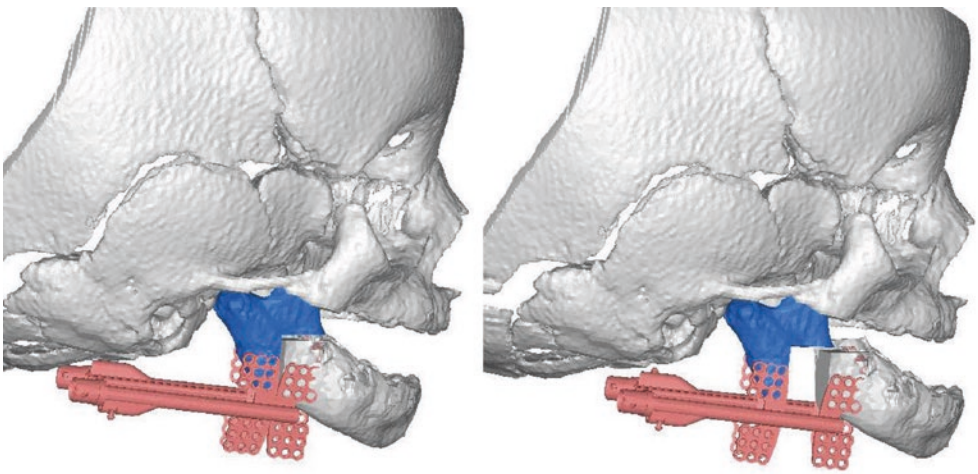


Fig. 5.8 Virtual surgical planning of mandibular distraction device placement

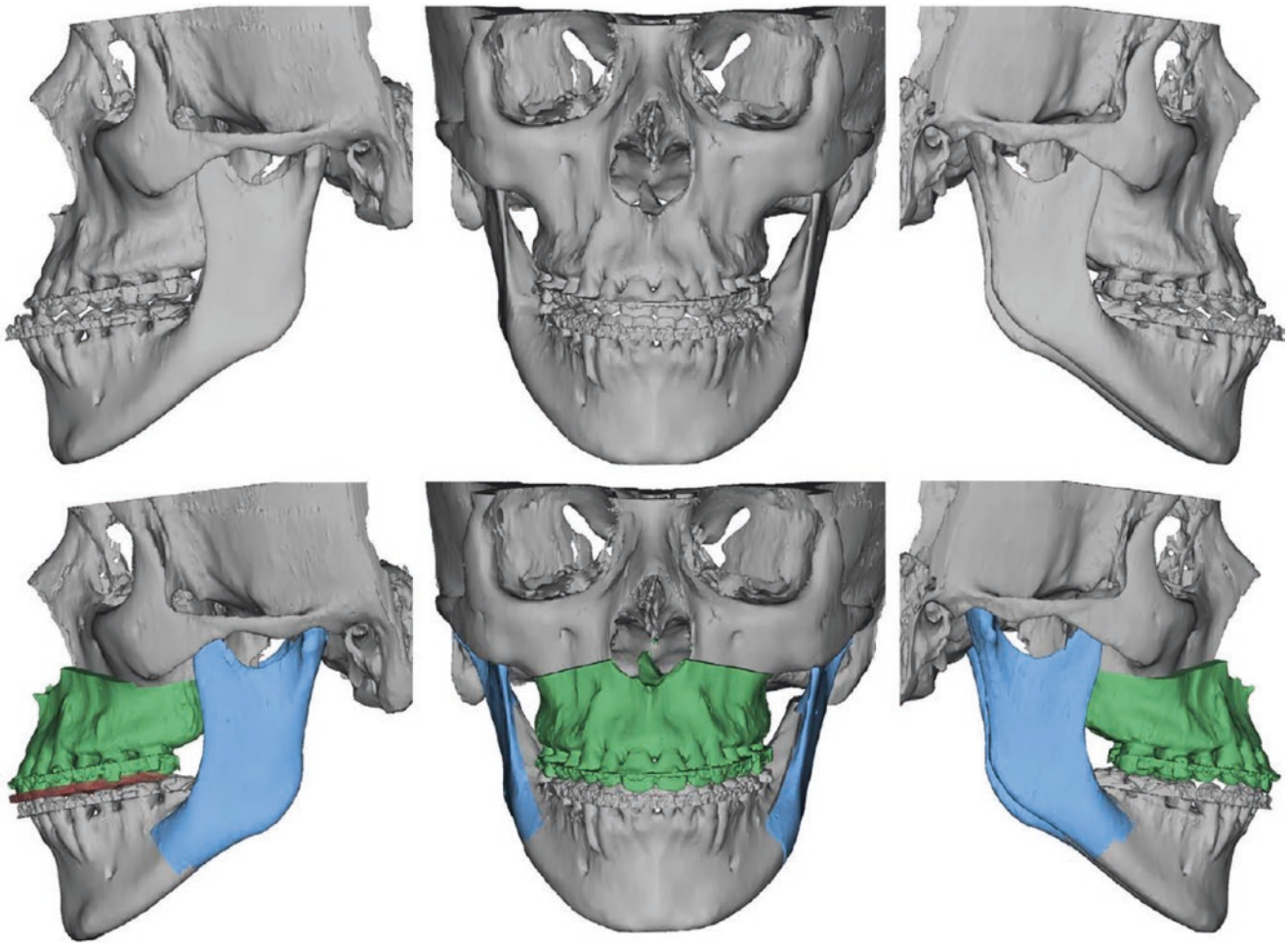


Fig. 5.9 Pre (top) and post (bottom) illustration from a virtual surgical planning session

Post-operative Course

As physicians and surgeons of other specialties, it is important to be generally familiar with the surgery and the typical post-operative course of patients who might undergo this type of procedure. In modern practice, most patients who have orthognathic surgery undergo 2–5 h of the procedure under general anesthesia and are often discharged the next day. During the procedure, the anesthesiologist often provides intentional hypotension with a Mean Arterial Pressure (MAP) of 60 to reduce bleeding when down fracturing the maxilla. The average length of hospitalization in orthognathic surgery is 1.7 days [24]. The hospital admission is used to evaluate post-operative anesthesia recovery as well as ensure the patient can maintain fluid intake requirements. As with any other surgical procedures, adequate fluid intake and early mobilization out of bed is vital to recovery. In the authors' experience, most patients complain of minimal pain due to the transient hypoesthesia following the procedure.

Patients are placed on a liquid diet for at least 4 weeks. Soft foods are reintroduced at weeks 4–6 and are slowly advanced over a period of 3 months. Patients need to avoid contact sports for at least 3–4 months following the procedure. While showering is okay, submerging the head while bathing or swimming needs to be avoided for at least 4 weeks. Patients are placed on scheduled ibuprofen and acetaminophen for control of pain and swelling as well as dexamethasone while admitted. Antibiotics maybe utilized if a bone graft was placed at the surgical site. Discharge medications typically include ibuprofen 600 mg q6h, acetaminophen 500 mg q6h, oxycodone 5 mg × 10 tabs, fluticasone and saline nasal sprays (if maxillary surgery performed), and

5 days of antibiotics if a bone graft was used (amoxicillin 500 mg Three times a day (TID) or clindamycin 300 mg TID). Most patients' major complaint following the procedure is facial swelling/discomfort and a sore throat.

Complications

The most common post-operative complication is nerve damage. While up to 80% of patients complain of immediate post-operative hypoesthesia, for the vast majority much or all of the sensation will return over a period of weeks to months. In a review by Sousa and Turrini in 2012, nerve damage was reported following 12.1% of surgeries. Infection was second most common post-operative complication, seen in 3.4% of cases. Problems arising from the plates and screws used during the surgery account for the third most common source of complications, at 2.5% of cases. This was followed by temporomandibular joint disorders at 2.1%, undue fractures at 1.8%, and scarring at 1.7% [25]. Permanent numbness of the lower lip at surgery is reported in the literature as low as 1% [26], while damage to the lingual nerve is very rare. One study investigated nerve damage in 100 patients and reported the incidence of permanent injury to the lingual nerve was 2/100 patients [27, 28], although the authors believe this is much higher than in the general population and is likely due to the small sample size.

Summary

Skeletal disharmony can be troublesome for patients. Discrepancy in the facial bones can be both an esthetic and functional issue. Orthognathic surgery to reposition the jaws can result in better skeletal harmony that can improve mastication, decrease temporomandibular joint pain, increase airway space, decrease risk of Obstructive sleep apnea (OSA), and provide better facial esthetics. While this chapter is not exhaustive in the diagnosis and treatment modalities of skeletal dysplasias, hopefully the medical practitioner is now more familiar with these disorders and the treatment modality. While the surgeries to correct these issues are invasive, typically result in a hospital admission, and require several weeks of healing, patients typically are very satisfied with the improved quality of life.

References

1. Pahkala RH, Kellokoski JK. Surgical-orthodontic treatment and patients' functional and psychosocial well-being. Am J Orthod Dentofac Orthop. 2007;132:158.
2. Proffit WR. Contemporary orthodontics. 5th ed. St. Louis, MO: Elsevier/Mosby; 2013.
3. Miloro M, Peterson LJ. Peterson's principles of oral and maxillofacial surgery. In: Online resource (2 volumes, xxi). 3rd ed. Shelton, CT: People's Medical Publishing House-USA; 2012. p. 1.
4. Ackerman JL, Proffit WR. The characteristics of malocclusion: a modern approach to classification and diagnosis. Am J Orthod. 1969;56:443.
5. Angles E. The upper first molar as a basis of diagnosis in orthodontics. Dent Items Interest. 1906;28:421.
6. Salzmann JA. The angle classification as a parameter of malocclusion. Am J Orthod. 1965;51:465.
7. Mageet A. Classification of skeletal and dental malocclusion: revisited. Stomatol Edu J. 2016;3:38.
8. Ngan P, Hu AM, Fields HW Jr. Treatment of class III problems begins with differential diagnosis of anterior crossbites. Pediatr Dent. 1997;19:386.
9. Simmons HC III, Oxford DE, Hill MD. The prevalence of skeletal class II patients found in a consecutive population presenting for TMD treatment compared to the national average. J Tenn Dent Assoc. 2008;88:16.
10. Bartzela TN, Carels C, Maltha JC. Update on 13 syndromes affecting craniofacial and dental structures. Front Physiol. 2017;8:1038.
11. Quintáns B, Pardo J, Campos B, Barros F, Volpini V, Carracedo A, Sobrido MJ. Neurofibromatosis without neurofibromas: confirmation of a genotype-phenotype correlation and implications for genetic testing. Case Rep Neurol. 2011;3:86.
12. Butow KW, Hoogendijk CF, Zwahlen RA. Pierre Robin sequence: appearances and 25 years of experience with an innovative treatment protocol. J Pediatr Surg. 2009;44:2112.
13. Suri S, Tompson BD, Cornfoot L. Cranial base, maxillary and mandibular morphology in down syndrome. Angle Orthod. 2010;80:861.
14. Cote A, Fanous A, Almajed A, Lacroix Y. Pierre Robin sequence: review of diagnostic and treatment challenges. Int J Pediatr Otorhinolaryngol. 2015;79:451.
15. Akram A, McKnight MM, Bellardie H, Beale V, Evans RD. Craniofacial malformations and the orthodontist. Br Dent J. 2015;218:129.
16. Posnick JC, Ruiz RL. Treacher Collins syndrome: current evaluation, treatment, and future directions. Cleft Palate Craniofac J. 2000;37:434.
17. Suda N, Handa S, Higashihori N, Ogawa T, Tsuji M, Ohyama K. Orthodontic treatment of a patient with stickler syndrome. Angle Orthod. 2007;77:931.
18. Acke FR, Dhooge IJ, Malfait F, De Leenheer EM, De Pauw GA. Cephalometrics in stickler syndrome: objectification of the typical facial appearance. J Craniomaxillofac Surg. 2016;44:848.
19. Hikita R, Kobayashi Y, Tsuji M, Kawamoto T, Moriyama K. Long-term orthodontic and surgical treatment and stability of a patient with Beckwith-Wiedemann syndrome. Am J Orthod Dentofac Orthop. 2014;145:672.
20. Kawafuji A, Suda N, Ichikawa N, Kakara S, Suzuki T, Baba Y, Ogawa T, Tsuji M, Moriyama K. Systemic and maxillofacial characteristics of patients with Beckwith-Wiedemann syndrome not treated with glossectomy. Am J Orthod Dentofac Orthop. 2011;139:517.
21. Oria A, Schellino E, Massaglia M, Fornengo B. [A comparative evaluation of Steiner's and McNamara's methods for determining the position of the bone bases]. Minerva Stomatol. 1991;40:381.
22. Ricketts RM. A foundation for cephalometric communication. Am J Orthod. 1960;46:330.
23. Beyer JW, Lindauer SJ. Evaluation of dental midline position. Semin Orthod. 1998;4:146.

24. Huamán ET, Juvet LM, Nastri A, Denman WT, Kaban LB, Dodson TB. Changing patterns of hospital length of stay after orthognathic surgery. J Oral Maxillofac Surg. 2008;66:492.
25. Sousa CS, Turrini RNT. Complications in orthognathic surgery: a comprehensive review. J Oral Maxillofac Surg Med Pathol. 2012;24:67.
26. Choi BK, Lee W, Lo LJ, Yang EJ. Is injury to the inferior alveolar nerve still common during orthognathic surgery? Manual twist technique for sagittal split ramus osteotomy. Br J Oral Maxillofac Surg. 2018;56:946.
27. McLeod NM, Bowe DC. Nerve injury associated with orthognathic surgery. Part 3: lingual, infraorbital, and optic nerves. Br J Oral Maxillofac Surg. 2016;54:372.
28. McLeod NM, Bowe DC. Nerve injury associated with orthognathic surgery. Part 2: inferior alveolar nerve. Br J Oral Maxillofac Surg. 2016;54:366.

Salivary Glands

6

Arthur R. Hand

Abbreviations

AQP5	Aquaporin-5
CFTR	Cystic fibrosis transmembrane regulator
CMV	Cytomegalovirus
Cyclic AMP	3′,5′-cyclic adenosine monophosphate
EB	Epstein-Barr virus
EGF	Epidermal growth factor
FGF-10	Fibroblast growth factor-10
FGFR2b	Fibroblast growth factor receptor-2b
HIV-1	Human immunodeficiency virus-1
IgG	Immunoglobulin G
IgG4-RD	Immunoglobulin G4-related disease
IgM	Immunoglobulin M
IP_3	Inositol trisphosphate
LADD	Lacrimo-auriculo-dento-digital syndrome
MMR	Measles-mumps-rubella vaccine
PKA	Protein kinase A
PKC	Protein kinase C
PRPs	Proline-rich proteins
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
S-IgA	Secretory immunoglobulin A
SLPI	Secretory leukocyte protease inhibitor
SS	Sjögrens syndrome
TFF3	Trefoil factor 3
TGFα	Transforming growth factor alpha
TLRs	Toll-like receptors
VEGF	Vascular endothelial growth factor

A. R. Hand (✉)
Department of Craniofacial Sciences, School of Dental Medicine, UConn Health, Farmington, CT, USA
e-mail: hand@uchc.edu

Introduction

The salivary glands are exocrine glands that secrete *saliva*, a watery fluid that contains electrolytes, proteins, mucins, and other substances that create and regulate the environment of the oral cavity and serve to protect the oral tissues and facilitate taste, mastication, swallowing, and speech. There are three *major salivary glands*—the *parotid*, *submandibular*, and *sublingual* glands—that are located bilaterally outside the oral cavity and have long ducts that convey the saliva to the mouth. Except for the gingivae, the anterior dorsum of the tongue, and some regions of the hard palate, the mucosal lining of the oral cavity also contains hundreds of small glandular aggregates, the *minor salivary glands*, with ducts that open individually onto the mucosal surface. Saliva secretion is regulated by both branches of the autonomic nervous system and stimulated mainly by activation of taste receptors and oral mechanoreceptors. The salivary glands can be affected by local and systemic conditions, including neoplasms. The most common patient complaint related to the salivary glands is a "dry mouth" due to reduced secretion of saliva as a result of damage to the glands by autoimmune diseases or radiation, or by the use of drugs that affect salivary function.

This chapter reviews the anatomy of the salivary glands, their histology and development, the secretion, composition and functions of saliva, and its potential role as a diagnostic fluid. Also discussed are some of the more common pathological conditions of the glands, including salivary hypofunction and its causes, duct obstruction, infections and inflammation, and neoplasms.

Anatomy

The largest salivary gland, the parotid gland, is located on the side of the face, anterior to the external ear and superficial to the masseter muscle (Fig. 6.1). A portion of the gland wraps around the posterior edge of the mandibular ramus

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_6

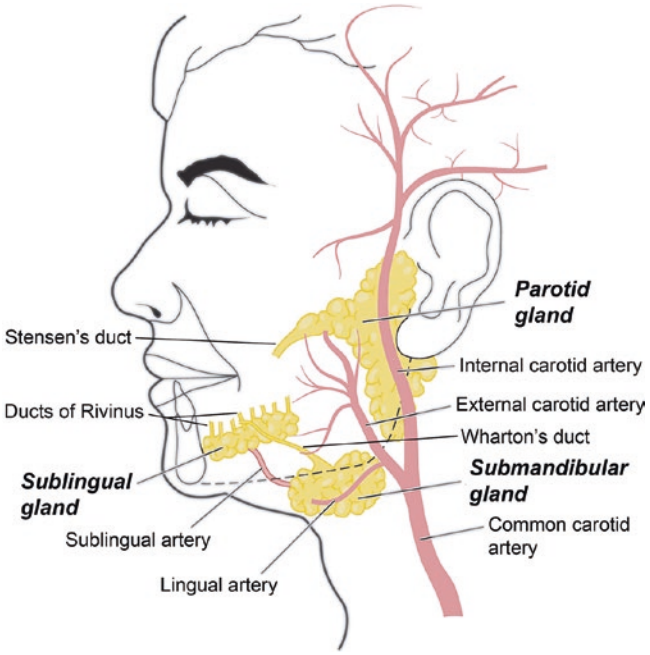


Fig. 6.1 Location of the major salivary glands. (Modified from Blamb/Shutterstock.com)

and neck. The main duct (*Stensen's duct*) extends anteriorly over the masseter muscle, then penetrates the buccinator muscle and opens at the parotid papilla on the buccal mucosa opposite the maxillary second molar. Branches of the facial nerve (cranial nerve VII) course through the gland, and branches of the carotid artery provide the blood supply. The parasympathetic secretory innervation is derived from the glossopharyngeal nerve (cranial nerve IX) via the otic ganglion and the auriculotemporal nerve. The sympathetic secretory innervation originates from the upper thoracic spinal cord, synapses in the superior cervical ganglion, and accompanies the blood vessels supplying the gland.

The submandibular gland is located in the submandibular space, inferior to the mylohyoid muscle (Fig. 6.1). A portion of the gland extends posterior and superior to the mylohyoid. The main duct (*Wharton's duct*) travels anteriorly below the floor of the mouth and opens at the sublingual caruncle by the lingual frenum. Branches of the lingual artery provide the blood supply of the gland. The parasympathetic secretory innervation travels via the facial (cranial nerve VII), chorda tympani, and lingual nerves, synapsing in the submandibular ganglion. Like the parotid, the sympathetic secretory innervation travels with the blood vessels supplying the gland.

The sublingual gland is located below the floor of the mouth (Fig. 6.1). The main duct (*Bartholin's duct*) opens with the submandibular duct at the sublingual caruncle, and several small ducts (*ducts of Rivinus*) open along the sublingual fold. The sublingual artery provides the blood supply of the gland. Similar to the submandibular gland, the sublingual gland receives its parasympathetic secretory innervation from the submandibular ganglion, and its sympathetic innervation accompanies the blood supply.

Histology

A fibrous connective tissue capsule encloses each of the major salivary glands [1]. Septa of connective tissue extend into the gland, dividing it into *lobes* and smaller *lobules* (Fig. 6.2). Blood vessels, nerves, lymphatic vessels, and excretory ducts are present in the septa. The parenchymal tissue within the lobules is organized into *secretory endpieces*, or *acini*, and a system of intralobular *ducts* that modify the secretory product of the acinar cells, primary saliva, and convey it to the interlobular excretory ducts (Fig. 6.2). The secretory endpieces consist of a roughly spherical or tubular arrangement of secretory cells around a central lumen that is confluent with the initial part of the duct system. The intralobular ducts consist of a simple cuboidal or columnar epithelium. All of the parenchymal components are surrounded by loose connective tissue within which reside fibroblasts, plasma cells, mast cells, macrophages, dendritic cells, and the occasional lymphocyte. The smallest branches of the vascular system, arterioles, capillaries, and venules, and the unmyelinated fibers of the autonomic nerves innervating the secretory and duct cells, also are found in the connective tissue between the individual parenchymal components.

There are two types of secretory cells found in salivary glands, *serous cells* and *mucous cells* (Fig. 6.3). Serous cells secrete a variety of proteins and glycoproteins, electrolytes, and water. Their structure is characterized by the presence of a spherical nucleus located in the basal cytoplasm, abundant rough endoplasmic reticulum, a prominent Golgi complex, and dense secretory granules stored in the apical cytoplasm (Fig. 6.4). The luminal surface of serous cells has a few small microvilli and is expanded by *intercellular canaliculi* that extend along the lateral surfaces between adjacent cells toward the basal surfaces of the cells. Junctional complexes, consisting of a tight junction, adhering junction, and one or more desmosomes, hold adjacent cells together and separate the luminal surface from the lateral and basal cell surfaces. Gap junctions involved in cell–cell communication are present on the lateral cell surfaces.

The main secretory product of mucous cells is mucin; only a few other organic substances have been identified as

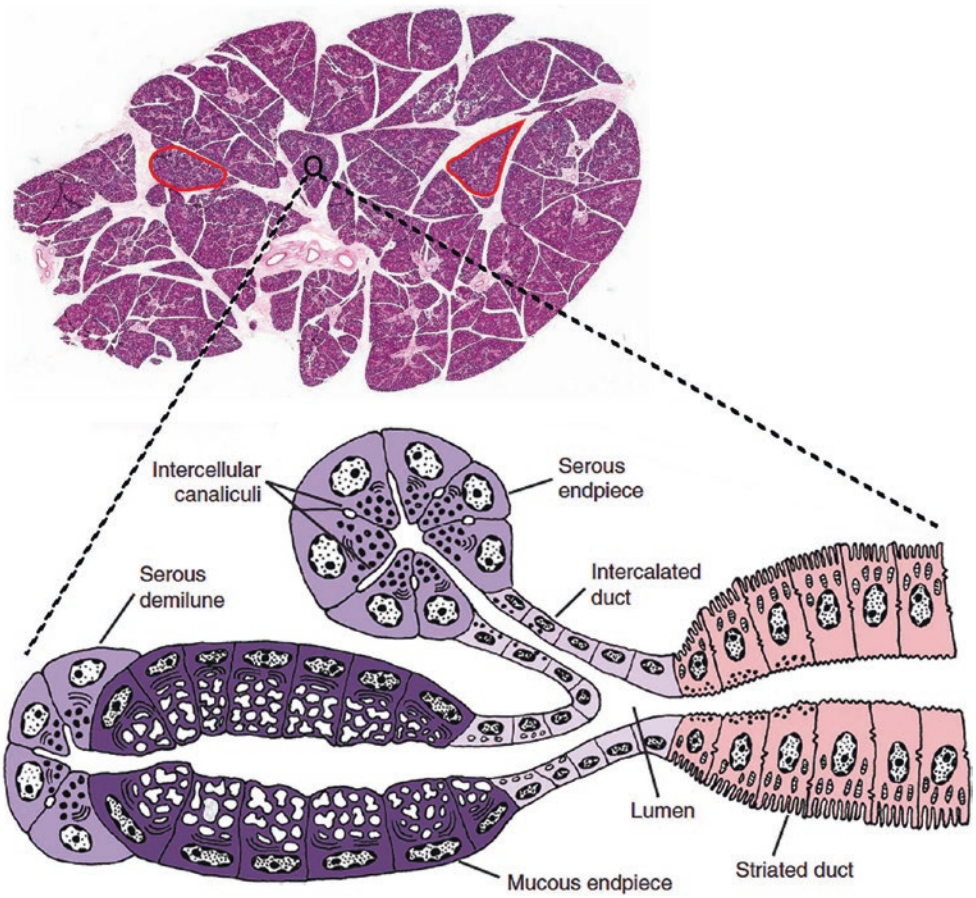


Fig. 6.2 Low-magnification view of human submandibular gland section with two lobules outlined in red. The diagram shows serous and mucous secretory endpieces and the intralobular components of the duct system. (Modified from [1]; reprinted with permission from Wiley-Blackwell)

mucous cell products. In typical histological preparations, mucous cells are characterized by a large apical mass of often fused, pale secretory granules; a flattened, dense nucleus; rough endoplasmic reticulum; and a large Golgi complex located in the basal cytoplasm (Fig. 6.5). However, this appearance has been shown to be an artifact of the chemical fixatives used to prepare tissue samples. In samples prepared by rapid cryofixation, mucous cell structure is similar to that of serous cells, with distinct, relatively compact secretory granules.

A third epithelial cell type present in the endpieces is the *myoepithelial cell* (Fig. 6.6). These are stellate-shaped contractile cells that are located between the basal lamina and the basal surfaces of the secretory cells. Processes originating from the cell body are filled with actin and myosin filaments and extend around the endpieces. The myoepithelial cells function to support the endpieces, and their contraction forces saliva from the endpiece lumen into and along the duct system. Myoepithelial cells also are located along the initial part of the duct system where they have a spindle shape and extend along the longitudinal axis of the duct. Their contraction serves to shorten and maintain the patency of the ducts.

The secretory endpieces are connected to the first part of the duct system, the *intercalated ducts* (Fig. 6.7). These ducts consist of small cuboidal cells that have a relatively simple structure with few organelles. In cross-section, the diameter of these ducts is always smaller than that of the secretory endpieces, and their lumina also have a small diameter. The cells nearest the endpieces may contain a few secretory granules in their apical cytoplasm; they contribute a few proteins and/or mucins to the saliva. The initial intercalated ducts usually join with other intercalated ducts, forming a larger intercalated duct, which may merge again before joining a striated duct.

The *striated ducts* form the main part of the intralobular duct system (Fig. 6.8). These ducts consist of a simple columnar epithelium surrounding a lumen larger than that of the intercalated ducts, and their overall diameter is as large as or larger than that of the secretory endpieces. The cells have a centrally placed nucleus, and at the light microscopic level the basal region appears to have vertical striations due to the

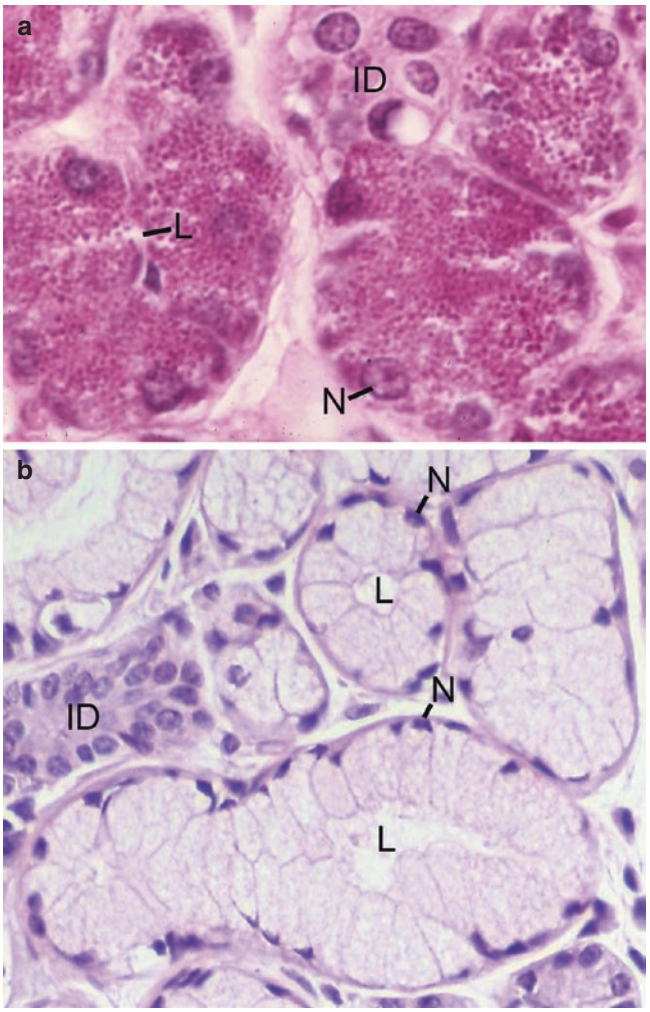


Fig. 6.3 (**a**) Serous cells: Three serous endpieces are seen, each consisting of several serous cells filled with densely stained secretory granules. A small lumen (L) is visible in the center of the endpiece at the left. Nuclei with prominent nucleoli are round to oval and located in the basal cytoplasm. (**b**) Mucous cells: Portions of several mucous endpieces, typically exhibiting a tubular configuration, are present. Lumina (L) are large and the lateral membranes of the mucous cells are distinct. The mucous cell cytoplasm is filled with pale mucous granules and their nuclei are dense and flattened against the basal cell surface. *ID* intercalated duct

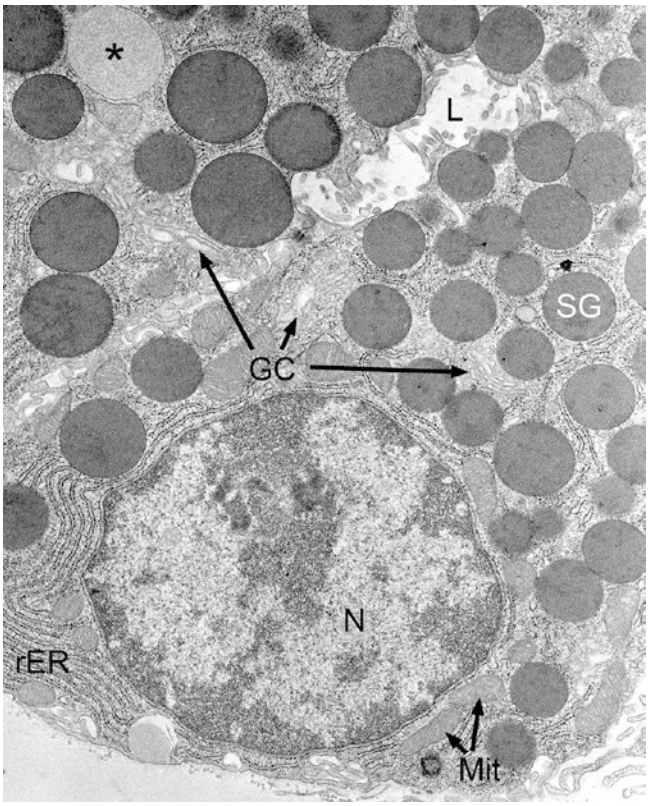


Fig. 6.4 Electron micrograph of a serous cell. The round nucleus (N) is located in the basal cytoplasm along with abundant rough endoplasmic reticulum (rER). The Golgi complex (GC) is in the supranuclear cytoplasm along with numerous dense secretory granules (SG). * immature secretory granule, *L* lumen, *Mit* mitochondria. (Modified from [1]; reprinted with permission of Wiley-Blackwell)

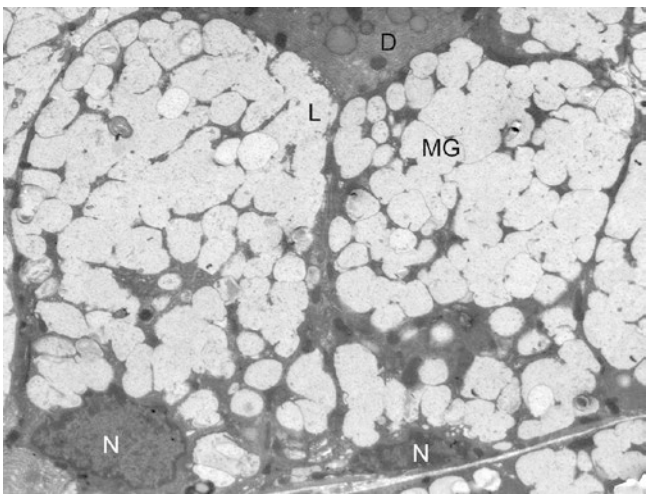


Fig. 6.5 Electron micrograph of two mucous cells. Their cytoplasm is filled with mucous granules (MG) with a light flocculent content. Most of the granules are fused with neighboring granules. The nuclei (N) are dense and located close to the basal cell membrane. A portion of a serous demilune cell (D) is visible at the top. *L* lumen

highly infolded basal cell membrane with numerous mitochondria aligned between the infoldings. The cytoplasm contains a few cisternae of rough endoplasmic reticulum, a small perinuclear Golgi complex, a few lysosomes and peroxisomes, and tubules of smooth endoplasmic reticulum and small vesicles in the apical cytoplasm. In some cells small dense secretory granules are present in the apical region. A few basal cells may be present in larger striated ducts, along with occasional dendritic cells. In addition to conveying the saliva toward the mouth, a significant function of the striated ducts (as well as the excretory ducts) is modification of the primary saliva secreted by the endpieces.

As the striated ducts leave the lobules and enter the interlobular connective tissue, they become *excretory* (or *interlobular*) *ducts* (Fig. 6.9). These ducts typically consist of a pseudostratified epithelium, with small basal cells and columnar cells that extend from the basal lamina to a large lumen. The columnar cells are similar in appearance to striated duct cells, but have fewer basal infoldings, and usually lack apical secretory granules. Occasional dendritic cells may be present, as well as mucous goblet cells in the larger ducts. Tuft cells with prominent microvilli that likely have chemosensory functions are scattered throughout the epithelium. As the excretory ducts merge and eventually form the *main excretory duct*, they increase in size and close to the oral cavity the epithelium may become stratified.

The parotid gland is a *pure serous gland with* all of its secretory endpieces consisting of serous cells (Fig. 6.10). The submandibular and sublingual glands are *mixed glands*, consisting of both serous and mucous cells. The submandibular gland consists predominantly of serous secretory endpieces, but also has mucous secretory endpieces arranged mainly in a tubular configuration (Fig. 6.11). The mucous tubules typically have a few serous cells attached to the end

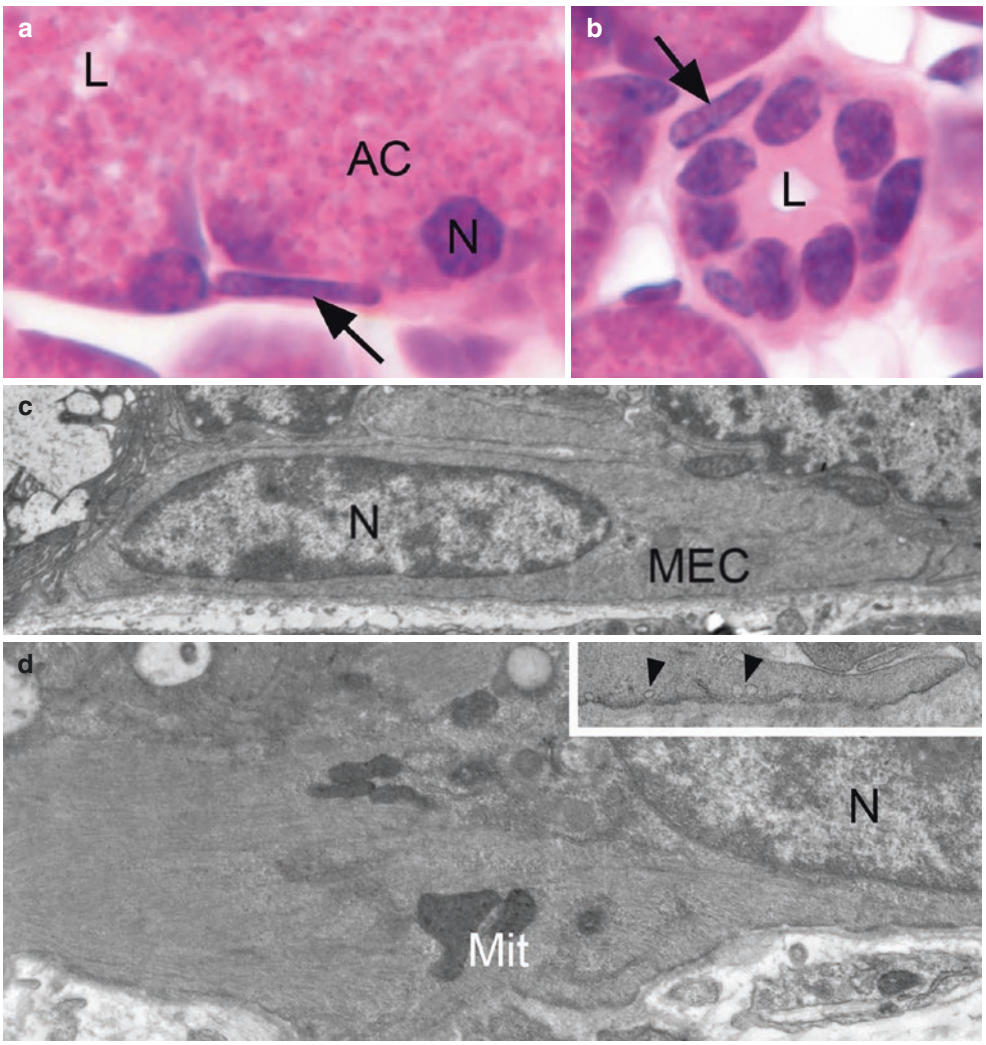


Fig. 6.6 Myoepithelial cells. (**a**) Myoepithelial cell (arrow) along the basal surface of serous acinar cells (AC). (**b**) Myoepithelial cell (arrow) associated with an intercalated duct. (**c**, **d**) Electron micrographs of myoepithelial cells (MEC) at the basal surfaces of mucous acini. The cytoplasm is filled with actin and myosin filaments. The inset in (**d**) shows caveolae (arrowheads) along the basal membrane of the myoepithelial cell. (Image courtesy of Dr. Zaki Hakami). *L* lumen, *Mit* mitochondria, *N* nucleus

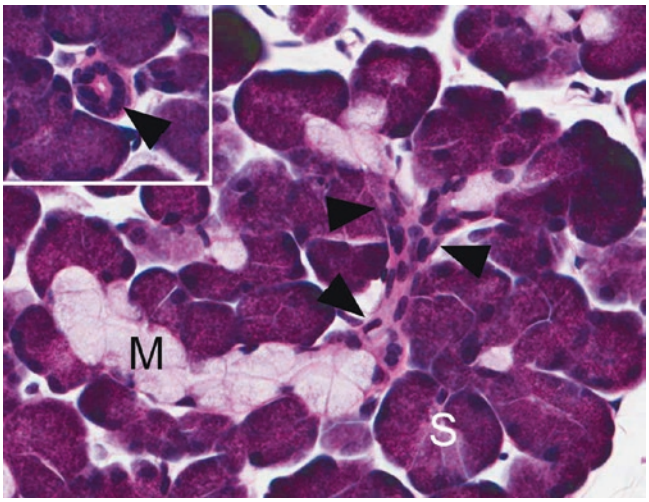


Fig. 6.7 Intercalated ducts. Longitudinal and cross (inset) sections of intercalated ducts (arrowheads). The ducts are smaller in diameter than the endpieces and consist of a simple cuboidal epithelium. A small lumen can be seen in the cross-sectioned duct. *M* mucous endpiece, *S* serous endpiece

of the tubule. This configuration is called a *serous demilune*. The products of the demilune cells reach the main lumen of the mucous tubule via intercellular canaliculi. The sublingual gland consists predominantly of mucous tubules with serous demilunes (Fig. 6.12); a few serous endpieces may be present. With age, an increase in the number of adipocytes present in the loose connective tissue occurs, especially in the parotid and submandibular glands. The main structural features of the major salivary glands are given in Table 6.1.

In addition to the three major glands, hundreds of small *minor salivary glands* are present in the mucosa throughout the oral cavity except for the gingivae, anterior dorsum of the tongue, and parts of the hard palate (Table 6.2) [1, 3]. These glands are located in the lamina propria or submucosa, or between muscle fibers of the tongue, and their ducts open directly onto the surface of the mucosa (Fig. 6.13). Most of the minor glands consist of mucous secretory endpieces; in some glands the mucous endpieces may have associated serous demilunes. An exception is the *lingual serous glands* (of *von Ebner*), associated with the circumvallate and foliate papillae on the posterior dorsal and lateral regions of the tongue (Fig. 6.13c). These are pure serous glands whose ducts open into the troughs of the papillae; they are thought to function in the taste process and maintenance of taste buds. The duct cells of the minor glands are similar to intercalated duct cells. Striated ducts usually are not present in these glands. The minor glands secrete continuously and play an important role in the moistening, lubrication, and protection of the oral mucosa.

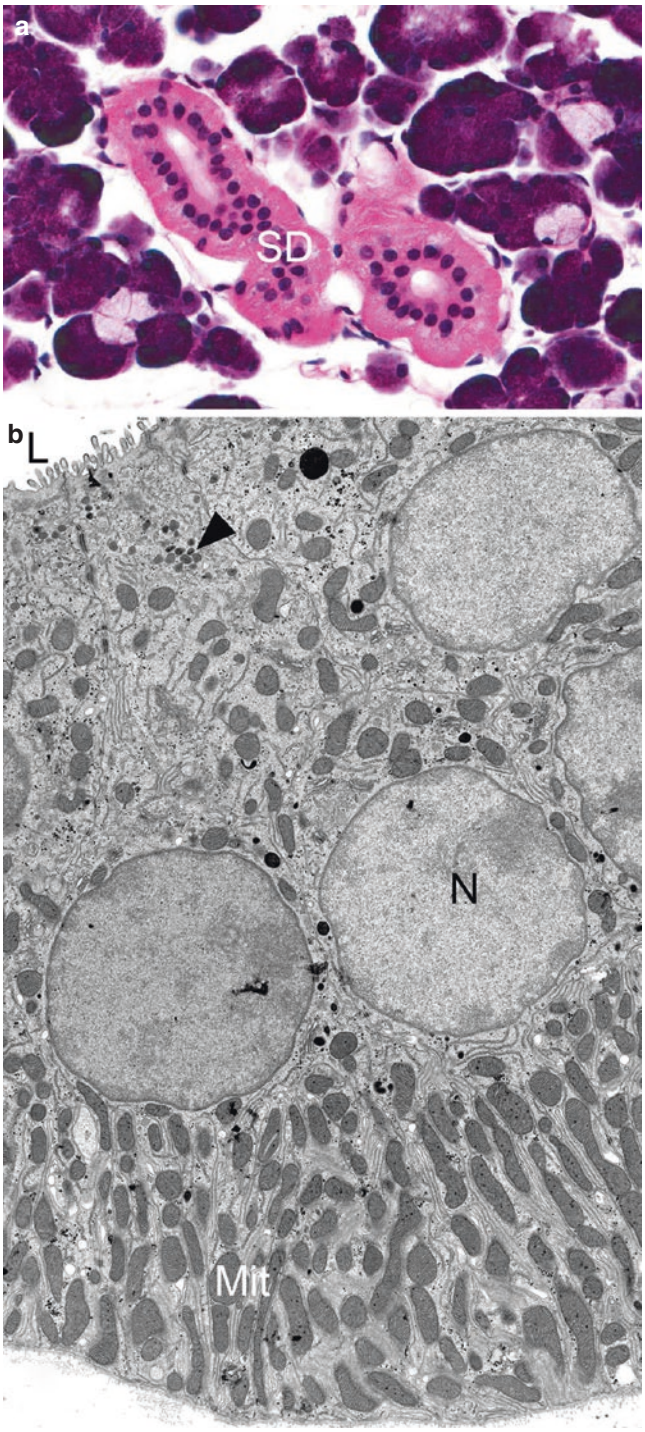


Fig. 6.8 Striated ducts. (**a**) Striated ducts (SD) are lined by a simple columnar epithelium. (**b**) Electron micrograph of striated duct cells. Numerous mitochondria (Mit) are located between infoldings of the basal cell membranes. A few small secretory granules (arrowhead) are present in the apical cytoplasm. *L* lumen, *N* nucleus. (Panel **b**, modified from [2]; reprinted with permission from the American Society for Biochemistry and Molecular Biology)

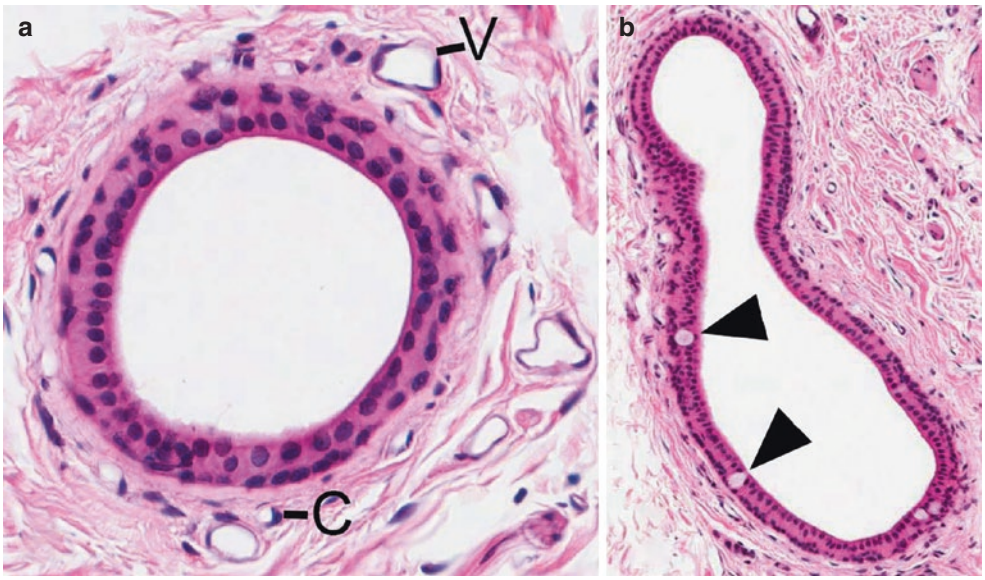


Fig. 6.9 Excretory ducts. (**a**) Medium, and (**b**) large excretory ducts with pseudostratified epithelium. A few goblet cells (arrowheads) are present in the epithelium of the large duct. Numerous small venules (V) and capillaries (C) are present in the connective tissue around the ducts

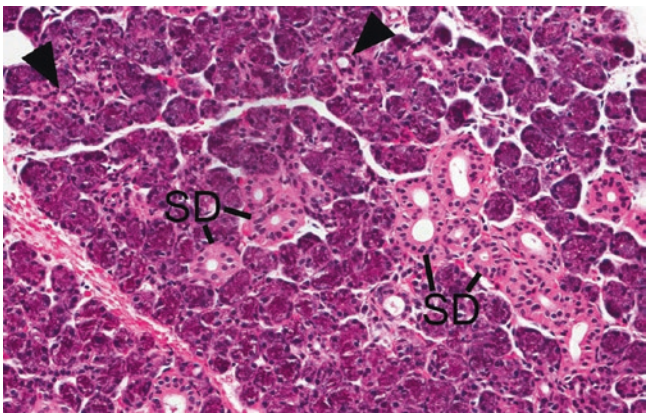


Fig. 6.10 Parotid gland: The parotid consists entirely of serous endpieces. Striated ducts (SD) are numerous and a few intercalated ducts (arrowheads) are visible

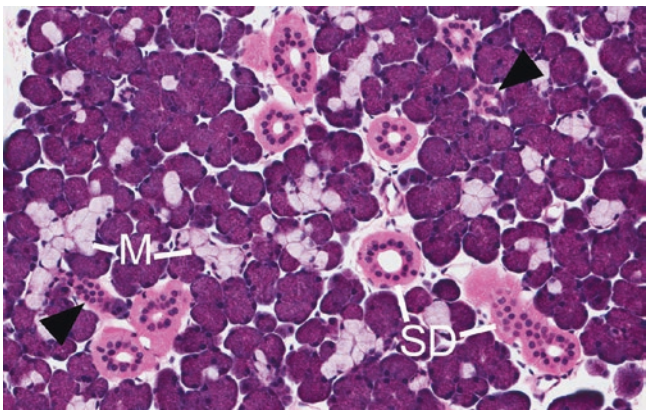


Fig. 6.11 Submandibular gland: The submandibular gland consists mainly of serous endpieces with some mucous endpieces (M). Striated ducts (SD) are prominent and a few intercalated ducts (arrowheads) are visible

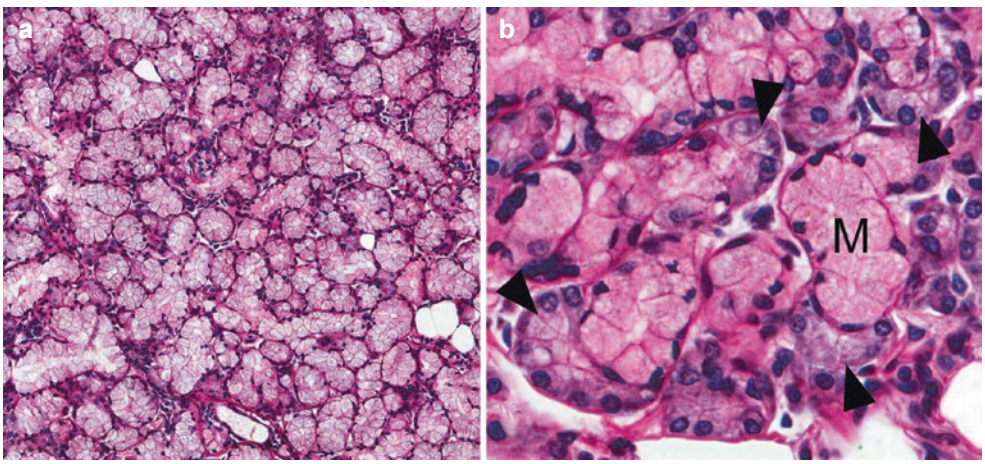


Fig. 6.12 Sublingual gland. (**a**) The sublingual gland consists predominantly of mucous endpieces and has fewer striated ducts than the parotid and submandibular glands; none are seen in this micrograph. (**b**) Higher magnification showing serous demilunes (arrowheads). *M* mucous endpiece

Table 6.1 Major salivary glands

Component	Parotid	Submandibular	Sublingual
Acini	All serous	Mostly serous; some mucous with serous demilunes	Mainly mucous with serous demilunes; a few serous acini may be present
Ducts			
Intercalated	Long, branching	Moderate length	Short, relatively few
Striated	Numerous, well developed	Numerous, well developed	Short, poorly developed
Main excretory	Stensen's; opens at parotid papilla on cheek opposite maxillary second molar	Wharton's; opens at sublingual caruncle at ventral tongue	Bartholin's; opens with submandibular duct at sublingual caruncle; ducts of Rivinus open along sublingual fold
Connective tissue capsule	Well defined	Well defined	Poorly developed
Blood supply	Branches of external carotid artery	Lingual artery	Sublingual artery
Nerve supply			
Parasympathetic	Cranial nerve IX via lesser petrosal nerve, otic ganglion, and auriculotemporal nerve	Cranial nerve VII via chorda tympani nerve, lingual nerve, and submandibular ganglion	Cranial nerve VII via chorda tympani nerve, lingual nerve, and submandibular ganglion
Sympathetic	Superior cervical ganglion with blood supply	Superior cervical ganglion with blood supply	Superior cervical ganglion with blood supply
Development begins	4th–6th fetal week	6th–8th fetal week	8th–12th fetal week

Modified from [1]

Table 6.2 Minor salivary glands

Gland	Location	Histological structure
Labial	Submucosa of lips	Mucous acini, serous demilunes
Buccal	Submucosa of cheeks	Mucous acini, serous demilunes
Palatine		
Hard palate	Posterior lateral submucosa	Mucous acini, serous demilunes
Soft palate	Submucosa of soft palate and uvula	Mucous acini, serous demilunes
Glossopalatine	Isthmus of palatoglossal fold	Mucous acini
Lingual		
Anterior	Ventral submucosa of tongue	Mucous acini, serous demilunes
Posterior	Lamina propria and between muscle fibers posterior to circumvallate papillae	Mucous acini, serous demilunes
Lingual serous	Lamina propria and between muscle fibers of posterior and lateral regions; ducts open into troughs of circumvallate and foliate papillae	Serous acini
Minor sublingual	Submucosa of floor of mouth	Mucous acini, serous demilunes

Modified from [1]

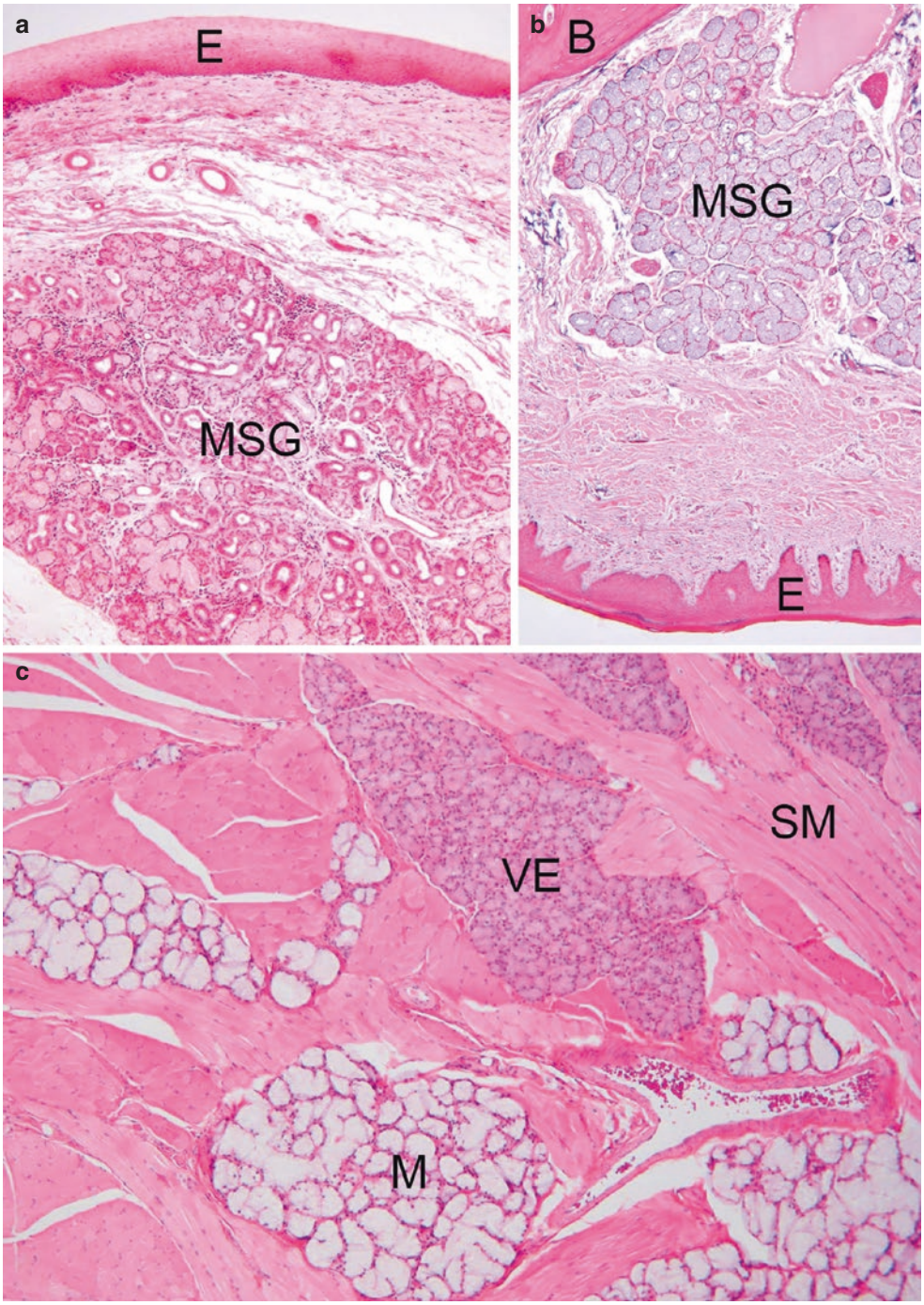


Fig. 6.13 Minor salivary glands. (**a**) Minor salivary gland (MSG) in the submucosa of the lip. (**b**) Minor salivary gland in the submucosa of the hard palate. (**c**) Lingual serous (von Ebner's, VE) glands and mucous (M) glands located between skeletal muscle fibers (SM) of the tongue. *B* bone, *E* oral epithelium. (Panel **c** modified from [1]; reprinted with permission from Wiley-Blackwell)

Development

The salivary glands begin their development as a proliferating bud of epithelial cells of the primitive oral mucosa at the sites where the main ducts will eventually open on the mucosal surface (Fig. 6.14a) [5–7]. The parotid gland arises from ectoderm; the submandibular and sublingual glands originate from the floor of the mouth at the transition between ectoderm and endoderm. A solid cord of cells formed by continued proliferation grows into the mesenchyme underlying the mucosa. Under the paracrine influence of several growth factors produced by the mesenchymal and epithelial cells, and the activity of specific transcription factors, the initial cell cord begins the process of *branching morphogenesis*, with repeated dichotomous branches, that eventually results in a bush- or tree-like structure (Fig. 6.14b). The inner cells of the terminal end buds and connecting cell cords then undergo apoptosis to create lumina, leaving a two-cell-thick

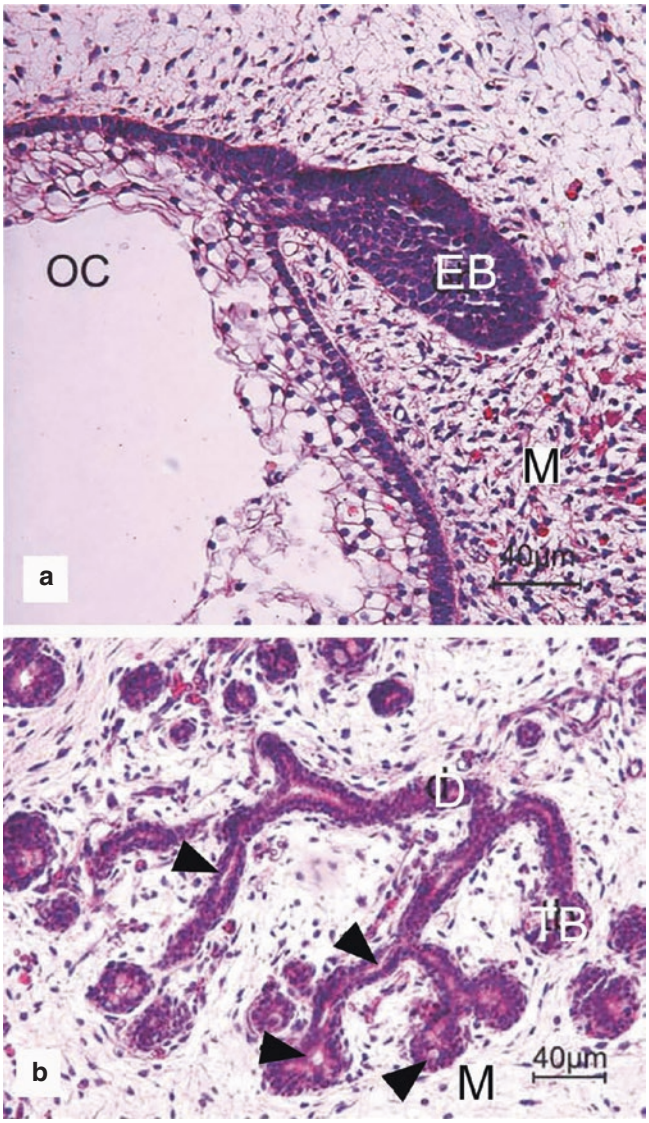


Fig. 6.14 Developing parotid gland. (**a**) An epithelial bud (EB) of proliferating cells from the oral epithelium grows into the underlying mesenchyme (M). Oral cavity (OC). (**b**) Repeated branching of terminal buds (TB) results in a bush-like structure with secretory endpieces and ducts (D) derived from the connecting cell cords. Lumina are forming in the ducts and some terminal buds (arrowheads). (Modified from [4]; reprinted with permission from Wiley-Liss, Inc.)

layer of epithelium. Cytodifferentiation of the cells of the inner layer produces the secretory cells of the endpieces and eventually the cells of the intercalated and striated ducts, whereas the cells of the outer layer differentiate into myoepithelial cells. The secretory cells develop the intracellular organelles of the secretory system and accumulate secretory granules. With the development of the autonomic innervation and functional neurotransmitter receptors on the secretory cells, the ability to secrete saliva is attained.

The development of the parotid gland begins at 4–6 weeks of embryonic life, the submandibular gland at 6–8 weeks, and the sublingual and minor glands at 8–12 weeks. Maturation of the secretory and duct cells is completed in the final 2 months of gestation, and the glands continue to increase in size postnatally.

Salivary Secretion

Secretion of saliva from the three major glands occurs at a low rate in awake individuals in the absence of an external stimulus [1, 8–11]. This *"unstimulated"* or *"resting"* secretion is due to input to the salivary nuclei in the brainstem from higher centers. In healthy adults the resting saliva flow rate ranges from 0.2 to 0.4 mL/min. The submandibular and sublingual glands contribute about two-thirds of the resting saliva, somewhat less than one-third comes from the parotid glands, and only a few percent from the minor glands. Saliva secretion is subject to a circadian rhythm, with peak flow in mid-afternoon and low flow in the early morning. During sleep and anesthesia, there is little to no secretion from the major glands, although the minor glands continue to secrete at a low rate.

Stimulation of taste receptors by taste substances in food and drink provides the most potent stimulus for salivary secretion. Mechanoreceptors in the periodontal ligament and oral mucosa, activated by chewing and movement, also provoke secretion, as do olfactory stimuli. *Stimulated* saliva flow rates may be five- to tenfold greater than resting rates, with the parotid gland making a greater contribution than the submandibular and sublingual glands. The total daily secretion of saliva typically is in the range of 0.6–1.0 L, most of which is swallowed.

The glands receive and respond to both sympathetic and parasympathetic innervation. The unmyelinated autonomic nerve fibers travel in the connective tissue in bundles supported by Schwann cells. In the parotid and submandibular gland, the acinar cells receive a dual sympathetic and parasympathetic innervation, whereas the mucous cells of the sublingual and minor glands are innervated predominantly by parasympathetic fibers.

The secretion of protein by serous cells occurs predominantly by exocytosis at the luminal cell surface of stored secretory granules, mainly in response to sympathetic nerve stimulation. Noradrenaline released by nerve terminals binds to β-adrenergic receptors on the serous cells. These G-protein-coupled receptors activate adenylyl cyclase, which generates cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). The subsequent activation of protein kinase A (PKA) initiates an intracellular signaling cascade involving other proteins and intracellular Ca^{2+} that results in docking of the granules and fusion of their membranes with the luminal cell membrane and discharge of their contents (Fig. 6.15). Parasympathetic nerve stimulation also results in

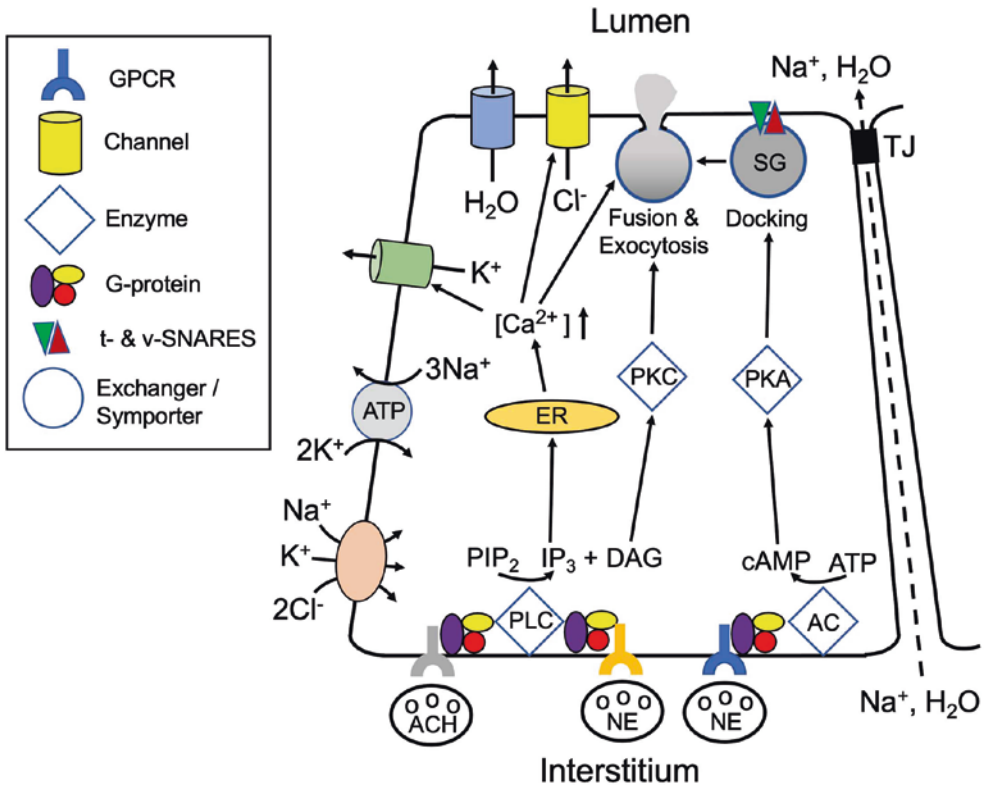


Fig. 6.15 The main pathways regulating fluid and protein secretion in salivary gland acinar cells. Fluid secretion is stimulated primarily by binding of acetylcholine (ACH) released from parasympathetic nerve endings to muscarinic M_3 G-protein coupled receptors (GPCRs) in the basolateral cell membranes. Norepinephrine (NE) released from sympathetic nerve endings elicits a smaller amount of fluid secretion by binding to α_1-adrenergic GPCRs. The $G_{q/11}$ G-protein activates phospholipase C (PLC), which hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to inositol 1,4,5-trisphosphate (IP_3) and 1,2-diacylglycerol (DAG). IP_3 binds to receptors on the endoplasmic reticulum (ER), resulting in release of stored Ca^{2+}. The elevated level of intracellular Ca^{2+} opens Cl^- channels in the luminal cell membrane and K^+ channels in the basolateral membrane. Cl^- efflux creates an electrochemical gradient that pulls extracellular Na^+ into the lumen via the paracellular pathway through tight junctions (TJ). The resulting osmotic gradient causes water to enter the lumen through tight junctions and via aquaporin 5 channels in the luminal membrane. During strong stimulation leading to high salivary flow rates, HCO_3^- efflux via luminal Cl^- channels can contribute to the luminal electrochemical gradient. The Na^+/K^+-ATPase and $Na^+/K^+/Cl^-$ co-transporter in the basolateral membrane, along with other channels and transporters, maintain the cell's pH and ionic equilibria. Protein secretion is stimulated mainly by NE binding to β_1-adrenergic GPCRs. The G_s G-protein activates adenylyl cyclase (AC), which forms cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). cAMP activates protein kinase A (PKA), which phosphorylates other proteins leading to docking of secretory granules (SG) at the luminal cell membrane through interactions of vesicle-associated Soluble *N*-ethylmaleimide-Sensitive Factor Receptor (v-SNARE) and target-associated t-SNARE proteins. Increased Ca^{2+} levels cause fusion of the granule and cell membranes and formation of a pore, resulting in release of the granule content by exocytosis. ACH binding to M_3 receptors, activation of protein kinase C (PKC) by DAG, and increased intracellular Ca^{2+} also result in exocytosis, but at a lower level than β_1-adrenergic receptor stimulation

some protein secretion, at much lower levels than sympathetic stimulation, through protein kinase C (PKC) activation and Ca^{2+} release. Secretion of mucus from mucous cells occurs mainly in response to parasympathetic stimulation.

Fluid and electrolyte secretion by the acinar cells is stimulated predominantly by the parasympathetic nervous system. Acetylcholine released from nerve terminals binds to G-protein-coupled muscarinic M_3 receptors, leading to activation of phospholipase C and the hydrolysis of phosphatidylinositol bisphosphate into diacylglycerol and inositol trisphosphate (IP_3). Binding of IP_3 to its receptor on the endoplasmic reticulum releases Ca^{2+} to the cytoplasm. The increased intracellular [Ca^{2+}] opens Cl^- channels on the luminal membrane, leading to an increase in luminal [Cl^-], which draws extracellular Na^+ into the lumen via the paracellular pathway. The resulting increase in luminal osmotic pressure draws water into the lumen via the paracellular route and also through aquaporin 5 (AQP5) water channels in the luminal membrane (Fig. 6.15). Noradrenaline, binding to G-protein-coupled α-adrenergic receptors, also stimulates some fluid and electrolyte secretion. Sympathetic and parasympathetic stimulation also results in contraction of myoepithelial cells, propelling the saliva into and through the duct system.

This *primary saliva*, which contains the organic products of the acinar cells as well as some substances present in

blood plasma and the extracellular fluid that are transported or diffuse across the epithelium, is essentially isotonic with respect to Na^+ and Cl^- concentrations. As the primary saliva moves through the duct system, it is modified by reabsorption of Na^+ and Cl^- and secretion of K^+ and HCO_3^- by the striated duct cells. Important for this process are the Na^+/K^+/ATPase in the infolded basolateral cell membranes and the abundant mitochondria between the infoldings, along with co-transporters, ion exchangers, and channels in the basolateral and luminal cell membranes, including the cystic fibrosis transmembrane regulator (CFTR). Because the striated ducts are relatively impermeable to water, the resulting saliva that enters the mouth is hypotonic. Na^+ and Cl^- reabsorption also occurs in the excretory ducts, but to a lesser extent than in the striated ducts.

In addition to modifying the electrolyte content of saliva, striated ducts also modify the protein content. The small apical granules present in cells in the first part of the ducts contain *kallikrein*, a serine protease, which is released into saliva. Experimental animal studies have shown that the duct cells are capable of endocytosing salivary and exogenous proteins from the lumen; whether this occurs in human glands is unknown.

Saliva Composition and Function

Saliva consists of about 99% water; the remaining 1% consists of proteins, glycoproteins, mucins, small molecules, and electrolytes (Table 6.3) [1, 8, 11–14]. Its composition varies depending upon the source of the saliva (*glandular saliva*, collected from the main duct of a major gland, or *whole* or *mixed saliva*, the fluid present in the mouth), the specific stimulus evoking secretion, and the physiological condition of the subject. In addition to the components present in glandular saliva as noted above, whole saliva contains oral microorganisms, desquamated oral epithelial cells, and food remnants, as well as molecular components, white blood cells, and fluid derived from the gingival crevice that surrounds each tooth.

Table 6.3 Composition of whole saliva

Parameter	Characteristics
Volume	600–1000 mL/day
Flow rate: resting/stimulated	0.2–0.5 mL per min/2 ≥ 6 mL per min
pH	6.7–7.4
Osmolality	~50–75 mOsm/kg
Electrolytes	Na^+, K^+, Cl^-, HCO_3^-, Ca^{2+}, Mg^{2+}, HPO_4^{2-}, SCN^-, F^-, I^-
Protein concentration	0.5–1.5 mg/mL
Major proteins	Amylase, PRPs, cystatins, mucins, S-IgA, statherin, carbonic anhydrase VI, histatins, lysozyme
Small molecules	Glucose, amino acids, urea, uric acid, lipids
Other components	Growth factors, cytokines, insulin, cyclic AMP-binding proteins, serum albumin

Modified from [1]

The flow of saliva around the oral cavity and swallowing result in the dilution and clearance of food, cellular debris, non-adherent microorganisms, and the metabolic substrates and products of adherent microorganisms. In individuals with reduced salivary function, the prolonged presence of these substances increases the risk of disease. The volume of saliva present in the mouth before a swallow averages 1.1 mL. This volume is spread over the entire surfaces of the teeth and oral mucosa, resulting in a thin film that varies in thickness (0.07–0.1 mm) and rate of movement in different regions of the oral cavity. On the lingual side of the mandibular incisors and the facial side of the maxillary molars, movement of saliva is rapid due to the openings of the ducts of the major salivary glands. In contrast, the presence of only minor glands in the lips results in slow movement of saliva along the facial surfaces of the maxillary incisors.

Saliva also moistens and lubricates the soft and hard tissues of the oral cavity and the pharyngeal and esophageal mucosae. Individuals with reduced salivary function typically complain of a dry mouth and difficulty with chewing, swallowing, and speech. Salivary mucins (mainly the large gel-forming *MUC5B* mucin and the small soluble *MUC7* mucin) bind water and coat the teeth and mucosa, making them slippery. Other salivary constituents contributing to tissue lubrication include *glycosylated proline-rich proteins* (PRPs) and *statherin*, along with the *salivary pellicle* (described below).

The pH of whole saliva ranges from 6.7 to 7.4. Bicarbonate (HCO_3^-), secreted by the major salivary glands, is the main buffering system in saliva; HCO_3^- serves to neutralize acid ingested in food and drinks and produced by oral microorganisms. *Carbonic anhydrase VI*, secreted by serous cells of the salivary glands, catalyzes the reaction:

$$H^+ + HCO_3^- \rightleftarrows H_2CO_3 \rightleftarrows H_2O + CO_2 \uparrow$$

Phosphate (HPO_4^{2-}) makes a small contribution to saliva buffering, as do some cationic salivary proteins. Ammonia, derived from salivary urea by the action of urease secreted by some oral bacteria, also serves to neutralize acid.

Salivary proteins, glycoproteins, mucins, and lipids adsorb onto the teeth and mucosa, and, along with cellular and serum proteins, create a thin film (up to 1 μm thick) of organic material called the salivary pellicle. While numerous salivary proteins are found in the pellicle, the major ones include statherin, *histatins*, *cystatins*, *acidic PRPs*, *carbonic anhydrases*, *amylase*, and mucins. The pellicle formed on tooth surfaces, also called the *acquired enamel pellicle*, has been most studied. It begins to form within seconds after the tooth surface is cleaned. Although thin, it may serve in a

small capacity as a diffusion barrier, slowing the penetration of acid into the enamel and the loss of mineral from the enamel. As saliva is supersaturated with respect to Ca^{2+} and PO_4^{3-}, the pellicle also prevents mineral deposition on the enamel surface. However, during the initial formation of dental caries, the presence of calcium-binding proteins in the pellicle, such as statherin, histatin 3, and acidic PRPs, provides a reservoir of Ca^{2+} and PO_4^{3-} at the tooth surface, which can remineralize early subsurface lesions. In the presence of F^-, the remineralizing enamel crystals form as fluoroapatite, which is less soluble than carbonate substituted hydroxyapatite. The tooth and mucosal pellicles also help protect the teeth from abrasion by acting as a surface lubricant. Finally, several pellicle components serve to bind oral microorganisms, initiating the formation of a *bacterial plaque* on the tooth surfaces.

Many salivary proteins and peptides have antimicrobial activity. These antimicrobial factors, along with good oral hygiene, contribute to the maintenance of oral health even in the presence of the hundreds of species of microorganisms in the normal oral flora. Histatins, a family of small cationic proteins, inhibit the growth of *Candida albicans*, and also have antibacterial activity. *β-Defensins*, small peptides that can insert into bacterial membranes and cause lysis, are secreted by epithelial cells and neutrophils that enter the mouth via the gingival crevice. *Lysozyme* hydrolyzes the peptidoglycan of bacterial cell walls causing lysis, and *lactoferrin* binds iron, inhibiting the metabolic activity of several microorganisms. In the presence of hydrogen peroxide (H_2O_2), *salivary peroxidase* secreted by salivary acinar cells and *myeloperoxidase* released by white blood cells convert thiocyanate (SCN^-) to hypothiocyanite ($OSCN^-$), which can enter and kill bacterial cells; myeloperoxidase also produces the more potent hypochlorite ion (OCl^-). Cystatins and *secretory leukocyte protease inhibitor* (SLPI) can inhibit bacterial proteases, preventing metabolism of salivary proteins to amino acids. Several salivary proteins bind and agglutinate microorganisms, preventing their attachment to the teeth and mucosa and facilitating their removal by swallowing. MUC7, PRPs, *salivary agglutinin* (also known as *GP340* and *DMBT1*), synthesized and secreted by salivary gland epithelial cells, and dimeric *secretory immunoglobulin A* (S-IgA), produced by salivary gland plasma cells and transferred across the gland epithelium into saliva, act in this manner. While a small amount of pentameric *immunoglobulin M* (IgM) is transferred into saliva by this route, both IgM and *immunoglobulin G* (IgG) enter saliva via the gingival crevice. Finally, a number of salivary proteins have antiviral activity; these include defensins, cystatins, PRPs, MUC7, S-IgA, lactoferrin, peroxidases, SLPI, *thrombospondin 1*, and *cathelicidin LL37*. Some of these proteins have been shown in vitro to inhibit the infectivity of the human immunodeficiency virus-1 (HIV-1), and recent studies have demonstrated that the early post-symptom immune response to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection results in neutralizing S-IgA antibodies in saliva and at other mucosal surfaces.

It is well known that injuries to the oral mucosa heal more rapidly and with less scar formation than skin injuries [8, 15]. Several factors in saliva have been shown to enhance wound healing. Mucins keep the mucosa moist, tissue factor accelerates blood clotting, and salivary antimicrobial components help to prevent infection. Growth factors in saliva that may contribute to oral wound healing include *epidermal growth factor* (EGF), *transforming growth factor alpha* (TGFα), and *vascular endothelial growth factor* (VEGF). *Trefoil factor 3* (TFF3), a small peptide secreted by mucous cells, promotes mucosal healing, and histatin 1 stimulates epithelial cell and fibroblast migration.

Saliva makes a modest contribution to the digestion of food. Saliva, and particularly mucins, helps to form a food bolus and facilitate swallowing. *α-Amylase*, secreted by serous cells, is the main digestive enzyme in saliva. It hydrolyzes starch into maltose and other small oligosaccharides. Its activity is largely confined to the oral cavity and esophagus, as it is inactivated by gastric acid. *Lingual lipase*, produced in small amounts by the lingual serous glands and pharyngeal glands, makes a minor contribution to lipid digestion. *Ribonuclease* and *deoxyribonuclease* are present in saliva, but their contribution to nucleic acid digestion is unknown. Kallikrein is secreted by striated duct cells, although a specific role in digestion has not been described.

Certain salivary proteins have been shown to bind toxic substances in food, and in response to these substances, the synthesis of the proteins is increased. Tannins inhibit growth and have toxic effects and are found in many plant-derived foods. Basic PRPs and histatins bind tannins and inhibit their uptake by intestinal epithelial cells; experimental studies in rodents have shown a marked increase in PRP synthesis in animals fed food containing tannins. Cystatins, cysteine peptidase inhibitors, may help protect against plant-derived papain-like enzymes. The synthesis of other salivary proteins may be modified by other food constituents or drugs. The sugar substitute xylitol increases salivary peroxidase activity, and treatment of rodents with β-adrenergic agonists increases PRP synthesis.

Saliva is essential for taste. It solubilizes taste substances in food and distributes them to the taste buds located on fungiform, circumvallate, and foliate papillae of the tongue, as well as the soft palate and epiglottis. Saliva in the mouth is hypotonic, with low Na^+ and Cl^- concentrations, which allows tasting of dilute salty solutions. Bicarbonate in saliva neutralizes acid thus decreasing sour taste. The concentrations of other substances present in saliva that potentially could stimulate taste receptors, such as glucose, glutamate, and urea, are below their taste thresholds.

Salivary Diagnostics

It has long been appreciated that certain substances present in saliva can offer information about the physiological status and health of the individual [8, 16–18]. Steroid hormones (cortisol, testosterone, estrogen) are readily detectable in saliva; cortisol in particular has been used as an indicator of stress. The concentration of α-amylase in saliva, released by sympathetic nerve stimulation and adrenal activity, also has been correlated to stressful situations. Changes in salivary concentrations of cortisol and/or α-amylase frequently are used in psychological studies of stressful situations. Numerous drugs, including drugs of abuse (e.g., cocaine, marijuana, barbiturates, amphetamines), are transferred into saliva. Their presence in saliva is determined by their lipid solubility, size, dissociation constant, and plasma-protein-binding characteristics. The use of saliva for drug testing often is more convenient, and less prone to sample substitution, than urine. Commercial devices and kits are available for the detection of several drugs in saliva.

Saliva is a convenient fluid for diagnosis of several viral infections as well as certain bacterial and parasitic infections [19, 20]. A number of viruses have been detected in saliva using molecular methods (e.g., polymerase chain reaction [PCR]) or antigen-based immunodetection. Although the majority of oral viruses are bacteriophages, several pathogenic viruses can be detected using these methods (Table 6.4). For some pathogens, antibodies present in saliva are used for diagnosis. Specialized collection devices as well as detection kits for some of these organisms are commercially available.

During the last two decades an emphasis has been placed on enumerating all of the proteins present in saliva, i.e., the *salivary proteome* [21]. The rationale is that if changes in the presence or quantity of specific salivary proteins can be detected, saliva could be used as an alternative or supplement to blood plasma/serum analyses for diagnosis of disease or monitoring physiological conditions [8, 16, 22]. More recently the presence of DNA, RNA, and microRNAs in saliva, as well as the ability to collect and analyze salivary *exosomes* (small cell-derived membrane-bound vesicles), has broadened the diagnostic possibilities. Current research is focused on identification of biomarkers for specific disease conditions. These include oral conditions such as periodontal disease and oral cancer, and systemic diseases such as pancreatic cancer, Parkinson's disease, and Alzheimer's disease. The ease and non-invasive nature of saliva collection make its use as a diagnostic fluid an attractive option.

Saliva also has important uses in forensic medicine [18]. The oligosaccharide groups present on salivary mucins are identical to ABO and Lewis blood group substances in about 80% of the population, making it possible to determine the blood type of an individual from a sample of saliva. Genetic polymorphisms in the PRPs, α-amylase, and several other salivary enzymes have been used for personal identification and paternity tests. The PRPs, including acidic, basic, and glycosylated forms, constitute a family of over 100 members derived by alternative splicing of 6 genes; PRPs account for greater than 50% of the protein secreted by the parotid gland. DNA derived from desquamated mucosal epithelial cells is frequently used to determine genotype and to positively identify an individual.

Table 6.4 Pathogenic organisms detectable using saliva

By PCR or immunodetection	By salivary antibodies
HIV-1	HIV-1, -2
Zika	West Nile
SARS-CoV-1, -2	Rotavirus
Influenza	Norovirus
Rabies	*Helicobacter pylori*
Epstein-Barr	*Campylobacter jejuni*
Human herpesviruses	*Entamoeba histolytica*
Human papilloma virus	*Toxoplasma gondii*
Herpes simplex 1	*Ascaris lumbricoides*
Hepatitis A, B, C	*Trichinella spiralis*
Measles	*Taenia solium*
Mumps	
Cytomegalovirus	
Dengue	
Ebola	
Chikungunya	
Nipah	

From [19]

Clinical Correlations

Altered salivary gland function, especially dry mouth, is a relatively common patient complaint. The feeling (subjective sensation) of a dry mouth is *xerostomia* [8]. The objective measurement of a reduced amount of saliva is termed *salivary hypofunction*; usually this is defined as <0.1 mL/min whole saliva. Much less common is the subjective feeling or objective measurement of too much saliva, termed *salivary hyperfunction* or *sialorrhea*. *Salivary gland dysfunction* is the general term applied to such alterations of gland function.

There are several potential causes for salivary hypofunction including drugs with central or peripheral effects on the autonomic nervous system, autoimmune diseases, and damage to gland tissue from therapeutic radiation for head and neck cancer. In addition to reduced salivary flow, the electrolyte and/or protein composition of saliva may be altered in many of these conditions. The consequences of salivary hypofunction include dental caries; mucosal infections and ulcerations; difficulties in swallowing, chewing, and speaking; and an overall reduced quality of life.

The most common cause of dry mouth is prescribed medications, over-the-counter drugs, and illegal drugs [23–25]. Categories of drugs causing salivary hypofunction or xerostomia are given in Table 6.5. Strong to moderate clinical evidence has identified as many as 100 drugs that are associated with salivary hypofunction. Weaker evidence implicates nearly 50 additional drugs as causing salivary hypofunction. Fewer drugs cause objective (clozapine, olanzapine, venlafaxine, clobazam) or subjective (quetiapine, risperidone, enalapril, haloperidol, methyldopa) sialorrhea. Animal studies have shown that clozapine may cause both sialorrhea and reduced salivation by stimulation of muscarinic M1 receptors and by inhibition of muscarinic M3 and α_1-adrenergic receptors, respectively. Dry mouth has been reported as a side effect of some chemotherapeutic agents, e.g., 5-fluorouracil, cisplatin, or bevacizumab. Prescribing an alternative medication or, if feasible, reducing the dosage may help to alleviate the symptoms.

Autoimmune diseases may damage the salivary glands and result in salivary hypofunction. *Sjögren's syndrome* (SS) is the most common autoimmune disease affecting the salivary glands, with a preponderance of cases in females [8, 26–28]. Lymphocytic invasion of the glands occurs with destruction especially of the secretory cells. The loss of fluid secretory capacity and the protection offered by salivary proteins and buffering cause dry mouth; difficulty in speaking, chewing, and swallowing food; and the risk of dental caries, mucosal infections, and ulcers. In *primary SS*, or *sicca syndrome*, lacrimal glands also are affected, resulting in dry eyes. *Secondary SS* includes the presence of other autoimmune diseases, such as rheumatoid arthritis, lupus erythematosus, or systemic sclerosis. Although a few antigens have been linked to the onset of SS, and several viral infections are thought to be predisposing factors, a specific cause has not been unequivocally identified. Recent studies indicate that the activation of toll-like receptors (TLRs) on salivary gland epithelial cells and immune cells plays a significant role in the pathogenesis of SS. TLRs recognize exogenous (microbial) as well as endogenous ligands, including nucleic acids. Diagnosis of SS often can be confirmed by measurement of whole saliva flow rates, biopsy of a labial minor salivary gland with microscopic examination, and the presence of serum anti-Ro/SSA and anti-La/SSB antibodies in 70% and 45% of patients, respectively.

Table 6.5 Categories of drugs causing salivary gland hypofunction

By pharmacologic classification	By system
Anticholinergics	Alimentary tract and metabolism
Sympathomimetics	Cardiovascular system
Skeletal muscle relaxants	Genitourinary system and sex hormones
Antimigraine agents	Musculoskeletal system
Benzodiazepines, hypnotics, opioids, drugs of abuse	Anti-neoplastic and immunomodulating agents
H2 antagonists, proton pump inhibitors	Nervous system
Cytotoxic agents	Respiratory system
Retinoids	Sensory organs
Anti-HIV agents	
Cytokines	

From [23, 25]

IgG4-related disease (IgG4-RD) is an autoimmune condition most often occurring in middle-aged to elderly males that affects many organs, including the salivary glands [27, 29]. It is characterized by elevated serum IgG4 levels (≥135 mg/dL), gland swelling, storiform tissue fibrosis, obliterative phlebitis, a lymphoplasmacytic infiltrate with abundant IgG4-positive plasma cells, and tissue eosinophilia. Salivary secretion may or may not be reduced, with xerostomia occurring in about 30% of patients. IgG4-RD usually responds well to immunosuppressants such as glucocorticoids.

Hematopoietic stem cell transplantation resulting in graft-vs.-host disease also can affect salivary gland function. Early effects include salivary gland inflammation, salivary flow reduction, and decreases in some antimicrobial components in saliva, including S-IgA. At later times after transplantation, other antimicrobial proteins showed an increase, particularly SLPI, lactoferrin, and β_2-miroglobulin.

Salivary glands are particularly sensitive to damage from radiation therapy for head and neck cancer [27, 30]. Loss of acinar secretory cells and damage to vascular tissues result in reduced secretion of fluid and protective salivary proteins. Dental caries, mucosal infections, and ulcers are common. Radioactive iodine treatment for thyroid cancer also can damage salivary glands [31]. The striated duct cells express the Na^+/I^- symporter and are most commonly affected, resulting in damage to the ducts and surrounding tissue with subsequent inflammation and fibrosis. Serous cells also concentrate I^-; thus the parotid gland is more affected by radioactive iodine therapy than the submandibular and sublingual glands. Radioactive iodine therapy also poses an increased risk of developing a secondary primary malignancy in the salivary glands. Patients should have any necessary dental treatment done prior to the radiotherapy, and post-treatment follow-up with particular attention to oral hygiene, regular dental checkups, and fluoride treatments.

Treatment of salivary hypofunction is generally palliative, e.g., sipping water, use of artificial saliva. If functional gland tissue remains, chewing sugar-free gum, use of a saliva substitute containing a topical stimulus such as malic acid, or prescribing oral parasympathomimetic drugs (low-dose pilocarpine, cevimeline, bethanechol) may increase salivary flow. Considerable research into the use of gene therapy to improve salivary function, as well as a phase 1 clinical trial, has been conducted, although currently it is not in general

use [32]. The procedure involves retrograde ductal infusion of an adenovirus or adeno-associated virus containing the gene for human aquaporin-1 to increase fluid secretion. Also being studied are means to prevent radiation damage with radioprotective compounds (e.g., tempol), biologicals (growth factors, cytokines), and apoptosis inhibitors (dasatinib). In appropriate patients, surgical transfer of one submandibular gland to a region not included in the field of radiation (e.g., submental space, parotid region) has been shown effective in reducing post-radiation hypofunction. Finally, therapeutic uses of stem cells derived from salivary glands or other tissues (e.g., mesenchyme, adipose tissue, dental follicle, dental pulp) to regenerate the glands, as well as tissue engineering approaches, are being studied [33].

True sialorrhea is a rare condition. Drooling, due to poor oral motor control and swallowing impairment, frequently is associated with neurological disorders, such as Parkinson's disease, amyotrophic lateral sclerosis, stroke, and cystic fibrosis [34]. Besides embarrassment and reduced quality of life, the inability to swallow saliva can result in skin infection, choking, and aspiration. Behavioral therapy for mild drooling may be successful. Pharmacologic approaches to control drooling include anticholinergic drugs, e.g., scopolamine, benztropine, glycopyrrolate, tropicamide, or injection of botulinum toxin into the parotid or submandibular gland. Surgery to remove the submandibular glands, ligate or re-route the ducts, or ligation or re-routing of the parotid ducts, may be appropriate for children.

Other factors also may affect salivary flow and/or composition [8, 27, 35]. Obstruction of the main duct of a gland due to a stricture, mucous plug, or calcified stone (*sialolith*) will reduce salivary flow and cause gland swelling and pain, especially during eating. Stones most commonly occur in the submandibular duct due to the higher content of calcium and phosphate salts in submandibular saliva. Duct obstruction also may occur after an injury to the duct. A common occurrence is an accidental lip bite, which may sever the duct of a minor salivary gland. The pooling of mucus in the connective tissue results in a swelling called a *mucocele*. Trauma to one of the minor ducts (Rivinus) of the sublingual gland results in submucosal mucus accumulation called a *ranula*. Dehydration causes reduced salivary flow rates and increased saliva osmolality and can lead to retrograde bacterial infection from the oral cavity. Elderly patients often complain of a dry mouth, which may or may not be a side effect of medications. While many studies have shown a decline in salivary function with aging, some well-conducted studies suggest that stimulated salivary secretion in healthy non-medicated elderly individuals is comparable to that of younger people. Aplasia or hypoplasia of the salivary glands, associated with some genetic syndromes (e.g., lacrimo-auriculo-dento-digital syndrome [LADD], trisomy 21) or mutation of the fibroblast growth factor-10 (FGF-10) gene or its receptor, FGFR2b, can result in a dry mouth. Parotid gland aplasia (~1:5000 live births) occurs much more frequently than submandibular gland aplasia.

Inflammation of the salivary glands, *sialadenitis*, can occur with bacterial or viral infections [8, 19, 27, 35]. Bacterial infections, most common in the parotid gland (*acute parotitis*), typically are caused by *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus* species, or anaerobic Gram-negative bacilli and result in swelling, pain, and suppuration. Prior to vaccine (MMR: measles-mumps-rubella) introduction, the most common viral infection of salivary glands was mumps. Patients with mumps experience a prodromal period with flu-like symptoms and subsequent unilateral or most frequently bilateral gland swelling and pain, especially the parotid. Although cases of mumps are now rare, occasional outbreaks have occurred even in vaccinated populations. Swelling, reduced salivary flow, benign lymphoepithelial cysts, diffuse infiltrative lymphocytosis syndrome, and salivary gland lymphomas may occur in HIV-infected patients, even those on antiretroviral therapy, and in immunocompromised individuals. HIV-associated salivary gland disease is linked to infection with the BK polyoma virus. Epstein-Barr (EB) virus replicates in the salivary glands and is present in 90% of the population. Although primary infections are usually asymptomatic, EB causes infectious mononucleosis, is associated with nasopharyngeal carcinoma, oral hairy leukoplakia, and Burkitt's lymphoma, and is considered a predisposing factor for SS. Cytomegalovirus (CMV) infections are present in as many as 70% of adults; the virus infects and replicates in the salivary glands. After the initial infection CMV patients may exhibit mononucleosis and few or no other symptoms, and the virus remains latent. In immunocompromised patients the virus may reactivate, and cause liver failure, inflammation in several organs, atherosclerosis, and possibly some cancers.

Sialadenosis (*sialosis*) is a bilateral, non-neoplastic, asymptomatic, painless swelling of the salivary glands, most frequently the parotid glands [27, 35]. It can occur in diabetic patients, alcoholics, in bulimia nervosa, and as a consequence of chronic malnutrition. The gland enlargement is due to acinar cell hypertrophy, with accumulation of secretory granules, possibly related to an underlying neuropathy.

Although relatively rare, several different neoplastic lesions may occur in the salivary glands [27, 35–37]. They possess a wide range of histological characteristics and clinical behavior, and generally present as slow-growing painless masses. Most tumors occur in the parotid gland, and most of these are benign. While only 5–8% of tumors occur in minor salivary glands, the majority occur in the palate and most of them are malignant. The most common benign parotid tumors are *pleomorphic adenoma*, *papillary cystadenoma lymphomatosum* (*Warthin tumor*), and *oncocytoma*. The most common malignant parotid tumor is *mucoepidermoid carcinoma*, and the most common malignant submandibular

and minor gland tumor is *adenoid cystic carcinoma*. Metastatic tumors also occur in the salivary glands, the most common being *squamous cell carcinoma*.

Summary

The three major salivary glands, parotid, submandibular, and sublingual, along with minor glands in the oral mucosa, produce and secrete saliva that creates and regulates the oral environment. Saliva secretion occurs in response to taste and olfactory stimulation, as well as mechanical stimulation of the periodontium and oral mucosa, conveyed via both sympathetic and parasympathetic fibers of the autonomic nervous system. The products of the serous and mucous secretory cells of the glands serve to moisten and lubricate the oral tissues, solubilize food, initiate digestion, facilitate mastication, taste, and swallowing, and protect the oral tissues through the actions of antibacterial and antiviral components, calcium-binding proteins, and the bicarbonate buffering system. In addition to substances secreted by the glands, whole saliva in the mouth contains substances transferred from blood plasma, gingival crevicular fluid, oral microorganisms and their products, and food debris.

Saliva frequently is used in forensic medicine, and increasingly being used as a diagnostic fluid to determine health and physiological conditions. Several hormones and drugs of abuse can be detected in saliva, and a variety of viral and bacterial pathogens can be detected using immunological and molecular methods. Protein, DNA, RNA, and microRNA biomarkers present in saliva are being studied for the diagnosis of several oral and systemic diseases.

Salivary dysfunction leading to dry mouth is a common clinical complaint. Side effects of prescribed medications can reduce saliva secretion, and autoimmune diseases and radiation therapy for head and neck cancer can destroy the secretory cells of the glands. Infection or inflammation of the glands, blockage of a duct, or, rarely, glandular aplasia, also may lead to a dry mouth. The consequences of salivary dysfunction include dental caries, mucosal infection and ulceration, difficulty swallowing and speaking, and a reduced quality of life. Although not common, benign and malignant tumors may occur in the major and minor salivary glands and must be differentiated from gland enlargement caused by infection, inflammation, or non-inflammatory processes.

References

1. Hand AR. Salivary glands, saliva secretion, and saliva. In: Hand AR, Frank ME, editors. Fundamentals of oral histology and physiology. Ames, IA: Wiley-Blackwell; 2014. p. 223–40.
2. Evans RL, Park K, Turner RJ, Watson GE, Nguyen HV, Dennett MR, et al. Severe impairment of salivation in Na^+ /K^+ /$2Cl^-$ cotransporter (NKCC1)-deficient mice. J Biol Chem. 2000;275:26720–6.
3. Hand AR, Pathmanathan D, Field RB. Morphological features of the minor salivary glands. Arch Oral Biol. 1999;44:S3–10.
4. Zhou J, Wang H, Yang G, Wang X, Sun Y, Song T, et al. Histological and ultrastructural characterization of developing miniature pig salivary glands. Anat Rec. 2010;293:1227–39.
5. Harunaga J, Hsu JC, Yamada KM. Dynamics of salivary gland morphogenesis. J Dent Res. 2011;90:1070–7.
6. Hauser BR, Hoffman MP. Regulatory mechanisms driving salivary gland organogenesis. Curr Top Dev Biol. 2015;115:111–30.
7. Emmerson E, Knox SM. Salivary gland stem cells: a review of development, regeneration and cancer. Genesis. 2018;56:e23211. https://doi.org/10.1002/dvg.23211.
8. Ligtenberg AJM, Veerman ECI, editors. Saliva: secretion and functions, Monographs in oral science, vol. 24. Basel: Karger; 2014.
9. Proctor GB. The physiology of salivary secretion. Periodontol 2000. 2016;70:11–25.
10. Pedersen AML, Sörensen CE, Proctor GB, Carpenter GH, Ekström J. Salivary secretion in health and disease. J Oral Rehabil. 2018;45:730–46.
11. Pedersen AML, Sörensen CE, Proctor GB, Carpenter GH. Salivary functions in mastication, taste and textural perception, swallowing and initial digestion. Oral Dis. 2018;24:1399–416.
12. Tabak LA. In defense of the oral cavity: the protective role of the salivary secretions. Pediatr Dent. 2006;28:110–7.
13. Brandtzaeg P. Secretory immunity with special reference to the oral cavity. J Oral Microbiol. 2013;5:20401. https://doi.org/10.3402/jom.v5i0.20401.
14. Dawes C, Pedersen AML, Villa A, Ekström J, Proctor GB, Vissink A, et al. The functions of human saliva: a review sponsored by the World Workshop on Oral Medicine VI. Arch Oral Biol. 2015;60:863–74.
15. Waasdorp M, Krom BP, Bikker FJ, van Zuijlen PPM, Niessen FB, Gibbs S. The bigger picture: why oral mucosa heals better than skin. Biomol Ther. 2021;11:1165. https://doi.org/10.3390/biom11081165.
16. Dawes C, Wong DTW. Saliva and salivary diagnostics in the advancement of oral health. J Dent Res. 2019;98:133–41.
17. Giacomello G, Scholten A, Parr MK. Current methods for stress marker detection in saliva. J Pharm Biomed Anal. 2020;191:113604. https://doi.org/10.1016/j.jpba.2020.113604.
18. Chatterjee S. Saliva as a forensic tool. J Forensic Dent Sci. 2019;11:1–4.
19. Corstjens PLAM, Abrams WR, Malamud D. Saliva and viral infections. Periodontol 2000. 2016;70:93–110.
20. Moreira VM, Mascarenhas P, Machado V, Botelho J, Mendes JJ, Taveira N, et al. Diagnosis of SARS-Cov-2 infection by RT-PCR using specimens other than naso- and oropharyngeal swabs: a systematic review and meta-analysis. Diagnostics. 2021;11:363. https://doi.org/10.3390/diagnostics11020363.
21. Denny P, Hagen FK, Hardt M, Liao L, Yan W, Arellanno M, et al. The proteomes of human parotid and submandibular/sublingual gland salivas collected as the ductal secretions. J Proteome Res. 2008;7:1994–2006.
22. Malamud D. Saliva as a diagnostic fluid. Dent Clin N Am. 2011;55:159–78.
23. Scully C. Drug effects on salivary glands: dry mouth. Oral Dis. 2003;9:165–76.
24. Scully C, Bagan J-V. Adverse drug reactions in the orofacial region. Crit Rev Oral Biol Med. 2004;15:221–39.
25. Wolff A, Joshi RK, Ekström J, Aframian D, Pedersen AML, Proctor G, et al. A guide to medications inducing salivary gland dysfunction, xerostomia, and subjective sialorrhea: a systematic review sponsored by the World Workshop on Oral Medicine VI. Drugs R D. 2017;17:1–28.
26. Matthews SA, Kurien BT, Scofield RH. Oral manifestations of Sjögren's syndrome. J Dent Res. 2008;87:308–18.

27. Mandel L. Salivary gland disorders. Med Clin N Am. 2014;98:1407–49.
28. Proctor GB, Shaalan AM. Disease-induced changes in salivary gland function and the composition of saliva. J Dent Res. 2021;100:1201. https://doi.org/10.1177/00220345211004842.
29. Maritati F, Peyronel F, Vaglio A. IgG4-related disease: a clinical perspective. Rheumatology. 2020;59(Suppl 3):iii123–31.
30. Jensen SB, Vissink A, Limesand KH, Reyland ME. Salivary gland hypofunction and xerostomia in head and neck radiation patients. J Natl Cancer Inst Monogr. 2019;53:lgz016.
31. Singer MC, Marchal F, Angelos P, Bernet V, Boucai L, Buchholzer S, et al. Salivary and lacrimal dysfunction after radioactive iodine for differentiated thyroid cancer: American Head and Neck Society Endocrine Surgery Section and Salivary Gland Section joint multidisciplinary clinical consensus statement of otolaryngology, ophthalmology, nuclear medicine and endocrinology. Head Neck. 2020;42:3446. https://doi.org/10.1002/hed.26417.
32. Baum BJ, Alevizos I, Chiorini JA, Cotrim AP, Zheng C. Advances in salivary gland gene therapy – oral and systemic implications. Expert Opin Biol Ther. 2015;15:1443–54.
33. Lombaert I, Movahednia MM, Adine C, Ferreira JJ. Concise review: salivary gland regeneration: therapeutic approaches from stem cells to tissue organoids. Stem Cells. 2017;35:97–105.
34. Potulska A, Friedman A. Controlling sialorrhea: a review of available treatment options. Expert Opin Pharmacother. 2005;6:1551–4.
35. Ogle OE. Salivary gland diseases. Dent Clin N Am. 2020;64:87–104.
36. Eveson JW. Salivary tumours. Periodontol 2000. 2011;57:150–9.
37. Guzzo M, Locati LD, Prott FJ, Gatta G, McGurk M, Licitra L. Major and minor salivary gland tumors. Clin Rev Oncol Hematol. 2010;74:134–48.

Part II

Infection

Elie M. Ferneini

Dental Caries

7

Melissa E. Ing

Introduction

Dental caries, commonly known as tooth decay, remains one of the most prevalent chronic, if not THE most prevalent chronic, disease in the world [1]. Yet, caries is 100% preventable. If recognized and caught in its early stages, caries can also be reversed.

Clinicians probably spend more time treating the outcomes of dental decay rather than placing more emphasis on understanding the mechanisms of the caries process and on educating patients about the prevention of dental caries.

Dental caries is the resultant localized destruction of tooth structure which is caused by acidic byproducts, metabolized by bacteria that utilize sucrose and simple carbohydrates as energy sources [1]. Caries initiates within a film of dental plaque that adheres to tooth structure. First, there is destruction or "demineralization" of the hardest outer enamel crown of the tooth structure. Deeper caries can involve the inner and softer dentin of the tooth. More extensive caries can involve the central/pulpal portions of the tooth which include the nerves and connective tissues. Dental caries can also affect the root and the cementum areas of tooth structure.

Caries is a multifactorial and a polymicrobial disease. Caries is considered an infectious disease since it is invoked by bacteria, and it is a transmissible disease.

There are multiple risk factors that drive carious activity. These risk factors can include socioeconomic reasons such as poverty level, salivary flow, oral hygiene, and amount and prevalence of sugar consumption.

Carious activity is a complex process. The following four factors must exist and interplay to drive carious activity: (1) host factors which consist of a susceptible tooth, (2) bacteria/biofilm responsible for producing acid, (3) substrate: fermentable carbohydrate/sucrose which bacteria use as a source of energy, and (4) time.

M. E. Ing (✉)
Brookline, MA, USA

Repeated acid attacks on the teeth will likely result in caries breakdown if there is less change to balance the neutral environment in the oral cavity. The factors that influence caries initiation and progression are shown in what is known as the "Keyes-Jordan Venn Diagram" which is demonstrated in Fig. 7.1.

Who Is Susceptible?

Patients are susceptible to caries throughout their lifetime [2]. Statistically, approximately 92% of adults [3] and 60–90% of school children have caries [4].

According to the World Health Organization (WHO) dental caries is considered the single most prevalent chronic disease [5], yet it is totally preventable. WHO data demonstrate that as many as 60% of school children have caries and in certain countries of the world the caries percentage can jump up to 90% [4, 6].

Childhood caries negatively impacts self-esteem and nutritional habits. Furthermore, there is a demonstrated correlation between caries and childhood obesity [6].

Despite many advances in medical science in industrialized countries, oral disease such as dental caries remains the fourth most expensive disease to treat, taking up to 10% of health care budgets [4].

Dental Anatomic Features and Cariology Related Terminology

In order to understand dental caries pathogenesis, it is important to have a preliminary understanding of characteristic, healthy tooth structure as well as dental anatomy.

Most human mouths have 20 deciduous teeth and up to 32 permanent teeth. These are designated anterior and posterior teeth. The anterior teeth consist of the central and lateral incisors, and the canines. The posterior teeth consist of the premolars and the molars. Each tooth type assists with bit-

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_7

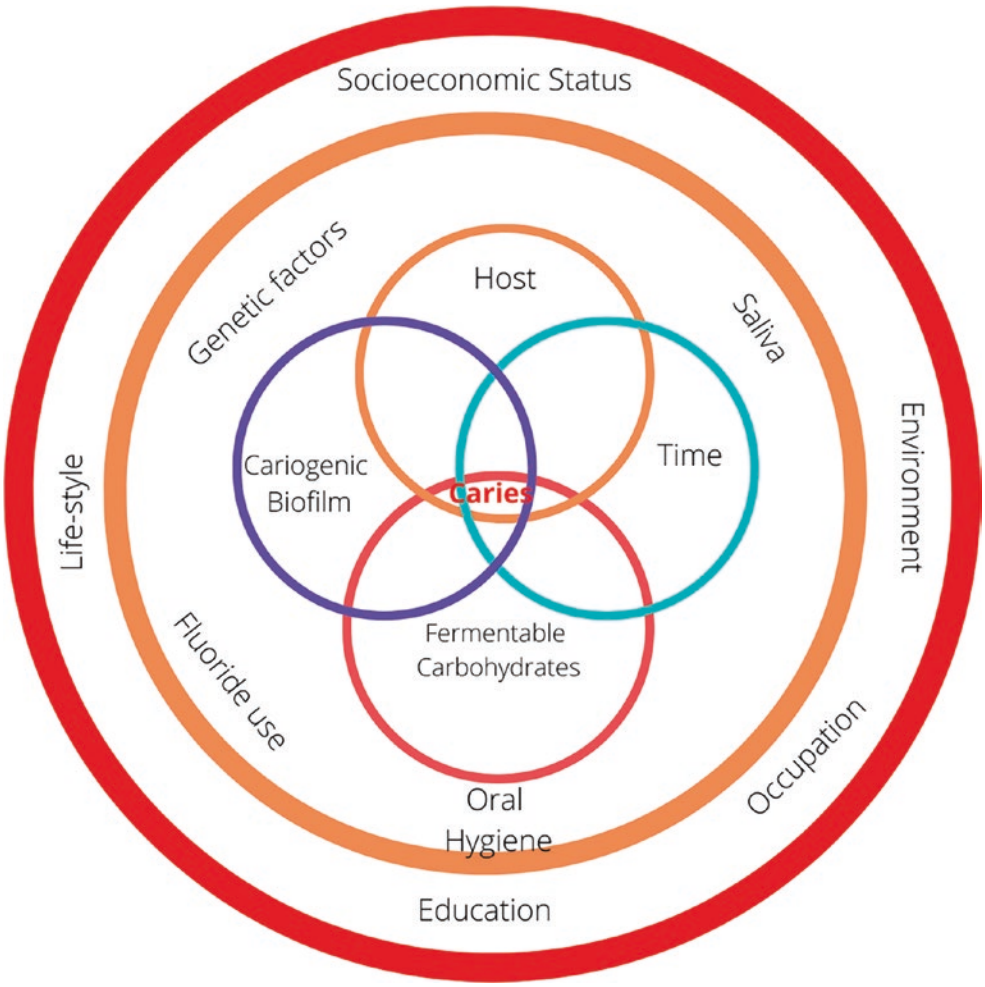


Fig. 7.1 Keyes-Jordan Venn Diagram. (Courtesy of the author, Dr. Melissa Ing)

ing, mastication and speech. Each tooth has a **crown** and a **root** portion. The anatomic features of tooth structure are shown in Fig. 7.2.

Dental enamel is the outer translucent shell of the tooth. Dental enamel is the hardest substance of the human body. Enamel color can vary from white to grayish white to light yellow. It is comprised of 96% inorganic and 4% organic material. Its inorganic content consists of a calcium phosphate mineral which is also called hydroxyapatite. Enamel does not consist of living cells. If it is damaged by carious activity or is fractured, enamel has little means to repair itself and if the damage is severe, the dental team may need to intervene with appropriate methods.

The dentin is the inner or middle layer adjacent to the enamel and makes up the bulk of tooth structure. Dentin is softer than dental enamel and is yellow in color. Dentin is highly organic, consisting of 70% apatite, 20% collagen, and 10% water. Dentin is made up of thousands of microscopic hollow tubes called dentinal tubules, which carry sensations from the outer to the inner portion of the tooth. When patients complain of tooth pain and sensitivity, it is due to these dentinal tubules transmitting a stimulus. It is possible for dentin to heal itself to some degree, and it is dependent on the degree of bacterial insult.

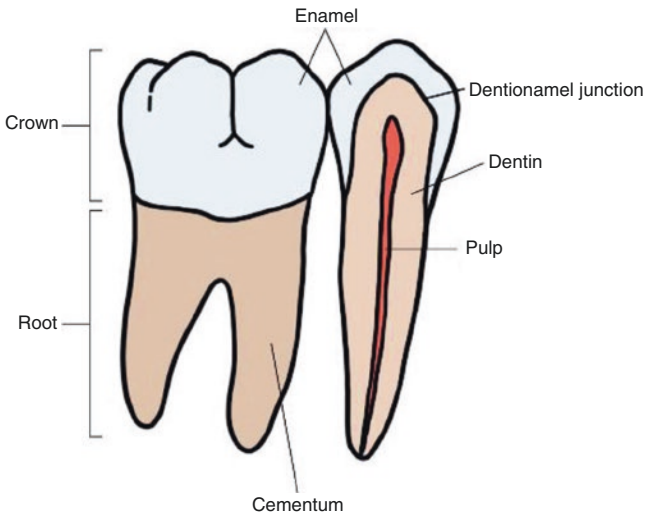


Fig. 7.2 Anatomic features of tooth structure. (Courtesy of Dr. John Syrbu)

The pulp is the center part of the tooth that is comprised of the neurovascular bundle and contains living connective tissue. The pulp nourishes the dentin with its living cells, nerves, and blood vessels.

The cementum is a thin coating that covers the root of the tooth and resembles bone structure. It is approximately 50% organic. Cementum connects fibers from teeth to alveolar bone and continuously forms throughout the life of a tooth.

Dental biofilm (plaque) is a sticky, mostly colorless layer that easily adheres to oral surfaces and houses a community of microorganisms, comprised mostly of bacteria. Biofilm adhering to tooth surfaces is where carious activity initiates.

The dentinoenamel junction, which is often also termed the **"**DEJ," is where the enamel meets the dentin.

Tooth Surfaces and Dental Caries

In general, dental caries can be found in several distinct different areas of a tooth. Carious lesions can be found on *smooth* surfaces of the tooth which include: the crown, the root, or the approximal surfaces. The other area that caries can be commonly found is within the *occlusal* areas of the posterior teeth in the indentations of the occlusal surfaces called "pits" and "fissures."

There are five "surfaces" to each tooth: occlusal, the approximal surfaces, which consist of the mesial and distal, and the buccal and lingual surfaces. The surfaces of the tooth are shown in Fig. 7.3.

Occlusal surface The chewing surfaces of the posterior teeth found on premolars and molars are called the "occlusal" surfaces. As part of the occlusal surface, premolars and molars will have indentations called pits and fissures. Debris, plaque, and bits of food adhere easily to these hard to cleanse areas. Pits and fissures are the most vulnerable areas for caries. Some anterior teeth have similar pits and fissures that are called "cingulum pits."

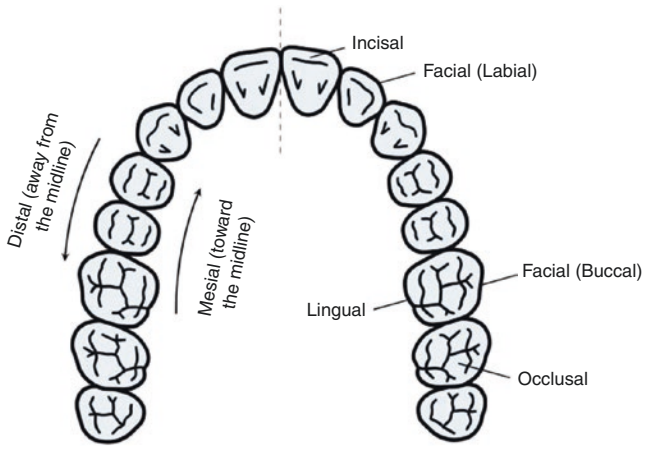


Fig. 7.3 Surfaces of the tooth. (Courtesy of Dr. John Syrbu)

Incisal surface Anterior teeth (central incisors, lateral incisors, and canines) have incising surfaces and are not called occlusal surfaces like the posterior teeth.

Approximal surfaces These surfaces were also known as "interproximal surfaces" and form point contacts between adjacent teeth. There are two approximal surfaces to each tooth. The **mesial** surface is the one closest to the front of the mouth. The **distal** surface is the one toward the back of the mouth.

Buccal surface The surface on the cheek side of the tooth. Generally, the buccal surface is smooth except molars can possess buccal grooves or pits which are places that can harbor plaque and debris. The buccal surface closer to the gumline (gingiva) is called the "cervical" area, which is an area for potential carious activity.

Lingual surface The surface of the tooth that faces the tongue.

The Carious Process/Pathogenesis

The mouth contains more than 700 species of bacteria, fungi, and protozoa. Some bacteria are beneficial, and some can be harmful [6, 7]. Dental biofilm contain specific oral bacteria that produce harmful acids that are able to dissolve tooth enamel. For many decades it has been believed that specific acid-producing bacteria form this dynamic biofilm, which colonize on the tooth surface, and are considered the main etiology behind caries. Caries is considered an infectious disease because it is caused by bacteria.

Microbial Agents Responsible for Dental

Modern research demonstrates that there may be many more microorganisms contributing to the progression of caries than the previously identified specific gram-positive bacteria thought to be mainly responsible for caries [8, 9].

However, in this chapter we will discuss the most well-recognized and main bacterial contributors to cariogenesis: *Streptococcus mutans*, *Streptococcus sobrinus, Lactobacillus* spp., and *Actinomyces* spp. [10] Cariogenic bacteria thrive on sugar and simple carbohydrates which are used as a molecular energy source. The enzyme glucansucrase converts sucrose into a tacky polysaccharide, allowing plaque to

form and stick to enamel surfaces and produce lactic acid byproducts. These acids are responsible for the destruction of tooth structure.

At birth, babies possess the "good bacteria" *Streptococcus sanguis* and *Streptococcus salivarius*. When a baby is at approximately 12 months of age *Streptococcus mutans* is introduced [11]. Research demonstrates that caries can be acquired at a very early age, most likely from the mother, but emerging theories also show that caries is non-communicable [11].

Streptococcus mutans is considered the main etiologic microbiological organism of dental caries initiation and progression. *Streptococcus mutans* is an anaerobic, gram-positive bacterium that metabolizes carbohydrates and sugars to create an acidic environment in the mouth.

This microbe can adhere and multiply on tooth surfaces. *Streptococcus mutans* is often acquired through "vertical transmission," by being passed down from caregivers, usually the mother, to infant. Examples of bacterial transmission include when the mother kisses the child, puts mouth on pacifier to cleanse and then gives it back to the baby, or tastes milk or shares food before giving to the baby [12].

While *Streptococcus mutans* is considered the main bacteria responsible for dental decay there are also some other main players responsible for producing caries. There are some studies demonstrating that the profiles of bacteria may differ between pediatric and adult dentitions [8].

Streptococcus sobrinus is closely related to *Streptococcus mutans* and is found in approximately 8–35% of human mouths in different countries. *Streptococcus mutans* and *Streptococcus sobrinus* can cohabitate in the mouth [8, 9].

***Lactobacillus* spp.** are gram-positive anaerobic rod-shaped bacteria that do not colonize well on smooth enamel surfaces [9]. This is considered one of the main bacteria for initiating pit and fissure caries.

***Actinomyces* spp**. are gram-positive pleomorphic rod-shaped bacteria that are implicated to be responsible for root caries [13].

Acid Production, the Critical pH, and the Stephan Curve

The pH measurement of the oral environment is an important factor that can drive the carious process [14]. The pH level can rise or drop in the mouth, depending on what kinds of foods and beverages are being consumed. For instance, when individuals intake foods or beverages with high sugar or fermentable carbohydrate content, tooth enamel will then be bathed in an acidic environment. This acid can adhere to the tooth surface.

Bacteria in plaque react to fermentable carbohydrates and/or sweet foods. When patients consume foods and beverages consisting of fermentable sugars dental plaque produces organic lactic acid byproducts. The acid causes the mineral dissolution [14].

The concept of "critical pH," as it pertains to dentistry, was introduced by Robert Stephan in the 1940s [15]. The critical pH is the point at which saliva is no longer saturated with calcium and phosphate, which are essential minerals in enamel and help strengthen tooth structure. At the critical pH enamel and dentin will start to dissolve or "demineralize" because the enamel is losing these important minerals. This process where minerals leach out of tooth enamel is termed "demineralization." [14, 15]. This process can reverse itself, when enamel can gain the same important minerals back and the pH will rise. This is called "remineralization." [14, 15].

Many researchers designate the critical pH when tooth enamel is exposed to a pH being a fixed value of 5.5; but other researchers, such as Dawes, have demonstrated that the critical pH can fluctuate higher or lower than this number [14]. The variance of the critical pH is dependent on an individual's salivary concentrations of calcium and phosphate [14, 16].

If the calcium and phosphate concentration are increased, then it is possible that the critical pH can be decreased, and teeth can possibly withstand an acidic environment without demineralizing [16].

Caries is caused by an imbalance of "demineralization" and "remineralization" of hard tooth structure. When there is an imbalance to this cycle where there is more loss of minerals than net gain [17], a cavitation (cavity or carious lesion) will occur. This process is initiated by acids in the bacteria within the dental biofilm.

In 1943, Robert Stephan created a graphical representation of the critical pH concept to illustrate how eating and drinking fermentable carbohydrates and sugars impacts caries formation [14, 15]. Stephan also demonstrated how frequent introduction of food equates to acid attacks to the oral environment. His graphs show what is called "The Stephan Curve," as depicted in Fig. 7.4**.**

The Stephan Curve demonstrates that the pH level drops rapidly after food or drink has been consumed and that it will take time for the pH to rise again to resting level [14, 15]. The time it takes for the pH to neutralize again can often take up to at least half an hour, depending on what has been consumed. In addition, the Stephan Curve demonstrates that the more frequently food or drink is consumed throughout the day the critical pH threshold will be affected for longer periods of time, thereby impacting a patient's risk for caries initiation [14, 15].

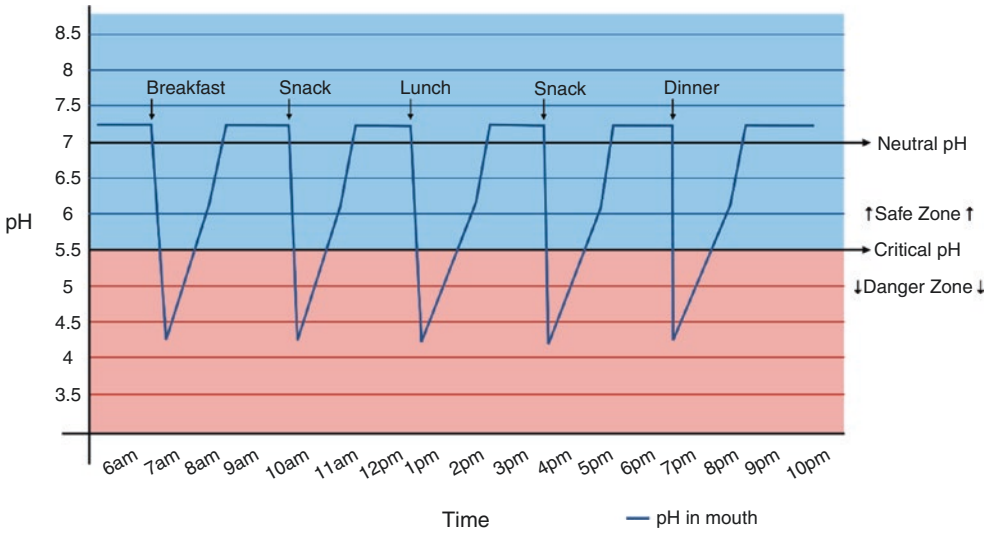


Fig. 7.4 The Stephan Curve. (Courtesy of Dr. John Syrbu)

Sugars, Free Sugars, and Dental Caries

Nutrition, oral health, and systemic health are closely aligned. Caries is a sugar-driven and sugar-induced disease. Dietary sugars and simple carbohydrates are the primary energy sources utilized by the bacteria responsible for caries.

Statistics demonstrate that western developed countries have a higher rate of caries as compared to the caries rate in less developed countries. This observation is thought to be due to the increased amount of refined sugar consumption within many developed countries [18].

Sugar consumption has tripled in the past 50 years and this trend is expected to continue to grow due to cultural and modern lifestyles shift [19]. More people eat out and eat conveniently prepared "fast foods." More and more consumers are eating processed foods and sweetened beverages due to their convenience, lower cost, and their taste [20]. Both sugary drinks and processed foods contain significant amounts of added sugars. Manufacturers add sugar to foods because consumers enjoy the taste of foods with the added sugars; sugar can act as a preservative by extending the lifespan of many processed foods. Together, sweetened beverages and processed foods account for staggeringly more amounts of refined sugar content consumed than those found within desserts and sweets [19]. Consumers may not realize that added sugar is easily found in processed foods such as chips, packaged breads, condiments, and salad dressings [19]. It is therefore very important to read nutrient packaging labels while food shopping.

There are different forms of dietary sugars. These include the monosaccharides such as fructose, glucose, and galactose, and the disaccharides such as sucrose which is common table sugar. There are "intrinsic" sugars and there are "free" sugars [21]. Intrinsic sugars are those found within intact fruit and vegetables. Sugars are also naturally found in honeys, syrups, fruits, and fruit juices [21]. Sugar in the form of lactose is found in milk. Free sugars are sugars **added into foods and beverages** by the manufacturer, the cook, and the consumer [21]. These include table sugar found in cane, beet, and other sources. In addition, free sugars also include the sugars naturally present in syrups, honey, fruit juices, and fruit juice concentrates. These sugars are "free" because they are not located within the cells of the food consumed; therefore, when fruit is extracted into fruit juice and the sugars come out of their cells they become free sugars. Free sugars are primarily responsible for dental caries, even with preventive measures such as fluoride [21].

In 2015, the Federation Dentaire Internationale (FDI) World Dental Federation, which serves to develop and improve oral health policies, released a health providers' toolkit, to document the global rise in sugar consumption [21]. The FDI reported that quantity and frequency of free sugar intake influence dental caries so clinicians should counsel patients on the importance of BOTH factors to help control dental caries [21]. Free sugar intake above 60 g per person a day has been demonstrated to increase the rate of dental caries in teenagers and adults [21]. The FDI also warns that consuming free sugars more than four times a day increases the risk of dental caries [21].

Similarly in 2015, the WHO created sugar intake guidelines for both adults and children [22]. The WHO suggests that the daily intake of free sugars be less than 10% of the total energy intake. This equates to approximately 50 g or 12 teaspoons of sugar. Furthermore, the WHO suggests that the daily intake of free sugars be reduced to less than 5% of total energy intake to provide even more health benefits and to minimize dental caries risk for a lifetime.

The Role of Saliva

Saliva is the body's natural built-in protection against caries. Saliva is a glandular secretion, comprised mostly of water with a primary value of being able to flush debris and bacteria from the teeth. Saliva possesses a buffering quality and is therefore able to neutralize the oral environment after patients have consumed food and beverages [23]. In a healthy mouth saliva has a pH of approximately 6.2–7.6, with an average of 7.1, which makes it slightly more basic than water.

Once food or beverage is consumed bacteria breakdown carbohydrates resulting in acid release and lowered salivary pH. It can take from 15 min to an hour or more for the pH to normalize, depending on the acidity of the food and drink. Saliva contains specific proteins which provide a buffering quality [23].

Important minerals found in saliva include calcium, phosphate, and fluoride, which help to remineralize the enamel [23]. In addition, saliva also contains different enzymes including amylase, which helps break down carbohydrates and starches [23].

Genetics, the Environment, and Caries

Genetics and the environment are considered as risk factors in caries formation [24]. A systematic review of the literature demonstrated that different protein phenotypes found in saliva can influence caries risk [24]. In another systematic review, the oral microbiome of monozygotic twins was compared to that of fraternal twins from 1959 to 2013. The oral microbiome of monozygotic twins was found to be very similar as compared to that of fraternal twins, especially when compared among approximal carious lesions. The microbiome of pit and fissure type carious lesions did not yield similar results [25].

Genetics scientists feel that several other genes, such as those involved with enamel development and immune response, tend to influence caries risk [26]. Later studies have found that environmental factors possibly play a larger role in influencing caries risk than genetics [27]. Patients living in areas without fluoridated water are at more risk for caries [27]. Maternal obesity [27] and mothers who lack vitamin D during pregnancy [28] have demonstrated greater carious activity in their offspring.

Dental Caries and Systemic Disease

The oral cavity is the window to the general health of an individual. It is estimated that at least 100 systemic diseases have oral manifestations [29]. Currently, there is limited definitive evidence that oral bacteria are responsible for systemic disease. Similarly, there is limited research that correlates dental caries with systemic disease. More research studying the relationships between oral disease and systemic disease is necessary.

Dental caries can reveal a lot about general bodily health. Untreated decay can lead to pain, infection, and missing teeth which, in turn, can lead to problems with mastication. When patients have trouble chewing, their diets can become compromised by the selection of processed or soft foods, which often contain high amounts of sugar and yield poor nutritional value. Patients with painful or missing teeth may not be able to chew fresh fruit, vegetables, lean meats, nuts, and whole grains which are healthful foods required for a balanced diet. Poor diets can lead to unhealthy weight loss or weight gain.

The consequences of being unable to maintain a good diet will cause a domino effect or a bidirectional effect with serious systemic conditions such as high blood pressure, high cholesterol, diabetes, cardiovascular diseases, and cancer [29, 30].

Xerostomia and Dental Caries

"Xerostomia" is derived from the Greek words: Xeros = dry; Stoma = mouth [31, 32] (see Chap. 23). Xerostomia is an abnormally dry mouth condition resulting from salivary gland dysfunction, systemic diseases, fungal infection, post-radiation treatment, or certain prescription medications. Patients with xerostomia are at higher risk of dental caries since there is little saliva to wash away debris and bacteria. Senior populations can be particularly affected by xerostomia and are more prone to caries [33].

Medications that can cause xerostomia include: antidepressants, anticholinergic (tricyclic antidepressants), antipsychotics, antihistamines, antihypertensives, diuretics, H2 antagonists, opioids, decongestants, incontinence medications, chemotherapy [33].

It is important for healthcare providers to recognize patients suffering from xerostomia. These patients should be promptly referred to dental clinicians who can work with physicians and nurses to suggest alternate medication prescriptions that may not be as mouth drying. Patients with dry mouth need to drink more water during the day and perhaps chew sugarless gum to encourage salivary function. There are also saliva substitutes currently available on the market for patients that may offer some temporary comfort.

Diabetes and Dental Caries

There are studies demonstrating that diabetic patients are more at risk for periodontal disease [34] and for dental caries [35, 36]. Diabetes mellitus patients have a decreased salivary

flow rate caused by hyperglycemia. Diabetic patients possessing poor metabolic control will have dry mouth conditions which facilitate aciduric bacterial generation. This can lead to more caries and more severe carious lesions. Poor oral health can lead to a high sugar diet resulting in a negative effect on diabetic glycemic control.

Oral Cancer and Caries

Methods used to eradicate cancer have lasting detrimental effects on hard and soft oral tissues. Cancer patients who have received radiation and chemotherapy treatments often end up with a dry mouth. Radiation destroys salivary glands, resulting in xerostomia, and can easily culminate in what is coined: "radiation-induced caries." [37].

After radiation treatment caries can progress rapidly, often within 3 months time, and can be very destructive [37, 38]. Clinicians can recommend saliva substitutes for cancer patients to use at home as they will suffer from xerostomia. Xylitol gum, mints, and sprays may be helpful. In addition, cancer patients would greatly benefit from using topical fluoride, especially a prescription strength one. Patients would also benefit from having in-office fluoride varnish applied on teeth every few months. To wash away debris and combat dry mouth patients should constantly sip plain water during the day.

Cardiovascular Diseases, Vascular Disease, and Caries

There have been multiple studies examining the association between cardiovascular disease, vascular disease, and poor oral care. Some of the earliest research associating patients with dental caries, periodontal disease and myocardial infarction date back to studies published in 1989 by Mattila et al. [39]

Furthermore, there is a strong correlation of tooth loss to stroke incidence. Studies support that stroke patients may have lost their teeth at a younger age [30].

Classification and Characteristics of Caries

How Caries Is Classified: Historically (Traditional G.V. Black Method) vs. Currently (Preservation of Tooth Structure Based ICDAS and ICCMS Method)

G.V. Black, the grandfather of U.S. dentistry, is credited with the traditional and perhaps the most common method of classifying caries, which dates from the early 1900s [40]. Most dentists are familiar with the G.V. Black classification and treatment of caries, which he based on the anatomical location of the tooth. According to G.V. Black there are six classifications for carious lesions [40].

Class I caries: Involve the pits and fissures of the teeth. These are located on the occlusal surface of a tooth, so these are also called "occlusal caries."
Class II caries: Involve the interproximal/approximal surfaces of posterior teeth (premolars and molars) and is best detected with bitewing radiographs.
Class III caries: Interproximal/approximal surfaces of anterior teeth and can be detected clinically and or with radiographs.
Class IV caries: Interproximal/approximal surface of anterior teeth plus the incisal edge.
Class V caries: Involve the 1/3 of the buccal surface of the tooth, anterior or posterior.
Class VI caries: are those involving only the cusp tips of teeth. Class VI caries are not commonly found.

ICDAS/ICCMS: Classification of Caries International Caries Detection and Assessment System

A paradigm shift began in the early 2000s. Dental researchers realized that the longevity and strength of a tooth depend on the amount of remaining tooth structure. Clinicians sought methods to preserve, to minimize surgical intervention, and to form a more standardized caries classification system.

In 2002 the International Consensus Workshop on Caries Clinical Trials was held, and the International Classification of Detection and Assessment System (ICDAS) was born. ICDAS provides a more accurate assessment of caries by grading the severity of the caries. ICDAS allows for better management and outcomes of carious situations [41]. ICDAS method of classification relies on specific seven-point ordinal coding system which ranges from sound to extensive caries. The ICDAS coding system is as listed below:

1. Sound.
2. First visual change into enamel.
3. Distinct visual change into enamel.
4. Localized enamel breakdown.
5. Underlying dark shadow visualized (from dentin).
6. Distinct cavity including visible dentin.
7. Extensive distinct cavity including visible dentin.

Characteristics of, Symptoms of, and Progression of Caries

It can take many months to years for a fully cavitated carious lesion to appear clinically and radiographically. The progression of caries is gradual in most patient situations. On average, it takes approximately 18 months (give or take 6 months) for a smooth surface carious lesion to progress from non-cavitated to cavitated [38]. Pit and fissure lesions progress more rapidly than smooth surface caries [38]. However, caries development can vary from patient to patient and breakdown and pain can possibly progress over several months' time, depending on mitigating factors. Caries can form rapidly with acute systemic conditions such as cancer and associated radiation treatments [38].

Patients with early dental caries usually present with no pain. In the beginning the carious lesions may not be very noticeable. There may be the appearance of what is called a "white spot lesion." [42]. White spot lesions can be found often under a layer of accumulated plaque. Primary caries shows up as subsurface demineralization and this is where the crystalline structure begins to break down. Due to how light reflects off the enamel they appear as chalky, opaque and, rough, hence the term "white spot" as shown in Fig. 7.5.

Once the caries progresses closer toward the dentinal layer or penetrates the dentin, the patient may begin to have sensitivity to sweets. As carious lesions become larger and deeper toward the pulpal/root area, the patient will often feel pain reaction to hot or cold temperatures. Eventually, constant and throbbing pain can accompany the deep carious lesion if it has progressed into the pulp. An abscess and/or swelling could accompany as well.

The Progression of Caries is diagrammed in Fig. 7.5 for occlusal surface (pit and fissure caries) pattern vs. smooth surface approximal surface pattern**.** Demineralization follows the direction of the enamel rods, spreading laterally, so a triangular pattern is formed such that the base of the triangle will be at the dentinoenamel junction (DEJ). As occlusal caries progresses beyond the DEJ and into the dentin the caries will then form another triangular shape with the base of the triangle being at the DEJ and the apex toward the pulpal area. Deep caries approaching the pulpal area will form a diamond shape from the two triangles.

Approximal caries also follow the pattern of the enamel rods with the base of a triangular shape towards the outer surface of the tooth as diagrammed in Fig. 7.6. The caries forms the apex of a triangular shape as it reaches the DEJ. Once caries spreads into the dentin a second triangular shape forms with the base of the triangle at the DEJ area and the apex toward the pulp (Fig. 7.7).

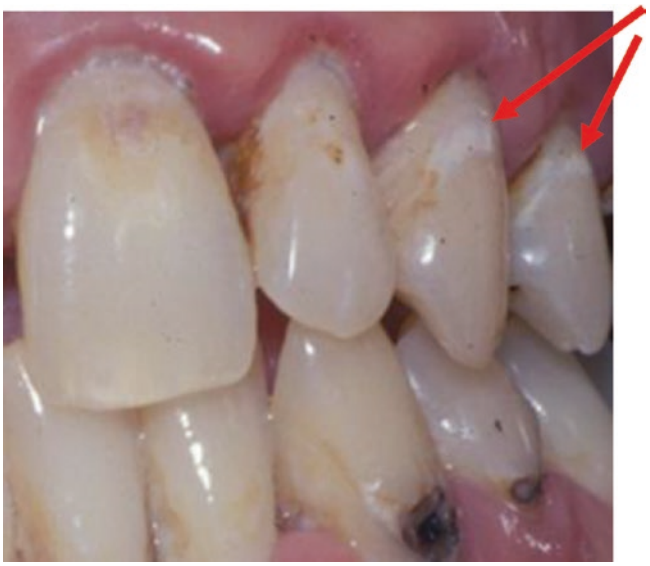


Fig. 7.5 Depicting white spot lesions. (Courtesy of Dr. Jonathan C. Meiers)

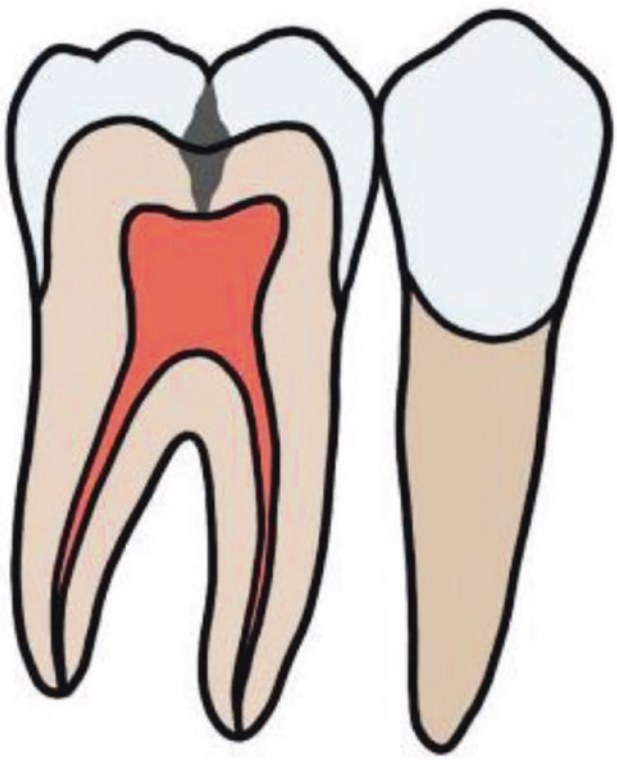


Fig. 7.6 Depiction of occlusal caries progression. (Courtesy of Dr. John Syrbu)

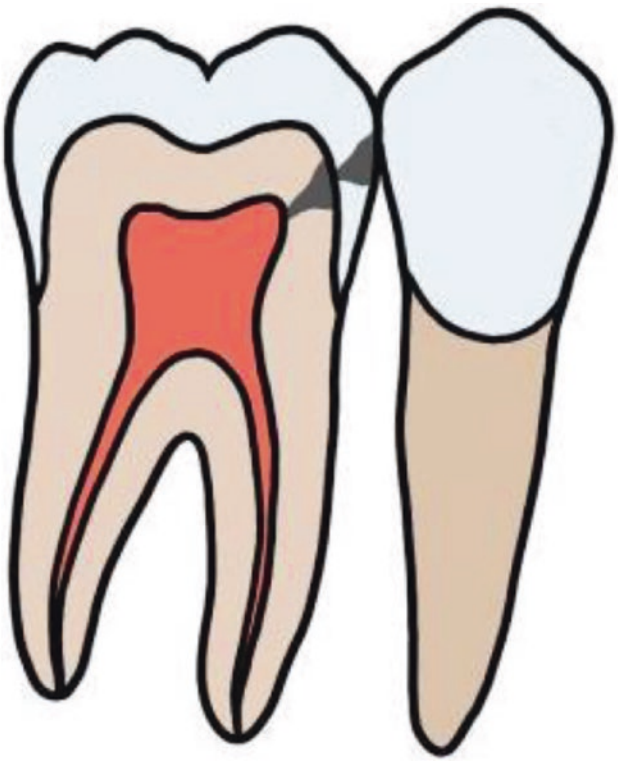


Fig. 7.7 Depiction of approximal caries progression. (Courtesy of Dr. John Syrbu)

The Interprofessional Roles in Dental Caries Management

Sometimes patients may see a medical practitioner before seeing a dentist. It is important for physicians, physician assistants, and nurses to recognize signs of xerostomia, fractured teeth, white spot lesions, and frank caries. Interprofessional referrals provide prompt benefits for the patient. Working together, the health teams' overall goals are to improve health and quality of life.

Proper management of caries requires:

1. A prior very accurate diagnosis of caries.
2. Followed by a good treatment plan.
3. Understanding of the modern caries paradigm and best/most conservative treatment options to maintain tooth structure.

CAMBRA (Caries Management by Risk Assessment)

"The best restoration is NO restoration."

At a lecture 130 years ago, G.V. Black stated: "the day surely is coming and perhaps within the lifetime of you young men before me when we will be engaged in practicing preventive rather than reparative dentistry." [43]. G.V. Black would have been pleased that his predictions eventually did lead to the modern caries paradigm. Evidence has now been established that caries isolated to the enamel does not require operative removal [44]. Even with evidence-based research demonstrating more conservative treatment for carious lesions with minimally invasive methods, dentists surveyed worldwide are still resistant to forgo traditional concepts of "drilling and filling." [45]. In fact, Innes et al. report that 40–80% of dental clinicians would still prefer to surgically remove tooth structure with a handpiece [45]. Innes et al.'s research found that there were three basic reasons why clinicians refused to change their habits which are summarized as: "Don't know, can't do, won't change." [45]. The study found that dental clinicians choose not to learn more about the topic so that is why this updated chapter on caries is so significant to share with our medical colleagues.

CAMBRA, the acronym for "Caries Management by Risk Assessment," is an evidence-based standard for making decisions to treat carious lesions. CAMBRA includes a methodology of assessing caries risk factors on each individual patient; management of the patient with behavioral and chemical means. If surgical intervention is required, then the most minimally invasive treatments would be recommended. CAMBRA includes behavioral, environmental, protective, and preventive considerations [46].

Caries risk is defined as "the probability of future caries development." [44]. There are different factors, called "caries risk factors," that can affect caries development. Over the patient's lifetime caries risk factors can change [44].

In more recent times a growing list of caries risk factors have been identified. Caries risk factors can include the following [47]:

1. Age, sex, and race,
2. Sugar consumption, amount of sugar consumption, and frequency of sugar consumption,
3. Inadequate salivary flow,
4. Poor oral hygiene,
5. Inadequate fluoride exposure,
6. Socioeconomic reasons including community status, environment, and geography,
7. Pre-existing medical conditions such as diabetes, Sjogren's disease, or medications that cause xerostomia,
8. Form and arrangement of teeth.

Diagnosing/Detection of Caries: Visual-Tactile/ Radiology and the Use of Newer Technology

Diagnosing caries is not just about seeing stain in or on a tooth but also about visualizing a change in tooth texture.

The oldest and most traditional ways of diagnosing caries which are still commonly used, are tactile and visual methods. Tactile method consists of using the explorer hand instrument while visual methods include eye vision, supplemented by use of the X-ray (radiography) unit [44]. "Bitewing" radiographs are considered a reliable source for detecting approximal caries, as demonstrated in Figs. 7.8, 7.9, and 7.10.

Anterior approximal carious lesions can often be visualized clinically by "transillumination." This consists of shining a bright light over the facial surfaces of the teeth and a mouth mirror placed on the lingual (tongue side) to show the dark carious lesion shadows as depicted in Fig. 7.11.

While posterior approximal carious lesions may be easily identified with bitewing radiographs they are not easily visualized clinically in the mouth *until* approximal caries become rampant, Figs. 7.12 and 7.13.

Prior to visual examination for caries, teeth should be cleaned of plaque and thoroughly dried of saliva and water. It would be impossible to accurately examine if debris is lodged in the occlusal surfaces. Clinicians need excellent overhead lighting and should wear high powered magnification lenses to allow for optimum caries detection.

Accurate diagnosis of occlusal caries can be more difficult to confirm than that of smooth surface caries. Caries diagnosis is a combination of texture and stain. When viewed clinically, occlusal caries can appear to lose enamel translu-

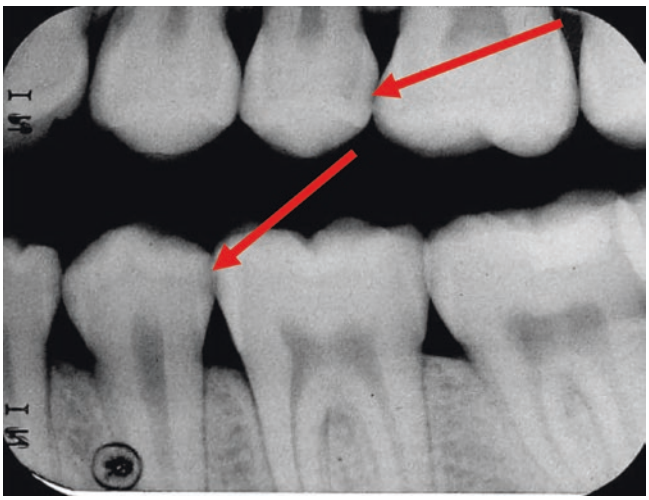


Fig. 7.9 Bitewing radiograph demonstrating approximal caries on maxillary second premolar and mandibular second premolar. (Courtesy of Dr. Howard Strassler)

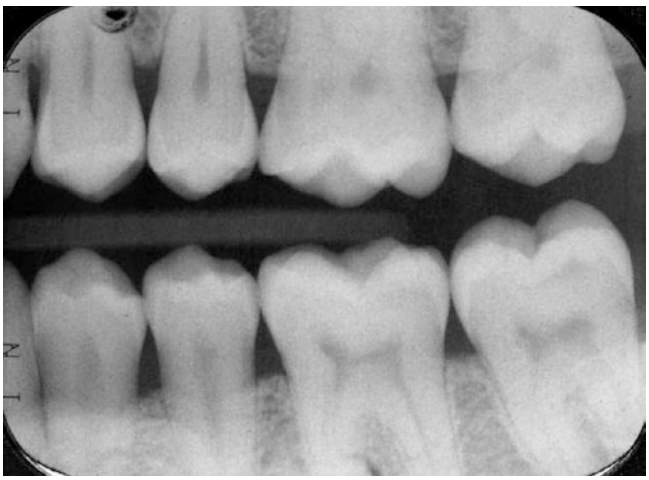


Fig. 7.8 Bitewing radiograph demonstrating healthy mouth without caries. (Courtesy of Dr. Howard Strassler)

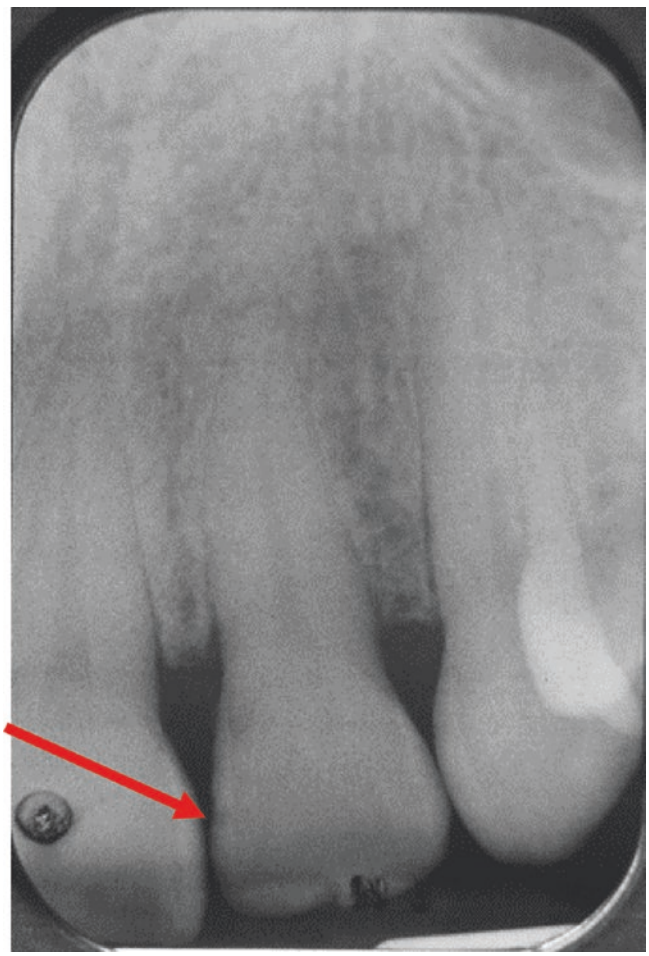


Fig. 7.10 Radiograph demonstrating approximal caries on an anterior tooth. (Courtesy of Dr. Howard Strassler)

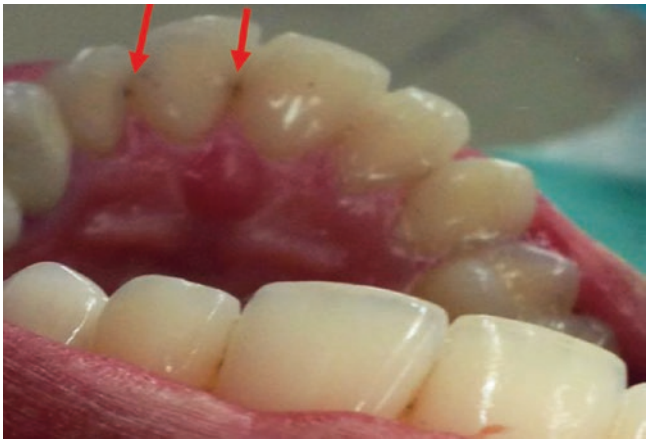


Fig. 7.11 Transillumination to detect anterior approximal carious lesions as demonstrated by arrows. (Courtesy of the author, Dr. Melissa Ing)

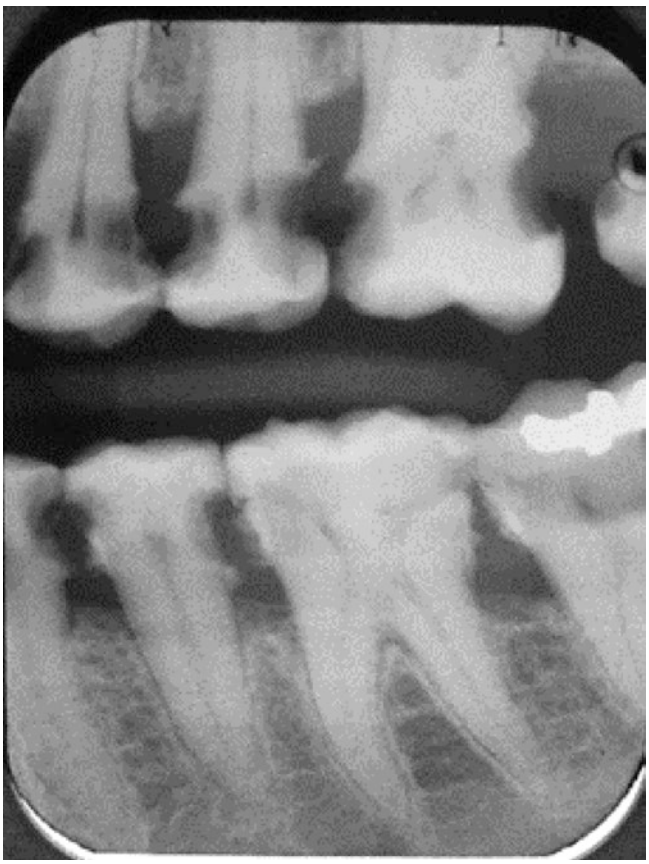


Fig. 7.12 Bitewing radiograph of rampant approximal caries. (Courtesy of Dr. Howard Strassler)

cency and often are accompanied by dark staining as demonstrated in Fig. 7.14. Occlusal and deep occlusal caries on second molar. Note dark coloration and lack of translucency. Figure 7.15 After caries removal**.**

Traditionally, probably for the last 50 years, sharp explorer hand instruments were utilized to explore into pits

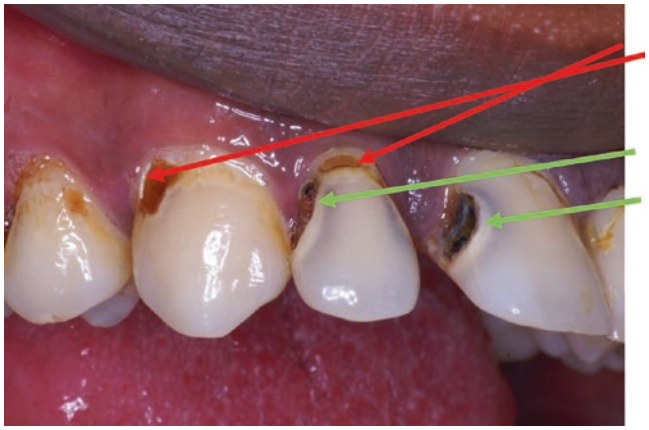


Fig. 7.13 Rampant approximal and cervical caries. Red arrows depict cervical caries. Green arrows point to approximal caries. (Courtesy of Dr. Howard Strassler)

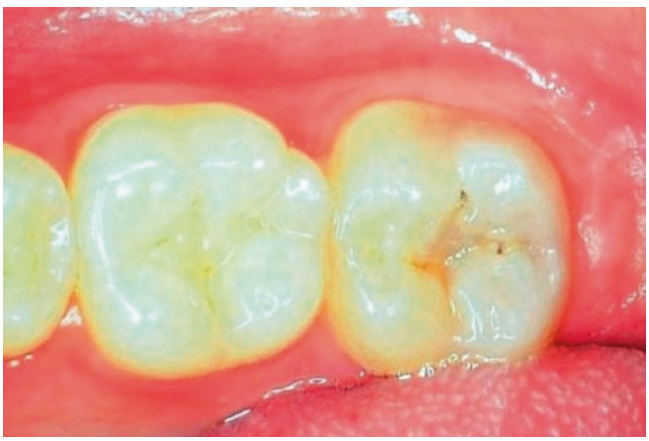


Fig. 7.14 Occlusal caries.

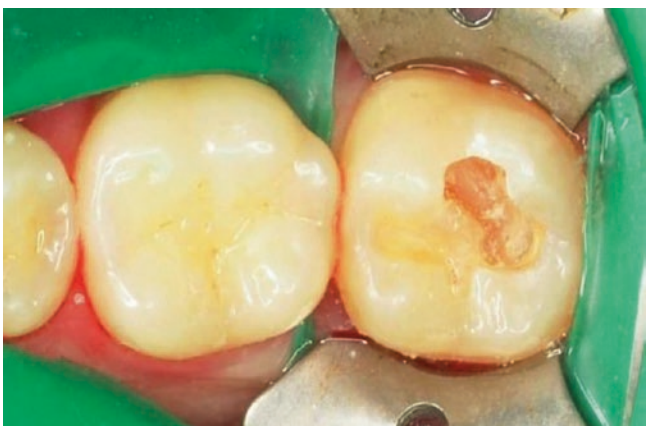


Fig. 7.15 After caries excavation. (Courtesy of Dr. Howard Strassler)

and fissures of teeth for caries. However, sharp explorers are not recommended for caries detection, especially with teeth that have demineralized enamel [40]. Electron micros-

copy has demonstrated that the use of sharp explorers can cause iatrogenic damage to pits and fissures. The use of a blunt probe can be used to clean debris out of deep crevices but the modern caries paradigm demonstrates that there is not much to be gained by pushing an explorer in to find a "sticky fissure."

There are newer and interesting methods of detecting caries that involve the use of technology [40, 44]. In the last 20 years various manufacturers have introduced computerized equipment that incorporates lasers (e.g., The Canary System), transillumination (e.g., DEXIS CariVu), or light fluorescence (e.g., Diagnodent) to detect and quantify the amount of enamel mineral. This technology relies on the scattering of fluorescing light, giving clinicians the ability to detect very minute enamel caries [40, 44]. However, detecting the smallest enamel caries has been shown to cause overdiagnosis with subsequent over-treatment of carious lesions that would normally be monitored, instead of surgically treated, according to ICDAS coding [44].

While not a diagnostic tool, an intraoral camera wand may be more of a useful piece of equipment that allows dentists to demonstrate carious lesions, cracked restorations, and teeth to patients.

The Inter-professionals' Role in Prevention of Caries

Dental caries is preventable. Knowledge of caries prevention should be a team investment by dental and medical professionals to curb oral disease, which in turn will improve overall systemic health. Prevention is an investment to allow healthy and functional teeth throughout the patients' lifespan.

There are three main strategies to prevent tooth decay. These include:

1. Nutritional counseling and reduction of sugar intake.
2. Administration of fluoride.
3. Proper oral hygiene instruction which includes proper daily tooth brushing and flossing techniques.

In some cases, more than one or all three preventative measures may need to be utilized for successful caries reduction [44].

Nutritional Counseling Including Reduction of Sugar Intake

Nutritional advice and diet modification are the most important approaches to caries prevention. After performing a caries risk assessment, it is important to supply each patient an individualized yet practical dietary plan that is geared towards better nutrition and promotes better oral health [44].

Most consumers are unaware of how free sugars are added in as ingredients of many processed foods including packaged breads, chips, condiments, and salad dresses [19].

Health providers should discourage patients' frequent intake habits of sugary, sticky, starchy foods, and sugary beverages (including fruit juices and sport drinks). Snacking throughout the day should be discouraged since each introduction of food will promote acid attacks. Instead, suggest that snacks be eaten with meals and not allow foods to linger inside the mouth. Frencken emphasizes that it is prudent that children limit their sugar intake to no more than five times per day [44].

Caries Prevention and Treatment with Fluoride

For many decades, fluoride, a natural mineral that exists in the earth's crust, has been well recognized as a powerful preventive measure to fight dental caries [44].

Fluoride is the negatively charged ion of fluorine. It is the most highly electronegative element of the periodic table. Due to its electronegative quality, fluoride is able to substitute into bone and tooth hydroxyapatite crystals, which converts them to stronger fluorapatite crystalline structures. Fluorapatite crystals are able to form quicker than hydroxyapatite and they are stronger, making enamel more resistant to acid dissolution [48].

Systemic vs. Topical Fluoride

While all delivery systems of fluoride can be beneficial, health care providers should understand which type of fluoride and which strength would be most suitable for a patient situation; which are applied in a dental office; which are prescribed to patients; and which fluorides consumers may purchase over the counter.

In 1909 dentists Frederick McKay and G.V. Black found it very peculiar that Colorado Springs residential children's unsightly, chocolate brown colored, mottled enamel was resistant to caries. After years of studying the phenomenon, it was realized that the unesthetic staining was due to the excessive natural fluoride in the ground water. The enamel disorder was termed "dental fluorosis." With this discovery, dentists and other scientists decided to test a hypothesis that the addition of fluoride into city water systems would fight dental decay. In 1945, several pairs of cities in the United States and Canada were chosen to be the experimental lead sites to introduce community water fluoridation. This is the abridged story of how fluoride was discovered to be able to fight cavities.

When fluoride is ingested through natural or synthetic fluoride water supplies it is called "systemic fluoride."

Fluoride is naturally found in water, soil, and air in the form of calcium fluoride. This is "naturally occurring fluoride." In some parts of the world fluoride can be found in excessive amounts while in other areas natural fluoride is deficient. In areas where fluoride is insufficient synthetic fluoride is added to the municipal water [48].

Clinicians should understand the differences between (a) "*systemic fluoride*" and (b) "*topical fluoride*" and how each contribute toward caries prevention.

The addition of synthetic fluoride to public water supplies is called: "Community Water Fluoridation." The Centers for Disease Control considers community water fluoridation as one of the ten greatest public health achievements of the twentieth century [49]. Community water fluoridation is responsible for an 18–40% reduction in cariogenesis [49] and, therefore, is an efficient and cost-effective way to deliver fluoride to the public [48].

As of 2015 in the United States Department of Health and Human Services lowered Community Water fluoridation to 0.7 parts per million taking into account that consumers already receive fluoride by using fluoridated toothpastes, gels, varnishes, and mouthwash rinses. Also, there is halo or diffusion effect from the fluoride run off from multiple unanticipated community water sources. Virtually all foods and beverages contain fluoride, with crustaceans, fish, grapes, and tea possessing the highest levels [48].

When fluoride is administered at the dentist's office or applied to teeth at home from dentifrices, gels, varnishes, and mouth rinses it is considered "topical fluoride."

While systemic fluoride is ingested and is incorporated into enamel and dentin structure strength, topical fluoride is considered more effective for teeth that are already erupted into position in the mouth to make them resistant to caries.

Stannous vs. Sodium Fluoride

The two main types of fluoride are added to toothpaste dentifrices, gels, and varnishes are: "stannous fluoride" and "sodium fluoride." Both types of fluoride are effective at fighting caries.

- Stannous Fluoride—protects against gingivitis, plaque, tooth sensitivity, and protects against caries. Some formulations may cause slight staining.
- Sodium Fluoride—only protects against caries.

Following CAMBRA risk assessment a patient's risk factors are determined. Factor assessment allows clinicians to make decisions on which fluoride-containing therapeutic agents would be most suitable for their patients. These fluoride treatments can consist of in-office treatments (silver diamine fluoride and fluoride varnish), prescribed (within the United States) stronger fluoride toothpastes for at home use, or over-the-counter fluoride toothpastes, gels, and rinses. Certain patient cases may warrant a combination of these preventative therapeutic measures [44].

Fluoride for "Non-Surgical Treatment" of Carious Lesions.

It is possible to re-mineralize teeth with white spot lesions that are hard and non-cavitated, and if there is no acid erosion [14, 42].

38% Silver Diamine Fluoride (SDF): Non-Surgical in Office Treatment Contains 44800PPM Fluoride.

During the 1840s, G.V. Black created protocols to use silver nitrate to treat caries, since silver possesses antiseptic qualities. In 1917 Dr. Percy Howe of the Forsyth Institute added ammonia to silver nitrate, creating "diamine silver nitrate." The addition of ammonia allows silver nitrate to stabilize and concentrate, thereby allowing the material to stay in place better to arrest caries. By the early twentieth century many dental offices were mixing and creating their own "Howe's solutions." With the advent of local anesthesia and fluoride in the 1950s and 1960s, silver nitrate fell out of favor for use in North America. However, in countries such as Japan, Mexico, China, Brazil, and Australia, silver diamine fluoride has been in continuous use since the 1960s.

In 2014 the United States Federal Drug Administration cleared silver diamine fluoride (SDF) as a Class II medical device for the treatment of dentinal sensitivity but allows SDF to be used "off label" to non-surgically treat caries. Thirty-eight percent of silver diamine fluoride consist of: 25% silver, 5% fluoride, and 8% ammonia in solvent.

Since silver diamine fluoride does not require local anesthesia administration, or the removal of caries with hand or rotary instrumentation, trained health care workers may apply SDF in compromised communities such as nursing homes [44].

Using SDF allows for the preservation of tooth structure since there is no drilling. SDF increases dentinal hardness and prevents demineralization. The material reacts with hydroxyapatite to create calcium fluoride and silver phosphate. Note that patients may object to the post-treatment black/brown discoloration caused by SDF as demonstrated in Figs. 7.16 and 7.17 before and after SDF application showing black stain.

The use of SDF has been especially beneficial during the 2020 SARS-CoV-2 Coronavirus pandemic when dentists were forced to minimize the use of aerosols (particles less than 50 μm) produced by dental handpieces. It was hypothesized that dental aerosols were possibly linked to the transmission of COVID-19. Aerosol particles can possibly remain airborne for at least 30 min [50].

5% Fluoride Varnish.

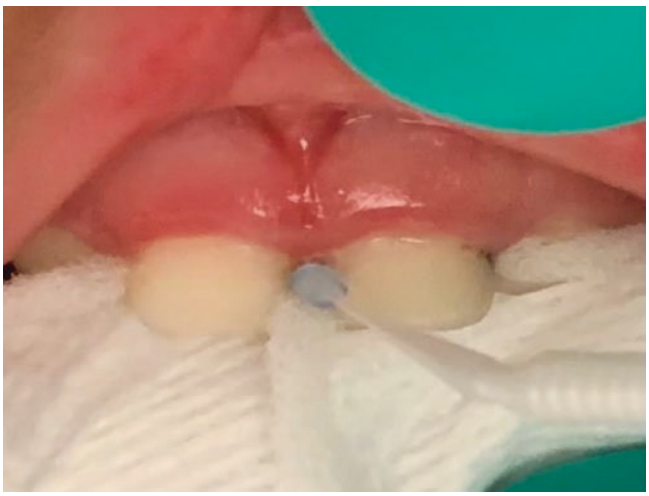


Fig. 7.16 Anterior teeth are isolated and silver diamine fluoride is applied as a clear liquid. (Courtesy of Dr. Shan Girn)

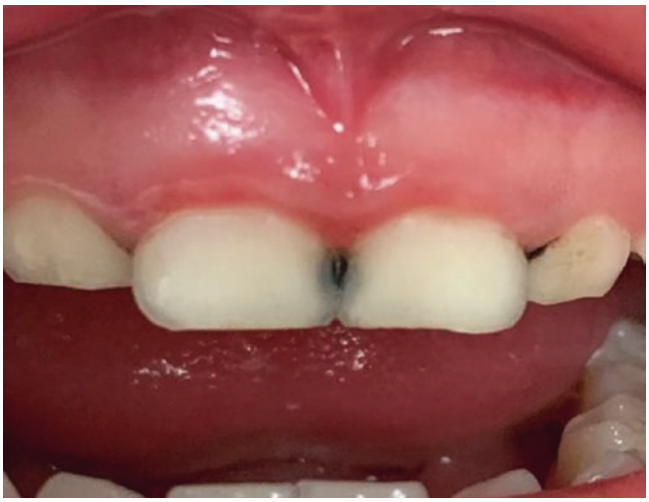


Fig. 7.17 Depiction 1 week post-operative black staining after silver diamine fluoride application. (Courtesy of Dr. Shan Girn)

Fluoride varnish is an in-office application containing 22,600 PPM Fluoride. Fluoride varnish applications have been demonstrated to decrease primary teeth caries by up to 37% [51]. It is therefore, imperative to expand administration to primary care physicians, especially pediatricians.

5000 PPM Fluoride Toothpaste.

Patients at high risk for caries may be given a high 5000 PPM fluoride toothpaste for at home use which is by prescription in the United States or over the counter in Canada.

Too Much Fluoride? Dental Fluorosis.

While dental fluorosis is a common oral disorder caused by ingesting fluoride it can only develop on children under the age of 8 years of age while their permanent teeth are forming [50]. Dental fluorosis may appear as white flecks or lacy white patterns on the enamel surface. More severe cases of fluorosis could include brown discoloration and pitting of the enamel [50] (Figs. 7.18 and 7.19).

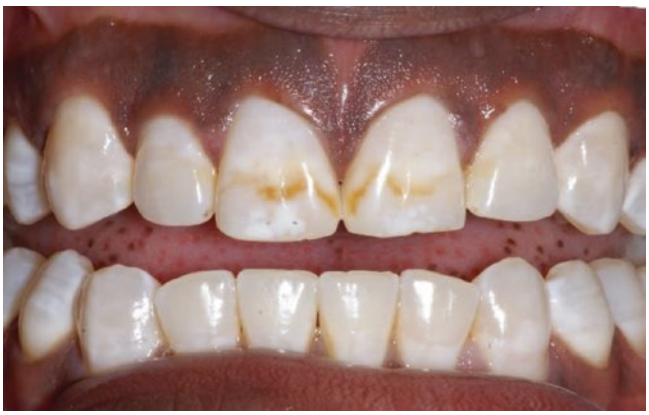


Fig. 7.18 Moderate fluorosis. (Courtesy Dr. Howard Strassler)

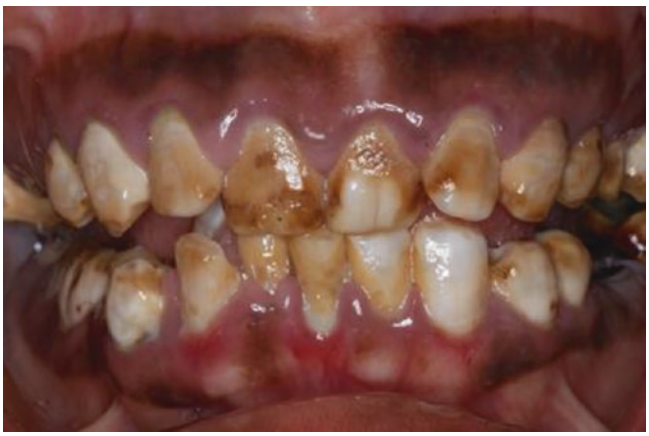


Fig. 7.19 Severe fluorosis. (Courtesy Dr. Howard Strassler)

Cases of mild over exposure to fluoride have been reported. Mild over exposure can cause mild to serious symptoms, mostly related to gastrointestinal discomfort such as vomiting, abdominal discomfort, diarrhea, and nausea [50].

There are multiple unanticipated sources of fluoride intake, including topical dentifrices, oral rinses, gels, and varnishes as well as within food and beverages. Therefore, in 2015, the United States Public Health Service updated its recommended optimal level of fluoride in drinking water and decreased it to 0.7 mg/L [50].

Sharing Teachable Moments in Good Oral Hygiene

Oral hygiene habits can influence the composition of the oral microbiome [29]. Patients with excellent oral hygiene will have a simpler colony population consisting of mostly gram-

positive cocci and rods and some gram-negative cocci. However, patients with poor oral hygiene tend to have a complex flora composed of anaerobic gram-negative bacteria [29]. Therefore, better oral hygiene habits will disrupt the biofilm and allow for cleaner tooth surfaces. When there is less bacteria there is less likely to be onset of caries incidence.

The entire healthcare team (dentists, physicians, physician assistants, nurses) needs to educate parents as early as possible to establish a good oral care regimen with proper toothbrushing habits for their babies, toddlers, and children. It is very important to encourage healthy sleep routines so that babies are never allowed to go to bed with a bottle in their mouths to prevent "baby bottle caries."

Often, parents will let their toddlers play with a toothbrush, not thoroughly cleaning the teeth. Health professionals must emphasize that toddlers and children should not be allowed to brush teeth without adult help and follow through. It is so important for the parents to thoroughly brush the teeth, assuming that parents have been taught proper technique. For children who are able to understand how to expectorate, it is beneficial to have them swish with a fluoride mouth rinse in case there are any unbrushed tooth surfaces.

Parents should brush teeth for children up to ages 4–5 years. Parents should monitor toothbrushing for children up to ages 9–10 years. In addition, parents should ensure that (1) the correct amount of toothpaste is utilized, (2) teeth in the entire mouth have been brushed, and that (3) teeth have been brushed for adequate amounts of time.

How Much Toothpaste Should Patients Use?

A 2019 report released by the Centers for Disease Control (CDC) [52] demonstrated that children are using too much toothpaste. The American Dental Association (ADA) recommends that children not overuse fluoride toothpaste while their enamel is still forming. In addition, it is best to delay the introduction of toothpaste until children can demonstrate they comprehend how to expectorate after brushing in order to prevent inadvertent swallowing of fluoride toothpaste.

Fluoride needs contact time with the tooth surface in order to be effective. Therefore, it is best to advise patients to brush thoroughly and then continue to spit out excess so as not to swallow any fluoride toothpaste but do NOT rinse with water if at all possible. Patients should be encouraged not to rinse off excess toothpaste so that the fluoride has time to permeate into the enamel surface.

It is recommended that toddlers under the age of 3 if able to expectorate, use a smear or rice-sized portion of toothpaste on their toothbrush for each brushing as shown in Fig. 7.20.

It is recommended that children over the age of 6 use a pea-sized dot amount of toothpaste on their toothbrush for each brushing as shown in Fig. 7.20.

Fig. 7.20 Demonstrating proper amount of toothpaste application for adults (thin ribbon), for children over the age of 6 (pea-sized dot), and for toddlers under the age of 3 who understand how to and can expectorate (smear or rice-sized amount). (Figure by Courtesy of Dr. Melissa Ing)

It is recommended that adults also not overload toothpaste quantities. Adults should place a thin ribbon amount of toothpaste on their toothbrush for each brushing as shown in Fig. 7.20.

How Long Should Patients Brush Their Teeth?

The American Dental Association instructs patients to brush their teeth for AT LEAST 2 min each time, twice a day, once in the morning and once at night. However, the Academy of General Dentistry suggests that patients brush longer, for about as long as a song playing on the radio [53].

There will be times when access to a toothbrush is not possible during the daily routine. At such times, physicians, nurses, and all health care providers should advise patients to chew sugarless gum and to drink water throughout the day which will encourage salivary function, help dislodge debris in the mouth, and keep the oral cavity moist.

Can Flossing Prevent Caries?

Flossing can disrupt interdental plaque. Hujoel et al. demonstrated that professional flossing done at a dental office can possibly reduce caries. However, Hujoel's research showed that patient self-flossing is more beneficial for gingival health but does not stop carious activity [54].

The Benefits of Xylitol, a Sugar Substitute.

Xylitol is a common sugar substitute shown to help reduce caries [44, 55]. Soderling et al.'s research from 2001 demonstrated that women who consumed xylitol significantly reduced mother–child transmission of streptococcus mutans [55]. In 1995 Makinen et al. released their study demonstrating that chewing gum stimulates saliva, which can help inhibit acid production and stop caries.

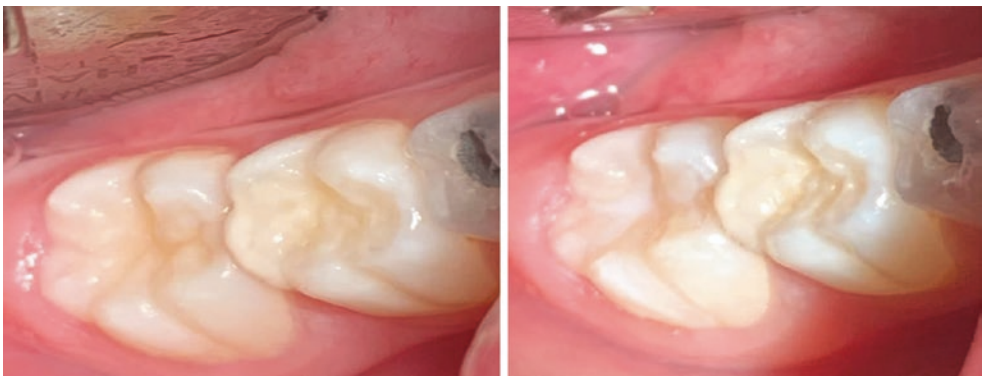


Fig. 7.21 Before and Fig. 7.16 After of sealant placement on permanent molar. (Courtesy of Dr. Shan Girn)

Makinen's study showed that xylitol containing gum was more effective than sorbitol containing gums at reducing caries [56].

Xylitol is considered a sugar alcohol, meaning it is a combination of sugar and alcohol molecules [57]. Acidogenic bacteria are unable to ferment xylitol, accounting for less acid production in plaque.

Xylitol gum (or mints) chewed for 5 min 3 times a day has been demonstrated to reduce caries. For effectiveness 5–6 g of xylitol is recommended daily. Since xylitol requires time to be absorbed by the large intestine, one of the noted side effects of xylitol intake is gastrointestinal discomfort where patients may complain of diarrhea [57].

Pit and Fissure Sealants

Dental sealant application can be utilized to prevent caries on the occlusal surfaces of permanent premolars and molars [44]. Due to their anatomical features, pits and fissures are prime areas for debris and food entrapment. They are more vulnerable to caries so sealant application fills in the voids, thereby making the occlusal surface smoother, easier for the patient to cleanse, and prohibiting bacteria from entering the deep fissures (see Figs. 7.21 and 7.22). Sometimes sealant material may be also applied to seal off deeply depressed lingual surfaces of the lateral incisors. Sealants are easily and painlessly applied to teeth without the need for pre-op anesthesia or drilling. Sealants are recommended to be placed as soon as children's permanent posterior teeth have erupted into position to protect the occlusal surfaces from acid dissolution.

Preventive sealants consist of either resin-based or glass ionomer-based material. Glass ionomer materials chemically bond to tooth structure and have the advantage of being a fluoride releasing material. Glass ionomer materials are easier to place in pediatric situations when clinicians must work quickly on a child and where there may be difficulty controlling moisture. Glass ionomer is hydrophilic. Glass ionomer traditionally have more retention problems and tend to dislodge after placement more than resin-based sealants.

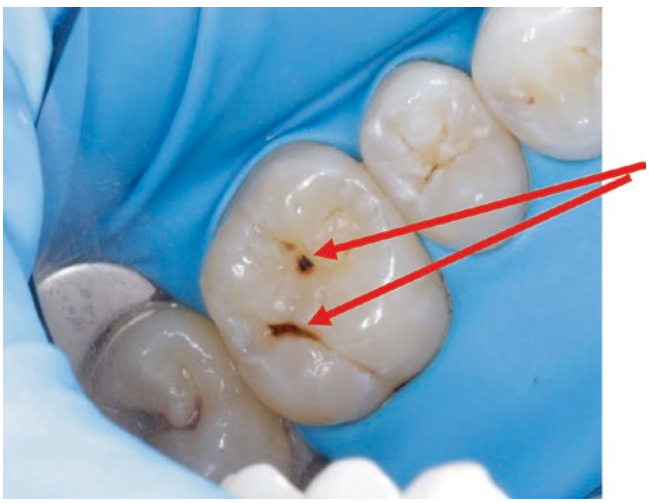


Fig. 7.22 Arrested caries on occlusal pits of maxillary first molar. Area is deeply stained but is hard, without any soft texture. (Courtesy of Dr. Aditi Jain)

Regardless, systematic reviews of recent research demonstrate that both materials still provide similar caries prevention efficacy [58].

Minimally Invasive Treatment of Caries

When isolated to the enamel layer caries can and should be reversed with fluoride as a conservative treatment. Understanding the balance between demineralization and remineralization is crucial to caries management. Surgical intervention is always considered as a last option.

The more that tooth structure can be preserved the stronger tooth will be in the long run with less chance for tooth and restoration fracture, and less chance for restoration failure in the future. Secondary carious complication situations can arise as noted below in: "Caries around the restoration" and "Defective restorations."

There are benefits to minimizing surgery for the patient. Patient anxiety can be provoked by local anesthesia, needles, the noise and sensation of dental handpieces, and the perception of discomfort and pain.

If surgery is necessary dentists should consider minimally invasive procedures [44].

Minimally Intervention Dentistry (MID) is a term that not only applies to the treatment of caries but rather to the care of the entire oral cavity including the periodontium. MID strategies include: early caries risk assessment; remineralization methods; minimally invasive operative treatments; repair rather than replacement methods [44].

Total removal of deep carious lesions should be avoided to prevent pulp exposure, if teeth are considered "vital." Research has demonstrated that during caries excavation "infected dentin" is removed but that it is possible to leave hard/leathery (previously coined "affected dentin") dentin remaining and place a permanent restoration to avoid a root canal. Endodontics is another traumatic procedure for patients [44, 45].

Arrested Caries

Caries can become "arrested" or stationery. The progression of caries stops even though the tooth structure appears deeply stained brown or black as in Fig. 7.22 with a polished appearance. Even though the area is deeply stained there is no accompanying soft texture. However, arrested caries should be regularly monitored with recommended applications of fluoride varnish. Surgical intervention can be avoided if there is no relapse of carious activity/cavitation.

Caries Around the Restoration

"Caries around the restoration" differ from primary caries and is the designated term for caries that form around the perimeter of an existing restoration. This terminology replaces the old terminology "recurrent caries" as depicted in Fig. 7.23. This patient situation will require removal of the old restoration, excavation of the caries, and a replacement restoration [44].

Defective Restorations

The "margin" of an existing restoration is the interface where the restoration meets the tooth structure. When the margin of an existing restoration is compromised by fracture or chipping the restoration is deemed as defective as demonstrated in Fig. 7.24. A defective margin can also be "ditched," meaning that the restoration is shallow at the interface. These scenarios will most likely require either repair or complete replacement of the restoration [44].

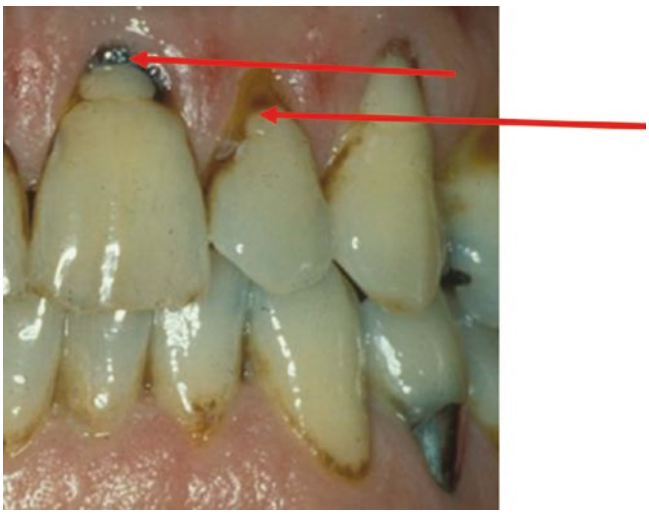


Fig. 7.23 Caries around the restoration. Leakage of restorative margins and caries is seen at the cervical area of the central incisor. (Courtesy of Dr. Jonathan C. Meiers)

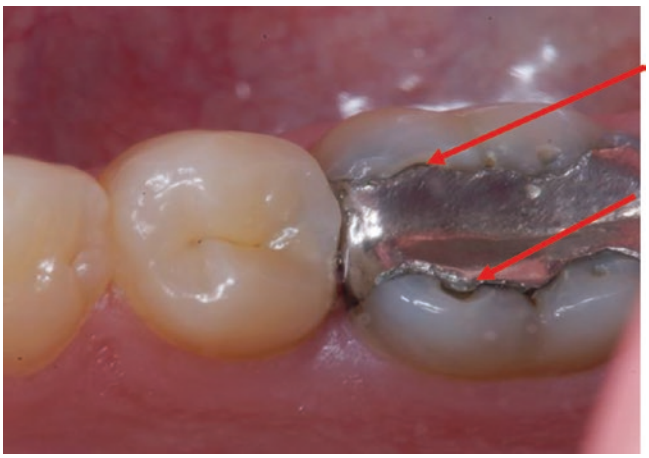


Fig. 7.24 Defective amalgam restoration with "ditched"/poor margins. (Courtesy of Dr. Howard Strassler)

Summary

Many chronic diseases show symptoms of xerostomia, periodontal disease, and caries. We know that there are associations, but more research is needed to link systemic and oral disease. The evidence of caries in multiple diseases are clues to intersection.

With the demographic shift where the geriatric population continues to quickly expand, it is essential for the entire health care team to recognize that the oral cavity is the inter-

section of medicine and dentistry. As the senior age group expands everyone can pitch in to diagnose pathology, treatment plan, and offer preventive dental care. In the meantime, there is opportunity and necessity for nurses, physicians, hygienists, dentists, and all health care practitioners to collaborate and optimize patient health for ALL ages.

Acknowledgments Dr. Ing would like to thank Dr. Jonathan C. Meiers for his contributions and for reviewing this chapter. Dr. Ing would like to thank Dr. Howard Strassler, Dr. John Syrbu, Dr. Shan Girn, Dr. Aditi Jain, and Dr. David Frantz for their contributions to this chapter.

Dr. Ing dedicates this book chapter to her late father, Dr. Tom Ing, who taught her early in life, to always love books and to appreciate how books can take you many places and always remain some of your best friends. Dr. Ing's father encouraged strength of purpose, duty above self, and she is very grateful for his wisdom.

References

1. Haumschild MS, Haumschild RJ. The importance of oral health in long-term care. J Am Med Dir Assoc. 2009;10(9):667–71.
2. Selwitz R, Ismail A, Pitts N. Dental caries. Lancet. 2007;369:51–9.
3. https://www.nidcr.nih.gov/research/data-statistics/dental-caries/adults.
4. https://www.fdiworlddental.org/sites/default/files/media/resources/sugar_toolkit-fdi-2016.pdf.
5. https://www.who.int/news-room/fact-sheets/detail/sugars-and-dental-caries.
6. Ling Z, Tao H. Dental caries and systemic diseases. In: Dental caries. Berlin: Springer. p. 129–55.
7. Kane S. The effects of oral health on systemic health General Dentistry. Self-instruction no. 411, 2017.
8. Aas J, Griffen A, Dardis S, Lee A, Olsen I, Dewhirst F, Leys E, Paster B. Bacteria of dental caries in primary and permanent teeth in children and young adults. J Clin Microbiol. 2008;46(4):1407–17.
9. Al-Shahrani, M. Microbiology of dental caries: a literature review. Ann Med Health Sci Res. 2019;9(4).
10. Faustova MO, Ananieva MM, Basarab YO, Dobrabolska OV, Vovk IM, Lobran GA. Bacterial factors of cariogenicity (literature review). Wiad Lek. 2018;71(2 pt 2):378–82.
11. Soderling E, Isokangas P, Pienihakkinen K, Tenovuo J. Influence of maternal xylitol consumption on acquisition of mutans streptococci by infants. J Dent Res. 2000;79:882.
12. Da Silva Bastos V, Freitas-Fernandes L, da Silva Fidalgo T, Martins C, Trindade Mattos C, de Souza I, Cople Maia L. Mother-to-child transmission of Streptococcus mutans: a systematic review and meta-analysis. J Dent. 2015;43(2):181–91.
13. Brailsford SR, Tregaskis RB, Leftwich HS, Beighton D. The predominant Actinomyces spp. isolated from infected dentin of active root caries lesions. J Dent Res. 1999;78:1525.
14. Dawes C. What is the critical pH and why does a tooth dissolve in acid? J Can Dent Assoc. 2003;69(11):722–4.
15. Bowen W. The Stephan curve revisited. Odontology. 2013;101:2–8.
16. Featherstone JD. Dental caries; a dynamic disease process. Aust Dent J. 2008;53(3):286–91.
17. Young D, Novy B, Zeller G, Hale R, Hart T, Truelove E. The American Dental Association Caries Classification System for clinical practice: a report of the American Dental Association Council of Scientific Affairs. J Am Dent Assoc. 2015;146(2):79.
18. Silk H. Diseases of the mouth. Prim Care. 2014;41(1):75–90.
19. Adam M. Stanford introduction to food and health, 2017.
20. Lama S. 4 reasons people choose junk food over healthy food. LiveSTRONGcom, 2019.
21. Sugars and Dental Caries. A practical guide to reduce sugars consumption and curb the epidemic of dental caries. https://preprod.fiworlddental.org/sites/default/files/2020-11/sugar_toolkit=fdi-2016.pdf.
22. Guideline: sugars intake for adults and children. The World Health Organization. https://www.who.int/nutrition/publications/guidelines/sugar_intake_information_note_en.pdf?ua=1.
23. Farooq I. The role of salivary contents and modern technologies in the remineralization of dental enamel: a narrative review. F1000Res. 2020;9:171.
24. Lips A, Antumes LS, Antunes LA, Pintor A, Baptista Dos Santos D, Bachinski R, Kuchler E, Alves G. Salivary protein polymorphisms and risk of dental caries: a systemic review. Braz Oral Res. 2017;31:e41.
25. Finn SB, Caldwell RC. Dental caries in twins: a comparison of the caries experience of monozygotic twins, dizygotic twins, and unrelated children. Arch Oral Biol. 1963;8(4):571.
26. Vieira AR. Genetics and caries-prospects. Braz Oral Res. 2012;26(Spec Issue 1):7–9.
27. Silva MJ. Genetic and early life environmental influences on dental caries risk. Pediatrics. 2019;143(5):e20183499.
28. Kong Y-Y, Zheng J-M, Zhang W-J, Jiang Q-Z, Yang X-C, Yu M, Zeng S-J. The relationship between vitamin D receptor gene polymorphism and deciduous tooth decay in Chinese children. BMC Oral Health. 2017;17:111.
29. Kane S. The effects of oral health on systemic health. Gen Dent. 2017;65(6):30–4.
30. Ling Z, Tao H. Dental caries and systemic diseases. Berlin: Springer-Verlag; 2016.
31. https://www.etymonline.com/word/xero-.
32. https://www.etymonline.com/word/stoma.
33. Tan E, Lexomboon D, Sandborgh-Englund G, Haasum Y, Johnell K. Medications that cause dry mouth as an adverse effect in older people: a systematic review and metaanalysis. J Am Geriatr Soc. 2018;66(1):76–84.
34. Liccardo D, Cannavo A, Spagnuolo G, Ferrara N, Cittadini A, Rengo C, Rengo G. Periodontal disease: a risk factor for diabetes and cardiovascular disease. Int J Mol Sci. 2019;20(6):1414.
35. Bhagashri RL, Kalburge JV, Birajdar SB, Latti RG. Evaluation of relationship between dental caries diabetes mellitus and oral microbiota in diabetics. J Oral Maxillofac Pathol. 2018;22(2):282.
36. Siudkiene J, Machiulskiene VN, Tenovuo J, Nedzelskiene I. Dental caries increments and related factors in children with type 1 diabetes mellitus. Caries Res. 2008;42(5):354–62.
37. Gupta N, Pal M, Rawal S, Grewal M, Garg H, Chauhan D, Ahlawal P, Tandon S, Khurana R, Pahuja A, Mayank M, Devnani B. Radiation-induced dental caries, prevention and treatment—a systematic review. Natl J Maxillofac Surg. 2015;6(2):160–6.
38. Ritter AV, Eidson RS, Donovan TE. Chapter 2: Dental caries etiology, clinical characteristics, risk assessment, and management. In: Sturdevant's art and science of operative dentistry. 6th ed. Amsterdam: Elsevier.
39. Mattila KJ, Nieminen MS, Valtonen VV, Rasi VP, Kesaniemi YA, Syrjala SL, Jungell PS, Isoluoma M, Hietaniemi K, Jokinen MJ. Association between dental health and acute myocardial infarction. Br Med J. 1989;298:779.
40. https://dentistryexplorer.com/g-v-black-classification-of-caries/.
41. Yilmaz H, Keles S. Recent methods for diagnosis of dental caries in dentistry. Meandros Med Dent J. 2017;17.
42. Bishara S, Osty A. White spot lesions: formation, prevention, and treatment. Semin Orthod. 2008;14(3):174–82.
43. Joseph R. The father of modern dentistry-Dr. Greene Vardiman Black (1836-1915). J Conserv Dent. 2005;8:5–6.

44. Frencken JE, Peters MC, Manton DJ, Leal SC, Gordan VV, Eden E. Minimal intervention dentistry for managing dental caries-a review. Report of a FDI task group. Int Dent J. 2012;62:223–43.
45. Innes N, Frenchken J, Schwendicke F. Don't know, can't do, won't change: barriers to moving knowledge to action in managing the carious lesion. J Dent Res. 2016;95:485.
46. Featherstone J, Chaffee BW. The evidence for Caries Management by Risk Management (CAMBRA). Adv Dent Res. 2018;29(1):9–14.
47. Hunter PB. Risk factors in dental caries. Int Dent J. 1988;38(4):211–7.
48. Ing M, Magnuson B, Frantz D. Fluoride content in Asian produced green teas. J Can Dent Assoc. 2021;87:13.
49. Centers for Disease Control and Prevention. Ten great public health achievements-United States, 1900-1999. MMWR Morb Mortal Wkly Rep. 1999;48(12):241–3.
50. Ing ME, Arsenault P. Part 1: patient assessment. Chapter 2. Office environment. "Office environment, infection control safety, eyewear safety, and ergonomics". In: Goupil MT, Ferneini EM, editors. Evidence-based oral surgery: a clinical guide for the general dental practitioner. Berlin: Springer; 2019.
51. Marinho V, Worthington H, Walsh T, Clarkson J. Fluoride varnishes for preventing dental caries in children and adolescents. Cochrane Database Syst Rev. 2013;(7):CD002279.
52. Thornton-Evans G, Junger M, Lin M, Liang W, Espinoza L, Beltran-Aguilar E. Use of toothpaste and toothbrushing patterns among children and adolescents-United States, 2013-2016. Morb Mortal Wkly Rep. 2019;68(4):87–90.
53. Know your teeth-infobites-don't rush, just brush to the beat!-search by keyword, letter or phrase. http://knowyourteeth.com/infobites/abc/article/?abc=B&iid=291&aid=1127.
54. Hujoel PP, Cunha-Cruz J, Banting DW, et al. Dental flossing and interproximal caries: a systematic review. J Dent Res. 2006;85:1147.
55. Soderling E, Isokangas P, Pienihakkinen K, Tenovuo J, Alanen P. Influence of maternal xylitol consumption on mother-child transmission of mutans streptococci: 6-year follow-up. Caries Res. 2001;35(3):173–7.
56. Makinen KK, Bennett CA, Hujoel PP, Isokangas PJ, Isotupa KP, Pape HR Jr, Makinen PL. Xylitol chewing gums and caries rates: a 40-month cohort study. J Dent Res. 1995;74(12):1904–13.
57. Xylitol: the decay-preventive sweetener. California Dental Association. https://www.cda.org/Portals/0/pdfs/fact_sheets/xylitol_english.pdf.
58. Mickenautsch S, Yengopal V. Caries-preventive effect of high-viscosity glass ionomer and resin-based fissure sealants on permanent teeth: a systematic review of clinical trials. PLoS One. 2016;11(1):e0146512.

Periodontal Infections: Gingivitis and Periodontitis

8

Christine E. Niekrash

Introduction

According to the Centers for Disease Control, more than 47% of adults aged 30 years or older have some form of periodontal disease [1]. These diseases are more frequent in adult males than in adult females (56.4% vs. 38.4%). The incidence of periodontal disease increases with age, with 70.1% of individuals in the United States aged 65 or higher manifesting periodontal disease. It is also observed more frequently in adults who smoke, in individuals with less than a high school education, and in people living under the federal poverty line. Although frequently observed, these diseases rarely present as an emergency situation.

This chapter will discuss the dental plaque-induced periodontal diseases, gingivitis and periodontitis. These conditions are widely prevalent, and usually painless, with the patients often unaware of their disease status. Gingival involvement not caused by dental plaque biofilm and associated with other systemic conditions or pharmaceutical agents are presented in various other chapters of this book.

Periodontal Disease Overview

Disease Development: Plaque-Induced Gingivitis and Periodontitis

Periodontal disease is the result of the interaction of the oral microbiome with the host's immune response, triggering an inflammatory response within the gingiva and other tissues that support and surround the teeth. For a description of these tissues in health, please see Chap. 3.

The oral cavity houses a complex microbiome, containing more than 800 oral specific species. The composition of the oral microbiome is unique to each individual, although a core content is thought to be shared.

In health, the community of microbes (oral microbiome) exists with symbiotic interactions among the various species within the ecosystem of the host. However, these conditions can become altered, destroying the symbiotic balance, and creating a state of dysbiosis which can result in disease. Variability in disease severity depends upon this host–microbe interaction. This interplay is influenced by shifts in the susceptibility of the host, the immune response of the host, the oral environment (general and local), and the microbiota. The dynamic environment of the host and microbiome is the basis for the current staging and grading of periodontal disease summarized later in this chapter.

Dental plaque is a soft, tenaciously sticky, yellowish-white biofilm visible on the surfaces of many teeth (Fig. 8.1). It is composed of microorganisms (primarily bacteria) and is easily visualized on the surfaces of teeth and intraoral restorations. When plaque mineralizes, it becomes a rigid deposit

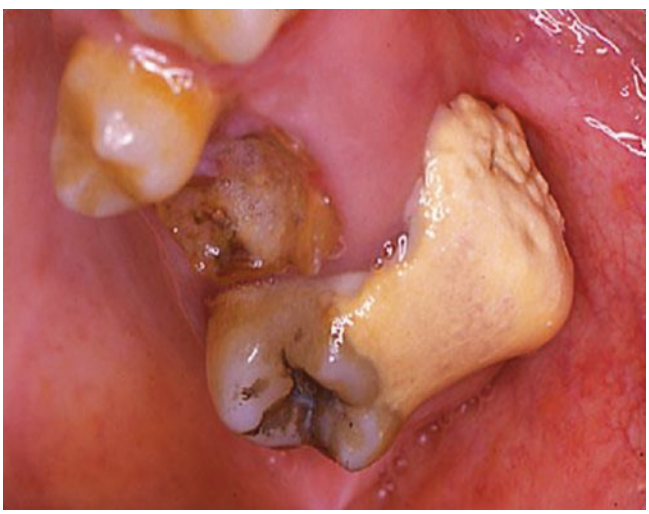


Fig. 8.1 Plaque biofilm and mineralized calculus have accumulated extensively on the surface of this molar. (Photo courtesy of Dr. Navid Knight, University of the Pacific)

C. E. Niekrash (✉)
Frank H Netter MD School of Medicine, Quinnipiac University, North Haven, CT, USA
e-mail: christine.niekrash@quinnipiac.edu

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_8

termed calculus, that is difficult to remove from the teeth and other hard surfaces in the oral cavity. Both dental plaque and calculus are removed from the teeth surfaces during a professional dental prophylaxis using special dental instruments.

Gingivitis and periodontitis result from the interaction of the microorganisms located in dental plaque with the host's immune and inflammatory response. These diseases are differentiated based on the extent of the inflammatory response and the resultant damage to the supporting structures of the teeth. Frequently, gingivitis cannot be distinguished from periodontitis by visual examination alone. Clinical examination with measurements of periodontal ligament attachment levels, radiologic imaging, and medical and dental history are essential in diagnosing disease status. Previous disease status, disease treatments, and clinical results are important in determining the prognosis, as a successfully treated, stable periodontitis patient is at a higher risk of disease recurrence than those without a history of periodontitis. Periodontal diseases are caused by the host's response to a consortium of organisms in a biofilm rather than by a single pathogen.

Gingivitis

Gingivitis involves inflammation of the gingival epithelium and the underlying connective tissue resulting from the accumulation of the oral microbial biofilm. Histologically, lymphocytes, neutrophils, macrophages, and other inflammatory cells infiltrate the tissue, vascular permeability increases, and tissue collagen levels decrease. Importantly, the alveolar bone and periodontal ligament are not affected in gingivitis, so there is no clinically detectable loss of periodontal attachment and no bone loss if the patient has no history of periodontitis. Clinically, the appearance of the gingiva varies depending on the severity of the inflammation and the anatomy of the host. Often, the gingiva displays the cardinal signs of inflammation and appear swollen, edematous, and red (Fig. 8.2). Bleeding is easily induced when the gingiva is challenged by friction from a toothbrush or periodontal probe. Other signs and symptoms that may be noted in the clinical presentation are listed in Table 8.1. Importantly, when the causative dental plaque and calculus are removed and are blocked from reaccumulating, gingivitis is reversible, and the gingiva return to a healthy appearance. Therefore, treatment consists of oral hygiene instructions to teach the patient to control dental plaque levels, and dental prophylaxis to remove dental plaque and calculus.

Periodontitis

Periodontitis involves a more extensive distribution of the inflammatory response involving the supporting structures of the teeth. As described in Chap. 3, teeth are held in their alveolar bone socket by periodontal ligament fibers which extend from the cementum covering the tooth root surface to the alveolar bone, and from the cementum to the attached gingiva. The host response to the dysbiosis of the oral microbiome in periodontitis leads to inflammation of these tissues with progressive tissue destruction resulting in the loss of periodontal attachment and alveolar bone, and ultimately loosening, drifting, and eventual loss of teeth. Signs of disease are the result of activated inflammatory and immune mechanisms rather than direct effects of bacteria. Clinically, this manifests in periodontal pocket formation and/or gingival recession. A periodontal pocket is a pathologic deepening of the gingival sulcus. In periodontitis, it is caused by apical migration of the junctional epithelium along the root surface due to the destruction of connective tissue attachment of the periodontal ligament by the inflammatory process (Fig. 8.3). Periodontal pocket depth is measured using a standardized periodontal probe which is inserted into the periodontal pocket and measures depth in millimeters. Periodontal attachment levels are measured in reference to the fixed cemento-enamel junction of the tooth (Fig. 8.4). Frequently, bleeding on probing and sometimes suppuration is observed

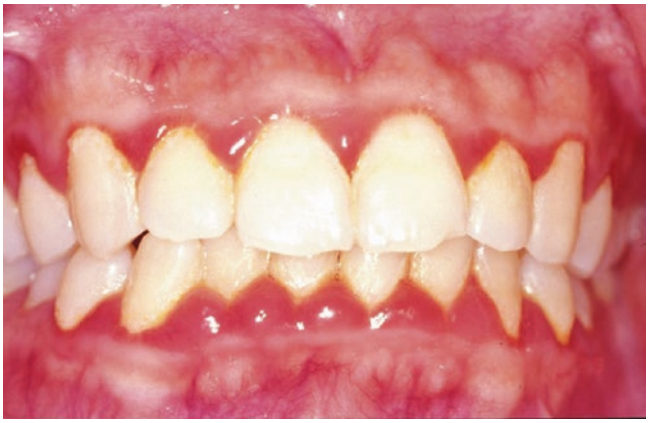


Fig. 8.2 Inflamed gingiva displays edema, swelling, redness, loss of gingival stippling, and easy bleeding upon challenge with a toothbrush or dental probe. (Photo courtesy of Dr. Navid Knight, University of the Pacific)

Table 8.1 Clinical signs and symptoms of gingivitis and periodontitis. Patients present with some of the following conditions

Swollen, edematous gingiva and gingival papillae
Red or blue gingiva
Loss of gingival stippling
Easy gingival bleeding upon challenge
Patient reports pink color of toothbrush when brushing teeth
Patient may spit out blood after brushing or flossing
Halitosis
Bad taste
Inflammatory exudate or suppuration expressed from gingival sulcus

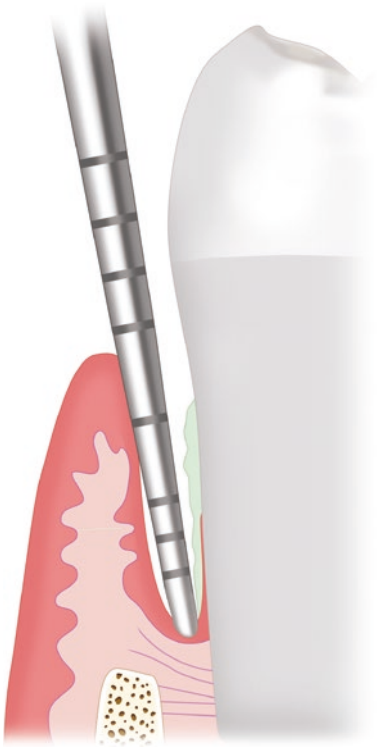


Fig. 8.3 Periodontal probe inserted in a periodontal pocket formed between the gingiva and the surface of the root of the tooth, measures the loss of periodontal attachment and the depth of the pocket. Calculus is present on the surface of the tooth root

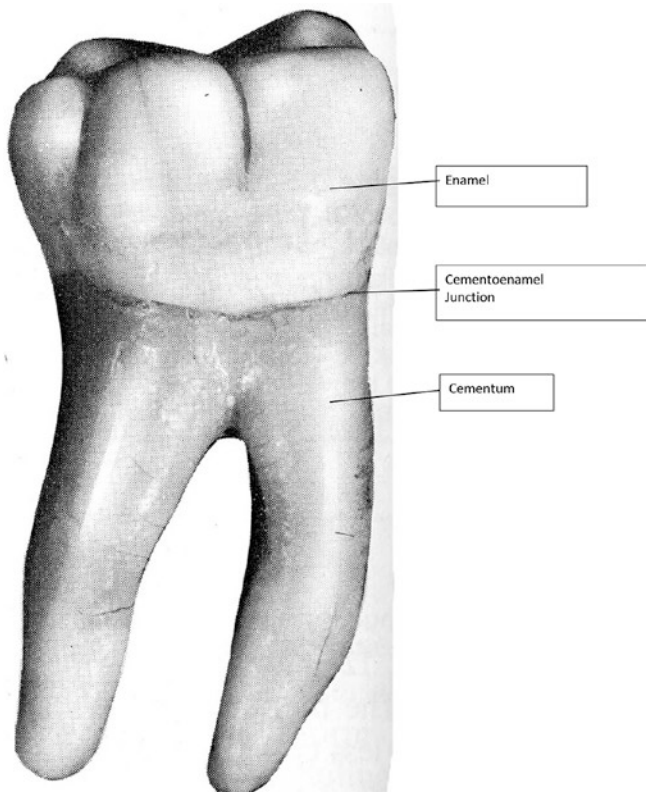


Fig. 8.4 Periodontal attachment levels are measured in reference to a fixed landmark, the cementoenamel junction, the location where the cementum covering the root and the enamel covering the crown meet

in periodontally involved pockets due to the inflammatory response to the oral microbiome.

Periodontitis is treated by removing dental plaque and calculus and keeping the bacterial microbiome reduced by instituting good oral hygiene practices. This may require surgical access to tooth root surfaces, recontouring gingival and bone anatomy, and methods to increase periodontal attachment to tooth surfaces.

Gingival recession is also a loss of connective tissue attachment due to the apical shift of the marginal gingiva, exposing the root of the tooth to the oral cavity. It is frequently associated with dentinal hypersensitivity and cervical carious lesions.

Alveolar bone loss is observed radiographically.

In summary, periodontitis is a dynamic disease state associated with dental plaque and calculus accumulation and destruction of the supporting structures of the teeth. Generally, the progression of the disease and the resultant loss of periodontal attachment is gradual, but it may accelerate due to increased risk factors, including systemic diseases such as diabetes mellitus, HIV infection, and other diseases which affect the host's defense mechanisms and, therefore, tissue destruction. Smoking and increased psychological stress also contribute to the progression of the disease. Genetics, environment, tooth anatomy, and restorations all add to the causal factors of this disease. Various predisposing factors associated with periodontitis are listed in Table 8.2. Their presence will contribute to the staging and grading of the disease as described below. Disease severity will vary depending on the microbe–host environment and interactions.

Table 8.2 Predisposing factors mediating periodontal disease occurrence and severity

Poor oral hygiene
Smoking
Use of chewing tobacco
Nutrition such as vitamin C deficiency
Xerostomia
Immune deficiency/immune suppression
Hyperglycemia (type 1 diabetes)
Leukemia
Defective restorations
Pharmacologic factors

Non-Biofilm-Induced Gingival Diseases

Gingival diseases not induced primarily by the dental microbiome are less frequent, and often associated with systemic disease manifestation. These have been subdivided into eight

categories summarized by Holmstrup et al. [2]. These categories are listed below and are described in more detail in other chapters in this book.

Categories of Non-Biofilm Induced Gingival Diseases

Genetic/developmental disorders (hereditary gingival fibromatosis, Papillon–Lefevre syndrome).
Specific infections (viral, fungal, bacterial).
Inflammatory and immune conditions, autoimmune diseases such as Pemphigus vulgaris, lichen planus, and pemphigoid.
Reactive processes.
Neoplasms.
Endocrine, nutritional, and metabolic diseases.
Traumatic lesions.
Gingival pigmentation.

Periodontitis as a Manifestation of Systemic Disease

Systemic disorders can influence periodontal diseases in many ways and may impact the inflammatory and immune processes and therefore modulate the destruction of periodontal tissues. For example, disorders affecting white blood cells have a direct impact on the inflammatory response. Some systemic diseases have direct effects on the oral mucosa (epidermolysis bullosa) or the connective tissue (Systemic lupus, Scleroderma, Ehlers–Danlos syndrome). Systemic inflammatory diseases such as inflammatory bowel disease and endocrine/metabolic disorders (diabetes, osteoporosis) may also impact periodontal disease pathogenesis. All of these systemic disorders will impact the grading and staging of periodontal disease.

Grading and Staging of Periodontal Disease [3]

Each individual supports a unique oral microbiome which plays a role in the etiology of disease. The systemic condition of the host, the status of the local environment, oral anatomy, restorations, trauma, and oral anatomical deformities influence this.

As a result, periodontal disease will progress differently for different individuals.

The current grading and staging classification of periodontal disease incorporates disease severity, extent of disease, history of disease, and systemic health status.

Biofilm-induced gingivitis is identified and graded by the extent of bleeding on probing.

Whereas, periodontitis staging depends upon the severity of disease, the extent of loss of function, and complexity of management of disease and causal factors. The grading of periodontitis utilizes the rate of disease progression, presence of risk factors (specifically smoking and diabetes), analysis of the individual's response to treatment, and the potential impact on general health of the individual.

Diagnosis and Treatment of Acute Gingival Disease

Patients are more likely to seek urgent care treatment for acute gingival diseases because these conditions are painful and have a more rapid onset with extensive tissue destruction.

The presentation of **Necrotizing Ulcerative Periodontal Disease** includes ulceration of the epithelium, bacterial invasion and necrosis of interdental papillae (often with pseudomembrane formation), and increased gingival bleeding (Fig. 8.5). It is characterized by fetid breath and results in painful, rapid bone loss often with bone exposure. Necrotizing ulcerative periodontal disease is associated with impairment of host immune system and is observed in individuals with HIV/AIDS, immunosuppression, severe malnutrition, high psychosocial stress, and/or viral infections.

A multifactorial approach is used to treat necrotizing periodontal disease. Initially, gentle superficial debridement, oral hygiene instruction, use of an antimicrobial mouthwash, and oral antibiotics (metronidazole) may be started. This is followed by a more comprehensive case management involving dental prophylaxis and treatment of underlying systemic contributing factors.

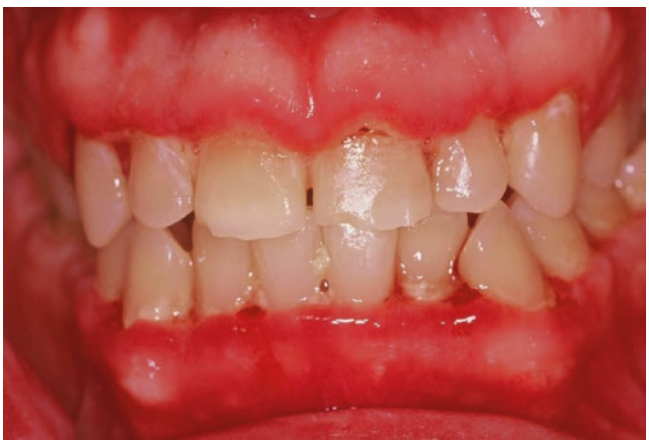


Fig. 8.5 Acute necrotizing ulcerative gingivitis exhibits ulcerated, necrotic dental papillae between the teeth. (Photo courtesy of Dr. Navid Knight, University of the Pacific)

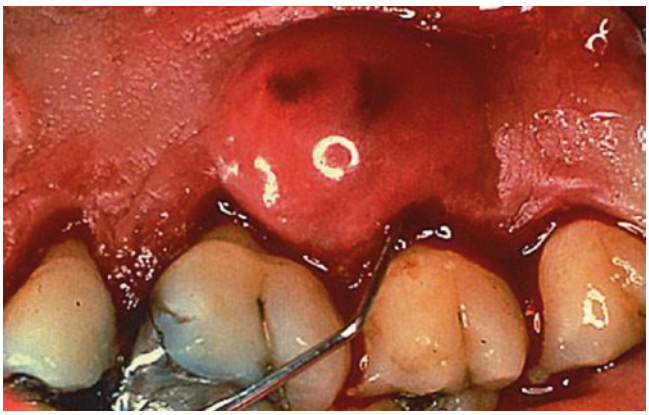


Fig. 8.6 Periodontal abscess: Gingival swelling is observed adjacent to the root surface of the tooth. A periodontal probe is inserted along the root of the tooth demonstrating the depth of the periodontal defect with immediate bleeding of the inflamed tissue. (Photo courtesy of Dr. Navid Knight, University of the Pacific)

Periodontal Abscesses are relatively common and constitute approximately 10% of all dental emergencies. It is a localized infection that presents as an area of swelling in the gingiva adjacent to the root of the tooth (Fig. 8.6). Bleeding and suppuration occur on probing. Abscesses involve loss of periodontal attachment, bone loss, and often increased tooth mobility. They may lead to tooth loss and acute systemic illness. Dental abscesses may be painful if the lesion is not draining, and the infections may involve the pulp of the tooth. Abscesses and their treatment are described in more detail in Chap. 10 of this book.

Peri-implant health and diseases are discussed in Chap. X.

Summary

Microbiome-induced periodontal diseases occur frequently in the adult population. Gingivitis involves inflammation of the gingiva as a result of the host's response to the oral microbiome visible as plaque and calculus. Periodontitis involves inflammation of the supporting tissues of the teeth including the gingiva, alveolar bone, and periodontal ligament. It involves loss of the periodontal attachment of the tooth. Necrotizing ulcerative periodontal disease is painful with ulceration and necrosis of the gingiva and is associated with impairment of the host's immune response.

References

1. Eke PI, Thornton-Evans G, Dye BA, Genco R. Advances in surveillance of periodontitis: the centers for disease control and prevention periodontal disease surveillance project. J Periodontol. 2012;83:1–9.
2. Holmstrup P, Plemons J, Meyle J. Non-plaque-induced gingival diseases. J Periodontol. 2018;89(Suppl 1):S28–45.
3. Tonetti M, Greenwell H, Kornman K. Staging and grading of periodontitis: framework and proposal of a new classification and case definition. J Clin Periodontol. 2018;89(Suppl 20):S149–61.

Third Molars and Pericoronitis

9

Gabriel M. Hayek and Elie M. Ferneini

Introduction

Pericoronitis is the inflammation of soft tissue surrounding the crown of a partially erupted tooth [1, 2]. The soft tissue flap overlying the tooth is referred to as a pericoronal flap or gingival operculum and is notoriously difficult to maintain adequate oral hygiene. Although this process can occur with any partially erupted tooth, it is by far most common among the mandibular third molars or lower "wisdom teeth" [3, 4]. The highest incidence is in the adolescent and young adult population [5]. Approximately 25–30% of impacted mandibular third molars are removed because of pericoronitis [6–10]. It is the most common reason for removal after age 20. There is a strong correlation between oral hygiene and the severity of the disease.

The general health of the patient is not a predisposing factor; however, seasonal variation is seen with peak incidence occurring during June and September. In one study, upper respiratory tract infection preceded 43% of cases. Pregnancy and fatigue have also been linked to an increased occurrence of pericoronitis. Bilateral pericoronitis is rare and is suggestive of underlying infectious mononucleosis [11]. Pericoronitis can range in symptoms and severity, but should not be underestimated. One study noted that 37% of almost 500 patients found the symptoms severe enough to seek surgical expertise for third molar removal before symptoms recurred [12].

Classification

Pericoronitis can be either acute or chronic [11]. Acute pericoronitis presents with the sudden onset of symptoms. Systemic signs are often present. Patients usually have poor to moderate oral hygiene. Chronic pericoronitis presents as repeated episodes of acute pericoronitis. Pain is often dull or mild, lasting a few days at a time, and is often less severe than acute pericoronitis. These patients usually have moderate to good oral hygiene.

Etiology

The most common site for pericoronitis is around partially erupted mandibular third molars [2]. It has been theorized that bacterial ingress into the follicular space initiates this process. Pericoronal inflammation is usually the result of dental plaque and food debris between the crown of the tooth and the gingival operculum, as well as occlusal trauma of the pericoronal tissues by an opposing maxillary tooth. This site is difficult to keep clean and is an ideal place for bacteria to grow. Once the drainage of exudate from the gingival pocket is blocked by the impaction of foreign bodies or by trauma-induced swelling of the operculum, an acute infection may occur. This results in the release of pericoronal inflammatory fluid and cellular exudate, which can spread to adjacent tissues and ultimately neighboring fascial spaces and the systemic vasculature. Systemic conditions, including influenza, upper respiratory tract infections, and stress, result in a compromised host immune system and can allow the chronic condition to become opportunistic. Risk factors for pericoronitis are presented in Table 9.1.

G. M. Hayek (✉)
Division of Oral and Maxillofacial Surgery, Department of Craniofacial Sciences, University of Connecticut, Farmington, CT, USA

E. M. Ferneini
Division of Oral and Maxillofacial Surgery, University of Connecticut, Farmington, CT, USA

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_9

Table 9.1 Risk Factors for Pericoronitis

- Vertical or distoangular impacted teeth
- Periodontal pockets adjacent to unerupted or partially erupted teeth
- Opposing tooth or teeth adjacent to pericoronal tissues of unerupted or partially erupted teeth
- Previous history of pericoronitis
- Poor oral hygiene
- Respiratory tract infections
- Tonsillitis

Clinical Features

Acute pericoronitis manifests as an erythematous, edematous, suppurative site with tenderness and throbbing pain that radiates to adjacent tissues [1, 2, 11]. It is not uncommon for the pain to disturb sleep. Patients may complain of dysphagia and a foul taste. Physical examination may reveal signs of occlusal trauma on the gingival operculum, including ulceration or indentation of the maxillary molar cusps. Systemic signs and symptoms are often present including fever, leukocytosis, malaise, lymphadenopathy, and loss of appetite.

Chronic pericoronitis is characterized by dull pain for a short period with remission between episodes that can last weeks to months. A chronic area of ulceration can sometimes be identified. Patients may complain of a foul taste.

Microbial Flora

Pericoronitis is associated with normal oral flora that is predominately anaerobic, with species largely similar to periodontitis [5, 13–17]. This includes *Peptostreptococcus*, *Fusobacterium*, *Bacteroides,* and *Porphyromonas* [14, 18, 19].

Management

The management of pericoronitis involves an assessment of the severity of inflammation, the presence of systemic involvement, and the prognosis of the associated teeth. If the cause of pericoronitis is not addressed then recurrent disease should be expected to develop.

Initial treatment is usually aimed at debridement of the gingival operculum pocket by irrigation or by mechanical means; disinfection of the pocket with an irrigation solution such as sterile saline, hydrogen peroxide, or chlorhexidine; and elimination of occlusal trauma by removal of the opposing maxillary third molar and, occasionally, of the offending mandibular third molar [1, 2, 20]. If a pericoronal abscess is present, drainage should be established with a standard incision and drainage procedure. Severe cases of pericoronitis with systemic symptoms or cases in which facial swelling or trismus (an inability to fully open the mouth) are present warrant systemic antibiotic therapy as an adjunctive treatment [1, 2, 21]. The antibiotic of choice is penicillin or azithromycin in the case of penicillin allergy. Prevention of recurrent pericoronitis is achieved by removal of the involved mandibular third molar. Patients should be instructed on appropriate oral hygiene for long-term maintenance.

Controversy still exists as to whether the mandibular third molar should be removed during the acute phase. The consensus is that if the pericoronitis is mild and the tooth can be removed straightforwardly, then immediate extraction may be performed [2]. In the face of severe pericoronitis, removal is not recommended due to the increased incidence of complications.

Others have advocated for operculectomy via removal of the overlying soft tissue to be performed during the acute phase. Unfortunately, no research is available that supports or condemns this treatment. Soft tissue regrowth following operculectomy is a frequent occurrence due to the lack of space between the anterior border of the ramus and the erupting tooth crown [20].

Complications

Although usually a localized condition, pericoronitis can spread posteriorly toward the oropharynx and base of the tongue, resulting in a severe fulminating infection that requires hospitalization and an aggressive surgical course of treatment. The rapid spread of infection to adjacent fascial spaces can occur because of the anatomic location of the mandibular third molar roots at the crossroads of the masticator, submandibular, and buccal spaces [22].

This can result in deep fascial space infections including parapharyngeal abscess or Ludwig's angina, both of which can become life-threatening due to the potential for airway compromise [1, 2, 20, 21]. Ludwig's angina is characterized by fever, malaise, elevation of the tongue and floor of mouth, difficulty swallowing, slurred speech, and a board-like swelling of the anterior neck. Parapharyngeal abscess is characterized by fever, malaise, severe pain in swallowing, dyspnea, and deviation of the larynx. Both of these conditions require urgent surgical intervention so that the airway can be secured along with draining and decompressing the affected tissue spaces.

If a patient has severe trismus with an inability to open the mouth more than 20 mm, a temperature of greater than 101.5 °F, facial swelling, pain, and malaise, the patient should be referred to an Oral-Maxillofacial Surgeon, who is likely to admit the patient to the hospital for intravenous antibiotic administration, careful monitoring, and surgical treatment.

Conclusion

Pericoronitis is an extremely common oral infection. It is usually localized to the soft tissues immediately surrounding the mandibular third molars and results in significant pain, discomfort, and a decrease in quality of life. Although rare, its potential for spread into adjacent deep fascial spaces should not be ignored and can become life-threatening. A proper diagnosis should be made based on a thorough history, clinical examination, and radiographic assessment.

The primary prevention of pericoronitis is the removal of third molars that are at high risk for developing inflammation and maintenance of excellent oral hygiene. Initial treatment of acute pericoronitis is performed utilizing debridement of the gingival operculum pocket, disinfection of the pocket with an irrigation solution, and elimination of occlusal trauma by extraction of the opposing maxillary third molar. Systemic antibiotics are recommended only for cases with systemic symptoms present. Whether done during the acute phase or upon its resolution, removal of the offending tooth is usually performed to prevent future recurrence.

References

1. Newman MG, Takei HH, Klokkevold PR, Carranza FA. Carranza clinical periodontology. 10th ed. St. Louis: Saunders Elsevier; 2006.
2. Hupp JR, Ellis E, Tucker MR. Contemporary oral and maxillofacial surgery. 7th ed. St. Louis: Mosby Elsevier; 2018.
3. Vent I, Turtola L, Muftomaa H, Ylipaavalniemi P. Third molars as an acute problem in Finnish university students. Oral Surg Oral Med Oral Pathol. 1993;76:135–40.
4. Leone SA, Edenfield MJ, Cohen ME. Correlation of acute pericoronitis and the position of the mandibular third molar. Oral Surg. 1986;62:245–50.
5. Nitzan DW, Tal O, Sela MN, Shteyer A. Pericoronitis: a reappraisal of its clinical microbiologic aspects. J Oral Maxillofac Surg. 1985;43:510–6.
6. Lysell L, Rohlin M. A study of indications used for removal of the mandibular third molar. Int J Oral Maxillofac Surg. 1988;17:161–4.
7. Norderam A, Hultin M, Kjellman O, Ramstrom G. Indications for surgical removal of the mandibular third molar. Swed Dent J. 1987;2:23–9.
8. Stanley HR, Alattar M, Collett WE, et al. Pathological sequelae of "neglected" impacted third molars. J Oral Pathol. 1988;17:113–7.
9. von Wowern N, Nielsen HO. The fate of impacted lower third molars after the age of 20. Int J Oral Maxillofac Surg. 1989;18:277–80.
10. Schroeder DC, Cecil JC III, Cohen ME. Retention and extraction of third molars in naval personnel. Mil Med. 1983;148:50–3.
11. Maloney J, Stassen L. Pericoronitis: treatment and a clinical dilemma. J Ir Dent Assoc. 2009;55:190–2.
12. Slade GD, Foy SP, Shugars DA, Phillips C, White RP Jr. The impact of third molar symptoms, pain, and swelling on oral health-related quality of life. J Oral Maxillofac Surg. 2004;62:1118–24.
13. Hurlen B, Olsen I. A scanning electron microscopic study on the microflora of chronic pericoronitis of lower third molars. Oral Surg Oral Med Oral Pathol. 1984;58:522–32.
14. Mombelli A, Busser D, Lang NP, Berthold H. Suspected periodontopathogens in erupting third molar sites in periodontally healthy individuals. J Clin Periodontal. 1990;17:48–54.
15. Moloney J, Stassen LF. The relationship between pericoronitis, wisdom teeth, putative periodontal pathogens and the host response. J Ir Dent Assoc. 2008;54:134–7.
16. Weinberg A, Nitzan DW, Sheteyer A, Sela MN. Inflammatory cells and bacteria in pericoronal exudates from acute pericoronitis. Int J Oral Maxillofac Surg. 1986;15:606–13.
17. Wade WG, Gray AR, Absi EG, Barker GR. Predominant cultivable flora in pericoronitis. Oral Microbiol Immunol. 1991;6:310–2.
18. Heimdahl A, Nord CE. Treatment of orofacial infections of odontogenic origin. Scan J Infect Dis Suppl. 1985;46:101–5.
19. Van Winkelhoff AJ, Carlee AW, de Graaff J. Bacteroides endotonalis and other black-pigmented bactericides species in odontogenic abscesses. Infect Immun. 1985;49:494–7.
20. Fonseca RJ. Oral and maxillofacial surgery. St. Louis: Saunders Elsevier; 2018.
21. Miloro M, Ghali GE, Larsen P, Waite P. Peterson's principles of oral and maxillofacial surgery. 3rd ed. Shelton CT: People's Medical Pub; 2012.
22. Oshima A, Ariji Y, Goto M, et al. Anatomical considerations for the spread of odontogenic infection originating from the pericoronitis of impacted mandibular third molar: computer tomographic analyses. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;98:589.

Fascial Planes and Spaces and Deep Space Infection

10

Christine E. Niekrash

Introduction

Odontogenic infections arise from tooth-related sources and are among the most commonly occurring illnesses in the US population. According to the Centers for Disease Control and Prevention, 13.2% of US children aged 5–19 years have untreated dental caries (2015–2018). This percent rose to 25.9% in adults aged 20–44 years. Odontogenic infections may lead to serious, even life-threatening outcomes since infections may spread from the oral cavity through fascial planes to deeper areas in the head and neck and inferiorly to the mediastinum and heart. Infection may also spread in the head through veins and result in involvement of the cranium. Therefore, it is essential that odontogenic infections are identified and treated as early as possible.

Dentoalveolar Infection and Abscess Formation

Dental infections originate from the dental pulp (endodontic), periodontal tissues, or impacted or fractured teeth. These infections will vary in their progression and disease expression, depending upon the number and virulence of the organisms (usually a consortium of bacteria), the anatomy of the area involved, and the immune resistance and systemic health of the individual.

In the case of a carious lesion invading the pulp of the tooth, bacteria may spread from the infected pulp within the crown and roots of the tooth into the neighboring deeper periodontal tissues and alveolar bone. See Chap. 7 for a comprehensive presentation regarding dental caries. These deeper tissues may also be infected by the progression of periodontal diseases or trauma. Once present in the deep tissues, infection and the resultant inflammatory response spread along the path of least resistance. The inflammatory response intended to destroy the pathogen contains enzymes that erode through normal tissue including bone. This response may be extremely robust and cause extensive damage to the host.

If the odontogenic infection remains localized at the apex of the root, a chronic periapical infection may persist. These areas are visualized radiographically by the presence of a radiolucency at the apex of the root (periapical radiolucency). Rarely, infection invasion into the supporting bone and deeper spaces may result in osteomyelitis (see Chap. 11). Usually, the infection and the concomitant inflammatory response localizes at the apex of the root to form a thick-walled cavity containing pus (a periapical abscess) with fistulous tracts that course through the alveolar bone and the surrounding soft tissues. The fistula often passes ultimately through the skin or mucosa allowing the abscess to drain, often diminishing the associated pain (Fig. 10.1). However, this dentoalveolar infection and the intense inflammatory response may also spread through the soft tissue as a diffuse, firm, subcutaneous, or submucosal infection termed cellulitis.

If the infection remains localized, the abscess and fistulous tract are usually located close to the tooth of origin and are related to the anatomic location of the affected tooth root. Most of the time, oral abscesses drain into the oral cavity on the buccal (cheek) or labial (lip) surface of the mucosa overlying the root of the tooth. These infections and inflammatory exudate erode through bone on the facial surface of the maxilla or mandible. If the tooth is tipped or the palatal or lingual bone is thin, abscesses may form on the palatal or lingual mucosa (Fig. 10.2).

C. E. Niekrash (✉)
Frank H Netter MD School of Medicine, Quinnipiac University, North Haven, CT, USA
e-mail: christine.niekrash@quinnipiac.edu

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_10

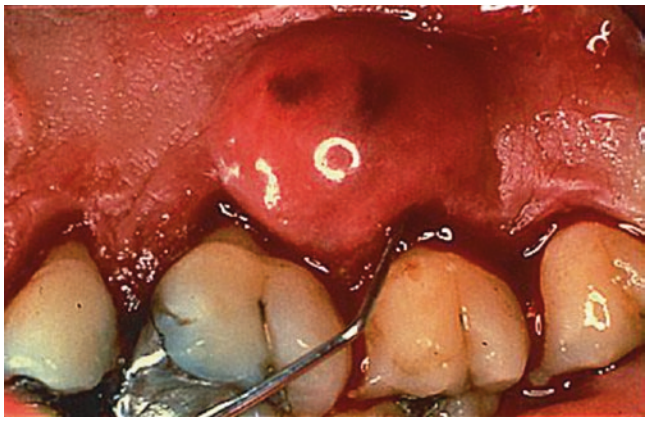


Fig. 10.1 Intraoral abscess draining into the oral cavity after eroding through the buccal bone. (Photo courtesy of Dr. Navid Knight, University of the Pacific)

Treatment of Odontogenic Infections

Treatment involves the elimination of the causative organisms and relief from the inflammatory process. This is accomplished by removal of the carious lesion (may involve endodontic treatment or extraction), with gingival curettage, incision, and drainage, and antibiotic treatment as adjunctive therapy if needed. The treatment is primarily surgical.

Fascial Infection Spread in the Face

After the infection erodes through bone, it may then spread through loose connective tissue and potential spaces formed by fascial planes throughout the head and neck regions and

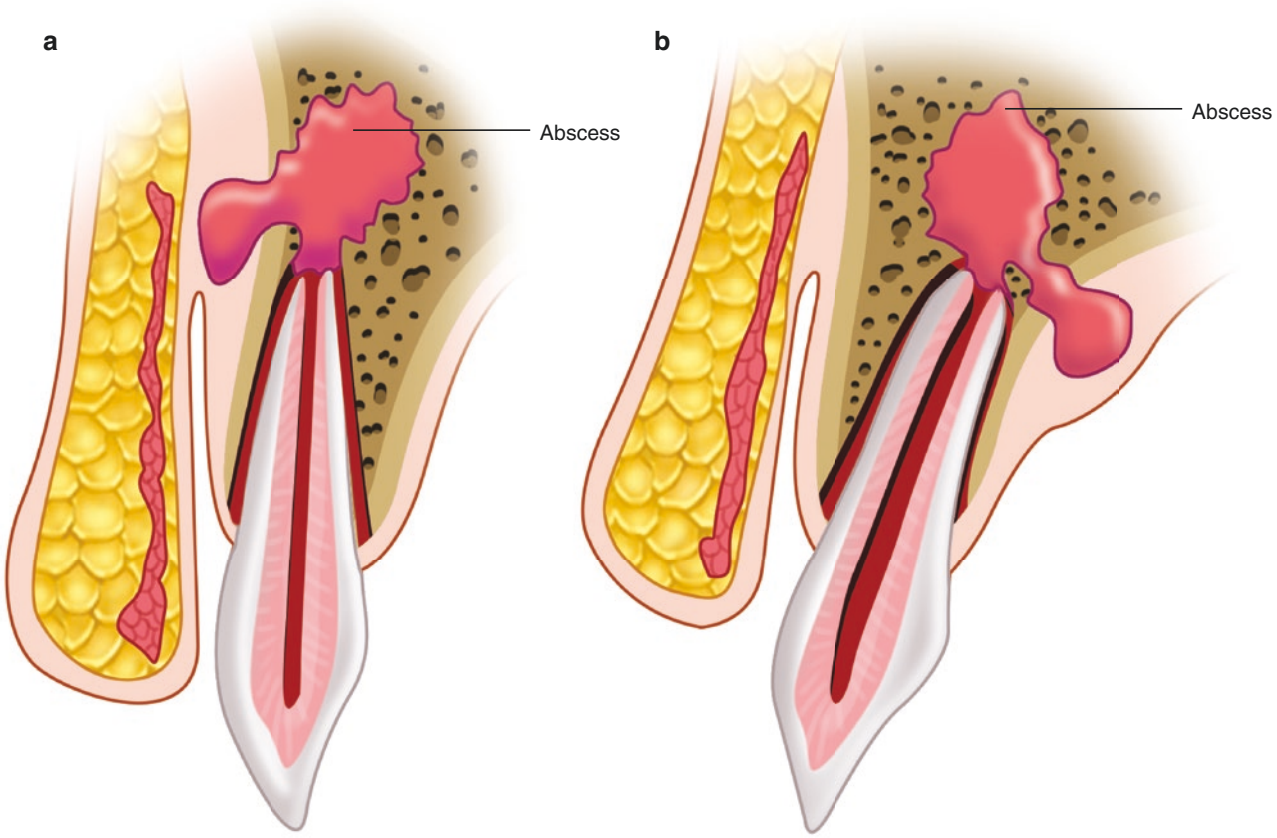


Fig. 10.2 The path of oral abscess drainage is influenced by the location of the tooth root and thickness of bone. In (**a**) drainage occurs on the buccal surface. In (**b**) the tooth is tipped so drainage occurs on the palatal surface

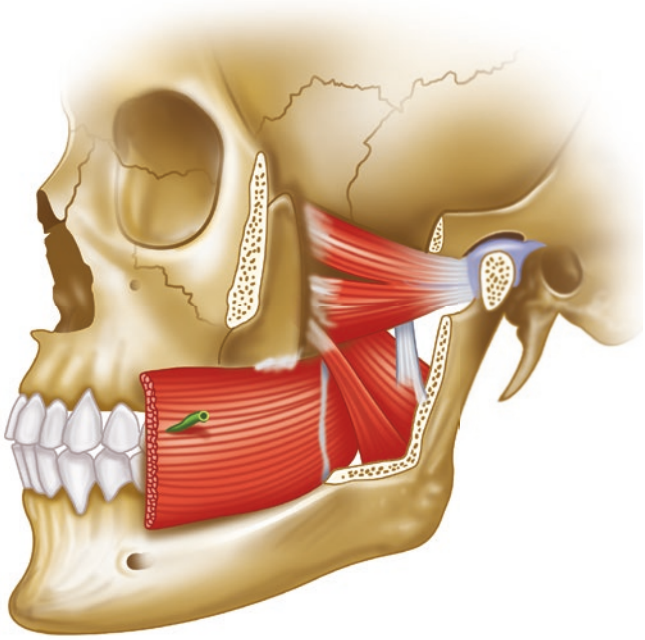


Fig. 10.3 Buccinator muscle

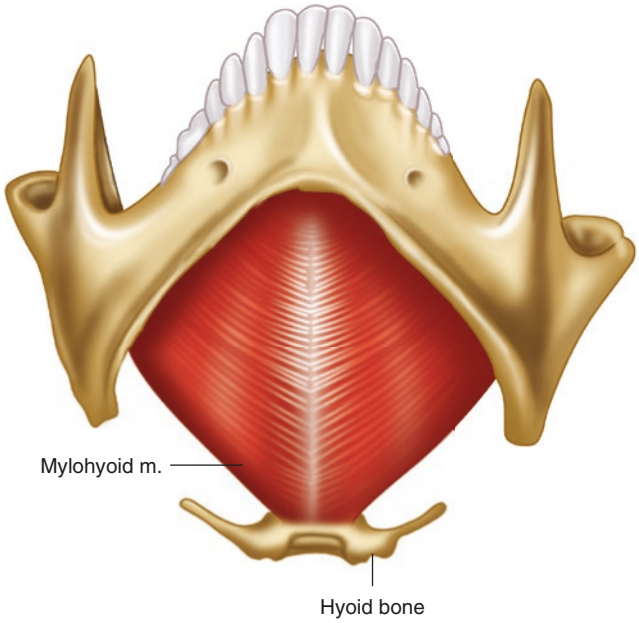


Fig. 10.4 Mylohyoid muscle

inferiorly to the mediastinum. This may happen rapidly and can be a life-threatening situation. Fascia is composed of dense connective tissue, and it surrounds muscles and neurovascular structures. In the face, these potential spaces are defined by the muscle attachments of various muscles of facial expression, especially the buccinator (Fig. 10.3) and the mylohyoid muscles (Fig. 10.4). These potential spaces contain loose connective tissue and expand only when invaded by infection, edema, blood, inflammatory exudate, or a surgeon's fingers. These spaces are described as independent entities; but in reality, they communicate with adjacent spaces, so infection can spread from one space to a contiguous one, sometimes quite easily. As a result, more than one potential space may be involved.

Buccal Space Involvement

Infection and inflammation of the buccal space is characterized by a prominent, distinct swelling of the cheek near the involved tooth. This is the cardinal sign of involvement of the buccal space.

The buccinator muscle arises from a line of attachment on the maxilla and the mandible connected by the pterygomandibular raphe in the posterior oral cavity. This muscle makes up the bulk of the thickness of the cheek. The location of the root apex of an infected tooth in relation to the boney attachment of the buccinator muscles determines whether an infection will drain into the oral cavity or will travel into the buccal space. If an infection from a maxillary tooth erodes through bone superior to the attachment of the buccinator muscle to the maxilla, the infection and swelling enters the buccal space (Fig. 10.5), lateral to the muscle. If it erodes inferior to this muscle attachment, the infection will drain into the oral cavity vestibular area.

Infection of mandibular teeth may also involve the buccal space if the infection erodes through bone on the buccal surface of the teeth, and the apex of the involved roots is inferior to the attachment of the buccinator muscle (Fig. 10.5).

Importantly, buccal space swelling and erythema may occur in association with otitis media without an odontogenic cause.

Canine Space Involvement

Infection and inflammation of the canine space presents as a characteristic swelling superior to the upper lip and lateral and inferior to the nose, usually obliterating the nasolabial crease. This space is involved with infections of the maxillary canine tooth and is not frequently encountered.

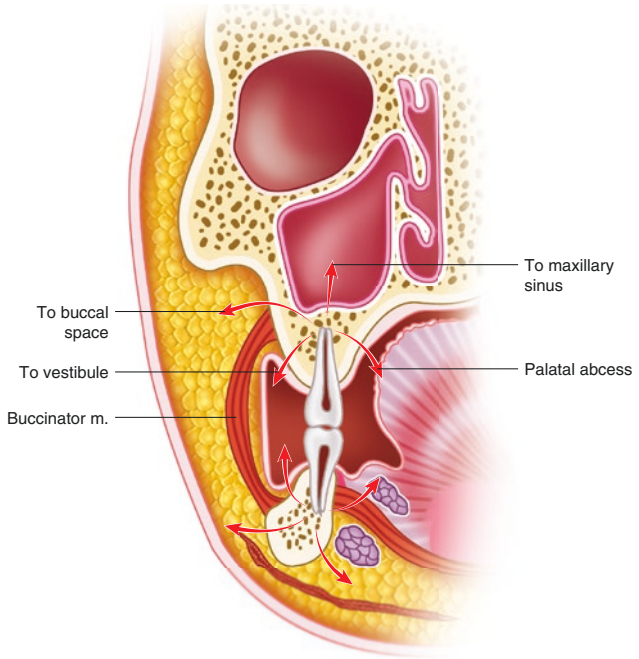


Fig. 10.5 Oral abscess drainage depends on the length of the tooth root, the thickness of bone, and the location of muscle attachments. Infections of maxillary molars may drain into the vestibule of the oral cavity, into the buccal space lateral to the buccinator muscle, into the maxillary sinus, or on the palate. Mandibular molar infections may drain into the oral cavity, the buccal space, superior to the mylohyoid muscle in the floor of the mouth (sublingual space), or under the mylohyoid muscle (submandibular space)

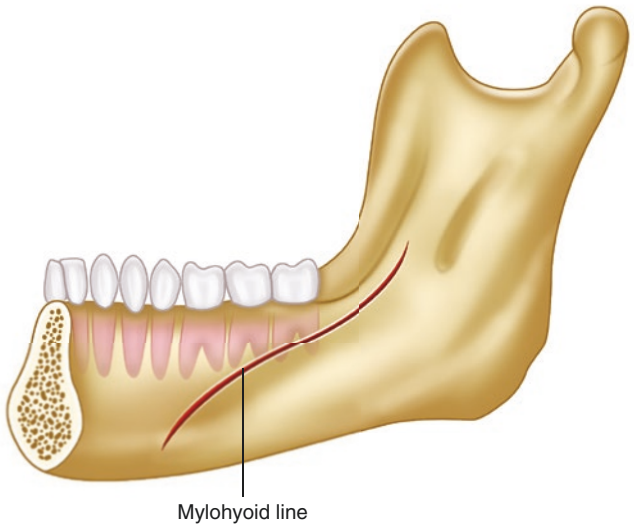


Fig. 10.6 Mylohyoid muscle line of attachment on the interior surface of the mandible. The position of the apex of the roots of the mandibular teeth in relation to the mylohyoid muscle attachment line determines the space involved with the infection and inflammation. Roots that terminate superior to the muscle line drain into the sublingual space. Infections involving root apices that end below (caudal to) the muscle attachment will involve the submandibular space

Submandibular, Sublingual, and Submental Space Involvement

Infections arising from mandibular posterior teeth will often drain into the submandibular and/or sublingual space. The mylohyoid muscle forms the floor of the oral cavity and arises from an attachment line on the interior surface of the mandible (Fig. 10.6). The sublingual space is superior to the broad, flat mylohyoid muscle and under the tongue. Inflammation in this area will be visible intraorally and often elevates the tongue. The submandibular space is inferior to the mylohyoid muscle, between this muscle and the platysma and submandibular skin. Swelling appears in the neck area under the mandible (Fig. 10.7). The relationship of the apex of the roots of mandibular teeth with the location of the mylohyoid muscle determines which space is involved. If the roots terminate above the mylohyoid muscle (usually mandibular premolars and first molar), the sublingual space is involved. However, if the root ends below the mylohyoid muscle (usually mandibular second and third molars), the submandibular space is involved.

The submental space is a small potential space in the middle region of the chin. It may become involved with infections of the mandibular incisors. When involved, the chin

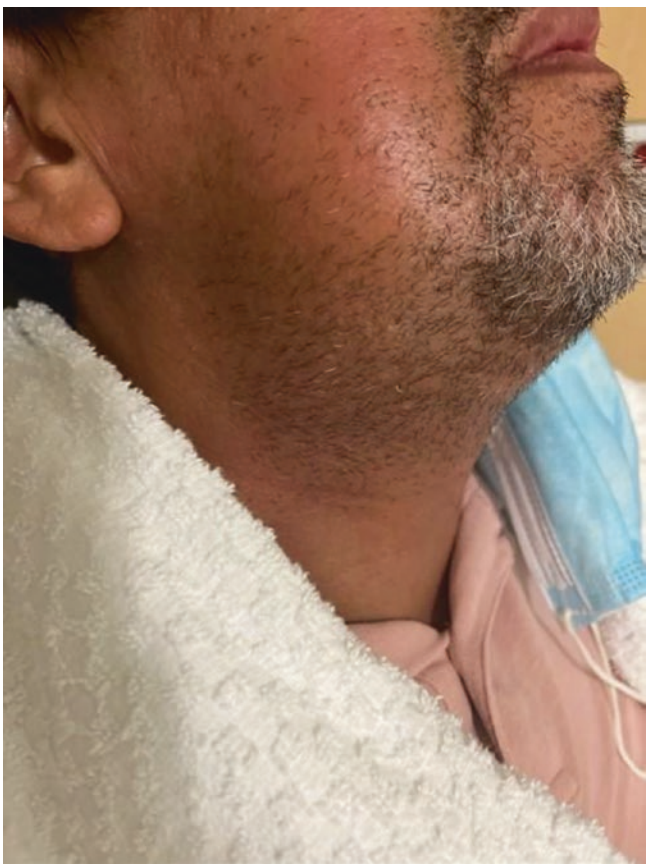


Fig. 10.7 Submandibular space inflammation is inferior to the mylohyoid muscle and in the anterior neck. (Photo courtesy of Dr. Steven Halepas, New York-Presbyterian/Columbia University Irving Medical Center)

region is swollen and often firm and erythematous. The submental space communicates easily with the submandibular spaces bilaterally.

Ludwig's Angina

Ludwig's angina occurs rarely and consists of bilateral firm cellulitis of the submandibular and sublingual spaces and the submental space in the midline. This is a life-threatening, emergency situation that requires immediate hospitalization. Individuals with Ludwig's angina have massive neck swelling, an elevated floor of the mouth and tongue, difficulty breathing, swallowing, and speaking, and pain on opening the mouth. Most of the time, it arises from an odontogenic infection although it may be caused by trauma or submandibular salivary gland inflammation. Treatment consists of immediate airway maintenance, surgical draining, extraction of involved teeth, and extensive antibiotic therapy.

Fascial Infection Spread Posteriorly Guided by the Muscles of Mastication and Their Associated Fascia

Masticator Space Involvement involves the spaces associated with the masseter, lateral pterygoid, and medial pterygoid muscles (Fig. 10.8), cradling the mandible. These spaces surround the ramus of the mandible and communicate freely with the buccal space, the submandibular spaces, and spaces located more posteriorly in the pharyngeal area. These spaces located deeper in the throat will be covered later in this chapter. Infections from the mandibular third molar expand most commonly into this space. Swelling may not be visible externally when the masticatory space is involved because the very large masseter muscle covers the space laterally. However, trismus (the inability to open the mouth) is a cardinal symptom of infection and inflammatory involvement of the masseteric space.

Fascial Spread to Deep Cervical Spaces

Infections and inflammation may spread beyond the facial, anterior neck, and masticatory spaces into deep cervical spaces surrounding the pharynx. These deep spaces may become involved due to the spread of infection and inflammatory exudate from odontogenic infections, but they also may enlarge as a sequela of tonsillitis, pharyngitis, otitis, mastoiditis, trauma, or tuberculosis.

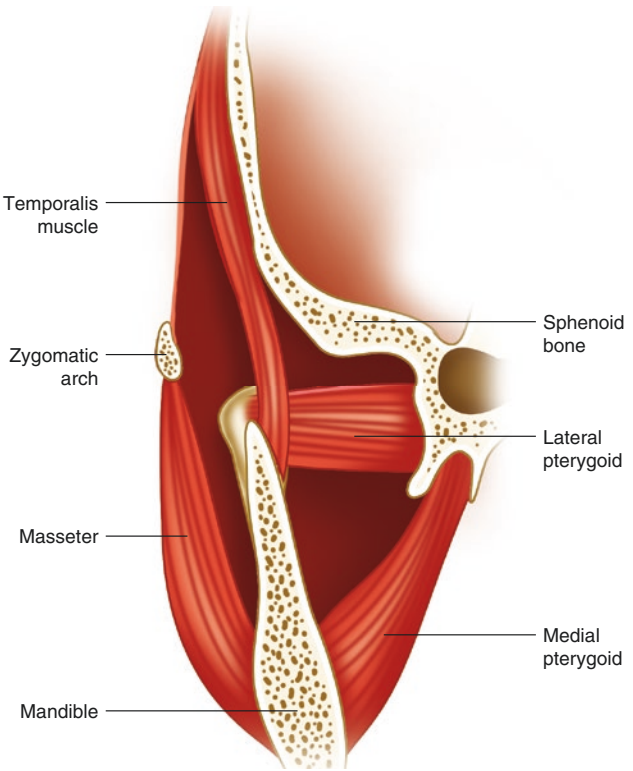


Fig. 10.8 Coronal section through the lateral portion of the face illustrating the muscles of mastication and the potential spaces that may be involved with infection spread

1. The **lateral pharyngeal space** lies deep to the constrictor muscles of the esophagus. Vital structures in this space (including the carotid sheath containing the carotid artery, internal jugular vein, and vagus nerve, and several other cranial nerves) are vulnerable to compression from swelling and erosion from the inflammatory exudate.

   When this space is involved, individuals present with pain, fever, enlargement of the pharyngeal wall, deviation of the uvula from the midline, and difficulty swallowing. Airway management is paramount and requires emergency care, and treatment ultimately involves incision and drainage, and antibiotic therapy.
2. The **retropharyngeal and prevertebral spaces** lie posterior to the pharynx and esophagus and anterior to the vertebral column and communicate inferiorly to the upper mediastinum. Swellings of these spaces may be visualized radiographically. Individuals with involvement of these spaces have difficulty breathing, swallowing, and speaking, and require urgent care for treatment. Infections and inflammation may spread through these spaces to involve the heart and mediastinum.

Venous Infection Spread

Odontogenic infections arising from the maxillary teeth as well as infections arising from the nose, the orbit, or the upper lip, may spread through the valveless facial veins to the cavernous sinus within the cranium. This may lead to a cavernous sinus thrombosis with extremely serious consequences. Involvement of the cavernous sinus leads to compression of the nerves which innervate the extraocular muscles and affect eye movements. Increased pressure may make eyes to protrude and cause engorgement of the conjunctiva.

Other veins in the face and head region communicate with the cranium via the pterygoid venous plexus and emissary veins across the skull and may be vehicles for infection spread.

Summary

Dentoalveolar infections arising from the teeth and/or surrounding periodontium are very common. If they are left untreated or undertreated, they have the potential to be life-threatening due to spread through the deep cervical spaces resulting in a compromised airway. Early recognition and appropriate surgical intervention are required.

Osteomyelitis of the Facial Skeleton

11

Peter F. James, Ronald Akiki, and Mohammad Banki

Osteomyelitis is an inflammatory and infectious process involving the medullary or cortical component of bone and may be acute or chronic in nature. While the advent of modern antibiotic therapies has vastly decreased the incidence of osteomyelitis in the general public, the condition is associated with considerable morbidity and mortality, especially when the head and neck is involved [1–3]. While the highly vascularized nature of the head and neck region encourages rapid healing and prompt response to invading pathogens, serious infections of the facial skeleton are possible, especially in sites exposed to the environment by trauma or surgical intervention [3, 4]. The mandible is of particular risk of infection owing to its limited vascular supply via the inferior alveolar artery as well as the dense nature of its cortices. The maxilla, conversely, is more resistant to infection as its bony matrix is more porous and several vessels provide perfusion to the area [5]. Osteomyelitis of the mandible is most frequently initiated by direct location extension of infection from the skin, sinuses, or the oral cavity [3]. Unlike in long bones, osteomyelitis of the facial skeleton is unlikely to be caused by a hematogenous source [5].

Acute Osteomyelitis of the Facial Skeleton

Acute osteomyelitis is characterized by acute pain, facial swelling, lymphadenopathy, fever, leukocytosis, and elevated erythrocyte sedimentation rate [6]. White blood cell counts may exceed 15,000 [3]. Diagnostic criteria specify that in order for osteomyelitis to be considered acute, symptom duration must be shorter than 4 weeks [7]. Most commonly, acute osteomyelitis of the facial bones is the result of a polymicrobial infection, typically comprised of normal oral flora including *Streptococcus, Fusobacterium*, and *Porphyromonas* [6]. Also occasionally implicated are the organisms *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Actinomyces*, and *Eikenella* [3, 4]. Clindamycin and methicillin-resistant organisms can be encountered in these patients as well. Given the diversity of possible causative organisms, initial treatment should include broad-spectrum antibiotics until results of wound cultures provide susceptibility data [8].

Development of acute osteomyelitis requires direct bacterial inoculation of the bone. This is most often the result of odontogenic sources such as periodontal or pulpal infection, or a penetrating event such as surgery (i.e., tooth extraction) or trauma [2, 3]. As the infection develops, so does inflammation of the surrounding medullary or osseus bone. Inflammatory edema results in vascular stasis, which both diminishes oxygen and nutrient delivery to the bone and impairs the host immune response to the infection by limiting leukocyte recruitment to the area. This unfortunate pattern leads to the development of a poorly perfused and immunologically deficient environment that is ideal for the growth of anaerobic bacteria [7]. The presence of systemic disease may further compound this issue; impaired immunologic response as in alcoholism or diabetes, reduced perfusion as in sickle cell disease or other hematological conditions, and abnormal bone as in osteopathies like osteopetrosis may all incite or worsen osteomyelitis [7, 9]. Seventeen percent of patients with osteomyelitis, however, have no underlying factors that predispose them to the condition [10].

Early in the disease process, plain radiographic imaging including orthopanoramic radiographs is of minimal diagnostic value. A loss of up to 50% of bone mineral density may be required in order for osteomyelitis to be detectable on radiographic imaging, meaning that these scans may appear normal for at least the first 4–8 days of disease and

P. F. James
Department of Otolaryngology, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

R. Akiki
Department of Plastic Surgery, Warren Alpert Medical School of Brown University, Providence, RI, USA

M. Banki (✉)
Department of Surgery, Warren Alpert Medical School of Brown University, Providence, RI, USA

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_11

potentially up to several weeks [1, 7]. As the disease progresses further, pathognomonic changes may become visible on radiographic imaging, with the most common finding being irregular radiolucency adjacent to an extraction socket or other odontogenic site [1, 11].

While plain films are of limited diagnostic utility early in the disease process, computed tomography (CT) and magnetic resonance imaging (MRI) are useful techniques for diagnosing and documenting progression of osteomyelitis. CT may depict early bony changes such as small sequestra of cortical bone and osteolysis of cancellous bone, as well as more clearly define the margins of the infectious process. MRI offers a high degree of sensitivity in the detection of intramedullary inflammation and is the modality of choice in the setting of high clinical suspicion of osteomyelitis despite prior inconclusive imaging. Subperiosteal disease will present with a high signal on T2 sequence and a low signal on T1, whereas sequestra will appear with a low signal on both sequences [1, 12]. Importantly, MRI has the potential to overestimate the extent of intramedullary disease due to the presence of associated edema, and this should be used with caution as a surgical planning tool. Radiolabeled isotope scintigraphy was historically favored for its ability to detect osteomyelitis at 2–3 days but has been replaced by more reliable techniques due to its relative lack of specificity [1, 11, 12].

Treatment of osteomyelitis should not be delayed and should be focused on removal of the offending microbial pathogens. Collection of contaminant-free specimens for culture and gram stain followed by early initiation of antibiotics is vital to preventing disease progression and further tissue damage. Empiric treatment with amoxicillin/clavulanic acid or clindamycin is appropriate until results of culture and gram stain are returned, and antibiotic therapy should be continued for 3–6 weeks [2, 8]. While antimicrobials are an integral component of effective osteomyelitis treatment, surgical intervention is the definitive treatment and is often required for complete resolution [13, 14]. Surgical approaches should be designed to restore appropriate blood supply to the area by means of medullary decompression, which may be achieved via sequestrectomy, decortication, and saucerization [10, 13, 14]. Furthermore, removal of contaminated bone via debridement or resection reduces the burden of infection and allows for improved host immune response and antibiotic penetration. Removal of infected teeth, in the event of an odontogenic origin of infection, may also be indicated.

Illustrative Case

The following case involves a male in his sixth decade of life with a history of recurrent pericoronitis involving a partially impacted right mandibular third molar (see Fig. 11.1). He underwent an uncomplicated removal of this symptomatic tooth. Postoperative course was significant for ongoing pain and trismus. The patient was treated symptomatically with muscle relaxants. Subsequently, on the third postoperative

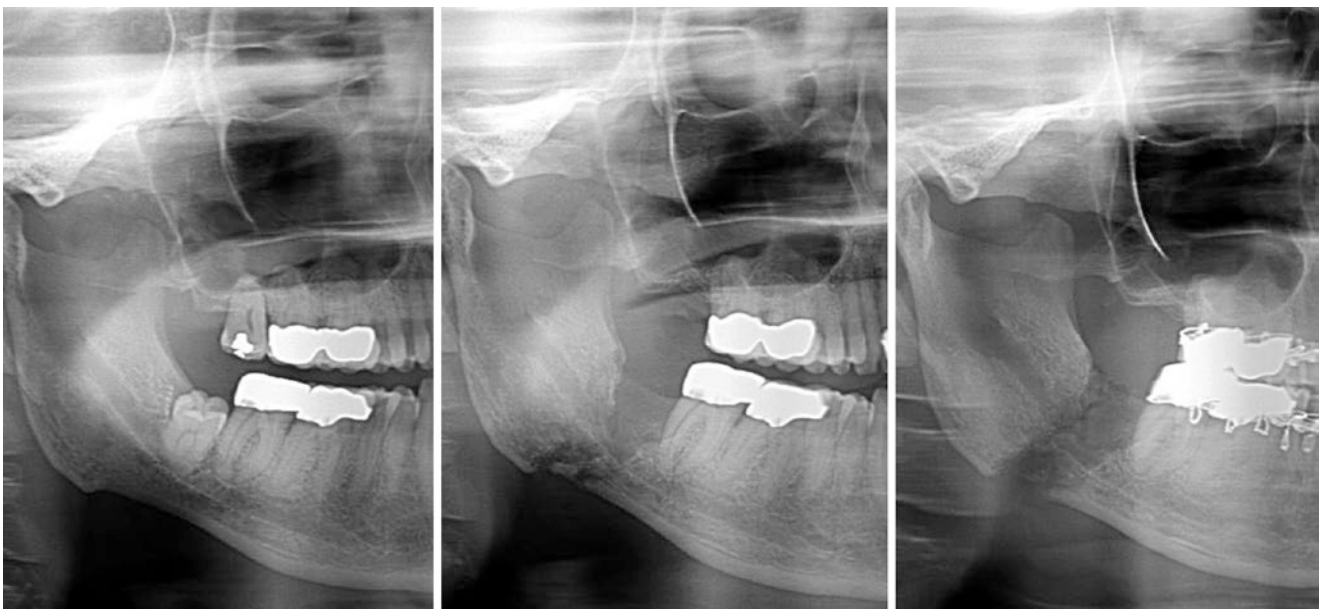


Fig. 11.1 Radiographs demonstrating mandibular osteomyelitis from left to right: impacted third molar tooth, osteomyelitis pathologic fracture of mandible at site of tooth removal, and treatment of fracture with debridement and intermaxillary fixation. (Radiographs courtesy of the author MB)

week a panoramic image of the mandible was obtained which revealed areas of radiolucency extending beyond the boundaries of the bony socket and extending to the inferior border. The site was surgically explored and copious granulation tissue along with small free-floating bone was removed and submitted for H&E staining. Additionally, the wound was swabbed and was submitted for culture and sensitivity. Pathology report was consistent with a possible diagnosis of osteomyelitis. The culture grew out mixed oral flora. A CT scan was obtained which was also read as osteomyelitis of the mandible. An infectious disease consult was obtained and the patient was placed on parenteral penicillin. Panoramic images continued to demonstrate exacerbation of the radiolucency with ragged bone edges, sequestration, and failure of the socket to heal properly. The patient eventually developed a pathological fracture of the right mandibular angle which did not respond favorably to closed reduction and maxillomandibular fixation. He ultimately underwent debridement of the fracture site, sequestrectomy, corticotomy, and saucerization followed by reduction and fixation via a locking-reconstructive plate that spanned the fracture defect. He remained on the intravenous course of penicillin for 4 months followed by an 8-week course of amoxicillin/clavulanate. The patient recovered fully with no adverse sequelae and remained symptom-free.

Chronic Osteomyelitis of the Facial Skeleton

Chronic osteomyelitis refers to a collection of inter-related disease processes of at least 1 month duration and includes both secondary and primary chronic osteomyelitis. Secondary chronic osteomyelitis (SCO), also referred to as chronic suppurative osteomyelitis, represents the persistence of acute osteomyelitis beyond 1 month of duration and may be related to inadequate treatment of that condition [1, 10, 15]. In contrast, primary chronic osteomyelitis (PCO), also called chronic diffuse sclerosing osteomyelitis or chronic nonsuppurative osteomyelitis, is a distinct entity with no association with the acute form of the condition [8, 14, 16, 17].

Patients suffering from SCO typically complain of pain, swelling, malaise, lymphadenopathy, and fever—symptoms similar to the acute phase of their condition. Intraoral or cutaneous fistulas may also be present, in collection of inter-related disease processes of at least one addition to pathologic fractures, exposed necrotic bone, and overlying soft tissue lesions [11]. Significant loss of bone can be easily appreciated with plain film, CT, or MRI in the form of contiguous radiolucent and radiodense lesions. Treatment failure of acute osteomyelitis may be multifactorial in nature; inappropriate antibiotic selection, insufficient dose or duration, or failure of the patient to seek care may all lead to progression to SCO. The development of SCO indicates that the condition can no longer be treated with antibiotics alone and that surgical intervention is required for collection of inter-related disease processes of at least one definitive treatment [7].

Surgical treatment of SCO should be focused on the removal of all necrotic or diseased bone and restoration of adequate blood flow to the area. Decortication of affected cortical bone and exposure of cancellous bone should be performed, followed by primary closure or healing by secondary intention. Further surgical techniques are identical to those used for treatment of the acute form of the disease, and may include saucerization, debridement, sequestrectomy, and resection in severe cases [13, 18, 19]. Due to demineralization and thinning of involved bone, care should be taken to avoid causing fractures intraoperatively for the collection of inter-related disease processes of at least one. Likewise, bone grafting or implant placement may be indicated to stabilize remaining healthy bone and prevent further injury.

As in acute osteomyelitis, antibiotic therapy is an important component in the treatment of SCO; however, different formulations and longer collection of inter-related disease processes of at least one duration may be required [1, 8]. The possibility of antibiotic resistance strains or atypical organisms should be explored, and care should be taken to perform in-depth microbiological analysis of bone samples. Antibiotic regimens should be selected with ample input from infectious disease experts. Regular monitoring during treatment and documentation of clinical signs and symptoms in addition to lab tests such as antibiotic level and C-reactive protein are important to ensuring resolution of SCO. There is some evidence that hyperbaric oxygen therapy (HBO) may be beneficial as a treatment adjunct for both acute and chronic forms of osteomyelitis. HBO improves oxygen delivery to diseased tissues, interrupts growth of anaerobic organisms, and promotes neoangiogenesis [20–22].

Primary chronic osteomyelitis (PCO) is a distinct and poorly understood condition which may present only on routine imaging and occasionally in the absence of symptoms [16, 17]. It is thought to be the result of chronic, low-grade infection, and in some cases has been associated with *Actinomyces* and *Eikenella* species [4]. Imaging is notable for multifocal areas of mixed radiolucency and radiodensity. The condition may be identical to a similar entity that occurs in children, known as juvenile mandibular chronic osteomyelitis (JMCO), which presents with pain and swelling unresponsive to antibiotic therapies. Treatment strategies for PCO are identical to those used for acute osteomyelitis or SCO but may have lower success rates [23].

References

1. Schuknecht B, Valavanis A. Osteomyelitis of the mandible. Neuroimaging Clin N Am. 2003;13(3):605–18. https://doi.org/10.1016/S1052-5149(03)00044-3.
2. Hudson J. Osteomyelitis of the jaws: a 50-year perspective. J Oral Maxillofac Surg. 1993;51(12):1294–301. https://doi.org/10.1016/S0278-2391(10)80131-4.
3. Krakowiak P. Alveolar osteitis and osteomyelitis of the jaws. Oral Maxillofac Surg Clin North Am. 2011;23(3):401–13. https://doi.org/10.1016/J.COMS.2011.04.005.
4. Marx R, Carlson E, Smith B, Toraya N. Isolation of Actinomyces species and Eikenella corrodens from patients with chronic diffuse sclerosing osteomyelitis. J Oral Maxillofac Surg. 1994;52(1):26–33. https://doi.org/10.1016/0278-2391(94)90008-6.
5. Bagheri SC, Jo C. Clinical review of oral and maxillofacial surgery. Amsterdam: Elsevier; 2013. p. 578.
6. Babu A, Santosh R, Ogle OE, Williams D, Woodbine EF. Epidemiology of oral and maxillofacial infections. Dent Clin North Am. 2017;61:217. https://doi.org/10.1016/j.cden.2016.11.003.
7. Baltensperger MM, Eyrich GKH. Osteomyelitis of the jaws. Berlin: Springer; 2009. p. 1–315. https://doi.org/10.1007/978-3-540-28766-7.
8. Dym H, Zeidan J. Microbiology of acute and chronic osteomyelitis and antibiotic treatment. Dent Clin N Am. 2017;61(2):271–82. https://doi.org/10.1016/J.CDEN.2016.12.001.
9. Marx RE. Chronic osteomyelitis of the jaws. Oral Maxillofac Surg Clin North Am. 1991;3(2):367–81. https://doi.org/10.1016/S1042-3699(20)30505-7.
10. Koorbusch G, Fotos P, Goll K. Retrospective assessment of osteomyelitis. Etiology, demographics, risk factors, and management in 35 cases. Oral Surg Oral Med Oral Pathol. 1992;74(2):149–54. https://doi.org/10.1016/0030-4220(92)90373-X.
11. Koorbusch G, Deatherage J, Curé J. How can we diagnose and treat osteomyelitis of the jaws as early as possible? Oral Maxillofac Surg Clin North Am. 2011;23(4):557–67. https://doi.org/10.1016/J.COMS.2011.07.011.
12. Schuknecht B. Diagnostic imaging - conventional radiology, computed tomography and magnetic resonance imaging. In: Osteomyelitis of the jaws. Berlin: Springer; 2009. p. 57–94. https://doi.org/10.1007/978-3-540-28766-7_3.
13. Bolognesi F, Tarsitano A, Cicciù M, Marchetti C, Bianchi A, Crimi S. Surgical management of primary chronic osteomyelitis of the jaws: the use of computer-aided-design/computer-aided manufacturing technology for segmental mandibular resection. J Craniofac Surg. 2020;31(2):E156–61. https://doi.org/10.1097/SCS.0000000000006121.
14. Hjorting-Hansen E. Decortication in treatment of osteomyelitis of the mandible. Oral Surg Oral Med Oral Pathol. 1970;29(5):641–55. https://doi.org/10.1016/0030-4220(70)90259-8.
15. Lew D, Waldvogel F. Osteomyelitis. Lancet. 2004;364(9431):369–79. https://doi.org/10.1016/S0140-6736(04)16727-5.
16. Matharu J, Taylor H, Sproat C, Kwok J, Brown J, Patel V. Diffuse sclerosing osteomyelitis: a case series and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020;129(5):437–46. https://doi.org/10.1016/J.OOOO.2019.11.010.
17. Buch K, Thuesen A, Brøns C, Schwarz P. Chronic non-bacterial osteomyelitis: a review. Calcif Tissue Int. 2019;104(5):544–53. https://doi.org/10.1007/S00223-018-0495-0.
18. Kim S, Lee S. Chronic non-bacterial osteomyelitis in the jaw. J Korean Assoc Oral Maxillofac Surg. 2019;45(2):68–75. https://doi.org/10.5125/JKAOMS.2019.45.2.68.
19. Bevin C, Inwards C, Keller E. Surgical management of primary chronic osteomyelitis: a long-term retrospective analysis. J Oral Maxillofac Surg. 2008;66(10):2073–85. https://doi.org/10.1016/J.JOMS.2008.06.029.
20. Ceponis P, Keilman C, Guerry C, Freiberger J. Hyperbaric oxygen therapy and osteonecrosis. Oral Dis. 2017;23(2):141–51. https://doi.org/10.1111/ODI.12489.
21. Van Merkesteyn J, Bakker D, Van der Waal J, et al. Hyperbaric oxygen treatment of chronic osteomyelitis of the jaws. Int J Oral Surg. 1984;13(5):386–95. https://doi.org/10.1016/S0300-9785(84)80063-0.
22. Lentrodt S, Lentrodt J, Kübler N, Mödder U. Hyperbaric oxygen for adjuvant therapy for chronically recurrent mandibular osteomyelitis in childhood and adolescence. J Oral Maxillofac Surg. 2007;65(2):186–91. https://doi.org/10.1016/J.JOMS.2005.11.106.
23. Renapurkar S, Pasternack M, Nielsen G, Kaban L. Juvenile mandibular chronic osteomyelitis: role of surgical debridement and antibiotics. J Oral Maxillofac Surg. 2016;74(7):1368–82. https://doi.org/10.1016/J.JOMS.2016.01.027.

Viral and Fungal Infections

12

Scott M. Peters

Introduction

The oral cavity is susceptible to a number of different viral and fungal infections. Some of these may be acute in nature and limited to the oral mucosa, while others may be chronic and represent manifestations of systemic diseases. This chapter will focus on some of the more commonly encountered oral viral and fungal infections, so that the medical professional may be able to accurately diagnose and manage these conditions.

Herpes Viruses

The **human herpesvirus (HHV) family** consists of a number of double-stranded (ds) DNA viruses, many of which can present with oral lesions. A complete listing of the HHVs and the oral lesions which they cause can be found in (Table 12.1). The text of this chapter will focus on the more commonly encountered oral and maxillofacial manifestations of these viruses.

Table 12.1 Diseases associated with human herpes viruses

Type	Name	Associated diseases
HHV-1 (HSV-1)	Herpes simplex virus type 1	Primary herpetic gingivostomatitis (initial infection only)
		Herpetic whitlow
		Herpes labials
		Recurrent intraoral herpetic ulcerations
HHV-2 (HSV-2)	Herpes simplex virus type 2	Genital herpes
HHV-3 (VZV)	Varicella zoster virus	Chicken pox/shingles
HHV-4 (EBV)	Epstein-Barr virus	Oral hairy leukoplakia, mono, & lymphoproliferative disorders such as African Burkitt's lymphoma, nasopharyngeal carcinoma and possibly some others
HHV-5 (CMV)	Cytomegalovirus	Symptomatic CMV infections usually only seen in neonates & immunocompromised
HHV-6	Human herpes virus type 6	Erythematous macular eruptions (roseola exanthema subitum), recurrences (usually only occur in the immunocompromised) can result in widespread multiorgan infection
HHV-7	Human herpes virus type 7	Roseola-like cutaneous eruptions, recurrences (usually only occur in the immunocompromised) can result in widespread multiorgan infection
HHV-8 (KSHV)	Kaposi's sarcoma herpes virus	Kaposi's sarcoma, small variety of lymphomas, Castleman's disease

S. M. Peters (✉)
Oral and Maxillofacial Pathology, Geisinger Health System, Wilkes-Barre, PA, USA
e-mail: smp2140@cumc.columbia.edu

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_12

Herpes Simplex Virus

Herpes simplex virus (HSV) is perhaps the best-known member of the HHV family. There are two HSVs, HSV1 and HSV2, which are similar in their structure and disease mechanisms but differ with regard to their epidemiology and site predilection for disease. HSV1 is classically spread via infected saliva or active oral or perioral lesions and is typically seen involving the head and neck region [1, 2]. HSV2 is spread via sexual contact and usually affects the genital area and skin below the waist, although changing patterns in sexual behavior are resulting in increasing cases of HSV2 being detected intraorally [3]. This chapter will focus on initial and recurrent infection with HSV1.

HSV will cause an initial infection in previously unexposed patients. This initial infection typically occurs at a young age, and in many patients may result in a subclinical level of disease. Patients who do develop symptoms frequently present with fever, chills, fatigue, malaise, decreased appetite, and cervical lymphadenopathy [1, 4, 5]. The oral lesions of an initial HSV infection will involve both the keratinized and nonkeratinized mucosa and present as multiple, clustered ulcerations with tan-grey pseudomembranes and surrounding erythema. In addition, the gingiva will typically appear inflamed, erythematous, and edematous (Fig. 12.1). This spectrum of findings is diagnosed as **primary herpetic gingivostomatitis** [5]. Most cases of primary herpetic gingivostomatitis are diagnosed between 6 months and 5 years of age. If a primary infection of HSV produces a clinical disease in older patients, it will more often involve the posterior oral cavity and oropharynx and present as a pharyngotonsillitis [5]. Treatment of primary HSV infection is palliative in most cases, as antiviral therapy is only effective if administered within the first 24 h of lesion onset [6]. Habits common for children of this age, such as thumb sucking, should be avoided as this may spread the active virus to the skin and result in conditions such as **herpetic whitlow**.

Following initial infection with HSV, the virus will undergo a period of latency where it remains dormant in sensory nerves, most often the trigeminal ganglion. Recurrences of HSV occur when the virus reactivates and travels along the sensory nerve, resulting in lesions of the skin or mucosa innervated by these nerve fibers [7]. There are numerous causes of reactivation of HSV, including but not limited to stress, environmental factors such as heat, wind, or cold, old age, pregnancy, ultraviolet light, dental treatment, systemic disease, respiratory tract infections, and menstruation [7, 8]. Recurrent or secondary infections of HSV are limited to keratinized tissues. When they involve the skin, they often appear near the vermillion border of the lip and are referred to as **herpes labialis**. This is colloquially referred to as a cold sore or a fever blister. Herpes labialis presents as multiple fluid-filled vesicles, which will subsequently rupture and crust [9]. Involvement of the oral cavity by recurrent HSV will appear as clustered vesicles, frequently 1–3 mm in size, which are acutely painful and typically limited to keratinized oral tissues such as the hard palate and gingiva (Fig. 12.2). Treatment of recurrent HSV infection is typically palliative

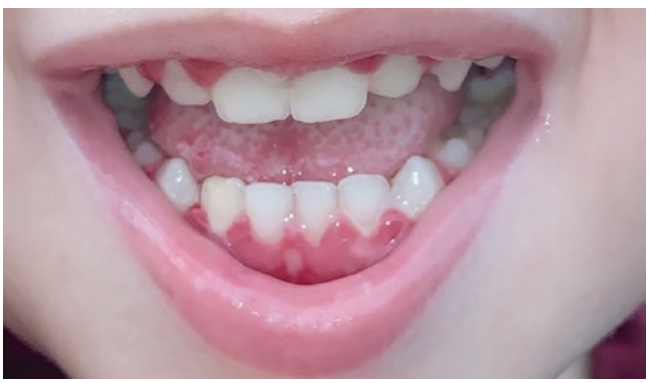


Fig. 12.1 Primary herpetic gingivostomatitis. The patient's gingiva appears erythematous and edematous. Focal tan-gray ulcerations can be seen involving the alveolar mucosa and tongue. (Courtesy of Dr. Jose Liens)

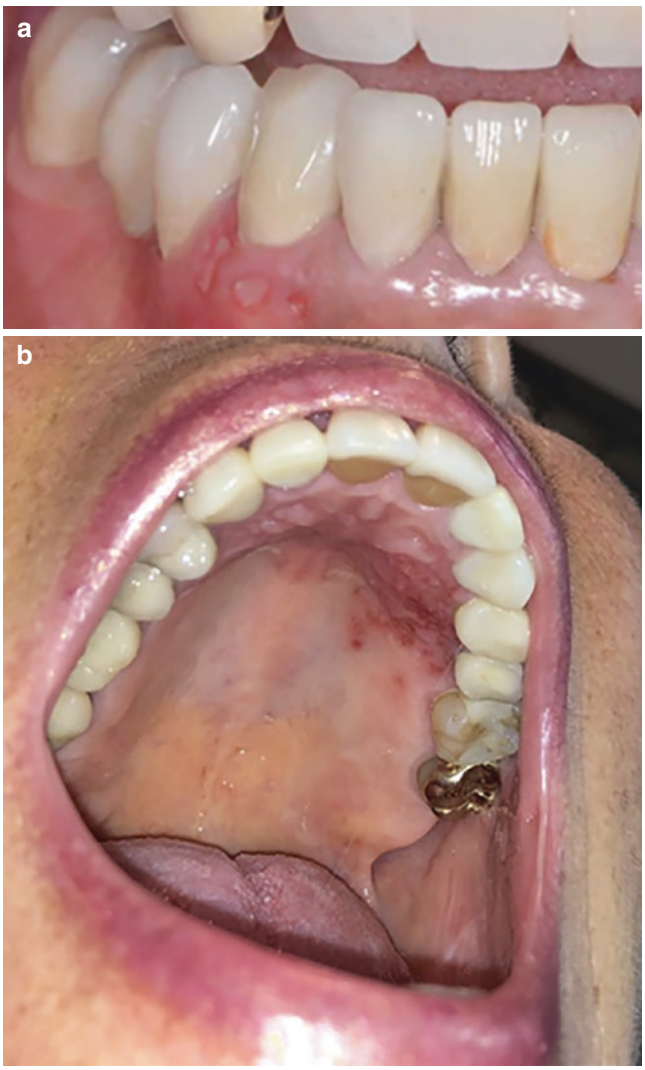


Fig. 12.2 Recurrent intraoral herpes. Small, clustered tan-grey ulcerated lesions involving the keratinized oral tissues, specifically the attached gingiva (**a**) and the hard palate (**b**)

in nature. Patients should be instructed not to touch active lesions as this may lead to autoinoculation of other body sites. Similarly, elective dental procedures should be delayed until the lesions resolve. Antiviral therapies, such as acyclovir, may be considered when a patient suffers from multiple recurrences, has an exacerbated erythema multiforme-like response to a recurrence, or when the condition is detected and diagnosed within the first 24 h of lesion onset [9].

Varicella Zoster Virus

Varicella zoster virus (VZV) is another member of the HHV family of viruses and is also referred to as HHV3. Initial infection with VZV results in **chickenpox**. Reactivation of the virus, which typically occurs later in adult life, will cause **herpes zoster (shingles)**. Chickenpox is primarily a disease of childhood and results in a pruritic exanthem that begins on the face and trunk and spreads to the extremities. The skin rash characteristically appears as vesicular lesions against an erythematous background. Treatment of chickenpox consists of antiviral and palliative therapies [10]. Following initial infection, VZV remains dormant in the dorsal root ganglion. Reactivation of the virus will result in herpes zoster (Shingles). The prevalence of shingles increases with patient age; this has been theorized to be related to an age-related decline in cell-mediated immunity. Similar to HSV, factors such as stress, immunosuppression, dental treatment, alcohol use, and advanced age may be associated with reactivation; however, unlike HSV, VZV will only recur once in a patient's lifetime [11]. Shingles has three distinct clinical phases. In the prodromal phase, initial replication of the virus begins, and ganglionitis with associated neuronal necrosis and neuralgia will develop [11]. This is followed shortly by the acute phase of shingles. The acute phase is heralded by the development of the classic cutaneous rash, which appears as vesicles set against an erythematous base (Fig. 12.3). This rash tends to involve a single dermatome, is typically unilateral, and terminates at the midline. The majority of cases of Shingles involve the thoracic dermatomes. When the head and neck region are involved, the rash may involve both the skin and oral mucosa [11, 12]. Oral involvement of shingles will present as multiple clustered ulcerated lesions with surrounding erythema, similar to the clinical appearance of recurrent HSV (Fig. 12.4). Unlike recurrent HSV, but similar to the cutaneous lesions of VZV, the lesions involving the oral mucosa will extend to but not cross the midline. Involvement of the external auditory canal and facial nerve by VZV may result in temporary facial paralysis and hearing loss and is referred to as **Ramsey Hunt syndrome** [13]. Following the acute phase of shingles, some patients may go on to develop chronic symptoms, termed postherpetic neuralgia. Risk factors for post-herpetic neuralgia include female gender, ophthalmic involvement, advanced age, prodromal pain, and a severe rash during the acute phase. Postherpetic neuralgia will last for a minimum of 1–3 months but may persist for years or decades. Treatment of shingles consists of expedient administration of antiviral therapy along with analgesics for pain relief [14].

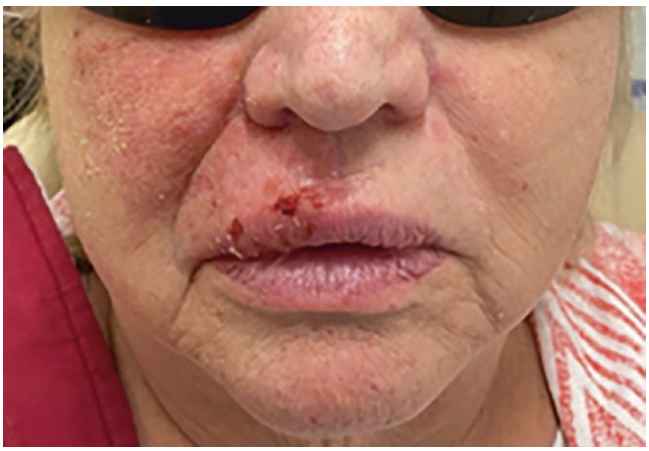


Fig. 12.3 Herpes zoster (Shingles) involving the facial skin. The cutaneous lesions appear as an erythematous rash extending to the patient's midline. (Courtesy of Dr. Jose Liens)

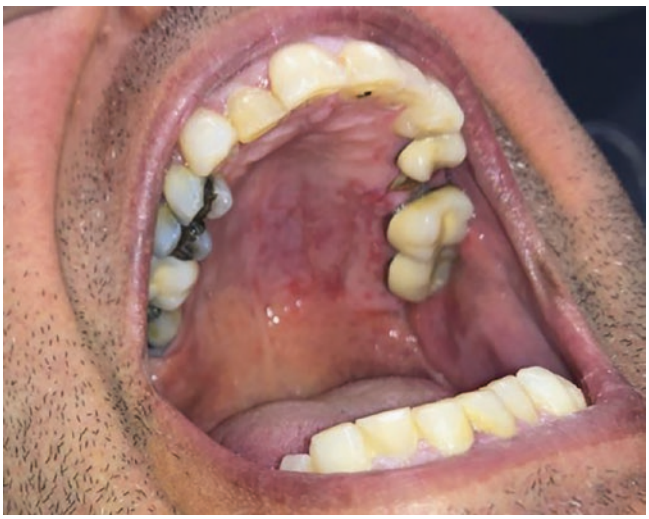


Fig. 12.4 Herpes zoster (Shingles) involving the palate. Tan-grey vesicular lesions and erythema extend to the midline of the palate. (Courtesy of Dr. Garrick Alex)

Of note, a vaccination for varicella zoster virus has been developed and is now routinely administered as part of pediatric care. It is a two-dose vaccination with the first dose given between 12 and 18 months and the second dose administered between 4 and 6 years of age. A similar two-dose vaccination for shingles has been developed for older adults and is recommended for all individuals above the age of 50 years [15, 16].

Epstein Barr Virus

Epstein Barr virus (EBV), also referred to as HHV4, is responsible for several different non-neoplastic and neoplastic conditions, which may manifest in the head and neck region. Some of the examples which are seen more frequently include infectious mononucleosis, oral hairy leukoplakia, EBV mucocutaneous ulcerations, NK-T Cell Lymphoma, and nasopharyngeal carcinoma.

Infectious Mononucleosis

Infectious mononucleosis, also referred to as "Kissing Disease," typically occurs through direct salivary transfer via sharing straws or kissing. In the United States, it is often a disease of young adults. In developing nations, EBV exposure occurs before age three and is often universal by adolescence [17]. In classic infectious mononucleosis in a young adult, patients will initially develop fatigue, malaise, and reduced appetite prior to the development of fever. The fever may last for up to 2 weeks and during this time patients will also develop prominent lymphadenopathy and tonsillar enlargement with diffuse surface exudates (Fig. 12.5). In addition to the observed tonsillar and lymphoid enlargement, other oral manifestations of infectious mononucleosis may include palatal petechiae and a necrotizing ulcerative gingivitis-like presentation [18]. Diagnosis of infectious mononucleosis is made by clinical presentation and the detection of **IgM heterophile antibodies**. Most cases resolve within 4–6 weeks. Patients should be encouraged to maintain adequate nutrition and fluid intake and analgesic therapy may be used for the management of symptoms.

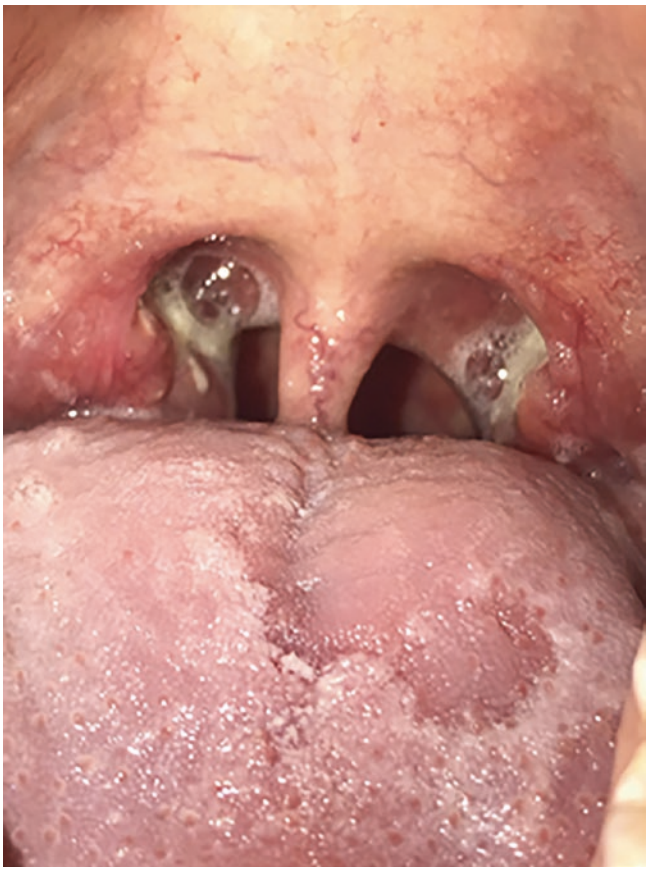


Fig. 12.5 Infectious mononucleosis. The tonsils appear enlarged and demonstrate a tan-grey pseudomembrane. (Courtesy of Dr. Alex May)

Oral Hairy Leukoplakia

Oral hairy leukoplakia (OHL) is an EBV-induced oral mucosal lesion seen in immunocompromised individuals, such as those who are HIV positive, status post organ transplant, or elderly (immune senescence). It classically presents as a nonremovable white lesion on the lateral border of the tongue (Fig. 12.6). It is clinically indistinguishable from other oral leukoplakia lesions; biopsy, therefore, is required to make the diagnosis of OHL. Treatment of OHL consists of managing the patient's underlying cause of immunosuppression. A more detailed discussion of OHL occurring in the setting of HIV can be found later in this chapter.

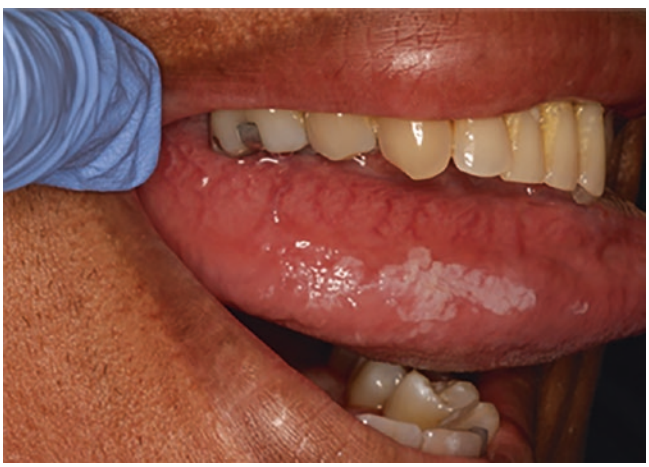


Fig. 12.6 Oral hairy leukoplakia. White, nonremovable lesion involving the lateral aspect of the tongue. The diagnosis was confirmed via tissue biopsy. The patient had a known history of HIV infection

EBV Mucocutaneous Ulcerations

The **EBV-associated mucocutaneous ulceration** (EBVMCU) is a persistent, nonhealing ulcer, which is caused by EBV (Fig. 12.7). It is most frequently seen in immune-compromised individuals, such as those who have received transplants, are HIV positive, or in the elderly [19]. The clinical presentation is non-specific, and a biopsy is required for the diagnosis.

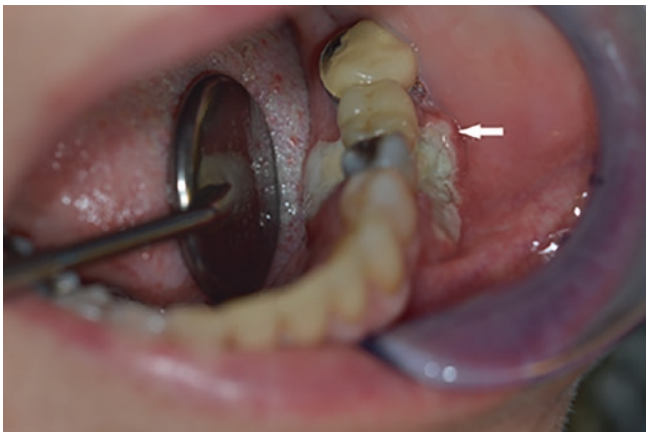


Fig. 12.7 EBV mucocutaneous ulceration. The patient's medical history was significant for recent single lung transplant. (Courtesy of Dr. Michael McKenzie)

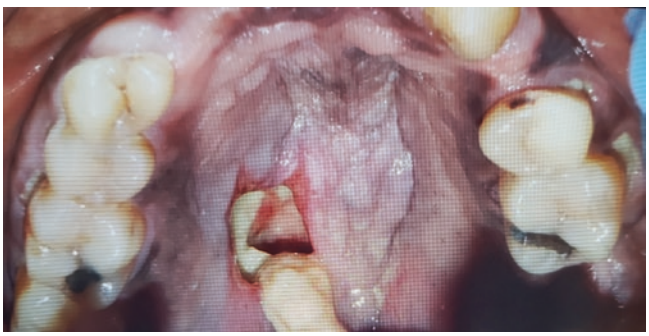


Fig. 12.8 NK-T cell lymphoma presenting as a palatal defect. (Courtesy of Dr. Riley Wedlake)

NK-T Cell Lymphoma

NK-T cell lymphoma is a malignant hematologic neoplasm characterized by aggressive destruction of the midline structures of the palate and the nasal fossa. EBV is theorized to play an important role in the pathogenesis of this condition, and EBV positivity in the lesional cells is required when rendering this diagnosis [20]. NK-T cell lymphoma is seen most often in East Asian, Peruvian, and Guatemalan populations, and may present as a midline palatal defect causing an oral-antral communication (Fig. 12.8). In the early stages of the disease, patients may report epistaxis and nasal stuffiness.

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) is a malignant neoplasm of epithelial origin. Many cases originate from the posterolateral pharyngeal recess, also known as the **fossa of Rosenmuller**. Infection with EBV, deficiencies in vitamin C, and consumption of salt fish are possible risk factors for NPC [21].

Cytomegalovirus

Cytomegalovirus (CMV) is also known as HHV5. It results largely in subclinical infection, with the majority of symptomatic cases involving neonates or the elderly. After initial infection, CMV resides latently in salivary gland tissue, endothelium, lymphocytes, or macrophages. It may be secreted in most bodily fluids. In the United States, CMV seroprevalence reaches almost 90% for those older than 80 years. CMV infections are frequently nonspecific and may exhibit clinical features of several other infectious processes, such as fever, headache, muscle aches, fatigue, decreased appetite, and gastrointestinal disturbances. Ganciclovir is the antiviral agent of choice for the treatment of symptomatic CMV infection [22].

Human Herpesvirus 8

HHV8, also referred to as Kaposi sarcoma-associated herpesvirus, is the etiologic agent responsible for **Kaposi sarcoma (KS)**. Kaposi sarcoma is a malignant neoplasm of vascular origin which although classically seen in middle-aged to older males of Mediterranean or Slavic origin, is better known as occurring in the setting of human immunodeficiency virus (HIV). KS in the context of patients with HIV is discussed in greater detail later in this chapter. This section will provide a brief review of the epidemiology and general features of KS.

Four distinct clinical forms of KS have been recognized: classic, endemic, iatrogenic, and epidemic. The classic form of KS occurs later in adult life, has a strong male predilection, and tends to involve the skin of the lower extremities, where it presents as blue to red cutaneous macules. The endemic form of KS is seen in sub-Saharan Africa and may involve either the skin or visceral organs. The iatrogenic variant of KS occurs in patients with a history of solid organ transplant and is theorized to be due to the use of immunosuppressive therapy in these patients. The epidemic form is seen in patients with HIV [23].

Additional clinical information is provided later in this chapter in the "Oral Manifestations of HIV" section.

Enterovirus Infections

Human enteroviruses have traditionally been subclassified as echoviruses, coxsackieviruses, and polioviruses. Most infections with enteroviruses produce a subclinical level of disease. The estimated incidence of symptomatic enterovirus infections in the United States is 10–15 million cases per year, with the majority of these affecting infants and children. Infections occurring in older individuals are often

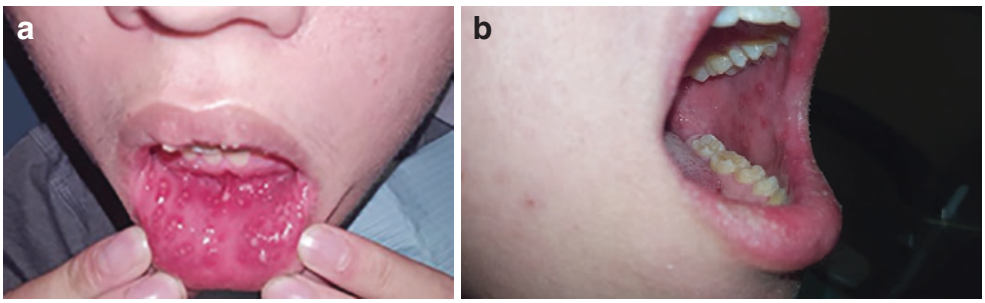


Fig. 12.9 The oral lesions of HFM appear as multiple, small ulcerated lesions of the lower labial mucosa (**a**) and buccal mucosa (**b**). (Courtesy of Dr. Kathleen Schultz)

attributed to caretakers of infected children. There are three patterns of enteroviral infections that are of particular importance with regard to head and neck manifestations: **hand-foot-and-mouth disease (HFM)**, **herpangina**, and **acute lymphonodular pharyngitis (ALP)** [24].

HFM presents with a skin rash and oral lesions occurring in association with flu-like symptoms, cough, rhinorrhea, decreased appetite, gastrointestinal disturbances, and headache. As the name of this disease suggests, the lesions tend to involve the hands, the feet, and the oral cavity, although in some older individuals affected with HFM, the presentation may be atypical and exclude one or more of these sites. The cutaneous lesions of the hands and the feet appear as vesicles involving the palms and the soles, respectively. Some surrounding erythema may also be observed. The oral lesions present as numerous aphthous-like ulcerations involving the anterior regions of the oral cavity such as the buccal mucosa, the labial mucosa, and the tongue (Fig. 12.9). The lesions are usually smaller than 1 cm in size, tend to ulcerate rapidly and heal over the course of a week [25].

Herpangina will present with flu-like symptoms and an associated sore throat, followed by the onset of oral lesions. Unlike HFM, the oral lesions of herpangina tend to involve the posterior zones of the oral cavity and oropharynx, such as the palate and tonsillar region. They appear as macular lesions, which form fragile vesicles which rupture and heal over the course of approximately 1 week (Fig. 12.10). Herpangina lacks the cutaneous component observed in HFM and the oral lesions are fewer in number when compared to those of HFM [24].

ALP has a similar clinical course and presentation when compared to herpangina. Patients will present with a fever, sore throat, and headache, along with yellow to pink-colored nodules of the posterior soft palate and tonsillar pillars. Unlike herpangina, these lesions will resolve without vesiculation or ulceration [26].

Diagnosis of HFM, herpangina, and ALP is rendered based on the clinical manifestations of these lesions. These conditions are self-limiting and will resolve without any therapeutic intervention. Palliative therapies can be given for the management of patient symptoms [24].

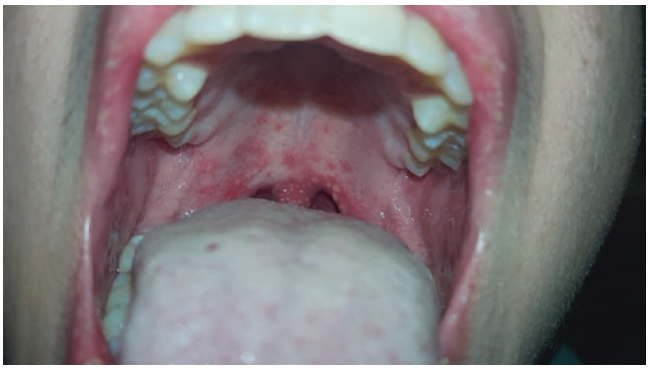


Fig. 12.10 Herpangina manifesting as yellow-tan vesicular lesions of the posterior soft palate and uvula. (Courtesy of Dr. Kathleen Schultz)

Human Papillomavirus-Related Lesions

Human papillomavirus (HPV) comprises a large group of double-stranded DNA viruses that belong to the Papillomaviridae family. HPV demonstrates a tropism for squamous epithelium and may produce infection of the skin or mucosa. Mucosal involvement has been noted to most frequently involve the anogenital region and upper aerodigestive tract [27]. Over 130 different types of HPV have been identified, and they are broadly categorized as low risk or high risk based on their ability to induce malignant changes. HPV subtypes 6 and 11 are some of the more frequently encountered low-risk strains of HPV, while subtypes 16, 18, 31, and 33 are the more commonly seen high-risk HPV strains. HPV may cause a variety of benign, premalignant, and malignant conditions; however most patients infected with HPV are asymptomatic and lack any clinically evident disease [28].

Proposed modes of transmission for oral HPV infection include both sexual and nonsexual person-to-person contact, autoinoculation, perinatal transmission, breast feeding, transfer from contaminated objects, and salivary transfer. Male gender, increased number of sexual partners, tobacco use, and diseases such as human immunodeficiency virus (HIV) are all considered risk factors for the increased preva-

lence of oral HPV infection [29]. This text will focus on some of the more commonly identified HPV-related lesions of the oral cavity.

Squamous Papilloma

Squamous papillomas are benign, HPV-induced proliferations of stratified squamous epithelium. Most cases are caused by low-risk HPV subtypes 6 and 11, however, the lesions themselves are typical of low virulence and infectivity rate.

Oral papillomas will typically appear as exophytic sessile or pedunculated masses (Fig. 12.11). Often times, they have a papillary or roughened surface, which has sometimes been described as having "cauliflower" or "wart-like" projections. Lesions may vary in color from pink-red to white depending on the degree of surface keratinization. Most papillomas are small and measure no more than a few millimeters in size. Although any oral mucosal site may be affected, papillomas are most frequently seen involving the soft palate, the tongue, and the lips. Papillomas are treated by simple excision. If the lesion is completely removed, then the risk of recurrence is low. Malignant transformation of squamous papilloma has not been reported [30, 31].

Condyloma Acuminatum

Condyloma acuminatum is an -induced proliferation of stratified squamous epithelium, which may be seen in the anogenital region, oral cavity, or oropharynx. It represents one of the more commonly diagnosed sexually transmitted diseases, and in most cases is caused by low-risk subtypes of HPV such as 6 and 11. In some instances, high-risk strains of HPV such as 16 and 18 have been identified [32]. Identification of a condyloma in a young child may be a sign of sexual abuse. Vertical transmission of condylomas from mothers with genital HPV has also been reported [32].

The clinical appearance of a condyloma is similar to that of a papilloma. Key differences are that it is typically larger in size and may be clustered with other lesions rather than presenting as a solitary entity. Condylomas appear as sessile, pink-colored, exophytic lesions. They often demonstrate short, blunted, papillary surface projections (Fig. 12.12). The most commonly affected oral sites include the labial mucosa,

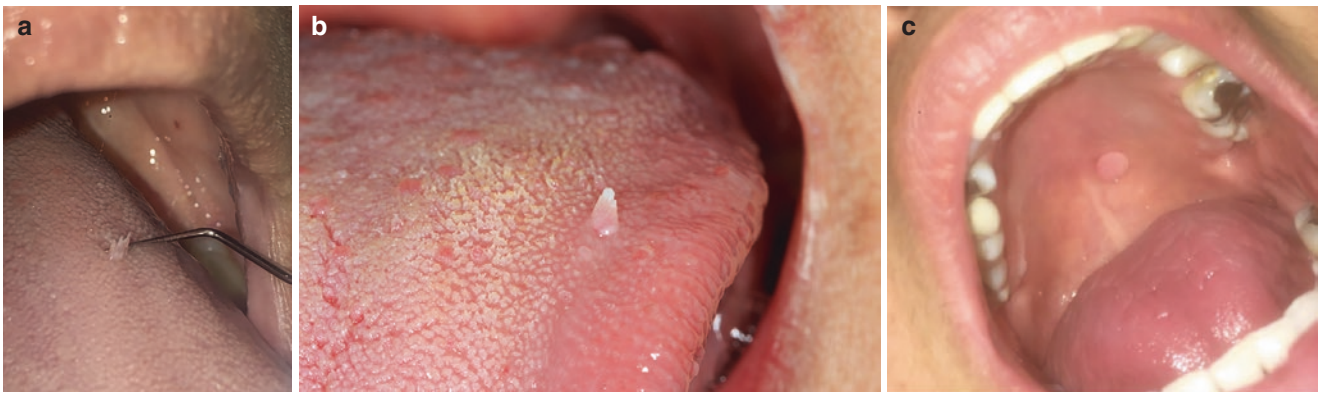


Fig. 12.11 (**a**, **b**) Papillomas of the dorsal tongue appearing as pedunculated, exophytic lesions with frond-like projections. ((**b**) Courtesy of Dr. Michele Bergen). (**c**) Papilloma of the palate presenting as an exophytic, sessile nodule. (Courtesy of Dr. Seth Greenberg)

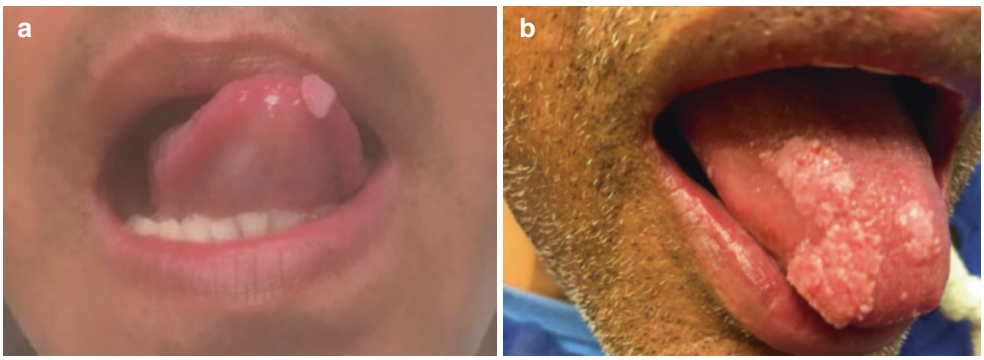


Fig. 12.12 (**a**) Condyloma involving the tip of the tongue. (Courtesy of Dr. Seth Greenberg). (**b**) Condylomata involving the dorsal aspect of the tongue. Note the shortened, blunted surface projections and the clustered nature of the lesions

tongue, and palate, and lesions are typically 1 cm or larger in size. Treatment consists of surgical excision of the lesion.

Heck Disease

Heck disease (HD), also known as **(multi)focal epithelial hyperplasia**, is an HPV-associated condition that results in multiple verrucae of the oral cavity. It is a rare, benign proliferation of the oral mucosa that presents primarily in Eskimo, Native American, and South American populations but is also seen in other ethnic groups. The frequency of this disease varies based on geographic location, ranging from 0.0002 to 35% [33]. The condition is characterized by multiple small, asymptomatic, raised plaques or papules in the oral cavity that are normally pink or whitish in color. These lesions are typically found on the lower lip, tongue, and buccal mucosa, and less commonly on the upper lip, palate, and gingiva (Fig. 12.13). The lesions are painless and tend to disappear spontaneously. This disease affects both sexes and all ages, but has a predilection for children and females, with the female-to-male ratio ranging from 1: 0.4 to 1:1. There is strong evidence that the low-risk subtypes 13 and 32 of HPV are associated with these lesions. There is also an association between HD and an HLA-DR4 (DRB1*0404) allele, which is frequently seen in Native Americans and Latin American populations [33, 34].

Clinically, HD presents as multiple, well-circumscribed, soft, flat-topped papules that vary in color from white to similar to that of the patient's normal mucosa. HD is considered to have two distinct clinical forms: **papulonodular** and **papillomatous**. The papulonodular form is more common and typically has lesions that are pink with smooth surfaces. A bilateral distribution on the labial and buccal mucosa and dorsolateral tongue is a common clinical presentation of this subtype. The papillomatous form usually appears on the masticatory mucosa of the tongue and attached gingiva and is white in color with a rough bumpy surface [35]. Treatment for HD is not always necessary if the lesions are asymptomatic because they will disappear spontaneously over time and do not have malignant potential. Surgical excision may be indicated for lesions that interfere with occlusion or are continuously traumatized. Other treatments include cryotherapy, laser ablation, topical application of 25% podophyllin resin, and vitamin therapy [36].

Oropharyngeal Carcinoma

Although many epidemiological studies will combine data on oral cavity cancer and oropharyngeal carcinoma into a single category, malignancies at these sites are distinct with regard to their etiology and location predilection. Oropharyngeal carcinoma, by definition, is a malignant epithelial neoplasm that may involve the soft palate, base of the tongue, tonsillar region, and posterior pharyngeal wall [37]. Of these locations, the tonsillar region is the most commonly affected subsite. HPV, which is rarely implicated in cases of oral cavity malignancies, represents a major etiologic factor in oropharyngeal carcinoma. To this end, the majority of oropharyngeal carcinomas in the United States are caused by HPV, and HPV-induced oropharyngeal carcinomas are predicted to outpace the development of anogenital region carcinomas by the year 2030 [38].

Due to their location, oropharyngeal carcinomas are often difficult to detect on intraoral examination until the lesion reaches a considerable size. Even then, the component of the tumor that is visible may represent only a small fragment of a much larger lesion (Fig. 12.14). Patients with oropharyngeal carcinoma will present with non-specific symptoms such as a persistent sore throat, difficulty swallowing, and pain in swallowing [37]. Metastases of HPV-associated oropharyngeal carcinomas are relatively common, and in some instances may be detected before a primary tumor has been identified. These metastases are frequently present as cystic lesions involving the anterior lateral neck clinically resembling a branchial cleft cyst (cervical lymphoepithelial cyst) [39]. As a general rule, metastatic oropharyngeal carcinoma should be included in the differential diagnosis of a cystic lateral neck mass occurring in any individual over the age of

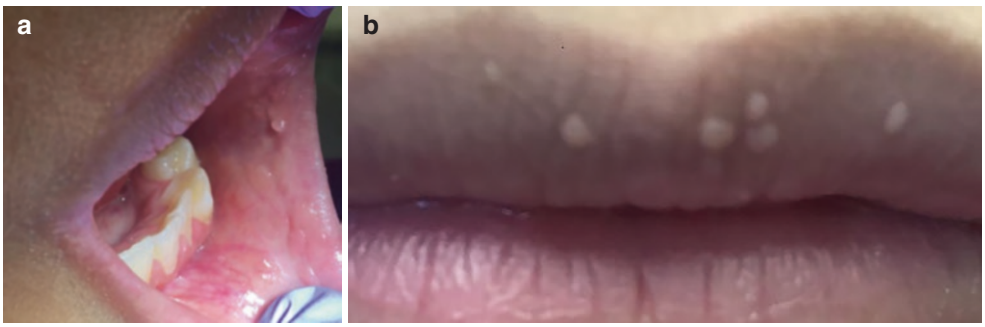


Fig. 12.13 Heck disease (multifocal epithelial hyperplasia) involving the buccal mucosa (**a**) and the labial mucosa (**b**)

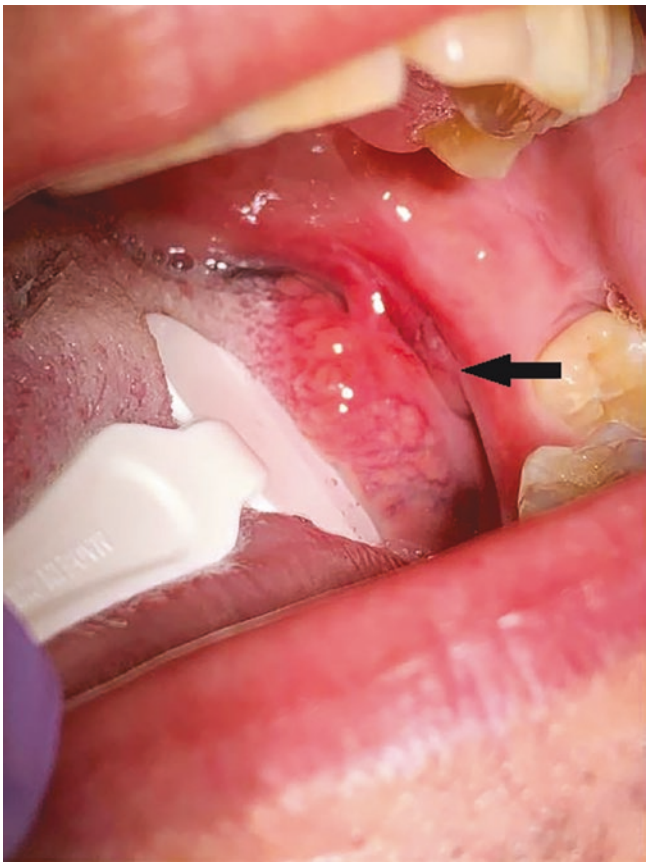


Fig. 12.14 Oropharyngeal carcinoma can be challenging to detect on intraoral examination. The component of the lesion that is visibly apparent often represents only a small portion of the larger lesion

40 years. Treatment of HPV-associated oropharyngeal carcinoma consists of radical surgical excision along with chemotherapy and radiation therapy, as needed.

HPV and Vaccination

HPV-induced lesions are preventable via vaccination. In the United States, the Food and Drug Administration has licensed two HPV vaccinations for use [40–42]. Gardasil, which is the more frequently administered of the two, provides protection against HPV subtypes 6, 11, 16, and 18. Cervarix vaccination targets HPV subtypes 16 and 18 only. Both have been shown to be more than 90% effective in preventing HPV-associated malignancies of the anogenital region and oropharynx. The Centers for Disease Control and Prevention recommend that the HPV vaccination be administered to all individuals on their 11th or 12th birthday but can be given as early as age nine. In this age group, it is administered in a two-dose schedule, with the second dose given 6 months to 1 year after the first dose [43].

Measles, Mumps, and Rubella

Measles, mumps, and rubella are examples of viral infections that were prevalent and sometimes lethal historically but have been nearly eradicated due to successful vaccination campaigns. However, as vaccination stringency begins to lessen, these diseases are unfortunately re-appearing in our population. This text will provide a brief discussion of the epidemiological data regarding these viruses, as well as an overview of some of the pertinent clinical features with an emphasis on the head and neck manifestations.

Measles (rubeola) is an infection caused by a virus in the paramyxoviridae family. Prior to vaccination, 90% of the United States population would be infected with measles by the age of 15, and it resulted in approximately 500 deaths per year [44]. Most cases of measles develop in the late winter or spring. There are three stages to the infection, each of which lasts 3 days. During the first 3 days, patients will develop a fever, brassy cough, runny nose, and conjunctivitis. The hallmark oral manifestation of measles, blue-white macules with surrounding erythema referred to as **Koplik spots**, also appear during this initial stage. After the first 3 days, a morbilliform rash will form; the rash first involves the face and later spreads to the trunk and extremities. In the final stage, the fever and rash will subside and patients may experience desquamation of the skin [44, 45].

Mumps is an infection also caused by a virus in the paramyxoviridae family. Similar to measles, it caused widespread disease in the United States prior to vaccination, with approximately 90% of the population affected by the age of 15 [46]. Mumps infection typically occurs in winter or spring, and the main target organs are the exocrine glands of the body. The most common head and neck manifestation is a painful, usually bilateral, swelling of the parotid glands (Fig. 12.15). This has been termed **epidemic parotiditis**, and

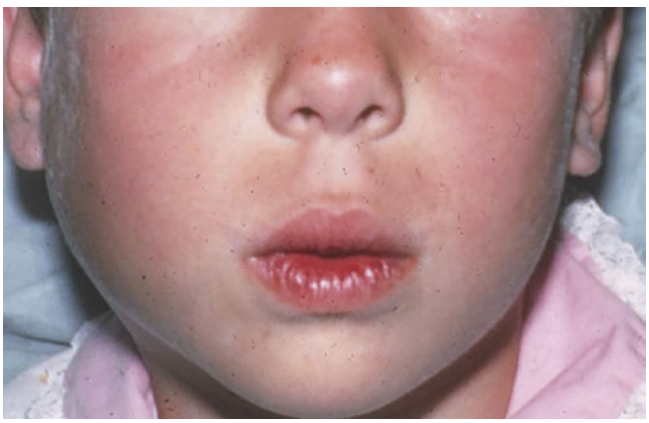


Fig. 12.15 Right parotid swelling in a child with mumps. (Courtesy of Dr. Louis Mandel)

it still represents the most common cause of pediatric-age parotid swellings worldwide [46]. Patients will report pain on chewing or after an activity that leads to increased salivation. Other common clinical findings in mumps include orchitis in males, headache, fever, malaise, and reduced appetite.

Rubella, also referred to as **German measles**, is caused by a virus in the Togavirus family. It is diagnosed most frequently in the winter and early spring. Prior to vaccination efforts, infection would occur in cycles with localized epidemics every 6–9 years, and larger pandemics every decade to 30 years [47]. Many patients who are infected with Rubella are asymptomatic, although individuals may present with nonspecific clinical findings such as fever, fatigue, malaise, decreased appetite, cough, runny nose, and lymphadenopathy. Patients may also develop a body rash that begins in the face and neck region and spreads to the trunk and extremities. This skin rash lasts for approximately 3 days before it resolves, which is why Rubella has sometimes been referred to as **3-day measles**. The oral lesions of Rubella appear as small discrete dark red papules of the soft palate and are termed the **Forchheimer sign**. Rubella is arguably more significant for its effects on the developing fetus than its ability to cause acute infection. Rubella is capable of crossing the placental barrier and inducing birth defects; this is known as **congenital rubella syndrome**. The classic triad of CRS consists of deafness, heart disease, and cataracts. Risk of developing CRS is highest if the mother is infected during the first 12 weeks of pregnancy [47, 48].

COVID-19

Coronaviruses are enveloped, nonsegmented, positive-sense, RNA viruses belonging to the coronaviridae family [49]. Although most coronaviruses cause mild cold or flulike symptoms, two betacoronaviruses (severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus) have resulted in more serious illnesses in 2002 and 2012, respectively [49]. Since December 2019, the novel strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19, has caused a global pandemic [50]. At the time of writing, much is still unknown regarding the full scope of the short, intermediate, and long-term effects of COVID-19 infection. To date, some potential COVID-19-associated oral lesions and complaints include (but may not be limited to) aphthous-like oral ulcerations, strawberry tongue, and dysgeusia (altered taste sensation) [51–53]. As our knowledge base continues to expand, new data may support an association between oral mucosal pathologies and COVID-19 infection.

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) is a single-stranded RNA virus belonging to the retroviridae family. It is responsible for causing **acquired immunodeficiency syndrome (AIDS)**. A detailed discussion of the epidemiology and pathogenesis of HIV/AIDS is beyond the scope of this text. Instead, a brief overview of the general features of the disease will be discussed. Then, the pertinent oral and maxillofacial manifestations of HIV will be reviewed in greater detail.

HIV infection occurs via sexual contact, injection drug use, perinatal exposure, and blood transfusion. In infected individuals, the virus can be detected in most bodily fluids, including serum, blood, saliva, semen, urine, tears, ear secretions, vaginal secretions, and breast milk [54]. The primary target of HIV is the $CD4^+$ T lymphocyte (helper T cell), which leads to a loss of normal immune function [55]. The clinical stages of HIV can be broadly divided into an acute phase, a chronic phase, and AIDS. The acute phase of HIV occurs within the first 6 weeks of exposure to the virus. While many patients may remain asymptomatic during this time, some will develop **acute retroviral syndrome**, a disease process with symptoms resembling infectious mononucleosis [56]. Patients typically have high viral loads and are at increased risk of spreading the infection during this time period. However, due to the lack of specificity of the clinical symptoms, HIV is usually not considered in the differential diagnosis at this time. Following the acute phase of HIV, patients will enter a latent period defined as the chronic phase of infection. This chronic phase can last from months to decades depending on factors such as whether a patient is actively obtaining treatment for HIV. Most patients are asymptomatic during this time period with the exception of a persistent enlargement of lymph nodes referred to as **persistent generalized lymphadenopathy** [57]. Eventually, the immune system will continue to decline and fail to control the virus. This leads to the development of AIDS, which is the final stage of HIV infection. The definition for AIDS is a reduction in the $CD4^+$ T lymphocyte count below 200 cells/mm^3, or the presence of an AIDS-defining illness [58]. In some patients, the onset of AIDS will be heralded by a period of fever, weight loss, gastrointestinal disturbances, candidiasis, shingles, and oral hairy leukoplakia. This is termed the **AIDS-related complex** [58].

Oral Manifestations of HIV

The following sections describe oral lesions, which may be seen in patients with HIV/AIDS. For each oral manifestation, the clinical features, diagnostic criteria, and relevance

to the patient's underlying HIV status will be discussed. It is important to remember that many of these entities can be seen in individuals without HIV/AIDS and are not necessarily indicative of an underlying immunocompromised status. In some patients, immunosuppression may alter the presentation of these lesions when compared to their immune-competent counterparts.

Candidiasis

Oral **candidiasis** will be discussed in greater detail later in this chapter. In the context of HIV, candidiasis marks one of the most commonly identified oral manifestations of the disease and may represent the presenting sign that leads to the initial diagnosis. Four clinical patterns of candidal infection have been described in HIV+ individuals: pseudomembranous, erythematous, hyperplastic, and angular cheilitis [59]. Pseudomembranous candidiasis is defined as white to yellow curd-like lesions that can be wiped off (Fig. 12.16). The underlying mucosa is often erythematous and bleeds easily. Erythematous candidiasis presents as red, non-wipeable plaques of the oral mucosa (Fig. 12.17). Hyperplastic candidiasis appears clinically as a leukoplakia; it is a white, nonremovable plaque or patch (Fig. 12.18). Angular cheilitis is a candida infection involving the bilateral labial commissures and presents as areas of cracking or fissuring (Fig. 12.19). Most cases of candidiasis can be diagnosed clinically; however, a fungal smear or culture can be performed to confirm the diagnosis. Hyperplastic candidiasis often is nonspecific in clinical appearance and requires biopsy for diagnostic confirmation. Erythematous candidiasis will be seen in HIV+ individuals whose $CD4^+$ counts drop below 400 cells/mm^3; pseudomembranous candidiasis will develop in those patients with CD^+ counts below

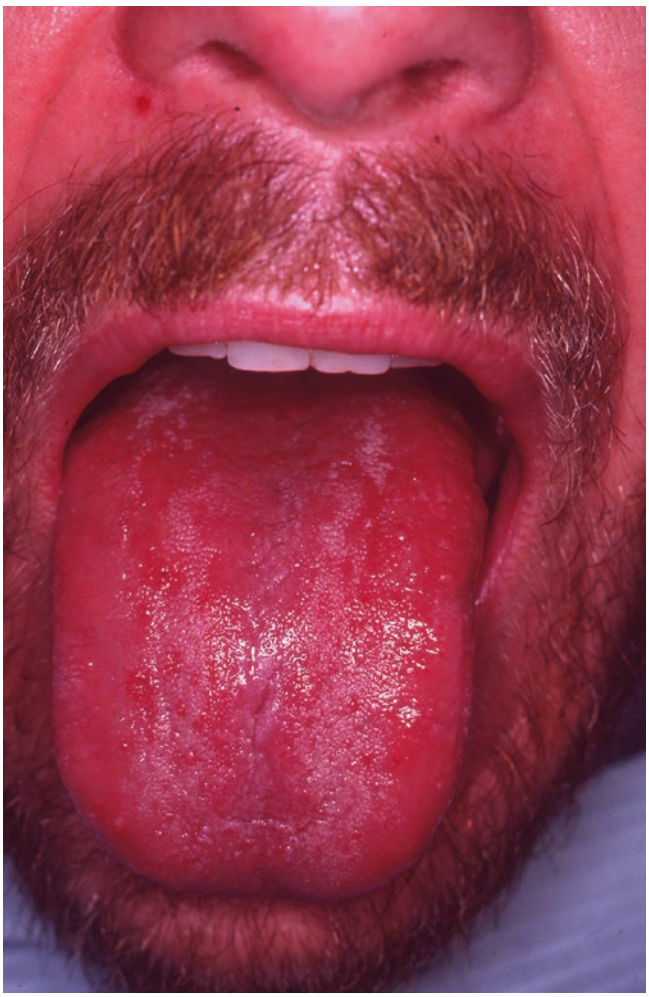


Fig. 12.17 Erythematous candidiasis involving the dorsal tongue. (Courtesy of Dr. Elizabeth Philipone)

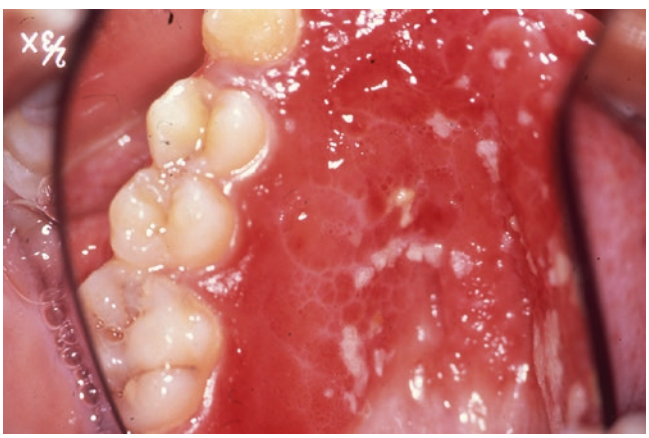


Fig. 12.16 Pseudomembranous candidiasis involving the palate. The curd-like, whitish lesions seen in the image were removable with gauze. (Courtesy of Dr. Elizabeth Philipone)

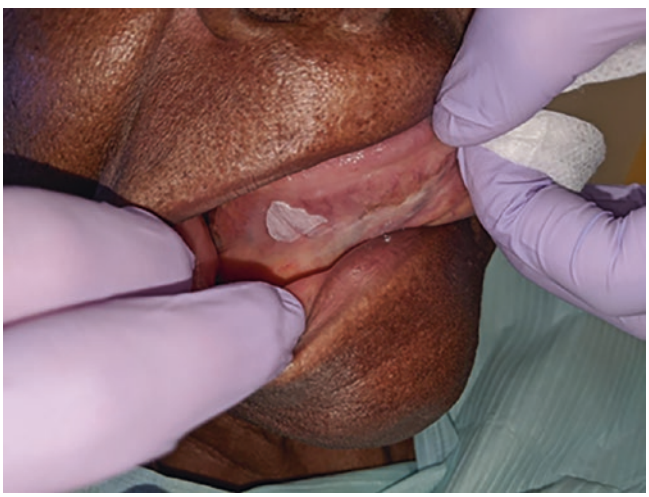


Fig. 12.18 Hyperplastic candidiasis will appear as an idiopathic leukoplakia clinically. Diagnosis can only be rendered on identification of the fungal organisms following tissue biopsy. (Courtesy of Dr. Austin Shackelford)

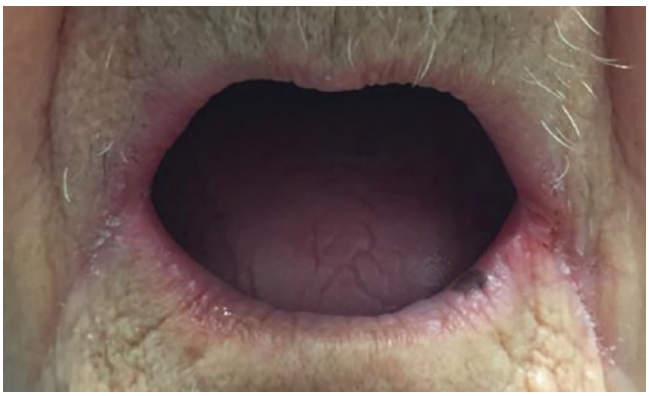


Fig. 12.19 Angular cheilitis. Bilateral cracking and erythema of the labial commissures in an edentulous patient with the collapsed vertical dimension of occlusion. (Courtesy of Dr. Jay Ponto)

200 cells/mm^3. Unlike the treatment of candidiasis in immunocompetent patients, topical agents such as Nystatin are typically ineffective in patients with HIV. Rather, treatment with a systemic antifungal such as fluconazole is recommended [60].

Oral Hairy Leukoplakia

Oral hairy leukoplakia (OHL) is an EBV-associated lesion that may be seen in patients affected with HIV/AIDS. As mentioned earlier in this chapter, OHL presents as a nonremovable white lesion of the oral mucosa, most often involving the lateral tongue (Fig. 12.6). It is nonspecific in its clinical appearance, and a biopsy is required to make the diagnosis of OHL. On microscopic examination, the EBV-infected cells appear as "balloon cells" with abundant cytoplasm and nuclear beading in the upper spinous layer of the epithelium [61]. OHL may be seen in patients with other causes of immunosuppression, such as a history of organ transplant or immune senescence, and diagnosis of OHL in a patient presumed to be immunocompetent should prompt evaluation for possible unidentified causes of immune compromise. Most lesions of OHL are asymptomatic and treatment is not necessarily indicated, although the presence of OHL in a patient known to have HIV/AIDS may be a sign of disease progression and worsening of immune function [61].

Plasmablastic Lymphoma

Patients with HIV/AIDS are at increased risk of developing hematologic malignancies; the category of **non-Hodgkin lymphoma (NHL)** represents the most common malignancy in the HIV/AIDS population in the United States. While many of these cases are diagnosed as diffuse large B cell lymphoma, there is a growing number of HIV/AIDS patients

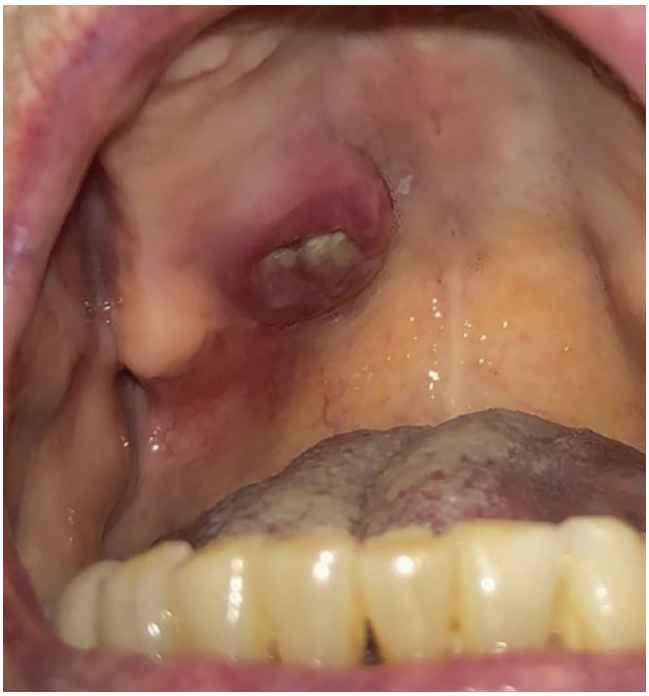


Fig. 12.20 Plasmablastic lymphoma. This patient presented with a large palatal swelling that had become secondarily ulcerated

developing **plasmablastic lymphoma (PBL)**. PBL is a B-cell lymphoma and a subtype of NHL. It has a predilection for the oral cavity and is seen most often in patients with HIV/AIDS (Fig. 12.20). Although the exact pathogenesis of PBL is still not fully understood, EBV is considered to be an important etiologic factor. PBL is an aggressive malignancy most commonly seen in middle-aged males, which can rapidly cause local invasion or spread to extraoral sites, and is generally associated with a poor prognosis [62].

Kaposi Sarcoma

Kaposi sarcoma (KS) is a vascular malignancy caused by HHV8. Although there are four different clinical categories of KS, the majority of patients in the United States who develop it do so in the context of underlying HIV infection. KS currently ranks as the second most common malignancy in people with AIDS in the United States [61]. In cases of AIDS-related KS, patients will present with multiple red to purple-tinged lesions of the skin and/or oral mucosa. The skin lesions have a predilection for the face and lower extremities, while oral lesions tend to involve the palate, gingiva, and tongue (Fig. 12.21). Oral lesions may invade bone leading to mobility of the surrounding teeth. KS is considered an AIDS-defining illness and usually is an indicator of the worsening of a patient's HIV status. Management of KS in individuals with HIV/AIDS is focused on the management of their underlying HIV status through antiretroviral therapy.

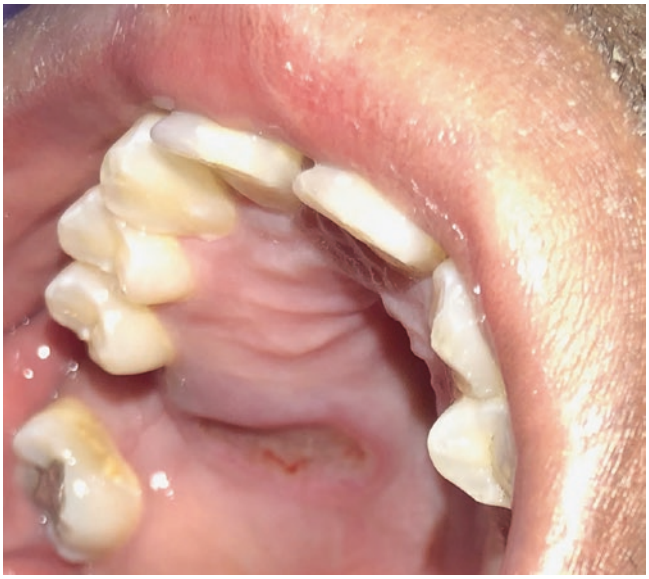


Fig. 12.21 Kaposi sarcoma presenting as an ulcerated palatal lesion with a violaceous border in an HIV+ male

In some cases, anti-neoplastic agents may also be employed [23, 61].

Linear Gingival Erythema

Linear gingival erythema (LGE) is a type of atypical periodontal disease seen in patients with HIV. It presents as a linear band of gingival erythema involving the free gingival margin. It does not correlate well with a patient's overall plaque status and does not respond to standard periodontal intervention predictably. Some have argued that LGE may represent an atypical form of candidiasis observed in patients with HIV [63]. LGE may progress to cause ulceration and necrosis of the interdental papilla without any bone loss or destruction of the periodontium. This condition is referred to as **necrotizing ulcerative gingivitis** [64]. NUG is not unique to patients with HIV and can be seen in several other conditions including stress, recent illness, smoking, poor oral hygiene, poor nutrition, and lack of sleep. In cases where NUG progresses to induce bone loss, the term **necrotizing ulcerative periodontitis** is used. In severe cases, patients with HIV may develop massive tissue destruction extending out from the alveolar processes; this pattern is called **necrotizing ulcerative stomatitis** (Fig. 12.22) [64, 65].

Other Viral Infections Occurring in the Setting of HIV

Members of the human herpesvirus and human papillomavirus families are responsible for a number of commonly

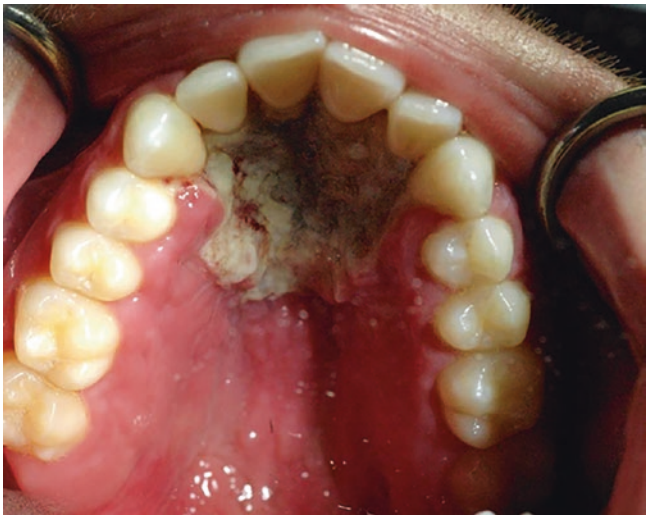


Fig. 12.22 Necrotizing ulcerative stomatitis in a patient with undiagnosed HIV infection

encountered lesions involving the oral cavity. In patients with HIV, these lesions may present atypically or demonstrate delayed healing. Recurrent HSV in patients with HIV increases significantly with reduced $CD4^+$ cell counts. While recurrent HSV in immunocompetent patients is limited to keratinized tissues, in those with HIV, the lesions may affect any oral mucosal site. Similarly, while an immunocompetent individual will clear a recurrent HSV infection in approximately 1–2 weeks, lesions in patients with HIV may persist for months without resolution. To this end, the persistence of HSV infection for more than 1 month in a patient with HIV is considered an AIDS-defining illness [66]. Recurrent VZV infection (shingles) may also be seen in patients with HIV/AIDS. Unlike infection in immunocompetent individuals, shingles in patients with HIV typically occurs at a younger age (less than 40 years old), is associated with increased morbidity and mortality rates, and may involve multiple dermatomes [67].

HPV lesions in patients with HIV/AIDS primarily involve the anogenital and oral regions. Unlike other viral infections which occur in the setting of HIV, the frequency of HPV-induced lesions, such as papillomas and condylomas, may actually increase following the initiation of successful antiretroviral therapy [68]. Although the etiology for this is not fully understood, it is theorized to be the result of **immune reconstitution syndrome**. In immunocompetent individuals, oral squamous papillomas classically appear as solitary, exophytic, frond-like lesions which harbor low levels of HPV subtypes 6 and 11. In patients with HIV/AIDS, the lesions are frequently multiple, flattened to dome-shaped, and may harbor high-risk HPV subtypes such as 16, 18, 31, and 33 (Fig. 12.23). As such, excision of these HPV-related lesions and in situ hybridization studies to detect HPV DNA for subtyping are strongly recommended.

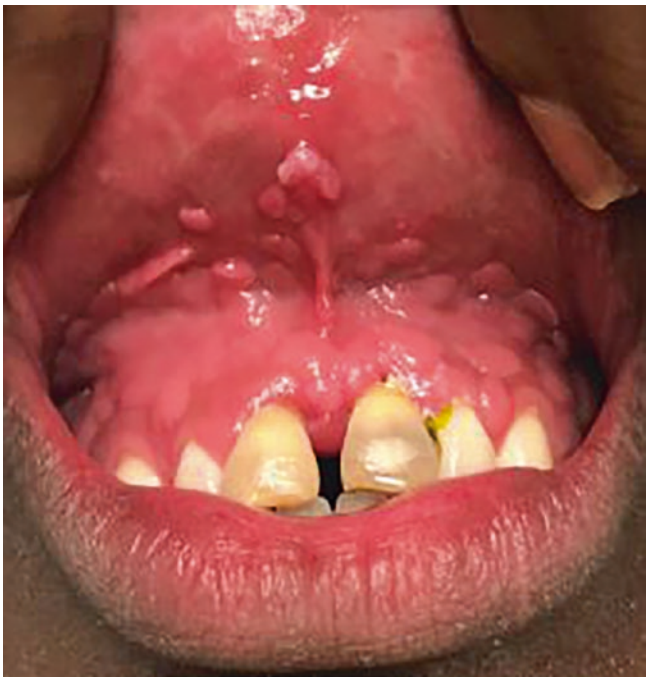


Fig. 12.23 Multiple papillomas in an HIV+ male undergoing antiretroviral therapy

Epithelial dysplasia has also been reported to occur more commonly in HPV-related lesions of the oral cavity involving immunocompromised hosts.

Molluscum contagiosum is an infection that is caused by the molluscum contagiosum virus (MCV), a member of the poxvirus family. Although molluscum infection can be seen in immunocompetent individuals, its presentation differs in those with HIV/AIDS. In both groups of patients, lesions typically appear as waxy, dome-shaped nodules. However, in immunocompetent hosts, molluscum contagiosum is self-limited and localized, while in those with HIV/AIDS, the lesions are much more widespread. The facial skin, which is infrequently affected by MCV, is commonly involved in individuals with HIV/AIDS [69]. As with many other opportunistic infections described, molluscum is best managed by controlling a patient's underlying HIV status.

Salivary Gland Disease

Clinically apparent salivary gland disease can be detected in approximately 5–10% of patients with HIV. In the majority of these cases, the parotid gland is most commonly involved. The two most frequently reported changes to the parotid gland are an increased prevalence of **lymphoepithelial cysts (LEC)** and a phenomenon known as **diffuse infiltrative lymphocytosis syndrome (DILS)**.

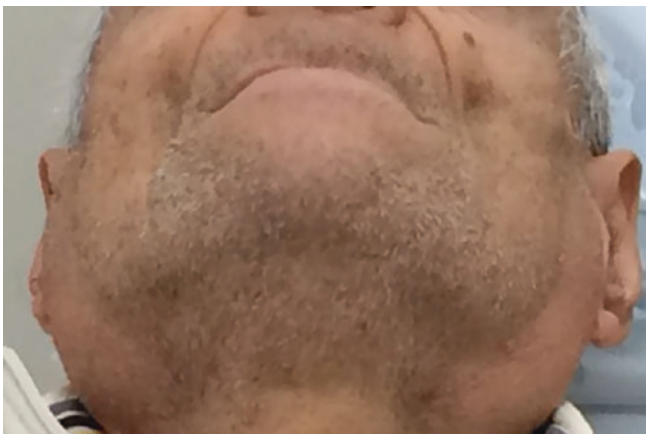


Fig. 12.24 Bilateral facial swellings in a patient with HIV. Imaging studies showed bilateral parotid cysts

LECs are benign, non-neoplastic entities characterized by an epithelial lining composed of stratified squamous epithelium, a lumen containing keratin debris, and a fibrous connective tissue wall containing lymphoid aggregates and occasionally activated germinal centers. Although LECs are commonly seen in immunocompetent patients, the parotid gland is rarely involved. In patients with HIV/AIDS, 5% will demonstrate bilateral parotid involvement with LECs. The pathophysiology of parotid LECs is unclear but two theories exist. In the first, it is hypothesized that HIV-infected cells migrate into the parotid glands, which triggers lymphoid proliferation, inducing metaplastic changes in the salivary ducts. Cysts then form due to ductal obstruction secondary to cellular proliferation. In the second theory, it is argued that HIV-related reactive lymphoproliferation occurs in the lymph nodes of the parotid gland. The parotid glandular epithelium subsequently becomes trapped in normal intraparotid lymph nodes, resulting in cystic enlargement [70]. In either case, patients will present with a painless, frequent bilateral facial swelling and possible cervical lymphadenopathy (Fig. 12.24). Treatment consists of cystic enucleation and drainage, although in some instances patients have been managed conservatively with continued observation and antiretroviral therapy.

DILS is characterized by lymphocytosis of $CD8^+$ T cells; the condition is not limited to the parotid glands and may also involve the lacrimal glands, lungs, liver, kidneys, and muscle and nerve fibers. DILS is seen less frequently when compared to LECs of the parotid; a prevalence of only 3% has been reported in the United States, with some studies showing rates of occurrence of less than 1%. Patients typically present with painless, bilateral facial swellings caused by enlargement of the parotid glands [71]. Effective antiretroviral therapy has been shown to reduce the parotid enlargement caused by DILS.

Squamous Cell Carcinoma

When compared to the general population, patients with HIV are at a twofold risk of developing a malignant neoplasm of the oral cavity. This is likely due both to the increased prevalence of squamous cell carcinoma (SCC) in an immunocompromised host and the use of other known risk factors for SCC, such as tobacco and alcohol, in this population group. While SCC tends to affect patients with HIV/AIDS at a younger age when compared to their immunocompetent counterparts, the presentation and management are otherwise similar. The lateral border of the tongue and the floor of the mouth are the most commonly affected sites, and treatment consists of surgical resection, radiation, and chemotherapy [72]. Patients with HIV tend to have a poorer prognosis due to advanced disease.

Candidiasis

*Candida albicans i*s a yeast-like fungal organism responsible for causing a superficial fungal infection referred to as **candidiasis**. Candida does not represent an invasive fungus but rather is considered part of the normal oral flora that may overgrow and cause superficial infection in some patients. In some larger studies, approximately 30–50% of the population harbors candida organisms at any given time without evidence of clinical disease [73]. Candida exists in two forms: yeast and hyphae; the yeast form is believed to be relatively harmless, with the hyphal form responsible for causing disease. The risk for infection with candidiasis is based on several factors including the immune status of the patient, the oral mucosal environment, and the pathogenicity of the candida strain. Oral candidiasis may exhibit a wide range of clinical presentations. It represents one of the most commonly diagnosed, and frequently misdiagnosed, oral infections. The following sections will focus on the different forms of oral candidiasis that the healthcare provider may encounter, as well as a discussion of some of their clinical mimics. After these different forms of candidiasis have been reviewed, general information on diagnosis and management of oral candida infections will be provided.

Pseudomembranous Candidiasis

Pseudomembranous candidiasis, also referred to as **thrush**, represents one of the most commonly identified forms of oral candida infection. Patients with pseudomembranous candidiasis demonstrate white to yellow curd-like lesions of the oral mucosa that typically resemble cottage cheese or curdled milk in appearance (Fig. 12.16). They are nonadherent to the oral mucosa and can be removed with gauze. The underlying mucosa will often appear erythematous and may occasionally bleed [74]. Patients with pseudomembranous candidiasis may describe altered taste sensations and complain of a burning or stinging discomfort of the oral mucosa. Lesions typically involve the buccal mucosa, palate, and tongue. Pseudomembranous candidiasis may be induced by changes in a patient's normal oral flora, such as antibiotic use or immunologic problems.

There are many white oral lesions that may superficially resemble pseudomembranous candidiasis and can potentially lead to improper diagnosis. White coated tongue, or white hairy tongue refers to a white coating of variable thickness involving the dorsal aspect of the tongue (Fig. 12.25). It is caused by an overgrowth of filiform papilla; the white coloration of the tongue is attributed to the keratin that the papilla produces. It may be partially removable, and in some cases may appear different colors (yellow, brown, black, etc.) due to the staining of the keratin by chromogenic material in food, beverages, or tobacco products [75]. Care should be given to avoid misdiagnosing white-coated tongue as pseudomembranous candidiasis and inappropriately prescribing antifungal therapy. Similarly, oral manifestations of autoimmune conditions, such as oral lichen planus, mucosal pemphigoid, and pemphigus vulgaris, may be occasionally misdiagnosed as thrush because they can appear as white to mixed red and white lesions causing burning and stinging discomfort. These lesions are not removable, however, and aside from patient subjective complaints do not share many objective clinical features of thrush.

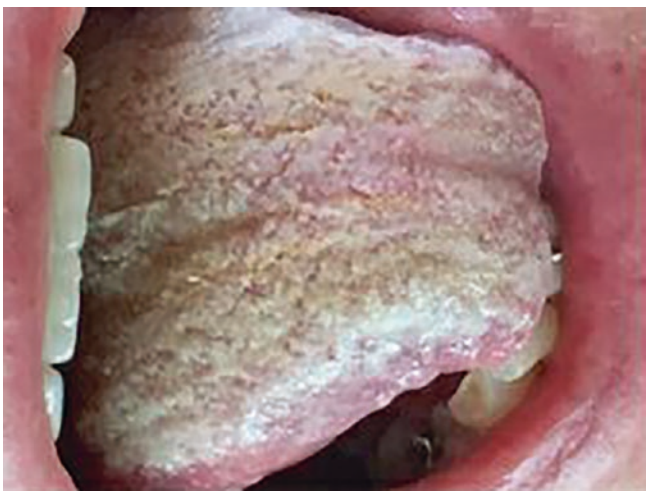


Fig. 12.25 White coated tongue. Often mistaken as thrush, white coated tongue represents an overgrowth of filiform papilla on the dorsal tongue

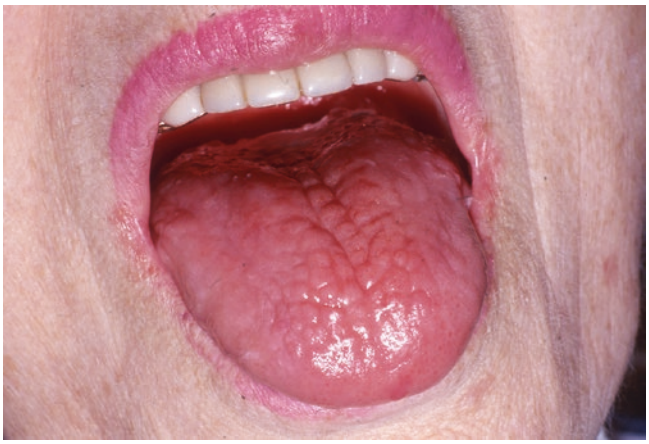


Fig. 12.26 Atrophic glossitis. The dorsal tongue appears bright red and lacks normal surface papilla. (Courtesy of Dr. Elizabeth Philipone)

Erythematous Candidiasis

Erythematous candidiasis is likely the most common form of candidiasis, although it may be overlooked clinically in many patients. Unlike pseudomembranous candidiasis, erythematous candidiasis lacks a white, removable component. Rather, it appears as either a solitary or multiple flat red patch(es) [74] (Fig. 12.17). Some patients will report a burning or stinging discomfort in association with the lesions, while others may be asymptomatic. Within the category of erythematous candidiasis, there are several subclassifications that exist. The term **acute atrophic candidiasis** refers to erythematous candidiasis following a course of antibiotic therapy that has disrupted the normal oral flora. It typically involves the dorsal aspect of the tongue, which appears as red, flat, and "bald" due to the loss of the filiform papilla (Fig. 12.26). **Chronic atrophic candidiasis**, sometimes referred to as **denture stomatitis**, is erythematous candidiasis occurring on the mucosal aspect of a poorly fitting denture or one that a patient wears 24 h a day without removing it. The underlying mucosa will appear bright red and classically the infection occurs in the shape of the overlying denture (Fig. 12.27). In many cases, patients with chronic atrophic candidiasis are asymptomatic. **Median rhomboid glossitis**, also known as **central papillary atrophy**, describes a form of erythematous candidiasis which presents as a square or rhomboid-shaped patch in the mid-dorsal aspect of the tongue (Fig. 12.28). The etiology is unknown, although historically it has been classified as a developmental defect. It has also been reported with increased prevalence in smokers. Most patients are asymptomatic. **Chronic multifocal candidiasis** refers to erythematous candidiasis, which has involved more than one oral mucosal site. A typical example of chronic multifocal candidiasis would be a patient with median rhomboid glossitis who develops a separate lesion of the palate. This is sometimes referred to as a "kissing lesion"

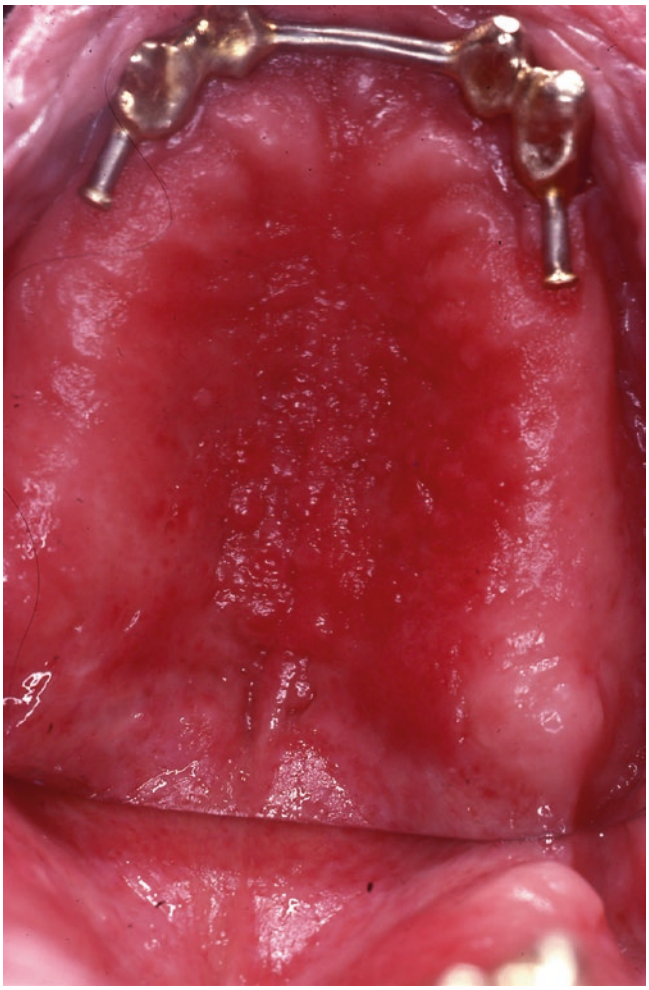


Fig. 12.27 Denture stomatitis. The mucosa appears bright red and resembles the outline of the patient's removable prosthesis (denture). (Courtesy of Dr. Elizabeth Philipone)

because it requires contact between the infected site of the tongue and the palatal mucosa to form.

Angular Cheilitis

Angular cheilitis refers to a candida infection that involves the corners of the mouth. Patients will present with redness, fissuring, and cracking of the bilateral labial commissures, occasionally extending to the adjacent skin (Fig. 12.19). Although it is categorized as a fungal infection, studies have shown that only 20% of cases of angular cheilitis are caused by candida alone, while approximately 60% are due to a combination of candida and superficial infection with the bacteria *Staphylococcus aureus*. The remaining 20% of cases are caused solely by *S. aureus* [74, 76]. Angular cheilitis is seen most often in elderly patients, due to loss of the vertical dimension of occlusion as they age and lose their teeth, leading to accentuated folding at the corners of the mouth where

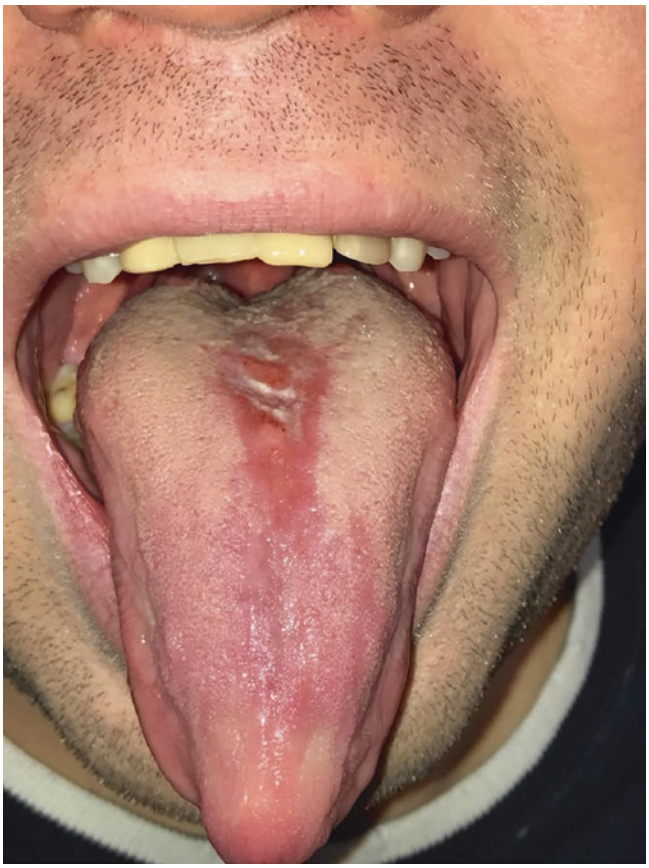


Fig. 12.28 Median rhomboid glossitis. A red, flat, rhomboidal-shaped lesion in the mid dorsal aspect of the tongue

saliva will pool. In some extreme cases of angular cheilitis, the infection will spread to form a ring-like erythema involving the perioral surfaces. This is referred to as **cheilocandidiasis**, and most often occurs due to patient habits, such as chronic lip licking, or inappropriate application of petroleum-based agents (Vaseline) to the area.

Hyperplastic Candidiasis

Hyperplastic candidiasis, also known as **candidal leukoplakia**, is a candida infection of the oral mucosa that presents as an adherent, nonremovable white lesion (Fig. 12.18). Although white in color, hyperplastic candidiasis differs from pseudomembranous candidiasis in that the latter can be wiped off. Hyperplastic candidiasis appears clinically as a leukoplakia, and the diagnosis can only be rendered through biopsy. It is unclear whether hyperplastic candidiasis is simply a fungal infection superimposed on a pre-existing leukoplakic lesion, or if the candida itself induced a leukoplakic change in the affected oral mucosa. Most cases involve the anterior buccal mucosa [77].

Hyperplastic candidiasis may be a component of a group of immunologic disorders; in this setting, it is referred to as **mucocutaneous candidiasis**. Most cases are sporadic, although an autosomal pattern of inheritance has been documented in some families. In most patients, mutations in the autoimmune regulator (AIRE) gene have been detected. These patients will present with endocrine disturbances as well as mucocutaneous candidiasis, and the condition has been referred to as **autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia (APECED) syndrome** [78].

Diagnosis and Treatment

Most forms of oral candidiasis can be diagnosed based on the clinical appearance of the lesion. If the diagnosis is uncertain, a fungal culture or smear of the affected tissues can be performed to test for candida organisms. Hyperplastic candidiasis is the sole exception to this rule; clinically, hyperplastic candidiasis presents as a leukoplakia, and therefore tissue biopsy is required for confirmation of the diagnosis.

Treatment of candidiasis will vary based on the specific form of the infection, but in general most patients respond well to topical antifungal therapies. The two most commonly prescribed topical antifungal therapies are nystatin and clotrimazole. Nystatin is a polyene antifungal most frequently prescribed as a rinse. Patients should be instructed to use it as a swish and spit for the management of a candida infection. Its primary relative contraindication is that formulations may contain high sucrose content, and it can lead to increased caries risk in patients who are xerostomic and prone to tooth decay [79]. Clotrimazole, also known as Mycelex, is an imidazole antifungal typically administered as a troche. It is contraindicated for use in patients who are diabetic [79]. Systemic antifungal therapies may be required in patients who are immune suppressed or in those who have oropharyngeal candidiasis, as a direct application of a rinse or troche to this location can be challenging. Fluconazole (Diflucan) is a triazole antifungal agent and the systemic medication of choice for these patients. Fluconazole is metabolized through the liver and may be contraindicated in patients with liver disease [79].

There is some slight nuance with regard to the treatment of the individual forms of candidiasis. Pseudomembranous candidiasis should respond well to topical antifungal therapies, but fluconazole should be considered if a patient presents with oropharyngeal involvement. Patients with erythematous candidiasis in the absence of a known history of antibiotic usage or xerostomia should be evaluated for vitamin and mineral deficiencies, as atrophic glossitis may be seen in patients with reduced levels of Vitamin B and iron.

In patients with chronic atrophic candidiasis (denture stomatitis), the denture itself should also be soaked in a solution of water and an antifungal agent such as nystatin. Patients with median rhomboid glossitis may only achieve partial resolution of the lesion following antifungal therapy or may experience recurrence of the area when the antifungal therapy is discontinued. Patients with angular cheilitis should be treated with an agent that has both antifungal and antibacterial properties, as a majority of cases are caused both by *C. albicans* and *S. aureus*.

Systemic Fungal Infections

Systemic fungal infections are infrequently seen in the oral cavity. When they occur, they often appear as poorly healing ulcerated lesions, which may clinically resemble squamous cell carcinoma or traumatic ulcerations (Fig. 12.29). These fungal organisms have distinct geographic or host predilections, which may help when trying to arrive at a diagnosis. Due to their relative rarity, the pertinent features of each will be discussed briefly.

Histoplasmosis

Histoplasmosis is the most common systemic fungal infection in the United States and is caused by the organism *Histoplasma capsulatum*. It is endemic to humid areas and caves with soil containing bat or bird droppings. Specifically, it is most commonly found in the Ohio and Mississippi River valleys. Oral lesions occur in patients with disseminated disease and tend to involve the tongue, palate, and buccal mucosa [80].

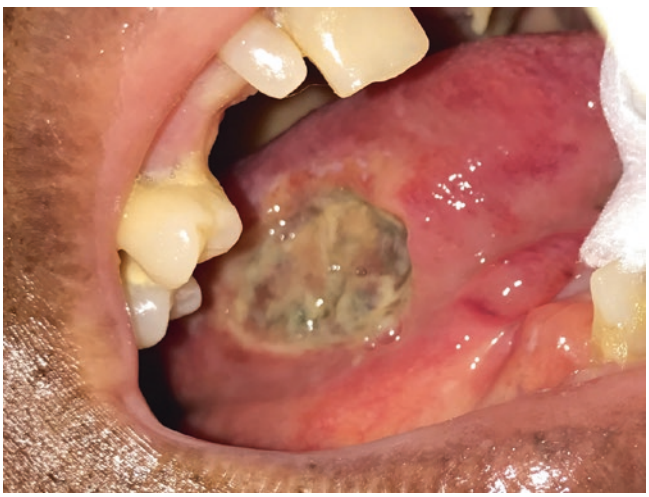


Fig. 12.29 Deep fungal ulceration. A large, tan-gray ulceration of the lateral tongue in a patient with poorly controlled diabetes mellitus. Biopsy showed fungal organisms belonging to the Mucor genera

Blastomycosis

Blastomycosis is caused by the organism *Blastomyces dermatitidis*. It is seen most frequently in the eastern half of the United States, as well as the Great Lakes region including Wisconsin, Minnesota, and parts of Canada. A strong male predilection has been historically reported, but it is unclear if these data are skewed by an association with outdoor activities such as hunting and fishing, which were more commonly male-gender-associated in the past. The organism itself is unique for having a double refractile cell wall [81].

Paracoccidioidomycosis

Paracoccidioidomycosis is caused by the organism *Paracoccidioides brasiliensis*. It is seen in areas of South and Central America and the nine-banded armadillo is a known host of the organism. A strong male predilection has been reported because the female hormone beta estradiol provides protection against infection. Oral lesions may be seen involving the gingiva or palate. The organism itself is described as having a "mariner" or "ship" wheel morphology [82].

Coccidioidomycosis

Coccidioidomycosis is caused by two different fungi, *Coccidioides immitis,* and *Coccidioides posadasii*. Infection is most frequently reported in the southwestern United States and Mexico [83].

Cryptococcus

Cryptococcus is a fungal infection most often caused by the organism *Cryptococcus neoformans*. It is seen in association with pigeon droppings. Although considered an uncommon disease, the incidence has increased substantially in the setting of HIV/AIDS, where it is considered an AIDS-defining illness. Oral lesions are rare, but skin involvement may be seen in up to 15% of patients with disseminated disease. The skin of the head and neck region tends to be affected frequently [84].

Aspergillosis

Aspergillosis is a fungal disease that has both noninvasive and invasive forms. Noninvasive forms are seen more commonly and tend to involve the sinuses. One such presentation is **allergic fungal sinusitis**, in which patients will present with allergy and thickened ("allergic") mucosa involving the

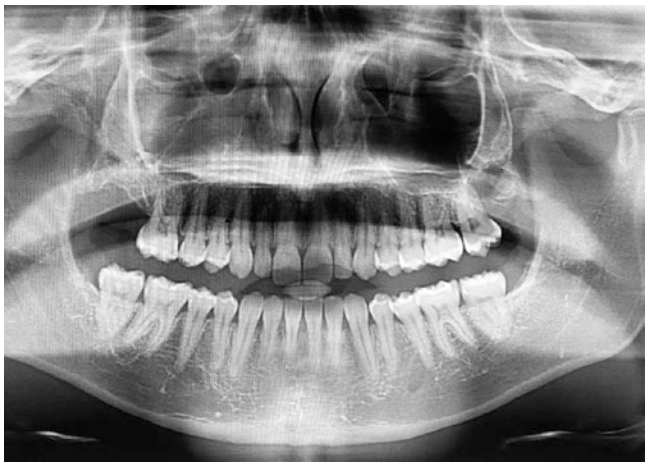


Fig. 12.30 Aspergillosis. Generalized hazy radiopacity of the right maxillary sinus

sinuses, but often without any readily identifiable organisms. Patients may also present with **aspergillomas**, or fungus balls, involving the sinuses. These will appear as somewhat hazy radiopacities of the involved sinuses (Fig. 12.30). These lesions are often discovered incidentally on routine imaging studies, as patients are frequently asymptomatic. Disseminated aspergillosis is an invasive form of disease seen mostly in immunocompromised hosts. Oral involvement is rare but may present as a swelling with a gray tinged hue [85].

Mucormycosis

Mucormycosis is an opportunistic fungal infection caused by organisms belonging to a variety of genera including Mucor, Rhizomucor, and Rhizopus. Its growth is enhanced by iron, and therefore it is seen most often in insulin-dependent diabetics with uncontrolled diabetes who are ketoacidotic and in patients with thalassemia who are being treated with blood transfusions. Mucormycosis has a propensity for the head and neck region and can be locally destructive. If the maxillary sinus is involved, patients may present with a swelling of the maxillary alveolar ridge and palate. This swelling will then ulcerate and form a black eschar. Infection can quickly spread to involve the nasal cavity, orbits, and cranial vault [86].

Summary: A variety of viral and fungal diseases though systemic in nature frequently have oral manifestations. Although an in-depth patient history and physical examination may illicit a diagnosis, further laboratory tests including a biopsy mat be required. Many of the viral conditions are self-limiting and treatment is not required.

References

1. Arduino PG, Porter SR. Herpes simplex virus type 1 infection: overview on relevant clinic-pathological features. J Oral Pathol Med. 2008;37:107–21.
2. Arduino PG, Porter SR. Oral and perioral herpes simplex virus type 1 (HSV-1) infection: review of its management. Oral Dis. 2006;12:254–70.
3. Centers for Disease Control and Prevention. Seroprevalence of herpes simplex virus type 2 among persons aged 14-49 years—United States 2005-2008. Morb Mortal Wkly Rep. 2010;59(15):456–9.
4. Juretic M. Natural history of herpetic infection. Helv Paediatr Acta. 1966;21(4):356–68.
5. Kolokotronis A, Doumas S. Herpes simplex virus infection, with particular reference to the progression and complications of primary herpetic gingivostomatitis. Clin Microbiol Infect. 2006;12:202–11.
6. Nasser M, Fedorowicz Z, Khoshnevisan MH, et al. Acyclovir for treating primary herpetic gingivostomatitis. Cochrane Database Syst Rev. 2008;(4):CD006700.
7. Usatine RP, Tinitigan R. Nongenital herpes simplex virus. Am Fam Physician. 2010;82:1075–82.
8. Woo SB, Challacombe SJ. Management of recurrent oral herpes simplex infections. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;103(1):S12.e1-18.
9. Raborn GW, Grace MGA. Recurrent herpes simplex labialis: selected therapeutic options. J Can Dent Assoc. 2003;69:498–503.
10. Badger GR. Oral signs of chickenpox (varicella): a report of two cases. J Dent Child. 1980;47:349–51.
11. Gershon AA, Gershon MD, Breuer J, et al. Advances in the understanding of the pathogenesis and epidemiology of herpes zoster. J Clin Virol. 2010;48(suppl 1):S2–7.
12. Vasilyeva D, Lee KC, Alex G, et al. Painful palatal lesion in a 90year-old female. Oral Surg Oral Med Oral Pathol Oral Radiol. 2021;131:626.
13. Adour KK. Otological complications of herpes zoster. Ann Neurol. 1994;35:S62–4.
14. Li Q, Chen N, Yang J, et al. Antiviral treatment for preventing postherpetic neuralgia. Cochrane Database Syst Rev. 2009;(2):CD006866.
15. Marin M, Guris D, Chaves SS, et al. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2007;56:1–40.
16. Schmader KE, Levin MJ, Gnann JW, et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. Clin Infect Dis. 2012;54:922–8.
17. Luzuriaga K, Sullivan JL. Infectious mononucleosis. N Engl J Med. 2010;362:1993–2000.
18. Courant P, Sobkov T. Oral manifestations of infectious mononucleosis. J Periodontol. 1979;40:279–83.
19. Will BM, Peters SM, Eisig SB, et al. Gingival ulceration in a 63-year-old lung transplant recipient. Oral Surg Oral Med Oral Pathol Oral Radiol. 2019;127(5):364–71.
20. Al-Hakeem DA, Fedele S, Carlos R, et al. Extranodal NK/T cell lymphoma, nasal type. Oral Oncol. 2007;43:4–14.
21. Xu FH, Xiong D, Xu YF. An epidemiological and molecular study of the relationship between smoking, risk of nasopharyngeal carcinoma, and Epstein-Barr virus activation. J Natl Cancer Inst. 2012;104:1396–410.
22. Bate SL, Dollard SC, Cannon MJ. Cytomegalovirus seroprevalence in the United States: the National Health and Nutrition Examination Surveys, 1988-2004. Clin Infect Dis. 2010;50:1439–47.
23. Fatahzadeh M. Kaposi sarcoma: review and medical management update. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113:2–16.

24. Khetsuriani N, Lamonte-Fowlkes A, Oberst S, et al. Enterovirus surveillance—United States, 1970-2005. MMWR Suveill Summ. 2006;55:1–20.
25. Buchner A. Hand, foot, and mouth disease. Oral Surg Oral Med Oral Pathol. 1976;41:333–7.
26. Steigman AJ, Lipton MM, Braspennickx H. Acute lymphonodular pharyngitis: a newly described condition due to coxsackie A virus. J Pediatr. 1962;61:331–6.
27. Gillison ML, Broutian T, Pickard RKL, et al. Prevalence of oral HPV infection in the United States, 2009-2010. JAMA. 2012;307:693–703.
28. Kreimer AR, Bhatia RK, Messegeur AL, et al. Oral human papillomavirus in healthy individuals: a systematic review of the literature. Sex Transm Dis. 2010;37:386–91.
29. Sanders AE, Slade GD, Patton LL. National prevalence of oral HPV infection and related risk factors in the U.S. adult population. Oral Dis. 2012;18:430–41.
30. Abbey LM, Page DG, Sawyer DR. The clinical and histopathologic features of a series of 464 oral squamous cell papillomas. Oral Surg Oral Med Oral Pathol. 1980;49:419–28.
31. Carneiro TE, Marinho SA, Verli FD, et al. Oral squamous papilloma: clinical, histologic, and immunohistochemical analysis. J Oral Sci. 2009;51:367–72.
32. Dunne EF, Friedman A, Darta SD, et al. Updates on human papillomavirus and genital warts and counseling messages from the 2010 Sexually Transmitted Diseases Treatment Guidelines. Clin Infect Dis. 2012;53(suppl 3):S143–52.
33. Archard HO, Heck JW, Stanley HR. Focal epithelial hyperplasia: an unusual oral mucosal lesion found in Indian children. Oral Surg Oral Med Oral Pathol. 1965;20(2):201–12.
34. García-Corona C, Vega-Memija E, Mosqueda-Taylor A, et al. Association of HLA-DR4 (DRB1*0404) with human papillomavirus infection in patients with focal epithelial hyperplasia. Arch Dermatol. 2004;140(10):1227–31.
35. Said AK, Leao JC, Fedele S, et al. Focal epithelial hyperplasia - an update. J Oral Maxillofac Pathol. 2013;42(6):435–42.
36. Dave AK, Shackelford AJ, Canterbury CR, et al. Focal epithelial hyperplasia (Heck's disease): a case series and review of the literature. J Clin Ped Dent (In Press).
37. Van Dyne EA, Henley SJ, Saraiya M, et al. Trends in human papillomavirus-associated cancers: United States, 1999-2015. MMWR Morb Mortal Wkly Rep. 2018;67:918–24.
38. Tota JE, Best AF, Zumsteg ZS. Evolution of the oropharynx cancer epidemic in the United States: moderation of increasing incidence in younger individuals and shift in the burden to older individuals. J Clin Oncol. 2019;37(18):1538–46.
39. Goldenberg D, Begum S, Westra WH, et al. Cystic lymph node metastasis in patients with head and neck cancer: an HPV-associated phenomenon. Head Neck. 2008;30:898–903.
40. Villa A, Patton LL, Giuliano AR, et al. Summary of the evidence on the safety, efficacy, and effectiveness of human papillomavirus vaccines: umbrella review of systematic reviews. J Am Dent Assoc. 2020;151:245–54.
41. Cutts FT, Franchesi S, Goldie S, et al. Human papillomavirus and HPV vaccines: a review. Bull World Health Organ. 2007;85:719–26.
42. FDA approves nine-valent HPV vaccine for the prevention of certain HPV-related head and neck cancers: Gardasil 9 now approved for the prevention of HPV-related cervical, vaginal, vulvar, anal, oropharyngeal, and other head and neck cancers, 10 July 2020. https://www.ascopost.com/news/june-2020/fda-approves-nine-valent-hpv-vaccine-for-the-prevention-of-certain-hpv-related-head-and-neck-cancers/.
43. Centers for Disease Control and Prevention. You Call The Shots: web-based training course. https://www.cdc.gov/vaccines/ed/youcalltheshots.html.
44. Centers for Disease Control and Prevention. Measles—United States, 2011. MMWR Morb Mortal Wkly Rep. 2012;61:253–7.
45. Koplik H. The diagnosis of the invasion of measles from a study of the exanthema as it appears on the buccal mucosa membrane. Arch Pediatr. 1896;13:918–22.
46. Hviid A, Rubin S, Muhlemann K. Mumps. Lancet. 2008;371:932–44.
47. Centers for Disease Control and Prevention. Elimination of rubella and congenital rubella syndrome—United States, 1969-2004. MMWR Morb Mortal Wkly Rep. 2005;54:279–82.
48. Centers for Disease Control and Prevention. Progress toward control and prevention of congenital rubella syndrome—worldwide, 2009. MMWR Morb Mortal Wkly Rep. 2010;59:1307–10.
49. Weiss SR, Navas-Martin S. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. Microbiol Mol Biol Rev. 2005;69:635–64.
50. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.
51. Brandão TB, Gueiros LA, Melo TS, et al. Oral lesions in patients with SARS-CoV-2 infection: could the oral cavity be a target organ? Oral Surg Oral Med Oral Pathol Oral Radiol. 2021;131:e45.
52. Halepas S, Lee KC, Myers A, et al. Oral manifestations of COVID-19 related multi-system inflammatory syndrome in children: a review of 47 pediatric patients. J Am Dent Assoc. 2021;152(3):202–8.
53. Lozada-Nur F, Chainani-Wu N, Fortuna G, et al. Dysgeusia in COVID-19: possible mechanisms and implications. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020;130(3):344–6.
54. Centers for Disease Control and Prevention. HIV surveillance—United States, 1981-2008. MMWR Morb Mortal Wkly Rep. 2011;60:689–93.
55. Voldberding P, Greene W, Lange JMA, et al. Sande's HIV/AIDS medicine: medical management of AIDS 2013. 2nd ed. Philadelphia: Elsevier/Saunders; 2012.
56. Macneal RJ, Dinulos JGH. Acute retroviral syndrome. Dermatol Clin. 2006;24(4):431–8.
57. Abrams DI, Kaplan LD, McGrath MS, et al. AIDS-related benign lymphadenopathy and malignant lymphoma: clinical aspects and virologic interactions. AIDS Res. 1986;2(Suppl 1):S131–40.
58. Waymack JR, Sundareshan V. StatPearls: acquired immune deficiency syndrome. Treasure Island: StatPearls Publishing; 2021.
59. Egusa H, Soysa NS, Ellepola A, et al. Oral candidosis in HIV-infected patients. Curr HIV Res. 2008;6:485–9.
60. Thompson GR, Patel PK, Kirkpatrick WR, et al. Oropharyngeal candidiasis in the era of antiretroviral therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;109:488–95.
61. Webster-Cyriaque J, Duus K, Cooper C, et al. Oral EBV and KSHV infection in HIV. Adv Dent Res. 2006;19:91–5.
62. Lopez A, Abrisqueta P. Plasmablastic lymphoma: current perspectives. Blood Lymphat Cancer. 2018;4(8):63–70.
63. Hofer D, Hammerle CH, Grassi M, et al. Long-term results of supportive periodontal therapy (SPT) in HIV-seropositive and HIV-seronegative individuals. J Clin Periodontol. 2002;29:630–7.
64. Horning GM, Cohen ME. Necrotizing ulcerative gingivitis, periodontitis, and stomatitis: clinical staging and predisposing factors. J Periodontol. 1995;66:990–8.
65. Peters SM, Heinz MJ, Koslovsky DA, et al. Necrotizing ulcerative stomatitis as initial presentation of undiagnosed HIV infection: a case report and review of literature. J Oral Maxillo Fac Surg Med Pathol. 2017;29(6):570–4.
66. Flaitz CM, Nichols CM, Hicks MJ. Herpes viridae-associated persistent mucocutaneous ulcers in acquired immunodeficiency syndrome: a clinicopathologic study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1996;81:433–41.

67. Blank LJ, Polydefkis MJ, Moore RD, et al. Herpes zoster among persons living with HIV in the current antiretroviral therapy era. J Acquir Immune Defic Syndr. 2012;61:203–7.
68. Cameron JE, Hagensee ME. Oral HPV complications in HIV-infected patients. Curr HIV/AIDS Rep. 2008;5:126–31.
69. Fornatora ML, Reich RF, Gray RG, et al. Intraoral molluscum contagiosum: a report of a case and a review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001;92:318–20.
70. Shivhare P, Shankarnarayan L, Jambunath U. Benign lymphoepithelial cysts of parotid and submandibular glands in a HIV-positive patient. J Oral Maxillofac Pathol. 2015;19(1):107.
71. Mandel L, Kim D, Uy C. Parotid gland swellings in HIV diffuse infiltrative CD8 lymphocytosis syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;85:565–8.
72. Butt FMA, Chindia ML, Rana F. Oral squamous cell carcinoma in human immunodeficiency virus positive patients: clinicopathological audit. J Laryngol Otol. 2012;126:276–8.
73. Arendoff TM, Walker DM. The prevalence and intra-oral distribution of *Candida albicans* in man. Arch Oral Biol. 1980;25:1–10.
74. Holmstrup P, Axell T. Classification and clinical manifestations of oral yeast infections. Acta Odontol Scand. 1990;48:57–9.
75. Funahara M, Yanamoto S, Soutome S, et al. Clinical observation of tongue coating of perioperative patients: factors related to the number of bacteria on the tongue before and after surgery. BMC Oral Health. 2018;18:223.
76. Ohman SC, Dahlen G, Moller A, et al. Angular cheilitis: a clinical and microbial study. J Oral Pathol. 1986;15:213–7.
77. Sitheeque MAM, Samaranayake LP. Chronic hyperplastic candidosis/candidiasis (candidal leukoplakia). Crit Rev Oral Biol Med. 2003;14:253–67.
78. Kisand K, Wolff ASB, Podkrajsek KT, et al. Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. J Exp Med. 2010;207:299–308.
79. Thompson GR, Cadena J, Patterson TF. Overview of antifungal agents. Clin Chest Med. 2009;30:203–15.
80. Kauffman CA. Histoplasmosis. Clin Chest Med. 2009;30:217–25.
81. Bradsher RW, Chapman SW, Pappas PG. Blastomycosis. Infect Dis Clin N Am. 2003;17:21–40.
82. Ameen M, Talhari C, Talhari S. Advances in paracoccidioidomycosis. Clin Exp Dermatol. 2009;35:576–80.
83. DiCaudo DJ. Coccidioidomycosis: a review and update. J Am Acad Dermatol. 2006;55:929–42.
84. Li SS, Mody CH. Cryptococcus. Proc Am Thorac Soc. 2010;7:186–96.
85. Segal BH. Aspergillosis. N Engl J Med. 2009;360:1870–84.
86. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005;41:634–53.

Sinusitis

13

Derek Groskreutz and Danielle Bottalico

Introduction

Sinusitis is a heterogeneous group of diseases characterized by inflammation of the mucosal lining of the paranasal sinuses. It is one of the most common reasons for physician visits in the United States and it is one of the most frequent reasons for the prescription of antibiotics. Understandably, sinusitis has a substantial economic impact with epidemiologists reporting 73 million restricted workdays and $2.4 billion in medical spending in a 1-year period [1].

Sinusitis can be caused by allergens, irritants, bacteria, viruses, and fungi. The pathophysiology is complex and often involves a bidirectional interplay between a variety of both host and environmental factors. The specific factors involved, both direct and indirect, determine the time course, severity, presentation, potential complications, and treatment approach. The following chapter will delineate some of the most common forms of sinusitis, including acute sinusitis, chronic sinusitis, odontogenic sinusitis, and fungal sinusitis. Each classification of the disease will be defined, followed by an elucidation of the biologic, genetic, and molecular elements comprising its etiologic and pathophysiologic mechanisms. Subsequently, methods and guidelines for diagnosis and both medical and surgical treatment will be described.

D. Groskreutz
Frank H. Netter MD School of Medicine at Quinnipiac University, North Haven, CT, USA
e-mail: derek.groskreutz@quinnipiac.edu

D. Bottalico (✉)
Department of Otolaryngology - Head and Neck Surgery, Albert Einstein College of Medicine, Montefiore Medical Center, Medical Arts Pavilion, Bronx, NY, USA
e-mail: Dbottali@montefiore.org

Acute Sinusitis

Definition

Acute sinusitis is classified based on symptoms and objective evidence of inflammation with a time course of less than 4 weeks [2]. The diagnosis is clinical with the most classic and sensitive symptoms including purulent nasal drainage, nasal obstruction, and facial pressure and pain. Additional symptoms can include headache, aching teeth, halitosis, and fever. The presence of fever over 102 °F is likely associated with a bacterial etiology [3]. Additionally, persistence of symptoms for longer than 10 days or exacerbation of symptoms after a brief period of improvement also indicates a probable bacterial infection. Acute sinusitis caused by viruses is typically self-limited and resolves within three to 5 days.

Pathophysiology

The pathophysiology of sinusitis is best understood by highlighting normal sinus physiology. The sinuses serve to filter antigens from entering the nasal cavities. This function is primarily maintained by three elements: mucus secretion, functioning cilia, and a patent sinus ostia. These three elements function together to filter and limit the entrance of antigens. Mucus secreted by the sinus mucosa traps antigens and is propelled via the motile activity of the cilia, sweeping the mucus and antigen through the sinus ostia where it can be drained into the nasopharynx (Fig. 13.1). Dysfunction in any of these three elements can increase the risk of infection and sinusitis.

The layer of mucus produced by the sinus mucosa contains enzymes, lysozymes, and immunoglobulins. Thus, a deficiency in these components can decrease the immune response to potential infection. Additionally, qualitative changes in mucus viscosity can diminish the ability of cilia to clear mucus, allowing for a buildup of antigens or microorganisms.

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_13

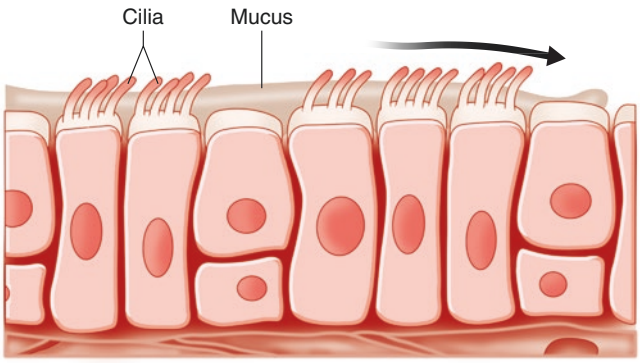


Fig. 13.1 Functional mucosal trapping and cilia motility

Similarly, dysfunction in cilia motility can also lead to mucus and antigen accumulation, increasing the likelihood of subsequent infection. Goblet cell metaplasia, allergens, pollutants, and direct viral cytotoxic effects have been linked to impaired cilia motility, thereby diminishing the ability to clear mucus and antigens.

Even with adequate mucus and functional cilia, a small or obstructed sinus ostium can limit drainage into the nasopharynx and predispose the sinus to obstruction. Moreover, regardless of where sinus dysfunction occurs, acute sinusitis occurs when the sinus is unable to effectively clear microorganisms and antigens, resulting in an inflammatory state.

Diagnosis

The diagnosis of acute sinusitis is clinical. Major and minor criteria have been described to comprise diagnostic criteria for acute sinusitis. Major criteria include facial pain, nasal congestion or discharge, diminished sense of smell, purulent drainage on anterior rhinoscopy, and fever. Minor criteria include headache, halitosis, fatigue, tooth pain, cough, and ear pain. A diagnosis of acute sinusitis can be made with the presence of two major criteria or with one major and two minor criteria. A positive diagnosis, for example, could therefore be made in a patient presenting with 2 weeks of purulent discharge and facial pain (two major symptoms) or in a patient presenting with 2 weeks of nasal congestion, ear pain, and headache (one major and two minor symptoms) [2].

Treatment

Medical

Intranasal Steroids

The use of intranasal steroids to treat acute sinusitis aims to reduce inflammation of both the sinus mucosa and ostia, subsequently promoting mucus clearance. Mometasone, fluticasone, flunisolide, and budesonide are all effective and recommended as standalone treatments for viral etiologies. If the etiology is thought to be bacterial, intranasal steroids should be combined with antibiotics [4].

Oral Steroids

Oral steroids are not effective as a monotherapy for acute sinusitis. When oral steroids are combined with antibiotics; however, there may be beneficial symptomatic relief. It is important to advise the patient of possible adverse effects such as nausea, vomiting, and gastric distress [4].

Antibiotics

Antibiotics are the primary treatment for acute bacterial sinusitis. Recent studies demonstrate the clinical benefit of antibiotics when compared to placebo. Antibiotics are associated with higher cure and symptom improvement at up to 15 days. However, there is a paucity in the literature regarding which patients will benefit more from antibiotics compared to others. In fact, the American Academy of Otolaryngology Guidelines currently considers antibiotics optional unless symptoms persist for more than 7 days or symptoms worsen within 48–72 h [2].

Amoxicillin with clavulanate is now considered first-line drug therapy. The use of clavulanate is a clinical decision based on the likelihood of B-lactam resistance as well as comorbidity and severity of infection. In patients with an allergy to penicillin or infection refractory to amoxicillin, doxycycline, respiratory fluoroquinolones, or clindamycin and a third-generation oral cephalosporin can be used. Antibiotics are given for 5–7 days. If symptoms fail to improve after an antibiotic course, the choice of drug should be changed [5].

Antihistamines

Treating acute sinusitis with antihistamines can decrease nasal secretions and sneezing, but has otherwise been determined to have questionable or unproven efficacy. Antihistamines should therefore only be used in patients with concomitant allergic exacerbation for mild symptomatic relief [6].

Surgery

Acute sinusitis is treated medically in the majority of patients. In extreme cases, surgery can be used to remove the infection at its source or to manually remove the obstruction to mucociliary clearance (Fig. 13.2). Endoscopic sinus surgery can be considered when acute sinusitis is complicated by infection that spreads to the orbit leading to abscess formation, vision changes, or failure to respond to antibiotic therapy after 72 h [7].

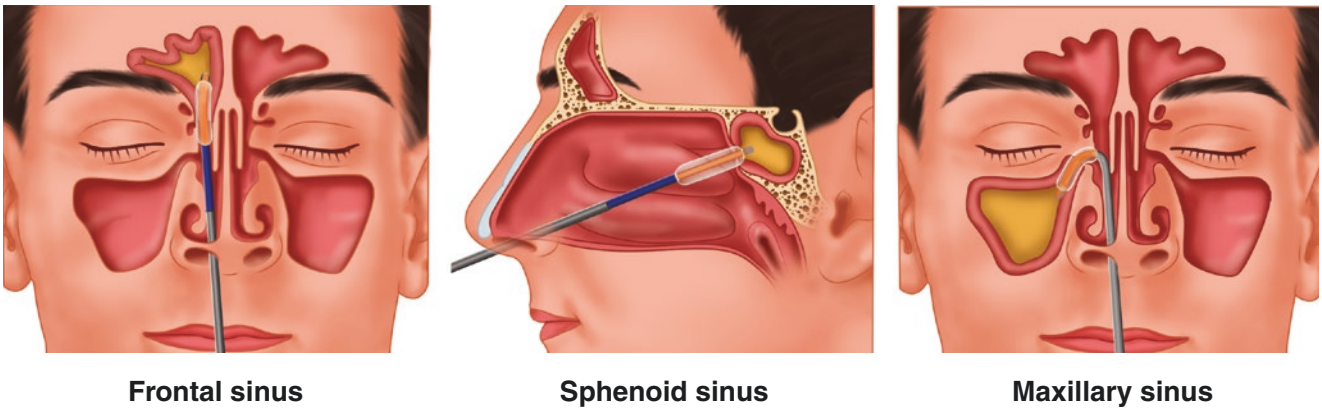


Fig. 13.2 Surgical removal of sinus obstruction

Chronic Sinusitis

Definition

Chronic sinusitis is also a clinical diagnosis with the duration of symptoms lasting 12 or more weeks [2]. For the purpose of this chapter, chronic sinusitis is discussed as a single entity. It should be noted, however, that as a disease, it is currently separated into three categories: chronic sinusitis with nasal polyps, chronic sinusitis without nasal polyps, and recurrent episodes of acute sinusitis.

Pathophysiology

The pathophysiology of chronic sinusitis is still being researched. With that said, a combination of both host and environmental factors likely plays important roles.

Environmental Etiologies

Superantigens

One theory regarding the etiology of chronic sinusitis involves the production of superantigen exotoxins by *Staphylococcus* within the nasal cavity [8]. The subsequent localized inflammation can result in polyp formation within nasal mucosa. Polyps often develop at the sinus ostia where they can obstruct nasopharyngeal drainage. Once mucosal remodeling occurs, the presence of polyps makes it more difficult for the body to clear infection, increasing the disease time course and the chance of recurrence.

External Disruption of Physiologic Nasal Flora

In recent decades, researchers have demonstrated that disruptions of the natural microbiome in the gastrointestinal tract and skin can give rise to chronic inflammation by facilitating the proliferation of pathogenic bacteria whose growth was previously suppressed by a variety of concomitant species. It has therefore been suggested that external modifications of the nasal microbiome by antibiotics or viruses may play a role in bacterial pathogenesis of certain cases of chronic sinusitis [9]. Thus, chronic sinusitis is likely to occur when the bacterial invasion is exacerbated by, and secondary to, the destruction of the natural flora within the nasal cavity which serves to compete with or limit bacterial expansion.

Host Factors

Eicosanoids

Various cell types are capable of metabolizing arachidonic acid into signaling eicosanoids. Dysfunction in this pathway that produces an imbalance in pro-inflammatory leukotrienes and anti-inflammatory prostaglandins has been associated with polyp formation found in aspirin sensitivity and in nasal polyps found in some cases of chronic sinusitis [8].

Immune Barrier

Microorganisms often implicated in chronic sinusitis, such as *Staphylococcus* and various fungi, are also considered normal, commensal inhabitants of healthy epithelium. It is therefore plausible that the development of chronic sinusitis caused by these organisms may derive from a diminished host tolerance [10]. Altered mechanical barriers as well as immunodeficiency are both potential examples of how the sinus mucosa can become overwhelmed by otherwise benign antigens.

Theories implicating the immune barrier are supported with various examples of genetic disorders and the increased prevalence of chronic sinusitis associated with them. Even subclinical cases of patients with cystic fibrosis, for example, demonstrate a higher prevalence of chronic sinusitis both with and without polyps, due to genetic defects in the transmembrane conductance channels and increased mucous viscosity. Likewise, inherited dysfunction of cilial motility in primary ciliary dyskinesia produces similar results.

Chronic sinusitis is a complex disease with multifactorial etiology. These etiologic factors coupled with mediating factors determine the time course, severity, presentation, and sensitivity to treatment. Further research is required to elucidate the specific roles and contributory extent of both environmental and host factors. While some of the hypotheses surrounding the pathophysiology of chronic sinusitis involve the same previously mentioned components noted in acute sinusitis, the theories mentioned here tend to involve persistent, intrinsic disruptions at the genetic or molecular level that are more likely to produce persistent or recurrent symptoms [10].

Diagnosis

While the diagnosis of chronic sinusitis also relies on clinical criteria, objective evidence such as imaging is also involved. Criteria for diagnosis require at least two of the following symptoms: nasal obstruction, nasal drainage, facial pain, and altered sense of smell [2]. In addition to symptomatic criteria, objective evidence of chronic sinusitis on physical exam (such as purulent drainage, edema, or polyps in the middle meatus) or on imaging (such as sinus computed tomography) is needed. Imaging should be obtained after a physical exam and only if the symptomatic criteria are met.

Treatment

Treatment of chronic sinusitis includes both medical and surgical options. Current guidelines suggest confirmation of the presence or absence of nasal polyps, testing for allergy and asthma, and screening for immune dysfunction before beginning therapy.

Medical

Nasal Irrigation

After confirming the presence or absence of nasal polyps, guidelines call for low-pressure, high-volume isotonic saline irrigation for symptom reduction. There is no evidence to support the efficacy of isotonic versus hypertonic solutions, though hypertonic is more likely to produce mucosal irritation and patient discomfort [11].

Intranasal Steroids

Topical steroids are considered effective in decreasing inflammation and there can alleviate symptoms of chronic sinusitis [12]. Moreover, decreasing inflammation can improve the endoscopic visibility of the sinus. There is minimal evidence that intranasal steroids may be more effective when polyps are present [13]. Nevertheless, intranasal steroid spray is considered first-line treatment in conjunction with isotonic saline nasal irrigation [2].

Oral Steroids

Oral steroids can be used for acute symptomatic relief in patients with chronic sinusitis with polyps presenting with severe symptoms, already being managed with nasal irrigation and intranasal steroids [2].

Antibiotics

Macrolides have both antibacterial and anti-inflammatory properties. Therefore, they are often used in the treatment of chronic sinusitis to both clear infection and decrease the size of nasal polyps [14]. However, there is no sound evidence supporting the efficacy of antibiotics. This lack of evidence, combined with the potential for adverse effects should be weighed when considering adding antibiotics to a treatment regimen.

Surgery

Once medical treatment has proven ineffective, endoscopic surgery is indicated [2]. Surgery can be used to increase ventilation and drainage of the paranasal sinuses through enlargement of the natural ostia. This can then allow improved access to topical pharmaceutical agents. Surgical intervention can quickly and significantly improve symptoms, but it does not often address the underlying cause of chronic sinusitis. Therefore, continued medical therapy is necessary.

Odontogenic Sinusitis

Definition

Acute sinusitis is distinguished from chronic sinusitis by disease time course. However, odontogenic sinusitis is defined by its anatomic origin. Similarly, odontogenic sinusitis is defined as inflammation of the sinus mucosa secondary to a dental lesion [15].

Pathophysiology

Trauma, complications following dental procedures, and periapical and periodontal disease are some of the most common causes of odontogenic sinusitis [16]. In these conditions, bacteria attached to the tooth are able to enter the pulp and colonize. From the tooth, infection and/or inflammation spread via the arteries, veins, or lymphatics to the maxillary sinus, then the maxillary ostium, and finally to the surrounding tissues (Fig. 13.3).

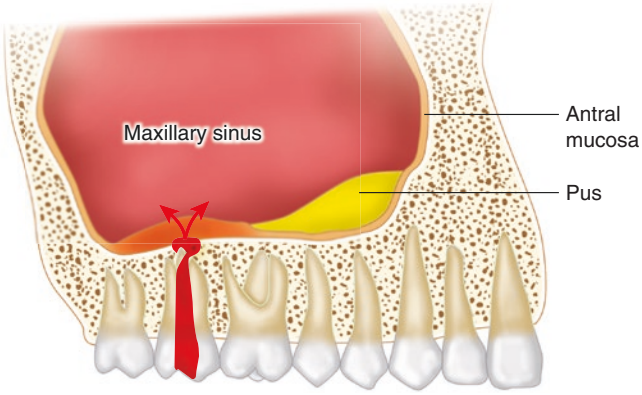


Fig. 13.3 Odontogenic sinusitis

Diagnosis

The diagnosis of odontogenic sinusitis often requires examination by both a medical and dental provider. Presentation can be similar to primary sinusitis and the odontogenic source is often inconspicuous. Significantly less research has been published investigating the diagnosis of odontogenic sinusitis as compared to nonodontogenic conditions. As a result, there are no formalized diagnostic criteria [16]. The treatment and outcome of odontogenic sinusitis, however, vary significantly from primary sinusitis, so a prudent physical exam, imaging, and history including dental history are important.

While no formal guidelines exist, the following findings can be considered indicators of potential odontogenic sinusitis: unilateral maxillary sinus opacification on CT, evidence of dental pathology on CT, nasal endoscopic evidence of unilateral purulence from the middle meatus, and culture of odontogenic bacteria from a nasal swab [16]. Once suspicion of odontogenic sinusitis is raised, both sinusitis and odontogenic pathology should be confirmed. Nasal endoscopy is generally considered the most reliable method to confirm sinusitis. In the absence of endoscopy, clinical symptoms or CT imaging are secondary.

Treatment

Because odontogenic sinusitis is, by definition, sinusitis caused by a primary odontogenic pathology, treatment should first target the identified dental pathology. Successful treatment often involves both a medical and surgical approach.

Medical

Since odontogenic sinusitis involves the migration of infection from the oral cavity, antibiotic therapy should cover both aerobic and anaerobic organisms. Amoxicillin with clavulanate is considered first line, while piperacillin, cefotaxime, cefuroxime and clindamycin, fluoroquinolones, and tetracyclines are also used as appropriate alternatives [16]**.** The majority of cases, however, do not resolve with antibiotic monotherapy and will often necessitate surgery as well.

Surgery

While endoscopic sinus surgery is considered to be the gold standard for surgical management of maxillary sinus disease, dental procedures with antibiotics should be performed first, with endoscopic sinus surgery reserved for refractory cases [17]. Specific dental intervention will vary but can include root canal, apicoectomy, or dental extraction.

Fungal Sinusitis

Inhalation of fungal spores can lead to colonization of sinus mucosa. There are various forms of fungal sinusitis that can be categorized as either noninvasive or invasive. Noninvasive fungal sinusitis can further be categorized into two subtypes, mycetoma and allergic fungal sinusitis [18]. Invasive fungal sinusitis can be divided into acute and chronic conditions.

Noninvasive Fungal Sinusitis

Mycetoma

A mycetoma is a collective mass of fungal organisms and fibrous exudate within the paranasal sinus following obstruction. Due to the slow growth of the mass, mycetomas are often asymptomatic and discovered incidentally via radiologic imaging. However, as the fungal mass grows, a mass effect can eventually compress adjacent structures.

Diagnosis

Because mycetomas usually present asymptomatically, diagnosis is usually made incidentally by imaging. CT shows a hyper-attenuated mass within the sinus surrounded by a hypointense mucosa due to inflammation. MRI will reveal a hypointense mass due to a composition of various metals and the absence of water. Histology with high-power microscopy can confirm a diagnosis, but the use of low-power microscopes can make differentiation from allergic fungal sinusitis difficult [19].

Treatment

Extraction of the fungal ball can sometimes be suctioned since there is no invasion of the mucosa. Endoscopic sinus surgery, however, is the treatment of choice for relieving

obstruction. Additionally, since there is no invasion of the mucosa, antifungal pharmaceuticals are not necessary [18].

Allergic Fungal Sinusitis

Allergic fungal sinusitis is a subtype of chronic sinusitis deriving from chronic allergic inflammation caused by fungal colonization. Most commonly implicated organisms include Aspergillus, Bipolaris, Drechslera, and Curvularia lunata [20]. Due to the geographic distribution of mold spores, allergic fungal sinusitis demonstrates a higher incidence in the Mississippi River basin and the southern United States.

Allergic fungal sinusitis is thought to develop after a prior sensitization to germinating fungal hyphae. Subsequent exposure results in an immune response with eosinophilic degranulation, with growth and inflammatory factors stimulating the formation of nasal polyps and the production of a thickened, viscous mucus. Damage to the mucosa combined with obstruction and impaired clearance facilitates secondary bacterial invasion and propagation of the inflammatory response.

Diagnosis

Allergic fungal sinusitis can have a similar presentation to chronic sinusitis. A diagnosis should thus be made using the following criteria: confirmed type 1 hypersensitivity with history, skin testing, or serology, presence of nasal polyposis, characteristic computed tomography signs, eosinophilic mucin without fungal invasion of the sinus mucosa, and positive fungal stain [21]. Minor criteria can also be considered such as asthma, unilaterality, bone erosion, fungal culture, Charcot-Leyden crystals, and serum eosinophilia.

Treatment

Medical treatment options for allergic fungal sinusitis can include oral glucocorticoids, topical steroids, and immunotherapy. As with other forms of sinusitis, oral steroids are a useful therapy to control inflammation and decrease the risk of recurrence. Moreover, when used prior to surgery, steroids can decrease bleeding and improve visualization of the sinus in the presence of nasal polyps [22]. In addition to the secondary inflammatory response, primary immune pathways can be medically targeted as adjuvant therapy. Monoclonal antibodies to IgE, IL 3, IL 4, and Il 5 may have clinical value [18].

Since surgery is often involved in diagnosis, concomitant intervention can serve two additional functions. First, manual removal of fungal debris, polyps, and mucus allows relief of the obstruction, with immediate improvement in symptoms while decreasing the risk of recurrence. Second, surgery can reverse osseous invasion.

Invasive Fungal Sinusitis

Acute Invasive Fungal Sinusitis

Acute invasive fungal sinusitis is a rare rapidly progressing infection seen predominantly in immunocompromised patients and patients with poorly controlled diabetes. It is the most lethal form of fungal sinusitis with a high mortality rate ranging from 50 to 80% [23]. Therefore, surgical intervention needs to happen quickly, sometimes requiring serial debridement and orbital exenteration. It develops rapidly and has a time course of less than 4 weeks [18]. It occurs when a fungal infection of the sinus invades beyond the mucosa into the proximal vasculature, nerves, or bone. Aspergillus, Mucorales, and Saprophyticus are commonly implicated [24]. It is rare for acute invasive fungal sinusitis to develop in immunocompetent individuals or in those without some form of underlying condition. Common risk factors include diabetes, hematologic diseases, steroid use, deferoxamine use, AIDS, intravenous drug use, and trauma.

Diagnosis

Acute invasive fungal sinusitis presents similarly to acute sinusitis, but one should be suspicious of fungal involvement when symptoms present in immunocompromised individuals or those with uncontrolled diabetes. Neutropenia is also a characteristic predictor. Given the high mortality rate, rapid diagnosis is crucial. It can be made via biopsy and histopathology. As the fungi invade the mucosa, their extension into the blood vessels causes thrombosis. Thus, histology will show visible necrosis and thrombosis of the mucosal vasculature [19]. Radiological imaging can also prove helpful in diagnosis, as necrotic and thrombosed tissue characteristically fail to take up the contrast and will be less visible.

Treatment

As acute invasive fungal sinusitis commonly develops secondary to another medical condition. While it is important to address and identify the predisposing factor, urgent surgical and medical interventions are necessary [25]. Tissue culture determines the pharmaceutical approach. Amphotericin B provides broad coverage, but the confirmation of Aspergillus necessitates treatment with voriconazole and echinocandin [18, 25]. Once clinical symptoms improve, treatment can transition to oral itraconazole, posaconazole, or isavuconazole.

Chronic Invasive Fungal Sinusitis

Whereas acute invasive sinusitis is associated with a rapid onset and spread, chronic invasive sinusitis progresses slowly

and has a time course of over 4 weeks. Aspergillus and brown molds are implicated in chronic fungal sinusitis, but Mucorales is not [18].

Diagnosis

Diagnosis can be made based on the time course of symptoms and a serum (1,3)-beta-D-glucan or aspergillus galactomannan assay [26]. Histopathology will show necrosis and thrombosis, similar to acute invasive fungal sinusitis [19].

Treatment

The treatment of chronic invasive fungal sinusitis is similar to acute invasive fungal sinusitis with debridement and antifungal medications. However, since Mucorales does not cause the chronic condition, triazoles play no role in treatment [18].

Complications of Rhinosinusitis

Because the paranasal sinuses are in close proximity to the brain, orbits, and craniofacial structures, sinusitis can result in complications via spread to these adjacent structures. The specific nature of the complications depends on the particular sinus that is involved but can generally be thought of as manifesting within the local osseous, orbits, or intracranially.

Osseous

Chronic inflammation stimulates bone remodeling and can result in osteitis, osteomyelitis, and osteoneogenesis. Mucoceles can obstruct the sinus, erode adjacent bone, and cause headache. Additionally, subperiosteal abscesses can develop secondary to osteomyelitis of the frontal sinus, presenting as edema, swelling of the forehead, and fever. Pott's puffy tumor is a rare complication characterized by subperiosteal abscess secondary to osteomyelitis of the frontal bone. It presents with a localized swelling of the forehead. Pott's puffy tumor can lead to intracranial abscess, cortical vein thrombosis, epidural abscess, and subdural empyema through contiguous or hematogenic spread inwards [27].

Orbital

Orbital complications are the most common complication of sinusitis [28]. Cellulitis of the tissue anterior to the septum can cause lid edema without orbital signs. Posterior to the septum, free blood flow between the valveless ophthalmic and ethmoid veins or direct invasion through the lamina papyracea can result in orbital involvement. Proptosis, chemosis, increased intraocular pressure, pupillary defects, and vision changes are signs this form of spread has occurred (Fig. 13.4) [29].

The Chandler classification is the most commonly used system for delineating the progression of orbital complications (Table 13.1). Stage I is preseptal orbital cellulitis with inflammation and edema anterior to the orbital septum. Stage II is orbital cellulitis with the extension of inflammation and edema beyond the orbital septum. Stage III is the development of a subperiosteal abscess beneath the periosteum of the lamina papyracea. Stage IV is an orbital abscess within the orbit. Last, stage IV, also categorized as an intracranial complication, is cavernous sinus thrombosis. This develops through the posterior extension of the superior ophthalmic veins and is associated with cranial nerve III, IV, V, and VI palsies (Fig. 13.5) [18].

Intracranial

Intracranial involvement of sinusitis is potentially life-threatening and can present as intracranial pressure, headache, fever, lethargy, malaise, seizure, cranial nerve paralysis, nausea, and vomiting. Specific manifestations include meningitis, epidural abscess, subdural empyema, cerebral abscess and, as previously discussed, cavernous sinus thrombosis [30]. Suspicion of intracranial complications requires immediate and urgent diagnosis [29]. Neurosurgical consultation and surgery are often necessary.

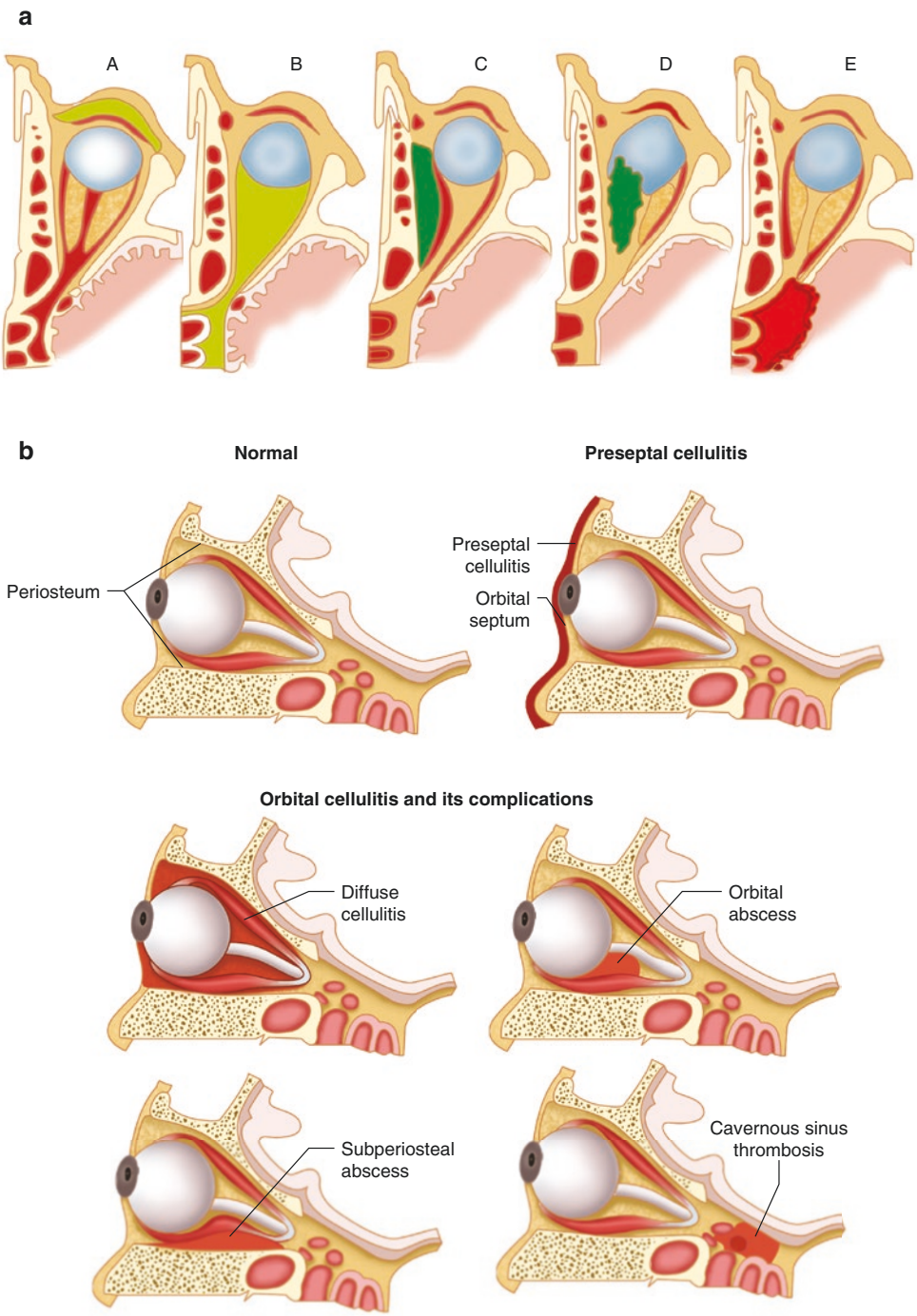


Fig. 13.4 Progression of orbital involvement

Table 13.1 Chandler classification of orbital complications of sinusitis

Stage I	*Preseptal cellulitis*	Inflammation and edema anterior to the orbital septum
Stage II	*Orbital cellulitis*	Extension of inflammation to the orbital contents posterior to the septum
Stage III	*Subperiosteal abscess*	Development of abscess between the bony orbital wall and periorbita
Stage IV	*Orbital abscess*	Development of abscess within the orbit
Stage V	*Cavernous sinus thrombosis*	Development of retrograde phlebitis and coagulation of vascular contents extending to the cavernous sinus

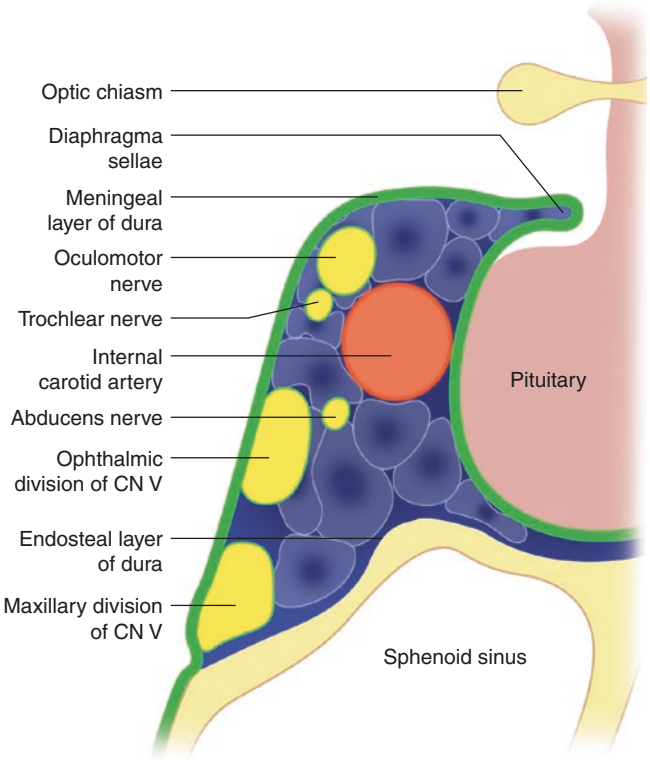


Fig. 13.5 Cavernous sinus

Summary

Sinusitis can be caused by a variety of microorganisms and is classified by both its etiology and time course. The diagnosis of sinusitis varies according to subtype, but often involves major and/or minor criteria, imaging, or histology. Therapeutic approach also varies by subtype, but oral steroids, topical steroids, antimicrobials, as well as endoscopic sinus surgery play predominant roles. Untreated sinusitis can lead to complications involving the bone, orbits, and intracranial structures. With the involvement of these nearby structures, uncontrolled sinusitis can be potentially fatal. However, with prudent and appropriate management, the prognosis of sinusitis tends to follow a favorable course.

References

1. Battisti AS. Sinusitis. 2020. https://www.ncbi.nlm.nih.gov/books/NBK470383/. Accessed 7 Aug 2021.
2. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update). Otolaryngol Head Neck Surg. 2015;152(4):598–609. https://doi.org/10.1177/0194599815574247.
3. Wald ER, Applegate KE, Bordley C, et al. Clinical practice guideline for the diagnosis and management of ACUTE bacterial sinusitis in children aged 1 to 18 years. Pediatrics. 2013;132(1):e262. https://doi.org/10.1542/peds.2013-1071.
4. Desrosiers M, Evans GA, Keith PK, et al. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. Allergy, Asthma Clin Immunol. 2011;7(1):2. https://doi.org/10.1186/1710-1492-7-2.
5. Sindwani R. Clinical practice guideline: adult sinusitis. Yearb Otolaryngol Head Neck Surg. 2008;2008:214–5. https://doi.org/10.1016/s1041-892x(08)79112-1.
6. Slavin R, Spector S, Bernstein I, et al. The diagnosis and management of sinusitis: a practice parameter update. J Allergy Clin Immunol. 2005;116(6):S13. https://doi.org/10.1016/j.jaci.2005.09.048.
7. Leung R, Almassian S, Kern R, Conley D, Tan B, Chandra R. Patient level decision making in recurrent acute rhinosinusitis: a cost-benefit threshold for surgery. Laryngoscope. 2012;123(1):11–6. https://doi.org/10.1002/lary.23504.
8. Tomassen P, Zele TV, Zhang N, et al. Pathophysiology of chronic rhinosinusitis. Proc Am Thorac Soc. 2011;8(1):115–20. https://doi.org/10.1513/pats.201005-036rn.
9. Lam K, Schleimer R, Kern RC. The etiology and pathogenesis of chronic rhinosinusitis: a review of current hypotheses. Curr Allergy Asthma Rep. 2015;15(7):41. https://doi.org/10.1007/s11882-015-0540-2.
10. Kern RC, Conley DB, Walsh W, et al. Perspectives on the etiology of chronic rhinosinusitis: an immune barrier hypothesis. Am J Rhinol. 2008;22(6):549–59. https://doi.org/10.2500/ajr.2008.22.3228.
11. Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. Cochrane Database Syst Rev. 2007;(3):CD006394. https://doi.org/10.1002/14651858.cd006394.pub2.
12. Mullol J, Obando A, Pujols L, Alobid I. Corticosteroid treatment in chronic rhinosinusitis: the possibilities and the limits. Immunol Allergy Clin N Am. 2009;29(4):657–68. https://doi.org/10.1016/j.iac.2009.07.001.
13. Joe SA, Thambi R, Huang J. A systematic review of the use of intranasal steroids in the treatment of chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2008;139(3):340–7. https://doi.org/10.1016/j.otohns.2008.05.628.
14. Soler ZM, Oyer SL, Kern RC, et al. Antimicrobials and chronic RHINOSINUSITIS with or without polyposis in adults: an evidenced-based review with recommendations. Int Forum Allergy Rhinol. 2012;3(1):31–47. https://doi.org/10.1002/alr.21064.
15. Chiu A, Suh J, DeConde A. Odontogenic sinusitis. In: Sataloff's comprehensive textbook of otolaryngology: head and neck surgery (rhinology/allergy and immunology), vol. 2; 2016. p. 479. https://doi.org/10.5005/jp/books/12714_33.
16. Craig JR, Tataryn RW, Aghaloo TL, et al. Management of odontogenic sinusitis: multidisciplinary consensus statement. Int Forum Allergy Rhinol. 2020;10(7):901–12. https://doi.org/10.1002/alr.22598.
17. Yoo BJ, Jung SM, Lee HN, Kim HG, Chung JH, Jeong JH. Treatment strategy for odontogenic sinusitis. Am J Rhinol Allergy. 2020;35(2):206–12. https://doi.org/10.1177/1945892420946969.
18. Senior BA, Chan Y. Fungal sinusitis. In: Rhinology and allergy: clinical reference guide. San Diego: Plural Publishing; 2018. p. 219–33.
19. Granville L, Chirala M, Cernoch P, Ostrowski M, Truong LD. Fungal sinusitis: histologic spectrum and correlation with culture. Hum Pathol. 2004;35(4):474–81. https://doi.org/10.1016/j.humpath.2003.10.024.
20. Schubert MS. Allergic fungal sinusitis: pathophysiology, diagnosis and management. Med Mycol. 2009;47(Suppl 1):S324. https://doi.org/10.1080/13693780802314809.

21. Ponikau JU, Sherris DA, Kern EB. Role of fungi in allergic fungal sinusitis and chronic rhinosinusitis: in response. Mayo Clin Proc. 2000;75(5):540–1. https://doi.org/10.4065/75.5.540-a.
22. Landsberg R, Segev Y, Fliss DM. Targeted endoscopic surgery for allergic fungal rhinosinusitis. Oper Tech Otolaryngol Head Neck Surg. 2006;17(2):117–20. https://doi.org/10.1016/j.otot.2006.01.014.
23. Waitzman AA, Birt BD. Fungal sinusitis. J Otolaryngol. 1994;23(4):244–9.
24. Aribandi M, McCoy VA, Bazan C. Imaging features of invasive and noninvasive fungal sinusitis: a review. Radiographics. 2007;27(5):1283–96. https://doi.org/10.1148/rg.275065189.
25. Nam SH, Chung Y-S, Choi YJ, Lee JH, Kim JH. Treatment outcomes in acute invasive fungal rhinosinusitis extending to the extrasinonasal area. Sci Rep. 2020;10(1):3688. https://doi.org/10.1038/s41598-020-60719-7.
26. Kumar M, Mugunthan M. β-D-glucan and Aspergillus galactomannan assays in the diagnosis of invasive fungal infections. Med J Armed Forces India. 2019;75(4):357–60. https://doi.org/10.1016/j.mjafi.2017.10.005.
27. Costa L, Mendes Leal L, Vales F, Santos M. Pott's puffy tumor: rare complication of sinusitis. Braz J Otorhinolaryngol. 2020;86(6):812–4. https://doi.org/10.1016/j.bjorl.2016.08.005.
28. Tewfik T. What are the orbital complications of acute sinusitis? Latest Medical News, Clinical Trials, Guidelines - Today on Medscape. 2020. https://www.medscape.com/answers/861646-95423/what-are-the-orbital-complications-of-acute-sinusitis. Accessed 7 Aug 2021.
29. Carr TF. Complications of sinusitis. Am J Rhinol Allergy. 2016;30(4):241–5. https://doi.org/10.2500/ajra.2016.30.4322.
30. Wagenmann M, Naclerio R. Complications of sinusitis. J Allergy Clin Immunol. 1992;90(3):552–4. https://doi.org/10.1016/0091-6749(92)90184-4.

Dental Implants

14

Harrison Spatz and Peter Pasciucco

Introduction: What Are Dental Implants?

Despite advances in dental care, many people still suffer from tooth loss due to various processes such as dental decay, periodontal disease, or injury.

A dental implant is a metal post that is surgically placed within a patient's jaw bone to replace the root portion of a missing tooth and create a stable foundation for a fixed or removable dental prosthesis. While dental implants provide the obvious aesthetic benefit of replacing missing teeth, they also provide many functional benefits. Dental implants can increase chewing efficiency compared to removable dentures, preserve bone and prevent bone resorption, help support facial structure, and allow the preservation of tooth structure by avoiding the need to restore adjacent teeth with conventional bridgework [1, 2].

Many studies have been done with different follow-up periods after dental implant placement, but most clinical studies show at least a 95% success rate of modern dental implants [3].

History of Dental Implants

Humans have always faced problems associated with tooth loss. The methods of managing tooth loss have evolved over many of years.

Ancient civilizations in Egypt and South America fabricated implants from animal bones, seashells, or carved ivory to replace teeth. Teeth replacements were most often placed post mortem, while others were placed during the lifespan of the recipient patient. These replacements were held together by gold ligature wire to create a fixed bridge and most likely resulted in early failure of the supporting teeth. From the 1500s to about 1800, teeth in Europe were collected from the underprivileged or from cadavers for the purpose of allotransplantation. Eventually, supragingival removable prostheses and tooth-borne fixed partial dentures became the mainstay of tooth replacement care [4, 5].

Modern implantology was made possible thanks to Dr. Per-Ingvar Brånemark, a Swedish physician. He established the basis of implantology (which he called osseointegration) accidentally in 1952 when he was studying blood flow in rabbit femurs by placing titanium chambers in their bones. Over time, the chamber became firmly affixed to the bone and could not be removed. He concluded the bone actually bonded to the titanium surface and the living bone could become so fused with the titanium oxide layer that forms on the implant that the two could not be separated without fracture [6]. Since then, there have been many changes in the research and development of dental implants trying to capitalize on achieving a faster and stronger bone-to-implant connection via different implant shapes, sizes, threading, surface treatments or coatings, materials, etc.

Biology of Osseointegration

Since Dr. Brånkmark coined the term osseointegration there have been some changes to the definition. The current definition of osseointegration in the Glossary of Prosthodontic Terms is, "the apparent direct attachment or connection of osseous tissue to an inert, alloplastic material without intervening fibrous connective tissue" [7].

The healing process in the implant system is similar to primary bone healing. Following the placement of the implant, a blood clot forms between the surface of the implant and the walls of the osteotomy site. Plasma proteins are attracted to the area accompanied by platelet activation and release of cytokines and growth factors. Angiogenesis begins and mesenchymal stem cells migrate via the fibrin scaffold of the clot to the osteotomy site and the surface of the implant. These cells differentiate into osteoblasts and

H. Spatz (✉)
Yardley Prosthodontics, Yardley, PA, USA

P. Pasciucco
Hartford Hospital, Hartford, CT, USA

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_14

begin to deposit bone on the surface of the implant and the walls of the osteotomy site leading to the anchorage of the implant in bone via immature woven bone, which eventually remodels into lamellar bone [8, 9].

The implant's primary stability comes from the mechanical engagement of cortical bone. It is a function of local bone quality and quantity, the geometry of the implant, and the placement technique. Secondary stability is biologic and established through remodeling and regeneration of surrounding bone resulting after the formation of secondary woven and lamellar bone. A dip in stability is observed about 3–4 weeks after implant placement, as the initially stabilizing bone is replaced [10].

Risks Associated with Implant Placement

The placement of dental Implants is considered an elective surgical procedure. Implant insertion can be performed in a dental office with local anesthesia, or if warranted due to the patient's medical complexities, in a hospital operating room. Over the past few decades, technological advancements have improved implant design, restorative options, imaging, and surgical techniques. These advances have increased the number of patients whose lives can be positively impacted by a more consistent solution than conventional dentistry could offer.

Most providers use two categories to define the types of risks associated with the placement of implants. Absolute contraindications are considered the most critical when deciding whether to place implants. Relative risks may impact the success rates, but the benefits outweigh the risks associated with the procedure.

Absolute contraindications may prevent a surgeon from performing surgery. These contraindications include radiation therapy, greater than 55 Gy, to treat malignancies in specific locations of the mandible or maxilla. Consultations are recommended with the radiation therapist prior to discussing any possibility of treatment with the patient. The risk of a surgical procedure initiating osteoradionecrosis must be avoided. The affected sites will not allow osseointegration due to decreased blood flow and decreased osteoclastic activity in the exposed bone. This is a permanent condition. Patients with long-term use of oral and I.V. Bisphosphonates due to metastatic disease (prostate, lung, and breast cancers) must also avoid dental implants. In these patients, the inability of the bone to metabolize prevents osseointegration and increases the chance of developing MRONJ (medicine-related osteonecrosis of the jaw) (See Chap. 29). Osteonecrosis disease, which may result from these procedures, is extremely invasive and could require major surgical procedures resulting in facial deformities. Other medical complexities and comorbidities that may prevent Implant placement are patients classified as ASA IV/V including patients with terminal disease and patients on permanent drug therapy for chronic medical conditions (immunosuppressed). This demographic may be successfully treated, but the overall risks outweigh the benefits.

The lack of proper jaw bone width or height to adequately place an implant fixture was always a major obstacle for implant placement. New techniques involving bone augmentation have improved these deficient areas and implants can now be placed in these areas with more than a 90% success rate [11].

Relative precautions are situations that can be modified and implants can then be placed, achieving a more optimal result. Periodontal disease and smoking are two local factors, which can be altered to gain a better result. Smoking more than 20 cigarettes per day and the presence of active periodontal disease, together or individually, adversely affects the ability of the implant fixture to osseointegrate. This is due to chronic bone loss, limited blood flow, and the presence of invasive pathogens producing inflammation. If corrected prior to placement, the oral environment will readily accept the procedure and produce normal success rates (90–100%). Bruxism (i.e., grinding of the teeth) can also impact the dental implant and the restorative fixture. Daily exposure of the restoration to micro-trauma can be very damaging, resulting in bone loss. These occlusal issues must be addressed prior to implant placement and restorative work. Diabetes is also a contributing factor to produce poor surgical results. Diabetes is associated with decreased peripheral blood flow and altered immune response. Osseointegration is dependent on the bone's ability to constantly metabolize. Most studies suggest A1c levels that are lower than 6.5 contribute to success rates in the acceptable range. Bleeding issues that are congenital or acquired can also affect the surgical placement. All medications affecting coagulation, whether prescribed or OTC should be monitored and altered depending on the primary care physician's recommendation. All patients who have been taking Coumadin should have their INR tested prior to surgery. An acceptable result of 3.5 or less is in the range accepted by most practitioners. Osteoporosis is another condition that has been reviewed and findings indicate that the levels of success mirror the placement in the healthy patient [12].

In conclusion, the placement of surgical implants in high-risk patients presents difficult choices for both the surgeon and the patient. If dental and medical guidelines are followed, success can be achieved. Both the patient and surgeon must review all these issues and decide if the risks outweigh any potential harm to the patient [13].

Failures

Implant failures can be attributed to many factors. Even with ideal placement in healthy tissue, a lack of osseointegration may occur and the fixture may be rejected. This phenomenon

is rare but when it occurs it is very discouraging for both the patient and the provider. These failures are usually due to nonosseointegration. Often these sites can be augmented with bone and after 3–6 months can receive a new implant. In these circumstances, it may be wise to request a medical consultation including blood tests to confirm that there is no underlying systemic disease.

Another reason for implant failure is technical error. Surgeons may encounter poor bone quality, and proximity to nerves, or the maxillary sinus, which result in non-optimal placement. Inadequate bone support is a leading factor in premature loss of the implant. Systemic or local factors previously mentioned may also contribute to increased failures [14].

Restorative procedures of the implant fixture by other team members can also contribute to short-term failure. Occlusal overloads can occur on areas that may not be able to support a new appliance. Fractures of titanium implant fixtures, fractures of screw-retained crowns, and failure to remove excess cement in cementable restorations can contribute to the early loss of a surgical implant.

Today, any licensed dentist is considered to be qualified to place implants. However, this has the potential to contribute to success/failure rates. It is strongly recommended that patients do their research when choosing an implantologist. The restorative dentist and local dental societies and friends can all help in choosing the doctor with the technical expertise to achieve the most successful results.

In conclusion, many issues should be addressed prior to choosing an implant as part of the treatment plan. Select a skilled restorative dentist whose opinion you respect, evaluate the patients' health status, and select an implant surgeon who is an experienced practitioner who devotes a major portion of their practice to implant placement. Medical practitioners will be asked to review consultations for this patient population, and their input will only enhance patient care [15].

Dental Maintenance of the Implant Patient

The patient who has received an implant (s) must follow the proper normal post-op protocol, which consists of 2–3 dental visits per year. The patient must be regularly evaluated. Implants following crown placement are very difficult to identify unless radiographs are available. Special care must be taken when scaling the implant crown. Titanium is easily scratched by conventional instruments, and this must be avoided. These areas if scratched form areas that may then harbor plaque and debris leading to local inflammation. This is referred to as peri-implantitis. Failure to treat this properly can lead to bone loss and subsequent failure. Occlusion also is a key component that must be regularly evaluated. Implants do not move once placed. The adjacent teeth can migrate and lead to malocclusion and parafunctional habits, such as grinding or bruxism. These issues if untreated may produce extreme stress on the implants resulting in bone loss. An occlusal guard may be recommended to prevent damage to the dentition/implant crowns while sleeping.

The recall visits may include X-rays to evaluate for dental caries in natural teeth and bone loss in the area of the implant. Dental prophylaxis will also be administered. Ideally, patients should be seen by their surgeon to examine their implants. The expertise offered by two doctors will help to proactively evaluate any potential problem. Patients who had implants placed to retain dentures or partial dentures (i.e., Hybrid) which are screw retained must still have the underlying tissue evaluated. They should have the restorative dentist remove the hybrid denture on a timely basis as recommended by the restorative dentist/surgeon.

Homecare should consist of brushing (manual /electrical toothbrushes), flossing, and other aids recommended by their general/restorative dentist. Disciplined use of these techniques will help ensure that both the natural dentition and restored implants stay healthy.

In the future. 3D imaging will be performed on all patients along with the production of a stent for surgical guidance. This new technology will assist in identifying potential pitfalls in the anatomical configurations. This will make implant surgery more predictable. However proper patient selection and a well thought out treatment plan will always be essential. Success rates now run between 85 and 95%. We again cannot underestimate the need for comprehensive and accurate health histories. If there is any uncertainty, we insist that an open dialogue between the Implant team and the PCP and other specialties proceed.

Summary

Dental implants have greatly improved the lives of millions of patients. Restored function, improved esthetics, and better health and quality are many of the positive results of dental implant placement. As technology continues to improve, more patients' lives will be impacted in a positive way.

References

1. Prasad D, Swaminathan A, Prasad D. Current trends in surface textures of implants. J Dent Implants. 2016;6(2):85.
2. Misch C. The importance of dental implants. Gen Dent. 2001;49(1):38–45.
3. Buser D, Janner S, Wittneben J, Brägger U, Ramseier C, Salvi G. 10-Year survival and success rates of 511 titanium implants with a sandblasted and acid-etched surface: a retrospective study in 303 partially edentulous patients. Clin Implant Dent Relat Res. 2012;14(6):839–51.
4. Abraham C. A brief historical perspective on dental implants, their surface coatings and treatments. Open Dent J. 2014;8(1):50–5.

5. Block M. Dental implants: the last 100 years. J Oral Maxillofac Surg. 2018;76(1):11–26.
6. Branemark P. Osseointegration and its experimental background. J Prosthet Dent. 1983;50(3):399–410.
7. The glossary of prosthodontic terms. J Prosthet Dent. 2017;117(5):C1–e105.
8. Dhinakarsamy V, Jayesh R. Osseointegration. J Pharm Bioallied Sci. 2015;7(5):228.
9. Mavrogenis A, Dimitriou R, Parvizi J, Babis G. Biology of implant osseointegration. J Musculoskelet Neuronal Interact. 2009;9(2):61–71.
10. Raghavendra S, Wood M, Taylor T. Early wound healing around endosseous implants: a review of the literature. Int J Oral Maxillofac Implants. 2005;20(3):425–31.
11. Hwang D, Wang H-L. Medical contraindications to implant therapy: part I absolute contraindications. Implant Dent. 2006;15(4):353–60.
12. Cordaro, L., Terheyden, H. ITI Treatment Guide: Ridge Augmentation Procedures Approach in Implant Patients. Volume 7. Berlin (Germany): Quintessence Publishing Co.; c2014. Medical History; p. 20–22.
13. Hwang D, Wang H-L. Medical contraindications to implant therapy: part II relative contraindications. Implant Dent. 2007;16(1):13–23.
14. Bragger, U., Heitz-Mayfield, LJA. ITI Treatment Guide: Biological and Hardware Complications in Implant Dentistry. Volume 8. Berlin (Germany): Quintessence Publishing Co.; c2015. Prevention of Peri-Implant Infections; p. 90.
15. Wittneben, J.G., Weber, H. P. ITI Treatment Guide: Extended Edentulous Spaces in the Esthetic Zone. Volume 6. Berlin (Germany): Quintessence Publishing Co.; c2012. Causes of Complications; p. 194–96.

Prophylactic Antibiotics

15

Steven Halepas, Brian Quinn, and Benjamin A. Miko

Introduction

Antibiotic use in dentistry falls into two major categories. First, antibiotics may be used to treat or prevent local infections in the head and neck. Second, they may be used for the prevention of transient bacteremia that can result in systemic infections such as infective endocarditis or seeding prosthetic valves and joints. Antibiotic use is either prophylactic (used to prevent) or therapeutic (used to treat an active infection). Unlike some fields of medicine, there is generally a shortage of quality randomized controlled trials in dentistry, and much of the antibiotic use is rooted in expert opinion. Given the limited available data, the optimal strategies for prophylaxis remain controversial [1]. Physicians are generally not well versed in the field of dentistry but are frequently consulted regarding antibiotics and medical optimization for dental procedures. This chapter aims to educate medical practitioners with the best-available evidence pertaining to antibiotic prophylaxis prior dental procedures. In order to provide sufficient background, common dental procedures will be described. The first section of this chapter will discuss preventing surgical site infections; the second will discuss preventing systemic bacteremia and seeding.

Many dental procedures are noninvasive, often having no interaction with the systemic vasculature, and staying within the confines of the tooth. More invasive procedures include oral biopsies, extraction of teeth, and other dental surgeries that involve mixing of blood with the oral flora. Logically, there seems to be a difference between a single instance of bacteremia following a dental procedure and chronic transient bacteremia, with the latter having a higher risk of systemic complications. Individuals with a higher burden of bacteria in the oral cavity are at higher risk of bacteremia when they brush their teeth [2]. Patients with poor dental hygiene have inflamed gingiva that can bleed when during brushing or flossing. Studies have demonstrated that home teeth brushing alone can result in a transient bacteremia [3, 4]. For most people, this is completely harmless. It is well established that brushing ones teeth results in a transient bacteremia, but, no direct link has been discovered between tooth brushing and infective endocarditis [5].

In 1991, a study was preformed where blood was drawn 5 min after patients with orthodontic appliances (braces) brushed their teeth. All blood samples taken prior to brushing demonstrated no bacterial growth. Five of the twenty patients (25% of the samples) demonstrated both anaerobic and aerobic bacterial growth in the samples taken after brushing [3]. All patients in the study had good oral hygiene and they could not attribute the bacteremia to a higher dental plaque bacterial load. A similar study was preformed 5 years earlier that demonstrated nine out of the 16 patients grew anaerobic bacteria from blood cultures taken 15 min after brushing [6]. Interestingly, 10 out of the 16 patients had positive cultures before brushing. The positive cultures pre-brushing had higher plaque scores, but the sample size was small.

Routine dental procedures can reduce the risk of this transient bacteremia by controlling the bacterial levels and reducing the repetitive transient bacteremia that the patient causes daily. In order to understand the antibiotic coverage of the oral cavity, it is important to review the microbiome of that exists in the oral cavity.

S. Halepas (✉)
Division of Oral and Maxillofacial Surgery, NewYork-Presbyterian/Columbia University Irving Medical Center, New York, NY, USA
e-mail: sh3808@cumc.columbia.edu

B. Quinn
College of Dental Medicine, Columbia University, New York, NY, USA

B. A. Miko
Division of Infectious Diseases, NewYork-Presbyterian/Columbia University Irving Medical Center, New York, NY, USA
e-mail: bm2266@cumc.columbia.edu

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_15

Microbiology

The microbiome of the oral cavity is second only to that of the gastrointestinal tract in its size and diversity [7]. Comprised of bacteria, fungi, and protozoa, the oral microbiome exists in a complex, dynamic equilibrium related to several host factors including genetics, physiological processes, medical comorbidities, and environmental/lifestyle factors (diet, smoking status, oral hygiene) [8]. Over 700 species of bacteria are known to colonize the hard and soft tissues of the mouth [8]. Only a small proportion of these are associated with clinical infection and are therefore targeted by antimicrobial prophylaxis. Streptococci represent approximately 30% of the resident flora of the gingival crevice and the majority of these are viridans group streptococci (VGS) [9]. VGS represent many streptococcal species that fall into several additional subgroups. These are the *Streptococcus anginosus* group, *S. mitis* group, *S. sanguinis* group, *S. salivarius* group, *S. bovis* group, and *S. mutans* group [10]. In general, VGS are low in pathogenicity but can cause local and systemic infections including infective endocarditis. As such, they are the focus of most antibiotic prophylaxis strategies discussed below. Other common genera constituents of the oral flora include *Fusobacterium, Lactobacillus, Peptostreptococcus, Prevotella, Proprionibacterium, Veillonella*, and *Actinomyces*, among others [11]. These may also be impacted by various antibiotic prophylaxis regimens discussed.

Dental Procedures

Dental procedures have different levels of invasiveness and therefore have different risks of infection and consequently vary in their requirement for antibiotics prophylaxis (see Table 15.1). The following discussion is intentionally rudimentary as most medical health practitioners have minimal education about dentistry and the teeth. If the reader is versed in the field of dentistry, he or she should feel free to skip ahead. The maxilla is the upper jaw and the mandible is the lower jaw. The gums are referred to as the gingival tissue. The adult has 32 teeth, while children have 20 teeth. There are several different types of teeth: incisors, canines, premolars, and molars (see Fig. 15.1). Each tooth has an assigned number. Adult teeth are numbered in the United States from 1 to 32, starting with the first tooth on the posterior upper right as #1 and ending with the last tooth on the posterior upper left as #16. The most posterior lower left tooth is #17 and the numbering ends with the last tooth on the lower right as #32. Teeth #1, 16, 17, and 32 (wisdom teeth, also known as third molars) are often not visualized in the mouth as many patients get them extracted at a young age or they are impacted below the gingival tissue. It is important to number the teeth accurately and not just number them based on what is visualized. As an example, even if some teeth have been extracted, the front tooth on the upper right is always #8 and

Table 15.1 Summarizing which procedures require antibiotic prophylaxis. Some procedures may require antibiotic prophylaxis for the average patient population based on the practitioner's clinical judgment as the literature is still controversial

Dental procedures	Antibiotic indication
Fillings	No
Root canals	No
Biopsy	High risk patients
Cleanings/deep cleanings	High risk patients
Tooth exactions	High risk patients
Third molar extractions	High risk patients/depends
Pre-prosthetic surgery	High risk patients
Dental implants	High risk patients/depends
Bone augmentation	Often

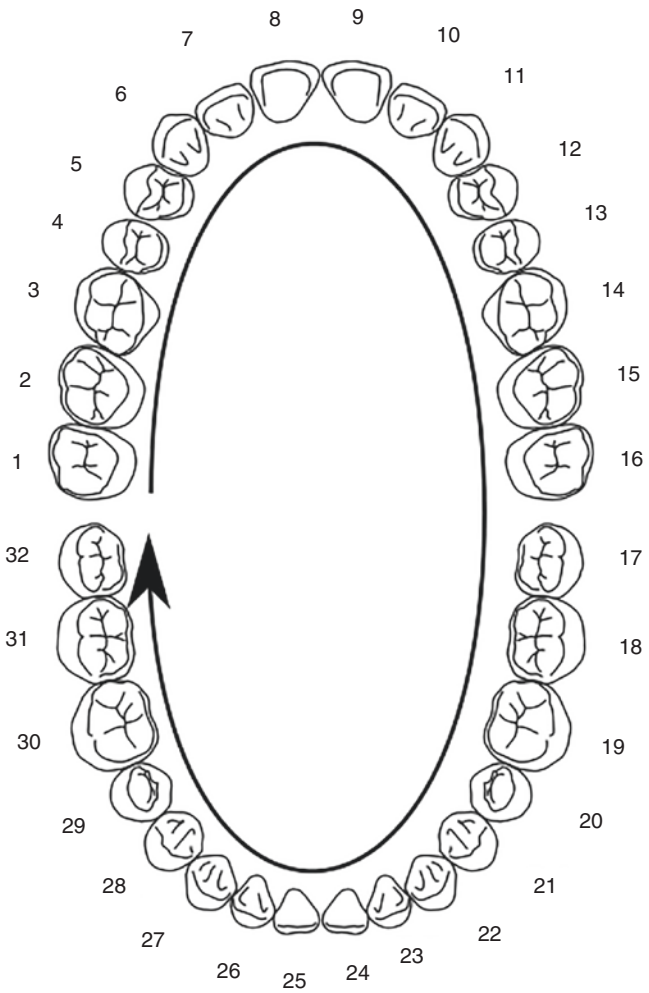


Fig. 15.1 An illustration of the adult dentition and universal teeth numbers used in the United States. (This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. Used without alterations. https://upload.wikimedia.org/wikipedia/commons/6/6c/Universal_Numbering_System.svg)

the upper left front tooth is always #9. This information can be helpful when being consulted by a dentist who may just include tooth numbers.

Restorative dentistry is the field of "fillings." In these cases, dentists use a drill to remove decayed tooth structure. Once all the bacteria are cleaned out of the tooth, the tooth is filled with a restorative material, often a resin composite. Restorative dentistry stays within the confines of the tooth. It does not enter the gingival tissue or the bone, and usually does not enter the pulp chamber of the tooth. The only manipulation of the gum tissue is when placing instruments around the tooth to keep the gingival tissue out of the way. Prosthodontics is a field of dentistry that includes fabricating fixed appliances (foreign materials that stay in the mouth permanently), such as a crown (or cap), and removable appliances, such as dentures. When fabricating a crown, the dental provider will again be drilling within the confines of the tooth, specifically within the enamel and dentin, so there is little risk of interaction with the systemic circulation via the bone or gingival tissue. Orthodontics (braces) is another field of dentistry that has a low risk of interaction with the systemic circulation and infection. Brackets are bonded to teeth by means of a resin composite glue and subsequently connected by wires that provide tension to move teeth in specific directions. These categories of dentistry, based on the level of invasiveness of the procedure, have exceedingly little risk of local or systemic infection as they do not increase the risk of transient bacteremia that could seed artificial joints or heart valves. They do not require antibiotic prophylaxis routinely, and their use in specific populations is likely unnecessary.

Biopsy

Biopsies of the oral cavity are like biopsies in other areas of the body. While biopsies do not routinely require antibiotic prophylaxis, they are invasive and have direct communication with the vasculature, so they could be a potential source of bacterial exposure to the systemic system. Therefore, patients undergoing biopsies are recommended to receive antibiotic prophylaxis only if they are in the high-risk populations discussed later in this chapter, not because of the procedure itself.

Dental Cleanings and Scaling/Root Planning

The infectious risk of dental cleanings is a controversial topic for a variety of reasons. Dental cleanings are important in patients who are at an increased risk of bacterial seeding from the oral cavity because this procedure will decrease the bacterial burden in the mouth. A dental cleaning includes supragingival scaling, where sharp instruments are placed where the tooth attaches to the gingival tissue. Scaling and root planning is sometimes called a "deep cleaning." In these instances, substantial bone loss in the setting of periodontitis requires cleaning down the root of a tooth several millimeters below the gingival tissue, which can result in more bleeding.

In 1982, a study was preformed to investigate transient bacteremia levels in patients undergoing dental cleanings. Of the 56 male patients, about half had a history of valvular heart disease and were given potassium penicillin G via intravenous infusion 30 min before the cleaning followed by every 4 h for 72 h. The other half of the patients did not receive antibiotics. Five minutes following the dental cleaning, 60.7% of the patients without penicillin were bacteremic, while only 10.7% of those who received the penicillin prophylaxis were bacteremic. However, by 30 min after the dental cleaning, there was a marked decline in prevalence of bacteremia in the group who did not receive antibiotics, resulting in no significant difference between the two groups [12]. No study participants developed infective endocarditis over the subsequent 18 months of follow-up. This study highlighted several key ideas. Dental cleanings result in a transient bacteremia even in healthy individuals. While prophylactic antibiotics may reduce the rate of this immediate bacteremia, they do not appear to alter that rate of sustained bacteremia or reduce the risk of infective endocarditis.

Patients with periodontal disease (periodontitis) have higher intraoral bacterial loads and therefore have an increased incidence of bacteremia after teeth scaling then in gingivitis patients or healthy patients with good oral hygiene [2]. Some believe that tooth brushing may be a greater concern for individuals at risk for distant site infections such as infective endocarditis or prosthetic joint infections because there is repeated transient bacteremia over time. Although the time of inoculation is higher with more tissue manipulation such as with tooth extractions, studies have demonstrated a higher percentage of positive cultures at 1 h after teeth brushing as compared to extractions [13]. This contrast between the isolated risk of bacteremia with tooth extraction and the repetitive risk of bacteremia with tooth brushing has complicated the formulation of antibiotic prophylaxis. While it is not efficacious to keep patients on antibiotics for tooth brushing, it is an interesting point to consider as appropriate guidelines on prophylaxis in high-risk populations are being developed.

General Extractions Versus Wisdom Teeth Extractions

Dental extractions are classified and coded into simple and surgical extractions. Put simply, whenever a gingival flap

needs to be raised, bone needs to be removed, or the tooth needs to be sectioned into pieces, practitioners will deem it a surgical extraction. In contrast, the procedure for a simple extraction begins with achieving local anesthesia, typically with 2% lidocaine with 1:100,000 epinephrine. The gingival tissue around the tooth is released with a periosteal elevator instrument. The tooth is then manipulated with instruments such as elevators. This manipulation allows for the periodontal ligaments (the fibers around the tooth) to stretch and break. Once the fibers around the tooth are broken, the tooth can be removed, generally with dental forceps. In a surgical extraction, the gingival tissue is general cut with a scalpel blade and a full thickness flap is raised, exposing the underlying maxillary or mandibular bone next to the tooth. Sometimes a surgical drill is used to remove bone adjacent to the tooth, often creating a purchase point for the elevator to engage both the tooth and the jawbone. Some teeth have more than one root. Mandibular molars typically have two roots, while maxillary molars often have three. In these instances, sometimes it is beneficial to section the tooth with a drill into the individualized roots. A single root is easier to extract then a tooth with three roots.

The point of this exercise is not to educate the reader on how to extract teeth, but to highlight the different levels of invasiveness during extractions. Simple extractions have very little manipulation of the patient's gingival tissue, as compared to raising a full thickness flap and removing bone in a surgical extraction. Although postoperative pain depends greatly on the patient's pain tolerance, the pain level is often greater after surgical extractions then with simple extractions.

In 2017, a systematic review was preformed to determine the effectiveness of systematic antibiotic prophylaxis in preventing a local complication after extraction of a tooth (excluding third molars—explained later). The study concluded there were no relevant randomized controlled trials highlighting the lack of evidence guiding this aspect of care [14]. The estimated incidence of infection in tooth extraction is extremely low, with a recent study from 2021 finding surgical site infection (SSI) after extraction of a non-third molar tooth of 0.8% (122/14,832). Out of the 8306 patients who received oral antibiotics, 0.76% (63 cases) had SSI, and 6526 patients who did not receive oral antibiotics had an SSI occurrence of 0.90% (59 cases). The SSI occurrence was not significantly different when compared with the presence or absence of oral antibiotic administration [15].

Third molars (wisdom teeth) are often placed in their own category in terms of extractions for several reasons. Third molars are often extracted because they are impacted and cannot erupt into occlusion. This means the wisdom teeth cannot become functional and are stuck in the jawbone. The teeth can partially erupt into the mouth, meaning the provider can see part of the tooth, but there is not enough space for it to erupt completely. In these instances, many patients undergo extraction of these impacted third molars. Impacted third molars are classified into soft tissue impaction, partial bony impaction, and full bony impaction. These extractions will more routinely require a full-thickness gingival flap that can be much larger than that for other surgical extractions, as well as needing removal of a significant amount of bone. The third molar location in the most posterior aspect of the jaws and near important structures like nerves, the airway, and the maxillary sinus can make these extractions more difficult and longer than extractions of other teeth in the mouth. This long explanation is provided to give the reader context to the following. Many oral and maxillofacial surgeons provide or used to provide a 5- to 7-day course of antibiotic prophylaxis for third molar extractions, even if they did not routinely provide antibiotics for extraction of other teeth. The reason for this thinking is multifactorial.

The rate of infection after third molar extraction is cited around 1–2% in the literature, although this reflects significant heterogeneity in antibiotic prophylaxis strategies. Many studies have stated that there is no significant difference in infection rates between the groups which underwent extractions with or without antibiotics [16]. Despite this, patients have become accustomed to receiving antibiotics following this procedure based on past personal experiences or those of close contacts. When an infection occurs, patients immediately assume it is because they did not receive antibiotics. Another reason that many dental practitioners prescribe antibiotics is to reduce the incidence of alveolar osteitis (a dry socket) [17]. Overall, there is a lack of scientific evidence to support routine antibiotic prophylaxis for third molar extractions. In a study by Reiland et al. involving 1895 patients undergoing third molar extractions, the authors found no statistical difference between an oral antibiotic regiment and a single dose intravenous peri-operative regiment in patients who developed alveolar osteitis or surgical site infections [18]. A single, peri-operative dose is adequate in reducing surgical infections [19, 20]. A systematic review involving ten studies found that a single oral dose of 2 g amoxicillin significantly decreased the incidence of surgical site infections and a single dose of 800 mg of penicillin V significantly decreased the incidence of alveolar osteitis [21].

In 2016, a meta-analysis was published by Moreno-Drada et al. to report on whether antibiotic prophylaxis is effective in preventing localized infections after undergoing oral procedures. They found that antibiotic prophylaxis with amoxicillin and clindamycin was effective in reducing local infection following tooth extractions but not effective following dental implant placement or endodontic surgeries [22]. In a prospective cohort study of 1877 patients having third molars extracted, the authors found a decrease in the risk of developing post-operative inflammatory complications ($p = 0.04$) [23].

In a systematic review and meta-analysis from 2017 by Menon et al., the authors reviewed 11 trials with a total of 1242 third molar extractions followed over a period of 2 months. The meta-analysis found that both amoxicillin–clavulanic acid and amoxicillin significantly reduced the risk of infection after third molar extraction (overall relative risk (RR) 0.25, $P < 0.001$) [24]. When separating out from amoxicillin-clavulanic acid, amoxicillin alone does not appear to reduce the risk of infection as the confidence interval contains 1 (RR 0.22, confidence interval [CI] 0.02–2.74, $P = 0.237$). For amoxicillin–clavulanic acid, the relative risk was 0.21 (95% CI 0.12–0.40, $P < 0.001$). In the amoxicillin group, the relative risk was 0.22 (95% CI 0.02–2.74, $P = 0.237$) for the parallel studies and 0.41 (95% CI 0.13–1.32, $P = 0.136$) for the split mouth studies [24]. They determined the adverse effects, such as diarrhea, nausea, and vomiting, was significantly greater with amoxicillin–clavulanic acid (RR 4.12, 95% CI 1.21–14.00, $P = 0.023$) but not with amoxicillin alone (RR 1.57, 95% CI 0.55–4.50, $P = 0.405$). When classifying into pre-surgery, post-surgery and mixed, the pre-surgery had a relative risk of infection of 0.32 (95% CI 0.12–0.85, $P = 0.023$ and the post-surgery group has a relative risk of 0.15 (95% CI 0.06–0.38, $p < 0.001$). While there was variability in the prophylactic strategies included in the meta-analysis, post-operative courses were most-commonly 4–5 days of antibiotics. This study demonstrates that antibiotic prophylaxis (specifically amoxicillin-clavulanic acid) in third molar extraction may reduce post-operative infections, but the use of amoxicillin-clavulanic acid is associated with more adverse events. Contrasting with this, Iguchi et al. reported in 2020 on 350 patients who received different types of antibiotics. Their findings suggested that preoperative administration of intravenous cefazolin was as effective as postoperative administration of broad-spectrum antibiotics such as piperacillin at reducing surgical site infections [25].

Antibiotic use in third molar extraction remains a controversial topic as individual studies generally contain a small sample size, the number of randomized controlled trials are limited, and there is a lack of split mouth design trials (studies that have one treatment arm on one side of the mouth and a control on the other side of the same patients mouth to minimize confounders) given the long washout period of the systemic antibiotics. Others have also stated that courses of amoxicillin do not reduce the risk of infection or dry socket [26, 27]. While 4-to-5-day courses of amoxicillin-clavulanic acid may reduce post-operative infection, it is likely unnecessary and not justified in the healthy patient and is associated with a higher degree of adverse reactions. A single peri-operative dose of cefazolin, ampicillin, amoxicillin, or penicillin V would likely provide as much benefit in reducing alveolar osteitis or surgical site infections as a post-operative course. Local measures such as placing chlorhexidine gels or doxycycline powder in the extraction socket have also been demonstrated to reduce the incidence of alveolar otitis [28].

Pre-prosthetic Surgery

Pre-prosthetic surgery are procedures done to prepare a patient for dentures. Some patients can easily be fabricated dentures, while others will need reshaping of the jaw bones or oral tissues. While the procedures themselves are outside the scope of this chapter, mandibular tori removal is a common example of pre-prosthetic surgery. Mandibular tori are a bony growth on the inside of the lower jaw, closes to the tongue. While the tori are benign, they often prevent a denture from seating tightly and, therefore, limit their stability. To remove the tori, a scalpel blade is used to make an incision in the gingival tissue and a full thickness flap is raised to expose the bony growths. A surgical bur is used to create a trough between the bony outgrowths and the mandibular jawbone. An osteotome (surgical chisel) is used to finish the separation. The bone is smoothed with surgical burs or files. While this is just one type of pre-prosthetic surgery, most of these procedures have this level of invasiveness.

Dental Implants

Dental implants utilize screws placed into the jaw bones to support replacement of lost teeth. As implants are increasingly common, providers of every medical specialty will likely encounter patients who have or will receive dental implants. In 2021, dental implants are made of titanium alloy that is biocompatible and results in osseous integration with the jaw bones. These implants are safe in computer tomography and magnetic resonance imaging, although they can create substantial artifact if the study involves the oral cavity. They are safe on airplanes and through airport security, a question you might get from a patient. As background, when a tooth is lost or removed via extraction, the bony socket undergoes remodeling. The jaw bones are unique in that the alveolus (the bone surrounding the teeth) serves only to hold the teeth in place. When a tooth is lost, that alveolar bone begins to resorb. When dental implants are placed at the proper time, the implants can act as the tooth roots, and the stress from occlusion (the teeth coming together and chewing), results in enough pressure for the alveolar bone to remain. After a tooth is extracted, the extraction socket may be grafted with bony particulate or may be left to remodel on its own accord. Generally, after 3–6 months a dental implant can be placed in the missing tooth site. The gingival tissue is incised with a scalpel blade and a full thickness flap is elevated to expose the bone. There are instances where provid-

ers will perform "flapless surgery" for dental implants, but the majority are performed with full exposure of the jawbone. A drill is then used to make holes in the bone of increasing diameter (osteotomy). These holes act like pilot holes if one were to drill into wood before placing a screw. The pilot holes are created to less than a millimeter from the dimension of the final implant being used. Typical implant sizes will range from 3 to 5 mm in diameter, and 8–14 mm in length. After the osteotomy is complete, the implant is screwed into the jaw and the amount of torque needed (N*cm) is recorded, as this helps the practitioner evaluate for primary stability. Just as in any other surgical field, a loose screw in a bone will not heal and often gets infected. When surgeons place titanium plates and screws to repair fractures, they ensure the screws are stable without being over torqued. The same principles apply in the mouth. In most instances, the dental implants are then allowed to heal for 3–6 months before placing the new tooth (crown) on top. The mouth is highly vascularized and osseointegration in this area is quite successful, with success estimates over 85% [29]. Procedures in the oral cavity occur in an area with a large bacterial load and because implantable devices in the body are at high risk of seeding bacteria, most practitioners placing dental implants provide at least a peri-operative dose of antibiotics, with many more providing a week-long course.

In 2018, a meta-analysis was conducted to determine whether antibiotic prophylaxis was needed with dental implant placement. Out of the seven randomized controlled trials including 1368 patients, no evidence was found to support the use of prophylactic antibiotics in reducing the risk of implant failure [30]. However, they determined the number needed to treat to prevent one implant failure was about 33 patients. Since dental implants are expensive and require months of healing time, many practitioners use antibiotic prophylaxis to prevent failures in their patient population even though initial evidence was not compelling. In 2020, a meta-analysis found a statistically significant reduction in early implant failures in patients who received antibiotic treatment (RR = 0.32 [0.20, 0.51], $P > 0.001$) [31]. While some benefit exists, antibiotic use with dental implants is controversial and should be left to the practitioner's clinical judgment until more controlled clinical trials have been performed.

Bone Augmentation

While there are several indications for using bone augmentation techniques in dentistry, most frequently it is used in the setting of dental implants. As discussed previously, in certain instances bone particulate is placed in the extraction socket to help facilitate enough bone for placement of a dental implant. Other times, a patient may not have enough supporting bone years after the tooth had been extracted, necessitating a bone grafting procedure. In cases of the posterior maxilla, the maxillary sinus can be too low and a sinus lift procedure may need to be performed to allow a dental implant to be placed without perforating the Schneiderian membrane (maxillary sinus membrane). Depending on the bone height and extent of sinus elevation needed, an "internal" sinus elevation may suffice (sometimes referred to as indirect), which means through the hole where one is to place the implant. The other approach is an external (sometimes referred to as lateral window, direct) sinus elevation, which is when a hole is created on the side of the maxilla above where the teeth would be to expose the sinus. This approach allows direct visualization and manipulation of the sinus. Regardless of the approach used, these procedures allow communication of the sinus cavity with the oral flora. This, in conjunction with the use of bone particulate, has resulted in most practitioners using antibiotic prophylaxis, typically with amoxicillin-clavulanate. In a study of 116 patients who received dental implants after sinus augmentation with bone grafting and clindamycin 300 mg every 8 h for 5 days, 4.3% still experienced maxillary sinusitis [32]. In a survey of periodontists (dentists who specialize in the treatment of gingival tissues), the practitioners were significantly more likely to prescribe antibiotics in periodontal surgeries that required bone grafting material [33]. Given the high degree of failure if the bone graft material becomes infected, the use of antibiotics is recommended based on the current available literature.

Medical Conditions

As stated earlier, antibiotic prophylaxis in dentistry generally falls into two categories: prevention of surgical site infections and prevention of transient bacteremia that can result in systemic infections such as infective endocarditis or prosthetic joints infections. The latter will be discussed in the section below and is often confusing. See Table 15.2 for current recommendations.

Cardiac

In 1923, Lewis and Grant suggested that transient asymptomatic bacteremia may be the cause of endocarditis in patients with valvular heart disease [34]. One of the most common reasons physicians prescribe antibiotic prophylaxis (AP) to patients before dental procedures is to prevent infective endocarditis (IE) [35]. IE is a devastating disease with an in-hospital mortality rate of 15–20% and a 1-year mortality rate of almost 40% [36]. In the United States, IE can also be financially devastating, with the average hospital stay cost-

Table 15.2 Medical conditions that are "high risk" requiring antibiotic prophylaxis for invasive dental procedures

Medical condition	Antibiotic prophylaxis
Mitral valve prolapse	No
Heart valve repair (mechanical/prosthetic)	Yes
Heart valve repair (allograft/xenograft)	No
Unrepaired congenital heart disease	Yes
Repaired congenital heart disease (prosthetic)	Yes—At least 6 months following or until endothelization has occurred
Cardiac stents	No
Ventricular assist devices	No
Heart transplants with valvulopathy	Yes
Diabetics	No
Orthopedic joint replacements	Depends—Usually no
Pregnancy	No
Bisphosphonates	Yes
Immunosuppressed	Depends

ing over $160,000 [37]. However, IE is relatively uncommon. In 2011 there were 15 hospital admissions for IE for every 100,000 people in the United States [38]. For patients where AP is indicated, the American Heart Association (AHA) recommends administering 2 g of Amoxicillin or 600 mg of clindamycin orally 30–60 min before the procedure. Other antibiotics may be given intramuscularly or intravenously for patients allergic to or unable to take oral antibiotics. The complete recommendations may be found in the AHA guidelines [39].

Although the pathogenesis of IE is complex, it normally occurs when there is damage to the endocardium, leading to non-bacterial thrombotic endocarditis (NBTE). Platelets and fibrin are deposited as part of NBTE and provide a substrate for bacterial adherence and proliferation [40]. Several medical conditions have been shown to predispose patients to IE, but the AHA does not recommend AP before invasive dental procedures for all of them. AP is only recommended for those patients at the highest risk of adverse outcomes from viridans group streptococci (VGS) [39, 41]. Known to be part of the normal oral flora, VGS is the most isolated organism in studies that have examined bacteremia after invasive dental procedures and is the target of AP [42, 43]. It has been estimated that VGS accounts for 17% of all IE cases [36]. However, the bacteria responsible for IE vary significantly by region. For example, VGS accounts for 26% of IE cases in South America but only for 9% of IE cases in North America [44].

It has long been theorized that bacteremia resulting from dental procedures contributes to IE [45]. However, no prospective randomized trials examine the efficacy of AP in reducing the incidence of IE itself [41]. Most evidence supporting AP is from observational and animal studies. As outlined earlier in the chapter, rates of bacteremia are often used as a corollary of IE risk. Because the incidence of IE is so low, a very large sample size would be required for an adequately powered clinical trial. In addition, even if a close temporal relationship were observed it would be difficult to rule out bacteremia from daily activities, such as chewing, brushing, and flossing, as the source of IE [39]. Although there is no strong evidence linking bacteremia from dental procedures to onset of IE, there is evidence that invasive dental procedures such as tooth extractions lead to bacteremia. Furthermore, evidence suggests that prophylactic antibiotics such as amoxicillin can reduce this bacteremia. A 2008 double-blinded, placebo-controlled study by Lockhart et al. examined blood cultures before and after dental extractions. All baseline pre-surgery blood cultures were negative except for 1% of the cultures ($n = 290$), which were likely contaminated from the patient's skin. Post-surgery, the overall incidence of bacteremia following tooth extractions with prophylactic amoxicillin was 56%, while the incidence of bacteremia following extraction with a placebo was 80% (χ^2 $P < 0.0001$) [13].

In 1955, the AHA first recommended using penicillin before dental procedures to prevent IE. Since then, antibiotic prophylaxis has remained the standard procedure to prevent infective endocarditis, but the recommended uses for AP have narrowed. In 2007 the American Heart Association (AHA) updated its recommendations for the prevention of infective endocarditis. A literature review concluded that very few cases of infective endocarditis may be prevented using prophylactic antibiotics before dental procedures [39]. Although strong evidence linking invasive dental procedures to IE is limited, most preeminent health organizations have determined that the potential benefits of prophylactic antibiotics outweigh the risks for at least a subset of patients with preexisting conditions. Therefore, by consensus opinion, the AHA recommends AP before invasive dental procedures in patients with the highest risk of adverse outcomes from IE. The guidelines of the American Heart Association (AHA), European Society of Cardiology (ESC), and National Institute for Health and Care Excellence (NICE) are outlined in Fig. 15.1.

After the AHA guidelines were updated in 2007, there was a significant reduction in AP use [46]. Most studies found that there was either no increase in the cases of IE or no change in the number of VGS IE cases in the United States [38, 47–53]. A few studies found an increase in IE after the guideline change, but there was no convincing evidence to suggest an increase in VGS IE after 2007 [41, 46, 54]. After the 2009 ESC guideline update which also restricted the use of AP before dental procedures, a few studies showed an increase in IE. However, those studies also failed to demonstrate an increase in VGS IE [55, 56].

While AHA and ESC guidelines have remained very similar, NICE recommendations diverged from the other organizations in 2008, no longer recommending AP before invasive dental procedures. Critics soon began to question the validity of the NICE guidelines. A 2014 study by Dayer et al. analyzed data of patients diagnosed with IE and data for AP use in England from 2000 to 2013. They found a significant decline in prescriptions for prophylactic antibiotics after NICE guidelines were updated in 2008 ($P < 0.0001$). In addition, they found that starting in March of 2008, IE cases had increased significantly above the projected trend ($P < 0.0001$). By March of 2013, 35 more cases per month of IE were reported than projected by the historical trend [57]. Although this study did not establish a causal relationship between the restricted use of AP and an increased IE incidence, it helped catalyze another change in the NICE guidelines. In 2016 the NICE guidelines were revised from "not recommended" to "not recommended routinely," indicating that in some cases, it was appropriate for the use of prophylactic antibiotics before dental procedures.

Based on the evidence available, it seems that current guidelines appropriately consider the benefits versus the risks when recommending AP before dental procedures. However, there is a lack of prospective studies on the subject and many of the recommendations are based on the consensus opinion of experts. Thus, questions remain about the efficacy of AP before dental procedures to prevent IE. From 2011 to 2015, more than 80% of AP before dental procedures were unnecessary, according to AHA guidelines [58]. Given the risks of antibiotic resistance, anaphylaxis, and *Clostridioides difficile*, this is a concerning statistic and highlights the need for more evidence to address physician concerns.

Mitral Valve Prolapse (MVP)

Mitral Valve Prolapse (MVP) is a common condition estimated to affect 2–3% of the population [59–61]. It is a major source of uncertainty for clinicians who are deciding whether to prescribe AP for patients undergoing invasive dental procedures [35]. Certain cases of MVP carry a higher risk of developing IE. To understand the risk of IE in MVP patients, MVP must be broken down into multiple categories [39]. The categories of consequence are MVP with regurgitation, MVP without regurgitation, and MVP with a flail leaflet. Several studies have found that MVP patients with an audible murmur of mitral regurgitation or with a flail leaflet were at a significantly higher risk of developing IE than MVP patients without these conditions [62–64]. In contrast, MVP patients without regurgitation or a flail leaflet have been shown to have a similar risk of developing IE as the general population [63]. Despite an increased risk of IE among some MVP patients, the AHA does not currently recommend AP before dental procedures for most MVP patients. The AHA only recommends AP before invasive dental procedures for patients with MVP that have been repaired or replaced with prosthetic material. Interestingly, a 2018 study by Isabel Zegri-Reiriz et al. found that patients with bicuspid aortic valve (BAV) and MVP had higher rates of VGS IE. They suggested that this VGS IE had a possible odontogenic origin, and that AP should be reconsidered in BAV and MVP patients undergoing invasive dental procedures [65]. The AHA, citing this same study, highlighted the fact that BAV and MVP patients who developed IE had significantly lower in-hospital mortality rates than patients with other high-risk conditions who develop IE [41]. Although the AHA acknowledges that certain patients with MVP are at a higher risk for developing IE, they do not recommend AP for most patients with MVP. They contend that lower mortality rates among BAV and MVP patients who develop IE, and the emerging threat of multidrug resistant microorganisms supports their decision to restrict the use of AP in this population [39, 41].

There are many ways in which heart valve defects may be remedied by surgical intervention. The valve may be repaired, or it may be replaced with a human valve, an animal valve, a mechanical valve, or a transcatheter aortic valve. There is a substantial body of evidence to suggest that patients with a valve that has been repaired or replaced with any prosthetic material are at a high risk of developing IE [63, 66]. Patients with prosthetic valves who develop IE are also at a high risk of mortality [67, 68]. For these reasons, the AHA and the ESC both recommend AP before invasive dental procedures for patients with a valve that has been repaired or replaced using prosthetic material [39, 69]. Neither the AHA or the ESC recommends AP before dental procedures for patients with repaired or replaced valves using human or animal tissue.

Congenital Heart Disease

In higher-income countries, congenital heart disease (CHD) is the most common underlying condition for children at risk for IE [41]. Several retrospective studies have shown patients with CHD to be at a higher lifetime risk of developing IE than the general population [70–72]. A study using the CONCOR Adult Congenital Heart Disease registry in the Netherlands found the incidence of IE in adults with CHD to be 110 per 100,000 person-years, well above the general population average of 1.5–6.0 per 100,000 person-years [73, 74]. However, CHD is a broad term encompassing many kinds of heart defects, each predisposing patients to a different likelihood of developing IE. Several retrospective case studies have shown an increased risk of IE in patients with cyanotic CHD and with CHD that has been repaired using prosthetic material, particularly prosthetic valves. One retrospective study using the Quebec CHD database found the incidence of IE in children with cyanotic CHD to be 207 per 100,000 person-years, significantly higher than the overall

incidence of IE in children with CHD, which was 41 per 100,000 person-years [75]. Another study found the incidence of IE in adults with CHD who had a prosthetically repaired heart valve to be 485 per 100,000 person-years [76]. The AHA and ESC recommend AP before invasive dental procedures for both conditions: unrepaired cyanotic CHD and CHD repaired with prosthetic material. AP is only recommended for 6 months after CHD has been repaired with prosthetic material in cases where endothelialization occurs. The ESC adds that AP should be provided to patients if residual regurgitation remains, and the AHA also recommends AP for patients with repaired CHD with residual defects that may inhibit endothelialization [41, 69].

Stents

In the mid-1980s, the first coronary artery stent was placed, and like any foreign material implanted into the body, concerns arose about the stent's role in promoting infection. Infected coronary artery stents are difficult to treat and have a high mortality rate, with 8 of the 17 available case studies resulting in mortality. While much is still unknown, the limited number of cases suggest that staphylococci (specifically *Staphylococcus aureus*) are most commonly responsible for coronary stent infections [77]. However, the incidence of stent infection is very low, estimated to occur in less than one in 10,000 cases. Between 1986 and 2012, only 17 cases of coronary stent infection were reported. These infections typically occurred soon after placement. Ten occurred within a week of placement, and 15 occurred within a month of placement. Only two cases of stent infection occurred more than a month after stent placement [77]. The lower long-term risk of infection is likely related to stent endothelialization. After the stent has denuded the endothelium, host proteins capable of binding to pathogens such as *Staphylococcus aureus* are exposed. Re-endothelialization prevents this process from occurring [78, 79]. Although data in humans are lacking, animal studies have shown that the endothelialization of stents generally occurs within 28 days [80]. Other studies have shown endothelialization of stents occurs up to 3 months after placement [77]. There is not sufficient evidence to suggest that invasive dental procedures lead to stent infections. Instead, stent infections likely result from implantation or an active infection [78]. Based on the rarity of stent infections and a lack of evidence linking invasive procedures to stent infection, the AHA does not routinely recommend antibiotic prophylaxis before dental procedures to prevent stent infections [39].

Ventricular Assist Devices (VAD)

Ventricular assist devices (VAD) have a very high rate of infection. The incidence of left ventricular assist device (LVAD) infection has been reported between 13 and 80% [78]. Gram-positive bacterial species, particularly staphylococci, usually cause these infections, while gram-negative bacteria and fungi are also implicated [81]. There are several different kinds of VAD infections, and the pathogenesis can depend upon the site infected. A VAD infection may involve the surgical site, the device pocket, the pump, or the driveline. Most infections involve the driveline, which connects the implanted pump to the external power supply and exits through this skin [78, 81, 82]. Trauma to the barrier between the driveline and the skin may promote an infection that can then spread down the driveline to the pump of the abdominal wall [83]. Driveline infections have been reported to occur in 14–48% of all LVAD cases [84]. As expected, the organisms responsible for driveline infections are commonly found on the skin, such as *Staphylococcus aureus* and coagulase-negative staphylococci [85]. VGS, the target for AP before invasive dental procedures, is not typically responsible for any kind of VAD infection [41]. However, once a VAD infection has occurred, the risk of morbidity and mortality is very high. One study found that the 1-year mortality rate in patients with LVAD infections was 5.6 times greater than LVAD patients without infections. Accordingly, the AHA determined that AP benefits outweigh the risks and recommend the use of AP before invasive dental procedures in VAD patients [41].

Heart Transplants

Since the first heart transplant was performed in 1967, the expected lifespans of heart transplant recipients have gradually increased with the advent of immunosuppressive drugs. While immunosuppressive drugs are lifesaving for transplant patients, this suppression may result in other health issues such as infection, chronic kidney disease, and malignancies [86]. Although the AHA and ESC provide similar guidance for most cases of prophylactic antibiotic use, they are at odds on the topic of prophylactic antibiotics for dental patients who have undergone a heart transplant. The AHA recommends using AP before invasive dental procedures for patients who have received a heart transplant and have developed cardiac valvulopathy [39]. The ESC, citing a lack of solid evidence, does not recommend AP for heart transplant patients with cardiac valvulopathy [69]. Both organizations agree that there is limited evidence supporting the usefulness of AP in these patients; however, the AHA supports their recommendation by pointing to the high risk of adverse outcomes in this patient population. The AHA references a 2005 study by Sherman-Weber et al. published in Transplant Infectious Disease, which followed 659 heart transplant patients. Among these patients, ten developed endocarditis and eight of those died. The median survival time of heart transplant recipients with endocarditis was 1.4 years, significantly shorter than the median survival time of the other heart transplant recipients, which was 9.3 years ($p < 0.001$) [87]. Therefore, while still controversial, clinicians should consider AP in patients who have received a heart transplant and have developed cardiac valvopathy.

Diabetics

Several studies have found an association between perioperative hyperglycemia and poor outcomes [88–90]. Hyperglycemia alters the innate and adaptive immune system in many ways, but the full effects are unknown. Several in vitro studies estimate that leukocyte dysfunction occurs when glycemic levels exceed 200 mg/dL [91]. Neutrophils, macrophages, and natural killer cells are all inhibited. In addition, cytokine production is suppressed, and the complement system is inhibited [92]. As a result, diabetic patients are more vulnerable to infection and are considered immunosuppressed [93]. It is natural to wonder if antibiotic prophylaxis would be appropriate in such a population; however, there is a lack of evidence to support the efficacy of AP in hyperglycemic patients undergoing invasive dental procedures [94, 95]. Several studies have found that well-controlled diabetic patients have similar outcomes as non-diabetic patients undergoing orthopedic and cardiac surgeries. However, the optimal range of glycemic control is still unclear [96, 97]. The American Association of Clinical Endocrinologists and the American Diabetes Association recommend keeping blood glucose levels below 180 mg/dL for non-ICU patients treated with insulin [98]. The endocrine society also recommends maintaining blood glucose levels below 180 mg/dL [99]. The Joint British Diabetes Societies recommends a target of 108–180 mg/dL but adds that blood glucose levels between 72 to 216 mg/dL are acceptable [100]. In a dental setting, where blood glucose levels probably won't be tightly managed, it may be prudent to delay non-emergency surgery for poorly controlled diabetics. A 1999 review study by Alexander recommends referring diabetic patients for improved control if their fasting glucose level exceeds 250 mg/dL [94]. It also must be noted that surgical strain and anesthesia have been shown to induce a hypermetabolic stress response that can result in hyperglycemia [101]. Anesthesia, particularly general anesthesia, is associated with an increase in catecholamines, glucagon, and cortisol [102]. Patients already unable to regulate glucose levels may be particularly susceptible to these effects [101]. This must be considered when managing diabetic patients undergoing invasive dental procedures under general anesthesia. Therefore, while AP is not indicated for well controlled diabetic patients, it is reasonable to consider delaying elective treatment if fasting blood glucoses exceed 250 mg/dL. If uncontrolled and emergency treatment is required, antibiotic use should be left to the practitioner's clinical judgement.

Orthopedic Prosthetics

The first hip prostheses were used in the 1950s, and postoperative infection rates were very high, ranging from 15 to 25% [103]. With the expansion of prosthetic joint surgeries came advances in infection prevention. Today, periprosthetic joint infections (PJI) have been reported to occur in approximately 1% of patients [104]. Managing PJI is reported to exceed $50,000 per case [105]. In the United States alone, over one million total joint arthroplasties (TJA) are performed yearly, and annual hospital costs incurred by PJI of the hip and knee are estimated to reach 1.85 billion dollars by 2020 [106]. Additionally, revisions of total joint arthroplasties result in significantly increased mortality rates. A recent study showed 2-stage revisions for total knee PJI carried a 1-year mortality rate of 4.33% [107]. Consequently, there is a huge potential benefit of further reducing the rate of PJI. The effort to do so has led to the investigation of dental procedures as a source of bacteremia leading to PJI.

While it has been established that dental procedures lead to bacteremia and that AP may reduce that bacteremia, a convincing link between PJI and dental procedures has not been made. The most well-conducted studies have found no association between PJI and dental procedures [108]. A 2010 case-control study by Berbari et al. enrolled 339 patients who underwent total hip or total knee replacements and developed a PJI, and 339 patients who underwent total hip or total knee replacements without developing an infection. Comparing those who underwent dental procedures with and without AP, the investigators found no statistically significant difference in PJI [105].

Several studies have examined the microorganisms responsible for PJI. The most common bacteria responsible for PJI are staphylococci, particularly *Staphylococcus epidermidis,* and *Staphylococcus aureus*, both of which typically originate from the skin [105, 109, 110]. VGS, the main target of AP, is rarely reported in the literature as the organism responsible for PJI. Berbari et al. found a 3% rate of PJI caused by VGS. Furthermore, they found that only 10.3% of PJI was caused by bacteria potentially resulting from the oral cavity [105]. Based on an overall incidence of PJI of 1%, only 0.03% of TJA patients will acquire VGS PJI. Thus, even if AP was effective at preventing a high number of these cases, the risks of AP must be weighed against the benefits.

In 2016, the American Academy of Orthopaedic Surgeons (AAOS) and the American Dental Association (ADA) reviewed the literature for the basis of the 2012 AAOS-ADA guidelines and the 2015 ADA guidelines and provided updated guidance on the use of prophylactic antibiotics, assessing the benefits versus the risks. They determined that, in most cases, it is not necessary to prescribe prophylactic antibiotics to patients with orthopedic implants undergoing dental procedures [108]. The ADA guide states "In general, for patients with prosthetic joint implants, prophylactic antibiotics are not recommended prior to dental procedures to prevent prosthetic joint infection." The AAOS says "The practitioner might consider discontinuing the practice of routinely prescribing prophylactic antibiotics for patients with hip and knee prosthetic joint implants undergoing dental pro-

cedures." However, the AAOS and ADA deemed the use of prophylactic antibiotics appropriate prior to invasive dental procedures for a small subset of patients, including severely immunocompromised patients with a history of prosthetic joint infection that required surgery within 1-year of surgery. Although it is a good reference, the AAOS and ADA guidelines are not meant to be comprehensive or fixed. The AAOS urges the clinician to use their own judgment and the patient's circumstances to guide treatment.

Despite recommendations to the contrary, the prescription of prophylactic antibiotics prior to dental procedures to prevent PJI remains a common practice [111–113]. One study surveyed orthopedic surgeons and dentists in the United States and found that 81% of respondents were aware of ADA and AAOS recommendations. Of those clinicians, nearly 75% stated that they would prescribe AP before invasive dental procedures for patients with prosthetic implants [112]. The risks of overprescribing antibiotics are hard to quantify and not as immediate to the clinician as the risk of infection. Often it seems the prescriber is taking a "better safe than sorry" approach.

Bisphosphonate

In the past two decades, the United States has seen a surge of bisphosphonate prescriptions. Bisphosphonates have proved useful for patients with osteoporosis, significantly reducing the risk of fracture in this population [114]. However, bisphosphonates have also been correlated with osteonecrosis of the jaw. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) was first reported by Marx in 2003 [115]. It is defined as exposed bone in the maxillofacial region for 8 or more weeks and a history of bisphosphonates with the absence of radiation therapy. Typically, BRONJ occurs after a dentoalveolar surgery such as a tooth extraction but occasionally occurs spontaneously [116]. Although the epidemiology is not well understood, one study found the prevalence of BRONJ to be 0.10% among patients receiving chronic oral bisphosphonate therapy [117]. In 2014, the AAOMS position paper reclassified BRONJ as medication-related osteonecrosis of the jaw (MRONJ) [118]. Several factors increase a patient's risk for developing MRONJ. The incidence of MRONJ increases with age and is more common in the mandible than in the maxilla. Patients on bisphosphonates for more than 3 years, corticosteroids, angiogenesis inhibitors, smokers, and patients with poor oral hygiene are at an elevated risk for MRONJ [119–121]. Evidence suggests that AP before invasive dental procedures may help to prevent MRONJ in patients taking oral or IV bisphosphonates [122–124]. The ADA acknowledges that AP may be useful to prevent MRONJ but cites a lack of controlled studies on the subject. They suggest that the clinician should decide on a case-by-case basis if AP is appropriate based on the patient's individual risk factors [116, 125]. The ADA emphasizes the importance of good oral hygiene and regular dental care to manage a patient's risk for MRONJ.

Immunosuppressed

As noted above, heart transplant recipients with valvulopathy may be considered for AP prior to dental procedures, although the data supporting this are lacking. The role of AP in other immunocompromised populations remains even less clear. Immunosuppression itself may or may not be a risk factor for the development of native valve endocarditis. While HIV infection had been suggested to be an independent determinant of infective endocarditis among intravenous drug users [126], this was not confirmed by subsequent studies. Furthermore, when presenting as an opportunistic infection in AIDS patients, endocarditis may be caused by unusual organisms such as *Salmonella* and *Listeria* rather than VGS [127, 128]. Despite a lack of evidence that immunosuppressed individuals suffer from a greater incidence of endocarditis, they may be at increased risk for complications of such infections. Therefore, AP can be considered on a case-by-case basis. In order to decide upon an optimal strategy, consultations between the patient's medical and dental providers are often helpful. Populations in which to consider AP (despite falling outside of official guidelines) include those with HIV infection, genetic immune deficiencies, neutropenia, cancer chemotherapy, solid organ transplants, and hematopoietic stem cell transplants [129].

Pregnancy

In 1979, the FDA began using a letter classification system to indicate medication safety for pregnant women. After 2015 this system was replaced with a more complex labeling system but remains a useful guide. The three most prescribed antibiotics by dentists—amoxicillin, clindamycin, and penicillin V—all fall into a pregnancy category rating of B from the FDA. This category is for medications that have failed to demonstrate a risk to the fetus in animal studies but lack well-controlled studies in pregnant women. Due to the ethical concerns of performing randomized controlled trials on pregnant women, category B is the safest classification the FDA has awarded for an antibiotic. Other less frequently prescribed antibiotics by dentists such as azithromycin, cephalexin, and amoxicillin/clavulanate were also given a category B rating by the FDA and are considered safe for use in pregnant women. Although class B antibiotics do not appear to have teratogenic effects, they likely affect the maternal microbiome [130]. Few published studies examine the effects of antibiotics on the maternal and fetal microbiome, so the consequences are largely unknown [131]. However, antibiotics may alter the microbiota of the birth canal and have longer-term effects on microbial colonization of the

baby [132]. In addition, a correlation has been found between antibiotic use in the second or third trimester and childhood obesity [133]. Given the many unknown effects of antibiotic use, it is important to avoid prescribing antibiotics to this patient population when not indicated. Infections are the most well-known reason a dentist is approached to treat a pregnant patient. The teratogenic potential has a wide range depending on the antibiotic of choice. Antibiotic prophylaxis is not required in pregnant patients, but often dental treatment is delayed until after pregnancy and is only preformed when an infection exists. It is recommended to use antibiotics such as amoxicillin or clindamycin in the pregnant patient when treating an infection [47].

Risk of Over-Prescribing

As noted above, widespread use of antimicrobial prophylaxis is not without negative consequences. These drawbacks can be divided broadly into adverse drug reactions (ADRs) and the development of antimicrobial resistance. Specific ADRs relate to the individual antibiotic being prescribed and to the patient's underlying health status (medical comorbidities, allergies, and intolerances). The overall risk of ADRs encountered from antibiotics utilized for AP is very low [41]. When it was utilized more regularly, clindamycin was associated with gastrointestinal side effects and *C. difficile* colitis [134]. Studies have estimated that up to 15% of incident cases of *C. difficile* colitis relate to AP prescribed for dental work [135]. Azithromycin is better tolerated than clindamycin but can be associated with prolongation of the QT interval on ECG. While the risk of resultant arrhythmias (including torsades des points) is quite low, the medication should be used with caution in individuals with a history of abnormal electrophysiology [136]. Single-dose doxycycline is largely free from life-threatening ADRs. Serious and fatal reactions to single doses of beta lactam and cephalosporin antibiotics are extremely rare. Most of these relate to underlying patient allergies, which should be assessed with a careful history prior to antibiotic prescription. Without a history of anaphylaxis or other serious allergies, the probability of life-threatening reactions to specific antibiotics is very low. It is estimated that fatal anaphylaxis from single-dose cephalosporin antibiotics occurs less than 1 in one million doses in individuals without a history of serious reactions to the class of medications [136]. While this risk is exceedingly low, it does emphasize that some degree of benefit should be expected prior to prescribing AP.

Antimicrobial resistance secondary to unnecessary antibiotic use poses a threat to both individual patients and the public at large. According to the US Centers for Disease Control and Prevention, at least 2.8 million Americans are infected with resistant bacteria each year, resulting in 35,000 deaths [137]. While there are several strategies to combat this, antimicrobial stewardship is of prime importance. This entails using antibiotics only when necessary, selecting the most appropriate agent, and choosing the correct dose and duration of therapy. The role of AP in driving antibiotic resistance in the larger population is unclear. Still, there is particular concern that AP may result in selection of resistant VGS strains [41]. Several studies have demonstrated an increase in VGS resistance following a single dose of amoxicillin, although the magnitude/significance of this has varied [138, 139]. As this effect is thought to wane by 3–4 weeks, authors have suggested waiting at least 4 weeks between procedures or altering the AP regimen. Although the impact of AP on antibiotic resistance remains in question, judicious use of antibiotics in an evidence-based manner is clearly essential [41].

Summary

The use of antibiotics as a prophylaxis in dentistry remains controversial in several areas. For simplicity purposes, "invasive" dental procedures can result in a transient bacteremia and generally include dental cleanings and deep cleanings, tooth extractions, biopsies, as well as surgical procedures such as dental implants, bone grafting, pre-prosthetic surgeries, and third molar extractions. Generally, fillings and root canals are not invasive and do not result in bleeding or an increased risk of transient bacteremia. If the provider believes bleeding will occur from the procedure or from obtaining isolation on the teeth, he or she can consider antibiotic prophylaxis in high-risk patient populations. Providers often over-prescribe antibiotics to patients undergoing dental treatment, but AP is recommended in only select patient populations. The American Heart Association (AHA) recommends routine antibiotic prophylaxis in patients with unrepaired cyanotic congenital heart disease (CHD) and CHD repaired with prosthetic material. AP is only recommended for 6 months after CHD has been repaired with prosthetic material in cases where endothelialization occurs. The AHA also recommends antibiotic prophylaxis in patients with VADs and heart transplants. Patients who have a history of infective endocarditis in the past, in most cases, require antibiotic prophylaxis. Other instances may require antibiotic prophylaxis, and this is left to the practitioner's own clinical judgement.

References

1. Stein K, Farmer J, Singhal S, Marra F, Sutherland S, Quiñonez C. The use and misuse of antibiotics in dentistry: a scoping review. J Am Dent Assoc. 2018;149(10):869–84.e5.
2. Forner L, Larsen T, Kilian M, Holmstrup P. Incidence of bacteremia after chewing, tooth brushing and scaling in individuals with periodontal inflammation. J Clin Periodontol. 2006;33(6):401–7.

3. Schlein RA, Kudlick EM, Reindorf CA, Gregory J, Royal GC. Toothbrushing and transient bacteremia in patients undergoing orthodontic treatment. Am J Orthod Dentofac Orthop. 1991;99(5):466–72.
4. Akbulut Y, Goymen M, Zer Y, Buyuktas MA. Investigation of bacteremia after debonding procedures. Acta Odontol Scand. 2018;76(5):314–9.
5. Martin M. Is there a link between tooth brushing and infective endocarditis? Int Dent J. 2003;53(Suppl 3):187–90.
6. Chung A, Kudlick EM, Gregory JE, Royal GC, Reindorf CA. Toothbrushing and transient bacteremia in patients undergoing orthodontic treatment. Am J Orthod Dentofac Orthop. 1986;90(3):181–6.
7. Deo PN, Deshmukh R. Oral microbiome: unveiling the fundamentals. J Oral Maxillofac Pathol. 2019;23(1):122–8.
8. Kilian M, Chapple IL, Hannig M, Marsh PD, Meuric V, Pedersen AM, et al. The oral microbiome - an update for oral healthcare professionals. Br Dent J. 2016;221(10):657–66.
9. Lockhart PB, Durack DT. Oral microflora as a cause of endocarditis and other distant site infections. Infect Dis Clin N Am. 1999;13(4):833–50, vi.
10. Doern CD, Burnham CA. It's not easy being green: the viridans group streptococci, with a focus on pediatric clinical manifestations. J Clin Microbiol. 2010;48(11):3829–35.
11. Sutter VL. Anaerobes as normal oral flora. Rev Infect Dis. 1984;6(Suppl 1):S62–6.
12. Baltch AL, Schaffer C, Hammer MC, Sutphen NT, Smith RP, Conroy J, et al. Bacteremia following dental cleaning in patients with and without penicillin prophylaxis. Am Heart J. 1982;104(6):1335–9.
13. Lockhart PB, Brennan MT, Sasser HC, Fox PC, Paster BJ, Bahrani-Mougeot FK. Bacteremia associated with toothbrushing and dental extraction. Circulation. 2008;117(24):3118–25.
14. Marchionni S, Toti P, Barone A, Covani U, Esposito M. The effectiveness of systemic antibiotic prophylaxis in preventing local complications after tooth extraction. A systematic review. Eur J Oral Implantol. 2017;10(2):127–32.
15. Yoshida K, Kodama Y, Nagai T, Estacio Salazar AR, Kaneko S, Saito C, et al. Clinico-statistical survey of oral antimicrobial prophylaxis and surgical site infection regarding ordinary tooth extraction and mandibular wisdom tooth extraction in the dental outpatient clinic. J Infect Chemother. 2021;27(2):192–7.
16. Menon RK, Kar Yan L, Gopinath D, Botelho MG. Is there a need for postoperative antibiotics after third molar surgery? A 5-year retrospective study. J Investig Clin Dent. 2019;10(4):e12460.
17. Ren YF, Malmstrom HS. Effectiveness of antibiotic prophylaxis in third molar surgery: a meta-analysis of randomized controlled clinical trials. J Oral Maxillofac Surg. 2007;65(10):1909–21.
18. Reiland MD, Ettinger KS, Lohse CM, Viozzi CF. Does administration of oral versus intravenous antibiotics for third molar removal have an effect on the incidence of alveolar osteitis or postoperative surgical site infections? J Oral Maxillofac Surg. 2017;75(9):1801–8.
19. Halpern LR, Dodson TB. Does prophylactic administration of systemic antibiotics prevent postoperative inflammatory complications after third molar surgery? J Oral Maxillofac Surg. 2007;65(2):177–85.
20. Poeschl PW, Eckel D, Poeschl E. Postoperative prophylactic antibiotic treatment in third molar surgery--a necessity? J Oral Maxillofac Surg. 2004;62(1):3–8; discussion 9.
21. Marcussen KB, Laulund AS, Jørgensen HL, Pinholt EM. A systematic review on effect of single-dose preoperative antibiotics at surgical osteotomy extraction of lower third molars. J Oral Maxillofac Surg. 2016;74(4):693–703.
22. Moreno-Drada JA, García-Perdomo HA. Effectiveness of antimicrobial prophylaxis in preventing the spread of infection as a result of oral procedures: a systematic review and meta-analysis. J Oral Maxillofac Surg. 2016;74(7):1313–21.
23. Morrow AJ, Dodson TB, Gonzalez ML, Chuang SK, Lang MS. Do postoperative antibiotics decrease the frequency of inflammatory complications following third molar removal? J Oral Maxillofac Surg. 2018;76(4):700–8.
24. Menon RK, Gopinath D, Li KY, Leung YY, Botelho MG. Does the use of amoxicillin/amoxicillin-clavulanic acid in third molar surgery reduce the risk of postoperative infection? A systematic review with meta-analysis. Int J Oral Maxillofac Surg. 2019;48(2):263–73.
25. Iguchi R, Moroi A, Saito Y, Takayama A, Hiraide R, Yoshizawa K, et al. Evaluation of intravenous prophylaxis antibiotics for third molar extraction under general anesthesia. Odontology. 2020;108(4):681–7.
26. Isiordia-Espinoza MA, Aragon-Martinez OH, Martínez-Morales JF, Zapata-Morales JR. Risk of wound infection and safety profile of amoxicillin in healthy patients which required third molar surgery: a systematic review and meta-analysis. Br J Oral Maxillofac Surg. 2015;53(9):796–804.
27. Arteagoitia MI, Barbier L, Santamaría J, Santamaría G, Ramos E. Efficacy of amoxicillin and amoxicillin/clavulanic acid in the prevention of infection and dry socket after third molar extraction. A systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal. 2016;21(4):e494–504.
28. Dobson M, Pillon L, Kwon O, Innes N. Chlorhexidine gel to prevent alveolar osteitis following mandibular third molar extractions. Evid Based Dent. 2018;19(1):16–7.
29. Simonis P, Dufour T, Tenenbaum H. Long-term implant survival and success: a 10-16-year follow-up of non-submerged dental implants. Clin Oral Implants Res. 2010;21(7):772–7.
30. Singh Gill A, Morrissey H, Rahman A. A systematic review and meta-analysis evaluating antibiotic prophylaxis in dental implants and extraction procedures. Medicina (Kaunas). 2018;54(6):95.
31. Canullo L, Troiano G, Sbricoli L, Guazzo R, Laino L, Caiazzo A, et al. The use of antibiotics in implant therapy: a systematic review and meta-analysis with trial sequential analysis on early implant failure. Int J Oral Maxillofac Implants. 2020;35(3):485–94.
32. Chirilă L, Rotaru C, Filipov I, Săndulescu M. Management of acute maxillary sinusitis after sinus bone grafting procedures with simultaneous dental implants placement - a retrospective study. BMC Infect Dis. 2016;16(Suppl 1):94.
33. Hai JH, Lee C, Kapila YL, Chaffee BW, Armitage GC. Antibiotic prescribing practices in periodontal surgeries with and without bone grafting. J Periodontol. 2020;91(4):508–15.
34. Lewis T, Grant R. Observation relating to subascute infective endocarditis. Heart. 1923;10:21–9.
35. Lockhart PB, Hanson NB, Ristic H, Menezes AR, Baddour L. Acceptance among and impact on dental practitioners and patients of American Heart Association recommendations for antibiotic prophylaxis. J Am Dent Assoc. 2013;144(9):1030–5.
36. Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler VG Jr, Bayer AS, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the international collaboration on endocarditis-prospective cohort study. Arch Intern Med. 2009;169(5):463–73.
37. Lone AN, Khan M, Khan MU, Khan SU, Balla S. Abstract 28: health care cost burden of infective endocarditis in United States: a nationwide study. Circ Cardiovasc Qual Outcomes. 2020;13(Suppl_1):A28-A.
38. Pant S, Patel NJ, Deshmukh A, Golwala H, Patel N, Badheka A, et al. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. J Am Coll Cardiol. 2015;65(19):2070–6.
39. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al. Prevention of infective endocarditis: guide-

lines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007;116(15):1736–54.
40. Sullam PM, Drake TA, Sande MA. Pathogenesis of endocarditis. Am J Med. 1985;78(6b):110–5.
41. Wilson WR, Gewitz M, Lockhart PB, Bolger AF, DeSimone DC, Kazi DS, et al. Prevention of Viridans group streptococcal infective endocarditis: a scientific statement from the American Heart Association. Circulation. 2021;143(20):e963–e78.
42. Hall G, Heimdahl A, Nord CE. Bacteremia after oral surgery and antibiotic prophylaxis for endocarditis. Clin Infect Dis. 1999;29(1):1–8; quiz 9–10.
43. Heimdahl A, Hall G, Hedberg M, Sandberg H, Söder PO, Tunér K, et al. Detection and quantitation by lysis-filtration of bacteremia after different oral surgical procedures. J Clin Microbiol. 1990;28(10):2205–9.
44. Hubers SA, DeSimone DC, Gersh BJ, Anavekar NS. Infective endocarditis: a contemporary review. Mayo Clin Proc. 2020;95(5):982–97.
45. Pallasch TJ, Wahl MJ. Focal infection: new age or ancient history? Endod Top. 2003;4(1):32–45.
46. Garg P, Ko DT, Bray Jenkyn KM, Li L, Shariff SZ. Infective endocarditis hospitalizations and antibiotic prophylaxis rates before and after the 2007 American Heart Association guideline revision. Circulation. 2019;140(3):170–80.
47. Rogers AM, Schiller NB. Impact of the first nine months of revised infective endocarditis prophylaxis guidelines at a university hospital: so far so good. J Am Soc Echocardiogr. 2008;21(6):775.
48. Desimone DC, Tleyjeh IM, Correa de Sa DD, Anavekar NS, Lahr BD, Sohail MR, et al. Incidence of infective endocarditis caused by viridans group streptococci before and after publication of the 2007 American Heart Association's endocarditis prevention guidelines. Circulation. 2012;126(1):60–4.
49. Pasquali SK, He X, Mohamad Z, McCrindle BW, Newburger JW, Li JS, et al. Trends in endocarditis hospitalizations at US children's hospitals: impact of the 2007 American Heart Association antibiotic prophylaxis guidelines. Am Heart J. 2012;163(5):894–9.
50. Bikdeli B, Wang Y, Kim N, Desai MM, Quagliarello V, Krumholz HM. Trends in hospitalization rates and outcomes of endocarditis among Medicare beneficiaries. J Am Coll Cardiol. 2013;62(23):2217–26.
51. DeSimone DC, Tleyjeh IM, Correa de Sa DD, Anavekar NS, Lahr BD, Sohail MR, et al. Incidence of infective endocarditis due to Viridans group streptococci before and after the 2007 American Heart Association's prevention guidelines: an extended evaluation of the Olmsted County, Minnesota, population and nationwide inpatient sample. Mayo Clin Proc. 2015;90(7):874–81.
52. Toyoda N, Chikwe J, Itagaki S, Gelijns AC, Adams DH, Egorova NN. Trends in infective endocarditis in California and New York state, 1998-2013. JAMA. 2017;317(16):1652–60.
53. Bates KE, Hall M, Shah SS, Hill KD, Pasquali SK. Trends in infective endocarditis hospitalisations at United States children's hospitals from 2003 to 2014: impact of the 2007 American Heart Association antibiotic prophylaxis guidelines. Cardiol Young. 2017;27(4):686–90.
54. Sakai Bizmark R, Chang RR, Tsugawa Y, Zangwill KM, Kawachi I. Impact of AHA's 2007 guideline change on incidence of infective endocarditis in infants and children. Am Heart J. 2017;189:110–9.
55. van den Brink FS, Swaans MJ, Hoogendijk MG, Alipour A, Kelder JC, Jaarsma W, et al. Increased incidence of infective endocarditis after the 2009 European Society of Cardiology guideline update: a nationwide study in The Netherlands. Eur Heart J Qual Care Clin Outcomes. 2017;3(2):141–7.
56. Keller K, von Bardeleben RS, Ostad MA, Hobohm L, Munzel T, Konstantinides S, et al. Temporal trends in the prevalence of infective endocarditis in Germany between 2005 and 2014. Am J Cardiol. 2017;119(2):317–22.
57. Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB, Thornhill MH. Incidence of infective endocarditis in England, 2000-13: a secular trend, interrupted time-series analysis. Lancet. 2015;385(9974):1219–28.
58. Suda KJ, Calip GS, Zhou J, Rowan S, Gross AE, Hershow RC, et al. Assessment of the appropriateness of antibiotic prescriptions for infection prophylaxis before dental procedures, 2011 to 2015. JAMA Netw Open. 2019;2(5):e193909.
59. Freed LA, Levy D, Levine RA, Larson MG, Evans JC, Fuller DL, et al. Prevalence and clinical outcome of mitral-valve prolapse. N Engl J Med. 1999;341(1):1–7.
60. Delling FN, Vasan RS. Epidemiology and pathophysiology of mitral valve prolapse: new insights into disease progression, genetics, and molecular basis. Circulation. 2014;129(21):2158–70.
61. Devereux RB, Jones EC, Roman MJ, Howard BV, Fabsitz RR, Liu JE, et al. Prevalence and correlates of mitral valve prolapse in a population-based sample of American Indians: the Strong Heart Study. Am J Med. 2001;111(9):679–85.
62. Katan O, Michelena HI, Avierinos JF, Mahoney DW, DeSimone DC, Baddour LM, et al. Incidence and predictors of infective endocarditis in mitral valve prolapse: a population-based study. Mayo Clin Proc. 2016;91(3):336–42.
63. Steckelberg JM, Wilson WR. Risk factors for infective endocarditis. Infect Dis Clin N Am. 1993;7(1):9–19.
64. MacMahon SW, Hickey AJ, Wilcken DE, Wittes JT, Feneley MP, Hickie JB. Risk of infective endocarditis in mitral valve prolapse with and without precordial systolic murmurs. Am J Cardiol. 1987;59(1):105–8.
65. Zegri-Reiriz I, de Alarcón A, Muñoz P, Martínez Sellés M, González-Ramallo V, Miro JM, et al. Infective endocarditis in patients with bicuspid aortic valve or mitral valve prolapse. J Am Coll Cardiol. 2018;71(24):2731–40.
66. Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Prosthetic valve endocarditis after surgical aortic valve replacement. Circulation. 2017;136(3):329–31.
67. Ferrieri P, Gewitz MH, Gerber MA, Newburger JW, Dajani AS, Shulman ST, et al. Unique features of infective endocarditis in childhood. Pediatrics. 2002;109(5):931–43.
68. Manne MB, Shrestha NK, Lytle BW, Nowicki ER, Blackstone E, Gordon SM, et al. Outcomes after surgical treatment of native and prosthetic valve infective endocarditis. Ann Thorac Surg. 2012;93(2):489–93.
69. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36(44):3075–128.
70. Dodo H, Child JS. Infective endocarditis in congenital heart disease. Cardiol Clin. 1996;14(3):383–92.
71. Martin JM, Neches WH, Wald ER. Infective endocarditis: 35 years of experience at a children's hospital. Clin Infect Dis. 1997;24(4):669–75.
72. Coward K, Tucker N, Darville T. Infective endocarditis in Arkansan children from 1990 through 2002. Pediatr Infect Dis J. 2003;22(12):1048–52.
73. Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, Veen G, et al. Turning 18 with congenital heart disease:

prediction of infective endocarditis based on a large population. Eur Heart J. 2011;32(15):1926–34.
74. Mylonakis E, Calderwood SB. Infective endocarditis in adults. N Engl J Med. 2001;345(18):1318–30.
75. Rushani D, Kaufman JS, Ionescu-Ittu R, Mackie AS, Pilote L, Therrien J, et al. Infective endocarditis in children with congenital heart disease: cumulative incidence and predictors. Circulation. 2013;128(13):1412–9.
76. Kuijpers JM, Koolbergen DR, Groenink M, Peels KCH, Reichert CLA, Post MC, et al. Incidence, risk factors, and predictors of infective endocarditis in adult congenital heart disease: focus on the use of prosthetic material. Eur Heart J. 2017;38(26):2048–56.
77. Myles O, Thomas WJ, Daniels JT, Aronson N. Infected endovascular stents managed with medical therapy alone. Catheter Cardiovasc Interv. 2000;51(4):471–6.
78. Baddour LM, Bettmann MA, Bolger AF, Epstein AE, Ferrieri P, Gerber MA, et al. Nonvalvular cardiovascular device-related infections. Circulation. 2003;108(16):2015–31.
79. Que YA, François P, Haefliger JA, Entenza JM, Vaudaux P, Moreillon P. Reassessing the role of Staphylococcus aureus clumping factor and fibronectin-binding protein by expression in Lactococcus lactis. Infect Immun. 2001;69(10):6296–302.
80. Belle EV, Tio FO, Couffinhal T, Maillard L, Passeri J, Isner JM. Stent endothelialization. Circulation. 1997;95(2):438–48.
81. Gordon RJ, Quagliarello B, Lowy FD. Ventricular assist device-related infections. Lancet Infect Dis. 2006;6(7):426–37.
82. Gordon RJ, Weinberg AD, Pagani FD, Slaughter MS, Pappas PS, Naka Y, et al. Prospective, multicenter study of ventricular assist device infections. Circulation. 2013;127(6):691–702.
83. Trachtenberg BH, Cordero-Reyes A, Elias B, Loebe M. A review of infections in patients with left ventricular assist devices: prevention, diagnosis and management. Methodist Debakey Cardiovasc J. 2015;11(1):28–32.
84. Pereda D, Conte JV. Left ventricular assist device driveline infections. Cardiol Clin. 2011;29(4):515–27.
85. Leuck AM. Left ventricular assist device driveline infections: recent advances and future goals. J Thorac Dis. 2015;7(12):2151–7.
86. Söderlund C, Rådegran G. Immunosuppressive therapies after heart transplantation--the balance between under- and over-immunosuppression. Transplant Rev (Orlando). 2015;29(3):181–9.
87. Sherman-Weber S, Axelrod P, Suh B, Rubin S, Beltramo D, Manacchio J, et al. Infective endocarditis following orthotopic heart transplantation: 10 cases and a review of the literature. Transpl Infect Dis. 2004;6(4):165–70.
88. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab. 2002;87(3):978–82.
89. Kotagal M, Symons RG, Hirsch IB, Umpierrez GE, Dellinger EP, Farrokhi ET, et al. Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. Ann Surg. 2015;261(1):97–103.
90. Frisch A, Chandra P, Smiley D, Peng L, Rizzo M, Gatcliffe C, et al. Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. Diabetes Care. 2010;33(8):1783–8.
91. Clement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, et al. Management of diabetes and hyperglycemia in hospitals. Diabetes Care. 2004;27(2):553.
92. Berbudi A, Rahmadika N, Tjahjadi AI, Ruslami R. Type 2 diabetes and its impact on the immune system. Curr Diabetes Rev. 2020;16(5):442–9.
93. Jafar N, Edriss H, Nugent K. The effect of short-term hyperglycemia on the innate immune system. Am J Med Sci. 2016;351(2):201–11.
94. Alexander RE. Routine prophylactic antibiotic use in diabetic dental patients. J Calif Dent Assoc. 1999;27(8):611–8.
95. Lockhart PB, Loven B, Brennan MT, Fox PC. The evidence base for the efficacy of antibiotic prophylaxis in dental practice. J Am Dent Assoc. 2007;138(4):458–74; quiz 534–5, 437.
96. Wukich DK. Diabetes and its negative impact on outcomes in orthopaedic surgery. World J Orthop. 2015;6(3):331–9.
97. Navaratnarajah M, Rea R, Evans R, Gibson F, Antoniades C, Keiralla A, et al. Effect of glycaemic control on complications following cardiac surgery: literature review. J Cardiothorac Surg. 2018;13(1):10.
98. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care. 2009;32(6):1119–31.
99. Umpierrez GE, Hellman R, Korytkowski MT, Kosiborod M, Maynard GA, Montori VM, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(1):16–38.
100. Dhatariya K, Levy N, Kilvert A, Watson B, Cousins D, Flanagan D, et al. NHS diabetes guideline for the perioperative management of the adult patient with diabetes. Diabet Med. 2012;29(4):420–33.
101. Duncan AE. Hyperglycemia and perioperative glucose management. Curr Pharm Des. 2012;18(38):6195–203.
102. Duggan EW, Carlson K, Umpierrez GE. Perioperative hyperglycemia management: an update. Anesthesiology. 2017;126(3):547–60.
103. Seymour RA, Whitworth JM. Antibiotic prophylaxis for endocarditis, prosthetic joints, and surgery. Dent Clin N Am. 2002;46(4):635–51.
104. Perfetti DC, Boylan MR, Naziri Q, Paulino CB, Kurtz SM, Mont MA. Have periprosthetic hip infection rates plateaued? J Arthroplast. 2017;32(7):2244–7.
105. Berbari EF, Osmon DR, Carr A, Hanssen AD, Baddour LM, Greene D, et al. Dental procedures as risk factors for prosthetic hip or knee infection: a hospital-based prospective case-control study. Clin Infect Dis. 2010;50(1):8–16.
106. Premkumar A, Kolin DA, Farley KX, Wilson JM, McLawhorn AS, Cross MB, et al. Projected economic burden of periprosthetic joint infection of the hip and knee in the United States. J Arthroplast. 2021;36(5):1484–9.e3.
107. Lum ZC, Natsuhara KM, Shelton TJ, Giordani M, Pereira GC, Meehan JP. Mortality during total knee periprosthetic joint infection. J Arthroplast. 2018;33(12):3783–8.
108. Watters W III, Rethman MP, Hanson NB, Abt E, Anderson PA, Carroll KC, et al. Prevention of orthopaedic implant infection in patients undergoing dental procedures. J Am Acad Orthop Surg. 2013;21(3):180–9.
109. Rosteius T, Jansen O, Fehmer T, Baecker H, Citak M, Schildhauer TA, et al. Evaluating the microbial pattern of periprosthetic joint infections of the hip and knee. J Med Microbiol. 2018;67(11):1608–13.
110. Kotzé MJ. Prosthetic joint infection, dental treatment and antibiotic prophylaxis. Orthop Rev (Pavia). 2009;1(1):e7.
111. McNally CM, Visvanathan R, Liberali S, Adams RJ. Antibiotic prophylaxis for dental treatment after prosthetic joint replacement: exploring the orthopaedic surgeon's opinion. Arthroplast Today. 2016;2(3):123–6.
112. Ward KA, Brundo GC, Nunn M, Wee AG. Current practices of the 2012 antibiotic prophylaxis recommendations for orthopaedic implants in a mid-West City. Int J Health Sci. 2015;3.
113. Colterjohn T, de Beer J, Petruccelli D, Zabtia N, Winemaker M. Antibiotic prophylaxis for dental procedures at risk of causing bacteremia among post-total joint arthroplasty patients: a

survey of Canadian orthopaedic surgeons and dental surgeons. J Arthroplast. 2014;29(6):1091–7.
114. Cummings SR, Lui LY, Eastell R, Allen IE. Association between drug treatments for patients with osteoporosis and overall mortality rates: a meta-analysis. JAMA Intern Med. 2019;179(11):1491–500.
115. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg. 2003;61(9):1115–7.
116. Hellstein JW, Adler RA, Edwards B, Jacobsen PL, Kalmar JR, Koka S, et al. Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis: executive summary of recommendations from the American Dental Association Council on Scientific Affairs. J Am Dent Assoc. 2011;142(11):1243–51.
117. Lo JC, O'Ryan FS, Gordon NP, Yang J, Hui RL, Martin D, et al. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. J Oral Maxillofac Surg. 2010;68(2):243–53.
118. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. J Oral Maxillofac Surg. 2014;72(10):1938–56.
119. Tsao C, Darby I, Ebeling PR, Walsh K, O'Brien-Simpson N, Reynolds E, et al. Oral health risk factors for bisphosphonate-associated jaw osteonecrosis. J Oral Maxillofac Surg. 2013;71(8):1360–6.
120. Nicolatou-Galitis O, Schiødt M, Mendes RA, Ripamonti C, Hope S, Drudge-Coates L, et al. Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment. Oral Surg Oral Med Oral Pathol Oral Radiol. 2019;127(2):117–35.
121. Jeong HG, Hwang JJ, Lee JH, Kim YH, Na JY, Han SS. Risk factors of osteonecrosis of the jaw after tooth extraction in osteoporotic patients on oral bisphosphonates. Imaging Sci Dent. 2017;47(1):45–50.
122. Montefusco V, Gay F, Spina F, Miceli R, Maniezzo M, Teresa Ambrosini M, et al. Antibiotic prophylaxis before dental procedures may reduce the incidence of osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates. Leuk Lymphoma. 2008;49(11):2156–62.
123. Bermúdez-Bejarano EB, Serrera-Figallo M, Gutiérrez-Corrales A, Romero-Ruiz MM, Castillo-de-Oyagüe R, Gutiérrez-Pérez JL, et al. Prophylaxis and antibiotic therapy in management protocols of patients treated with oral and intravenous bisphosphonates. J Clin Exp Dent. 2017;9(1):e141–e9.
124. Poxleitner P, Engelhardt M, Schmelzeisen R, Voss P. The prevention of medication-related osteonecrosis of the jaw. Dtsch Arztebl Int. 2017;114(5):63–9.
125. Dental management of patients receiving oral bisphosphonate therapy: expert panel recommendations. J Am Dent Assoc 2006;137(8):1144–50.
126. Nahass RG, Weinstein MP, Bartels J, Gocke DJ. Infective endocarditis in intravenous drug users: a comparison of human immunodeficiency virus type 1-negative and -positive patients. J Infect Dis. 1990;162(4):967–70.
127. Bestetti RB, Figueiredo JF, Da Costa JC. Salmonella tricuspid endocarditis in an intravenous drug abuser with human immunodeficiency virus infection. Int J Cardiol. 1991;30(3):361–2.
128. Riancho JA, Echevarría S, Napal J, Martin Duran R, Gonzalez MJ. Endocarditis due to Listeria monocytogenes and human immunodeficiency virus infection. Am J Med. 1988;85(5):737.
129. American Academy of Pediatric Dentistry. Antibiotic prophylaxis for dental patients at risk for infection. The reference manual of pediatric dentistry. Chicago, III: American academy of pediatric dentistry; 2022:500–6.
130. Zhang M, Differding MK, Benjamin-Neelon SE, Østbye T, Hoyo C, Mueller NT. Association of prenatal antibiotics with measures of infant adiposity and the gut microbiome. Ann Clin Microbiol Antimicrob. 2019;18(1):18.
131. Kuperman AA, Koren O. Antibiotic use during pregnancy: how bad is it? BMC Med. 2016;14(1):91.
132. Stokholm J, Schjørring S, Eskildsen CE, Pedersen L, Bischoff AL, Følsgaard N, et al. Antibiotic use during pregnancy alters the commensal vaginal microbiota. Clin Microbiol Infect. 2014;20(7):629–35.
133. Mueller NT, Whyatt R, Hoepner L, Oberfield S, Dominguez-Bello MG, Widen EM, et al. Prenatal exposure to antibiotics, cesarean section and risk of childhood obesity. Int J Obes. 2015;39(4):665–70.
134. Bombassaro AM, Wetmore SJ, John MA. Clostridium difficile colitis following antibiotic prophylaxis for dental procedures. J Can Dent Assoc. 2001;67(1):20–2.
135. Thornhill MH, Dayer M, Lockhart PB, Prendergast B. Antibiotic prophylaxis of infective endocarditis. Curr Infect Dis Rep. 2017;19(2):9.
136. Hancox JC, Hasnain M, Vieweg WV, Crouse EL, Baranchuk A. Azithromycin, cardiovascular risks, QTc interval prolongation, torsade de pointes, and regulatory issues: a narrative review based on the study of case reports. Ther Adv Infect Dis. 2013;1(5):155–65.
137. CDC. Antibiotic resistance threats in the United States. Atlanta: US Department of Health and Human Services; 2019.
138. Rammelkamp CH. Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections. Circulation. 1957;15(1):154–8.
139. Mortimer EA, Rammelkamp CH. Prophylaxis of rheumatic fever. Circulation. 1956;14(6):1144–52.

Part III

Perioral Pathology

Michael T. Goupil

Benign Lumps and Bumps

16

Easwar Natarajan

Introduction

Oral soft tissue masses are among the most common oral lesions in clinical practice. Patients presenting with oral masses may be understandably concerned about a malignant process, i.e., oral cancer. Fortunately, most oral masses are benign and result from epithelial and/or mesenchymal tissue proliferation. Oral swellings can have varied clinical appearances, present in various oral locations, and represent a range of pathological processes: reactive/inflammatory, benign neoplasm, malignant neoplasms, developmental/genetic, or rarely, the manifestation of an underlying systemic condition.

Oral Soft Tissue Masses/Nodules: The Diagnostic Process

When developing a differential diagnosis for oral soft tissue masses, clinicians must consider the following: *common things occur commonly*. This is true when faced with any diagnostic dilemma and more so when faced with a new oral mass. As with other problem-focused complaints, the clinical assessment and diagnostic approach to oral masses should proceed in a disciplined, step-wise manner (Fig. 16.1). The diagnostic process must begin with the patient's presenting complaint and gathering information relative to the chief complaint. New oral soft tissue growths can be alarming to patients, especially if they have grown rapidly and associated with symptoms of pain/discomfort/bleeding/discharge, or other symptoms. On the other hand, patients with a history of slow-growing, asymptomatic masses may be aware of them, but not overly concerned. Regardless, clinicians should approach diagnosis by fleshing out a thorough history. The questions listed in Table 16.1 may be used to obtain during the first phase of clinical assessment. Patient responses to questions posed in Table 16.1 provide the clinician valuable information in developing a differential diagnosis. Among these, the following parameters are of paramount importance in determining whether a discovered mass represents a benign growth (exuberant hyperplasia or benign neoplasm) or a malignant neoplasm:

- *Location*: Certain pathological processes occur in specific locations.
- *Duration*: Benign growths are generally long-standing and painless. Malignant neoplasms tend to be more recent in history.
- *Rate of growth*: Benign growths typically grow slower than malignant neoplasms.
- *Surface characteristics*: Benign growths are typically non-ulcerated and smooth-surfaced, while malignant tumors are often ulcerated.
- *Symptoms*: Benign growths tend to be painless. Malignant tumors are often associated with pain, paresthesia, and functional compromise.

The above information should help clinicians determine the appropriate diagnostic and management approach (see Fig. 16.1).

The vast majority of oral soft tissue masses are the result of the following pathological processes:

1. Reactive/inflammatory—Exuberant inflammatory and/or reactive hyperplastic lesions
2. Benign neoplasms—genetic deregulation leading to benign proliferation of epithelial/mesenchymal tumor tissue
3. Malignant neoplasms—cumulative genetic deregulation leading to proliferation and infiltration of epithelial/mesenchymal derived tumor proliferation and infiltration of epithelial/mesenchymal tumor tissue

E. Natarajan (✉)
Section of Oral and Maxillofacial Pathology, University of Connecticut Health Center, Farmington, CT, USA
e-mail: natarajan@uchc.edu

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_16

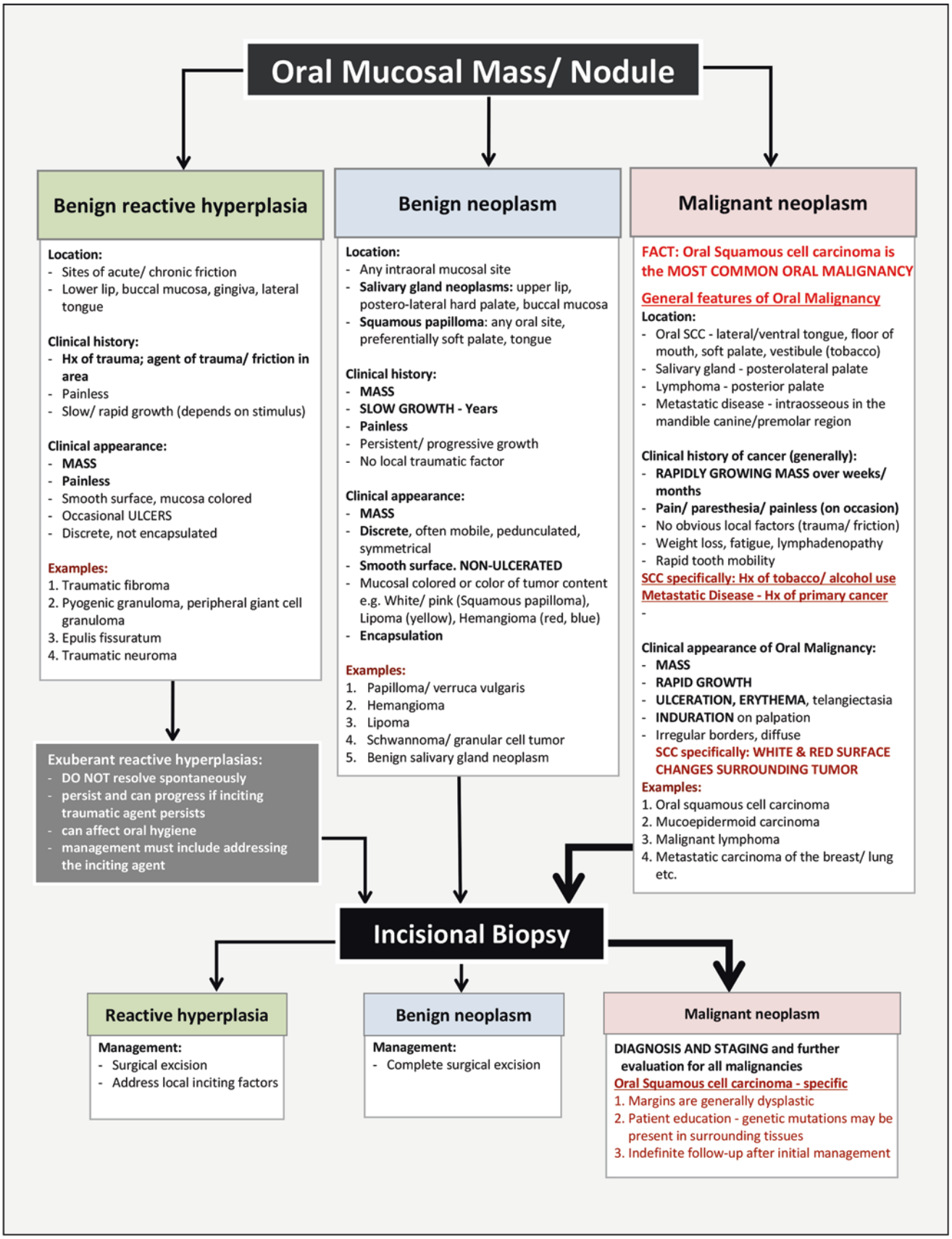


Fig. 16.1 Oral lumps and bumps—diagnostic flowchart

Table 16.1 Oral soft tissue lumps/bumps—patient assessment questions

Subject	Questions
Duration	• When did you discover this lump/mass? • How long have you been aware of this lump/mass?
Progression	• Has the lump grown in size? Has it reduced? Has it fluctuated in size? • Has the lump grown faster in the past few weeks or months? Any changes to the surface?
Location and distribution	• Is this the only such lump in your mouth? Do you have similar lumps in your mouth? How about outside your mouth—on the skin or face?
Stimuli/trigger	• Do you recall a history of trauma? • Are you aware of any parafunctional habit? Cheek biting/chewing/friction? • Any new dental restorations or prostheses? • If you wear prostheses, do they fit well? How long have you had them?
Signs/appearance	• Has the surface of the mass changed in character? Color? Ulcer/sore? • Have you noted any bleeding or discharge? Any foul taste/smell?
Symptoms	• Do you have any pain/discomfort/paresthesia associated with this bump?
Alleviating/aggravating factors	• Have you identified any factors that make the bump grow bigger or smaller? • Have you tried to manage the bump with medications or other means?

Exuberant Inflammatory/Reactive Hyperplasias

Nodules/masses that are reactive/inflammatory are typically masses of acute inflammation (abscesses), chronic inflammation (granulomatous nodules), or tissue repair related. The latter is often in response to a local inciting agent and associated with exuberant granulation tissue. Patients are generally aware of an underlying parafunctional habit, report a local traumatic agent, or present with a chronic, persistent tissue irritant. With a few exceptions, these lesions tend to be painless and grow very slowly over months/years. The surface mucosa is typically intact and similar to the color of the surrounding mucosa. If these lesions are secondarily traumatized, ulcerations and white surface plaques may be seen. Examples include traumatic fibromas (Fig. 16.2a) on the buccal or labial mucosa secondary to biting and epulis fissuratum secondary to denture flange impingement. In lesions caused by granulation tissue hyperplasia involving a vascular component, the mass may appear red, blue, or purple. Granulation tissue-related masses grow faster in response to local irritants. Examples include pyogenic granulomas (and related granulation tissue hyperplasias) (Fig. 16.2b) in response to trauma/local plaque/ill-fitting restoration/extraction sockets. Given their relatively rapid growth rate and vascular component, pyogenic granulomas (and related granulation tissue hyperplasias) tend to present with ulcerated surfaces and occasional bleeding.

Although benign, clinicians need to recognize that exuberant reactive hyperplastic lesions do not resolve spontaneously. Reactive nodules may require surgical excision as they can persist and progress to grow if an inciting agent persists. Clinicians must attempt to address the inciting agent. The best way to determine the cause is to submit excised hyperplastic specimens for histopathological examination and specific diagnosis.

Benign Neoplasms

Benign neoplasms are caused by genetic mutations (acquired/germline) that result in a benign, clonal proliferation of the affected tissue (epithelial/mesenchymal). Unlike exuberant reactive hyperplasias, benign neoplasms can arise in any oral mucosal location and are unrelated to specific traumatic insults/chronic irritants. Benign neoplasms present as slow-growing, painless masses with intact surface mucosal tissue. Patients often know of a slow-growing mass for several months to years and report no associated symptoms. They may be aware of an abnormal color or texture.

Clinically, benign neoplasms are discrete, often mobile (encapsulation), and may be pedunculated (stalk). They tend to be symmetrical and smooth-surfaced. Benign neoplasms may be ulcerated if patients have secondarily traumatized them. Depending on the tumor cell composition, benign neoplasms can range from being mucosal colored (e.g., schwannoma, leiomyoma, true fibroma, neurofibromas) or white/pink (e.g., low-risk HPV-associated squamous papilloma/verruca vulgaris) (Fig. 16.2c), yellow (e.g., lipoma, lymphoid proliferation), red/blue (e.g., vascular malformation, hemangioma), or other color depending on the underlying proliferative component.

As with exuberant reactive hyperplasias, benign neoplasms must be surgically excised. They often lend themselves to easy excision given their discrete, often encapsulated nature.

Malignant Neoplasms

Malignant neoplastic processes result from cumulative genetic defects over years/decades. As described in Chap. 19 on oral and oropharyngeal squamous cell carcinoma the cumulative genetic deregulation within cells and tissues is often driven/accelerated by risk factors. A wide range of malignant neoplasms can present as soft tissue masses on the oral mucosa, including squamous cell carcinomas, salivary gland malignancies (e.g., mucoepidermoid carcinoma, adenoid cystic carcinoma), malignant lymphoma, and oral manifestation of metastatic disease. With this in mind, it must be emphasized that squamous cell carcinoma (OC-SCC) is the

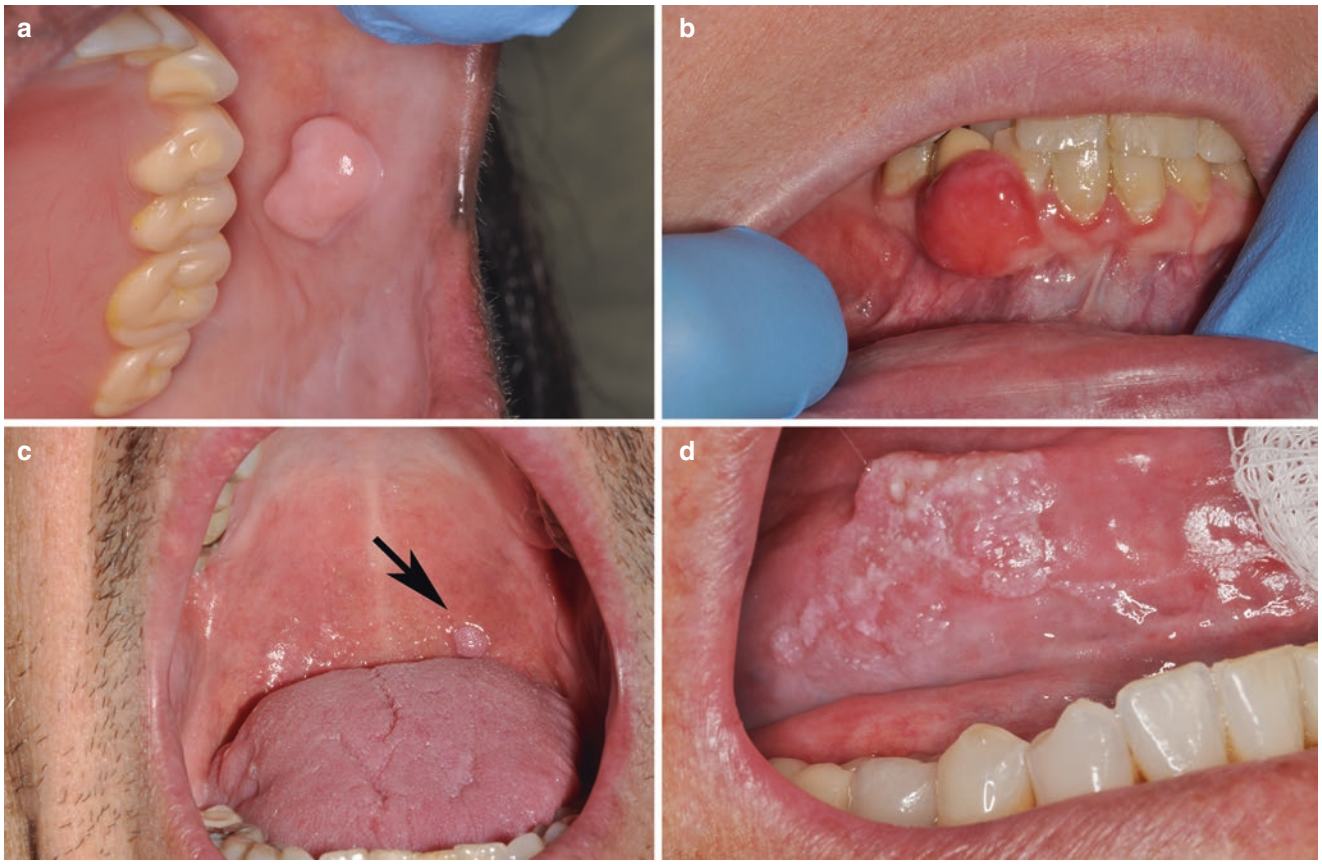


Fig. 16.2 Oral soft tissue swellings—reactive hyperplasia and neoplasia. (**a**) Reactive hyperplasia. *Traumatic fibroma.* Smooth-surfaced, intact, mucosa-colored well-demarcated nodule on the buccal mucosa, a trauma-prone location. (**b**) Granulation tissue hyperplasia. *Peripheral giant cell granuloma.* An erythematous gingival nodule associated with chronic local irritation (plaque accumulation). (**c**) Benign neoplasm. *Squamous papilloma.* A well-demarcated polypoid white-pink corrugated nodule on the soft palatal mucosa (black arrow). (**d**) Malignant neoplasm. *Squamous cell carcinoma.* Irregular surfaced, ulcerated, red + white heterogeneous mass on the right lateral-ventral tongue. Unrelated to local trauma

most common oral malignancy that arises from the mucosal lining that lines the oral cavity. OSCC comprises more than 95% of all oral malignancies.

Regardless of the individual entity, malignant neoplasms of the oral cavity share certain general clinical features that are important for clinicians to recognize and act on. Almost all oral malignant neoplasms present as masses that grow relatively rapidly. Due to their rapid and infiltrative character, tumors are often ulcerated and exhibit varying degrees of erythema and/or necrosis on the surface (Fig. 16.2d). Malignant tumors are frequently ill-defined, asymmetrical, and have a lobulated/lumpy-bumpy character. Various surface changes that may be noted include prominent white/red plaques surrounding the masses (as seen in OC-SCC), bluish hue with secretions (as seen in mucoepidermoid carcinoma), or vascular surface marking/surface bleeding (resulting from the underlying angiogenesis and desmoplastic stroma associated with malignancies). Malignant tumors are frequently hard/indurated on palpation. Patients may present with symptoms of pain/paresthesia (i.e., numbness, tingling, burning), weight loss, lymphadenopathy, rapid tooth mobility, and difficulty swallowing. They may also report unintentional weight loss and fatigue, which may indicate systemic disease (metastatic spread). When clinicians encounter ulcerated masses on oral mucosal surfaces, it is essential to gather information on the lesion's duration and rule out local inciting factors. It is also important to ask patients if they currently have a history of other primary cancers or in the past. If an ulcerated mass has persisted longer than 3–4 weeks and the surface exhibits suspicious changes, representative incisional biopsy/biopsies must be obtained. Based on the specific diagnosis, patients diagnosed with malignant neoplasms must be referred to specialty teams for further evaluation, staging, and management. Furthermore, patients diagnosed with malignant neoplasms of the oral cavity must be followed up indefinitely following management.

The current chapter will focus on lumps and bumps associated with reactive or benign neoplastic etiology. Malignant neoplasms, particularly oral and oropharyngeal squamous cell carcinomas, are discussed in Chap. 19.

Reactive/Inflammatory Masses

As described above, masses of reactive/inflammatory origin are typically composed of stromal tissue hyperplasia with varying degrees of surface mucosal involvement. The pathogenesis and character of almost all reactive/inflammatory masses or overgrowths are attributable to the spectrum of findings associated with inflammatory and repair processes. Therefore, this section will start with a brief review of the fundamental mechanisms of inflammation and tissue repair.

Inflammation is a response of vascularized tissues to infections, necrotic tissue, foreign bodies, or immune hypersensitization that brings cells and molecules of the host defense from the circulation to the sites where they are needed. The ultimate goal of inflammation is to eliminate or address the offending agent and return the affected tissues to a state of normalcy. Inflammatory reactions follow a series of sequential steps: (1) the offending agent/agents/triggers are recognized by host cells and sensory molecules; (2) leukocytes and plasma proteins are recruited to the location of the offending agent; (3) activated leukocytes, host proteins, and enzymes work in synchrony to destroy and eliminate the offending agent; (4) the body launches a concurrent response to control, contain, and terminate the inflammatory response in an attempt to prevent dissemination of an inflammatory process; (5) the damaged tissue is either restored to its original state (architectural and functional) through tissue *regeneration* or returned to a state of partial function through incomplete tissue restitution, i.e., *repair* (scar tissue) [1].

The morphological patterns of inflammation-related and repair-associated benign oral mucosal/stromal overgrowths are the consequence of one of the following inflammation-related scenarios.

Acute Inflammation Outcomes and Related Masses

The inflammatory process begins with initiation (TNF, IL-1), vascular dilatation, stasis, and increased vascular permeability (vasoactive amines; histamine), allowing for the recruitment and transmigration of leukocytes (endothelial integrins and ligands; selectins, ICAMs, PECAMs) responding to a triggering insult (infection/necrosis). Leukocytes, specifically neutrophils (the cell of acute inflammation), once recruited, are activated, migrate (chemotaxis), and acquire the ability to ingest/destroy (phagocytosis, intracellular destruction of microbes/debris, lysosomal enzymes, neutrophil extracellular traps, release of reactive superoxides/ROS) microbes or dead cells or undesirable material present in the tissues. This initial rapid response, acute inflammation, develops within minutes or hours and ideally lasts for several hours or a few days. This protective response, mediated largely by short-lived neutrophils, is often accompanied by collateral damage to the surrounding normal tissue resulting from inflammatory enzymes. There is a simultaneous attempt by the body to contain, localize, and "wall-off" this inflammatory focus with elements of fibrovascular granulation tissue (VEGF, bFGF, TGF-beta, PDGF) and macrophages (M1-macrophages: pro-inflammatory and phagocytic; M2-macrophages: anti-inflammatory, repair oriented). While acute inflammation aims to neutralize offending agents, the body attempts to dial down the inflammatory response by producing specific mediators that terminate inflammatory mechanisms. The typical outcomes of acute inflammation are:

- *Complete resolution*—the offending agent is eliminated/neutralized and the tissue is restored to normal function and structure through tissue regeneration. Resolution involves removal of cellular debris by pro-inflammatory M1 macrophages (microbicidal and phagocytic), down-regulation of inflammation by M2-anti-inflammatory macrophages (repair oriented), resorption of tissue edema by local lymphatics, and stimulation of parenchymal cells triggering a regenerative response.
- *Healing by connective tissue replacement* (fibrosis/organization/scar)—in the case of substantial tissue destruction or in the setting of a persistent chronic inflammatory reaction, regeneration and complete tissue replenishment are not possible. In this situation, connective tissue (collagen produced by fibroblasts within local granulation tissue) grows into the damaged area, converting it into a mass of fibrous tissue, i.e., *organization.*
- *Progression to chronic inflammation*—the offending agent is not fully addressed. This leads to the initiation of adaptive immune responses and chronic inflammatory mediators (addressed in a later section) and leads either to foci with persistent chronic inflammatory states or an abnormal proliferation/hyperplasia of granulation tissue (fibrovascular connective tissue).
- *Persistence of an acute inflammatory focus:* the offending agent is persistent and continues to trigger acute inflammatory mediators leading to purulent (suppurative) inflammation and the formation of an abscess. Purulent inflammation is characterized by the production of *pus,* an exudate containing neutrophils (Fig. 16.3a), the liquefied necrotic debris, and edematous fluid. In the orofacial region, purulent inflammation is most frequently caused by infectious organisms (*pyogenic/pus-producing* bacteria like staphylococci/streptococci/bacteria associated with oral infections). Abscesses are localized collections of neutrophils within a confined space bordered by fibrovascular connective tissue. In an anatomically complex region like the oral cavity, abscesses can present with a clinically visible mass.

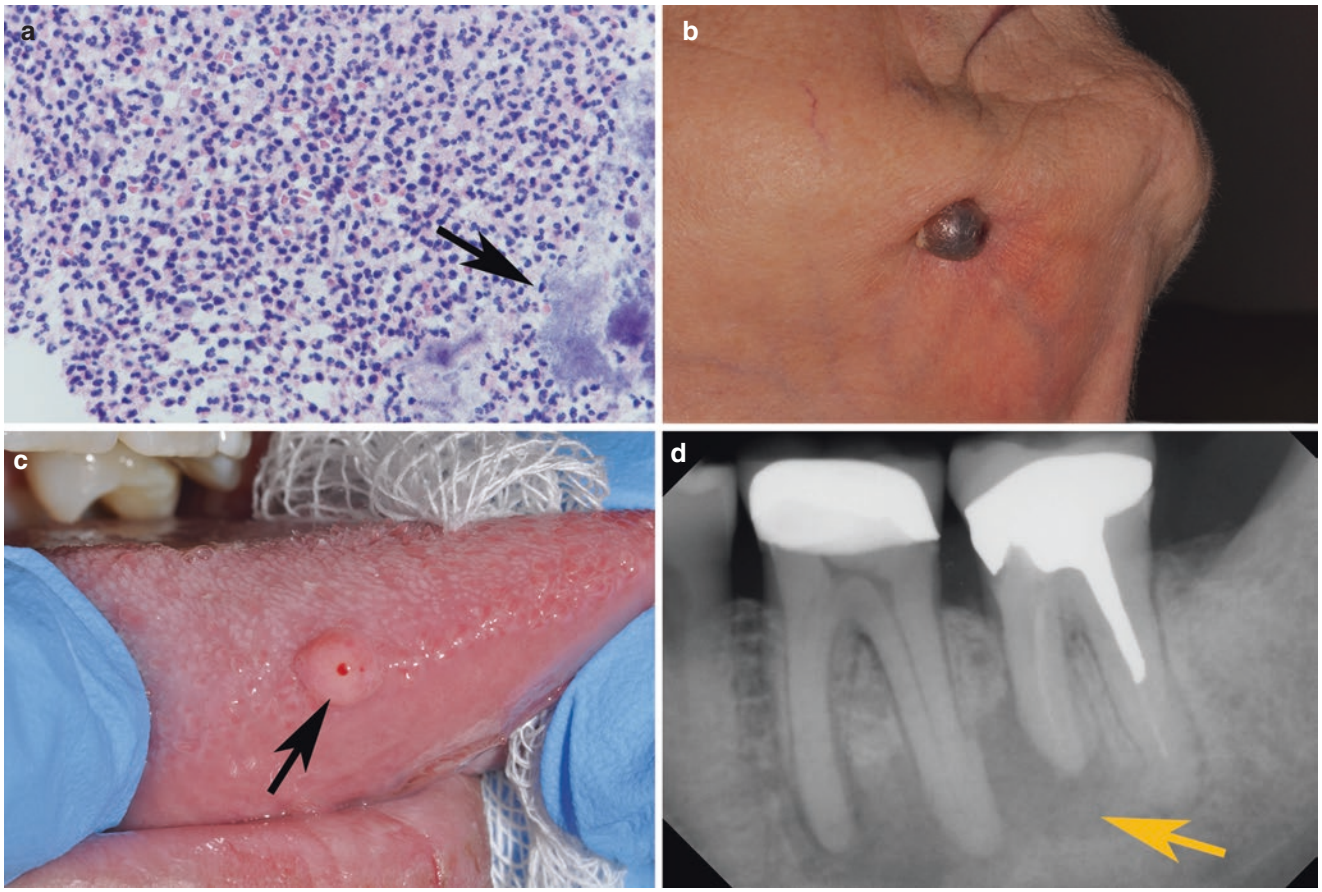


Fig. 16.3 Oral swellings associated with acute inflammation. Abscesses. (**a**) Abscess. An aggregate of neutrophils in response to microbial and necrotic debris (black arrow). (**b**) Cutaneous fistula. Oral abscess originating from an odontogenic infection presenting with extraoral drainage. The erythematous/purple nodule represents the fistulous tract opening. Note the surrounding cutaneous erythema consistent with the disseminated inflammatory process. (**c**) Soft tissue abscess. A raised yellow-pale, fluctuant nodule on the right lateral tongue with a central erythematous punctum. (**d**) Periapical abscess. Periapical radiolucency (yellow arrow) associated with the mesial root of an endodontically treated left mandibular molar. Note the lytic change (lack of trabeculation) with lack of cortical definition

Oral Abscesses

Abscesses are among the most common causes of oral swellings. The oral cavity is prone to a range of infectious processes, the majority of which arise secondary to an infected or necrotic tooth, or tooth-related tissues (odontogenic sources). The two major sources of odontogenic abscesses are (1) infections arising in the gingiva (gum) and periodontium (soft tissue and alveolar bone surrounding the tooth root); and (2) inflammation of the dental pulp resulting from infection and/or pulp necrosis that spreads through the root canal system to tooth apices (apical periodontitis). Other causes of oral abscesses could be soft tissue abscesses arising from embedded foreign bodies or an abscess arising in an infected salivary duct system (salivary duct abscess).

Abscess: Clinical History Clinically, regardless of the specific source, patients with oral abscesses present with a set of common complaints, signs, and symptoms. In general, abscesses are acute clinical lesions. Patients typically report being aware of a progressive oral soft or hard tissue swelling of relatively short duration (a few days to <2–3 weeks duration). The patient may be aware of discharge, bleeding, or a "bad/salty taste" from the swelling. They may report a specific history of trauma/irritation (embedded foreign debris; blow to the face; fall; food impaction) or may be aware of a specific tooth-related problem (recent restoration; gingival or periodontal disease; root canal therapy; extraction; surgical procedure). Patients with locally disseminated disease may report constitutional signs of fever, lymphadenopathy, and malaise. Depending on the specific abscess and location, patients may present with acute, severe pain (described as throbbing, sharp, piercing), dull pain, or discomfort on a decreasing scale (if there is evidence of drainage/discharge). If said abscess is of odontogenic origin and involves the bone, there is a risk of dissemination within the jaw bones and into the surrounding fascial spaces. This may be associ-

ated with extraoral facial swelling, facial asymmetry, and reports of extraoral drainage, sinus tract formation (Fig. 16.3b), cutaneous erythema, and spread beyond the point of origin.

Abscess: Clinical Presentation On clinical assessment and examination, oral abscesses present as yellow-red-colored masses, having either a sessile (broad base) appearance or as a discrete papule/polyp (draining fistulous tracts/parulis). The center of the mass may exhibit a yellow-red punctum indicative of drainage (Fig. 16.3c). Soft tissue abscesses are typically fluctuant on palpation. Deeper abscesses arising from odontogenic sources may present with a more "board-like" or indurated consistency. The degree of pain, tenderness, and discomfort depends on the specific anatomic location, point of origin, extent of involvement, and proximity to structures. Clinical examination and assessment of dentoalveolar tissues will help narrow down the origin of oral abscesses. To this end, it is essential to evaluate for tooth mobility, periodontal pocket depths, dental caries, and tooth/pulp vitality status (cold test and/or electronic pulp testing).

Abscess, Radiographic Presentation Odontogenic abscesses (periodontal, periapical, pericoronal) originate within the dentoalveolar bone. An acute inflammatory process within the bone has the potential to cause bone resorption. Odontogenic abscesses typically present as radiolucencies that lack defined borders (Fig. 16.3d). Radiographs may help pinpoint the specific odontogenic source. For example, periodontal abscesses are associated with observable horizontal and/or vertical bone loss and alveolar bone loss; periapical abscesses present as a demarcated or ill-defined radiolucencies surrounding the root apex of a clinically necrotic tooth (with a large restoration or deep dental caries); pericoronal abscesses may present as radiolucent defects distal to or surrounding a partially impacted mandibular third molar.

Abscess: Microscopic Presentation The histological presentation of all abscesses, regardless of location, is similar. Specimens show large aggregates of neutrophils, edematous granulation tissue, and varying amounts of necrotic and/or microbial debris. Foreign debris (vegetable or food matter; wood splinters; exogenous foreign material) may be evident in the specimen (Fig. 16.4a). If the specimen is obtained from within the bone, viable and/or necrotic bone fragments may be evident along with pockets of chronic inflammation. In salivary duct abscesses, salivary gland lobules with secondary reactive changes (interstitial fibrosis, acinar destruction, microbial debris, mucinous debris) and fragments of sialoliths (acellular, concentric appearing salivary stone fragments) may be evident.

Specific Oral Abscesses: Characteristics

Regardless of subtype and location, oral abscesses share several pathogenetic, clinical, microscopic, and management-related features. Following are the specific oral abscesses presenting with clinical masses and their respective unique features:

- *Gingival abscess*: Gingival abscesses form as the result of infection or entrapment of debris that originates in the gingival sulcus. Common causes of gingival abscesses include the traumatic introduction of food/debris into the gingival soft tissues or heavy plaque/calculus build-up with microbial invasion into the gingival sulcus (Fig. 16.4b). The resulting acute, purulent inflammatory response may present as a painful gingival mass. The underlying periodontal dentoalveolar structures are not involved. Periodontal pocketing depths may be within the range of normal. Hence, there is no visible radiographic change.
- *Periodontal abscess*: Periodontal abscesses, similar to gingival abscesses, are the result of either microbial invasion or introduction of foreign material into the gingival sulcular epithelium. The resulting acute, purulent inflammatory infiltrate causes a painful, fluctuant gingival swelling that also involves the periodontal ligament and associated dentoalveolar osseous tissue. Patients may present with rapidly progressing tooth mobility, constitutional signs, deep periodontal pockets, purulent discharge from the gingival sulcus, furcation involvement, and visible radiographic findings (Fig. 16.4c). Radiographic evaluation may show severe horizontal and vertical alveolar bone loss, lytic radiolucent findings with potentially ill-defined borders.
- *Periapical abscess*: Pulpal necrosis resulting from infection (deep caries or restorations) or trauma causes intrapulpal inflammation. The spread of this inflammatory process through the root canal complex and into the periapical space is defined as apical periodontitis. Depending on the individual tooth, the host response, or microbial virulence, the necrotic debris exiting the apical region has the potential to trigger an acute, purulent inflammatory response at the apex. Although the body tends to contain most periapical inflammatory processes with resolution or organization, some progress into chronic processes (periapical granulation tissue, periapical cysts, periapical scars). Those few that persist as acute inflammatory foci have the potential to burrow their way through the alveolar bone and into the oral cavity proper: a fistulous tract. Thus, periapical abscesses from the apex of a tooth have the potential to present intraorally as a gingival or buccal vestibular mass. Such masses are typically red, often with yellow-white puncta, and may have

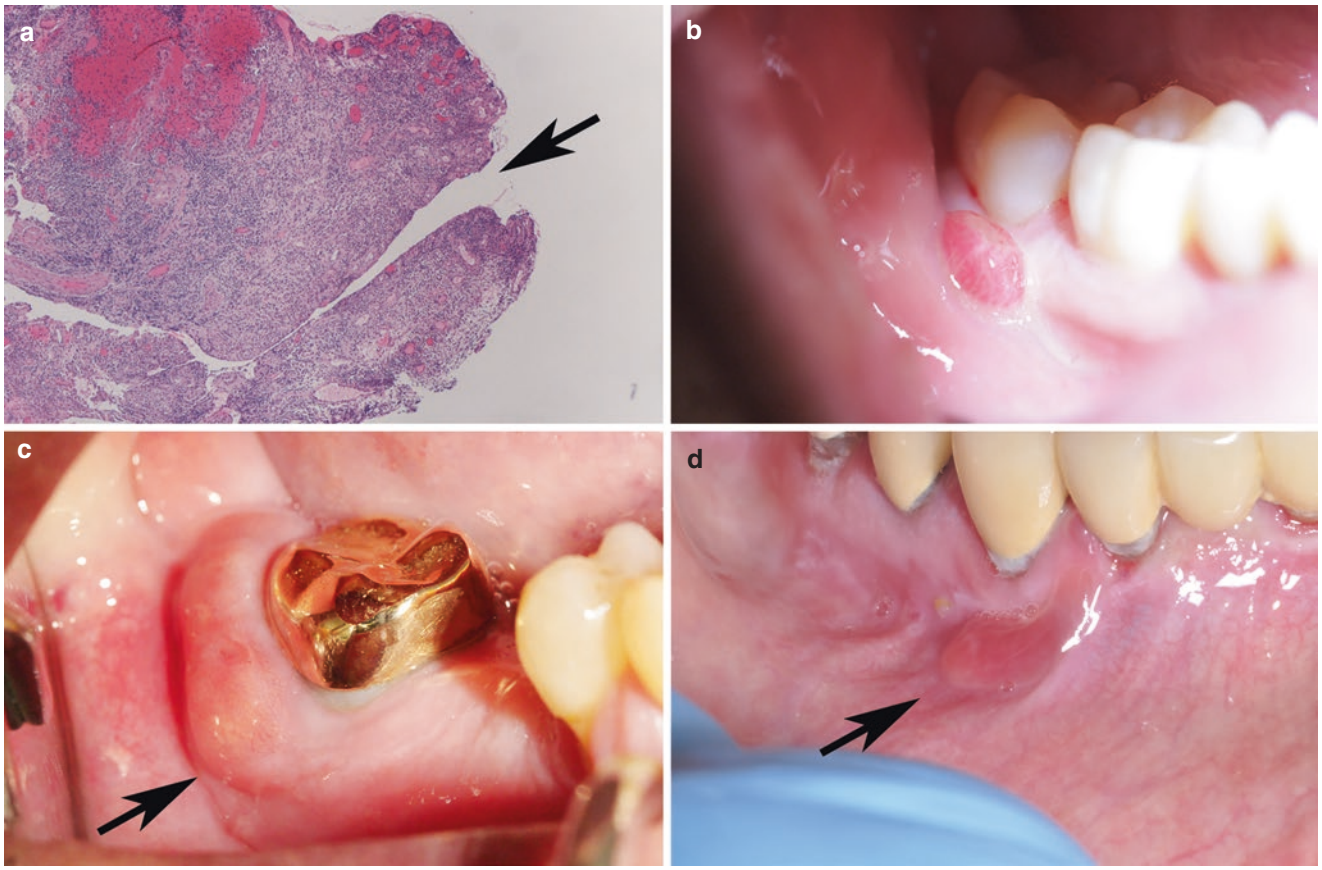


Fig. 16.4 Oral swellings associated with acute inflammation. Specific oral abscesses. (**a**) Histological features of an abscess with draining tract. Soft and hard tissue abscesses often create fistulous tracts lined by granulation tissue walls to facilitate drainage. Note the granulation tissue-lined channel that represents the opening of the sinus tract (black arrow). (**b**) Gingival abscess. Erythematous, fluctuant nodule on the lower right mandibular attached gingiva. Note the yellow center representing an area of purulent discharge. (**c**) Periodontal abscess. Raised, yellow fluctuant nodule facial aspect of mandibular right posterior tooth. The patient presented with severe pain and deep periodontal pockets toward the distal/posterior aspect of the crowned molar. (**d**) Draining periapical abscess/"parulis." Intraosseous periapical abscess associated with endodontically and restored right mandibular canine. Drainage into the right buccal vestibule results in a draining fistula associated with a soft tissue swelling, i.e., "parulis"/gum boil. The patient may present with a history of discharge or foul taste in the region

evidence of purulent discharge (Fig. 16.4d). They are often called a "gum boil" or "parulis." The discovery of a "parulis" should trigger a thorough dental and radiographic evaluation to determine the tooth of origin in order to initiate appropriate treatment (restoration, root canal therapy, or extraction). Periapical abscesses may also spread along fascial spaces (submandibular; sublingual; infraorbital etc.), predisposing to disseminated infection—in some cases, this may constitute a medical surgical emergency.

- *Pericoronal abscess/pericoronitis*: Teeth erupting into the oral cavity are invested with a soft tissue envelope, i.e., follicular tissue. This remnant of tooth development typically disintegrates upon full tooth eruption. Frequently, primarily associated with partially erupted or impacted third molars, the follicular tissue becomes contiguous with the developing periodontal sulcular epithelium and oral mucosal tissue. The pocket that results from redundant soft tissue encompassing/lying over the occlusal surface (operculum) of the incompletely erupted tooth traps food and microbial debris. This predisposes to inflammation (pericoronitis) and abscess formation. Pericoronal abscesses present as erythematous, broad-based swellings, typically toward the posterior mandibular/retromolar pad region and in association with a partially erupted or impacted third molar. Purulence may be expressed on palpation of the soft tissue operculum. Pericoronal abscesses can be exquisitely painful, and may be associated with constitutional signs, lytic radiographic changes, potential soft tissue and fascial space extension, and can be associated with dentigerous cysts (a developmental cyst that arises from follicular epithelium that invests an erupting/impacted tooth). A thorough clinical and radiographic examination is indicated before initiating management. Management may range from conservative antimicrobial rinses to incisional drainage, surgical

extraction of the impacted tooth, and surgical removal of the redundant soft tissue flap.

- *Other soft tissue abscesses*: Abscesses may be seen along any oral surface if there is a history of trauma and entrapment of either foreign or microbial material in the soft tissue. Salivary duct abscesses are often seen in the setting of an impacted salivary duct stone (sialolith) and microbial entrapment in the ductal system. This may present as a swelling of the labial mucosa (typically upper), buccal mucosa, or floor of the mouth. The patient may present with an uncomfortable, fluctuant swelling in the area and report the size of a presenting mass fluctuating in size at meal times. Patients may also report gritty or sandy material (sialolith fragments) emanating from the salivary duct opening.

Abscess: Management The principles of abscess management are the same, regardless of anatomic location. It is essential to attempt to drain the accumulated purulent, microbial, and necrotic debris while addressing the underlying etiology. Unlike visceral and internal organs, the orofacial region is readily accessible and lends itself to surgical treatment. Depending on the specific oral abscess, the management could range from conservative antimicrobial rinses (pericoronitis), to surgical incision and drainage (gingival, salivary, periapical, periodontal abscesses) with or without additional dental management (periodontal debridement or root canal therapy), to systemic antibiotic therapy to address deep-seated infections with accompanying constitutional signs (signs of disseminated infection).

Chronic Inflammation Outcomes and Related Masses

Chronic inflammation is a prolonged inflammatory response that may have started as an acute inflammatory process or in response to a hypersensitized adaptive immune system. It is a response that typically runs weeks, months, or years in which inflammation, tissue injury, and attempts at repair coexist in varying combinations, with the balance constantly shifting. In contrast to acute inflammation, chronic inflammation is characterized by infiltration with mononuclear cells, which include macrophages, lymphocytes, and plasma cells. The adaptive immune system regulates the response, i.e., CD4+ T lymphocytes. It may swing between periods of tissue destruction induced by a persistent offending agent and attempts at healing accomplished by connective tissue deposition (fibrosis) and vascular proliferation (angiogenesis). The latter constitutes granulation tissue and is a central concept in tissue repair; it accounts for the majority of benign oral bumps and will be discussed in the following section.

Chronic inflammation typically arises in the following settings: (1) hypersensitivity diseases; (2) prolonged exposure to toxic agents; (3) persistent infections or irritants. The chronic inflammatory process is tied in with acute inflammation and is often the mechanism by which acute inflammatory processes are wound down. The primary mediator, the lymphocyte, is typically activated during acute inflammatory responses: microbes and environmental antigens activate T and B lymphocytes, which amplify and propagate chronic inflammation. The CD4+ T lymphocytes, in particular, act as a master regulator of adaptive immune and chronic inflammatory responses. They can activate several chronic inflammatory cells: (1) CD8+ cytotoxic T lymphocytes that are critical in cell-mediated killing; (2) they activate macrophages through IFN-gamma (interferon) production—the classical M1 macrophages that are pro-inflammatory and phagocytic; (3) B lymphocyte differentiation and propagation to promote the humoral immune response (antibody production); (4) eosinophils and neutrophils through IL-17 and other critical chemokines; (5) activate M2 macrophages through the alternate pathway to promote repair and dial-down inflammatory processes. Macrophages are considered to be dominant cells in the chronic inflammatory response. They contribute significantly to promoting and propagating chronic inflammatory responses through their vast array of chemokines. They are involved in phagocytic activity and enzymatic microbial killing, but through the alternate pathway (M2 macrophages inhibit inflammatory responses (IL-10) and promote tissue repair (TGF-beta; bFGF)). The spectrum of chronic inflammatory reactions and associated diseases is vast and beyond the scope of this particular chapter. Among the types of chronic inflammatory processes, granulomatous inflammation is the one that frequently presents as a benign oral swelling. It is important not to confuse granulomatous inflammation (a specific type of macrophage-rich, chronic inflammatory process) with the process of granulation tissue formation (fibrovascular repair-related tissue).

Granulomatous inflammation is a specific form of chronic inflammation characterized by nodular aggregations of activated macrophages along with lymphocytes and fibrosis. Granuloma formation is the body's attempt to contain and wall off (fibrosis) an antigen or irritant that is difficult to eradicate. This results in a T lymphocyte-mediated activation of phagocytic macrophages, promoting their aggregation around an offending agent (or perceived offending agent). Occasionally, macrophages fuse together to form multinucleated giant cells (Fig. 16.5a). Broadly speaking, there are two types of granulomatous diseases:

- Foreign body granulomas: formed in response to inert foreign material like suture material, silicone, dental restorative material, or embedded foreign debris.

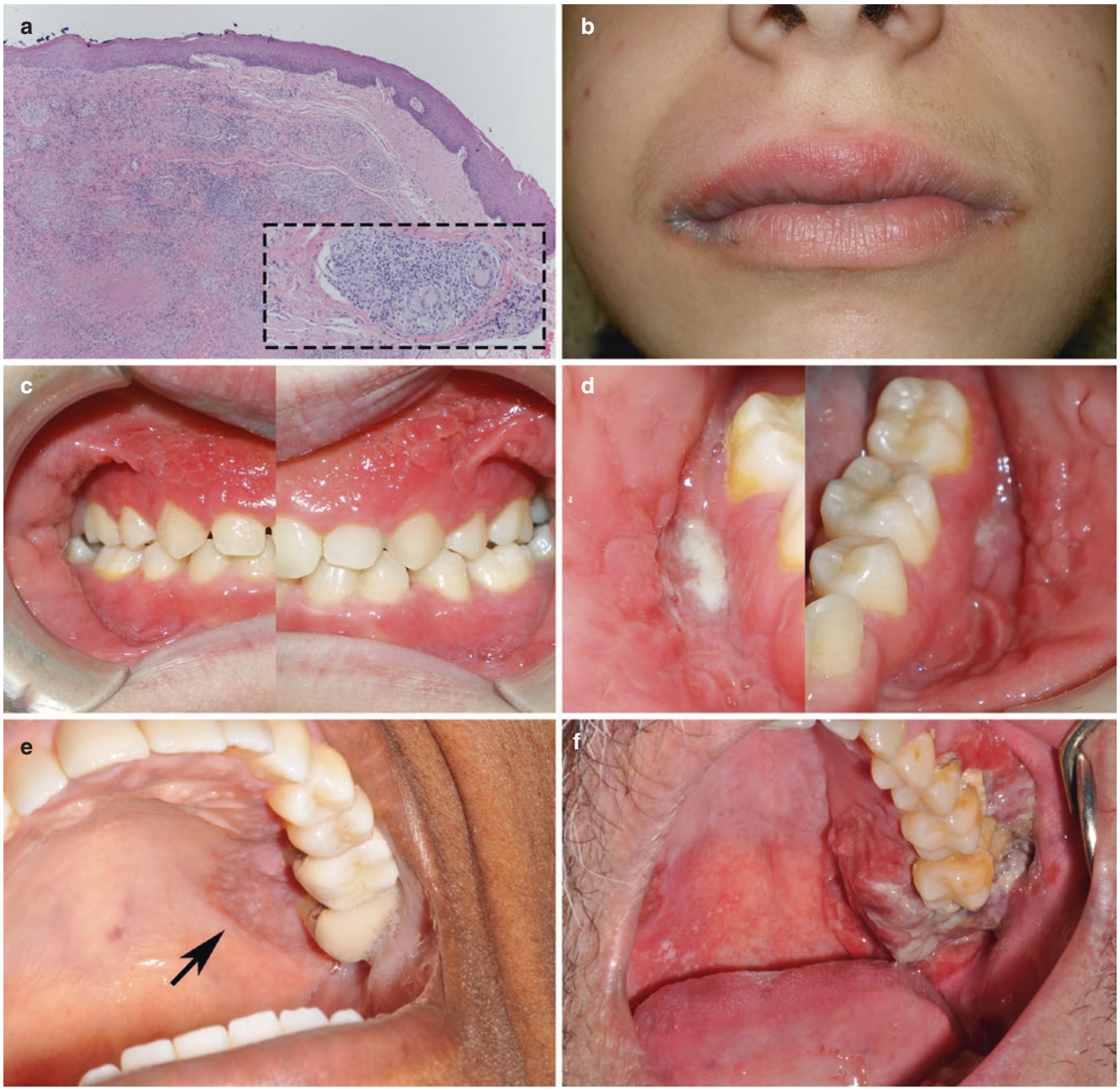


Fig. 16.5 Oral swellings associated with chronic inflammation. Granulomatous disorders. (**a**) Histological features of granulomatous stomatitis. Multiple nodular aggregates of activated macrophages, lymphocytes, and fibrosis in the stromal tissue. *Inset*—nodular histiocytic aggregates with multinucleated giant cells. (**b**) Cheilitis granulomatosa, manifestation of Crohn's disease. A young patient presenting with a several months history of swollen, uncomfortable upper and lower lip swellings. The swellings are doughy on palpation. Note the erythematous vermilion and angular fissuring. (**c**) Granulomatous stomatitis, manifestation of Crohn's disease. Cobblestone-like swellings of the upper buccal vestibule (R & L) and buccal mucosa + aphthous-like ulcers. (**d**) Granulomatous stomatitis, manifestation of Crohn's disease. Fissuring ulcers in the L and R lower buccal vestibules. Note the redundant soft tissue folds bilaterally; ulcers present at the depth of these fissures. Also noted are cobble-stone like nodules on the buccal mucosa. (**e**) Granulomatous stomatitis, manifestation of sarcoidosis. The patient had a long-standing history of dyspnea, chronic cough, and a recent pulmonary work-up suspicious for sarcoid. Oral exam revealed pebbly, mildly uncomfortable nodules with intervening erosion on the upper left palatal and facial gingiva. Biopsies revealed orofacial granulomatosis in the setting of pulmonary sarcoidosis. (**f**) Granulomatous stomatitis, manifestation of histoplasmosis infection. Multifocal fungating oral ulcerative swelling. The differential diagnosis includes a malignant neoplasm (lymphoma or other). This HIV-positive patient with multisystem histoplasmosis presented with multiquadrant ulcerated oral masses. Biopsies revealed granulomatous stomatitis with abundant histoplasmosis organisms

- Immune granulomas: formed in response to persistent microbes, specific antigens, or perceived antigens. This is an active T lymphocyte-mediated process. Examples include granulomas seen in the setting of tuberculosis, deep fungal infections, sarcoidosis [2], and Crohn's disease.

Oral Masses: Foreign Body Granulomas

Benign oral masses that are the result of foreign body granulomas are uncommon. Most oral masses attributable to foreign body granulomas result from the accidental or unintentional introduction of inert foreign material into oral soft tissues. Occasionally, soft tissue masses result from intentional implantation of cosmetic filler material or ornamental piercing/implantation material [3–5].

Foreign Body Granuloma: Clinical History Clinically, patients with foreign body granulomas are aware of a triggering event, accident, or procedure leading up to the oral swelling. Patients may point to the mass and report a history of an accident/injury/procedure at the site with the introduction of materials like wood splinters, surgical suture, dental restorative material, or others. Alternately, there may be a history of cosmetic tissue injections/filling procedures (silicone or other lip/cheek filling material) in the area. Patients may be asymptomatic or report various symptoms—discomfort, pain, burning, tingling, or discharge. There may be a history of progressive growth, change in the texture or form of the mass over a period of time, or change in surface coloration; occasionally, there may be reports of discharge [6].

Foreign Body Granulomas: Clinical Presentation On clinical assessment, the masses are solitary, small, nodular/lobular, and smooth-surfaced. The color may vary from normal to erythematous, or take on the color of the embedded material (yellow-lipid/cosmetic filler; gray/black—metallic fragments, amalgam; pale—scar around crystalline material). Masses associated with cosmetic filler material may appear diffuse and spread out over the area of the procedure. Occasionally, the surface may be ulcerated or exhibit a punctum/opening with associated purulent discharge. Foreign body granulomas are typically painless on palpation but may vary depending on the situation. The masses may be fluctuant, soft, firm, or hard, depending on the embedded material and the degree of scarring around it.

Foreign Body Granuloma: Microscopic Presentation The histopathological appearance of foreign body granulomas is characterized by nodular aggregates of activated macrophages (histiocytes) and multinucleate giant cells around foreign debris or material. Depending on the specific situation, the foreign material may appear as granular brown-black, crystalline (visualized by polarized light), or clear. The area is generally surrounded by varying degrees of collagenous scar tissue deposition. Scattered lymphocytic infiltrates may or may not be evident—suture granulomas are typically devoid of lymphocytes. In the case of cosmetic filler, lipid-, or medicament-associated granulomas, the granulomatous aggregates are spread out more diffusely through the specimen. Macrophages with phagocytized cosmetic filler material or lipid-containing foreign debris may mimic adipose tissue—the clear vacuoles and spaces appear more haphazard and vary considerably in size and shape.

Foreign Body Granulomas: Management and Prognosis Foreign body granulomas are best managed with surgical removal. The remaining foreign material, if any, should be debrided. Once removed, the area should heal uneventfully or may resolve with scar tissue formation.

Oral Masses: Immune Granulomas

Oral swellings resulting from immune granulomatous disorders are uncommon. They generally present as an oral manifestation of an underlying systemic condition: Crohn's disease, sarcoidosis, and rarely, an infectious disease (e.g., tuberculosis, syphilis, deep fungal infections) [7, 8].

Immune Granulomas: Clinical History Oral masses seen in the setting of immune granulomatous conditions vary in presentation and depend on the specific systemic condition. Given their systemic origin, immune granulomas are likely to present with multifocal distribution within the mouth and/or extraorally. Patients may either present with a history of a known systemic illness (Crohn's disease, sarcoidosis, etc.) or present with an oral swelling (as the first clinical manifestation) that reveals granulomatous inflammation. The latter triggers a systemic evaluation to rule out a specific granulomatous condition.

Immune Granulomas: Clinical Presentation Oral findings in the setting of systemic immunological or infectious granulomatous conditions include:

- *Lip swelling:* nodular or diffuse; progressive or intermittent; asymptomatic, uncomfortable, burning, or painful. This symptom complex is referred to as *cheilitis granulomatosa* (see Fig. 16.5b) and requires biopsies for diagnostic confirmation [9, 10]. The presence of granulomas should trigger a systemic work-up.
- *Buccal mucosal or vestibular growths*: redundant fissured vestibular growths; cobblestone-like nodules/polypoid or broad-based; asymptomatic, uncomfortable, or painful; ulcerated or non-ulcerated.
- *Mucosal ulcers, erosions, nodular surface changes (any oral mucosal site)*: aphthous-like, nonhealing ulcers; fissures; indurated nodules; symptoms vary from no symptoms to discomfort or pain.

Following is a list of systemic granulomatous conditions, their clinical presentation, and respective orofacial manifestations:

- *Crohn's disease*: young patients (teens to young adults), history of Crohn's disease, or gastrointestinal symptoms (cramping, diarrhea, bloating, blood in the stool). Oral findings include nodular or diffuse doughy labial tissue swellings, gingival erythema, buccal vestibule fissures, redundant tissue flaps and ulceration, oral aphthous ulcers, cobblestone-like swellings around the buccal mucosa and vestibules (Fig. 16.5c, d).
- *Sarcoidosis:* patients with a history of sarcoidosis or pulmonary signs (chronic cough, hilar lymphadenopathy, dyspnea), cutaneous nodules [2]. Oral findings include diffuse or nodular labial mucosal swellings, pebbly/nodular oral soft tissue growths, chronic erosions/ulcerations [2] (Fig. 16.5e).
- *Tuberculosis or fungal infections*: patients with a history of tuberculosis or deep fungal infection (e.g., histoplasmosis) or systemic pulmonary complaints (chronic cough, dyspnea), or immune depletion. Oral findings include nonhealing ulcerations and erythematous soft tissue growths (Fig. 16.5f).

Patients presenting with multiple nodular growths suggestive of granulomatous disease may require additional clinical laboratory work-up and potential oral soft tissue biopsies. When present, oral nodules present an easy-to-access site to evaluate for an underlying granulomatous condition.

Immune Granulomas: Microscopic Presentation Immune granulomas are comprised of nodular histiocytic aggregates with lymphocytes, fibroblasts, and varying numbers of multinucleated giant cells. Depending on the specific systemic condition, the granulomas may be either necrotizing or non-necrotizing. Lesions diagnosed with granulomatous stomatitis must be evaluated for the presence of mycobacterial organisms (to rule out tuberculosis) using special microbial stains (i.e., Acid-fast bacillus stain, Gram, GMS Silver, PAS fungal). Following is a summary of microscopic findings seen in oral biopsies obtained in specific immune granulomatous disorders:

- *Crohn's disease*: lymphocyte-rich, non-necrotizing granulomatous aggregates, perivascular lymphocytic infiltration, fissured mucosal ulcerations, peri-granuloma fibrosis, no evidence of microbes on special stains.
- *Sarcoidosis*: non-necrotizing granulomatous aggregates in the deep stromal tissues that are often arranged in sheets, scattered lymphocytes, surface erosion or ulcerations, no evidence of microbes on special stains
- *Microbial etiology:* tuberculosis granulomas are characteristically necrotizing with central caseous (cheese-like), amorphous appearance, surrounding lymphocytes, and fibrosis. AFB stains reveal mycobacterial bacilli within central necrotic foci. Granulomas seen in deep fungal infections like histoplasmosis are described as "dirty" owing to the presence of numerous lymphocytes. Fungal stains will highlight the capsulated forms of *Histoplasma capsulatum.*

Oral Masses Related to Tissue Repair/Granulation Tissue Outcomes

Most oral soft tissue masses result from benign hyperplastic inflammatory responses or exuberant overgrowths of epithelial, fibrous, and/or vascular connective tissue. They are caused by local, chronic/persistent trauma, inflammation, or irritation. The oral cavity is host to a variety of labile soft tissue (mucosal epithelium, gingival and periodontal ligament tissue, salivary glands, lymphoid tissue) and stable connective tissue (muscle, neurovascular structures), in close proximity to teeth, bone, dental restorations, prostheses, and appliances. In addition, all oral tissues are laden and coated with normal and potentially pathogenic microflora. Daily function (speaking, biting, chewing) subjects these tissues to constant wear and tear, as well as low-grade chronic inflammation from gingival plaque and calculus. This constant "abuse" renders the oral tissues susceptible to the upregulation of tissue repair mechanisms: this results in oral soft tissue masses. There are a plethora of oral exuberant reactive hyperplastic entities described. Many, if not all, of them, share their origin in foundational principles of injury-related tissue repair, organization, and resolution. Hence, this section will start with a discussion on the foundational characteristics of tissue repair.

Repair refers to the restoration of tissue architecture and function after an injury. The initiators of repair are woven into inflammatory responses. Chronic inflammatory cells, especially macrophages (M2-anti-inflammatory) and regulatory T lymphocytes, can initiate and promote tissue repair pathways by releasing growth factors and cytokines. Repair of damaged tissues can involve:

- *Regeneration:* replenishment of labile parenchymal cells through proliferation
- *Organization:* deposition of granulation tissue, connective tissue to replenish tissue regions that are incapable of restitution, or in areas with chronic irritation or inflammatory aggregation

Both regeneration and connective tissue deposition occur in varying proportions following injury. Both processes involve the proliferation of cells that replenish the paren-

chyma (epithelium, salivary glands) and connective tissue (blood vessels, fibroblasts). Cell proliferation and tissue deposition are driven by growth factors or the extracellular matrix signals. Injury sites are filled with growth factors that macrophages, epithelial, and stromal cells produce. Growth factor activity, mediated through cell surface receptors, influences the expression of genes that can: (1) promote cell cycle activity and proliferation; (2) relieve blocks on the cell cycle—promoting replication; (3) enhance biosynthesis of cellular components and protein production. Common growth factor signaling pathways that play a role in forming oral tissue masses are:

- *Epidermal growth factor (EGF)*: *produced by macrophages and epithelial cells.* Stimulates epithelial and fibroblast proliferation; promotes granulation tissue formation.
- *Transforming growth factor-beta (TGF-β): produced by macrophages, platelets, T lymphocytes, fibroblasts, smooth muscle cells, endothelial cells, and epithelial cells.* Stimulates extracellular matrix (ECM) protein synthesis (collagen deposition); suppresses acute inflammation; chemotactic for fibroblasts.
- *Vascular endothelial growth factor (VEGF)*: *produced by mesenchymal stromal cells.*

Stimulates proliferation of endothelial cells and increases vascular permeability. Promotes capillary sprouting and branching.

- *Platelet-derived growth factor (PDGF)*: *produced by macrophages, platelets, endothelial cells, and epithelial cells.* Stimulates proliferation of fibroblasts, endothelial cells, and promotes ECM synthesis. Chemotactic for inflammatory cells and fibroblasts.
- *Fibroblast growth factor-basic (bFGF or FGF-2)*: *produced by macrophages, endothelial cells, and mast cells.* Stimulates angiogenesis and ECM synthesis.

A centerpiece of tissue organization, repair, and the composition of the bulk of injury-related oral soft tissue masses is *granulation tissue* and *fibrosis* (scar). Sustained injury or inflammation stimulates angiogenesis modulated by VEGF, which promotes new, but leaky blood vessel formation. This results in vascular permeability and localized interstitial edema. In a chronic inflammatory environment, M2 macrophages and other cells release TGF-beta, PDGF, bFGF, EGF, and VEGF. This promotes the migration and proliferation of fibroblasts (producing collagen scaffolds, ECM matrix), together with endothelial cells (forming a new capillary meshwork). This rich fibrovascular matrix helps fill tissue voids and builds scaffolds for regenerating parenchyma or future scar tissue (Fig. 16.6a). The outcome and resolution of this repair process depend on the balance between synthesis and degradation (remodeling) of ECM scaffolds built in response to injury. Tissue remodeling is accomplished by matrix metalloproteinases (MMPs), which include collagenases, gelatinases, and stromelysins. Granulation tissue (GT), through its fibrovascular composition, serves the following functions during tissue injury + repair:

- *Scaffold/bridge building*:
  - *Reepithelialization:* GT forms the bridge along which migrating and proliferating epithelial cells come together to close ulcers/wounds.
  - *Bone healing*: GT forms scaffolds along which a fractured bone or a tooth socket forms fibrovascular calluses (frameworks) to facilitate bone replenishment.
  - *Scar formation*: GT forms scaffolds for fibroblast to lay down collagenous scar.
- *Containment*:
  - *Walling off inflammatory foci*: Fibroblasts in GT form collagenous walls to contain inflammation and prevent dissemination.
  - *Wall off interstitial tissue spillage*: Fibroblasts in GT form collagenous walls to contain interstitial "spills," e.g., mucous, exocrine secretions, abscesses, necrosis, hemorrhage.

Changes in the balance of this tissue repair process, especially factors that promote exuberant or excessive formation of either epithelium, ECM, or granulation tissue, account for the inflammatory/reactive oral masses described in this section.

Pyogenic Granuloma

Pyogenic granulomas (PG) are benign, reactive masses composed of exuberant, hyperplastic granulation tissue [11]. In etiology, presentation, and microscopy, they are identical to pyogenic granulomas in other parts of the body (e.g., skin, mucosal membranes). The name *pyogenic granuloma* is a misnomer; PGs are neither *pyogenic (pus-forming)* nor are they *granulomas (a specific chronic inflammatory process characterized by nodular aggregates of macrophages)*. The author believes that a more appropriate name would have been "exuberant hyperplastic granulation tissuomas," but that would be a mouthful for any clinician! Oral PGs are fairly common in daily practice. PGs go by different names when they occur in specific clinical situations. PGs that extrude out of recent tooth extraction sockets as hemorrhagic, mushroom-like masses are referred to as *Epulis Granulomatosum.* PGs that arise during pregnancy are called *Pregnancy Tumors of the Gum or Granuloma Gravidarum*. It is important to understand that hormonal flux, either in the setting of pregnancy or in the teen years, has nothing directly

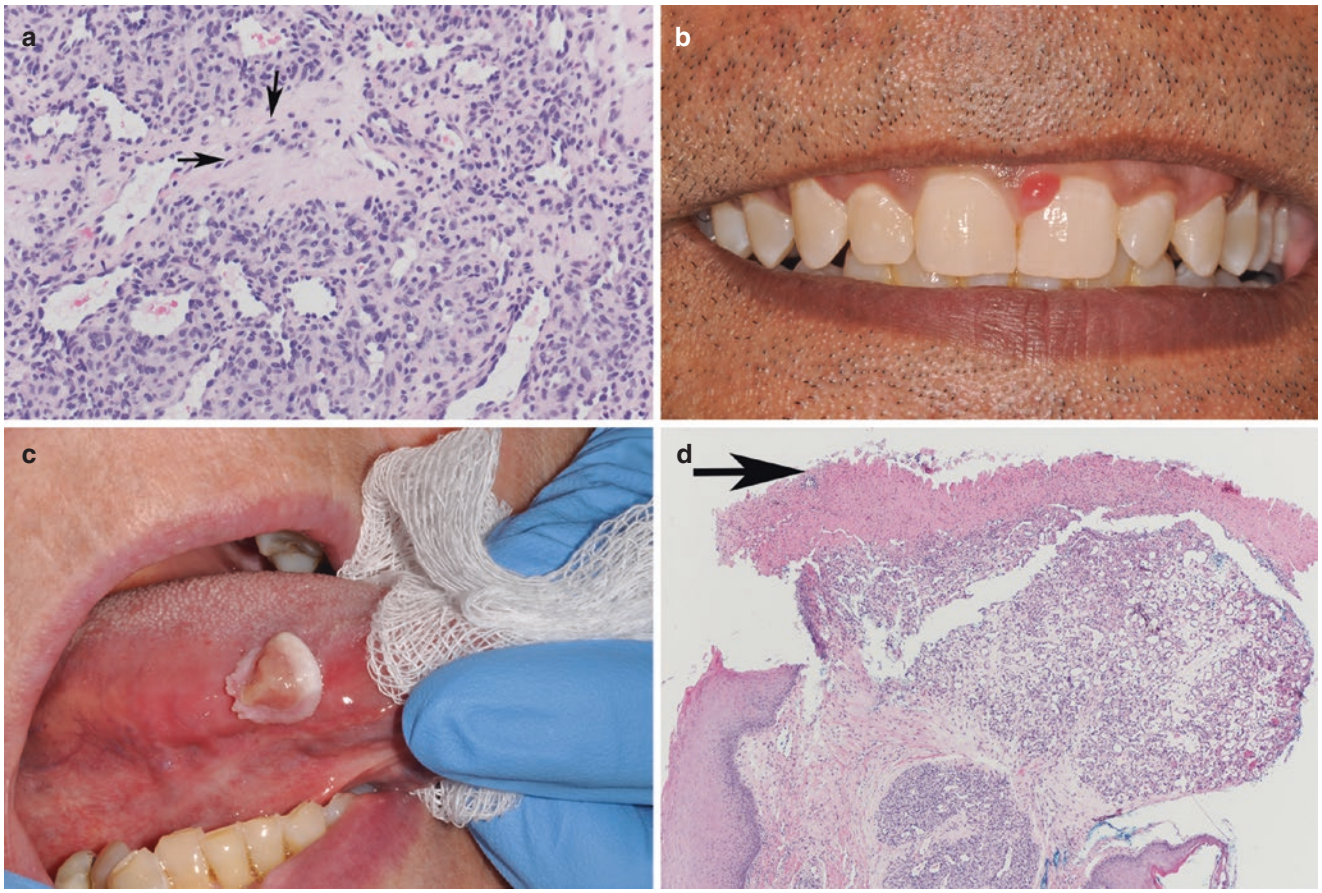


Fig. 16.6 Granulation tissue-related masses. Pyogenic granuloma. (**a**) Granulation tissue. Proliferation of small endothelial-lined capillaries and new, plump fibroblasts (spindle-shaped—two black arrows). This is a hallmark of repair-related tissue throughout the body. (**b**) Pyogenic granuloma, gingiva. A focally ulcerated, erythematous nodule on the gingival margin of tooth # 9 associated with local food impaction. The erythema corresponds to the vascular component of hyperplastic granulation tissue. (**c**) Pyogenic granuloma, right ventral-lateral tongue. An ulcerated nodule covered by a prominent yellow-white fibrinopurulent pseudomembrane. This 70-year-old woman presented with bilateral, painless pyogenic granulomas on the tongue secondary to repeated low-grade trauma from two sharp mandibular posterior teeth. She reported occasional bleeding on biting or contact. (**d**) Pyogenic granuloma, microscopic features. An ulcerated nodule covered by abundant fibrinopurulent surface material (black arrow). The bulk of the nodule is composed of cytologically benign hyperplastic fibrovascular granulation tissue

to do with PG formation. Presumably, PGs occurring in these populations (adolescence, puberty, pregnancy) is a combination of poor oral hygiene and a build-up of growth factors (VEGF, TGF-beta, PDGF, bFGF). In individuals going through puberty or pregnancy (with higher growth factor availability and demand), it is likely that a little irritation/stimulation goes a long way, tipping the balance of tissue repair toward granulation tissue hyperplasia. Contrary to general belief, PGs can be seen in patients of any age and sex and occurs on all oral mucous membranes that may be subject to or have a history of chronic irritation and/or trauma. They result from excessive VEGF, PDGF, bFGF, and TGF-beta availability, resulting in masses composed of granulation tissue [12–14].

Pyogenic Granulomas: Clinical History and Presentation

Pyogenic granulomas occur in patients of all ages and sexes and can involve any oral site subject to chronic irritation or trauma. The gingiva (margin, sulcus, and attached surface) is the most common location in the oral cavity, followed by the buccal mucosae, tongue, and labial mucosa [11, 15]. Patients present with a painless, rapid or slow-growing mass, typically on the gingiva (or other site). There is no discomfort, pain, or burning associated with the lump. Patients may report occasional bleeding when brushing, eating, or touching the nodule. There is often a known history or obvious source of trauma (sharp tooth cusp or irregular restoration/prosthesis), chronic irritation from plaque/calculus, or ill-fitting crown margin.

On examination, PGs present as ovoid or irregularly shaped masses adjacent to an area of irritation/trauma/source of inflammation. They are characteristically irregularly/pebbly surfaced (described as "raspberry-like), ulcerated, and reddish-yellow in color [15] (Fig. 16.6b, c); they may occasionally appear smooth when there is abundant fibrinopurulent surface debris. The surrounding tissues are intact and generally of normal color and texture, or may exhibit mild

erythema. PGs are typically nontender palpation and feel soft, supple, or focally firm. Bleeding spots may be noted. PGs that are a few weeks or months old may feel firmer owing to organization and fibrosis. Gingival PGs are typically associated with teeth with abundant plaque, food impaction, or ill-fitting restorative crown margin.

Pyogenic Granuloma: Microscopic Presentation
On histopathological examination, PGs present as frequently ulcerated nodules composed of abundant granulation tissue. The nodules vary in shape from being sessile to polypoid, ovoid to irregular. The ulcerated surface is typically covered by abundant fibrinopurulent debris (correlating with the yellow-red surface color) (Fig. 16.6d). The marginal epithelium is typically hyperplastic. Occasionally, PGs are surfaced by atrophic but intact stratified squamous epithelium and may exhibit prominent edematous/spongiotic change. The bulk of the nodule is composed of hyperplasia of small, endothelial-lined capillaries surrounded by an abundance of plump and stellate fibroblasts in an edematous stromal background. The fibrovascular proliferation occasionally exhibits a lobular pattern (this has earned PGs the inaccurate moniker, *lobular capillary hemangioma*). Varying amounts of acute and/or chronic inflammatory cells may be evident. Older PGs exhibit more organization and foci of fibrosis.

Pyogenic Granuloma: Management and Prognosis
Pyogenic granulomas are treated with conservative surgical excision. An integral part of the management is to address the underlying traumatic/reactive cause—this may involve plaque removal, addressing a sharp restoration or crown margin, tooth extraction, or smoothing of sharp tooth surfaces. PGs are notorious for recurrence, in large part due to clinicians not identifying and managing the causative factor. Therefore, the surgical wound of PGs should be curetted, and adjacent reactive elements addressed as efficiently as possible. Surgical options include sharp steel or laser-based excision. Overall, the prognosis for PGs is excellent. If PGs are left untreated, they have the potential to "organize," fibrose, and turn into irritation fibromas or exuberant gingival fibrotic hyperplasias.

Peripheral Giant Cell Granuloma

Peripheral giant cell granulomas (PGCG) are benign, reactive masses of exuberant, hyperplastic granulation tissue containing abundant multinucleated osteoclast-type giant cells [16–20]. They arise from the soft tissues of the periodontal ligament and occur *exclusively on the marginal and attached gingival tissues*. As with pyogenic granulomas, they do not represent a true granulomatous inflammatory mass. They are reactive and secondary to local irritants along the gingival sulcus or periodontal soft tissue: plaque, calculus, ill-fitting restoration/crown margins, food entrapment, or chronic inflammation. PGCGs are essentially pyogenic granulomas with a smattering of osteoclast-type giant cells that arise from syncytial fusion of monocytes. Monocytic preosteoclasts are found within the periodontal soft tissue and the adjacent periosteum. Chronic irritation and inflammation trigger growth factors that promote angiogenesis (VEGF, PDGF), fibroblasts (bFGF, TGF-beta), and factors like GM-CSF that promote monocytic differentiation. Studies have demonstrated the osteoclastic expression profile of the giant cells seen in PGCGs, but they do not possess the bone resorptive capacity of functional osteoclasts. In light of this, it is essential to distinguish PGCGs from central giant cell granulomas (CGCGs), which are located within the jaw bones. The latter is associated with benign but locally aggressive behavior; CGCGs have the potential to cause bone resorption and present as osseous swellings with well-demarcated, expansile radiolucencies.

Peripheral Giant Cell Granuloma: Clinical History and Presentation
The clinical presentation of PGCGs is almost identical to that of PGs, with one important difference. PGCGs are, by definition, found ONLY on the gingiva. PGCGs occur in patients of all ages and sexes and are seen along gingival tissues subject to localized chronic irritation or trauma [19, 20]. The gingival margin, sulcus, or attached gingiva may be involved. Patients present with a painless, slow-growing mass. Patients may report occasional bleeding on brushing or eating. There is often a history of a sharp restoration margin, prosthesis, or plaque/calculus accumulation.

On examination, PGCGs are practically indistinguishable from pyogenic granulomas. They present as yellow-red or occasionally purple-red, frequently ulcerated, smooth-surfaced masses on the gingival surfaces adjacent to a poorly restored tooth crown or in an area of heavy plaque accumulation (Fig. 16.7a). PGCGs are nontender and feel firm on palpation. Occasionally, PGCGs contain foci of metaplastic bone or cementum formation; this may make the mass feel hard or "crunchy" on palpation.

Peripheral Giant Cell Granuloma: Microscopic Presentation
On histopathological examination, PGCGs are composed of an unencapsulated diffuse stromal proliferation of dense, cellular granulation tissue filled with plump fibroblastic cells and endothelial cells with abundant fresh hemorrhage and hemosiderin deposition (Fig. 16.7b, c). In this background are numerous osteoclast-like multinucleated giant cells with benign cytology. The overlying epithelium is typically ulcerated and covered by fibrinopurulent debris. Chronic inflammatory aggregates may be present. A PGCG may contain foci of edematous granulation tissue (resembling PG) and metaplastic cementum/bone formation may be noted (so-called peripheral ossifying fibroma). This reflects the common

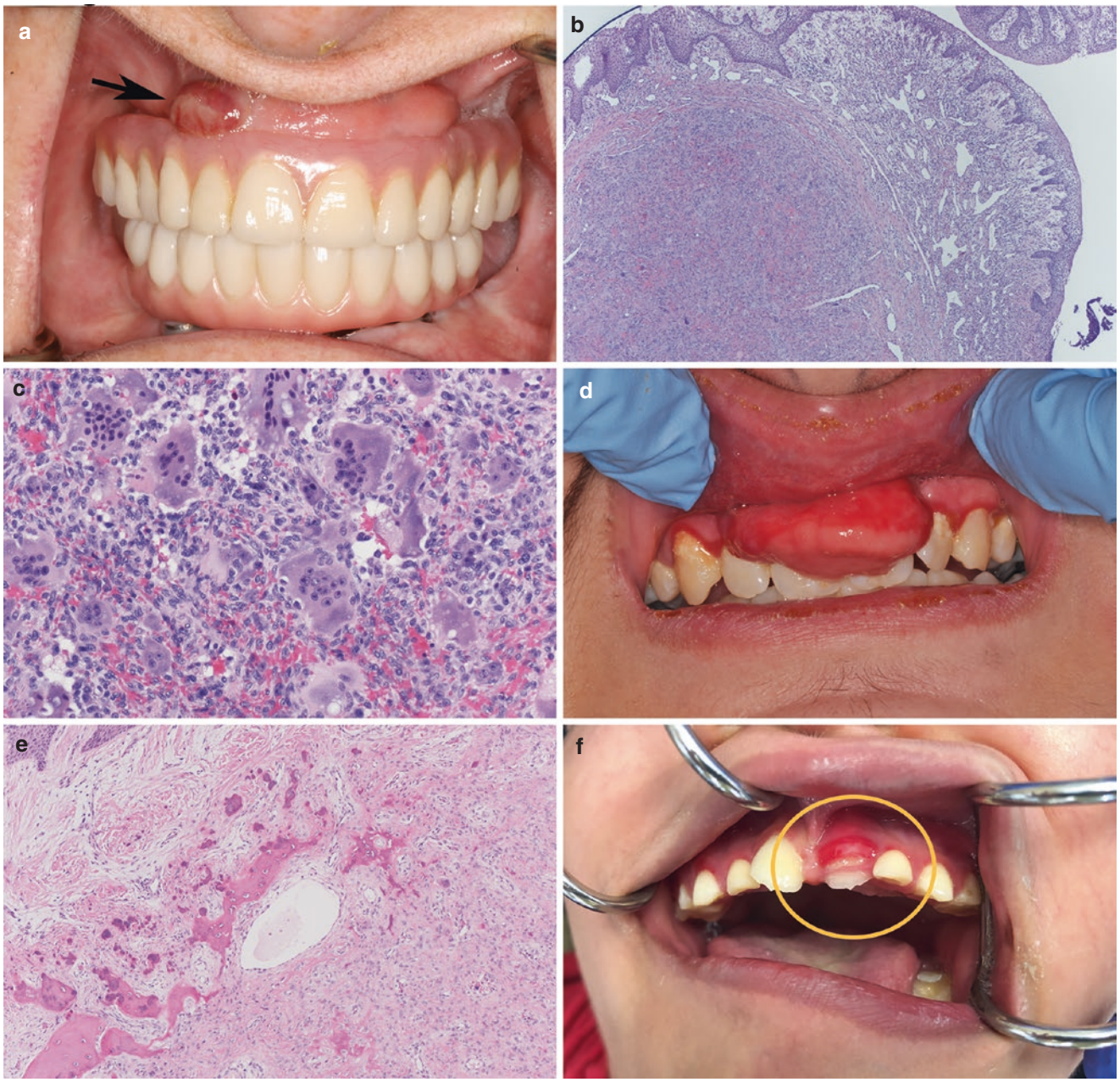


Fig. 16.7 Granulation tissue-related masses. Gingival nodules and their histological spectrum. (**a**) Peripheral giant cell granuloma (PGCG). An atrophic, painless, reddish-brown nodule on the right upper alveolar ridge (black arrow) associated with an implant-supported denture. On exam there was evidence of local irritation from food accumulation/impaction around the implant. PGCGs are seen exclusively on the gingiva and alveolar ridge. (**b**) PGCG, microscopic features (*low mag*). The nodule is composed of hyperplastic granulation tissue (see the area close to the epithelium) with a central area containing abundant multinucleated giant cells, poorly formed young capillaries, and plump fibroblasts. The overlying epithelium is intact but atrophic. (**c**) PGCG, microscopic features (*high mag*). Numerous osteoclast-type multinucleated giant cells in a background of hyperplastic granulation tissue. Note the erythrocyte extravasation and poorly formed capillaries—broken down hemosiderin corresponds to the maroonish clinical hue associated with PGCGs. (**d**) Peripheral ossifying fibroma (POF). The patient presented with a painless, long-standing (1.5 years), slow-growing, ~4 × 2 cm firm-to-hard erythematous gingival nodule in the anterior maxilla. There was generalized heavy plaque/calculus accumulation. The patient's last dental hygiene visit was over 3 years ago. POFs are exclusive to the gingiva. (**e**) POF/exuberant gingival hyperplasia with ossification, microscopic features. POFs are composed of hyperplastic fibrovascular granulation tissue dominated by plump fibroblasts. Areas of osteoid deposition and bone/cementum formation are noted. (**f**) Juvenile spongiotic gingival hyperplasia. Demarcated, granular, edematous appearing region of gingival erythema associated with the facial gingiva of tooth # 9. Seen in children and associated with local irritants (food impaction, incompletely erupted tooth)

hyperplastic granulation tissue origins of PG, PGCG, and peripheral ossifying fibromas (described in the next section).

Peripheral Giant Cell Granuloma: Management and Prognosis
PGCGs are treated with conservative surgical excision and curettage of the surgical bed. As with all reactive granulation tissue hyperplastic responses, it is essential to manage the underlying irritant or source of trauma—plaque removal, addressing poorly contoured restoration margins or prosthetic clasps, or food debridement. As with PGs, the prognosis for PGCGs is excellent, with the potential for recurrence if the underlying causative factors are not addressed. Older PGCGs can become fibrotic (irritation fibroma) or demonstrate foci with prominent osseous metaplasia.

Peripheral Ossifying Fibroma/Exuberant Fibrous Hyperplasia with Osseous Metaplasia

Peripheral ossifying fibromas (POF) are benign, reactive masses of exuberant, mesenchymal fibroblastic tissue with varying amounts of unmineralized or mineralized cementum or bone [21–23]. Like PGCGs, POFs arise from soft tissues of the periodontal ligament and occur *exclusively on the marginal and attached gingival tissues*. POFs, contrary to their name, "ossifying fibroma," are not benign neoplasms. The name "*Peripheral ossifying fibroma"* is a misnomer and symptom of the proliferation of diagnostic terms to describe entities that lie on the spectrum of granulation tissue formation, mesenchymal repair, and tissue organization. Some pathologists use the descriptive diagnosis "exuberant fibrous hyperplasia with osseous metaplasia" instead of POF and note that the mass represents a reactive and benign process. POFs are reactive and occur secondary to local irritants along the gingival sulcus or periodontal soft tissue: plaque, calculus, ill-fitting restoration/crown margins, food entrapment, or chronic inflammation. POFs are essentially cellular and fibrotic pyogenic granulomas in which pluripotent stem cells adjacent to the periosteum are triggered by growth factors (bFGF and TGF-beta) to transform into osteoblasts, cementoblasts, or fibroblasts.

Peripheral Ossifying Fibroma: Clinical History and Presentation
Peripheral ossifying fibromas, like PGCGs, occur only on gingival tissues. While some retrospective studies show that POFs show a predilection for younger patients and females [21–23], there are others where POFs occur in patients of all ages and sexes. POFs are seen along gingival tissues that are subject to localized chronic irritation or trauma. Patients present with a painless, slow-growing mass. They may be aware of the nodule growing progressively firm or hard over a period of months or years.

On examination, POFs are practically indistinguishable from PGCGs and irritation fibromas. They present as lobulated pink or yellow-red gingival masses. Early lesions may be ulcerated; older lesions tend to be surfaced by intact mucosa and are the color of normal oral tissues. The masses are typically seen on the gingival surfaces adjacent to a poorly restored tooth crown or in an area of heavy plaque accumulation (see Fig. 16.7d). POFs are nontender and can feel firm to bony hard on palpation.

Peripheral Ossifying Fibroma: Microscopic Presentation
POFs are composed of an unencapsulated, diffuse cellular proliferation of plump mesenchymal cells with minimal inflammation. The cells resemble fibroblasts or osteoblasts. Foci of unmineralized osteoid may be seen. Several areas of bone trabeculae and/or droplet-like mineralized cementum may be seen (Fig. 16.7e). The cytology of all cells is banal. Granulation tissue elements (resembling PG) and foci with multinucleated giant cells (PGCG) may also be evident. Zones of dense, acellular fibrosis may also be apparent and consistent with the granulation tissue and repair continuum.

Peripheral Ossifying Fibroma: Management and Prognosis
POFs are treated with conservative surgical excision, curettage of the wound site, and addressing the sources of local irritation.

Juvenile Spongiotic Gingival Hyperplasia

Juvenile spongiotic gingival hyperplasia is a relatively recently described benign reactive entity [24]. It is characterized by exuberant epithelial and stromal granulation tissue hyperplasia. It is seen along the gingival margins and almost exclusively in children aged 12–13 years or below. As with pyogenic granulomas, it tends to occur on the gingiva adjacent to areas prone to local irritation. It is presumably an outward eversion of the sulcular epithelium toward the facial aspect subjecting the junctional epithelium to the "outside environment." For all practical purposes, juvenile spongiotic gingival hyperplasia (JSGH) is a pyogenic granuloma with a few extra features: edematous epithelial hyperplasia, gingival location, pediatric population [24].

Juvenile Spongiotic Gingival Hyperplasia: Clinical History and Presentation
JSGH is seen in the first two decades of life. Most JSGH lesions are located on the anterior maxillary gingiva and are thought to be secondary to inadvertent mouth breathing or anterior gingival margin irritation (Fig. 16.7f) [25, 26]. Patients or their parents report discovering an asymptomatic red bump on the upper gum margin. They may not be aware

of any specific trauma. The finding is usually fairly quick in its manifestation, going from nothing to a visible change within weeks to a month. Patients or their parents may report occasional bleeding on brushing.

JSGH is typically a well-demarcated and defined elevated zone of erythema that has a granular or corrugated surface texture. The findings generally are between 3–8 mm in height and up to 1.5 cm in width (larger areas are rare). It occurs almost exclusively along the facial gingival margins of maxillary anterior teeth with potential extension onto the attached gingival region [24]. The area is asymptomatic. Bleeding on probing may be noted.

Juvenile Spongiotic Gingival Hyperplasia: Microscopic Features

The microscopic findings in JSGH are characterized by notable epithelial hyperplasia with no evidence of ulceration. The epithelium is spongiotic, edematous, and exhibits neutrophilic infiltration. The mass is composed of edematous granulation tissue and numerous congested blood vessels. In summary, the microscopic findings mimic that seen in PGs except for the overlying spongiotic epithelial hyperplasia.

Juvenile Spongiotic Gingival Hyperplasia: Management

Conservative surgical excision and follow-up are all that is required. Addressing home oral hygiene measures or potential mouth breathing issues is essential for patient education.

Traumatic Fibroma/Irritation Fibroma/Reactive Fibrous Hyperplasia

Traumatic fibromas are ubiquitous in daily practice. They are benign reactive submucosal nodules of hypocellular fibrous tissue [27–29]. The endpoint of most tissue repair-related processes is scar tissue comprised of hypocellular and hypovascular collagen deposition, i.e., fibrosis. The oral mucosal tissue is subject to daily friction and inadvertent trauma and is, therefore, a prime site for masses comprised of reactive fibrous tissue/scar. These extremely common, benign, reactive nodules are called irritation fibromas or traumatic fibromas (TF, a.k.a. *fibrovascular polyp*, *fibroepithelial polyp*, *bite fibroma*, *reactive fibrous hyperplasia*). A TF is a submucosal response to chronic irritation that results in initial pockets of granulation tissue formation and eventual organization through deposition of Type I and III collagen (regulated by bFGF, TGF-beta, and TGF-alpha). TFs may start as either pyogenic granulomas, PGCGs, or mucoceles in some patients. If left unmanaged, these entities could undergo scarring/fibrosis (as a fibrotic endpoint of granulation tissue) and appear as traumatic fibromas. Inflammatory fibrous hyperplasia associated with dental prostheses may take on different forms—epulis fissuratum or inflammatory papillary fibrous hyperplasia but represent essentially the same process.

Traumatic Fibroma: Clinical History and Presentation

Traumatic fibromas are common with no age or sex predilection. They occur commonly in trauma-prone oral cavity locations: buccal mucosa, lateral tongue, lower lip, and gingiva. There is no age or sex predilection. Patients present with a painless, long-standing nodule. Patients are generally aware of chronic friction or trauma, especially with TFs that present on the buccal mucosa along the occlusal plane (bite line) or at the anterior labial commissure. TFs on the lower labial mucosa may have started as mucoceles (following inadvertent lip trauma); those on the gingiva may have started as PGs or exuberant fibrous hyperplastic responses to local trauma/irritation.

On clinical examination, TFs present as round or ovoid, broad-based or polypoid, smooth-surfaced, mucosa-colored (pink) masses. The surface may appear white from reactive frictional keratosis or focally ulcerated from repeated trauma (Fig. 16.8a, b). The surrounding tissues are intact and generally of normal color and texture. TFs are nontender and feel soft to firm.

Fibrous hyperplasias or traumatic fibromas of the buccal vestibule and alveolar mucosa associated with ill-fitting dentures are referred to as *Epulis fissuratum (epulis = gingival growth; fissuratum = fissured morphology).* This is a form of denture-related hyperplasia that presents as redundant, linear masses along and around the flanges of ill-fitting partial or complete dentures. The repeated, chronic impact on the soft tissues from these flanges results in the characteristic shape and form. EF appears as painless, pink or red flabby-appearing redundant folds of firm tissue in the vestibules.

Traumatic Fibroma: Microscopic Presentation

At the microscope, traumatic fibromas present as sessile or pedunculated nodules composed of diffusely distributed, unencapsulated, hypocellular, and hypovascular fibrocollagenous tissue. The surface stratified squamous epithelium could be either hyperplastic or atrophic (Fig. 16.8c). The epithelium may exhibit surface corrugation and benign, frictional hyperkeratosis; epithelial maturation is generally normal. Fibromas may exhibit variable vascularity, focal granulation tissue formation, and scattered chronic inflammation. *Epulis fissuratum* is microscopically similar with the exception of more chronic inflammatory aggregates seen around the stroma. EFs also have the potential to have foci of surface ulceration and have a folded, fissured appearance in the areas where the denture flange is seated. Fibromas on the buccal mucosa may have areas of mature adipose tissue and are referred to as *fibrolipomas* (not to be mistaken for benign neoplasms of adipose tissue). Occasionally, fibromas on the gingiva, tongue, and hard palate exhibit a hypercellular

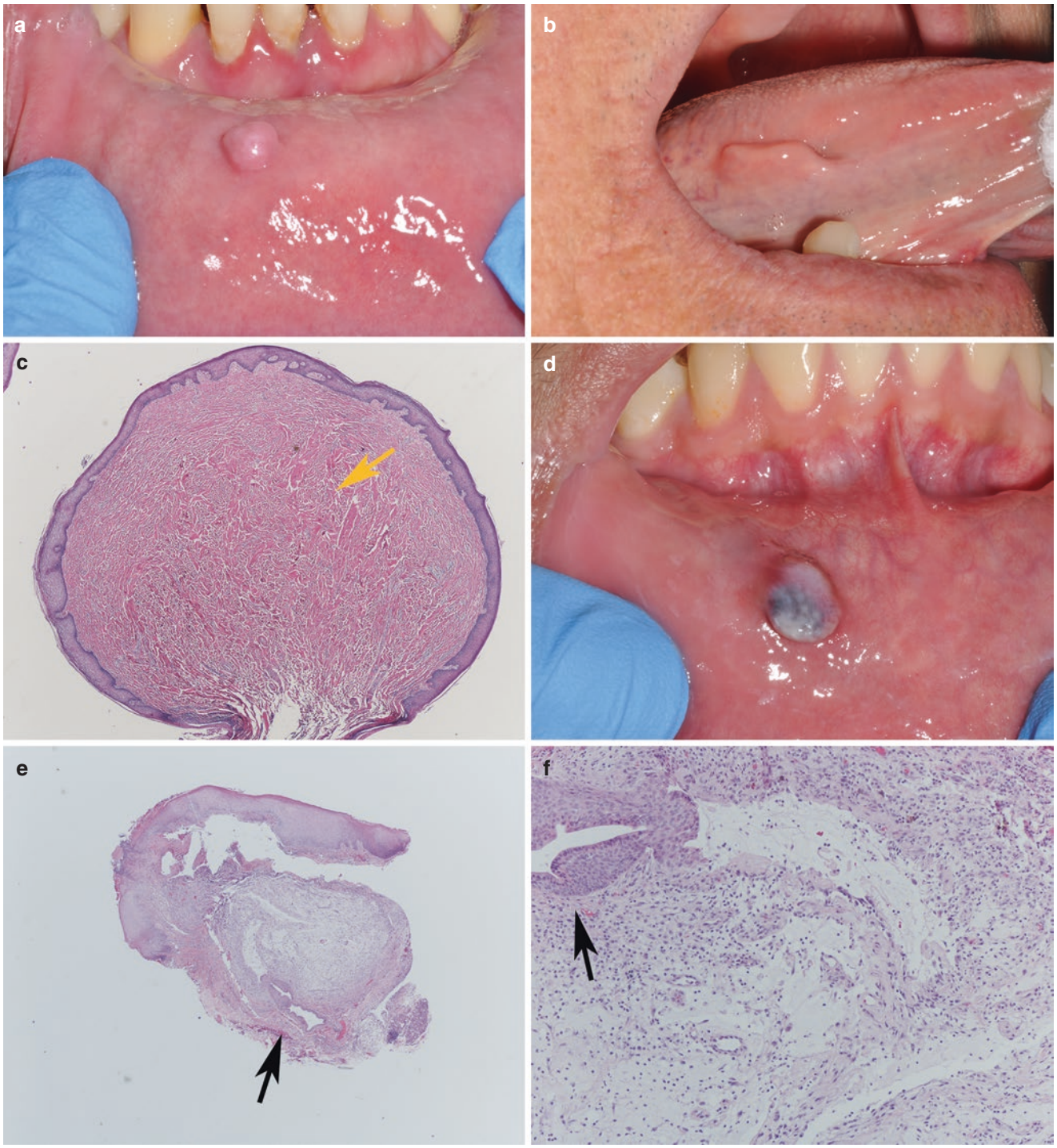


Fig. 16.8 Granulation tissue-related masses. Fibroma and mucocele. (**a**) Traumatic fibroma. A painless, discrete mucosa-colored nodule on the lower labial mucosa secondary to local trauma (lip biting). (**b**) Traumatic fibroma. A painless, firm-textured, mucosa-colored, sessile nodule on the right lateral tongue secondary to unintentional tongue biting. (**c**) Traumatic fibroma microscopic features (*low mag*). A polypoid nodule composed of dense, hypocellular fibrous connective tissue (yellow arrow)—an endpoint of organizing granulation tissue. The overlying epithelium is atrophic but intact. (**d**) Mucous extravasation phenomenon, mucocele. A painless, bluish-red, fluctuant mass on the right lower labial mucosa. The patient reports having bitten their lip a few days ago. (**e**) Mucocele, microscopic features (*low mag*). Submucosal mucin extravasation resulting from a severed duct (black arrow). Note the gray-blue region of mucinous beneath the surface epithelium (intact). (**f**) Mucocele, microscopic features (*high mag*). Mucin extravasation from a severed duct (black arrow). The spilled mucin initiates inflammation and is accompanied by a granulation tissue response. Depending on the duration from the traumatic incident, the inflammatory response can range from acute (neutrophils and edema) to chronic (muciphages + fibrovascular organization)

appearance. The fibroblasts are large, angulated, and stellate in appearance. The overlying epithelial rete pegs are tapered and jagged. These fibromas are referred to as *giant cell fibromas* [30].

Traumatic Fibroma: Management and Prognosis

Traumatic fibromas (or reactive fibromas by any other name) are treated with conservative surgical excision. Surgical options include sharp steel or laser-based excision. As with all reactive processes, clinicians should try and address any potential chronic irritant or source of trauma. For patients with epulis fissuratum, the treatment may involve relining or replacing their ill-fitting denture and surgical excision of redundant soft tissue. The overall prognosis for reactive fibrous hyperplasia is excellent, with low recurrence rates.

Mucocele/Ranula/Mucous Extravasation Phenomenon

Mucoceles (mucous extravasation phenomenon) are extremely common, trauma-related oral masses that occur in sites containing minor salivary gland lobules. Mucoceles result from the disruption of a minor salivary gland ductal system and extravasation of mucin into the surrounding connective tissue. The spilled mucin, an exocrine section, is regarded as a "foreign substance" by the body's innate immune system. It triggers an inflammatory and corresponding granulation tissue reaction. The initial acute, and subsequent chronic, inflammatory infiltrates attempt to lyse (neutrophils) and phagocytose (macrophages/muciphages) the spilled mucin and debris. The fibrovascular granulation tissue response (triggered by M2-macrophages) attempts to build scaffolds and a fibrous wall to contain the inflammation and the spilled mucin while working toward repairing and reorganizing the ductal system. Mucoceles can be seen in patients of any age and sex and occurs on all oral mucous membranes that contain submucosal minor salivary gland tissues; the marginal and attached gingival tissues as well as the hard palate do not contain minor salivary glands.

Mucocele: Clinical History and Presentation

Mucoceles are extremely common and occur in trauma-prone locations. The most common location is the lower labial mucosa. Other oral sites where mucoceles occur are the buccal mucosa, vestibule, and occasionally on the soft palate or floor of the mouth [28, 29, 31, 32]. The upper lip is not a common location for mucoceles but may be a location for mucous retention cysts or benign salivary gland neoplasms. Patients present with a painless, clear or bluish-colored, soft swelling/bubble on the lower lip or buccal mucosa (Fig. 16.8d). They typically present with a recent history of trauma to the area (e.g., biting lip while eating or speaking; a blow to the lips, cheek, or commissure). Occasionally, mucoceles may present in the floor of the mouth region following trauma or obstruction—this is common in children and adolescents and referred to as a *ranula.* In this setting, patients present with bluish, or pinkish swelling in the anterior floor of the mouth that may elevate the ventral tongue surface in and around the Wharton's duct region. Regardless of location, patients may report that the mass fluctuates in size or shape during the course of the day or week. As a rule, mucoceles do not present on the attached gingiva or hard palate in zones where there are no minor salivary glands.

On clinical exam, mucoceles present as round to ovoid, bluish/reddish/translucent, fluctuant (fluid-filled) sessile masses on the lower labial mucosa, buccal mucosa, or vestibule. Lesions that are ruptured may appear erythematous, ulcerated, or collapsed. They may vary in size from a few millimeters to a centimeter or more. Mucoceles that have been present for longer may feel firmer or "fibrotic," resulting from fibrous organization. Ranulas in the floor of the mouth region appear similar (bluish, fluctuant). They may push on the ventral tongue and obscure the morphological features of the anterior floor of the mouth region.

Mucocele: Microscopic Presentation

Mucoceles contain pools of gray-blue mucinous material with varying numbers of muciphages (macrophages with foamy intracytoplasmic mucin), neutrophils, and lymphocytes (Fig. 16.8e, f). The muciphages are typically at the periphery of mucin pools. In intact mucocele specimens, a condensed granulation tissue wall with fibrous tissue and numerous dilated and congested capillaries (correlating with the bluish-purple hue of mucoceles) are typically evident. In fragmented specimens, the granulation tissue wall may appear collapsed with mucin dispersion. The surrounding stromal tissue typically contains minor salivary gland lobules with varying amounts of chronic inflammatory infiltrates, interstitial fibrosis, and reactive acinar changes. Occasionally, a severed excretory duct may be evident in the specimen, confirming the disruptive origin of mucoceles. Mucoceles that are older or "chronic" contain minimal spilled mucin and may contain more organizing granulation tissue and foci of dense hypocellular fibrosis.

Mucocele: Management and Prognosis

Small, superficial mucoceles may resolve spontaneously. For larger mucoceles, it is essential to educate patients not to "puncture" or rupture mucoceles in an attempt to "drain" them. This often results in fibrosis and scar tissue formation, or recurrent mucoceles. Larger, deeper mucoceles are treated with definitive surgical excision of the nodule and the surrounding minor salivary gland. If left untreated, mucoceles may organize, fibrose, and appear as a traumatic/irritation

fibroma. Floor-of-mouth mucoceles (ranulas) may be large and occasionally "plunge" below the mylohyoid muscle and present as an extraoral swelling. This may require a more extensive surgical approach.

Traumatic Neuroma

Traumatic neuromas result from a simultaneous reactive proliferation of nerve fibers and scar tissue following trauma/damage to a peripheral nerve [33, 34]. A severed peripheral nerve attempts to regenerate and send unmyelinated axonal processes distally to reestablish a neural network. This is often accompanied by repair-related granulation tissue. The admixture of organizing granulation tissue and proliferating nerve trunks can form a knotted mass of regenerating nerve trunks and fibrous scar tissue. This results in the formation of a submucosal ball of scarred nerve tissue that manifests as an oral mucosal papule or nodule referred to as a *traumatic neuroma*. This entity is reactive and distinct from benign neural/perineural neoplasms like mucosal neuromas, schwannomas, and neurofibromas.

Traumatic Neuroma: Clinical History and Presentation

Traumatic neuromas are uncommon and occur in trauma-prone locations. The most common sites include the lateral tongue, lower lip mucosa, and the gingiva overlying the mental foramen region. Patients typically present with a small papule or nodule measuring 5 mm or less (larger masses are rare). Unlike most trauma/irritant-associated hyperplasias, traumatic neuromas can be symptomatic [33, 34]. Patient symptoms may range from a dull ache, to paresthesia (burning, tingling), to a shooting pain that may be triggered when the papule/nodule is touched. Traumatic neuromas in the mental foramen region are typically seen in edentulous patients (partial or complete).

On exam, traumatic neuromas are indistinguishable from a small traumatic fibroma or fibroepithelial polyp. They present as ovoid or round papules or nodules (5 mm or less) with intact pink/ normal-colored mucosal surfaces. On palpation, traumatic neuromas are soft to firm. Patients may report discomfort, tenderness, or extreme pain on palpation.

Traumatic Neuroma: Microscopic Presentation

Traumatic neuromas present as either polypoid or sessile nodules containing multiple nerve fibers arranged haphazardly in a dense, hypocellular fibrous (scar) background. Scar tissue is present between small and large nerve fibers and appears to splay them apart. Degenerating nerve fibers and elements of organizing granulation tissue may be evident at the periphery. Minimal to moderate chronic inflammatory aggregates may be evident. The nodular proliferation is generally diffuse and non-encapsulated. The overlying mucosa is usually intact and matures normally.

Traumatic Neuroma: Management and Prognosis

Traumatic neuromas are treated with conservative surgical excision. Addressing the surrounding scar tissue and larger peripheral nerve trunk may be required in larger lesions. The overall prognosis is excellent, with occasional recurrence.

Soft Tissue Cysts and Other Lesions

Gingival Cyst of the Adult

The gingival cyst of the adult is a developmental cyst that arises from ectodermally derived epithelial rests (dental lamina) that are left behind in the gingival soft tissues during and after tooth formation [35, 36]. Acquired developmental defects post-tooth eruption can cause cystification of these rests and present as a bump on the gingival tissues. Gingival cysts may mimic the appearance of mucoceles, but it is important to note that mucoceles do not occur on gingival tissues, given the absence of minor salivary glands on the gingival tissues.

Gingival Cyst: Clinical History and Presentation

Gingival cyst of the adult is an uncommon cyst. It typically presents in patients in their fourth or fifth decades as a painless, soft tissue nodule on the gingival tissues. The most common locations are on the facial aspects of the mandibular or maxillary canine-premolar region. Patients may report slow growth and no other clinical symptoms [35, 36].

On exam, gingival cysts are solitary and present as dome-shaped, translucent to bluish, fluctuant, or soft swellings on the alveolar mucosa or attached gingiva in the canine-premolar region, or the lateral incisor region (mandibular or maxillary) (Fig. 16.9a). The majority of gingival cysts are 5 mm or less in size. On palpation, the swellings are non-tender, fluctuant, or soft. There is no discharge or bleeding noted. The cyst is located exclusively in soft tissue and exhibits no bone involvement.

Gingival Cyst: Microscopic Findings

On microscopy, gingival cysts are lined by attenuated non-keratinized stratified squamous epithelium (Fig. 16.9b). The cyst lining may exhibit nodular epithelial thickenings [35]. The cyst wall is typically uninflamed. The overlying gingival epithelium is usually present in the specimen and is in close proximity to the cyst lumen. The gingival epithelium may appear atrophic, accounting for the translucent appearance of gingival cysts.

Gingival Cyst: Management

Gingival cysts are managed with conservative surgical enucleation and excision with an excellent prognosis.

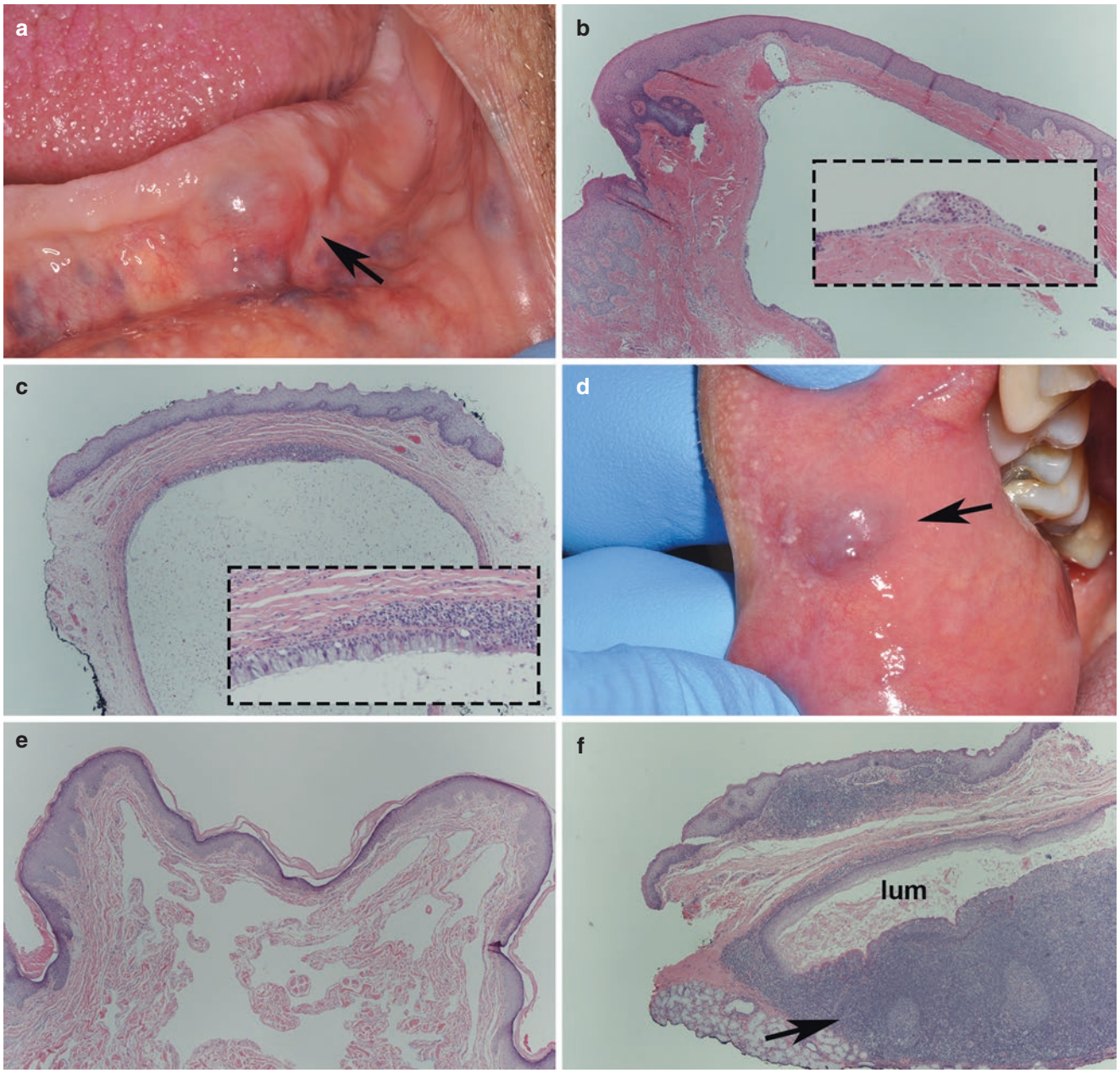


Fig. 16.9 Soft tissue cysts and other lesions. (**a**) Gingival cyst of the adult. A clear to bluish-colored, painless, slow-growing fluctuant nodule on the gingiva. The patient was unable to wear their lower denture. There was no evidence of bone involvement. (**b**) Gingival cyst, microscopic features. A soft tissue cyst located just beneath the intact gingival mucosa. The cyst is lined by attenuated, non-keratinized stratified squamous epithelium with occasional nodular epithelial thickenings (inset). (**c**) Mucous retention cyst, microscopic features. A soft tissue cyst located just beneath intact upper labial mucosal tissue. The cyst is lined by simple columnar epithelium with mucous producing goblet cells (see inset). There is no mucin spillage. (**d**) Venous lake/solitary varix: a long-standing, solitary, painless, slow-growing bluish-purple mass on the right buccal mucosa close to the commissure. On palpation the nodule was soft to firm; on pressure, the area blanched. (**e**) Solitary varix, microscopic features. Excision specimen from the vermilion and skin of the upper lip. Large, dilated and "floppy" appearing venous channels just beneath an intact overlying epithelial surface. There is no sign of proliferation. (**f**) Benign lymphoepithelial cyst, microscopic features. Clinically, BLECs present as painless, yellowish nodules in the posterior ventral tongue/floor-of-mouth region. On microscopy, the cyst lumen (lum) is filled with keratin (corresponds to the yellow clinical appearance) and lined by stratified squamous epithelium. The wall, characteristically, exhibits abundant mature lymphoid/tonsillar tissue with mature germinal centers

Mucous Retention Cyst/Salivary Duct Cyst

Mucous retention cysts are generally the result of ductal obstruction within minor salivary gland lobule ductal systems. The obstruction may be the result of small sialoliths or mucous plugs. Presumably, this obstruction leads to localized inflammation, reactive change, and subsequent cyst formation within the salivary duct. Cyst formation within submucosally located minor salivary glands results in soft tissue swellings that closely resemble the clinical appearance of mucoceles (mucous extravasation). Mucous retention cysts are pathophysiologically different from mucoceles in that there is no mucous spillage, associated inflammation, and granulation tissue responses.

Mucous Retention Cyst: Clinical History and Presentation
Mucous retention cysts typically occur on the upper labial mucosa, buccal mucosa, and other intraoral sites that bear submucosal minor salivary gland lobules. The lower labial mucosa is not a common location for mucous retention cysts. Patients present with a slowly enlarging, painless, translucent or bluish, ovoid/dome-shaped swelling. Patients may report fluctuations in size or shape during meals. On palpation, mucous retention cysts (similar to mucoceles) are nontender and fluctuant to soft. Larger mucous retention cysts may be associated with a palpable sialolith; or the patient may report occasional "grains of sand" emanating from a duct opening.

Mucous Retention Cyst: Microscopic Findings
Mucous retention cysts are characterized by a cystic cavity that resembles a dilated salivary duct. The cyst is typically lined by cuboidal or columnar epithelium (Fig. 16.9c) with apical goblet cells or apocrine snouting. The cyst lumen may contain pools of mucinous material. Occasionally, cysts may be partially lined by attenuated stratified squamous epithelium and are sometimes noted to be contiguous with an excretory duct with squamous metaplasia. Mild scattered chronic inflammation may be evident in the wall and surrounding minor salivary gland lobules. The overlying mucosal epithelium, if present, is generally intact and otherwise unremarkable.

Mucous Retention Cyst: Management
Mucous retention cysts are managed with conservative surgical enucleation of the cyst accompanied by removal of the associated minor salivary gland tissue to prevent recurrence.

Venous Lake

Venous lakes are the result of a solitary/focal venous dilation that results in vascular stasis [37]. It is either the result of trauma to a superficial venous channel or presumably a loss of "elasticity" among the smooth muscle of a vein's *tunica adventitia* resulting in its dilation. The pooling of venous contents in close proximity to the oral mucosal surface results in a focal oral swelling that goes by various diagnostic names: *solitary varix*, *venous pool*, *venous aneurysm*, *traumatic angiomatous lesion*. This phenomenon must be distinguished from varicosities seen around the oral cavity, especially prominent lingual varices. Lingual varies, which present as multiple purplish-blue linearly arranged swellings on the ventral tongue, are considered as a variation of normal clinical findings.

Venous Lake: Clinical History and Presentation
Patients with venous lakes present with a history of a persistent or slow growing, painless mass on locations prone to trauma or irritation [37]. The most common locations include the upper or lower labial mucosa, labial/buccal commissure, the labial vermilion, lateral tongue, and buccal vestibule. A venous lake presents as a solitary, discrete, sessile nodule that is generally bluish/maroon/purple in color (Fig. 16.9d). The nodule is nontender and soft to firm on palpation. Depending on the location, the nodule may feel mobile (like a small pea) under the mucosal tissue. On pressure, superficially located solitary varices blanch and fill back on release. Venous lakes are generally small (<1.0 cm in diameter). Occasionally, venous lakes may contain thrombotic material with varying degrees of organization; this may make the nodule feel firmer than otherwise.

Venous Lake: Microscopic Findings
On microscopy, sections reveal dilated venous channels within the superficial stromal tissue. The venous channels may vary in muscular thickness but invariably appear "floppy" and irregularly shaped (Fig. 16.9e). Variable amounts of blood or thrombotic material may be present with the varix. The overlying epithelium is generally intact but may be atrophic; venous channels are seen in close proximity to the epithelium. Some venous lakes may contain thrombi with marked organization and recanalization. This is typically seen in venous lakes that are secondarily traumatized and may demonstrate chronic inflammatory cells in the wall. Venous lakes do not extend into the deeper skeletal muscle or adipose tissue layers.

Venous Lake: Management
The bluish swellings associated with venous lakes are fairly diagnostic. Given that solitary venous lakes are asymptomatic, static, and do not pose any impairment to function, patients may choose to monitor and not treat them. Surgical excision is optional and should be conservative.

Lymphoepithelial Cyst

Benign lymphoepithelial cysts (LeC) are reactive cysts that arise from crypt epithelium/*lymphoepithelium* (see Chap. 19 section on oropharyngeal anatomy) within tonsillar tissues. In the oral cavity, LeCs arise within the lingual tonsillar tissue from reactive changes within the crypt epithelium [38–40]. Inflammation and irritation within the crypt presumably lead to epithelial hyperplasia and hyperkeratosis. The opening to the crypts may be obstructed by abundant keratin, microbial, and necrotic debris. This may lead to cystification of the crypt lumen and on occasion separates from the surface to form a submucosal cyst. LeCs can form extraorally: branchial cleft cysts within the neck or within the parotid gland. This section focuses on the oral LeCs (OLeCs) that cause swellings in the lingual tonsillar region.

Oral Lymphoepithelial Cyst: Clinical History and Presentation

In the oral cavity, OLeCs are almost exclusively seen in the posterior ventral tongue/floor of the mouth involving lingual tonsillar tissue [38, 41]. Occasionally, OLeCs can involve the soft palate. Patients with OLeCs present with an incidentally discovered painless nodule in this region (typically at a dental hygienist or physician wellness visit). There is no history of pain, symptoms, difficulty swallowing, or other loss of function. On examination, OLeCs present as discrete, yellowish or pale round/ovoid, sessile nodules in the ventral tongue or floor-of-mouth region [39, 40]. They are nontender, soft, and mobile on palpation. Rarely, the cyst may have a punctum with keratinaceous debris emanating from it. The nodule is typically surfaced by intact mucosa with no surface erythema.

Oral Lymphoepithelial Cyst: Microscopic Findings

Sections typically reveal an intact mucosal surface with a submucosal nodule containing a cyst. The overlying mucosal epithelium may be atrophic. The cyst is lined by attenuated stratified squamous epithelium with a flat interface (Fig. 16.9f). The cyst lining can be composed of reticulated stratified squamous epithelium/*lymphoepithelium* (see ultrastructural details in Chap. 19). The luminal surface is hyperkeratotic with abundant keratin shedding into the lumen. Keratin debris can be seen filling the lumen and is occasionally accompanied by necrotic and microbial debris (especially if the lumen is contiguous with the surface). The cyst wall characteristically contains abundant lymphoid tissue often with secondary follicle/germinal center formation.

Oral Lymphoepithelial Cyst: Management

The yellow-white nodules in the lingual tonsillar region or soft palate region are fairly diagnostic for BLeC. Conservative excision to establish diagnosis is an option but not an emergency. BLeCs are not a sign of infection and have the potential to stay the same size or involute in some patients.

Osseous Masses

Torus/Tori

A torus is an anomaly of gnathic development and considered by most to be a variant of normal development. Oral tori have an inherited component and exhibit an autosomal dominant pattern in some families. By definition, there are two types of tori: (1) palatal torus; (2) mandibular lingual tori. A palatal torus is a bony growth that presents on the hard palatal midline. Mandibular lingual tori present on the lingual aspect of the anterior mandible from the lateral incisor to the canine-premolar region. Tori may be found in infancy and can continue to grow through a person's lifetime.

Clinically, tori present as glacially slow-growing bony hard masses on the hard palate and/or bilaterally on the lingual anterior-posterior mandible. Patients are generally aware of that they've had tori since their childhood. There is no pain, discomfort, or impact on everyday function. The masses are sessile and bosselated on the surface. The overlying mucosal tissues are intact and of normal color; tori may be secondarily ulcerated from trauma, causing discomfort.

Biopsies or excision of tori is not recommended. Rarely, tori may have to be surgically excised if they impact complete or partial denture construction; however, dentists have the means to work around tori with adequate tissue relief.

At the microscope, tori are composed of mature, viable lamellar bone. The overlying mucosal tissue is intact, thin, and normal.

Exostoses

Exostoses are benign, often reactive periosteal bony growths that present along the buccal/facial aspect of either maxilla or the mandible. They are hyperplastic osseous growths secondary to low-grade inflammation and often in areas of chronic periodontal disease. There appears to be a genetic predilection in people who develop prominent gnathic exostoses.

Clinically, buccal exostoses present as slow growing or static bony hard prominences on the buccal/facial gingival tissues. In patients with generalized periodontal disease, they tend to be distributed bilaterally and multifocally. In patients with a focal inflammatory source, a bony exostosis could be solitary (e.g., an endodontically treated tooth). Bony exostoses do not impede function unless the patient is edentulous and is being considered for removable prostheses that require relief. Exostoses do not require surgical excision.

At the microscope, bony exostoses are nodular, convex, and composed of mature lamellar bone with varying amounts of reversal lines (remodeling) secondary to periosteal deposition. The intervening connective tissue is uninflamed. The overlying mucosal tissue is generally intact unless secondarily ulcerated.

Benign Neoplasms

As described previously, benign neoplasms are caused by genetic deregulation (via acquired/germline mutations, gene fusion, loss of heterozygosity, protein transcription defects) that results in a benign, often-clonal proliferation of the affected tissue (epithelial/mesenchymal). Unlike exuberant reactive hyperplasias, benign neoplasms are unrelated to specific traumatic insults/chronic irritants. Hence benign neoplasms may be encountered in oral locations that may be otherwise trauma protected. When considering the general features of benign neoplasms, it is helpful to compare them to both reactive hyperplastic masses (discussed in the previous sections) and malignant neoplasms. Features that are shared by both benign and malignant tumors include a proliferative parenchyma (the transformed neoplastic cell) and a supporting, host-derived, non-neoplastic stromal component composed of blood vessels and a scaffolding framework. The latter is essential to all tumor survival and growth. The fundamental features that distinguish benign from malignant neoplasms are differentiation, invasion (lack thereof), and corresponding clinical behavior.

At a cellular and tissue level, benign neoplasms are well differentiated. They resemble the tissues they originate from. For instance, a hemangioma is composed of a proliferation of cytologically benign endothelial cells that form the recognizable structures they are programmed to make: blood vessels (capillaries, veins, arteries, etc.). At a cytological level, benign neoplasms do not exhibit pleomorphism, nuclear abnormalities, abnormal mitoses, or loss of polarity. Well-differentiated tumor cells may retain the functional capabilities of their normal counterparts.

As a rule, benign neoplasms do not invade surrounding tissues. Benign neoplasms grow as cohesive expansile masses that remain localized to their sites of origin. Given their slow growth, benign neoplasms develop a well-formed rim of compressed fibrous tissue: encapsulation. Fibrous capsules derive from the stromal tissue that accompanies the neoplasm; the origin of peritumor capsules can be traced back to the same signaling mechanisms and growth factors that give rise to granulation tissue in reactive processes. Encapsulation makes benign neoplasms discrete, mobile (if present in soft tissues), and amenable to surgical excision. Some benign neoplasms, like hemangiomas, may lack a true capsule and exhibit locally infiltrative behavior. Malignant neoplasms, unlike benign ones, have the potential to invade beyond their local site of origin, given their ability to produce lytic enzymes (metalloproteases, collagenases) and infiltrate into lymphatics and blood vessels.

Clinically, benign neoplasms of the oral soft tissues present as slow-growing, painless masses with intact mucosal surfaces. Patients are often aware of a nodule/lump growing symmetrically over several months or years. Benign neoplasms are typically discrete, symmetrical, potentially mobile (location dependent), and uniform in color and texture. Benign neoplasms tend to push against surrounding normal structures and do not impact their normal function. For instance, a salivary adenoma growing in the cheek may push against neurovascular bundles or a salivary duct but will not impair their respective functions.

Given the anatomic complexity of the orofacial region, a wide range of benign neoplasms occur on the oral soft tissues. This section will focus on the most commonly encountered benign neoplasms affecting oral soft tissues and discuss a few benign neoplasms that have a distinct clinical appearance and/or behavior. Discussing every single entity is beyond the scope of this chapter.

Benign Epithelial Neoplasms: HPV-Related

The most common benign neoplasms encountered in the oral cavity are viral warts caused by human papillomaviruses (HPV). Human papillomaviruses are small, non-enveloped, epitheliotropic, double-stranded DNA viruses with more than 200 strains that infect both cutaneous and mucosal surfaces. The Alpha family is the most clinically significant virus associated with benign and malignant neoplasms. The overwhelming majority of Alpha HPV strains cause *benign* cutaneous and mucosal neoplasms (warts); they are considered "low-risk" (LR-HPV). A small number of Alpha HPVs are "high-risk" (HR-HPV) [16, 18, 31, 33] and are associated with cancers of the cervix, oropharynx, and anogenital mucosae [42, 43]. The pathogenesis and clinical presentation of HR-HPV-associated cancer are presented in detail in Chap. 19.

The LR-HPV strains associated with oral mucosal warts are HPV6, 11, 13, 32, and 7. As an obligate intracellular parasite, HPV depends on a host's replicative machinery and protein transcription "factory." The cells best suited to HPV's viral transcription needs are proliferative and differentiating keratinocytes in stratified squamous epithelia; HPV is bound to the keratinocyte lifecycle from basal to spinous to superficial layers. Hence, the *oral basal epithelial cells of stratified squamous epithelium* serve as THE host cell of choice and the "portal of entry." During wart formation, the virus "hijacks" a host epithelial cell to transcribe its proteins and, in the process, promotes unregulated

epithelial proliferation. The virus harnesses the epithelial proliferation machinery, the cell cycle, to achieve its evolutionary end goal: to replicate, assemble millions of viral capsids, infect another host cell, and go on a repeat cycle. To understand HPV pathogenesis, one needs to appreciate HPV's structure and function. The mechanistic details of HPV pathogenesis are presented in the "HPV pathogenesis" section of Chap. 19 (Fig. 19.4).

An important concept, described in detail in Chap. 19, is the difference between the mechanisms leading to warts relative to those leading to HR-HPV-associated malignancy. The fundamental difference between viral warts and HPV-related cancer is the presence of a productive viral infection cycle during the formation of warts (benign epithelial neoplasms) compared to a non-productive viral cycle (no viral capsid release) noted in HPV-related cancers. The other critical difference is that benign viral warts DO NOT cause or progress to HPV-related SCC as the specific viral strains are very different: LR-HPV vs. HR-HPV.

The benign neoplasms associated with LR-HPV are caused by virally driven, clonal epithelial proliferation accounting for mucosal warts (verruca vulgaris, squamous papilloma, condyloma acuminatum). HPV6 and 11 share early pathogenetic mechanisms common to all viruses in the family (high and low risk). Upon entry into the trans-golgi network, LR-HPV strains, through E1, E2, E6, and E7 gene function, promote an initial genome amplification. This results in the establishment of a low copy number in infected basal stem cells. What follows is the orderly expression of viral E1, E2, E4, E5, and late spinous layer expression of E6 and E7; this results in clonal epithelial proliferation in a spire-like manner. Viral capsid protein assembly proceeds in order, with virions released at the epithelial surface. This productive viral life cycle accounts for the infectious nature of benign warts. All along, the viral E4 and E5 gene activity promotes angiogenesis and creates a sustaining fibrovascular stroma. By contrast, in HR-HPV (HPV16, 18) related cancers, the production of infectious virions is restricted to smaller numbers and is eventually shut down. HR-HPV strains demonstrate elevated and dysregulated levels of E6/E7 (oncogene) expression. This is in stark contrast to benign gene activity promoted by LR-HPV strains HPV6 and 11. Hence, viral warts caused by HPV 6, 11, and other LR strains are vastly different diseases from HPV16- and 18-related cancers [42, 43]. Notably, a patient with a history of HPV6- or 11-related warts is NOT at risk of developing an oral malignancy from a LR strain. The clonal epithelial proliferation and accompanying angiogenesis accounts for the oral mucosal polyps, lumps, and bumps. The benign HPV-related masses of the oral cavity are verruca vulgaris (common wart) (VV), squamous papilloma (SP), condyloma acuminatum (CA), and multifocal epithelial hyperplasia (MEH).

Squamous Papilloma/Verruca Vulgaris

Squamous papillomas (SP) and Verruca vulgaris (VV) are the diagnostic terms to describe LR-HPV-associated warts [44]. The two entities share the same pathogenesis but result from different LR-HPV strains. They also exhibit different clinical and microscopic characteristics. Oral mucosal squamous papillomas are associated with HPV6 and 11, whereas verrucae vulgaris are associated with HPV 2, 4 (a gamma HPV virus), and 40 [42, 45–48].

Squamous Papilloma and Verruca Vulgaris: Clinical History and Presentation

Oral SPs are ubiquitous and can occur at any age, including in children. Although any oral surface can be affected, the most common locations include the palate (including the soft palate) (Fig. 16.2c), tongue, labial mucosa, or buccal mucosa [44]. On exam, SPs are typically painless, pedunculated, exophytic masses with numerous delicate finger-like surface projections that may appear either pink or white due to heavy keratinization (see Fig. 16.10a, b). SPs are often described as having a delicate "haystack" or short and stubby cauliflower-like configuration. Patients with SPs are likely to have more than one lesion in their mouth. On palpation, SPs are soft, nontender, and do not bleed. Patients may report occasional bleeding if SPs are inadvertently traumatized.

Verruca vulgaris is relatively uncommon intraorally. It is caused primarily by LR-HPV strains that exhibit cutaneous tropism (HPV2, 4, 40) with the potential for mucosal involvement [47, 48]. Patients with VV may report a history of trauma or biting their skin. Autoinoculation is common, especially in children who suck on their fingers or thumbs. Clinically, VV of the oral mucosa can be seen in children and adults. The nodule or papule is typically seen on the vermillion of the lip, labial mucosa, tongue, or gingiva. VV presents as a painless, broad-based, exophytic, corrugated papule or nodule with either a mucosal- or white-colored surface, and can be indistinguishable from SPs. The surface of VVs is thrown into numerous corrugated/verruciform (peaks and troughs) folds with a bright white surface from the heavy hyperkeratosis (Fig. 16.10c). Both SP and VV tend to grow fairly rapidly and within a matter of weeks but seldom grow larger than 5–10 mm in greatest dimension. Both can undergo spontaneous involution and appear in other oral locations. Patients who are immunocompromised or immune-depleted, or patients with a history of HIV infection may present with multiple oral warts (Fig. 16.10c).

Squamous Papilloma and Verruca Vulgaris: Microscopic Findings

At the microscope, both SPs and VVs present as exophytic soft tissue nodules composed of hyperplastic and proliferative epithelium. SPs tend to have a narrower base and more likely to be pedunculated. In SPs, the epithelium is thrown

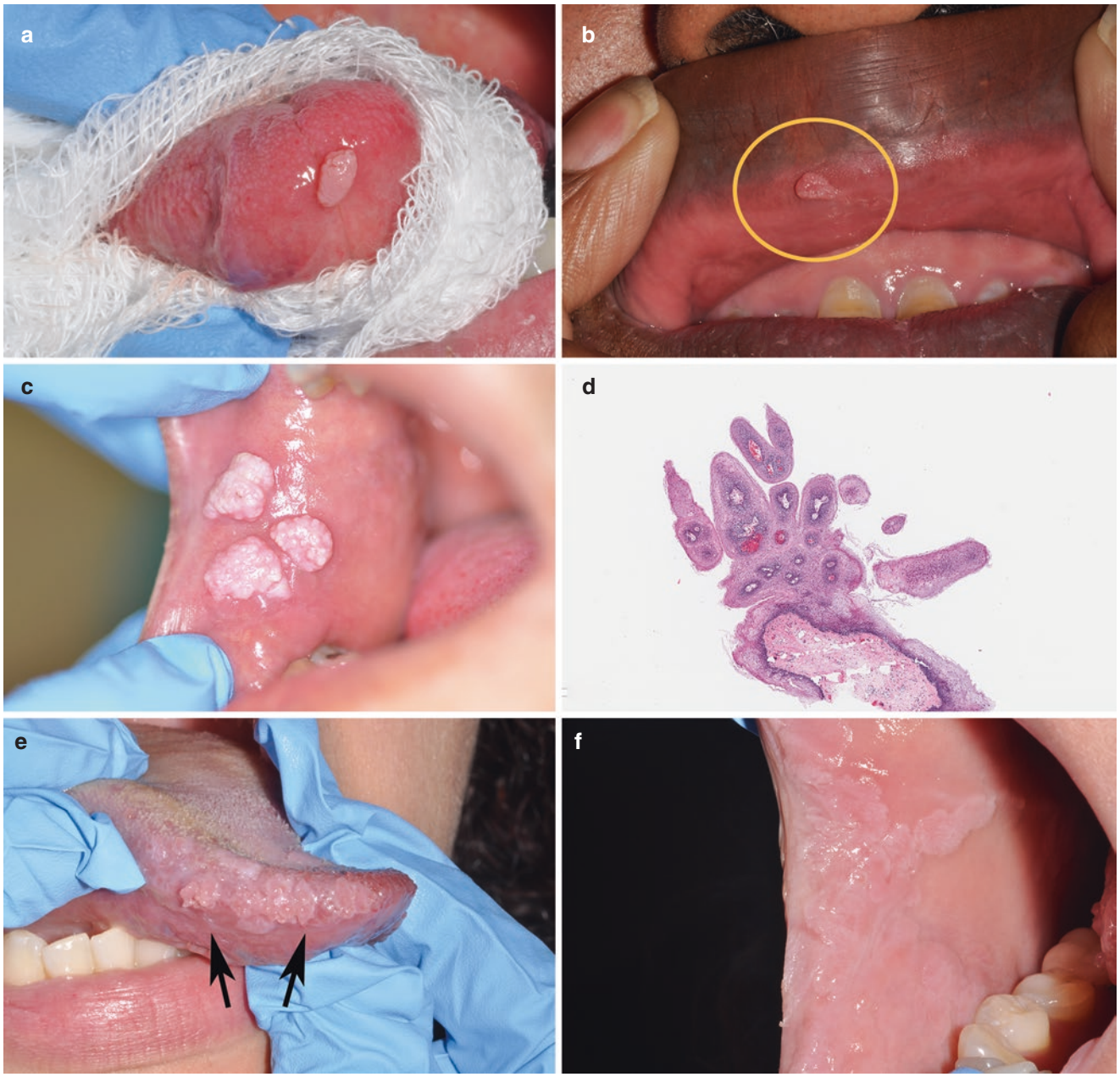


Fig. 16.10 Benign neoplasms. Low-risk Human Papillomavirus (LR-HPV) related oral swellings (viral warts). (**a**) Squamous papilloma. Associated with LR-HPV strains 6 & 11. Painless, long-standing, exophytic, pedunculated, polyp on the anterior dorsal tongue. The nodule has a papillary/corrugated surface, intact, and white-to-mucosa colored. (**b**) Squamous papilloma. Associated with LR-HPV strains 6 & 11. Painless, long-standing, exophytic, pedunculated, polyp on the upper labial mucosa. The nodule is papillary, intact, and mucosa colored. (**c**) Verruca vulgaris. Associated with LR-HPV strains 2, 4, & 40. Multiple, broad-based, white, corrugated masses on the right buccal mucosa. (**d**) Squamous papilloma, microscopic features. An exophytic, papillary epithelial proliferation with light surface keratinization. The proliferation is accompanied by a characteristic fibrovascular (angiogenesis) tissue within the papillary connective tissue cores. Note the surrounding normal epithelium and lack of endophytic growth. (**e**, **f**) Multifocal epithelial hyperplasia (MEH)/Heck's Disease. Associated with LR-HPV 13, 31. The patient presented with a long-standing history of multiple, painless, papillary growths bilaterally on the tongue, labial mucosa, buccal mucosa. The patient reported the lesions "moving" around her mouth—involuting in regions while appearing in others over a period of years

into multiple papillary folds (finger-like projections) (Fig. 16.10d). The epithelium is generally non-keratinized but could exhibit varying degrees of parakeratinization. The valleys between the papillary projections could be filled with keratin [44]. Virally modified cells (koilocytes) may be evident in some lesions. The basal epithelial and upward maturation is generally within the range of normal. The papillary connective tissue cores are prominently fibrovascular with

dilated capillaries. On microscopic examination, VVs are sessile, exophytic, and exhibit axial inclination (a cupping appearance of rete pegs at the edge of the lesion). VVs exhibit a verrucous, corrugated/wavy surface configuration and surfaced by a hyperorthokeratotic layer. VVs exhibit a prominent granular layer (see figure VV granular) [47, 48]. Koilocytes may be seen within the superficial spinous and granular layers. Despite the notable epithelial proliferation, maturation from the basal to superficial strata is within normal range.

Squamous Papilloma and Verruca Vulgaris: Management and Prevention

SP and VV are managed with conservative surgical excision that includes the base of the lesion. Frequently, benign warts left untreated can undergo spontaneous involution or remain the same with no spread to adjacent sites. The benignity of warts cannot be stressed enough. Patients must be educated about the infectious nature of LR-HPV-related warts and assured that there is no risk of transformation to cancer. It is also important to stress to patients that the presence of an oral wart does not translate to an increased risk of developing HPV-related oropharyngeal or cervical SCC.

A significant development in our management of HPV-related processes is the availability of highly effective HPV vaccines. Clinicians have an opportunity to discuss the benefits of HPV vaccines with their patients, especially those with young children. HPV vaccines are made from purified L1 virus-like proteins of various HPV strains. Multiple studies have shown that HPV vaccines have a high efficacy (close to 100%) in preventing cervical cancer. Studies have demonstrated the latest HPV vaccines to be effective in preventing other HR-HPV-related cancers: anal, oropharyngeal, vaginal, penile, and vulvar. The latest vaccine Gardasil® 9-valent is protective against several HR-HPV strains [16, 18, 31, 33, 45, 49, 50] as well as LR-HPV strains 6 and 11. Thus, HPV vaccines protect against both cancers and warts.

The indications and schedules for administering HPV vaccines are as follows:

- **Children:** routine HPV vaccination for all children at 11–12 years. The vaccine can be started at 9 years.
- *Two doses of HPV vaccine should be given at 0 and at 6–12 months.*
- **Adolescents and adults** (13–26 years): catch-up vaccination for those who have not been vaccinated.
- *Three doses of HPV vaccine should be given at 0, 1 to 2 (typically 2), and 6 months.*
- **Adults older than 27 years:** catch-up vaccination is not routinely recommended. Selected situations may apply (i.e., immunocompromised patients).
- *Three doses of HPV vaccine should be given at 0, 1 to 2, and 6 months.*

Multifocal Epithelial Hyperplasia

Multifocal epithelial hyperplasia (MEH) or "Heck's disease" is a benign HPV-related epithelial proliferative disorder. MEH is attributed to LR-HPV strains HPV13 and 32. It is defined by the presence of multiple virally induced epithelial papules and nodules with a propensity for people with a specific human leukocyte antigen subtype HLA-DR. Lesions of MEH are seen in Native Americans, indigenous people of Greenland, Brazil, and Pacific Islanders. MEH has also been documented in the elderly and in patients with HIV-AIDS [46, 51, 52]. It is considered to be highly contagious and is often seen affecting multiple members of a family.

Clinically, patients with MEH present with multiple pink-to-white, verrucous, papillary, and corrugated-appearing papules and/or nodules (Fig. 16.10e, f). Some lesions may be exophytic, while others are sessile. Lesions of MEH tend to coalesce, flatten, and form a carpet-like morphology. The nodules are painless and are distributed along the lips, buccal mucosa, tongue, and occasionally on the gingival tissues. The floor of the mouth and palate are typically uninvolved. MEH lesions are characteristically painless and cause no loss of function. Patients may report biting into lesions, causing bleeding. Occasionally, patients report spontaneous involution of viral warts in some areas with growth/ spread in others.

Microscopically, MEH presents with sessile papules and nodules composed of hyperplastic epithelium. The stratified squamous epithelium exhibits acanthosis and grows characteristically upward (broad-based) and above the plane of normal epithelium. The *rete pegs* are typically the same depth as the adjacent normal ones. Superficial epithelial cells may exhibit koilocytic change. Lesions of MEH exhibit so-called mitosoid bodies with degenerating nuclear chromatin, representing virally altered cells [46, 51, 52].

Patients with MEH are managed conservatively, especially as the multiple lesions do not impede daily function. As described, MEH lesions tend to involute and resolve with no intervention in most patients, only to appear in other locations. Selected surgical removal may be indicated for those lesions that are repeatedly traumatized or "in the way" of normal function. The overall prognosis for MEH is good, with no risk of progression to carcinoma.

Neural and Perineural Neoplasms

Benign neoplasms of peripheral nerve and perineural tissues in the orofacial region are rare. Unlike traumatic neuromas discussed earlier, neural and perineural tumors present as painless, mucosa-colored oral masses [53]. They present as solitary masses as seen with schwannomas and granular cell tumors or in multiples in the case of mucosal neuromas and neurofibromas. The former is a result of focal acquired genetic defects. The presence of multiple mucosal neural/

perineural neoplasms is often a manifestation of an underlying inherited systemic condition.

Schwannoma

Schwannomas are benign neoplasms of Schwann cells of the neural sheath. While the head and neck region is a common location for schwannomas, they are relatively uncommon in the oral cavity [53]. Most oral schwannomas are solitary; in rare instances, multiple schwannomas may be associated with neurofibromatosis 2 (NF-2) or schwannomatosis syndrome.

Clinically, schwannomas of the oral cavity present as slow-growing, painless, sessile mucosal-colored nodules with intact surfaces. Patients may report progressively slow growth. Solitary oral schwannomas present in adults between the third and sixth decade. The most common location is the dorsal and lateral tongue (Fig. 16.11a); other sites include the buccal mucosa, labial mucosa, and vestibule [49]. When schwannomas occur on the dorsal tongue, the overlying filiform papillae may exhibit atrophy or may be lost; this manifests as a "bald" appearing nodule. Solitary oral schwannomas are indistinguishable from the clinical appearance of irritation fibromas. The diagnosis is made on surgical excision and histological examination.

At the microscope, schwannomas present as encapsulated submucosal nodules composed of a proliferation of cytologically benign spindle-shaped cells arranged in two distinct patterns. The Antoni-A arrangement contains spindle-shaped Schwann cells arranged in parallel or palisading arrangement with blunt elongated nuclei; the cells are arranged around acellular amorphous eosinophilic areas [49] (Fig. 16.11b). Other regions within the nodule may exhibit Antoni-B arrangement that lacks the organized appearance described above. Cells are arranged haphazardly in a loose myxoid stroma. The tumor stroma is typically uninflamed, but there are examples of schwannomas with chronic inflammation and areas of fibrous organization. Tumor cells are positive on immunohistochemistry for S100, CD56, and SOX 10.

Schwannomas are excised with conservative surgery with minimal risk for recurrence. Patients with multiple schwannomas may need to be worked up for potential underlying syndromes (in patients with no prior history of a syndrome).

Granular Cell Tumor

The granular cell tumor (GCT) is a benign neoplasm of Schwann cell origin and is sometimes referred to as a granular cell schwannoma [54–57]. GCTs were originally thought of as tumors of striated muscle origin (originally called a granular cell myoblastoma) but are now accepted as originating in neuroectodermal tissue [58]. The tumor's characteristic eosinophilic cytoplasmic granules result from lysosomal accumulation within the tumor cells. GCTs are typically solitary and have a predilection for the head and neck region, oral cavity, and skin.

The oral cavity, especially the dorsal tongue, is a common location for GCTs. Clinically, an oral GCT presents as a slow-growing, painless, sessile, and dome-shaped nodule on the dorsal or lateral tongue. The mass is typically pink-to-pale white in color and is well demarcated from the surrounding dorsal tongue surface. The overlying mucosa is usually atrophic and "stretched" out (Fig. 16.11c). The tumor is firm to doughy on palpation. As with conventional schwannomas in this location, the overlying dorsal tongue papillae are lost or atrophic. GCTs can also present on other oral surfaces, including the buccal and labial mucosa.

On histological exam, GCTs present as discrete but unencapsulated submucosal masses composed of large polyhedral cells with indistinct cell membranes [58]. The tumor cell cytoplasm contains abundant fine-to-coarse eosinophilic granular material (Fig. 16.11d). The nucleus is typically eccentrically placed and vesicular. Cytological features are banal. The tumor cells are arranged in broad sheets and extend from the lamina propria deep into the skeletal muscle. Tumor cells are seen among striated muscle cells and may appear to blend in with individual myocytes. On the dorsal tongue, the tumor may exhibit a Grenz zone or come right up to the surface epithelium. Frequently, GCTs of the tongue are associated with prominent pseudoepitheliomatous hyperplasia; this should be recognized and not mistaken for a squamous cell carcinoma [54–57]. Tumor cells express S-100, neuron-specific enolase (NSE), and CD68.

GCTs are excised with conservative surgery with minimal risk for recurrence despite the lack of deep tissue capsulation.

Mucosal Neuroma

The mucosal neuroma is an example of benign neoplasm that arises in the setting of an inherited genetic disorder, Multiple Endocrine Neoplasia Type 2-B (MEN 2B) [50, 59]. Unlike most sporadic, solitary, acquired benign neoplasms, mucosal neuromas present in multiples [53]. They can affect the oral mucosal membranes in addition to other mucosae. Patients with MEN 2B develop tumors of the adrenal gland (pheochromocytoma), thyroid (medullary carcinoma), and intestine (ganglioneuromas) [50, 59]. Mucosal neuromas result from germline mutations in the RET protooncogene that promotes cell proliferation through the AKT, mTOR1 pathway.

The typical patient is a child or adolescent who presents with multiple painless oral mucosal nodules. The patients may already have a diagnosis of MEN 2B or present with a family history of the syndrome. Clinically, patients present with multiple pink-white, sessile nodules of the lips, tongue, and buccal commissures [50]. The nodules are painless, soft

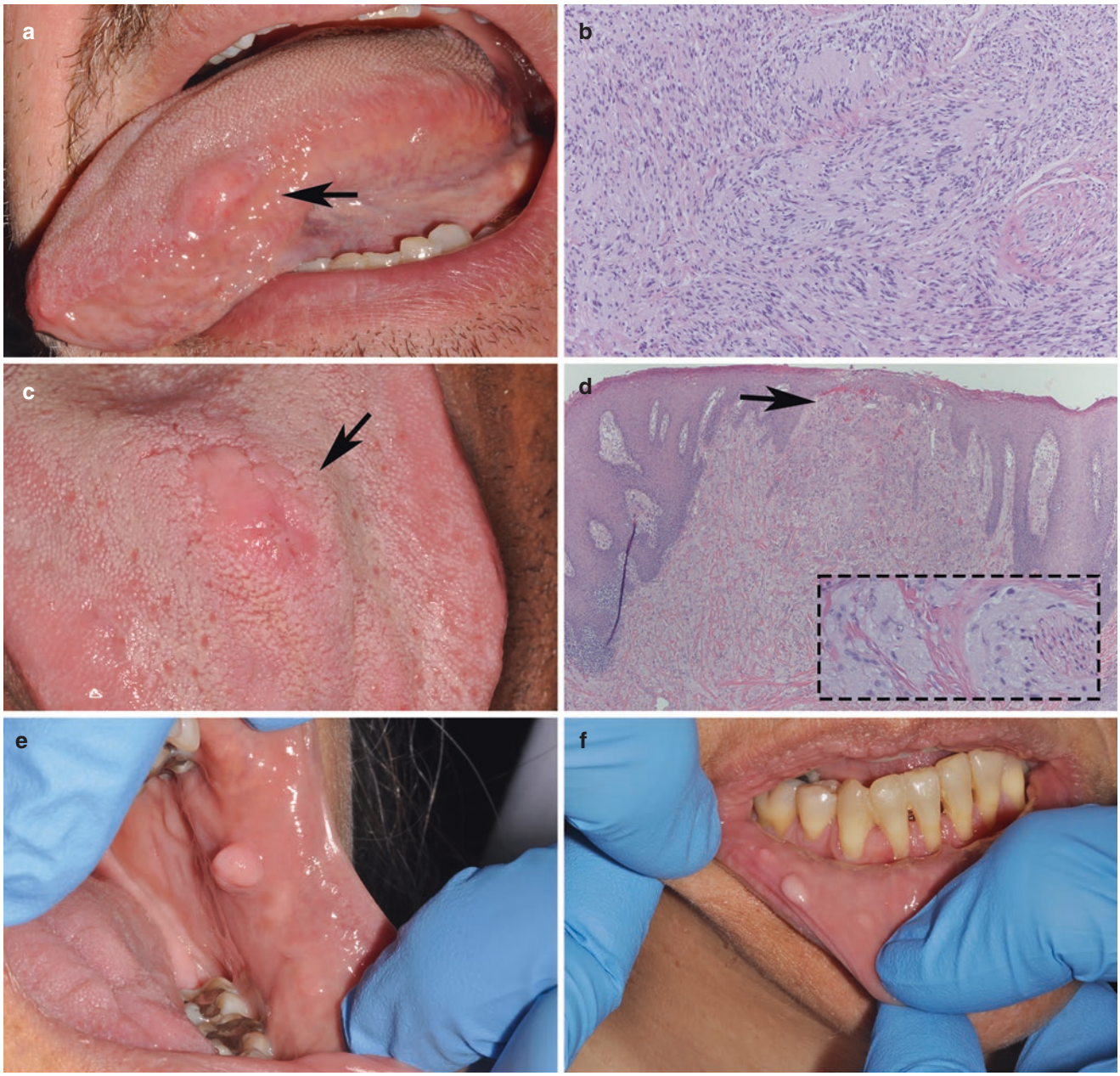


Fig. 16.11 Soft tissue nodules. Benign neural and perineural neoplasms. (**a**) Soft tissue nodule on the lateral tongue. The differential diagnosis for a smooth-surfaced, painless nodule on the left lateral-ventral tongue includes a traumatic fibroma or a benign perineural neoplasm (schwannoma). (**b**) Schwannoma, microscopic features (*high mag*). Proliferation of cytologically benign spindle-shaped Schwann cells arranged in a parallel or palisading arrangement surrounded by amorphous, hypocellular eosinophilic areas (Antoni A pattern). (**c**) Granular cell tumor (GCT). A painless, slow-growing, broad-based mass on the dorsal tongue. GCTs on the dorsal tongue are typically associated with a loss or atrophy of filiform papillae. (**d**) Granular cell tumor, microscopic features. An unencapsulated benign neoplastic proliferation of large polyhedral cells with abundant pale-eosinophilic, granular cytoplasmic material (inset) wrapping around peripheral nerve. The tumor causes mucosal atrophy (black arrow) and may be present with pseudoepitheliomatous hyperplasia. (**e**, **f**) Mucosal neuromas, MEN-2b. The patient presented with a slow-growing mass on the left buccal mucosa appearing similar to a traumatic fibroma. Examination revealed multiple similar oral mucosal nodules. Biopsies revealed mucosal neuroma. The patient reported having had thyroid and adrenal surgery as a child for "unknown tumors"—manifestation of MEN2b

on palpation, mobile, and rarely larger than 4–5 mm. Several reports describe the presence of clustered nodules on the dorsal tongue tip as a characteristic finding; this may not always be the case. The neuromas may be scattered around the oral mucosae. Occasionally, adult patients presenting with multiple oral neuromas may have a distant history of surgery or management of their endocrine neoplasms (Fig. 16.11e, f). In addition to oral mucosal neuromas, patients may present with neuromas of the eyelids, nose, and facial skin.

The diagnosis of mucosal neuromas is made on biopsies and/or laboratory values. If their endocrine tumors are active, patients present with elevated levels of VMA (vanillylmandelic acid) or serum calcitonin. Children whose endocrine tumors have not yet manifested may not demonstrate abnormal lab values necessitating a tissue biopsy. Microscopic examination of mucosal neuromas reveals discrete submucosal nodules comprised of a benign proliferation of mature, small nerves. The nodules are often partially encapsulated. The nerves are typically arranged in well-organized bundles (perineurium). Unlike traumatic neuromas, the intervening connective tissue is generally loose and organized; there is no evidence of scar tissue. The overlying epithelium is intact and may be focally atrophic. There is no evidence of inflammation.

Patients with multiple mucosal neuromas do not require surgical excision. Targeted excision may be necessary for traumatized nodules. Suppose a patient (with no prior history of MEN2B) presenting with multiple oral nodules is diagnosed with a mucosal neuroma (on biopsy), they should be referred to an endocrinologist for further work-up and management.

Neurofibroma

Neurofibromas are benign neoplasms of perineural fibroblasts and Schwann cells [60]. As with mucosal neuromas, neurofibromas are neoplasms that almost always arise in the setting of an inherited genetic disorder, neurofibromatosis type I (NF1). Solitary, sporadic neurofibromas are uncommon. Neurofibromatosis results from either germline mutations in the NF1 gene that are inherited or spontaneous at conception. The NF1 gene on chromosome 17 produces a protein neurofibromin, a growth regulator/tumor suppressor. Mutations in NF1 cause a loss of function of neurofibromin, which allows uncontrolled cell proliferation. In addition to potential oral mucosal and cutaneous nodules, patients with NF1 may present with mucocutaneous macular pigmentation (café au lait spots), axillary freckling, nodules of the iris (Lisch nodules), optic gliomas, skeletal deformities, and learning disabilities.

Neurofibromatosis is usually diagnosed during childhood or in patients with a known family history. Signs are often noticed at birth and often before the age of 10. Patients are not in significant discomfort but may present with one or several of the above findings. Clinicians who discover one of the above findings may proceed to work a patient up for the syndrome. In the oral cavity, neurofibromas present as slowly enlarging, painless, soft nodules on the tongue, cheek, or lips of young patients [60]. There are typically multiple oral mucosal nodules and likely evident cutaneous nodules [53]. The surface is typically intact. Oral nodules are rarely larger than 1cm in diameter. In addition, patients may present with enlarged dorsal tongue papillae.

The diagnosis of neurofibromas is made on biopsies. Neurofibromas are typically unencapsulated tumors of small ovoid to spindled cells with pointy (comma-like) nuclei arranged in a loose fibromyxoid stroma. The tumor cells exhibit bland cytological features; no mitoses or pleomorphism noted. Mast cells may be evident in the background. The overlying mucosal epithelium is generally intact and atrophic. Tumor cells are positive for S-100 and SOX10 on immunohistochemistry.

Solitary neurofibromas are not associated with a syndrome. Patients with multiple neurofibromas presenting with other phenotypic traits associated with NF1 should be worked up appropriately. Genetic counseling and evaluation of close family members may be indicated.

Lipoma

Lipomas are benign neoplasms of mature white adipocytes [61, 62]. They are the most common mesenchymal neoplasm in adults and are encountered in multiple anatomic sites. Truly neoplastic lipomas are uncommon in the orofacial region. Most swellings of the oral cavity that contain mature adipose tissue, especially those found on the buccal mucosa, result from herniated fat secondary to trauma. When lipomas occur in the oral cavity, they present as solitary masses later in life and are unrelated to traumatic etiology [63–65].

In the oral cavity, lipomas are slowly enlarging, discrete, smooth-surfaced masses arising in the submucosal tissues [63–65]. Patients may be aware of a long-standing oral mass that has grown to its current size over months or years. The most common locations are the buccal mucosa and buccal vestibule. Other sites include the tongue, labial mucosa, and the floor of the mouth. On examination, oral lipomas present as yellow-to-pale pink, sessile or pedunculated, smooth-surfaced, painless nodules [61–65]. They are nontender, mobile, and soft-to-doughy on palpation. Occasionally, surface vascular markings may be evident.

On gross examination, lipomas appear yellow and greasy. When excised, lipomas are circumscribed and occasionally encapsulated. The tumor is composed of cytologically benign and mature adipocytes with intervening delicate collagenous tissue (Fig. 16.12a). On low magnification, a lobular pattern divided by fibrovascular septae may be appreciated. There are several histological variants of lipoma. Among these, the spindle cell lipoma is the most common variant seen in the oral cavity.

Oral lipomas lend themselves to conservative surgical excision and seldom recur.

Benign Salivary Gland Neoplasms

The oral cavity contains numerous minor salivary glands just beneath the mucosal membranes. These predominantly seromucinous, unencapsulated glands are located throughout the

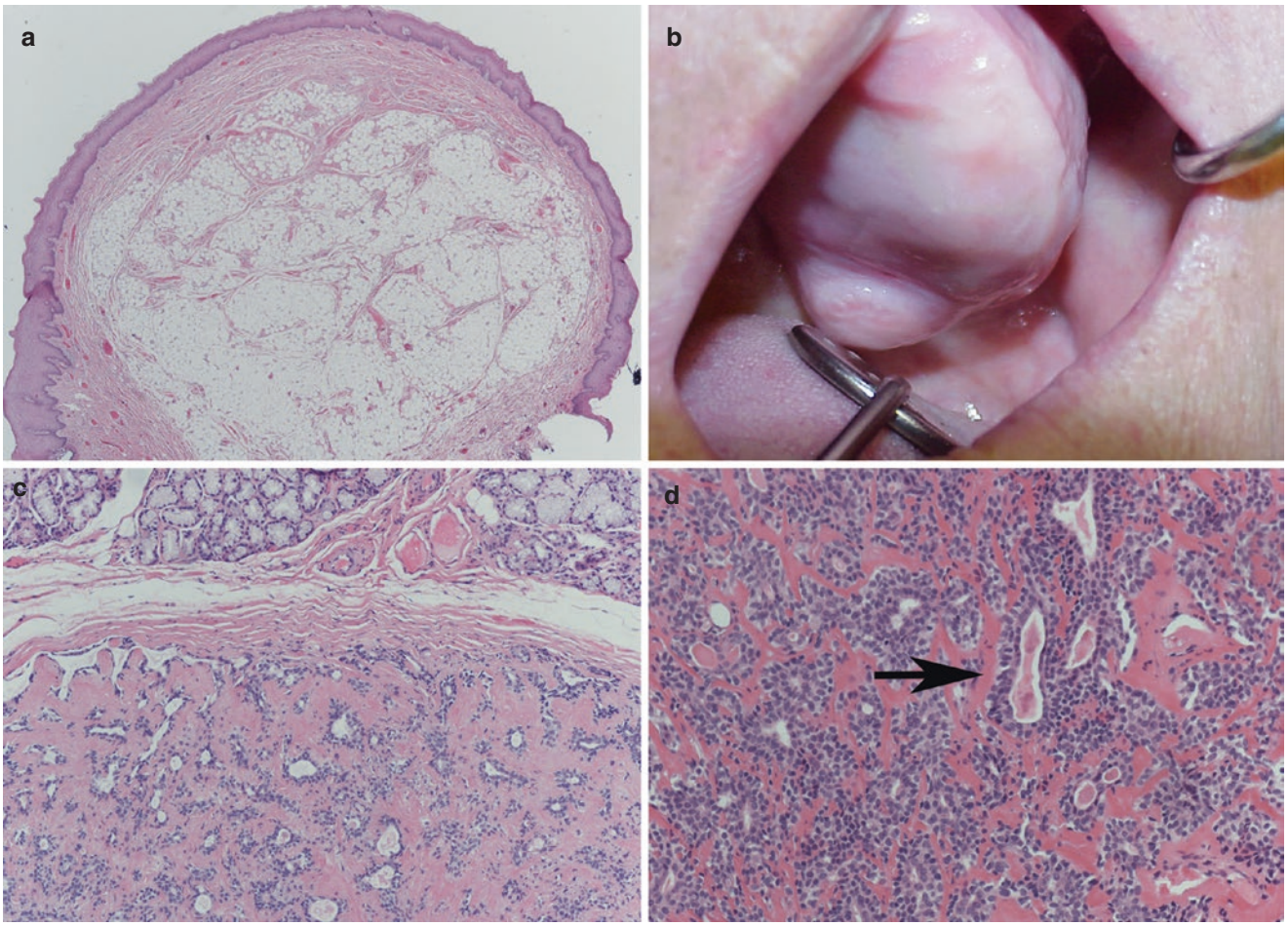


Fig. 16.12 Benign neoplasms. (**a**) Lipoma, microscopic features. An encapsulated mass of mature adipose tissue with intact overlying epithelium. (**b**) Benign salivary gland neoplasm. Pleomorphic adenoma. An elderly woman presents with a slow-growing, painless posterior-lateral palatal mass surfaced by intact, pink-colored mucosal tissue. The patient is unable to wear her upper denture. (**c**, **d**) Pleomorphic adenoma, microscopic features (low mag). An encapsulated proliferation of ductal epithelial and myoepithelial cells forming duct-like structures with a characteristic bilaminar arrangement (high mag, black arrow). The peritumor stroma is prominently hyalinized and acellular. The stromal tissue in pleomorphic adenomas can range from chondromyxoid to notably fibrocollagenous (seen in this field)

oral cavity, except for the anterior hard palate and attached gingival tissues. Groups of secretory units pour their secretions into the mouth through short ducts. The minor salivary glands are labile and have resident stem cells that are susceptible to neoplastic development. As with major salivary glands, the intraoral minor salivary glands can be the site of a range of benign and malignant neoplasms. The current WHO classification of salivary gland neoplasms [66] lists over 25–30 different (malignant and benign) neoplasms and their variants. Since salivary gland neoplasms of the oral cavity are generally uncommon, discussing every neoplasm and its details is beyond the scope of this section. Instead, the ensuing section will focus on the general principles and common presenting features of the following benign oral salivary gland neoplasms: pleomorphic adenoma and canalicular adenoma.

Benign salivary gland neoplasms exhibit a female predilection [66–68] and are typically seen in adults aged >40 years. The most common site affected is the posterior-lateral aspect of the hard and soft palate (the glandular zone of the palate), followed by the upper lip, buccal mucosa, and lower lip.

Pleomorphic Adenoma

Pleomorphic adenomas (PA) are benign neoplasms derived from the intercalated duct reserve cells that can differentiate into myoepithelial cells and ducts [66]. The majority of PAs demonstrate translocations with breakpoints on chromosomes 8q12 and 12q14-15. The translocations and gene rearrangements involve transcription factor genes PLAG1 and HMGA2; gain of function promotes unregulated proliferation. In the oral cavity, PAs present as painless, smooth-surfaced, mucosa-colored, broad-based masses on the posterior-lateral hard-soft palatal junction (Fig. 16.12b). Patients are typically aware of slowly progressive palatal swelling of several months or years duration. The masses

are soft to firm on palpation and nontender. There is typically no ulceration unless the mass is secondarily traumatized. The surrounding tissues are generally normal. PAs on the palate do not typically erode the underlying periosteum. PAs may also present on the upper lip, buccal mucosa, and other minor gland-bearing sites within the oral cavity.

At the microscope, the typical presentation of PAs is of a well-demarcated, potentially capsulated proliferation of myoepithelial and ductal cells in a chondromyxoid appearing background. The ductal and myoepithelial cells form ductal structures, cysts that exhibit a characteristic bilaminar arrangement (luminal ductal and abluminal myoepithelial cells). The lumens may contain dense eosinophilic proteinaceous material (Fig. 16.12c, d). The cells may also be arranged in strands, sheets, nests, and are typically surrounded by a dense hyalinized acellular stroma. PAs can have a polymorphic architecture and, interestingly, can contain a range of other tissue types: adipose tissue, bone, keratin, and hyaline cartilage. This speaks to the pluripotency of the stem cells that give rise to PAs. All cytological features are banal. PAs do not invade or infiltrate the surrounding stromal structures.

Oral PAs are treated with conservative surgical excision with negative margins. The prognosis is good, and recurrence rates are low.

Canalicular Adenoma

Canalicular adenomas (CA) are benign salivary gland neoplasms that are almost exclusive to the oral cavity. This is the second most common salivary neoplasm after pleomorphic adenoma. CAs present as painless, mobile, smooth-surfaced, broad-based nodules on the upper lip [66]. CAs can present on the buccal mucosa, lower lip, and the hard-soft palatal junction but not typically. The masses may be mucosa colored or appear bluish/purple, resembling a mucocele. On palpation, the nodules are nontender, firm to soft, and may be focally fluctuant. The surface is not ulcerated unless secondarily traumatized. CAs seldom grow more than 1.5–2 cm in diameter.

CAs are typically encapsulated but may show a lobulated arrangement. The tumor is composed of a proliferation of strands, chords, and trabeculae of cytologically benign, basaloid ductal cells. The basaloid-appearing cells are arranged in double rows of interconnecting chords and branching chords to form ducts and long canaliculi. The intervening stromal tissue is composed of loose, vascular connective tissue. CAs lack myoepithelial cells.

Canalicular adenomas are managed with conservative surgical excision with negative margins. Tumors with multiple lobules may pose minor surgical challenges. Recurrence is rare, and the overall prognosis is good.

Vascular Tumors/Malformations

Hemangiomas and Vascular Malformations

Tumors composed of vascular tissue are relatively common in the head and neck region. The diagnostic terms *hemangioma, venous/capillary/cavernous hemangioma, vascular malformation, and arteriovenous malformation* continue to be used interchangeably to describe a variety of orofacial vascular swellings. While all these terms imply benignity, it is essential to parse through and clarify the confusion generated by the array of terms. The current classification and terminology system used by the ISSVA (International Society for the Study of Vascular Anomalies) [69, 70] is based on a biological system proposed in 1982 by Mulliken and Glowacki [70]. Based on our understanding of the differences in pathogenesis, genetics, clinical features, and management outcomes, there are two major groups of vascular masses: (1) hemangioma and (2) vascular malformations.

Hemangiomas are considered true neoplasms and grow by endothelial cell proliferation and must be differentiated from vascular malformations, which are not true neoplasms. Based on ISSVA criteria, hemangiomas are classified into two main categories: (a) infantile hemangioma [71, 72] and (b) congenital hemangioma [69, 73]. Infantile hemangiomas are the most common type (>70% of all hemangiomas) [69] and are not present at birth but appear within days or weeks. Infantile hemangiomas exhibit rapid growth for ~6–12 months and gradually involute over 6–9 years. They exhibit a female prevalence of 5:1. Congenital hemangiomas account for ~30% of all hemangiomas and show an equal male: female prevalence. Congenital hemangiomas, by definition, are *clinically present as fully developed lesions at birth*. They undergo rapid involution within the first year of life or may never show involution; they do not grow larger than their original size.

Vascular malformations (previously called cavernous/venous hemangiomas/angiomas) are developmental anomalies of blood vessels with no evidence of endothelial cell proliferation [72]. They consist of progressively enlarging aberrant and ectatic vessels composed of a particular vascular architecture (veins, lymphatic vessels, venules, capillaries, arteries, or mixed vessel types). Vascular malformations (VM) are appropriately named by their predominant vessel type (e.g., venous malformation, arteriovenous malformation). Significantly, diagnosis and management are based on the individual flow characteristics (slow- or fast-flow lesions).

In this setting, how does one diagnose or classify vascular swellings in the orofacial region and the oral cavity? The vast majority of vascular lesions encountered in the oral cavity are vascular malformations (venous, capillary, arterial, or mixed vessel type). Although they may have been (and still) referred to as "*hemangiomas*," VMs do not exhibit

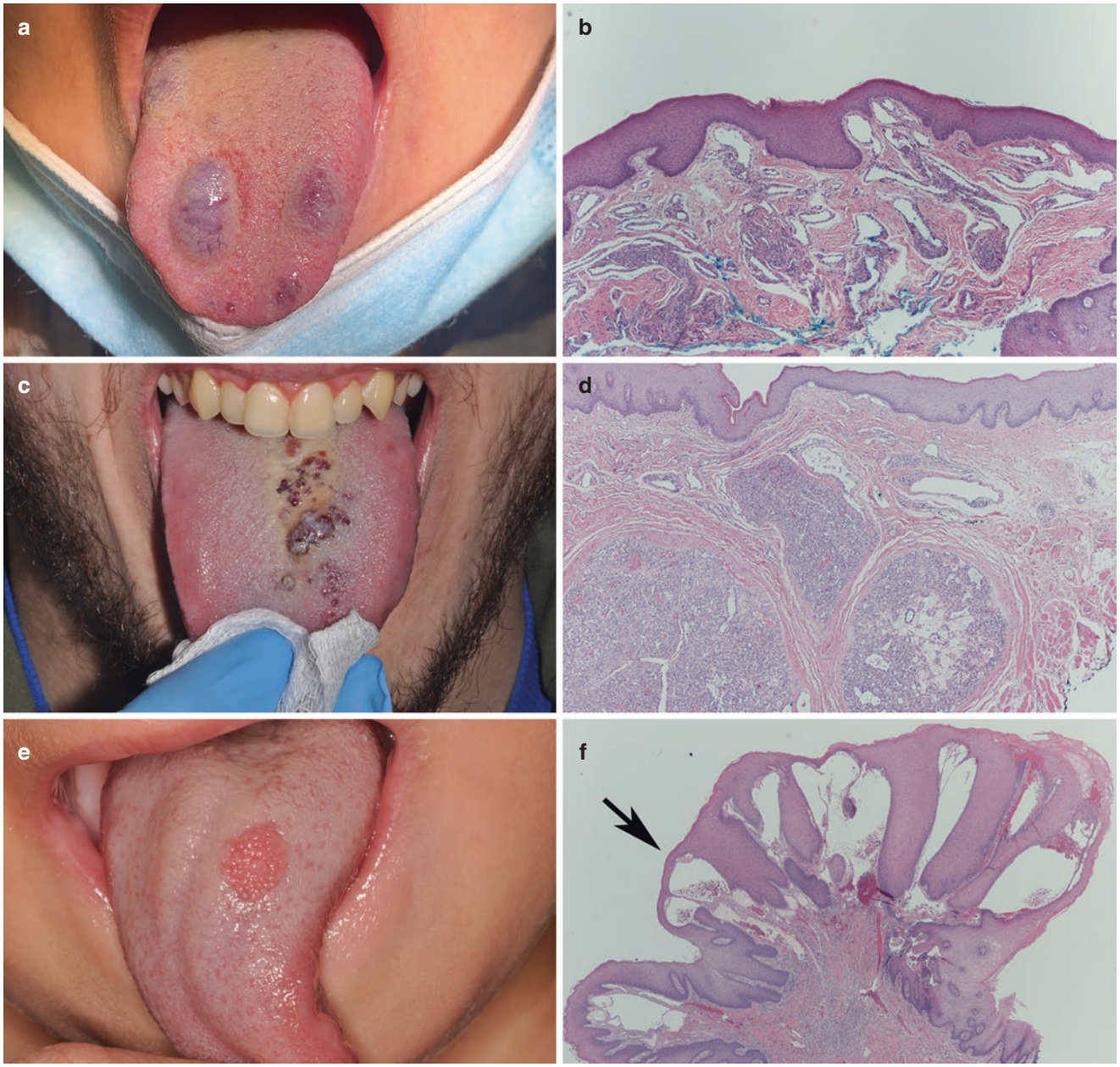


Fig. 16.13 Benign vascular tumors. (**a**) Vascular malformation, clinical. Multiple large painless and long-standing purple, broad-based masses on the dorsal and ventral tongue. The patient has been aware of them since her childhood with glacial growth. (**b**) Vascular malformation, microscopic features. Slow-flow, venous malformation. Large venous structures present within the superficial lamina propria and extend into the deeper tissues. There is no evidence of proliferation. (**c**) Infantile hemangioma persistent into adolescence. A teenager presents with multiple purple-red lobulated blister-like masses on the dorsal tongue. The findings have been present since infancy. Some tongue foci have involuted while others persist and extend into the deeper musculature (evident on imaging). (**d**) Hemangioma, microscopic features. Lobular proliferation of capillaries of various luminal sizes that extends into the deeper tongue musculature. Benign cytological features. (**e**) Lymphangioma. A 2-year-old boy presents with a well-demarcated pink to erythematous nodule with a microlobulated, vesicular surface. The tumor is slow-growing, painless, and does not impact function. (**f**) Lymphangioma, microscopic features. A well-demarcated proliferation of dilated and tortuous lymphatic channels that extend upward into the epithelium and close to the surface. The proliferation also extends downward into the musculature. The mass exhibits a papillary surface configuration

endothelial proliferation on microscopic examination. VMs persist from birth throughout life and typically do not involute (unlike true hemangiomas). VMs have the potential to grow proportionally with a child's growth. Clinically, VMs present as painless, slow-growing, purple/red/blue masses of the oral soft tissues. The surface is typically intact with no ulceration (Fig. 16.13a). VMs are generally soft to firm, nontender, compressible, and blanch on pressure. Patients

may report continued growth, typically without loss of function. The most common oral sites are the lips, tongue, and buccal mucosa. Depending on the vessel type and location relative to the surface, VMs may exhibit thrills and bruits (arterial VMs).

By contrast, hemangiomas are uncommon in the oral cavity. The type of hemangioma one is likely to encounter in most teens or adults is the infantile hemangioma. This is the hemangioma that appears shortly after birth. Although most infantile hemangiomas involute, some can remain well into adulthood. Larger infantile hemangiomas can be quite infiltrative and extend deep into tissues (Fig. 16.13c). Oral hemangiomas occur on the tongue, lips, and buccal mucosa (similar to VMs). They present as soft, lobulated, painless masses that are typically purple, bluish, or red depending on the type and depth of vessels comprising the process. Hemangiomas tend to blanch on pressure. Occasionally, patients may report bleeding following inadvertent trauma to the area.

Hemangioma and Vascular Malformation: Microscopic Features

At the microscope, VMs vary depending on the vessel caliber. Capillary malformations are composed of dilated capillaries and venules arranged in a fairly discrete arrangement. Venous malformations exhibit large, tortuous, and dilated veins lined by cytologically banal endothelial cells. These correspond clinically to slow-flow malformations (Fig. 16.13b). The resulting stasis may be accompanied by luminal thrombi with varying degrees of organization and recanalization. Arteriovenous malformations exhibit a mixture of arteries, veins, venules, and other vessel calibers. Regardless of the type of VM, there is no evidence of proliferation or mitotic activity.

Infantile hemangiomas are composed of a proliferation of capillaries in the submucosal tissue [71, 72]. Their proliferation lacks definition and capsulation. Infantile hemangiomas tend to be infiltrative and exhibit lobular extensions (Fig. 16.13d). Proliferative populations exhibit plump endothelial and pericytic cells. The proliferative cells of infantile hemangiomas are GLUT-1 positive, a marker used to differentiate between true hemangiomas and vascular malformations.

Hemangiomas and Vascular Malformations: Management

Management of vascular malformations depends on the size and location of the lesions. Small lesions are managed with conservative surgical excision. Large and infiltrative lesions may require sclerotherapy or laser ablation. Arteriovenous malformations may require embolization followed by surgery. Larger, infiltrative malformations may require targeted debulking; tissue preservation is prioritized.

Hemangiomas, if inconspicuous, are left untreated and allowed their natural course of proliferation and evaluation. Large and infiltrative hemangiomas may require nothing more than monitoring and addressing targeted problems. Pulse-dye lasers, intra-lesional sclerosing injections, and surgical excision are management options for persistent infantile hemangiomas.

Lymphangioma

Lymphangiomas are considered congenital malformations of lymphatic vessels or hamartomas. The majority of lymphangiomas occur in the head and neck region [70, 74]. Lymphangiomas are uncommon but, when discovered, are seen in infancy or early childhood, typically within the first 2 years of life. Lymphangiomas can present close to mucosal and cutaneous surfaces and present within the deep connective tissues and fascia. Most lymphangiomas present as solitary lesions.

Clinically, oral mucosal lymphangiomas are discovered in infancy during the first year of life. Reports show that half of all oral lymphangiomas are congenital; they continue to grow and become prominent as children grow. The most common location is the dorsal tongue, followed by the palate, buccal mucosa, gingiva, and lips [74, 75]. Lymphangiomas on the dorsal tongue appear pebbly, corrugated, and often exhibit a "small bubble wrap" texture. The surface vesicles and occasionally papillary appearance are pink or pale yellow (see Fig. 16.13e); they may appear bluish or red if filled with blood. The raised pebbly regions are generally discrete from the surrounding tissues and non-ulcerated. The nodules are nontender, do not bleed, and do not impact function. Patients or their parents may report progressive growth over months.

On microscopy, lymphangiomas present as a demarcated proliferation or collection of multiple, dilated, and tortuous lymphatic channels of varying size within the superficial lamina propria. The lymphatic vessels often come right up to the surface and may be within a layer of epithelium from the outside (see Fig. 16.13f). Multiple tortuous channels may extend into the deeper submucosal tissue and present among striated muscle bundles. The lymphatic channels are lined by cytologically bland, flattened endothelial cells. The lumens are generally clear or may contain sparse pale pink lymphatic proteinaceous material. Valve-like structures may be seen projecting into the lumen.

Superficially located lymphangiomas may be surgically excised conservatively (with sclerotherapy), especially if the lesions impact a child's function. Many lymphangiomas tend to be infiltrative and more profound than they appear on the surface. Complete surgical removal is not advised in this setting, especially as it may cause significant patient morbidity (in growing children). Targeted removal or debulking may be planned as a child grows.

Vascular tumors represent a wide variety of vessel abnormalities. Their management, especially large vascular tumors or anomalies, requires an understanding of pathogenesis, the correct classification criteria, appropriate diagnostic assessment, and referral to vascular anomalies teams.

References

1. Kumar V, Abbas AK, Aster JC, Perkins JA. Robbins basic pathology. 10th ed. Philadelphia: Elsevier; 2017. p. 935.
2. Suresh L, Radfar L. Oral sarcoidosis: a review of literature. Oral Dis. 2005;11(3):138–45.
3. Daley T, Damm DD, Haden JA, Kolodychak MT. Oral lesions associated with injected hydroxyapatite cosmetic filler. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;114(1):107–11.
4. Jham BC, Nikitakis NG, Scheper MA, Papadimitriou JC, Levy BA, Rivera H. Granulomatous foreign-body reaction involving oral and perioral tissues after injection of biomaterials: a series of 7 cases and review of the literature. J Oral Maxillofac Surg. 2009;67(2):280–5.
5. Owosho AA, Bilodeau EA, Vu J, Summersgill KF. Orofacial dermal fillers: foreign body reactions, histopathologic features, and spectrometric studies. Oral Surg Oral Med Oral Pathol Oral Radiol. 2014;117(5):617–25.
6. Gordon SC, Daley TD. Foreign body gingivitis: clinical and microscopic features of 61 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997;83(5):562–70.
7. Grave B, McCullough M, Wiesenfeld D. Orofacial granulomatosis–a 20-year review. Oral Dis. 2009;15(1):46–51.
8. Tilakaratne WM, Freysdottir J, Fortune F. Orofacial granulomatosis: review on aetiology and pathogenesis. J Oral Pathol Med. 2008;37(4):191–5.
9. Allen CM, Camisa C, Hamzeh S, Stephens L. Cheilitis granulomatosa: report of six cases and review of the literature. J Am Acad Dermatol. 1990;23(3):444–50.
10. van der Waal RI, Schulten EA, van der Meij EH, van de Scheur MR, Starink TM, van der Waal I. Cheilitis granulomatosa: overview of 13 patients with long-term follow-up–results of management. Int J Dermatol. 2002;41(4):225–9.
11. Jafarzadeh H, Sanatkhani M, Mohtasham N. Oral pyogenic granuloma: a review. J Oral Sci. 2006;48(4):167–75.
12. Bhaskar SN, Jacoway JR. Pyogenic granuloma–clinical features, incidence, histology, and result of treatment: report of 242 cases. J Oral Surg. 1966;24(5):391–8.
13. Daley TD, Nartey NO, Wysocki GP. Pregnancy tumor: an analysis. Oral Surg Oral Med Oral Pathol. 1991;72(2):196–9.
14. Zhang W, Chen Y, An Z, Geng N, Bao D. Reactive gingival lesions: a retrospective study of 2,439 cases. Quintessence Int. 2007;38(2):103–10.
15. Al-Khateeb T, Ababneh K. Oral pyogenic granuloma in Jordanians: a retrospective analysis of 108 cases. J Oral Maxillofac Surg. 2003;61(11):1285–8.
16. Bodner L, Peist M, Gatot A, Fliss DM. Growth potential of peripheral giant cell granuloma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997;83(5):548–51.
17. Buchner A, Hansen LS. The histomorphologic spectrum of peripheral ossifying fibroma. Oral Surg Oral Med Oral Pathol. 1987;63(4):452–61.
18. Katsikeris N, Kakarantza-Angelopoulou E, Angelopoulos AP. Peripheral giant cell granuloma. Clinicopathologic study of 224 new cases and review of 956 reported cases. Int J Oral Maxillofac Surg. 1988;17(2):94–9.
19. Lester SR, Cordell KG, Rosebush MS, Palaiologou AA, Maney P. Peripheral giant cell granulomas: a series of 279 cases. Oral Surg Oral Med Oral Pathol Oral Radiol. 2014;118(4):475–82.
20. Boffano P, Benech R, Roccia F, Gallesio C, Garzaro M, Pecorari G. Review of peripheral giant cell granulomas. J Craniofac Surg. 2013;24(6):2206–8.
21. Salum FG, Yurgel LS, Cherubini K, De Figueiredo MA, Medeiros IC, Nicola FS. Pyogenic granuloma, peripheral giant cell granuloma and peripheral ossifying fibroma: retrospective analysis of 138 cases. Minerva Stomatol. 2008;57(5):227–32.
22. Zain RB, Fei YJ. Peripheral fibroma/fibrous epulis with and without calcifications. A clinical evaluation of 204 cases in Singapore. Odontostomatol Trop. 1990;13(3):94–6.
23. Zain RB, Fei YJ. Fibrous lesions of the gingiva: a histopathologic analysis of 204 cases. Oral Surg Oral Med Oral Pathol. 1990;70(4):466–70.
24. Vargo RJ, Bilodeau EA. Reappraising localized juvenile spongiotic gingival hyperplasia. J Am Dent Assoc. 2019;150(2):147–53 e2.
25. Chang JY, Kessler HP, Wright JM. Localized juvenile spongiotic gingival hyperplasia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;106(3):411–8.
26. Darling MR, Daley TD, Wilson A, Wysocki GP. Juvenile spongiotic gingivitis. J Periodontol. 2007;78(7):1235–40.
27. Barker DS, Lucas RB. Localised fibrous overgrowths of the oral mucosa. Br J Oral Surg. 1967;5(2):86–92.
28. Bouquot JE. Common oral lesions found during a mass screening examination. J Am Dent Assoc. 1986;112(1):50–7.
29. Bouquot JE, Gundlach KK. Oral exophytic lesions in 23,616 white Americans over 35 years of age. Oral Surg Oral Med Oral Pathol. 1986;62(3):284–91.
30. Weathers DR, Callihan MD. Giant-cell fibroma. Oral Surg Oral Med Oral Pathol. 1974;37(3):374–84.
31. Bermejo A, Aguirre JM, Lopez P, Saez MR. Superficial mucocele: report of 4 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999;88(4):469–72.
32. Cataldo E, Mosadomi A. Mucoceles of the oral mucous membrane. Arch Otolaryngol. 1970;91(4):360–5.
33. Lee EJ, Calcaterra TC, Zuckerbraun L. Traumatic neuromas of the head and neck. Ear Nose Throat J. 1998;77(8):670–4.
34. Sist TC Jr, Greene GW. Traumatic neuroma of the oral cavity. Report of thirty-one new cases and review of the literature. Oral Surg Oral Med Oral Pathol. 1981;51(4):394–402.
35. Buchner A, Hansen LS. The histomorphologic spectrum of the gingival cyst in the adult. Oral Surg Oral Med Oral Pathol. 1979;48(6):532–9.
36. Nxumalo TN, Shear M. Gingival cyst in adults. J Oral Pathol Med. 1992;21(7):309–13.
37. Lazos JP, Piemonte ED, Panico RL. Oral varix: a review. Gerodontology. 2015;32(2):82–9.
38. Giunta J, Cataldo E. Lymphoepithelial cysts of the oral mucosa. Oral Surg Oral Med Oral Pathol. 1973;35(1):77–84.
39. Sykara M, Ntovas P, Kalogirou EM, Tosios KI, Sklavounou A. Oral lymphoepithelial cyst: a clinicopathological study of 26 cases and review of the literature. J Clin Exp Dent. 2017;9(8):e1035.
40. Yang X, Ow A, Zhang CP, Wang LZ, Yang WJ, Hu YJ, et al. Clinical analysis of 120 cases of intraoral lymphoepithelial cyst. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113(4):448–52.
41. Buchner A, Hansen LS. Lymphoepithelial cysts of the oral cavity. A clinicopathologic study of thirty-eight cases. Oral Surg Oral Med Oral Pathol. 1980;50(5):441–9.
42. Egawa N, Egawa K, Griffin H, Doorbar J. Human papillomaviruses; epithelial tropisms, and the development of neoplasia. Viruses. 2015;7(7):3863–90.
43. Taberna M, Mena M, Pavon MA, Alemany L, Gillison ML, Mesia R. Human papillomavirus-related oropharyngeal cancer. Ann Oncol. 2017;28(10):2386–98.
44. Abbey LM, Page DG, Sawyer DR. The clinical and histopathologic features of a series of 464 oral squamous cell papillomas. Oral Surg Oral Med Oral Pathol. 1980;49(5):419–28.

45. Snietura M, Lamch R, Kopec A, Waniczek D, Likus W, Lange D, et al. Oral and oropharyngeal papillomas are not associated with high-risk human papillomavirus infection. Eur Arch Otorhinolaryngol. 2017;274(9):3477–83.
46. Betz SJ. HPV-related papillary lesions of the oral mucosa: a review. Head Neck Pathol. 2019;13(1):80–90.
47. Eversole LR, Laipis PJ, Green TL. Human papillomavirus type 2 DNA in oral and labial verruca vulgaris. J Cutan Pathol. 1987;14(6):319–25.
48. Green TL, Eversole LR, Leider AS. Oral and labial verruca vulgaris: clinical, histologic and immunohistochemical evaluation. Oral Surg Oral Med Oral Pathol. 1986;62(4):410–6.
49. Handschel J, Heikaus S, Depprich R, Kubler NR, Yekta SS, Smeets R, et al. Intraoral schwannoma: review of the literature and presentation of a rare case. Cranio. 2012;30(2):150–3.
50. Lee MJ, Chung KH, Park JS, Chung H, Jang HC, Kim JW. Multiple endocrine neoplasia type 2B: early diagnosis by multiple mucosal neuroma and its DNA analysis. Ann Dermatol. 2010;22(4):452–5.
51. Archard HO, Heck JW, Stanley HR. Focal epithelial hyperplasia: an unusual oral mucosal lesion found in Indian children. Oral Surg Oral Med Oral Pathol. 1965;20:201–12.
52. Said AK, Leao JC, Fedele S, Porter SR. Focal epithelial hyperplasia - an update. J Oral Pathol Med. 2013;42(6):435–42.
53. Alotaiby FM, Fitzpatrick S, Upadhyaya J, Islam MN, Cohen D, Bhattacharyya I. Demographic, clinical and histopathological features of oral neural neoplasms: a retrospective study. Head Neck Pathol. 2019;13(2):208–14.
54. Chaudhry AP, Jacobs MS, SunderRaj M, Yamane GM, Jain R, Scharlock SE. A clinico-pathologic study of 50 adult oral granular cell tumors. J Oral Med. 1984;39(2):97–103, 18.
55. Mirchandani R, Sciubba JJ, Mir R. Granular cell lesions of the jaws and oral cavity: a clinicopathologic, immunohistochemical, and ultrastructural study. J Oral Maxillofac Surg. 1989;47(12):1248–55.
56. Ordonez NG, Mackay B. Granular cell tumor: a review of the pathology and histogenesis. Ultrastruct Pathol. 1999;23(4):207–22.
57. Stewart CM, Watson RE, Eversole LR, Fischlschweiger W, Leider AS. Oral granular cell tumors: a clinicopathologic and immunocytochemical study. Oral Surg Oral Med Oral Pathol. 1988;65(4):427–35.
58. Rejas RA, Campos MS, Cortes AR, Pinto DD, de Sousa SC. The neural histogenetic origin of the oral granular cell tumor: an immunohistochemical evidence. Med Oral Patol Oral Cir Bucal. 2011;16(1):e6–10.
59. Gorlin RJ, Sedano HO, Vickers RA, Cervenka J. Multiple mucosal neuromas, pheochromocytoma and medullary carcinoma of the thyroid–a syndrome. Cancer. 1968;22(2):293–9.
60. Angiero F, Ferrante F, Ottonello A, Maltagliati A, Crippa R. Neurofibromas of the oral cavity: clinical aspects, treatment, and outcome. Photomed Laser Surg. 2016;34(2):56–60.
61. de Visscher JG. Lipomas and fibrolipomas of the oral cavity. J Maxillofac Surg. 1982;10(3):177–81.
62. Epivatianos A, Markopoulos AK, Papanayotou P. Benign tumors of adipose tissue of the oral cavity: a clinicopathologic study of 13 cases. J Oral Maxillofac Surg. 2000;58(10):1113–7. discussion 8.
63. Fregnani ER, Pires FR, Falzoni R, Lopes MA, Vargas PA. Lipomas of the oral cavity: clinical findings, histological classification and proliferative activity of 46 cases. Int J Oral Maxillofac Surg. 2003;32(1):49–53.
64. Furlong MA, Fanburg-Smith JC, Childers EL. Lipoma of the oral and maxillofacial region: site and subclassification of 125 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;98(4):441–50.
65. Manor E, Sion-Vardy N, Joshua BZ, Bodner L. Oral lipoma: analysis of 58 new cases and review of the literature. Ann Diagn Pathol. 2011;15(4):257–61.
66. El-Naggar AK, Chan JKC, Takata T, Grandis JR, Slootweg PJ. The fourth edition of the head and neck World Health Organization blue book: editors' perspectives. Hum Pathol. 2017;66:10–2.
67. Wang D, Li Y, He H, Liu L, Wu L, He Z. Intraoral minor salivary gland tumors in a Chinese population: a retrospective study on 737 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;104(1):94–100.
68. Yih WY, Kratochvil FJ, Stewart JC. Intraoral minor salivary gland neoplasms: review of 213 cases. J Oral Maxillofac Surg. 2005;63(6):805–10.
69. George A, Mani V, Noufal A. Update on the classification of hemangioma. J Oral Maxillofac Pathol. 2014;18(Suppl 1):S117–20.
70. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg. 1982;69(3):412–22.
71. Adams DM, Ricci KW. Infantile hemangiomas in the head and neck region. Otolaryngol Clin N Am. 2018;51(1):77–87.
72. Buckmiller LM, Richter GT, Suen JY. Diagnosis and management of hemangiomas and vascular malformations of the head and neck. Oral Dis. 2010;16(5):405–18.
73. Eivazi B, Ardelean M, Baumler W, Berlien HP, Cremer H, Elluru R, et al. Update on hemangiomas and vascular malformations of the head and neck. Eur Arch Otorhinolaryngol. 2009;266(2):187–97.
74. Sunil S, Gopakumar D, Sreenivasan BS. Oral lymphangioma - case reports and review of literature. Contemp Clin Dent. 2012;3(1):116–8.
75. Sivasankari T, Jeelani S, Asokan GS, Parthiban J. Lymphangioma of the tongue - a case report and review of literature. J Clin Diagn Res. 2014;8(9):12–4.

Alterations in Color: Oral White, Red, and Brown Lesions

17

Ellen Eisenberg

A Few Words About Diagnosis

Pathogenetically diverse conditions often share similar clinical features: this can create a diagnostic challenge. Relative to red, white, and brown lesions, a combination of two or even all three colors in a single lesion could amplify that diagnostic challenge considerably. At times establishing a reasonable clinical diagnostic impression for an oral mucosal red, white, or brown lesion can test the acumen of even an experienced clinician (Box 17.1).

Box 17.1 Pathological Processes
- Variant of normal anatomy.
- Genetic/development anomaly.
- Reactive/inflammatory.
- Infection.
- Immune response—local, systemic.
- Neoplasm—benign, malignant.
- Manifestation of systemic influence.

Diagnosis is a distinguishing process. The ability to distinguish similar-appearing oral mucosal entities from one another—irrespective of color—requires a systematic, disciplined approach. The diagnostic process begins when the clinician notes an unusual finding, or when the patient brings a particular concern (chief/presenting complaint) to the clinician's attention. Taking a thorough history of the chief concern or presenting finding must always be the next essential step, followed by documentation of the patient's general health, past medical history, current medications, and social history (see Box 17.2—The Diagnostic Sequence). Only after all the baseline historical data is gathered, should the physical examination be performed and a thorough description of the finding(s) in question recorded. To describe clinical findings well is not only an art, it is also a key component of the diagnostic process. In most instances, a complete and accurate clinical description provides considerable diagnostic information. Therefore, knowing and applying the elements of a good description are requisite to becoming a good diagnostician [1, 2] (Box 17.3).

Box 17.2 The Diagnostic Sequence
- Chief/presenting complaint.
- History of chief complaint.
- General health and social history.
- Physical examination.
  - Extraoral.
  - Intraoral.
- Differential diagnosis.
- Further testing—if needed (e.g., Biopsy, cytology, serology).
- Definitive diagnosis.

Box 17.3 Clinical Description (Soft Tissue)
- Precise location(s)/distribution.
- *Lesion type* (e.g., plaque, papule, macule, nodule, ulcer, vesicle, bulla, erosion, atrophy).
- Size (mm, cm).
- Shape.
- Color(s).
- Texture (visual inspection, palpation).
- Surrounding tissues.

E. Eisenberg (✉)
Section of Oral and Maxillofacial Pathology, Division of Oral and Maxillofacial Diagnostic Sciences, Department of Oral Health and Diagnostic Sciences, University of Connecticut School of Dental Medicine, Farmington, CT, USA
e-mail: eeisenberg@uchc.edu

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_17

White Oral Mucosal Lesions: General Principles

Any barrier that increases the relative distance between the clinician's eye and the underlying vascular bed will block the reflection of light back from the underlying vascular bed to the observer's eye. This can effect a white or relatively pale appearance to the oral mucosa. With this in mind, there are three basic reasons (Table 17.1) why an oral mucosal lesion can appear white:

1. **Presence of superficial surface debris** (e.g., the fibrinonecrotic pseudomembrane covering an ulcer; cumulation of nonviable cellular/keratotic and/or microbial, food or mucoid debris; fungal colonization/ infection, etc.). Debris usually appears white or yellow-white and is *wipeable* (i.e., it can be removed with applied pressure from a tongue blade, gauze sponge, finger, dental explorer or periodontal probe). The roof of a collapsed mucosal blister is white and detaches readily with application of laterally applied pressure.
2. **An increase in the top-to-bottom width of the oral squamous epithelium** With or without an attendant increase in surface keratinization, these lesions appear clinically as plaques that are white and *non-wipeable* (i.e., they cannot be scraped off with a tongue blade or gauze). This important group comprises the *epithelial* or *keratotic* white oral lesions.
3. **Diminished submucosal vascular supply** or **an increase in the intervening submucosal tissue components** (e.g., an increase in fibrocollagenous stromal tissue, "reactive fibrous hyperplasia") essentially serves to distance or insulate the examiner's eye from the reflection of light off of the underlying vascular bed, resulting in a relatively pale or white mucosal appearance.

Table 17.1 White oral mucosal lesions

Etiology	Examples	Wipeable/ non-wipeable
Presence of superficial surface debris	• Fibrinonecrotic pseudomembrane (ulcer)	Wipeable
	• Debris—cellular/keratotic, microbial, food, mucin	
	• Fungal colonization/ infection	
Increase in epithelial width ("keratotic white lesions")	• Increase in epithelial width (± surface keratinization, ± acanthosis)	Non-wipeable
	• Normal maturation, cytology	
	• Abnormal maturation, cytology	
Diminished vascular supply or increase in intervening submucosal tissue	• Vascular ischemia	Non-wipeable
	• Increase in intervening stromal tissue (fibrosis, other submucosal tissue proliferation)	

In this chapter, we will focus primarily on the first two groups, namely, the *epithelial white lesions* and selected *white lesions due to surface debris*. First, we must address some key terminology and the clinical significance of that terminology referable to the oral stratified squamous epithelium.

"Keratinized" (Masticatory) and "Unkeratinized" (Lining) Mucosa; "Attached" and "Unattached" Oral Mucosa

All viable squamous epithelial cells contain intermediate keratin filaments. Like the poles of a tent, these filaments form an internal (intracellular) "cage" that gives the cell its shape. The keratin filaments change in configuration as the cells mature from their origin in the basal-most epithelial layer (the *stratum germinativum* or *stratum basale*) and progress upward through the *stratum spinosum* to the surface keratin layer (the *stratum superficiale*). The surface keratin layer consists of nonviable keratinocytes. Keratin is the ultimate destiny of squamous epithelium, and it exfoliates continuously from the mucosal surface as the epithelium constantly replenishes itself. Thus, keratotic debris is continuously being shed into the oral cavity.

It is important to recognize that there are certain locations in the oral cavity where the mucosal surface epithelium is naturally more heavily keratinized than in other locations. The *keratinized* oral mucosal locations include the attached gingivae, the hard palate, and the dorsal surface of the tongue. These locations are constantly subjected to friction; therefore, they require increased surface thickness for protection. Together, the more pronounced surface keratin layer and the wide top-to-bottom epithelial cellular compartment beneath are analogous to the texture and resiliency of an indoor-outdoor carpet. Additionally, both the maxillary and mandibular attached gingiva and the hard palatal mucosa are bound down to their respective underlying jawbone at the level of the periosteum (i.e., they are attached to the bone directly by a *mucoperiosteum*). For that reason, both the mandibular and maxillary attached gingival tissue and hard palatal mucosa are also termed *attached mucosa* [3, 4].

By contrast, the remaining squamous epithelium that lines the buccal and labial mucosae, floor of the mouth, lateral and ventral tongue, and the soft palate/uvula complex is naturally thinner, moveable, and keratinized minimally at its surface. The latter locations are termed the *non-keratinized*

Table 17.2 Attached ("Keratinized") and unattached ("Unkeratinized," "Lining") oral mucosa

Oral location	Attached ("*Keratinized*") mucosa	Unattached ("*Unkeratinized*") mucosa	Unattached, "*Keratinized*" mucosa
Attached gingiva	Yes—attached via mucoperiosteum		
Hard palate	Yes—attached via mucoperiosteum		
Dorsal tongue	Keratinized—but *not attached* to bone	Yes—but heavily keratinized (filiform papillae)	Yes; unattached, "specialized" and keratinized mucosa
Lateral/ventral tongue		Yes	
Buccal/alveolar/vestibular mucosae		Yes	
Labial mucosa		Yes	
Floor of mouth		Yes	
Soft palate		Yes	

oral mucosal locations, also referred to as the *lining, moveable* or *unattached mucosa* (i.e., oral mucosa that is not bound down to underlying jawbone). It is well to note that the *dorsal tongue* is also surfaced by *unattached*, albeit *heavily keratinized mucosa*, primarily in the form of the abundant hair-like filiform papillae (Table 17.2) The mucosa covering the dorsal and lateral tongue surfaces is also considered *specialized mucosa* because it is where taste receptors are found within three of the four types of lingual papillae, specifically, the fungiform and circumvallate papillae that occupy the anterior and posterior dorsal tongue surfaces, respectively; and the foliate papillae, on the posterior-lateral surfaces of the tongue [3, 4].

Trauma-Prone Oral Locations and Sources of Trauma/Friction

Several intraoral locations are naturally subject to friction or trauma: they include the buccal and labial mucosae, the dorsal and lateral-superior surfaces of the tongue, the attached gingiva, and the hard palate mucosa (Box 17.4). Clearly, the most common sources of chronic irritation, friction and trauma are the teeth, followed by rough dental restorations, ill-fitting dental prostheses (i.e., removable complete or partial dentures), aggressive toothbrushing injury, orthodontic appliances, and parafunctional habits (including the introduction and manipulation of foreign objects in the mouth).

Box 17.4 Trauma/Friction-Prone Oral Sites

- Buccal mucosa.
- Lower labial mucosa, vermilion.
- Gingiva.
- Dorsal and lateral surfaces of tongue; tip of tongue.
- Hard palate.

Non-Wipeable White Plaques and Papules (Epithelial White Lesions)

Developmental-Genetic White Epithelial Lesions

Leukoedema

Leukoedema is a benign, innocuous clinical variant of normal oral anatomy that is in a sense, an optical illusion. Most often encountered on the buccal mucosa of darker-skinned individuals, it presents when the buccal mucosa is relaxed (i.e., not stretched out or extended) as a diffuse, top-to-bottom, sometimes folded-appearing, milky-white/gray mucosal discoloration. By pulling forward and thus stretching out the buccal mucosa, the epithelial width is artificially diminished, so that the white-gray color disappears accordingly, only to reappear when the tissue is released from the stretch and is once again relaxed [5] (Fig. 17.1a, b).

Recognizing leukoedema clinically is important; it should not be confused with other white mucosal changes that may have more clinically significant implications. Although biopsies of leukoedema are unnecessary and rarely obtained, the histopathological features include a normal epithelial maturation pattern and benign cytology, acanthosis with intercellular edema and/or spongiosis, and mild surface parakeratosis (Fig. 17.1c).

White Sponge Nevus

White sponge nevus (WSN) is an uncommon benign, autosomal dominant genetic condition attributable to mutations in keratins 4 and 13 genes, critical to normal oral mucosal keratinization [6]. WSN typically manifests at birth or during early childhood as painless white non-wipeable mucosal changes that persist and become more pronounced throughout the patient's lifetime. Its classic presentation is bilateral. On the buccal mucosae, it is diffusely white, spongy or folded, and has a carpet-like appearance (Fig. 17.2a). The white changes usually extend contiguously to involve the adjacent vestibules, labial mucosa, the floor of mouth, and the tongue; other sites of involvement can include the soft

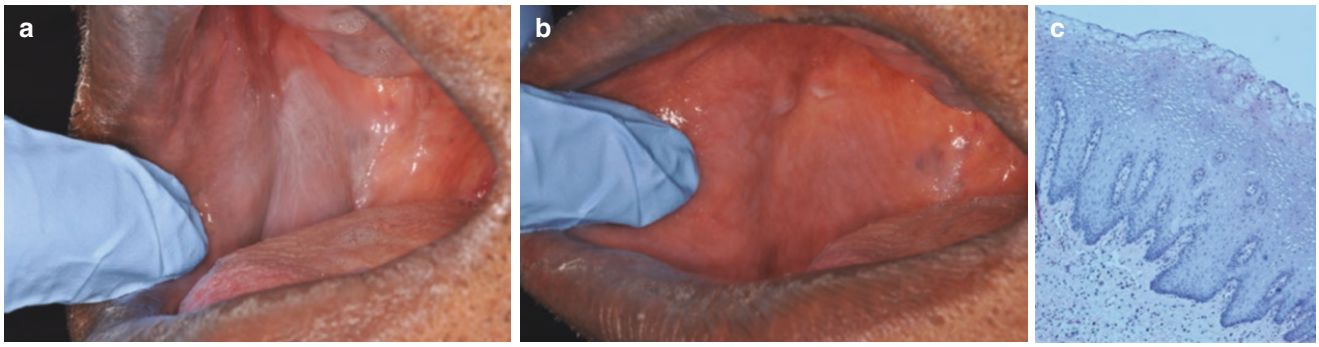


Fig. 17.1 Leukoedema. (**a**) Diffuse milky white appearance of relaxed buccal mucosa. (**b**) On stretching, the white change disappears. (**c**) The epithelial maturation and cytology are normal. There is spongiosis in the upper stratum spinosum (H&E ×40)

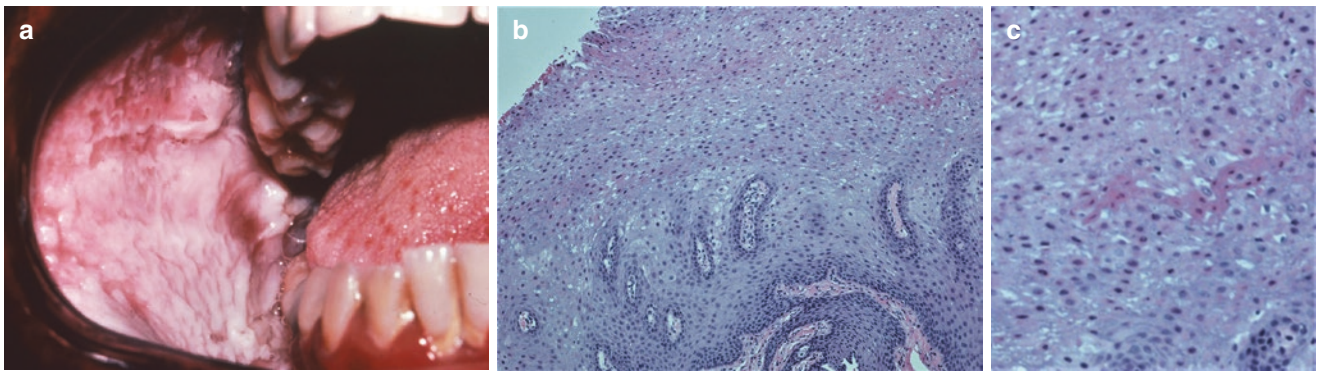


Fig. 17.2 White sponge nevus. (**a**) Buccal mucosa exhibits diffuse, corrugated, spongy-appearing non-wipeable white change. (**b**) The mucosal squamous epithelium is acanthotic with numerous dyskeratotic (individually keratinized) cells in the stratum spinosum. Maturation and cytology are otherwise normal (H&E ×10). (**c**) Higher magnification focusing on dyskeratotic cells with pink cytoplasm and hyperchromatic nuclei (H&E ×40)

palate, and other non-oral mucous membranes. There is usually a positive family history, although isolated cases of WSN can occur, presumably due to spontaneous mutations.

Histopathology reveals an abundance of individual cell keratinization (dyskeratosis) within the acanthotic stratified squamous oral epithelium. The cytology is otherwise normal, and there is no predisposition for malignant transformation (Fig. 17.2b, c).

Reactive White Epithelial Lesions

Benign Reactive Hyperkeratosis

Benign reactive hyperkeratoses are extremely common non-wipeable white oral lesions. They occur on the typical trauma- or friction-prone oral locations, presenting as painless, rough-surfaced plaques located directly opposed to and in contact with an offending source of chronic friction or irritation. Therefore, they can usually be diagnosed with confidence on clinical grounds alone and are not considered "leukoplakias" [7–9]. With elimination of the presumptive source of irritation, benign reactive hyperkeratoses will usually fade and disappear within several weeks or months, but they can reappear if the irritant is reintroduced. Biopsy is optional for lesions where an obvious source of friction or trauma is identified but may be indicated when the clinical diagnostic impression is unclear (Fig. 17.3a–c).

Under the microscope, benign reactive hyperkeratosis is characterized by ortho- or para-hyperkeratosis and/or acanthosis. There may be intercellular edema and plasma pooling within the stratum spinosum; the epithelial cytology and maturation are benign. There may or may not be a chronic inflammatory infiltrate within the superficial stroma [7] (Fig. 17.3d).

Linea Alba

Linea alba (*white line*) refers to a very common and highly specific presentation of benign, reactive hyperkeratosis that appears as a uniform, usually thin, non-wipeable, horizontal "white line" along the occlusal plane on the buccal mucosa. It results from perpetual friction caused by the repetitive interdigitation of the teeth during daily function [9]. Therefore, it is not the result of a parafunctional habit. Clinical recognition is sufficient for diagnosis; biopsy is not necessary (Fig. 17.4).

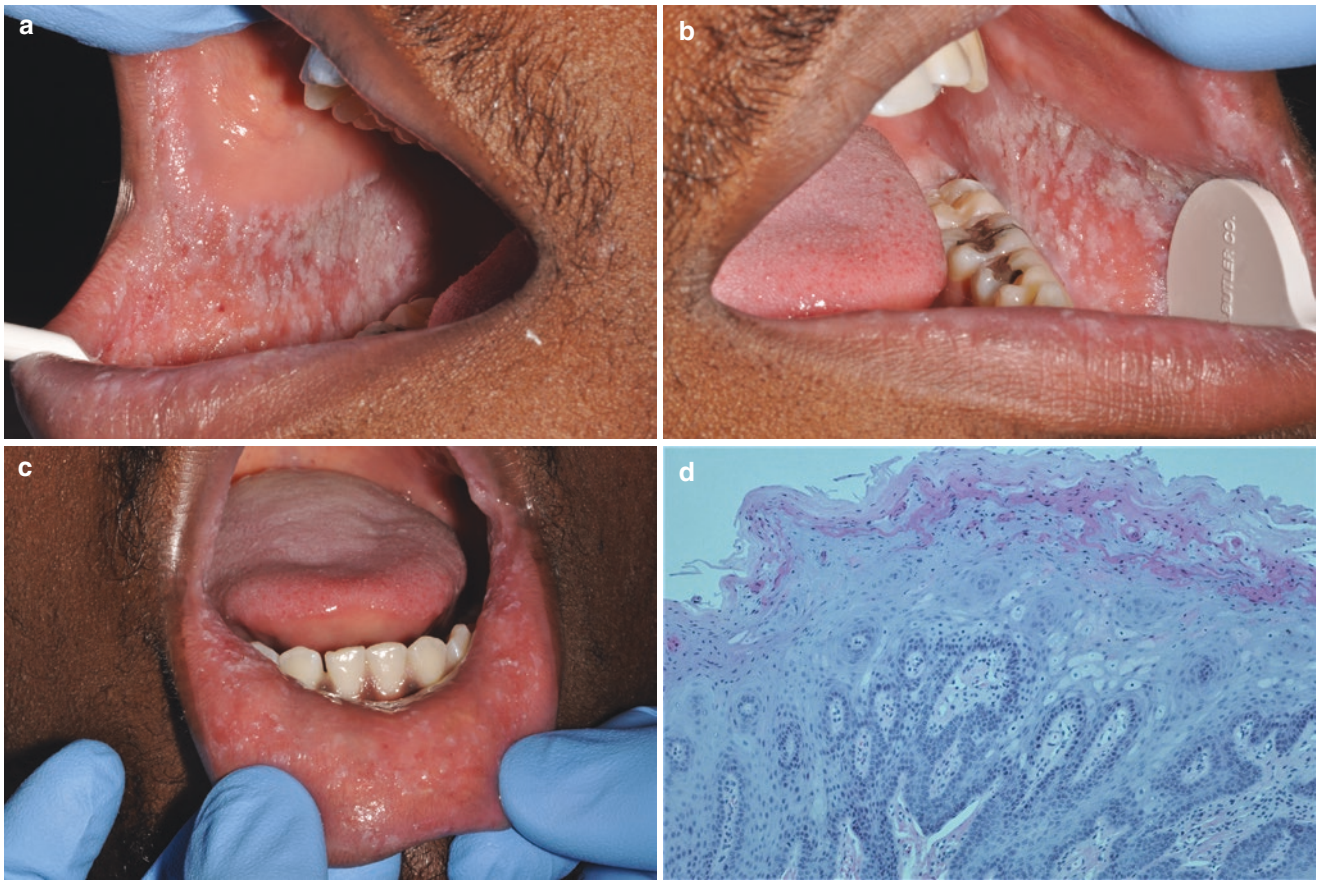


Fig. 17.3 Benign reactive hyperkeratosis. (**a–c**) Right and left buccal mucosae and lower labial mucosa in a chronic habitual cheek and lip chewer. From the commissures of the lips posteriorly along the mid-buccal mucosa bilaterally, and on the lower labial mucosa there are painless but extensive white, shreddy-appearing keratoses. (**d**) Benign reactive hyperkeratosis characterized by hyperparakeratotic surface epithelium with prominent stratum granulosum, plasma pooling. Normal cytology and maturation pattern (H&E ×10)

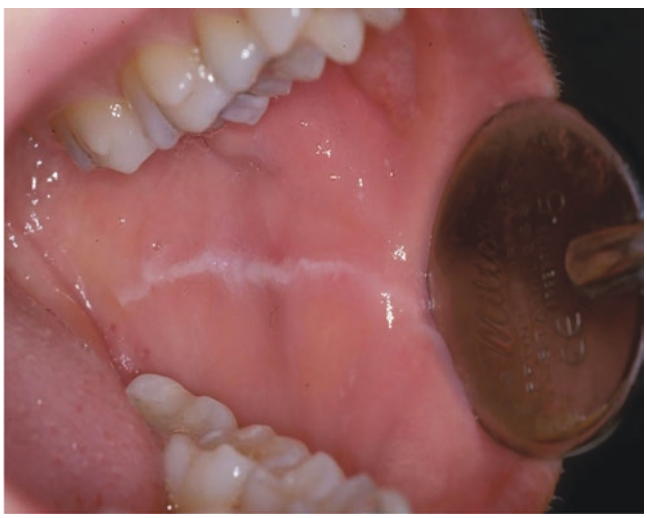


Fig. 17.4 Linea alba. Along the buccal mucosa there is a horizontal white, non-wipeable line indicative of benign reactive hyperkeratosis at the location where the teeth constantly interdigitate during daily function

Benign Alveolar Ridge Keratosis (BARK)

Benign alveolar ridge keratosis ("BARK"), the oral mucosal counterpart of cutaneous *lichen simplex chronicus*, is a reactive, hyperkeratotic entity. It presents as a homogenous rough, white, non-wipeable plaque, either on the retromolar pad or on the crestal portion of an edentulous region of the alveolar ridge in either jaw [10]. In the latter locations, the edentulous alveolar crest is the equivalent of an occlusal surface subjected to chronic friction from contact with an opposing tooth or teeth in the opposite jaw, or from abrasive foods. Although diagnosis of BARK usually can be made presumptively on the basis of clinical features alone [11], it is not uncommon for oral biopsy services to receive specimens of white plaques that fulfill the clinical and historical criteria for BARK (Fig. 17.5a).

On histopathological examination BARKs demonstrate hyperorthokeratosis, hypergranulosis, and cytologic normality. The epithelial rete pegs are elongated, tapered and occasionally their bases coalesce. There is minimal to no

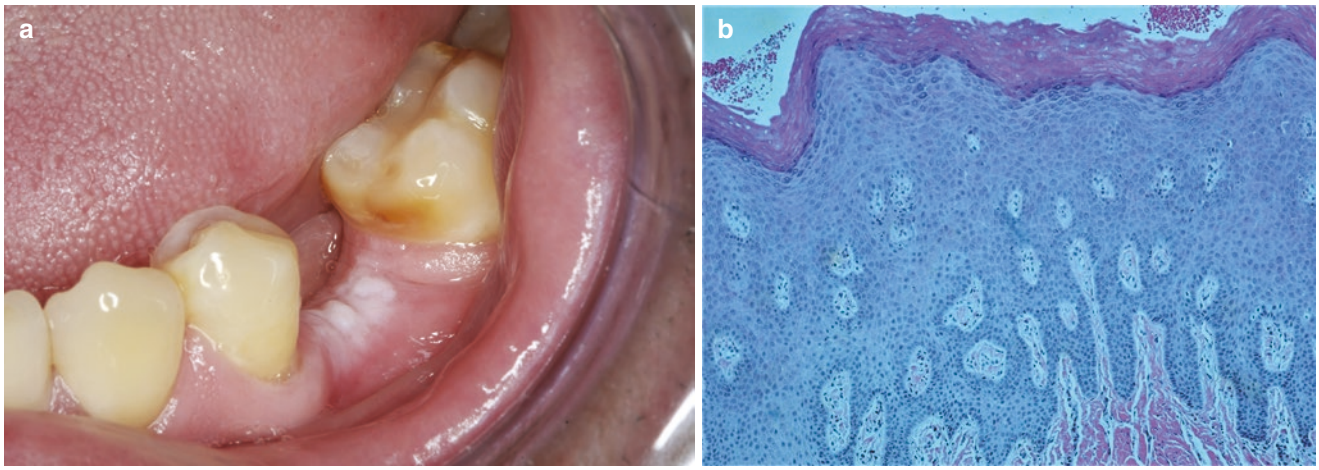


Fig. 17.5 Benign alveolar ridge keratosis (BARK). (**a**) In the edentulous space formerly occupied by the mandibular first permanent molar, there is a thick, white, non-wipeable plaque. The alveolar crestal mucosal epithelium here is subject to function-related friction. This is a benign, protective epithelial response to chronic low-grade frictional stimulation. (**b**) BARK. Hyperorthokeratosis and a prominent stratum granulosum with normal cytology and maturation pattern of the acanthotic surface epithelium (H&E ×20)

inflammation [12] (Fig. 17.5b). BARK lesions are benign, reactive and they do not transform to carcinoma. They do not require periodic biopsies.

Nicotine Stomatitis (*Stomatitis nicotina*, Smoker's Palate)

Individuals who smoke tobacco products that are thermally hot (e.g., cigars, pipes, several packs of cigarettes on a daily basis) [13] and those who indulge regularly in reverse smoking (i.e., habitual intraoral placement of the lit end of the cigarette or cigar) [14] may exhibit hard palatal mucosa that is diffusely white and non-wipeable, with an appearance that is often compared to a dried-up river bed. The white background is usually punctuated by small red puncta that represent irritated terminal excretory ducts of underlying submucosal mucus glands [15] (Fig. 17.6).

Although nicotine stomatitis is a well-recognized clinical entity and biopsies are rarely obtained, microscopic examination reveals hyperorthokeratosis and acanthosis with an essentially normal epithelial maturation pattern and benign cytology. The submucosal salivary glands' terminal ducts exhibit benign squamous metaplasia. There may or may not be attendant chronic inflammatory infiltrates.

It is important to bear in mind that the hard palate is surfaced by keratinized mucosa. Therefore, it already has a degree of natural protection from a variety of physical irritants. By contrast, the soft palatal mucosa is surfaced by unkeratinized, relatively thin, lining mucosa [3, 4]. Chronic, long-term exposure to both intense heat and the influence of carcinogens in tobacco specifically render it a susceptible site for epithelial dysplasia and carcinoma. For this reason, a white, or red-and-white mucosal plaque on the soft palate is an indication for biopsy, especially when there is a past or active tobacco history [1, 16] (Box 17.5).

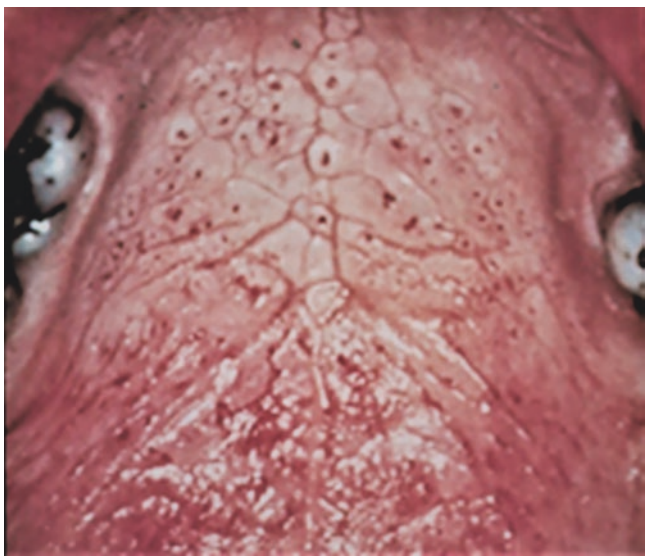


Fig. 17.6 Nicotine stomatitis ("Smoker's palate") . The hard palatal mucosa appears diffusely white and resembles a dried-up riverbed. The numerous red, punctate papules are the openings of irritated submucosal gland excretory ducts. The soft palatal mucosa appears irregularly red and white. The soft palatal mucosal changes must be biopsied to determine the epithelial status

Box 17.5 White Keratotic Epithelial Lesions: Indications for Biopsy for Definitive Diagnosis

Nonwipable white plaque

- Arises on a trauma-prone area and remains unchanged and/or persists after a reasonable period of time (i.e., 1–2 months) following eradication of the presumptive source of chronic friction or trauma.
- Increases in size without explanation.
- Develops a heterogeneous character (e.g., red and white color; nodular, pebbly, verruciform, papillary surface features, ulceration).
- Arises on a naturally trauma-protected area (e.g., floor of the mouth, ventral/lateral surface of the tongue, soft palate).

Clinically Indeterminate White Nonwipeable Plaques ("Leukoplakias")

What is *leukoplakia*? The term often is used generically to describe any "oral white plaque." But is that usage correct? Does leukoplakia refer to all oral white mucosal plaques, or only a select few? If it is the latter, then which white plaques qualify? Is *leukoplakia* another way of stating that a white oral lesion is malignant? Or premalignant? Is *leukoplakia* a definitive diagnosis? What are the actual implications of this term? These are important questions.

One way to put it is this: all leukoplakias are white lesions, but not all oral white lesions are leukoplakias. Therefore, *leukoplakia* should not be used to refer to any and all "white plaques." According to the WHO's definition of the term, *leukoplakia* is "a white patch or plaque that cannot be characterized clinically or pathologically as any other disease." [17] However, by stating that it is not possible to characterize a white plaque "pathologically" implies that there is simply no way to ever arrive at a diagnosis for that lesion. Therefore, it would seem reasonable to emphasize that the term *leukoplakia* should be reserved specifically for a white, non-wipeable mucosal plaque that cannot be diagnosed with confidence as any other specific disease, on clinical grounds alone (Fig. 17.7a, b). Hence, a white non-wipeable plaque in contact with an identifiable source of chronic friction can be clinically characterized as a benign, reactive keratotic lesion; it is not leukoplakia. By contrast, a white non-wipeable plaque for which a clinical diagnosis is indeterminate (i.e., no identifiable inciting agent, no history of trauma, no features characteristic of another specific keratotic disease), is considered *leukoplakia* until a definitive diagnosis can be established through representative biopsy and microscopic evaluation. Therefore, *leukoplakia* is only a provisional clinical diagnosis, and a biopsy is indicated for determining diagnostic specificity. Once a definitive diagnosis is established, the term *leukoplakia* no longer applies to that particular lesion [18].

A majority of white, non-wipeable lesions that best satisfy the leukoplakia rubric clinically are unifocal, and most often present on oral locations that are naturally fric-

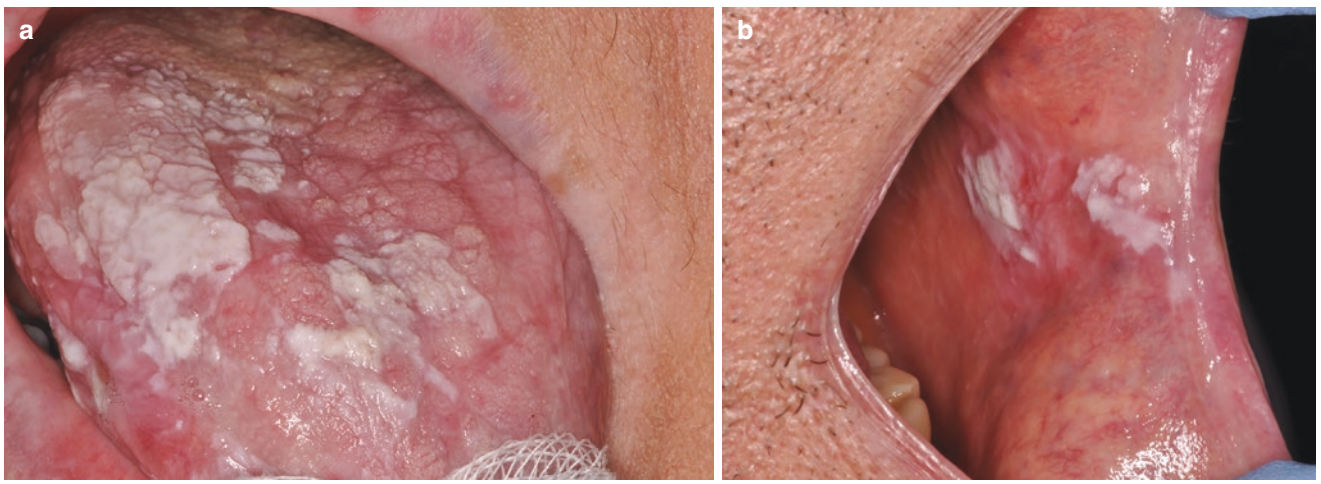


Fig. 17.7 Leukoplakia (Clinically indeterminate white plaques that require biopsies for diagnosis). (**a**) Extensive white, non-wipeable plaque with irregular surface features covering much of the dorsal and lateral surfaces of the tongue. Biopsy representative areas to determine diagnoses. (**b**) Left buccal mucosa with unexplained white and red non-wipeable plaque. There was neither a history, nor any obvious source of trauma

tion- or trauma-protected (i.e., floor of the mouth, lingual mandibular vestibules, ventral-lateral tongue, soft palate, uvula, tonsillar pillars). It is important to recognize that in the oral cavity, these locations are where a majority of oral cancers (squamous cell carcinomas) are also most likely to arise. Moreover, oral cancers are preceded in most cases by white, non-wipeable homogenous or heterogeneous plaques that demonstrate dysplastic (i.e., potentially premalignant) epithelial features on microscopic examination [16, 19].

Irrespective of what is stated above, *leukoplakia* is not a synonym for potentially premalignant or malignant epithelial change. On microscopic examination, a majority of clinically indeterminate white non-wipeable (keratotic) plaques exhibit features consistent with benign hyperkeratoses. The clinical features of keratotic lesions that are most likely to demonstrate potentially premalignant epithelial maturational disturbance (intraepithelial dysplasia) are summarized in Box 17.6. By now it should be clear that "*leukoplakia*" should only be applied as a temporary designation for a clinically indeterminate white non-wipeable plaque. Definitive diagnosis of such a lesion is established through obligatory microscopic examination of a representative tissue sample [1].

Box 17.6 Clinical Features of Premalignant Oral Keratotic White Lesions

- Located in "oral cancer-prone" site.
- No evident sources of trauma.
- Non-wipeable white plaque.
  - Homogenous, focal.
  - Homogenous, diffuse, borders obscure.
  - Heterogeneous (white, red, corrugated, pebbly surface texture).
  - >200 mm^2.
- Surface features suggestive of malignant progression.
  - Pebbly, verruco-papillary texture.
  - Ulceration, erosion.
  - Nodularity, irregular mass.
  - Induration.

Epithelial Dysplasia

The subject of epithelial dysplasia is covered extensively in this textbook's Chap. 19 on oral squamous cell carcinoma and premalignant oral epithelial disorders. Key points are reiterated here.

Epithelial dysplasia refers to a composite of atypical cytomorphologic and architectural changes above the basement membrane, indicative of maturation disturbance. It results from deregulation of the epithelial cell cycle, attributable to cumulative genetic mutations leading to abnormal function of critical control genes. The diagnosis of epithelial dysplasia signals potential for progression to squamous cell carcinoma. Therefore, epithelial dysplasia is considered a potentially premalignant (precancerous, preinvasive) epithelial lesion [16–20].

Pathologists often grade individual dysplastic lesions as *mild* (subtle), *moderate*, or *severe dysplasia/carcinoma*-in situ based in the extent of cytomorphologic abnormality observed from the epithelial basal cell layer upward to the surface, along with deviations from normal epithelial topography (e.g., blunted, bulbous or droplet-shaped rete pegs) [21]. The WHO grades dysplasia as mild, moderate, and severe and considers the term *carcinoma-in situ* synonymous with the latter [17].

However, it is well to note that histopathological grading of dysplasia can be highly subjective and inconsistent, not only among pathologists but sometimes relative to an individual pathologist reviewing the same specimen at another time. Although mild dysplasia is interpreted by some as less likely than moderate or severe dysplasia/*carcinoma-in situ* to progress to frank malignancy, the progression of any individual dysplastic lesion is actually unpredictable [22, 23]. This means that even mild epithelial dysplasia can evolve over time and gain the ability to violate the basement membrane (i.e., the epithelial-stromal boundary) to become an invasive squamous cell carcinoma. On the other hand, it is also possible that a markedly dysplastic/*carcinoma*-in situ lesion could remain confined to the surface epithelium and never invade the underlying stroma.

For these reasons, it is important to recognize that while any dysplastic epithelial lesion has the potential to advance to invasive squamous cell carcinoma, such transformation is unpredictable and independent of the degree of dysplastic change observed under the microscope [22, 23]. Furthermore, because dysplasia, like carcinoma, is a disease of genetic deregulation, it must be presumed that the entire mucosal field has been similarly affected and that the potential for disease persistence exists (the so-called "field effect"). That is why a "new" dysplastic lesion or carcinoma can, and often does re-emerge in the same location, even after the original lesion has supposedly been completely excised ("field cancerization") [24, 25]. It is therefore incumbent on clinicians to acknowledge that a diagnosis of epithelial dysplasia indicates risk for disease persistence and malignant progression, and mandates clinical monitoring at regular intervals, indefinitely. Re-biopsy is indicated if an existing or recurrent lesion exhibits clinically suspicious-appearing changes (e.g., size increase, corrugation, irregular or pebbly surface texture, erosion, erythema) at follow-up examinations [16].

Epithelial Atypia

What is *epithelial atypia*? How does it differ from epithelial dysplasia? What is the significance of a diagnosis of epithelial atypia?

Epithelial atypia, like dysplasia, is a histopathologic diagnosis. It refers to either abnormal cytologic features, such as nuclear enlargement with or without hyperchromatism, or dyskeratosis (i.e., premature, individual cell keratinization); or architectural disturbance (i.e., blunt or bulbous rete pegs in oral locations where they would normally be either tapered or absent). The blunted/bulbous appearance usually results from an increase in basaloid cells and is indicative of some degree of maturation disturbance [16].

As a diagnostic descriptive, atypia is admittedly a somewhat "gray area": while it could reflect evolving dysplastic change, it could, on the other hand, reflect an unusual but fundamentally benign response to intense inflammatory stimulation [26]. Even oral mucosal candidal infection or mere superficial fungal colonization can result in atypical epithelial histomorphology. Therefore, it can be challenging to determine the benign or possibly premalignant nature of an atypical epithelial lesion with the currently available diagnostic means to do so, namely conventional light microscopy and clinical findings. For this reason, until there are reliable and consistent molecular-genetic criteria identified for distinguishing between the two major discrepant possibilities, a diagnosis of epithelial atypia signals that clinical correlation and follow-up are essential [27]. Re-biopsy may be indicated if clinical findings are suspicious for dysplastic or carcinomatous change (e.g., cancer-prone oral location, pebbly or other surface irregularities, heterogeneity, increase in size of lesion, pain, induration) [16].

Proliferative Verrucous Leukoplakia

Proliferative verrucous leukoplakia (PVL) is a progressive, multifocal, potentially malignant oral epithelial disorder with a high rate of progression to squamous cell carcinoma. Therefore, it is considered a potentially malignant oral disease [28, 29]. The disease has a predilection for older women whose history is usually negative for the classic risk factors (i.e., tobacco use, alcohol) associated with conventional oral squamous cell carcinoma. PVL lesions are resistant to attempts at eradication.

The attached gingiva is often the first site of involvement, and the epicenter from which multicentric and eventually multifocal oral involvement develops. Initially, there are flat or corrugated-appearing homogenous white, non-wipeable plaques, often on the gingiva, or buccal mucosa, tongue or palate. In some cases, there is linear white, ring-like circumscription of the gingival margin(s) of one or several teeth [30]. Over time the disease becomes multicentric as the white changes radiate and extend onto contiguous mucosa (Fig. 17.8a–c). Lesions become progressively more rampant and heterogeneous in appearance, with verruciform/papillary, exophytic surface configurations and a generally more bulky, mass-type character (Fig. 17.8d). New PVL lesions often arise in sites separate and distinct from the initial site of origin, and in this way become multifocal. A majority of PVL lesions run a slow, insidious, unrelenting course. In about 50–70% of cases, there is transformation to verrucous, papillary, or barnaculate carcinoma or conventional invasive squamous carcinoma [28–32]. Oral locations that were initially uninvolved may also develop carcinoma, suggesting that PVL is an example of field cancerization [31].

Histopathology

Histopathology of the initial white plaques of PVL often reveals benign findings, with undulating or corrugated-appearing hyperortho- or para-hyperkeratosis with minimal or no epithelial dysplasia or atypia [31, 32]. Over time, as the lesions assume more clinically protuberant and variegated features with erythema and increasing surface irregularity, the microscopic features reflect the clinical changes: there are more voluminous, bulbous rete pegs, and surface invaginations including crypts with keratotic abscesses. Lesions may demonstrate both exophytic and "pushing" endophytic growth, often with minimally atypical or dysplastic epithelial maturation, consistent with verrucous, papillary or barnaculate carcinoma [31]. If there is invasion beyond the epithelial basement membrane and stromal infiltration, the lesion has undergone transformation to conventional squamous cell carcinoma.

Keratosis of Unknown Significance (KUS)

Keratosis of unknown significance (KUS) is a relatively recently described entity that refers to white, non-wipeable oral mucosal plaques whose origin cannot be confidently attributed to a local source of friction (i.e., they do not appear to be clinically consistent with reactive frictional hyperkeratoses), and where the diagnosis is indeterminate clinically (Fig. 17.9a, b). KUS lesions, in contrast to lesions of BARK (as described above), are clinically enigmatic and of uncertain etiology. Their potential for malignant progression is indeterminate [31, 33]. Therefore, a KUS lesion should be biopsied, especially when it is located on sites associated with PVL (e.g., gingiva, buccal mucosa) or a trauma-protected oral location but with a recognized predilection for oral epithelial dysplasia and/or squamous cell carcinoma [16] (i.e., lateral/ventral tongue, soft palate, floor of mouth).

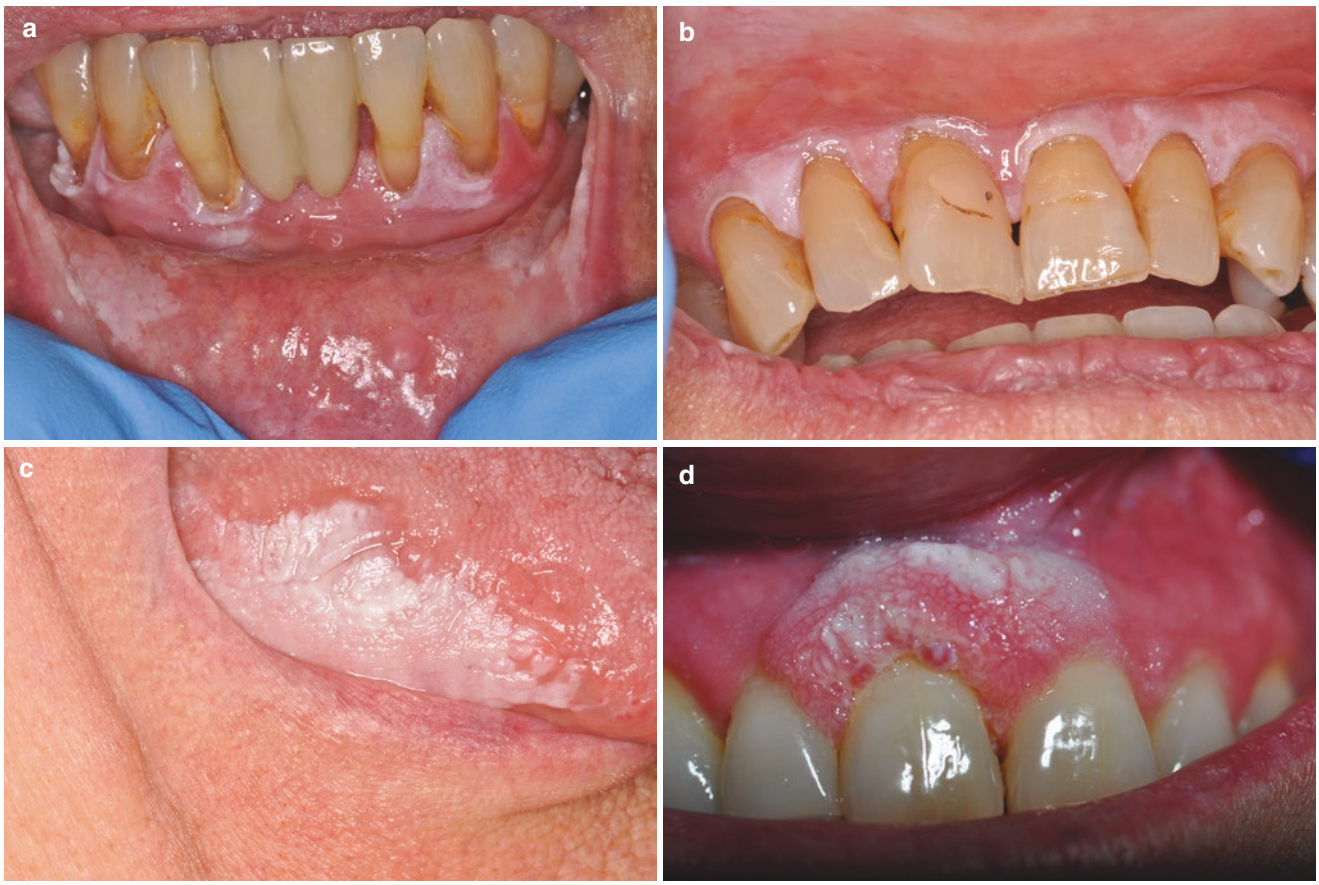


Fig. 17.8 Proliferative verrucous leukoplakia (PVL). (**a**) A 73-year-old white woman with multicentric white, non-wipeable plaques that involve the lower anterior gingiva, alveolar mucosa and labial vestibule and extend onto the lower labial mucosa. (**b**) Same patient with white, homogenous plaques involving the gingival margins of the maxillary anterior teeth circumferentially, with a "ring around the collar" effect. (**c**) Same patient with extensive white, rough homogenous plaque, right lateral-ventral tongue surface. (**d**) A 67-year-old Hispanic woman with long history of PVL. Bulky, pebbly, proliferative-appearing mass arose de novo on the maxillary gingiva. Biopsy revealed verruco-papillary squamous cell carcinoma

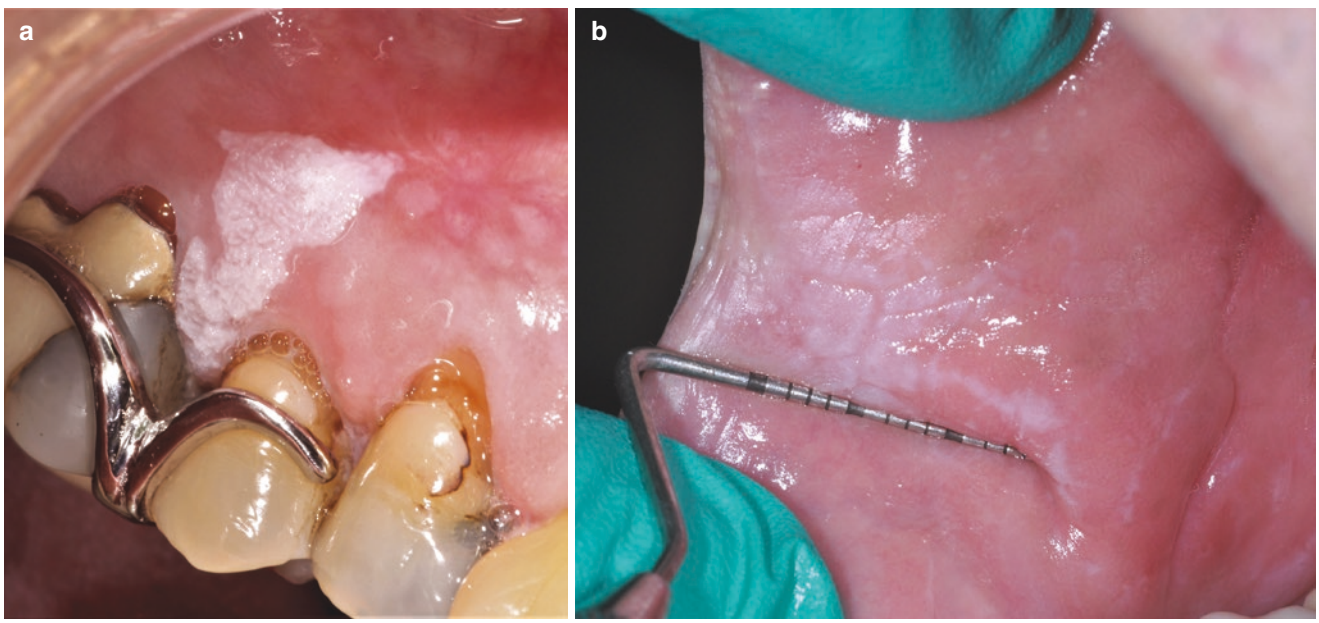


Fig. 17.9 Keratosis of uncertain significance (KUS). (**a**) Maxillary right interdental buccal gingiva and alveolar mucosa, premolar region. Homogenously white, corrugated plaque that is non-wipeable and does not appear to be reactive clinically. (**b**) White, dry-appearing plaque, right buccal mucosa. There was no evident source of trauma, no para-functional habits, nor was there a history of tobacco use

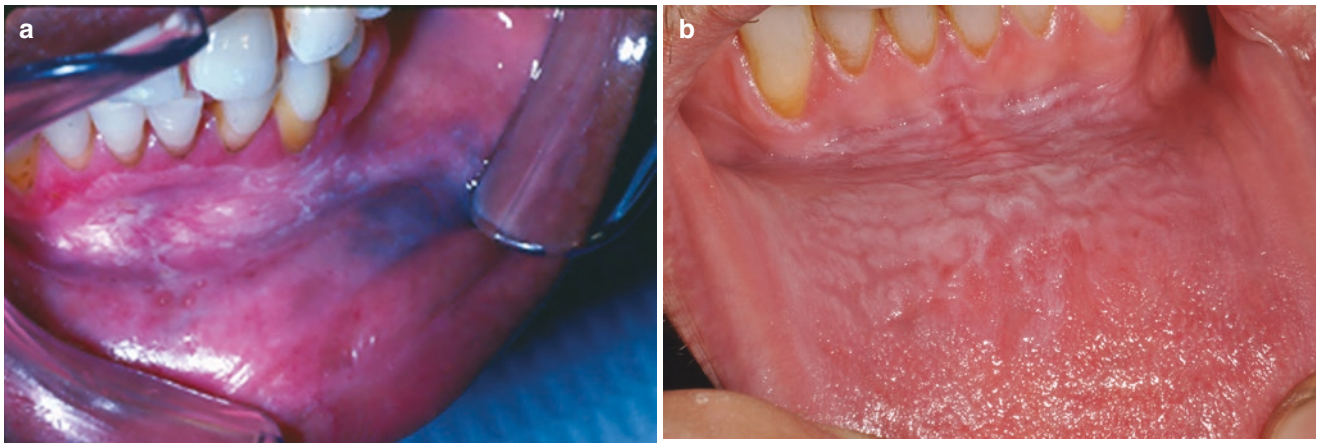


Fig. 17.10 Tobacco pouch keratosis. (**a**) This 72-year-old African American woman has been placing smokeless tobacco in this location since she was a small child. Biopsies revealed benign, reactive hyperkeratosis. (**b**) This 44-year-old Caucasian man has been placing smokeless tobacco in the lower labial vestibule daily since he was in high school. Biopsies revealed epithelial dysplasia

Histopathology

On biopsy a KUS lesion may demonstrate histopathologic features that can range from acanthosis with ortho- or parahyperkeratosis and an essentially normal maturation pattern, to benign verrucous hyperplasia, or epithelial atypia, or even epithelial dysplasia [33]. Given the unpredictable clinical course of KUS lesions, clinical follow-up and periodic biopsies are in order.

Smokeless Tobacco-Related Keratosis (Tobacco Pouch Keratosis)

Tobacco pouch keratosis refers to the composite clinical and histopathologic epithelial alterations attributable to habitual snuff or chewing tobacco use. Clinically, a grayish-white, often fissured mucosal patch develops at the site where smokeless tobacco is habitually placed and held in the oral cavity. The most common locations include the lower or upper labial or buccal mucosa including the contiguous vestibular and alveolar mucosa. Smokeless tobacco products are potentially carcinogenic [34]. Therefore, biopsies of tobacco pouch keratoses are often obtained for definitive diagnosis (Fig. 17.10a, b). In some cases, the clinical changes resolve over time, if the patient discontinues the habit, strictly avoiding tobacco placement.

In most instances, microscopy reveals a composite of benign findings: chevron-like hyperortho- or parakeratosis and acanthosis with both a normal epithelial maturation pattern and benign cytomorphology. However, in some cases epithelial atypia or dysplasia is observed [15, 31, 34]. In those cases where there are atypical or dysplastic epithelial changes, the patient should be advised to discontinue the habit, since long-term direct applications of a carcinogenic substance to the oral mucosa could evolve to frank squamous cell carcinoma over time.

Actinic Cheilitis

Actinic cheilitis refers to a composite of chronic sun exposure-induced, clinically white, non-wipeable, heterogeneous surface changes that are typically found on the vermilion border of the lower lip [35–37], which is neither an intraoral nor a trauma-protected location (Figs. 17.11a, b). Actinic cheilitis is characterized by a wide range of possible histopathologic features that can include benign epithelial hyperplasia or atrophy, atypia or dysplasia, and evidence of basophilic collagen degeneration within the superficial stroma, referred to as solar elastosis [16]. Actinic cheilitis is considered a potentially malignant condition because it usually precedes or accompanies squamous cell carcinoma (lip cancer) [35–37].

Oral Hairy Leukoplakia

Initially discovered in the early 1980s in patients with HIV/AIDS, oral hairy leukoplakia (OHL), is recognized as a clinical manifestation of advancing immune depletion. The name *oral hairy leukoplakia* (OHL) is an appropriate clinical description for these painless, white, non-wipeable, filiform plaques that are most often encountered on the dorsal-lateral and/or ventral surfaces of the tongue (Fig. 17.12a). OHL is attributable to opportunistic reactivation of latent Epstein-Barr virus (EBV, human herpesvirus 4, HHV-4) infection of oral epithelial cells. Presentation in a patient with documented HIV-infection signals the likelihood of more serious infections; in a patient whose HIV-serostatus is unknown, it may be among the first signs of compromised immunity and is an indication for serological testing [38, 39]. Since its discovery, OHL has been documented in a relatively small number of non-HIV-infected patients, some of whom were

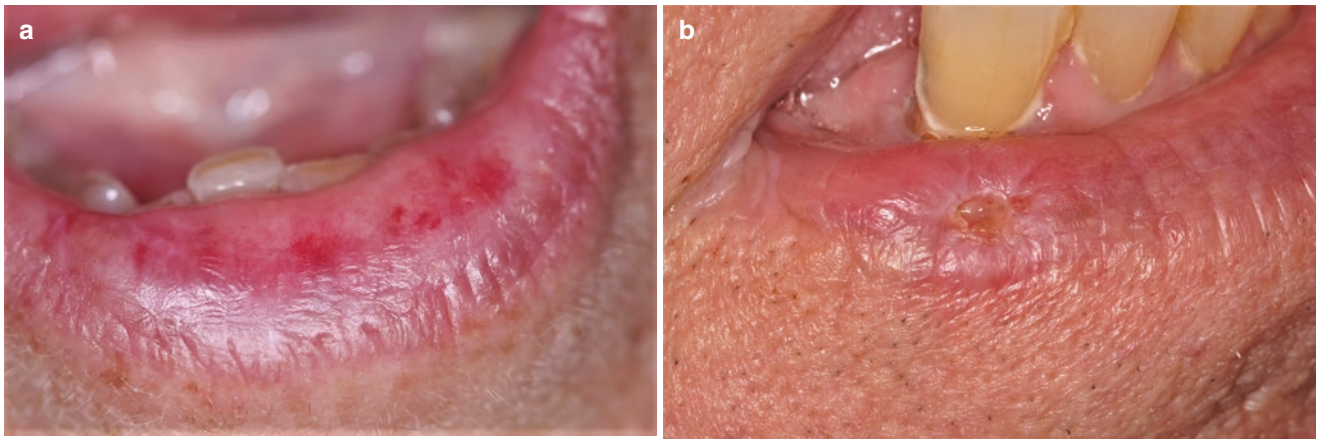


Fig. 17.11 Actinic cheilitis. (**a**) The lower lip vermilion border of this 64-year-old Caucasian woman exhibits atrophy with diffuse white change interrupted by foci of erythema. There is indistinct demarcation between the vermilion border and skin of the lower lip. (**b**) A 75-year-old Caucasian man with an ulceration surrounded by white starburst on the right side of the lower vermilion border. Surrounding vermilion tissue appears atrophic and there is no clear demarcation between vermilion border and skin

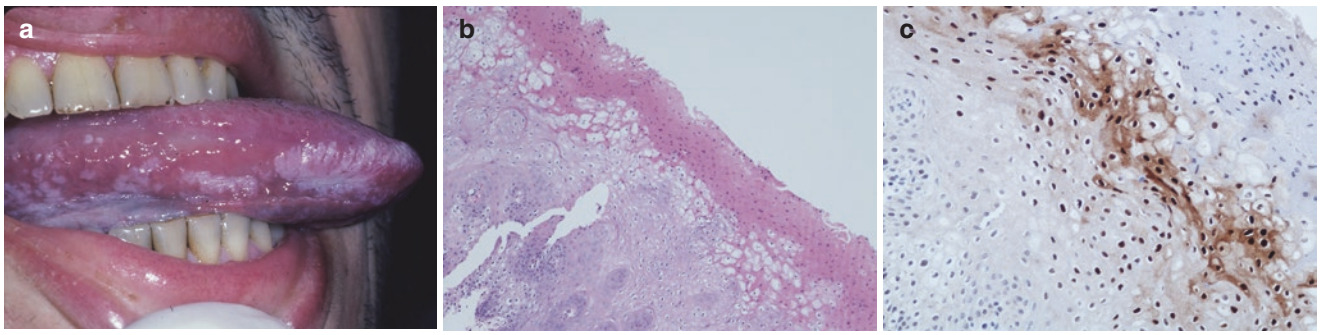


Fig. 17.12 Oral hairy leukoplakia. (**a**) HIV-infected a 32-year-old man with extensive, painless, non-wipeable white plaques on the lateral-ventral surfaces and dorsal surface of the tip of the tongue. (**b**) Biopsy revealed hyperparakeratotic epithelium with clear cytoplasm of subcorneal cells. There is perinuclear haloing generally in the upper stratum spinosum. The epithelium is hyperplastic but maturation is unremarkable. (H&E ×20). (**c**) Immunohistochemistry. EBV-in situ hybridization reveals EBER positivity (EBV-encoded small RNA) in the nuclei of the subcorneal cells

experiencing immune suppression of diverse etiologies, and in others in whom there was no identifiable immune compromise or modulatory circumstance. OHL can be a transient finding in a patient whose immune responses are restored. It often regresses in response to antiretroviral therapies and is rarely seen today in the age of HAART (highly active antiretroviral therapies) [40, 41].

Histopathology

At the microscope, OHL demonstrates unique features: peaks of hyperparakeratosis and cytoplasmic ballooning with perinuclear halos of the subcorneal epithelial cells. The surface epithelium is acanthotic, and its cytology and maturation are otherwise normal (i.e., neither dysplastic nor atypical). There are no Langerhans cells within the epithelium, and no appreciable inflammatory infiltrates within the submucosa or lamina propria. For diagnostic confirmation, Epstein Barr viral-encoded RNA (EBER) can be disclosed in the subcorneal cells with in situ hybridization immunohistochemistry analysis [38, 39] (Fig. 17.12b, c).

Candidal Leukoplakia (Chronic Hyperplastic Candidiasis)

This entity will be discussed in the section on candidiasis.

Red and White Oral Lesions

Lichen Planus and Oral Lichenoid Lesions

Lichen planus (LP) is a chronic systemic, immune-mediated mucocutaneous condition. It affects patients in midlife or older and exhibits a 3:1 preference for women. A patient with lichen planus may have exclusive involvement of either

the skin or of one or more mucous membranes (e.g., oral cavity, anogenital region). There is often multifocal disease presentation in which the oral mucosa, the anogenital region, the skin, or any combination of these sites is affected concomitantly or in succession. Disease activity can be synchronous or asynchronous in LP cases that involve more than one anatomic location.

The disease is aptly named for *lichens*, the ubiquitous blue-green or yellow-gold, scaly-appearing plants that propagate outdoors on trees, rocks, benches, and monuments. The classic cutaneous lesions of lichen planus present as linear or annular configurations of scaly (i.e., hyperkeratotic) papules on a violaceous background. The lesions most often involve the extremities, particularly the thighs, the pretibial skin, the ankles and wrists, and the skin on the trunk and on the back. The facial skin is rarely if ever affected. Lichen planus can also involve hair shafts and nails, resulting in foci of alopecia and paronychia, respectively. The cutaneous lesions are intensely pruritic, so that excoriation and perilesional brown-gray pigmentation from benign post-inflammatory melanin incontinence are not unusual clinical findings.

The classic oral mucosal lesions of LP are bilaterally distributed: buccal mucosa and gingiva are the most common oral locations, followed by the buccal vestibules and the tongue. Prototypical oral LP lesions are white, non-wipeable, keratotic papules that tend toward confluence to form characteristic lacy, spider web-like reticular networks that are frequently described as "striated" (Fig. 17.13a–d). In fact, the clinical descriptive term, "*lichenoid*" refers to the white, lacy, lattice-like pattern emblematic of classic oral LP. In addition to the classic white striations, there can be attendant foci of erythema, mucosal atrophy, erosion, or ulceration (Fig. 17.13e, f, g). LP patients tend to report long periods of asymptomatic quiescent disease activity interrupted periodically by symptomatic exacerbations. Such symptomatic flare-ups are usually attributable to erosive, ulcerative, or atrophic lesions [42–45].

Pathogenesis

Lichen planus, a prototypical *interface dermatitis/stomatitis*, involves a type 4 T cell-mediated hypersensitivity response [46] directed against epidermal (cutaneous) or epithelial (mucosal) basal keratinocytes. Recruited by antigen-presenting cells (APCs), CD4+ lymphocytes migrate to the epithelial-stromal interface. The sensitized lymphocytes perceive the basal cell surface antigenicity as foreign, signaling CD8+ cytotoxic T lymphocytes to attack the "alien" basal cells, resulting in basal cell destruction (cytolysis). This is consistent with a classic autoimmune process since the basal cell itself is targeted as a *self-antigen*. The histopathologic features of lichen planus reflect the condition's pathogenesis [43, 47].

Histopathology

Under the microscope, LP is an example of a classic interface dermatitis or stomatitis. A dense band-like, predominantly lymphocytic infiltrate (often referred to as a *lichenoid* infiltrate) occupies the lamina propria, obfuscating the epithelial-stromal interface region (the basement membrane zone/superficial lamina propria). The cytotoxic lymphocytes intermingle intimately with the epithelial basal cells. This results in basal cell liquefactive destruction (Figs. 17.13h, i). Consequently, there is a sharp, sawtooth-like appearance of the rete pegs. There is usually compensatory para- or orthohyperkeratosis, with normal epithelial cytology and maturation. With extensive basal cell liquefaction, the epithelial-stromal interface attachment can be disrupted and result in erosion/ ulceration of the surface epithelium. This is a significant clinical-pathological correlation, because symptomatic oral LP is typically associated with foci of erosion or ulceration [47–49]. Furthermore, given LP's chronicity, periodic recurrences of erosive or ulcerative flare-ups that alternate with cycles of healing can result in mucosal atrophy, especially noticeable as a smooth, shiny appearance of the normally stippled attached gingiva, and the papillated dorsal tongue. Atrophic changes can also be symptomatic [42–45].

Clinical Practice Point: Dysplasia with Lichenoid Inflammation

As a diagnostic criterion for LP, the importance of normal epithelial maturation and cytology cannot be overemphasized. Notwithstanding the presence of an interface band-like, lymphocytic (i.e., *lichenoid*) infiltrate in the superficial lamina propria, if the epithelium is dysplastic, the diagnosis is *epithelial dysplasia*, not LP [49–53] (Table 17.3). This is significant because historically, there have been assertions that erosive oral LP is inherently a premalignant condition [17, 20, 54, 55]. There are published cases of erosive oral LP transforming to carcinoma, yet the percentage of such cases relative to the prevalence of LP is so small that it belies erosive LP's repute as a precancerous condition. While remnants of the debate concerning LP's purportedly premalignant nature persist in some circles, it has become widely recognized over time that those cases of LP that transformed to SCCa were likely cases of mistaken identity [50]. In such cases unrecognized epithelial dysplasia accompanied by a lichenoid chronic inflammatory infiltrate was diagnosed erroneously as LP. Therefore, beyond recognizing the band-like lymphocytic infiltrate, careful evaluation of the epithelial architecture, cytology, and overall maturation pattern is essential for diagnostic accuracy [49–53, 56].

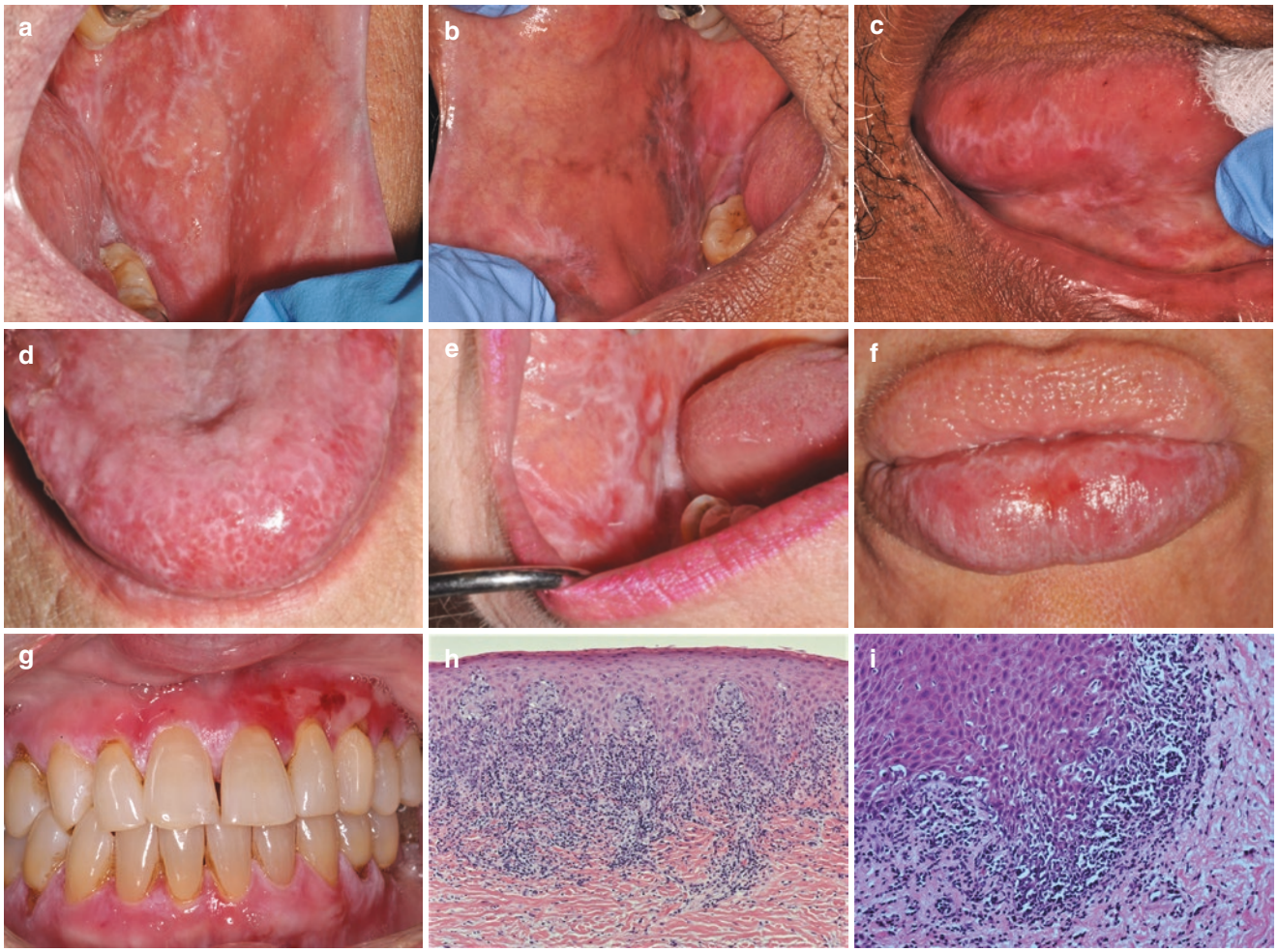


Fig. 17.13 Lichen planus. (**a**) A 61-year-old man with classic lacy white striations and papules on the left buccal mucosa. Similar striations were present on right buccal mucosa, lower vermilion border, dorsal tongue and gingiva, the latter accompanied by erosive changes. (**b**) White lacy striae and starburst-like pattern, right buccal mucosa of an Indian American man. Note the surrounding brown pigmentation consistent with benign inflammatory melanin incontinence, a common finding associated with lichen planus in trauma-prone oral locations. Similar findings were observed on the left buccal mucosa, characteristic of the bilateral distribution of lichen planus lesions. (**c**) Same patient as (**b**): right lateral-ventral tongue/floor of mouth exhibits white striations. (**d**) An 81-year-old white woman with oral lichen planus exhibits atrophy of filiform papillae accompanied by extensive white, lattice-like striations and foci of erythema on dorsal tongue. (**e**) This 74-year-old woman with erosive lichen planus complains of discomfort on eating spicy or acidic foods. Right buccal mucosa shows classic white striae with several foci of erythema (erosion) and ulceration covered by yellow pseudomembrane. (**f**) A 45-year-old woman with erosive lichen planus. Lower vermilion border exhibits painful erosive/ulcerative changes and generalized white striations. (**g**) Erosive lichen planus, gingiva. Lichen planus is one of the most common etiologies of gingival desquamation. (**h**) Lichen planus. Surface is parakeratinized; the epithelium demonstrates normal cytology and maturation. There is a band of lymphocytes occupying the epithelial-lamina propria interface, in intimate relation to the basal epithelial cells, many of which have undergone liquefactive degeneration (H & E ×20). (**i**) Higher magnification reveals obfuscation of the epithelial-stromal demarcation at the basement membrane zone due to CD8+ lymphocytic infiltration and liquefactive destruction of the basal cells (H&E ×40)

Other Oral Lichenoid Lesions

While LP is the prototypical lichenoid oral condition with characteristic clinical and histopathological findings, other oral mucosal entities with *clinically* lichenoid features are frequently encountered. Although these entities may be widely distributed in the mouth, unlike lichen planus they can be unilateral or isolated as opposed to bilateral in distribution. Under the microscope, they may or may not demonstrate a band-like chronic inflammatory infiltrate within the lamina propria; and basal cell liquefaction, requisite for LP, is not a consistent feature [42–45, 49].

Table 17.3 Oral lichenoid lesions: clinical-pathological correlations

Lichenoid oral condition	Clinical features	Histopathological features
Lichen planus[a]	• Bilateral distribution	• Parakeratosis
	• Lacy white keratoses ± erythema, erosive changes	• Normal cytology, maturation
	• Cutaneous lesions (scaly, pruritic papules), skin appendages and/or other mucous membranes involved	• Band-like lymphocytic infiltrate at epithelial-lamina propria interface intermingles with basal cells
		• Basal cell liquefaction
Lichenoid direct contact hypersensitivity reaction[a]	• On mucosal surface in protracted direct or repeated contact with sensitizing agent (e.g., amalgam restoration, cinnamon product)	• Hyperkeratosis ± surface erosion, ulceration
	• ± Discomfort, erosive changes	• Normal epithelial maturation
	• Resolves (in weeks, months) following complete elimination/ avoidance of precipitant/ sensitizing agent	• Basal cell destruction, ± ragged separation at basement membrane zone
		• Interface lymphocytic infiltrate
		• Perivascular inflammatory infiltrates in stroma
Lichenoid drug reactions[a]	• Follows introduction of medication	• Normal epithelial maturation
	• Can have bullous, erosive components	• Basal cell destruction, ± ragged separation at basement membrane zone (BMZ)[b]
	• May be accompanied by cutaneous, other mucosal involvement	• Interface lymphocytic infiltrate
	• Oral lesions may persist after withdrawal of medication	• ± Perivascular inflammatory infiltrates in stroma
Nonspecific lichenoid stomatitides[a]	• Oral mucosal involvement	• May or may not demonstrate microscopic features similar to those in lichen planus
	• Focal or multifocal	• ± Erosive changes
	• Lacy white keratoses ± erythema, erosions	
Systemic lupus erythematosus[a]	• Systemic autoimmune collagen vascular disease; oral lesions resemble CDLE lesions or are more nondescript and erythematous, erosive; ± radiating white striations	• Hyperkeratosis, keratin-plugged surface crypts
	• Palate often involved	• Basal cell destruction
	• Gingival erythema, bleeding	• Epithelial-stromal interface hyalinization
		• Lichenoid and perivascular lymphocytic infiltrates
		• D.I.F.- speckled IgG, C3 positivity at BMZs[b]
Chronic discoid (cutaneous) lupus erythematosus (CDLE)[a]	• Predominantly cutaneous involvement: hyperpigmented, hypopigmented plaques, scales, scar formation	• Similar to those seen in SLE, including findings on D.I.F. analysis
	• Oral lesions can be unilateral or multifocal, erythematous or erosive with white radiating striae peripherally	• Circulating antibodies (–)
	• ± Gingival erythema, bleeding	
Epithelial dysplasia[c] (epithelial maturation disturbance accompanied by interface lichenoid chronic inflammatory infiltrate)	• Isolated red-and-white lesion, ± striated white (i.e., clinically "lichenoid") component	• Epithelial architectural, cytological abnormalities
	• May be erosive or ulcerated	• Blunt, bulbous rete pegs
	• ± Indurated component on palpation	• Basal cells intact
	• Often but not exclusively on oral cancer-prone site	• Nuclear enlargement, hyperchromatism, pleomorphism, etc.
		• Interface (lichenoid) chronic inflammatory infiltrate

[a]Benign
[b]Basement membrane zone (BMZ)
[c]Potentially malignant (premalignant)

The other lichenoid oral lesions include:

- **Non-specific (often idiopathic) lichenoid stomatitides.** These are the most commonly occurring benign oral lichenoid lesions. Such lesions may present as a single focus of lacy white striations with or without erythema or ulceration; or they are distributed to varying degrees (even bilaterally) throughout the oral mucosa, but unlike some cases of lichen planus, there is no history of cutaneous or other mucous membrane lesions. Often it is difficult to identify an etiologic factor.
- **Lichenoid contact hypersensitivity reactions**. These are benign lichenoid responses that arise on oral mucosal sites consequent to their direct physical contact with an

irritant substance. Some lichenoid contact hypersensitivity responses can be symptomatic and include erosion or ulceration in conjunction with the white, lacy component at the site of contact. Recognized agents known to produce direct hypersensitivity responses include cinnamon products (chewing gums, candies, flavorings in beverages, sauces, etc.) or recently placed amalgam or other dental restorations [44] (Fig. 17.14a, b). A pathogenetic mechanism similar to that of LP applies. However, in addition to the interface stomatitis, there is notable perivascular inflammatory infiltration due to immune complex deposition at vascular basement membranes in the affected submucosal site [49] (Fig. 17.14c, d).

- **Lichenoid drug reactions**. Lesions in these cases are usually widely distributed throughout the oral cavity, and present in close temporal relationship and consequent to the introduction of a systemically ingested/administered medication. The oral eruption is usually associated with a symptomatic erosive or ulcerative component. Some oral lichenoid drug reactions involve additional, disparate anatomic regions concomitantly, with presentations on skin and other mucous membranes. Interface dermatitis/stomatitis would also characterize the histopathology [57].
- **Chronic discoid (cutaneous) lupus erythematosus (CDLE) and systemic lupus erythematous (SLE)** (See section "Lupus Erythematosus") (Fig. 17.15).
- **Oral manifestations of graft-versus-host disease (GVHD).** GVHD is a clinical syndrome with potential for considerable morbidity and even mortality. It follows allogeneic hematopoietic cell transplantation, resulting in attack of host tissues by donor-derived immunocompetent T cells and inflammatory responses [58–60]. The oral cavity is a potential site of GVHD involvement, often demonstrating hyperkeratotic plaques and/or symptomatic erosive lesions that resemble lichen planus both clinically and histopathologically [43, 45, 49, 58].

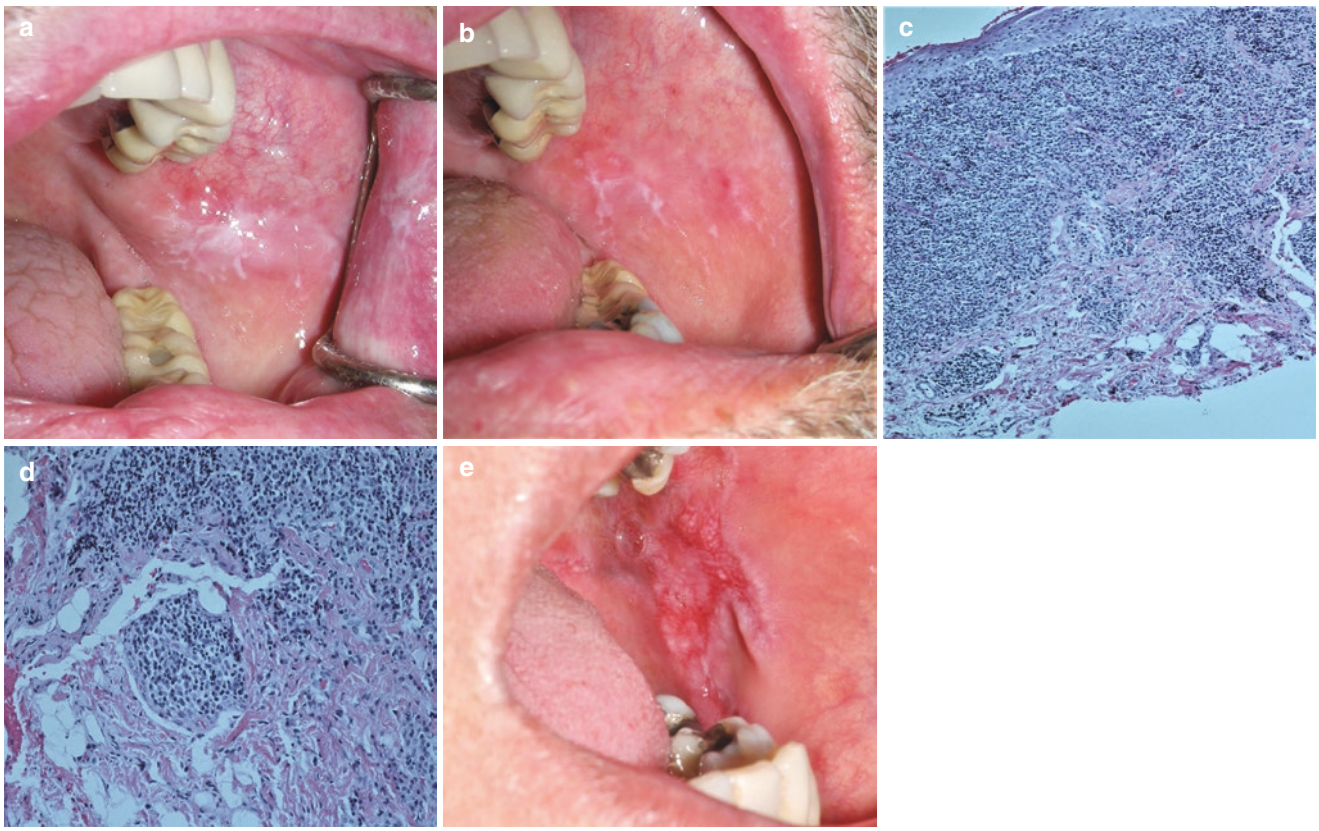


Fig. 17.14 Lichenoid stomatitis; Dysplasia /Carcinoma with lichenoid features. (**a**) The patient reports feeling "roughness" and mild discomfort in the left buccal mucosa. This solitary white, non-wipeable, starburst-shaped plaque with mild erythema arose in the area where patient habitually places cinnamon-flavor chewing gum. (**b**) At 6 weeks follow up after discontinuation of the chewing gum habit, the lichenoid changes are resolving and the patient is symptom-free. (**c**) Biopsy of lesion shown in (**a**) reveals atrophic surface epithelium and a dense band-like lymphocytic infiltrate in the lamina propria with basal cell obfuscation. In addition, there are dense perivascular chronic inflammatory infiltrates in the deeper stroma (H & E ×20). (**d**) Higher magnification of the perivascular infiltrate. (H & E ×40) (**e**) This 64-year-old woman complained of discomfort in the solitary, longstanding lichenoid lesion shown. She had been told this was "lichen planus." Heterogeneous, pebbly features of this isolated lesion were considered clinically suspicious. Biopsy demonstrated epithelial dysplasia with foci of invasive squamous cell carcinoma

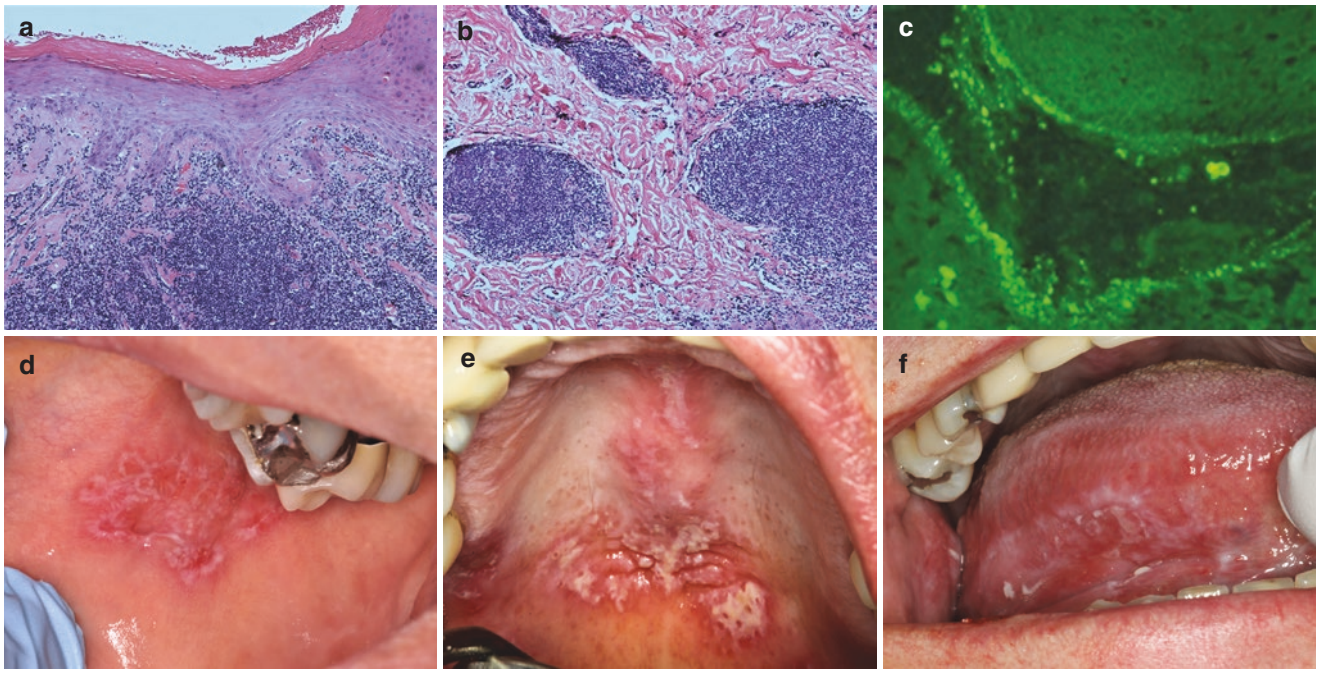


Fig. 17.15 Lupus erythematosus. (**a**) Buccal mucosal biopsy reveals hyperkeratosis and epithelial hyperplasia. The basement membrane region is markedly hyalinized. Basal cell liquefaction and lymphocytic infiltration are seen focally. Dense lymphocytic infiltrates are present in the stroma. These histopathological findings are characteristic of oral mucosal and cutaneous lesions in discoid and systemic lupus (H & E ×20). (**b**) Dense perivascular lymphocytic infiltrates accompany the changes noted in (**a**) (H & E ×40). (**c**) Direct immunofluorescence, discoid lupus erythematosus. Speckled positivity for IgG and C3 at basement membrane zones, both at the epithelial-stromal interface and perivascular. (**d**) Discoid LE lesion on right buccal mucosa. Discrete white, feathery-appearing border with internal erythema, possibly erosions. Such lesions may or may not be symptomatic. (**e**) Patient with history of systemic lupus developed painful lesions on the hard and soft palate. (**f**) Painful lupus lesion, right ventral-lateral tongue surface. Ulcerated, erythematous and with a white, clinically lichenoid border

- **Epithelial dysplasia**, previously discussed above as a potentially premalignant oral lesion, sometimes presents as a heterogeneous-appearing oral lesion with *clinically* lichenoid features. However, in contrast to lichen planus, dysplastic lesions are usually solitary and unifocal. They tend to favor the recognized oral cancer prone locations (floor of mouth, lateral-ventral tongue, soft palate) [16, 49–53, 56]. Importantly, dysplastic epithelial lesions are not exclusive to the latter sites; they can arise elsewhere in the oral cavity. In addition to the lichenoid lacy-white clinical appearance, any surface irregularities, including erythema, ulceration, erosive change, and pebbly texture, plus a history of exposure to a known risk factor (past or active tobacco use, betel chewing), must raise suspicion for dysplasia (Fig. 17.14e). In composite, the history and clinical features should prompt concern and are sufficient justification for one or more representative biopsies.

Histopathology

Under the microscope, *epithelial dysplasia with a band-like lymphocytic infiltrate in the lamina propria* (i.e., a lichenoid inflammatory pattern), previously referred to as "lichenoid dysplasia," is epithelial dysplasia: it must not be mistaken for lichen planus or any other benign lichenoid process [31, 50–53, 56] (Box 17.7).

Box 17.7 Clinical Practice Point: Dysplasia with Lichenoid Inflammation

Irrespective of whether a white oral lesion appears *clinically* lichenoid:

- Histopathological evidence of epithelial dysplasia militates against a diagnosis of LP and all other benign lichenoid entities.
- Epithelial dysplasia in a clinically or histologically lichenoid lesion is dysplasia. It reflects epithelial maturation due to genetic deregulation, and recognized as aberrant by T lymphocytes.
- It bears no pathogenetic relationship to LP.
- *These findings must not be interpreted as lichen planus with dysplastic change.*

Lupus Erythematosus

Lupus erythematosus is a group of autoimmune diseases that is typically classified into three subtypes:

- **Systemic lupus erythematosus (SLE)**—characterized by multisystem/multi-organ involvement.
- **Chronic cutaneous ("discoid") lupus erythematosus (DLE)**—characterized by mucocutaneous involvement exclusively.
- **Subacute cutaneous lupus erythematosus**—a form that may represent a transitional or intermediate form of SLE.

We will focus on SLE and DLE here because oral lesions are most likely to occur in these forms of lupus erythematosus [61, 62] (Table 17.3).

Systemic lupus erythematosus (SLE) is a commonly occurring, chronic, multisystem "collagen vascular" disease. It exhibits a predilection for women who are far more often affected than men (9:1), and the onset in women frequently occurs during the child-bearing years. However, the disease also can arise during childhood or in persons over the age of 65. In the latter cases, the female: male ratio is 2:1. There is also a notable preference for black and Hispanic patients.

A multitude of organ systems can be involved, including the joints, cutaneous tissues and mucous membranes. In particular, immune-mediated damage to the kidneys and heart are among the most serious complications, with organ failure and even death as potential endpoints.

Often regarded as the prototypic autoimmune disease, SLE is characterized by a wide array of autoantibodies that target tissues, cells, and nuclei. The antinuclear antibodies (ANAs) include antibodies against DNA, histones, non-histone proteins bound to RNA, and anti-nucleolar antigens. Aside from autoantibody-mediated type 2 hypersensitivity, in SLE there is also type 3 hypersensitivity characterized by circulating immune complexes that become bound to various tissues and basement membranes (perivascular, cardiac, renal) instigating inflammation and tissue destruction. Thus, the fundamental immunologic defect in SLE is the failure of mechanisms that maintain self-tolerance. Diagnosis is confirmed through correlation of physical findings, serological evidence of circulating autoantibodies, and positivity for a panel of ANAs, plus tissue-bound and circulating immune complexes [63–65].

The disease tends to run a long, insidious course with periodic exacerbations and remissions. Early diagnosis and intervention offer a more favorable prognosis. Over time, organ damage mounts in poorly-controlled disease.

The clinical spectrum of features potentially seen in SLE include:

- Relapsing constitutional signs (e.g., fever, extreme fatigue, malaise, weight loss).
- Immune-induced *arthritis* (with swelling of the PIPs).
- Raynaud disease (repeated transient vascular spasms and ischemia, often precipitated by cold, which can result in ulceration and eventual necrosis of peripheral structures like the digits).
- Cutaneous rashes (includes heliotropic, erythematous maculopapular rashes in sun-exposed regions (e.g., the midface).
- Pulmonary fibrosis.
- Coronary artery disease.
- Pericarditis.
- Libman-Sacks endocarditis (a non-bacterial endocarditis resulting in thrombus formation and valvular dysfunction).
- Glomerulonephritis, renal failure.

Oral mucosal lesions in SLE may be encountered, especially during disease flareups. On occasion they can be among the initial physical findings in undiagnosed disease. The range of oral lesions in SLE include erythematous patches, especially along the gingiva and on the palatal mucosa; ulcerations that can be variably asymptomatic or painful; and clinically lichenoid lesions with white lacy, non-wipeable and erythematous or ulcerative components. Oral lesions favor the palatal and buccal mucosae but can be seen on other intraoral locations [61, 62, 66].

Histopathology

The histopathological findings in lichenoid oral SLE lesions demonstrate hyperkeratosis often with keratin-plugged surface invaginations or crypts; basal cell destruction; hyalinization (thickening); and a lichenoid (i.e., band-like) chronic inflammatory infiltrate at the epithelial-stromal interface and perivascular basement membrane zones. Direct immunofluorescence (D.I.F.) reveals speckled-appearing positivity for IgG and C3 at the epithelial-stromal basement membrane zone indicative of tissue-bound immune complex deposition [48, 49, 61] (Fig. 17.15a–c).

In contrast to SLE, **chronic cutaneous (discoid) lupus erythematosus (DLE)** is an exclusively mucocutaneous condition with skin involvement predominantly. Affected patients may exhibit concomitant oral mucosal lesions or develop such lesions at a later time, but are otherwise systemically well. However, in some instances DLE can precede the onset of SLE.

Cutaneous lesions of DLE are most prominent on exposed skin, most especially the facial skin, the scalp, the pinnae of the ears, and vermilion borders of the lips. They present as round or ovoid, scaly, erythematous plaques with or without ulceration. The lesions also may demonstrate central depigmentation and scarring with hyperpigmented borders. Scalp lesions often present in association with focal alopecia.

Oral mucosal DLE lesions are seen in about 25% of affected patients. They are clinically reminiscent of LP

lesions, presenting with white, keratotic striations or plaques, erythema, occasionally erosive changes, and hyperpigmented borders. Favored sites are the buccal mucosa, the palate and the gingivae (Fig. 17.15d, e, f).

Like SLE, DLE is attributable to both type 2 and type 3 hypersensitivity [46]. However, in contrast to SLE, serology in DLE is inconsistent or frankly negative for circulating antibodies [61].

Histopathology

Oral mucosal biopsies reveal findings similar to those described above for SLE, on both conventional and D.I.F. microscopic analyses. Both demonstrate tissue bound immune reactants at vascular and epithelial-stromal basement membranes [49, 61, 62] (Fig. 17.15c).

Benign Migratory Glossitis ("Geographic Tongue"; Erythema Migrans)

Benign migratory glossitis (BMG, "geographic tongue," erythema migrans) is one of the most frequently encountered benign conditions affecting the lingual mucosa. For that reason alone, it is an important entity to recognize in all its various presentations. Among BMG's key characteristics is its tendency to migrate to different locations on the tongue at different times. It is also a transient phenomenon: lesions often change in appearance frequently, just as they appear and disappear inexplicably. Thus, there may be times when there is no clinical evidence of the condition, such that the surface of the tongue appears essentially unremarkable.

The underlying etiology and pathogenesis of BMG are unknown. The condition is frequently associated with fissured tongue. Both fissuring and BMG are sufficiently common that they are considered variants of normal lingual mucosal anatomy [67–69].

The patterns of BMG's presentation are distinctive, thereby making it readily recognizable. Typical locations of involvement are the dorsal and lateral lingual surfaces. Individual lesions may appear annular (ring-like), crescentic, or as serpiginous (serpentine) undulations, with erythematous or mucosa-color centers that are often bordered by white, non-wipeable keratotic margins. The erythema is attributable to transient focal atrophy of filiform papillae (i.e., depapillation). An important and consistent feature is each affected site's strikingly sharp demarcation from the adjacent normal-appearing lingual surface. The composite features of BMG often confer a map-like appearance to the mucosal surface (thus BMG's other descriptive name, "geographic tongue") (Fig. 17.16a–d). At any time, the number of BMG foci and the extent of lingual mucosal involvement in a single patient can vary considerably.

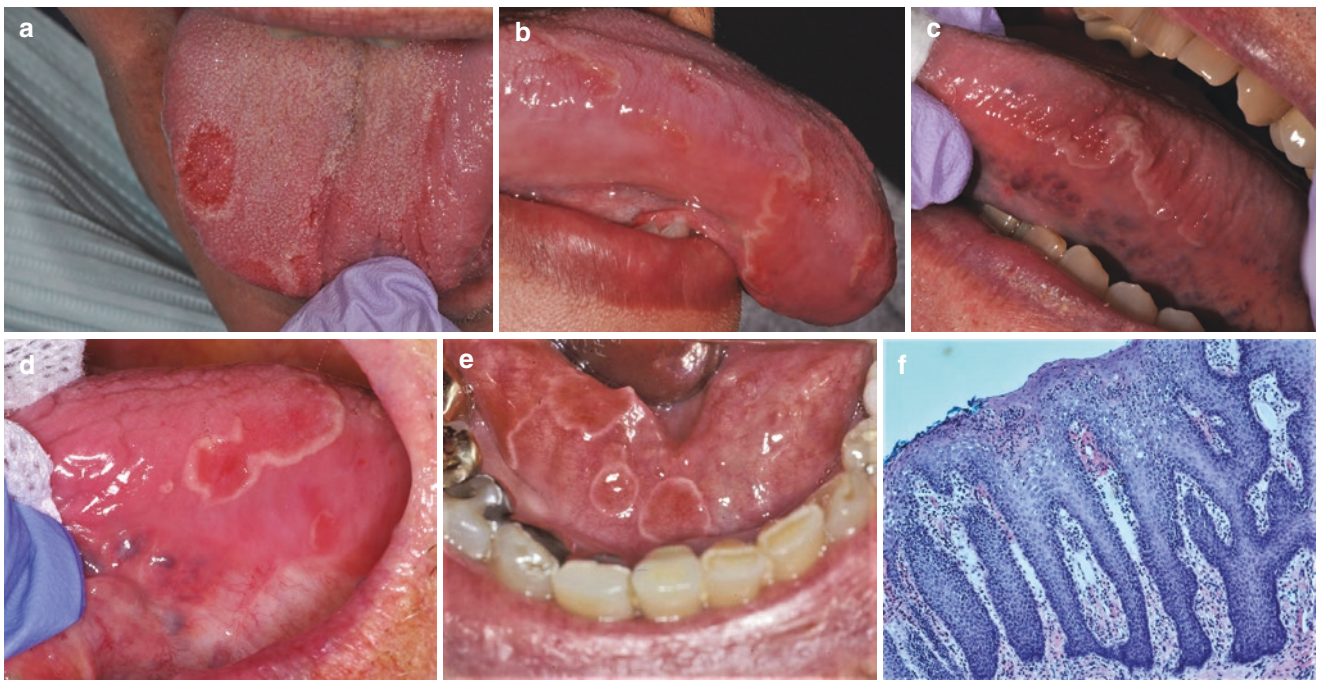


Fig. 17.16 Benign migratory glossitis (Geographic tongue). (**a–d**) Various clinical phenotypes of geographic tongue. Annular, serpiginous and arcuate patterns. (**e**) Erythema migrans (ectopic geographic tongue) on sublingual folds in floor of mouth. (**f**) Psoriasiform hyperplasia of the epithelium (elongated rete pegs), normal maturation. Microabscesses are seen in the stratum superficiale and upper stratum spinosum. Chronic inflammatory infiltrates and vascular dilatation are seen within the lamina propria (H & E ×40)

In the vast majority of affected patients, BMG is completely asymptomatic and treatment is unnecessary. In a small percentage of cases where filiform papillary atrophy is extensive, there may be temporary sensitivity to spicy or acidic foods or liquids. Natural fissures on the tongue surface obscured by a normal complement of filiform papillae may become more obvious in foci of BMG where the lingual surface is relatively thin due to transient filiform papillary atrophy. Occasionally patients will report sensitivity in these areas. It is essential to keep in mind that symptoms tend to be transient, and that there is no "cure" per se for BMG. Symptoms should be managed conservatively, by avoidance of aggravating triggers (e.g., spicy or acidic foods and liquids). Palliative rinses like dilute salt in water or baking soda in water or available over-the-counter topical analgesic oral care products can be soothing. Some recommend application of topical steroid ointment for treatment of symptomatic geographic tongue [67, 70]. However, corticosteroids, topical or systemic, should be avoided, as they can encourage further oral mucosal atrophy, only serving to compound a pre-existing problem [71].

Erythema Migrans ("Ectopic Geographic Tongue")

The term erythema migrans is another synonym for BMG, but it more often refers to a variation on the theme of BMG. Similar to the tongue lesions described above, erythema migrans describes well-demarcated, asymptomatic red, or red and white, annular or crescentic lesions on oral mucosal locations other than the tongue (e.g., floor of mouth, buccal and labial mucosa, soft palate) (Fig. 17.16e). Importantly, recognizing the lesions' patterns and appearance as clinically reminiscent of BMG is usually sufficient for diagnosis. However, in cases where the clinical diagnosis is uncertain, biopsy will reveal characteristic histopathologic features for diagnostic confirmation [67].

Histopathology

Biopsy is rarely necessary in most cases of BMG, because the diagnosis can be made presumptively and with confidence on clinical and historical grounds. However, if there is diagnostic concern about a red or red and white lesion on the tongue or anywhere else in the oral cavity, biopsy is an option for ruling out epithelial dysplasia and other possible pathological entities. Classic histopathological features of BMG and erythema migrans mimic those seen in biopsies of psoriasis, a cutaneous keratodermatosis. There is psoriasiform epithelial hyperplasia, hyperparakeratosis, elongated, slender rete pegs often with spongiosis, and notable microabscesses in the subcorneal upper portion of the stratum spinosum. Chronic inflammatory infiltrates are present in the papillary lamina propria and migrate into the epithelium (Fig. 17.16f). It is well to note that despite their resemblance to psoriasis at the microscopic level, both BMG and erythema migrans are separate and distinct from psoriasis, a cutaneous disease. Therefore, diagnosis of either BMG or erythema migrans should neither imply that a patient has psoriasis, nor does it predict that psoriasis is likely to develop, or vice versa. The occurrence of BMG or erythema migrans in a patient with psoriasis is coincidental [67, 72].

Wipeable White Plaques (Non-Keratotic White Oral Lesions)

White lesions that can be wiped away with a gauze sponge or a tongue blade consist of surface debris. Common examples include:

- Necrotic coagulum of thermally or chemically burned surface epithelium (e.g. aspirin burn)
- Collapsed roof of a bulla
- Fibrinopurulent pseudomembrane covering an ulcer base
- Pseudomembranous candidal colonies (Discussion and Table-see below)
- Accretions of nonspecific debris (including white coating on dorsal surface of tongue) [73]

Oral Candidiasis

Candida is a dimorphic fungus that exists in spore (yeast) and hyphal forms. Part of the normal oral flora, several candida species normally colonize the oral cavity in a clinically silent, commensal relationship with their host. This relationship is harmonious: it is not an example of fungal infection, because the interaction between the microorganism and its host has not altered the host in any way, nor has it resulted in harm to the host's living cells and tissues.

A number of local and systemic factors can upset the host-microbe equilibrium, rendering the host susceptible to opportunistic mycotic infection, mostly with *Candida albicans* (Box 17.8). Most oral candidal infections (candidiasis) are superficial affectations of the mucosal epithelium and/or perioral skin. In patients who are significantly immune-compromised, immune-depleted or otherwise debilitated (e.g., HIV/AIDS, patients deliberately immunosuppressed for organ or stem cell transplantation), candida infections can extend into the gastrointestinal and respiratory tracts and involve other visceral organs [74–78].

Box 17.8 Oral Candidiasis: Predisposing Factors

- Disequilibrium in balance of oral flora 2° to antibiotic treatment.
- Immunologic immaturity (infants).
- Local or systemic *immune dysregulation* 2° to disease, therapy, etc.
- Chronically *(true)* dry mouth; chronic wetting/drying of lips.
- *Anticholinergic* medications.
- Poor denture hygiene.
- Endocrinopathy (e.g., diabetes).

Oral candidiasis can present with a spectrum of possible features. What is important to bear in mind is that the clinical findings in candidiasis (i.e., infection) are distributed multifocally throughout the oral cavity, rather than confined to a single location.

The **four major phenotypic presentations of oral candidiasis** (Table 17.4) are as follows [73, 74]:

1. The **pseudomembranous** ("thrush") **type** is probably the most widely recognized presentation, characterized by white, wipeable curd-like accretions on an erythematous background (Fig. 17.17a). When they are undisturbed the white accretions are asymptomatic; however, once they are wiped away, leaving erythema, erosion or ulceration, the patient may complain of pain. The exfoliated white material can be stained with KOH and examined under the microscope for cytologic evaluation. Disclosure of fungal hyphae entangled with desquamated keratotic debris will confirm the clinical diagnostic impression (Fig. 17.17b).
2. The **erythematous** (atrophic) **type** appears as diffuse redness and atrophy that is usually distributed widely on multiple oral sites. This presentation is most striking on the dorsal surface of the tongue where atrophy of the filiform papillae renders the normally papillated surface smooth. The extent of papillary atrophy can vary: it may be extensive and diffuse, or focal and discrete. (**"median rhomboid glossitis"** a depapillated, sharply defined erythematous patch on the mid-dorsal tongue is an example of the latter focal presentation of erythematous oral candidiasis.) Atrophic tongue involvement is often accompanied by diffuse erythema on the hard palatal mucosa, directly opposite the dorsal tongue (Fig. 17.17c, d).

   Denture stomatitis (denture sore mouth) refers to what is presumed by many to be chronic erythematous (atrophic) candidiasis (but more likely, colonization by a spectrum of microbes rather than actual candidal infection) that develops in some patients who wear poor-fitting and/or inadequately cleansed removeable maxillary dentures. Poorly controlled diabetics, and especially those patients who habitually fail to remove their maxillary prosthesis at bedtime and wear it to sleep, are particularly prone to this condition [74, 79, 80]. The mucosal surface appears bright red, pebbly, or velvety; the affected area conforms to the shape of the denture base. The classic locations are the hard palatal and edentulous maxillary alveolar crestal mucosa. The mandible is not similarly affected (Fig. 17.17e). Diagnosis of erythematous candidiasis can be confirmed with culture on Sabouraud agar, rather than by cytologic smear [74].
3. **Angular cheilitis (*perleche*)** is almost always partly attributable to or complicated by candidal infection. The commissures of the lips appear chronically erythematous; they may be cracked, fissured, and crusty. The patient frequently reports discomfort or bleeding at the corners of the lips on opening the mouth. This form of candidal infection may be initiated by reduced occlusal vertical dimension either from loss of posterior teeth, failure to replace missing posterior teeth, or wearing down of denture teeth leading to collapse and deep cutaneous fissuring at the labial commissures, often extending inferiorly on the facial skin (Fig. 17.17d). Another source is a tendency in some patients to habitually lick the corners of the lips: the frequent wetting/drying cycle results in tissue disruption (i.e., cracking, fissuring) at the commissures. Oral secretions that accumulate in these cracks and fissures are colonized by fungal microorganisms that now find a ready portal of entry. The result is a candidal

Table 17.4 Phenotypic presentations[a] (types) of oral candidal infections

Type	Clinical/laboratory features
Pseudomembranous ("thrush")	• White, wipeable, curd-like accretions on erythematous mucosal background
	• Cytological smear reveals fungal hyphae, spores
Erythematous ("atrophic")	• Diffusely erythematous, atrophic surface, ± symptomatic
	• Often associated with chronic true oral dryness
	• Cytological smears contraindicated
	• Fungal culture (Sabouraud medium) + for candida
Angular cheilitis ("*perleche*")	• Crusting, erythematous, fissured labial commissures
	• Fungal culture (Sabouraud medium) + for candida
	• Streptococci, staphylococci + on bacterial cultures
Chronic hyperplastic ("candidal leukoplakia")	• Non-wipeable white, rough or pebbly-appearing plaques
	• ± Accompanied by other candidal clinical types
	• Diagnosis clinically indeterminate
	• Biopsy—abundant hyphae, spores within surface keratin

[a] Combinations of any and all types can be present in an individual episode of oral candidal infection

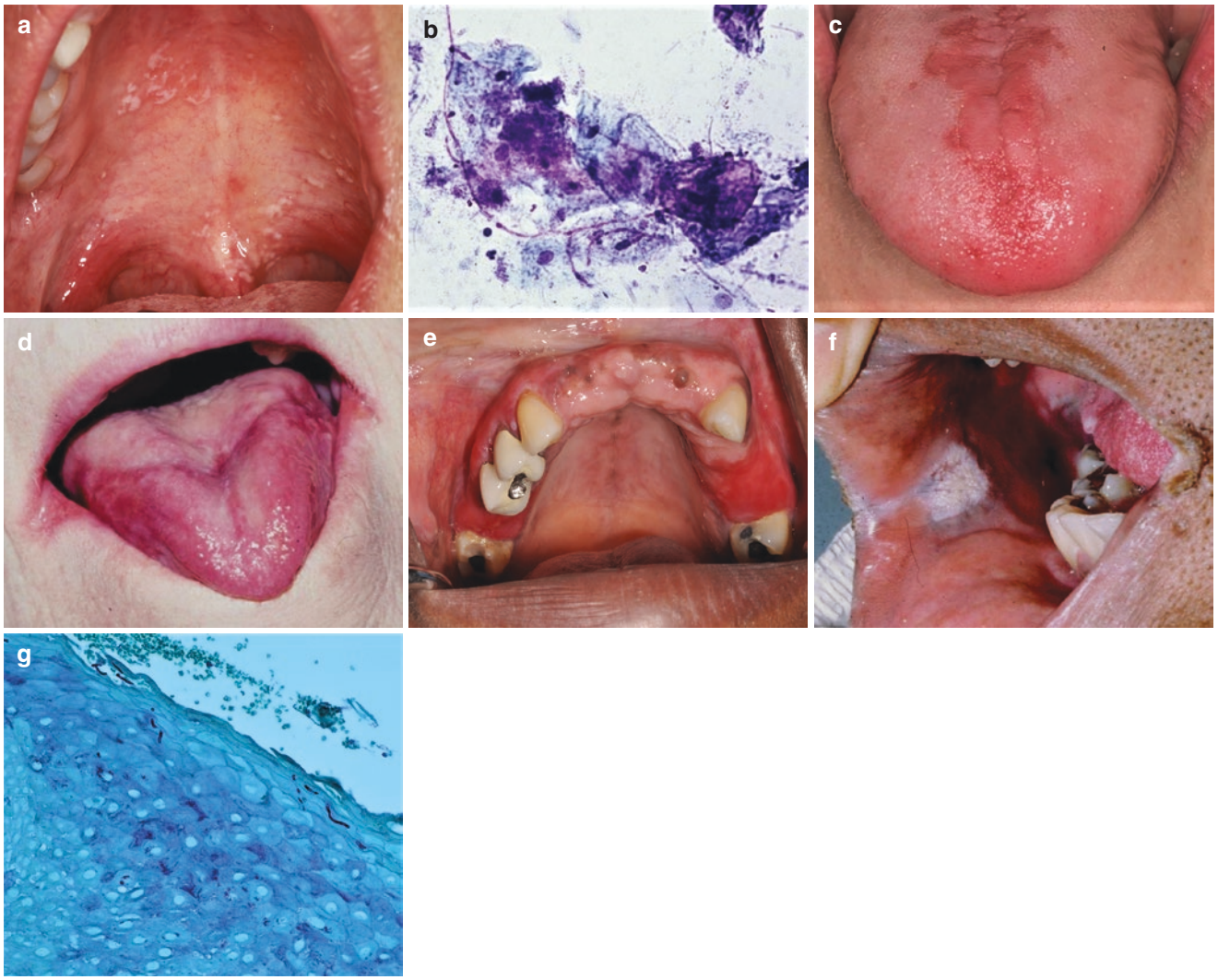


Fig. 17.17 Candidiasis. (**a**) Pseudomembranous candidiasis ("Thrush" phenotype). White, curd-like plaques can be wiped away. (**b**) Cytologic smear demonstrates candidal hyphae among desquamated epithelial cells. (KOH stain). (**c**) Erythematous (atrophic) form. On oral examination the erythema and atrophy of filiform papillae on the dorsal surface of the tongue (an example of "median rhomboid glossitis") were accompanied by other erythematous foci and pseudomembranous forms of candidiasis. (**d**) Angular cheilitis. Erythema and cracking at the commissures of the lips is another phenotypic manifestation of candidiasis in this elderly woman with a markedly dry mouth. Also note the atrophy and erythema of the filiform papillae on the anterior dorsal one third of the tongue. (**e**) Erythema on the removable partial denture-bearing maxillary alveolar ridges and extending into the buccal vestibules. Denture stomatitis ("denture sore mouth") may be a manifestation of erythematous candidiasis or a reaction to multi-microbial colonization in some patients who rarely remove or cleanse their maxillary prosthesis. (**f**) Chronic hyperplastic candidiasis. White, rough non-wipeable plaque was biopsied and revealed epithelial hyperplasia with candidal hyphae in the stratum superficiale and stratum spinosum. (**g**) Candidal hyphae in hyperplastic candidiasis appear vermiform within the keratin layer. (Gomori methenamine silver (GMS) ×60)

("yeast") infection. Impetiginization with *Staphylococcus aureus* (superficial bacterial infection with fissuring, erythema and amber color crusts) in addition to candidiasis may complicate angular cheilitis.

4. The least commonly encountered oral candidal phenotype is aptly termed **chronic hyperplastic candidiasis ("candidal leukoplakia").** In this presentation, the lesions appear as thick, pebbly or shaggy white, non-wipeable mucosal plaques, occasionally accompanied by erythema (Fig. 17.17f). The location of the plaques may vary, but the diagnosis cannot be made clinically. Therefore, biopsy is necessary to determine the diagnosis. On histopathological examination, abundant fungal hyphae penetrate the keratin layer, often accompanied by acute inflammatory cells (Fig. 17.17g). The squamous epithelium is hyperplastic, psoriasiform, and often exhibits a degree of cytologic atypia. The epithelial atypia here is reactive and benign in nature, and not an unusual finding in the setting of fungal infection. There is chronic inflammation within the underlying lamina propria.

Any attempts at treatment with antifungal topical or systemic agents must also call for identification of the underlying factor or factors that predisposed the patient to candidiasis initially. In cases of denture-associated candidiasis, "treatment" of the denture itself with antifungal or very dilute bleach solution is indicated [76, 81].

It is also important to reiterate that if only a single location in the oral cavity exhibits white, wipeable material, oral candidal infection is not likely. Frequent cumulations of debris on oral mucosal or tooth surfaces, or both, may be an indication of inadequate quality or quantity of salivary secretions. Clinically evident oral dryness may be attributable to inadequate daily plain water intake, anticholinergic medications, or a diverse range of possible factors, including immune-mediated systemic conditions with negative effects on exocrine glandular secretions.

Other Wipeable White Lesions

Non-specific Debris

Non-specific debris that settles and accumulates on the mucosal surface can be wiped away with either a tongue blade, gauze, or finger pressure, revealing essentially intact normal color mucosa underneath.

The abundant filiform papillae on the dorsal surface of the tongue constantly capture debris (e.g., keratotic debris, mucus, other non-specific debris) throughout the day and during sleep. However, the amassed material is naturally debrided and swallowed whenever the patient eats and drinks liquids. However, in patients who do not eat or drink for extended periods of time (e.g., fasting for many hours, skipping meals by choice or because severe oral pain makes it difficult to eat and drink for many hours or days), the debris remains stagnant, and the dorsal tongue develops a white coating. *White-coated tongue* is often mistaken for pseudomembranous candidiasis, so that many patients are prescribed antifungal treatments unnecessarily (Fig. 17.18a). However, the history and the solitary presentation of whiteness on the dorsal tongue but nowhere else in the mouth should militate against a diagnosis of candidiasis. Once a regular dietary schedule is resumed, the white coating disappears relatively expeditiously.

Filiform papillae can undergo hyperplasia under a variety of circumstances. One of them is through overuse of oxidizing mouthrinses (e.g., frequent rinsing with hydrogen peroxide). Innocuous dark-staining bacterial waste products, coffee, tea, and tobacco can also stain hyperplastic filiform papillae, or a white coating of debris, in shades of tan, yellow, brown, or black (Fig. 17.18b).

Necrotic White Lesions

Caustic chemicals, therapeutic or otherwise, applied directly to the oral mucosa can burn the epithelium leaving a white or yellow-white, wipeable coagulum that can be wiped away, leaving a red, raw, and often painful exposure of the submucosa (Fig. 17.19a, b). As an example, aspirin (acetylsalicylic acid) tablets placed directly on the oral mucosa in close apposition to a painful tooth or gingival lesion will dissolve and diffuse in all directions. At the epicenter of the tablet's placement, there will be a white, fragile membrane that can

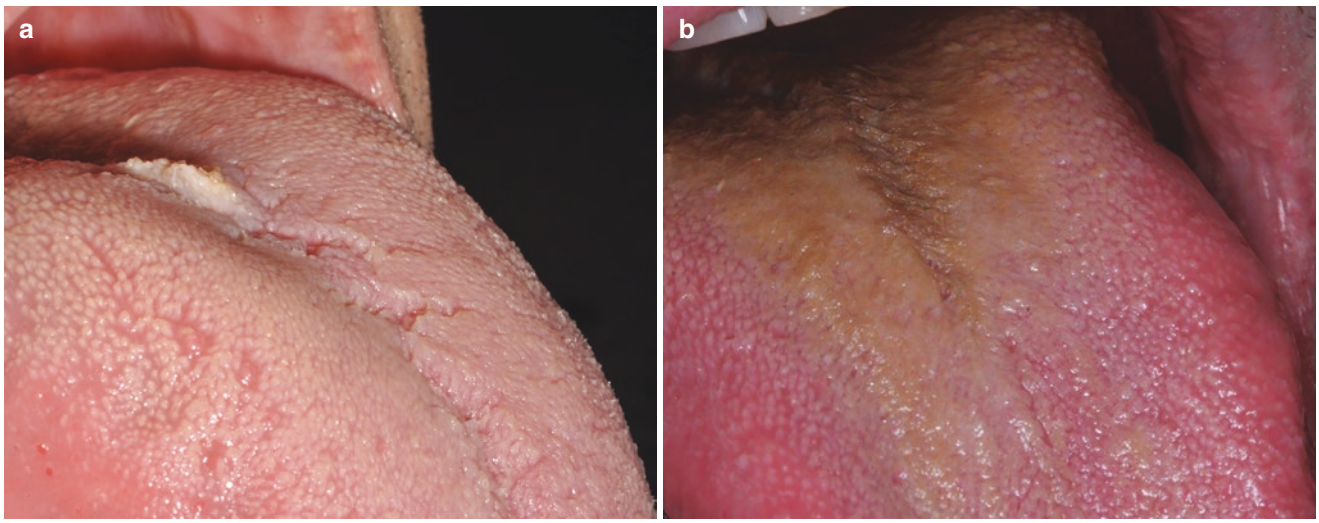


Fig. 17.18 Nonspecific debris; Black hairy tongue. (**a**) White coated tongue with hyperplastic filiform papillae that retain nonspecific debris. Patient habitually eats only a single daily meal in the evening. (**b**) Black hairy tongue. The patient is a smoker and heavy coffee drinker. He has been rinsing the mouth several times daily with hydrogen peroxide in water. Hyperplastic filiform papillae are extrinsically-stained yellow-brown

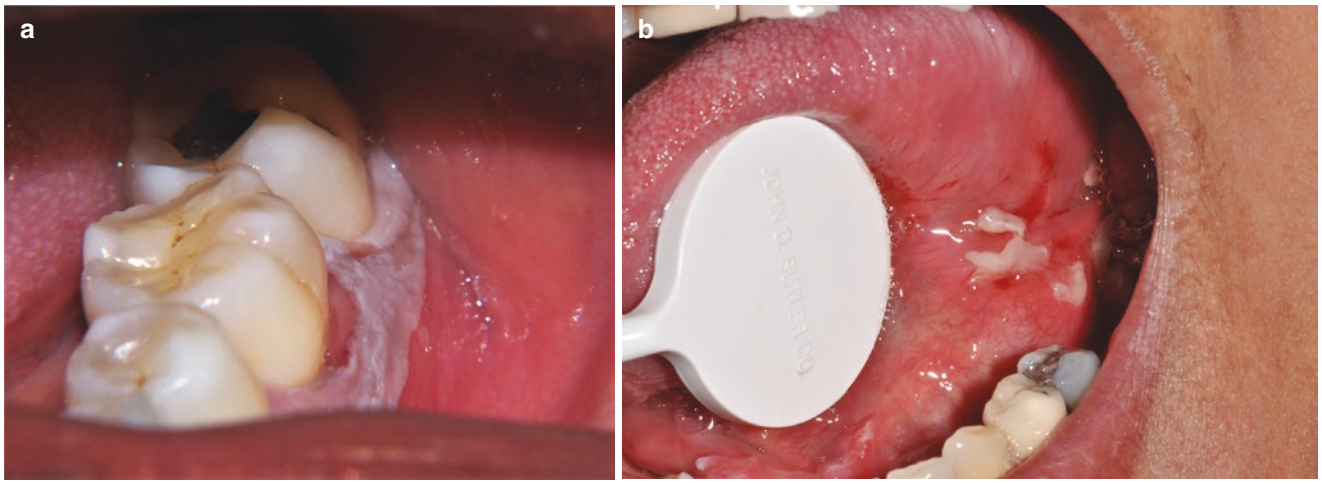


Fig. 17.19 Necrotic white lesions. (**a**) Painful white, wipeable necrotic lesion, buccal gingiva. Patient had applied a caustic home remedy repeatedly to the tissue adjacent to painful molar tooth. (**b**) Pemphigus vulgaris, positive Nikolsky sign. Necrotic surface epithelium had been the roof of a vesiculobullous lesion, lateral-ventral tongue. Note the intensely erythematous stroma exposed following desquamation

be readily stripped away exposing the painful, erythematous submucosal tissue. Other caustic chemical agents, including those intended for therapeutic purposes (e.g., some mouthwashes with phenol or alcohol), when applied directly and repeatedly to the oral mucosa, can also result in epithelial necrosis, ulceration, and pain.

Necrotic collapsed blister roof epithelium of a vesiculobullous oral lesion will also appear white and is wipeable.

Red Oral Lesions

Redness of the oral mucosa is usually attributable to:

1. Increased stromal vascularity.
2. Vascular dilatation (ectasia), congestion.
3. Fresh submucosal hemorrhage—macular, diffuse or pinpoint (petechial).
4. Reduction in width (atrophy) of the surface epithelium overlying the stromal vasculature.
5. Frank disruption (ulceration or erosion) of the integrity of the mucosal epithelium.

Benign, Reactive Erythematous Masses

This subject is also covered in Chap. 16 that addresses "Benign Lumps and Bumps." Readers are encouraged to visit that chapter for additional information on this topic.

Inflammatory responses as a consequence of traumatic injury or infection recruit richly fibrovascular granulation tissue to the site of tissue damage. Granulation tissue plays a critical role in the resolution and repair of tissue injuries and surgical wounds. Its young endothelial cells-lined vascular channels bring essential nutrients and oxygen to the site of injury, remove debris and, along with fibroblasts that elaborate collagen, serve as a matrix for restoration of tissue integrity, or replacement of damaged tissue by fibrous scar tissue.

Pyogenic Granuloma

Pyogenic granulomas are reactive (non-neoplastic) masses of exuberant, hyperplastic granulation tissue that can arise anywhere on the skin or oral mucosa in foci of chronic inflammatory stimulation. In the oral cavity, they are most often (but certainly not exclusively) encountered on the gingiva, especially in locations where there is plaque accumulation or periodontal pocketing. Occasionally, exuberant granulation tissue indistinguishable from pyogenic granuloma will extrude from a recent extraction site. This is often the case when there is osseous debris, a residual tooth fragment or other foreign material left within the post-extraction socket. Similarly, chronic hyperplastic pulpitis (*pulp polyp*) is an exuberant granulation tissue mass that arises in dental pulpal tissue that has been exposed through a large open carious lesion in the crown of a tooth. The "polyp" emerges from the open, cavitated pulp chamber as an exophytic erythematous or pink mass. Pulp polyps are not common; they tend to be seen more often in children than in adults.

Histopathology of pyogenic granuloma and its analogues, as described above, reveals an exophytic, either sessile or polypoid ulcerated mass of edematous fibrovascular granulation tissue with chronic or mixed inflammatory infiltration. The ulcer is usually surfaced by a fibrinopurulent pseudomembrane, and the marginal surface epithelium may be hyperplastic. It is interesting to note that even a pulp polyp demonstrates stratified squamous epithelium at the margins of the ulcer at its surface.

Peripheral Giant Cell Granuloma

Another specific example of an exuberant, hyperplastic granulation tissue mass is the peripheral giant cell granuloma (PGCG). PGCGs are located exclusively on the gingiva. In many instances, PGCGs are clinically indistinguishable from gingival pyogenic granulomas, and usually arise under circumstances similar to those associated with gingival pyogenic granulomas, in response to local irritants.

Definitive diagnosis of a peripheral giant cell granuloma is rendered on the basis of histopathological findings. Microscopy reveals numerous benign multinucleated giant cells reminiscent of osteoclasts widely distributed within a granulation tissue background. Often, there are extravasated erythrocytes and hemosiderin within the vascular granulation tissue stroma. The surface of the mass may or may not be ulcerated.

Appropriate management of these exuberant granulation tissue hyperplasias is twofold, and similar to the management of pyogenic granulomas: complete excision of the mass and eradication of the presumed irritant. Should the irritant persist or return, the lesion may recur.

Denture-Related Hyperplasia (Epulis Fissuratum, Inflammatory Papillary Hyperplasia, IPH)

Benign inflammatory tissue reactions (*Epulis fissuratum, inflammatory papillary hyperplasia*) can develop on the mucosal tissue surfaces (alveolar ridge, palatal mucosa, the labial, buccal and mandibular vestibules) that underlie and support removable dentures. These responses most often arise in patients who wear a removable partial denture or a complete denture prosthesis for extended periods of time, sometimes months or years. History often reveals that the denture has not been routinely removed for cleansing on a daily basis, or that the patient habitually wears the denture to bed, thus failing to allow the mucosal tissues to rest overnight. Maxillary removable prostheses tend to fit with greater retention, stability, and comfort than mandibular dentures. They also are more noticeable than mandibular dentures from a cosmetic standpoint. For those reasons, some patients tend to continue to wear their maxillary complete or partial dentures for protracted periods of time, even when the prostheses are old and ideally should be relined or replaced by a new prosthesis; and even when they no longer wear an unstable lower removable denture.

Epulis Fissuratum

The constant up-and-down and side-to-side movement of an ill-fitting, unstable, poorly-fitting denture mechanically stimulates the tissues it rests upon to produce flabby, folded ("fissured"), hyperplastic soft tissue masses in the vestibules and over the edentulous ridges. These mucosa colored or erythematous masses are called *epulis* ("on the gingiva") *fissuratum*, a term that perfectly describes their clinical features. The folds often capture superficial debris. To construct a better-fitting denture, epulis fissuratum must first be surgically excised.

Histopathology reveals bulky, mucosal masses, possibly with a surface invagination (equivalent to a clinical fissure) demonstrating exuberant squamous epithelial and fibrous hyperplasia, with varying degrees of chronic inflammatory infiltration. There may or may not be ulceration at the fissure's base.

Inflammatory Papillary Hyperplasia (IPH)

Clinically, inflammatory papillary hyperplasia presents as asymptomatic erythema, often with a noticeably pebbly texture, that conforms precisely to the shape of the ill-fitting or rarely removed denture base or therapeutic appliance (e.g., orthodontic retainer or bite plate, nightguard) that rests on the oral mucosa. IPH typically is seen on tissues that support maxillary prostheses or appliances, specifically the hard palatal mucosa and/or edentulous portions of the maxillary alveolar ridge. There is no need to surgically remove the IPH, unless there has been considerable fibrosis which could complicate construction of a better-fitting prosthesis.

At the microscope, IPH exhibits a papillary epithelial surface configuration with underlying fibrous hyperplasia. There is a robust chronic inflammatory infiltrate within the lamina propria that has an obvious granulation tissue component. In composite, this accounts for the characteristic pebbly, erythematous clinical appearance.

It is well to note that IPH and *denture sore mouth* are not one and the same entity (please refer back to our discussion of erythematous candidiasis, above). While in some cases there can be superficial candidal colonization of IPH (and/or epulis fissuratum), colonization alone does not fulfill the criteria for actual fungal infection (i.e., actual interaction with and alteration of living cells, tissues), nor is it to be construed as the primary etiology of either of these benign, reactive prosthesis-related conditions.

Hemangiomas Versus Varicosities

Benign vascular neoplasms (hemangiomas) can arise anywhere in either oral soft tissue or less commonly, within the jawbone. In the oral mucosa, they present as red, purple, or bluish papules or masses, depending on the composition, caliber and depth of the vessels comprising the neoplastic proliferation [82]. Mostly consisting of venous channels, or

capillaries, or a combination of both (or less commonly, arteriolar vessels accompanied by venous channels), oral mucosal hemangiomas may appear macular but more often they present as exophytic uni- or multinodular, grape-like surface configurations. These benign vascular neoplasms can vary in size considerably from just a few millimeters to several centimeters. Occasionally, what can be seen clinically may be the only the "tip of the iceberg," if the hemangioma involves much deeper submucosal tissues or underlying bone (Fig. 17.20a, b).

By contrast, oral varicosities are relatively superficial painless, dilated, thin-walled, tortuous venous channels whose walls have lost elasticity. They are encountered more commonly in older adults. They present as raised, bluish or purple nodules or papules with a smooth surface, and with a predilection for the lips, the sublingual region, the posterior-lateral and ventral tongue, and the anterior floor of the mouth [83] (Fig. 17.20c, d).

Histopathologic examination is often necessary for distinguishing hemangiomas from varicosities. The benign vascular neoplasms tend to be discrete, sometimes encapsulated aggregates of vascular channels of varying size, often with blood in their lumens. They are occasionally accompanied by lymphatic channels; in such cases they are best referred to as lymph-hemangiomas.

In contrast to hemangiomas, which can be located either in the superficial stroma or within deeper submucosa occasionally with extension into underlying muscle, varicosities are more superficial. They appear as one or more dilated, thin-walled, blood-filled veins often with evidence of an organizing thrombus in the process of recanalization [84] (Fig. 17.20e).

Erythema Due to Erosion, Ulceration, and Atrophy

Inflammatory and infectious processes and most mucocutaneous immune-mediated conditions and responses present clinically with mucosal erythema of varying degrees. This is often due to epithelial disruption that either originates at the interface between the superficial lamina propria and the basal most epithelial cells (as seen in lichen planus and lichenoid stomatitides) or at or below the basement membrane zone (as seen, for example, in antibody-mediated disruption that occurs in the pemphigoid group of diseases), or as a product of intraepithelial dyshesion (acantholysis). Some examples of conditions featuring acantholysis include the pemphigus group of vesiculo-bullous mucocutaneous diseases (e.g., pemphigus vulgaris, which most often affects the oral mucosa) and the alpha group of human herpesvirus (HHV) infections (Herpes simplex virus 1 and 2 [HSV/HHV-1 and 2] and Varicella zoster virus, VZV/HHV-3). Occasionally acantholysis can be seen in epithelial dysplasia and in squamous cell carcinoma.

Repeated cycles of mucosal disruption and healing characteristic of chronic immune-mediated conditions like cicatricial pemphigoid and erosive lichenoid stomatitides often result in mucosal atrophy that presents as persistent erythema and fragility.

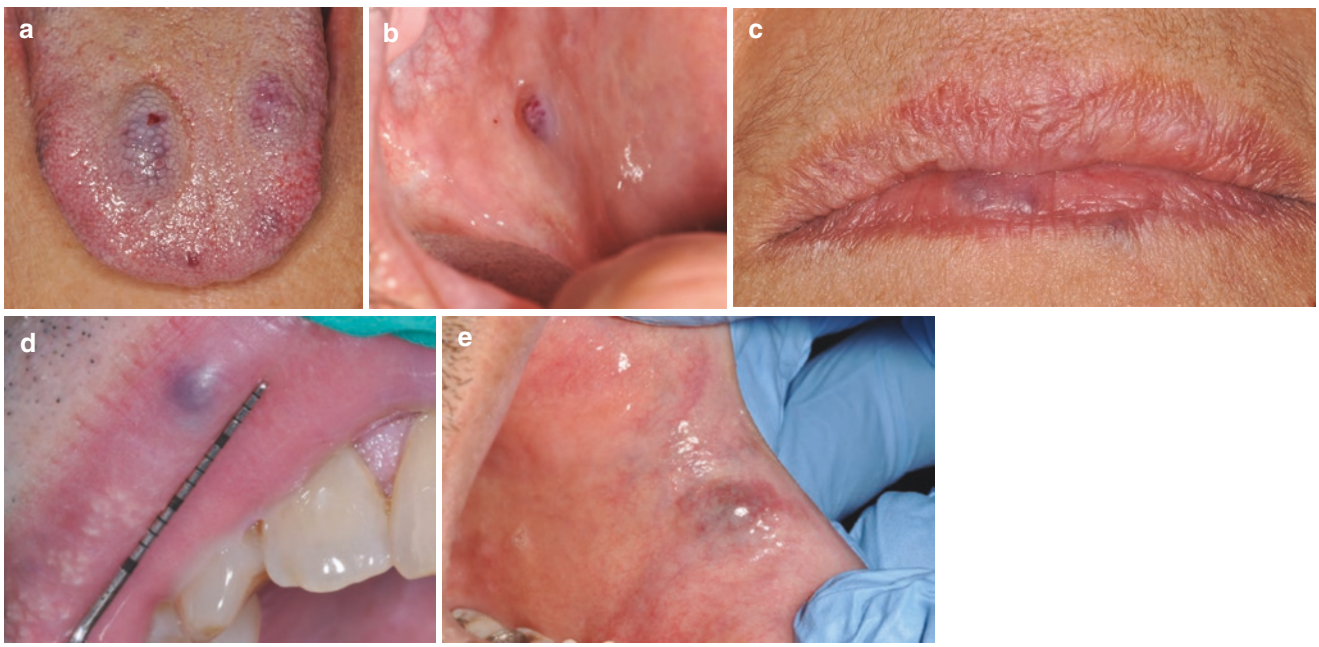


Fig. 17.20 Hemangioma, varicosities. (**a**) Large, deep venous hemangioma involving the anterior one third of the tongue. Raised, purple dome-like masses on dorsal and lateral tongue represent the "tip of the iceberg" as this vascular benign neoplasm infiltrated the underlying striated musculature. (**b**) Small hemangioma, left posterior buccal mucosa, discovered during routine oral examination. (**c–e**) Varicosities, biopsy confirmed. On lower lip vermilion border; upper vermilion-mucosal junction; and left anterior buccal mucosa

The immune-mediated vesiculobullous conditions and herpesvirus infections are discussed in detail in other chapters in this book. The lichenoid oral conditions are among the key immune-mediated mucocutaneous disorders that were discussed previously in this chapter.

As mentioned previously, **erythematous candidiasis** is also associated with atrophy of the filiform papillae. Of significance, over time, chronic true oral dryness due to inadequate quality and quantity of salivary secretions often results in atrophy of filiform papillae and erythematous lingual mucosa.

Anemia-Related Atrophy

Atrophy of the filiform papillae can occur in both iron-deficiency anemia and pernicious anemia [85, 86]. Iron deficiency anemia is not an uncommon phenomenon. It may be attributable to any of several possible scenarios: inadequate intake of dietary iron; impaired iron absorption in the gastrointestinal tract; chronic blood loss (e.g., menorrhagia, gastrointestinal bleeding); and during periods when there is an increased demand for iron, as in pregnancy and childhood.

Pernicious anemia involves a deficiency in vitamin B12 (extrinsic factor, "erythrocyte-maturing factor"), a nutrient essential for synthesis of DNA in rapidly dividing cells such as the bone marrow and the gastrointestinal tract. Parietal cells in the gastric mucosa are responsible for producing intrinsic factor, which complexes with vitamin B12 and is required for its transport across the intestinal mucosa. When there is a type 2 hypersensitivity immune attack on the parietal cells, intrinsic factor is lacking or inadequately produced, thereby disabling the absorption of vitamin B12 and resulting in pernicious anemia [46].

Erythema Multiforme

Erythema multiforme (EM) is an acute mucocutaneous reaction pattern that reflects combined type 3 and type 4 hypersensitivity reactions [46] triggered by an introduced precipitant. In susceptible patients, common precipitants include exposure to a recently introduced drug (prescribed, over-the-counter, or illicit); certain infections (Herpes simplex virus, mycoplasma, deep mycotic infections); selected immune-mediated conditions (e.g., lupus, polyarteritis, others); and selected malignancies (carcinomas, malignant lymphomas). Expeditious identification of the precipitant on initial presentation is one of the challenges EM poses. Recurrent episodes are likely if the offending agent is reintroduced, so that avoidance of the precipitant is critical. In previously affected patients, recurrent EM episodes can vary in terms of anatomic distribution, the spectrum of lesions manifested, and the intensity of symptoms [87, 88].

Pathogenesis

As indicated above, EM's pathogenesis is based in a cascade of types 3 and 4 immunologic responses to an introduced antigenic agent. The antigen becomes a component of circulating immune complexes that bind themselves to the walls of small vascular channels in the skin and mucosa. This instigates recruitment of CD4+ lymphocytes followed by CD8+ lymphocytes, which in turn results in release of lytic enzymes and TNF-α. The toxicity to epidermal and epithelial cells eventuates in epithelial cell necrosis.

In milder forms of EM that follow either primary Herpes simplex virus (HSV) infection or recurrent HSV outbreaks, similar pathogenetic mechanisms apply. However, in cases precipitated by herpesvirus, viral antigen-antibody complexes deposited in the vessels walls and keratinocytes of skin and mucosa initiate the cell-mediated immune reaction with recruitment of HSV-specific CD4+ lymphocytes that produce γ-interferon. The ensuing keratinocyte lysis in turn recruits NK T cells, with damage leading to necrosis of epithelial and epidermal cells [87, 89].

Histopathology

Diagnosis of EM is usually made on the basis of history and clinical findings. However, a biopsy obtained at a relatively early stage in the outbreak will reveal lymphocytic tagging at basement membranes, both perivascular and at the epidermal/epithelial-stromal interface. At later stages, biopsy reveals apoptosis of epidermal/epithelial cells, and epidermal/epithelial necrolysis that eventuates in ulceration from disruption of the epidermal/epithelial-stromal attachment [87, 88].

Clinical Manifestations

Manifestations of EM may range from relatively mild and limited to severe and generalized with widespread necrosis [89–91]. The clinical spectrum of EM is aptly described as polymorphous, with a wide range of possible lesions involving the skin or mucous membranes (Table 17.5), or a

Table 17.5 Erythema multiforme—cutaneous and oral mucosal clinical features

Cutaneous lesions	Mucous membrane lesions[a]
Erythema	Erythema
Vesicles, bullae; Nikolsky (+)	Vesicles, bullae; Nikolsky (+)
Ulcerations	Ulcerations, erosions
Target lesions	Hemorrhagic, scabbing lesions (lips)
Urticaria	Purpura
Purpura	

[a]Oral, nasal, conjunctival, anogenital

combination of both. A positive Nikolsky sign (i.e., epithelial or epidermal desquamation on lateral pressure) may or may not be featured.

One clinical manifestation that is frequently associated with EM is the so-called "target lesion," cutaneous lesions that resemble a bull's eye. The lesions consist of a central vesicle or bulla that ruptures and ulcerates, surrounded by a ring of erythema, which in turn is encircled by a wheal (hive), bounded by an erythematous border (Fig. 17.21a). Although target lesions are often considered the sine qua non of EM, they are among the many possible cutaneous manifestations of the condition that can present in a single episode. However, they are not necessarily a consistent finding. The absence of target lesions does not rule out EM if all other clinical-historical factors support that diagnostic impression.

Among the more impressive perioral manifestations of EM is involvement of the external lips. Painful swelling and ulceration with hemorrhagic crusting of the vermilion borders and perioral skin are considered classic features of EM, seen to some degree in many cases with oral involvement. Oral mucous membrane lesions of EM may start out as bullae that rapidly rupture leaving extensive painful ulcerations or sloughing erosions [87, 88, 91] (Fig. 17.21b–d).

The more severe forms of EM, Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) (precipitated by parenteral or otherwise systemically administered drugs), demonstrate widespread cutaneous and multiple mucous membranes involvement, accompanied by fever and malaise. SJS will occasionally require hospitalization for supportive care. In cases of TEN, the most extreme and potentially life-threatening presentation of EM, there is generalized cutaneous fragility and extensive sloughing of the skin and mucosa that requires hospitalization for significant medical intervention.

Clinical Differential Diagnosis

An important clinical differential diagnostic challenge may involve distinguishing between oral manifestations of EM and primary (acute) herpetic gingivostomatitis. While clinical history is paramount, in acute herpetic oral eruptions gingival erythema, ulceration, swelling and pain are consistently prominent features, whereas in EM, gingival involvement is usually minimal or altogether absent. In herpetic gingivostomatitis, lesions are intra- and perioral, whereas in EM, there may be accompanying cutaneous lesions on the extremities, trunk or back that the patient might not recognize as part of the presentation. Primary herpetic outbreaks are consistently accompanied by constitutional signs of systemic infection, whereas most outbreaks of EM usually are not.

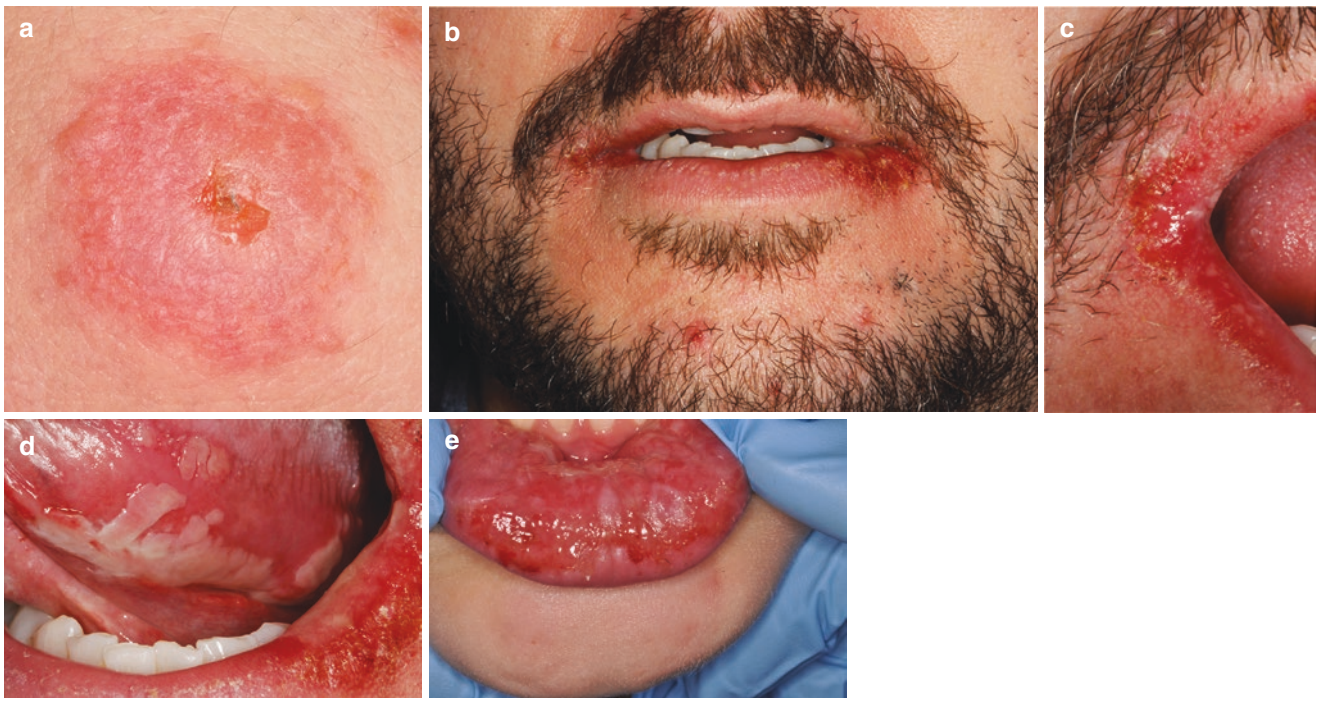


Fig. 17.21 Erythema multiforme. (**a**) Target lesion on the arm of a 32-year-old man with erythema multiforme. Ulceration resulted from rupture of central vesicle, surrounded concentrically by wheal and erythema. (**b–d**) Same 32-year-old man, erythema multiforme. Acute onset of painful oral mucosal lesions sparing only the gingiva. Crusty, ulcerated, hemorrhagic vermilion borders of lips with painful involvement of commissures. Painful ulcerations, ventral-lateral tongue; much of the remaining oral mucosa was similarly involved. (**e**) A 15-year-old boy with extensive painful ulcerations and erythema, lower labial mucosa. Similar findings were evident throughout the oral mucosa, with the exception of the gingiva

Management

Oral symptoms often render patients unable to tolerate foods or liquids. To pre-empt the possibility of dehydration, patients are advised to take in soft or pureed protein-rich food and to hydrate with water.

Oral presentations of minor forms of EM can be managed by elimination of the purported precipitant and applications of topical corticosteroid with or without a tapered systemic corticosteroid regimen of several weeks duration. For those cases of EM precipitated by herpesvirus infection, prophylactic systemic antiviral therapy is effective for preventing both reactivated viral outbreaks and subsequent episodes of EM [87–91].

In the most severe form of EM (TEN) where a considerable percentage of the body surface may have sloughed, patients are highly susceptible to both infection and negative nitrogen balance. This is an urgent medical status that requires hospitalization for intravenous administration of fluids, antibiotics, and immune modulators. SJS may require a similar approach to management, especially when cutaneous lesions are multifocal and multiple mucous membranes are involved. In such cases patients are vulnerable to infection, dehydration, and scarring. With severe conjunctival involvement, visual impairment is a potential complication unless appropriate professional intervention is initiated as early as possible [92].

Brown Oral Lesions

The overwhelming majority of brown-pigmented oral mucosal lesions are benign and harmless; far fewer have more ominous implications. A range of pathological processes that present themselves as brown lesions or discolorations on the oral mucosa derive from either endogenously-produced pigments, primarily melanin or hemoglobin; or from exogenously-introduced pigmented foreign materials or metabolic interactions with extrinsically-derived chemicals.

Hemorrhage

Following a traumatic incident resulting in submucosal hemorrhage, breakdown products of hemoglobin (hemosiderin, biliverdin, bilirubin) tend to remain for a period of time in the stromal interstitium, presenting clinically as ecchymoses or pinpoint-size petechiae. Discoloration from extravasated blood may range from red to green, blue-black or brown, depending on the length of time the hemorrhagic debris has been present and its depth within the submucosa. By several weeks post-hemorrhage, the mucosa will have reverted to normal color as the aging hemorrhagic debris is removed from the site of prior injury via the action of hemosiderin-laden macrophages (siderophages) and granulation tissue [93].

Foreign Material

Embedded foreign material, most notably dental amalgam, typically presents as a discrete gray-blue or black macule (Fig. 17.22a) or, less commonly as a papule (*amalgam tattoo*). A majority of amalgam tattoos are located in close proximity to a tooth that had had an amalgam restoration either removed by drilling or by drilling down an amalgam-restored tooth with a bur in preparation for a replacement restoration. During dental procedures that call for using a bur on a high-speed drilling instrument, micro-breaches in the adjacent mucosa may be inadvertently created when the bur nicks the adjacent soft tissue. These iatrogenic breaks in the integrity of the mucosa permit amalgam particles carried by the flutes of the drilling bur to be implanted directly into the stroma where they remain in an innocuous, inert, tissue-compatible state, permanently (Fig. 17.22b, c). Similarly,

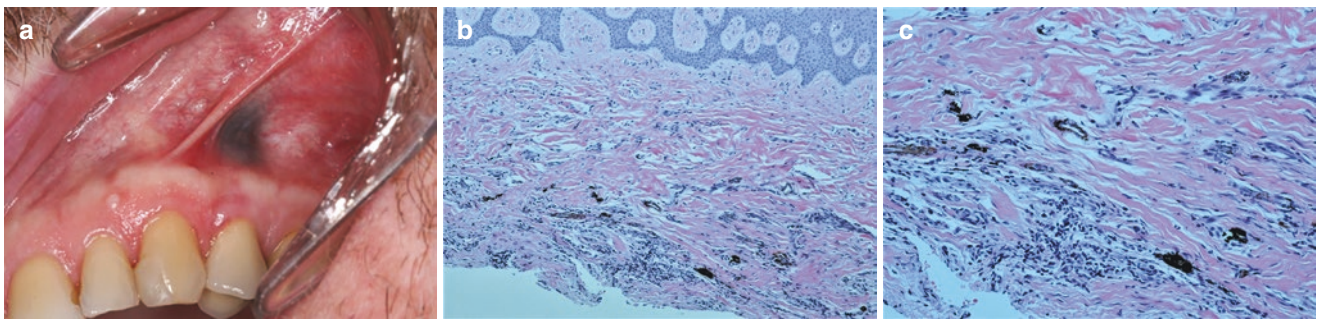


Fig. 17.22 Amalgam tattoo. (**a**) Amalgam tattoo, left maxillary buccal vestibule, first premolar area. Asymptomatic, discrete gray-blue macule. The adjacent tooth had been restored previously with amalgam, but the patient wanted the amalgam removed and replaced with a composite restoration for purely cosmetic purposes. (**b**) Black-brown particulate matter aggregates around vascular channels in the deep stroma (H&E ×20). (**c**) Higher magnification (H&E ×40)

graphite introduced into oral mucosa from traumatic injury (e.g., pencil chewing or stabbing) will result in a permanent tissue-compatible black or blue macule [94–97]. On clinical grounds alone it may not always be possible to determine either the source or the nature of a black, blue or brown lesion definitively without obtaining a biopsy for histopathological examination and diagnosis. Here we will focus our attention primarily on brown oral lesions attributable to melanin pigment.

Drug-Induced Pigmentations

An array of medications has potential to induce oral mucosal (and cutaneous) pigmentations (Table 17.6). While pigmentations varying from gray to black to shades of brown can arise anywhere on the oral mucosa, the most commonly affected sites include the palate, gingivae and tongue. The respective pathogeneses of mucosal hyperpigmentations are driven by various endogenous and exogenous mechanisms. These include drug-induced stimulation of melanin synthesis through ACTH and its deposition in the tissues; drug or metabolite accumulation in the tissues; deposition of the agent on oral mucosal surfaces; stimulation of bacterial metabolism; deposition of products of microbial metabolism; and vascular damage resulting in hemosiderin deposition [93, 95, 96].

Melanotic Oral Lesions

Pigmented lesions caused by increased melanin production or deposition may be tan, brown, blue, gray, or black, depending on the amount and location of melanin within the tissues. A majority of brown-pigmented oral lesions are attributable to melanin pigment based on history and clinical examination findings. Most such oral lesions are benign, and biopsy is optional. In those cases where the clinical diagnostic impression is uncertain and there is concern for the possibility of melanoma, biopsy for diagnostic confirmation is indicated.

Table 17.6 Medications associated with oral mucosal pigmentations

Antibiotics	Minocycline
	Tetracycline
	Clofazimine
Antiretroviral agents	Azidothymidine (AZT)
Antifungal agents	Ketoconazole
Antimalarial agents	Quinidine
	Quinacrine
	Hydroxychloroquine
	Chloroquine
Antineoplastic and alkylating agents	Busulfan
	Cyclophosphamide
	Bleomycin
	5-Fluorouracil
	Doxorubicin
Antiarrhythmic agents	Amiodarone
Others	Oral contraceptives
	Chlorhexidine oral rinses

What Is Melanin?

Melanin is a pigment elaborated by melanocytes, the pigment-producing cells that normally reside within the basal layer (*stratum basale*) of the epidermis or epithelium. During embryonal life, the melanocytes' pluripotent cellular precursors, *melanoblasts*, migrate from their origin in the neural crest to their ultimate destination among the basal epithelial keratinocytes in skin and oral mucosa. Melanocytes are characterized by lengthy dendritic processes that extend in all directions and allow for intimate contact with the neighboring keratinocytes; however, they lack desmosomes and tonofilaments. Therefore, despite living in close proximity with and among the keratinocytes, melanocytes undergo cell division independent of the basal keratinocytes, thereby maintaining a distinct, self-propagating population. Within the melanocytes' cytoplasm, melanin pigment is synthesized in organelles called *premelanosomes* through oxidation of tyrosine by tyrosinase, to 3,4-dihydroxyphenylalanine (DOPA). With increased production of melanin, premelanosomes mature into *melanosomes* which are then transported into the dendritic processes where they can be transferred into adjacent keratinocytes via phagocytotic inoculation. In tissue biopsies taken from darkly-pigmented individuals, aggregated melanosomes form coarse brown melanin granules that can be seen under the light microscope; however, they may not be visible in specimens obtained from more lightly-pigmented tissues without the aid of special stains (e.g., Fontana-Masson, argentaffin, Warthin-Starry).

In any particular site on the skin or oral mucous membranes, the number of melanocytes per unit area remains fixed, irrespective of whether an individual is dark- or light-skinned. Phenotypic differences in pigmentation result from the degree of melanin-producing activity of melanocytes and the rate of melanosome breakdown within the keratinocytes. These differences are largely determined genetically [98, 99].

The range of melanin-based oral lesions includes:

- Variants of normal mucosal coloration (physiologic (racial) melanosis, benign melanotic macules).
- Post-inflammatory melanin incontinence consequent to local trauma or chronic inflammatory stimulation (including smoker's melanosis).
- Benign and malignant neoplasms.
- Manifestations of selected systemic diseases (Table 17.7).
- Occasional interactions with selected drugs.

Table 17.7 Selected systemic conditions with brown macules

Condition	Etiology/pathogenesis	Clinical features	Diagnosis and management
Peutz-Jeghers syndrome	• Autosomal dominant	• Multiple hamartomatous intestinal polyps	• Melanotic macules persist
	• Mutation—STK11 tumor suppressor gene	• Predisposed to range of possible malignancies: GI, testicular, ovarian, thyroid, breast, pancreas	• Biopsy-increased melanin pigment in basal keratinocytes-benign
	• No sex predilection	• GI bleeding, obstruction	• Long term monitoring for the development of visceral malignancies
		• Early onset (childhood, adolescence) of numerous dark, *benign* melanotic macules: buccal mucosa, lips, skin of extremities	
Addison's disease	Adrenal cortical insufficiency	• Patchy, widespread oral melanosis	• Clinical findings
	• Decreased production of cortisol and aldosterone leads to increased pituitary secretion of ACTH and corresponding increase in melanocyte stimulating hormone	• Bronzing of skin	• Laboratory studies
	Causes	• Constitutional signs-weight loss, anorexia, diarrhea, vomiting, weakness, neurologic disturbances	• Management-corticosteroid replacement therapy
	• Immune-mediated adrenalitis, infection (e.g., TB), neoplasia	• Hypokalemia, hyponatremia	
Laugier-Hunziker syndrome	• Uncertain etiology	• Multiple brown-black macular pigmentations-vermilion borders of lips, labial and buccal mucosa, palate, gingiva, tongue	• Rule out GI pathology
	• Non-hereditary	• Other mucous membranes may be similarly involved	• Biopsy unnecessary-will demonstrate increase melanin pigment in basal keratinocytes
	• Progressive, benign	• ± Nail involvement—longitudinal streaks (melanonychia)	• Laser ablation optional
	• Acquired in early to mid-adult life		
	• Predilection for Caucasians		
	• F:M = 2:1		
McKune-Albright syndrome; Jaffe-Lichtenstein syndrome; Mazabraud syndrome	• GNAS gene mutations	• Benign, irregularly-shaped *café au lait* macules (tan-brown, homogenous) on extremities, trunk, back	• Clinical and radiographic findings
	• Benign, developmental, multisystem involvement	• Polyostotic fibrous dysplasia of multiple possible skeletal sites	• Biopsy of macules is unnecessary-increased melanin pigment in basal keratinocytes
	• Presents in early life	• Multiple possible endocrine hyperplasias/hyperfunction	
	• Impaired osteoblastic differentiation		
	• Overexpression of IL-6		
	• Melanocyte stimulation, increased melanin production		
Neurofibromatosis type I (Von Recklinghausen disease of skin	• Most cases are autosomal dominant-mutations in NF1 gene (abnormal tumor suppressor gene, neurofibromin)	• At least two neurofibromas-pendulous masses, soft nodules on skin	• Positive family hx (first-degree relative with NF1
		• Yellow tan to brown *café au lait* macules with smooth borders-vary in size (5–15 mm)	• Six or >yellow tan to brown café au lait macules
		• Axillary or inguinal freckling	• Biopsy unnecessary
		• Lisch nodules (hamartomas of the iris)	
		• Selected osseous lesions	

We will discuss several select benign oral melanotic entities, ones that are most likely to be encountered in clinical practice [93–95, 100–102]. (For these and other select entities, see Table 17.8.)

Physiologic Pigmentation

Physiologic (racial) pigmentation is most often seen in individuals with darker skin (e.g., those of African, Mediterranean,

Table 17.8 Benign macular oral melanotic macules

Entity	Etiology/pathogenesis	Clinical presentation	Diagnostic confirmation
Racial (physiologic) melanosis	• Genetically-determined increase in melanin production	• Darker-skinned individuals	• Clinical findings are sufficient
	• Onset may coincide with hormonal shifts (e.g., puberty); tends to increase with age	• Diffuse, macular tan to dark brown to black pigmentation	• Biopsy unnecessary-diffuse increase in melanocytic granules in basal keratinocytes ± melanin incontinence in lamina propria
		• Attached gingiva, lips, palate, buccal mucosa, tongue, especially fungiform papillae (papular-appearing)	
Smoker's melanosis	• Reactive and benign-heat from cigarette or pipe smoke stimulates increased melanin production in one or more foci	• Women > men	• Clinical presentation
	• Hormonal stimulation?	• Multiple macules (tan to brown to brown-black)	• + Smoking history usually sufficient for dx
		• Anterior portions of oral cavity mostly affected (anterior labial gingiva, tongue, buccal mucosa, hard palate)	• Biopsy optional-reveals findings identical to physiologic melanosis
Benign melanotic macule (focal melanosis)	• Common, benign, idiopathic	• Any age- middle age adults most often	• Clinical features-solitary, even-pigmented, defined, usually <2.0 cm macules
	• No racial predilection	• F > M	• Can be several
	• Increase in melanin production	• Caucasians > blacks = lip	• Histopathological features similar to above
	• ± Increase in number of melanocytes	• Darker skinned = intraoral (e.g., buccal mucosa, gingiva, palate)	
		• Lower lip macules–not responsive to sun exposure	
Inflammatory melanin incontinence	• Chronic inflammatory stimulation (local) results in disruption of basal keratinocytes; melanin spills freely into the lamina propria/superficial stroma; is engulfed by macrophages	• Any age	• Increased melanin in basal/parabasal keratinocytes
		• No gender predilection	• Free melanin
		• Solitary or multiple, sometimes confluent tan to dark-brown macules	• Melanin within melanophages in submucosa
		• Oral sites of chronic friction	
		• Lichenoid inflammation (including lupus erythematosus)	
Oral melanoacanthoma (Melanoacanthosis) (Fig. 17.24d)	• Benign, reactive • Trauma-induced?	• Females > males	• Biopsy advised
		• Young adults	• Acanthosis, spongiosis
		• Blacks > Caucasians, other persons of color	• Increased basal layer melanocytes
		• Brown macule develops over several weeks	• Increased numbers of dendritic melanocytes throughout the epithelium
		• Often several cm in size	
		• Usually asymptomatic	
		• Spontaneous resolution	

and Asian extraction). This form of pigmentation is characteristically diffuse, evenly distributed, and ranges in hue from light tan to dark brown (Fig. 17.23). The degree of pigmentation can deepen with age, and that intensification may become evident during adolescence. Classically, the marginal collar of gingiva is not involved, but garland-like diffuse melanosis involving the attached gingiva alone is apparent in both the maxilla and mandible. Physiologic pigmentation may also present as macular brown-gray patches on the buccal mucosa, tongue, labial mucosa and the keratinized portions of the palate.

Oral Melanotic Macules (Table 17.8)

Most oral melanotic macules are benign pigmented lesions with no potential for malignant transformation. They result from heightened production of melanin without a concomitant increase in the number of melanocytes. These discrete, tan-to-dark brown macules are typically under 1 cm in dimension, homogenous in color, and are most commonly encountered on the lower vermilion border and labial mucosa, the palate, gingiva, and the buccal mucosa (Fig. 17.24a–c). They favor young adults and women but can

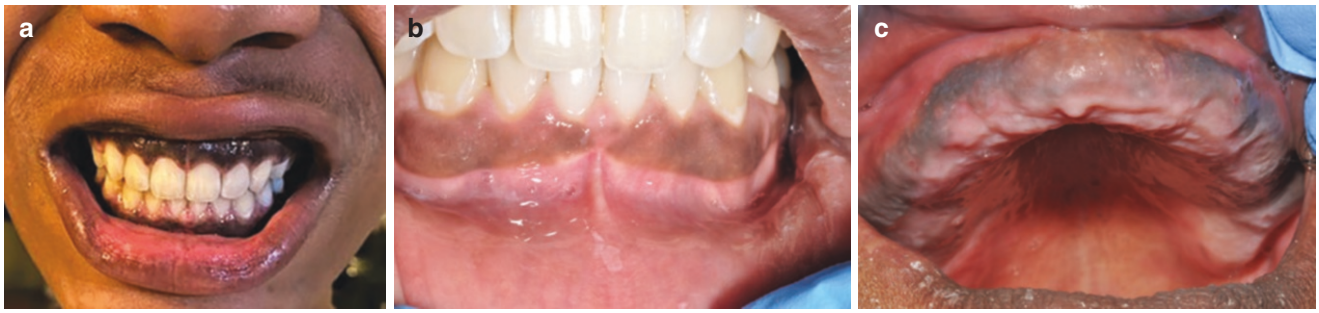


Fig. 17.23 Physiologic pigmentation (melanosis). (**a**) A 14-year-old African American boy. Note the diffuse dark brown pigmentation of both the maxillary and mandibular attached gingiva. According to the child's mother, the "dark brown coloration" appeared relatively suddenly within recent months. (**b**) A 29-year-old woman with light brown, evenly distributed physiologic pigmentation, mandibular labial attached gingiva. (**c**) A completely edentulous African American man. Similar findings were noted on the corresponding edentulous mandibular gingival tissue

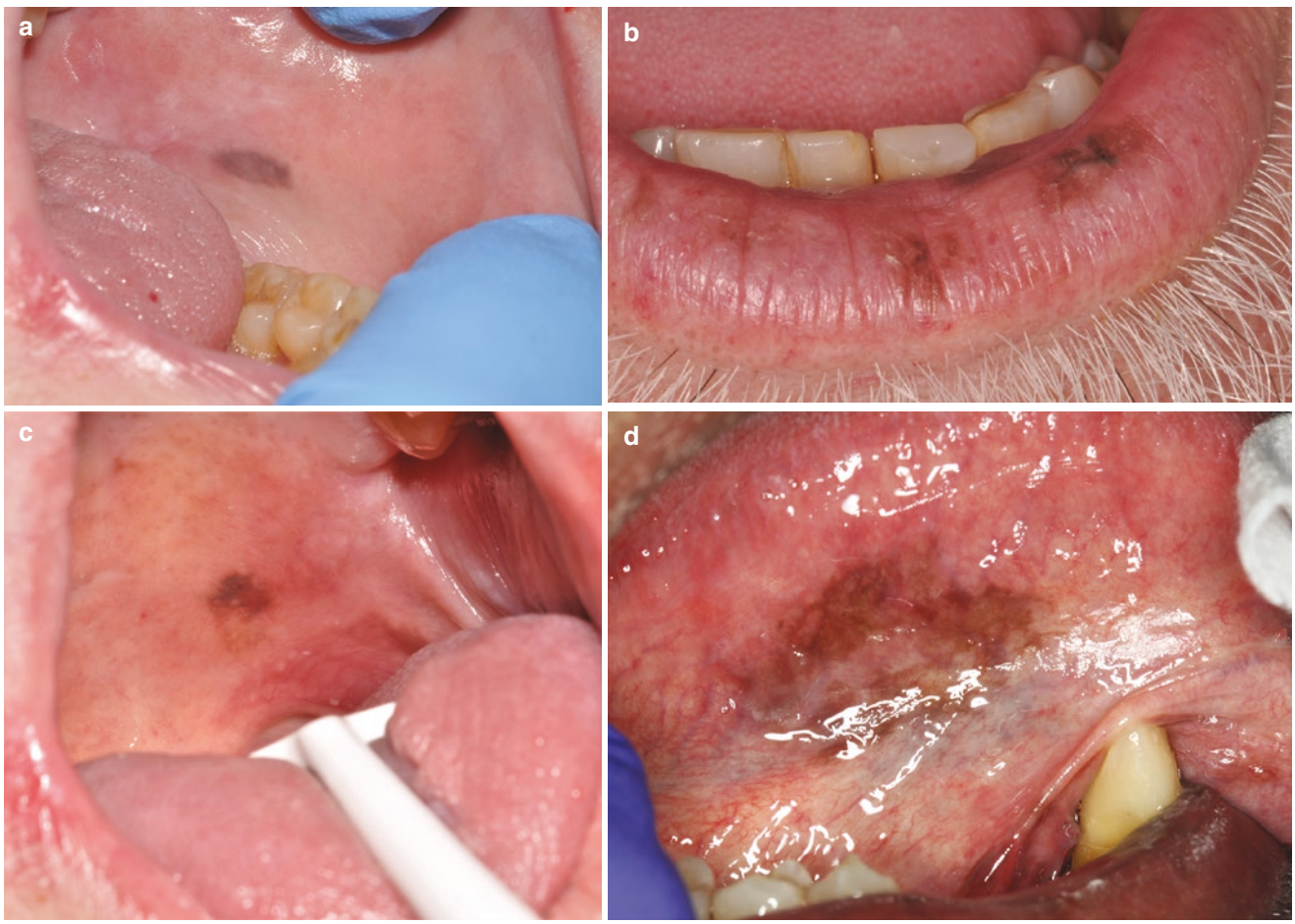


Fig. 17.24 Melanotic macules and melanoacanthoma. (**a–c**) Benign melanotic macules on buccal mucosa, lower lip vermilion border and on the soft palate, respectively. (**d**) This melanotic macule developed very rapidly on the lateral-ventral tongue of a 24-year-old woman. Melanoacanthoma was suspected. Biopsy revealed numerous benign-appearing dendritic melanocytes within the surface epithelium, confirming the diagnosis of melanoacanthoma

present at any age. In a single patient, there may be one isolated macule or several macules distributed on various intraoral locations and the external lips.

Melanoacanthoma, a benign, likely reactive and uncommonly occurring macular melanotic entity, is characterized by distribution of dendritic melanocytes

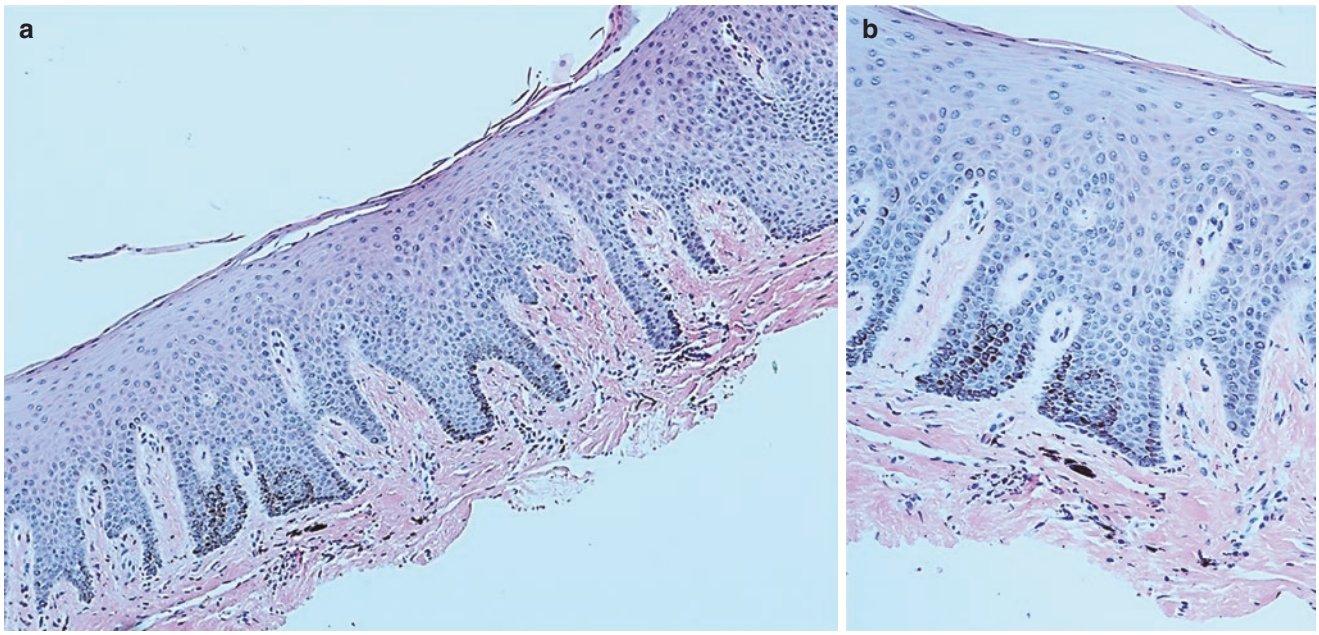


Fig. 17.25 Benign melanosis with melanin incontinence. (**a**) Melanin pigment appears along the epithelial basal layer. A few melanophages are present in the lamina propria region, indicative of benign melanin incontinence (H&E ×10). (**b**) Higher magnification of (**a**) (H&E ×20)

throughout the epithelium accompanied by an increase in the number of melanocytes within the basal most stratum. The lesions usually manifest themselves clinically in areas susceptible to or following trauma, as an asymptomatic brown macule that arises suddenly and spreads rapidly over the course of just a few weeks. Sites of involvement include the buccal and labial mucosa, the gingiva/alveolar mucosa (Fig. 17.24d) and palate. Lesions may be unifocal, bilateral, or widely distributed. A majority of affected patients are young adults, primarily darker-skinned women. Melanoacanthomas may regress spontaneously; they can recur. The rapid progression of melanoacanthomas can be alarming. Therefore, to rule out malignancy and confirm the clinical diagnostic impression and establish the benignity of the lesion, biopsy is often performed [93, 94, 102].

Biopsy is optional for diagnostic confirmation of most melanotic macules, but often is carried out to rule out any suspicion of malignant melanoma. On histopathology, the presence of melanin within benign-appearing basal keratinocytes is characteristic of oral melanotic macules, irrespective of location (Fig. 17.25a).

Post-inflammatory Melanin Incontinence

In oral mucosal locations where there had been prior inflammatory stimulation, or where there is chronic inflammation at the epithelial-stromal interface (e.g., lichen planus, lichenoid stomatitides, lupus lesions), disruption of melanin-containing keratinocytes may occur. This permits melanin to spill into the underlying superficial stromal tissue where it either remains free or is phagocytized and contained in macrophages (*melanophages*). This phenomenon is referred to as *benign melanin incontinence* or *inflammatory/post-inflammatory melanin incontinence* (Fig. 17.25b).

Oral Melanocytic Nevi (Table 17.9)

N*evus* (*nevi* = plural) is a generic term for a developmental anomaly or congenital malformation (hamartoma). Nevi present themselves as benign masses comprised of a particular cell type and tissue native to an anatomic site. Melanocytic nevi (commonly referred to as "moles") specifically are benign proliferations of melanocytes (or their close relatives) that normally reside in the basal layer of epidermis as well as oral and other mucosal epithelium. A majority of cutaneous melanocytic nevi are "acquired": this type of melanocytic nevus becomes clinically evident shortly after birth. The lesion slowly reaches its full dimension to no greater than 1.0 cm in diameter by the mid-fourth decade of life. "Congenital" melanocytic nevi are present at birth; on the skin they may also present as so-called *giant hairy nevi.* Melanocytic nevi have been classified both as hamartomas and as benign melanocytic neoplasms. In a substantial percentage of acquired nevi (and in malignant melanomas) BRAF mutations have been identified. This would support a (benign) neoplastic categorization for melanocytic nevi [101–103]. Cutaneous melanocytic nevi are among the most

Table 17.9 Oral melanocytic nevi vs. malignant melanoma

	Oral melanocytic nevi	Oral melanomas
History	Typically discovered in infancy or early childhood as a pigmented macule or nodule	– Arise later in life (middle-age to older adult) either in pre-existing pigmented macule or more typically, de novo
		– Depending on oral location, patient aware of "spreading" or nodular pigmented lesion
		± Bleeding
		± Pruritis, pain
Clinical features	– Palate, buccal mucosa, labial mucosa, gingiva	– Hard palate, maxillary gingiva (less often, mandibular gingiva, buccal mucosa, FOM)
	– Uniform in color, brown or tan, round to ovoid macule; may become raised over time	– Initially asymptomatic
	– Intact surface	– Variegated: macular tan-brown, dark blue to black, ± partially depigmented
	– Defined borders	Asymmetric, ill-defined borders
	– 1.0 cm or <in diameter	– Develop papules/nodularity, ulceration
	– Asymptomatic	– Satellite foci
		– Symptoms: pruritis, pain, bleeding
Histopathology	Junctional	In situ- (equivalent of acral lentiginous melanoma)
	– Clusters of benign nevus cells at the epithelial stromal junction ± pigment	– Individual atypical melanocytes, angular, large nuclei, ± pigment proliferate circumferentially within the epithelium above basement membrane
	Compound	± Melanin incontinence in lamina propria
	– Nests of benign nevus cells at the junction and within the submucosa, ± pigment	Superficial spreading
	Intramucosal	– Proliferate at junction and circumferentially in entire width of epithelium
	– Clusters of nevus cells, ± pigment, all within the submucosa	Nodular
		– Vertical growth beyond basement membrane, markedly atypical melanocytes in submucosa

commonly encountered cutaneous lesions; oral mucosal melanocytic nevi are far less common (Fig. 17.26a, b).

It is estimated that one third of cutaneous melanomas develop directly from benign melanocytic nevi. Yet most melanocytic nevi resulting from $BRAF^{V600E}$-activating mutations never progress to melanoma [104].

Clinical-Histopathological Correlations

About one third of oral melanocytic nevi involve the hard palate, followed almost evenly by the buccal mucosa, the vermilion border of the lip, and the gingiva. The two broad types of oral mucosal melanocytic nevi that can be distinguished from one another histopathologically are the *nevocellular type* (Fig. 17.26c) and the *blue type*, respectively. Both are benign with no predilection for transformation to malignant melanoma [95, 97, 98]. The nevocellular type evolves clinicopathologically. It begins as a collection of nevocellular melanocytes that proliferate at the basal layer and its intersection (junction) with the superficial lamina propria. These *junctional nevi* present clinically as light tan to dark brown, discrete, evenly colored, round to ovoid macules (Fig. 17.26d). As time passes, the nevus-cell nests proceed to fall from the junctional region into the lamina propria, and eventually into the deeper submucosa. Little, if any, junctional component remains. This results in an *intramucosal* melanocytic nevus that presents clinically as a raised, well-circumscribed mucosal nodule, no larger than 1.0 cm in diameter [97]. Melanocytic nevi can be melanotic (i.e., pigmented) or non-pigmented. Blue nevi consist of heavily pigmented, spindly melanocytes that proliferate along collagen bundles in the submucosa. These lesions present clinically as discrete, ovoid, evenly-colored blue macules. The blue color results from the Tyndall effect, attributable to the shrouding of melanotic pigment by the overlying vascular channels [95, 101].

Malignant Melanoma of Oral Mucosa (Table 17.9)

About 1–8% of all melanomas arise as primary tumors in the oral mucosa: they account for 0.5% of all oral malignancies. These neoplasms are even more aggressive and destructive than cutaneous malignant melanomas. The 5-year survival is around 15%, with locoregional spread to lymph nodes by 18 months following diagnosis. Molecular genetic analyses have revealed a number of frequently occurring genetic mutations in melanomas. These include alterations in Ras/Raf/MAPK and other signaling pathways. Related to these

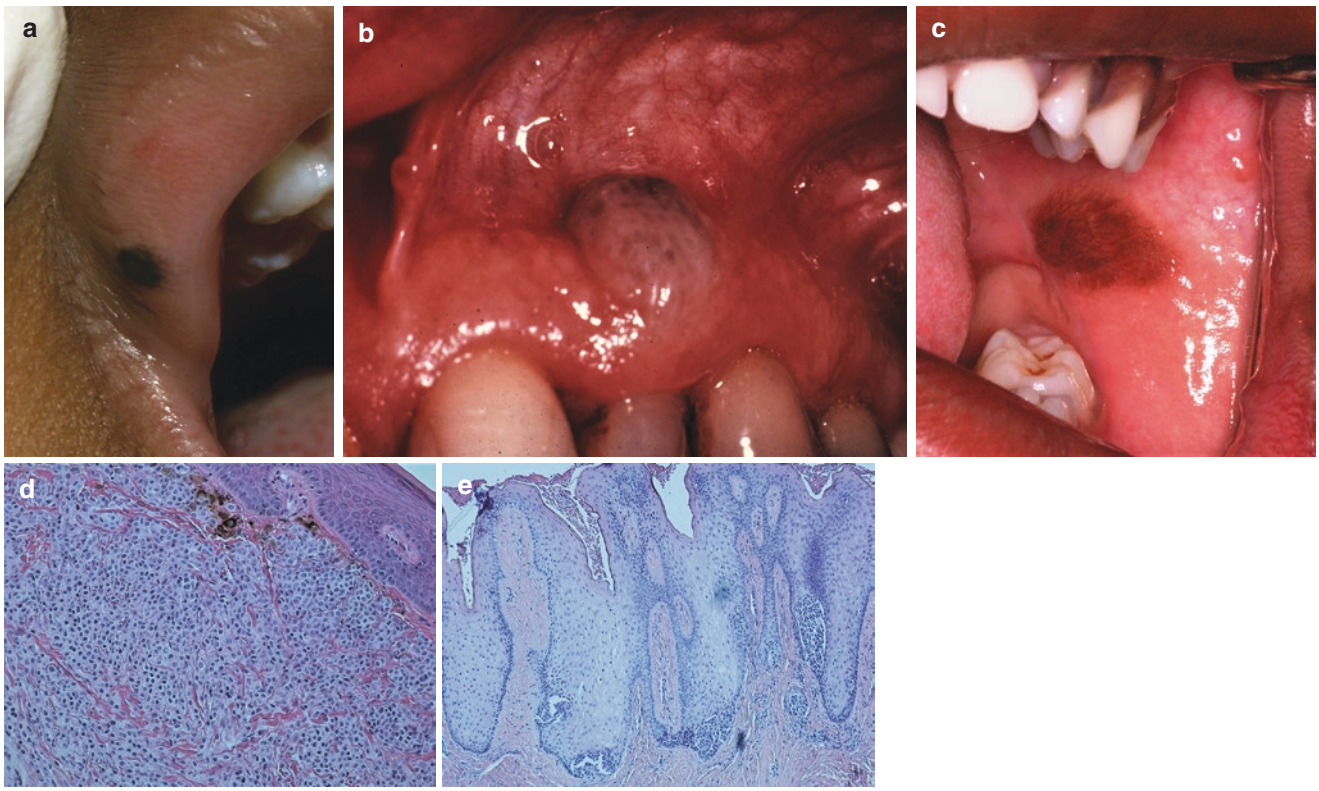


Fig. 17.26 Melanocytic nevi. (**a**) Pigmented mucosal melanocytic nevus, labial mucosa. (**b**) This painless nodule on the maxillary left alveolar mucosa had been present for many years. It was excised; biopsy revealed a partially pigmented benign mucosal melanocytic nevus. (**c**) A 6-year-old boy, left buccal mucosa. This asymptomatic, discrete, circumscribed brown macule was first noticed by the child's parents when he was 2 or 3 years old. It has not increased in diameter, but it has become slightly raised over time. The features are consistent with a benign, possibly congenital mucosal nevus. (**d**) Excised nodule from (**b**). Microscopy reveals a nevocellular mucosal nevus with minimal melanin pigment (H&E ×60). (**e**) Benign junctional melanocytic nevus (H&E ×60)

are BRAF mutations, which have been found in roughly half of melanomas. The C-KIT gene, associated with a receptor for tyrosine kinase interactions with Ras, is mutated in mucous membrane melanomas [104].

Clinical-Histopathological Correlations

Whereas cutaneous melanomas favor Caucasians, and UV radiation appears to be the most common identified risk factor, etiologic risk factors for mucosal melanomas remain obscure. There are four major classifications of cutaneous melanomas that reflect their respective clinical-pathological correlates [105]. They are:

1. Acral-lentiginous melanoma (analogous to the most common form of oral mucosal melanoma).
2. Lentigo maligna melanoma (begins on sun-exposed skin of older, fair-skinned adults, in a pre-existing *Hutchinson's freckle*).
3. Superficial spreading melanoma (the commonest cutaneous form, presenting with a maculopapular surface configuration).
4. Nodular melanoma (next most common type on skin; may begin de novo).

The general clinical features of cutaneous melanomas are often described according to the acronym, A, B, C, D and E: asymmetry, irregular borders, variegated color (including loss of pigment), and dimensions that exceed 0.6 cm. The E refers to the lesions' tendency to evolve over time. Often, there are satellite lesions that reflect the insidious contiguous progression of this tumor [105].

Acral cutaneous and oral mucosal melanomas, while rare, arise more often in adults. They appear to favor males over females, and Asians and blacks over Caucasians. The most common oral sites of involvement are the palatal and the gingival mucosa with potential for invasion into underlying jawbone. In general, oral (and other mucosal head and neck) melanomas tend to behave aggressively and exhibit a poorer

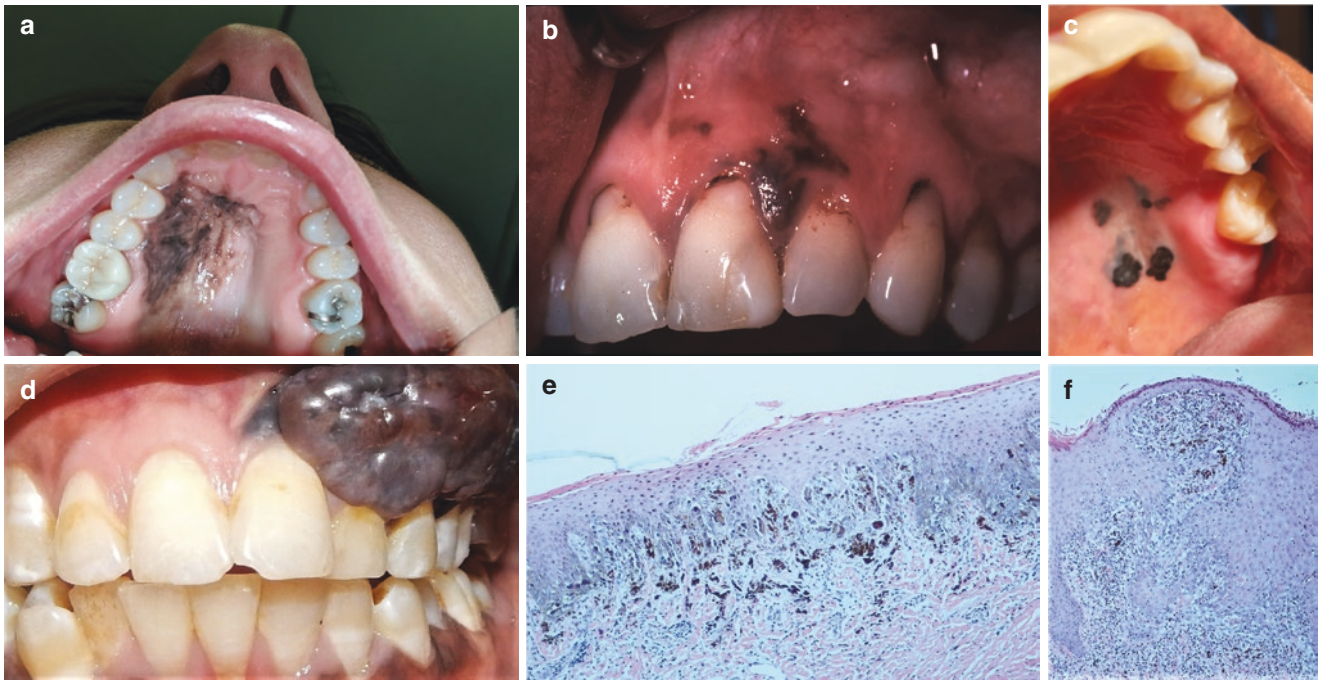


Fig. 17.27 Oral mucosal malignant melanoma. (**a–c**) Examples of clinically suspicious, predominantly macular oral pigmented lesions. All appear asymmetric, with ill-defined borders and variegated color. Their sizes are greater than 1 cm. Each of the pigmented lesions here had "evolved" clinically over time. All were melanomas on biopsy. (**d**) Nodular oral malignant melanoma. Black-brown, irregularly surfaced, ulcerated nodule arose in a previously existing black-brown diffuse gingival macule. (**e**) Biopsy of pigmented lesion seen in 27c reveals markedly atypical melanocytic proliferation along the basal layer with extension both superiorly into the surface epithelium and within the superficial lamina propria. The process is also spreading horizontally and is highly suspicious for melanoma (H&E ×40). (**f**) Nodular mucosal melanoma. Vertical spread: malignant melanocytes invade underlying stroma (H&E ×40)

prognosis than their cutaneous counterparts [93, 105–107]. Although it appears that acral and mucosal melanomas share many clinical, histopathologic and pathogenetic attributes, the overall rarity of these melanomas clouds full understanding of the biological mechanisms underpinning their respective differences in response to various therapeutic interventions [108].

The clinical presentation of oral melanomas varies widely, as does their rate of growth. Lesions initiate in situ (i.e., within the epithelium) as atypical melanocytic proliferations [106]. They are typically asymptomatic and present as asymmetric, variegated pigmented macules that usually include tan-brown, brown, black, and depigmented foci. The borders of the macule are poorly defined. As the malignant process spreads horizontally within the epithelium (circumferential spread), there can be extensive, diffuse involvement of the contiguous mucosa (Fig. 17.27a–d).

Under the microscope, clinically macular lesions (mucosal in situ melanomas) demonstrate radial (i.e., circumferential, horizontal) proliferation of atypical melanocytes along the epithelial-stromal junction. This presentation is the equivalent of cutaneous *acral lentiginous melanoma* (Fig. 17.27e). Upward spread of the malignant melanocytes into the more superficial epithelial strata can appear clinically as a papular component of the lesion, analogous to cutaneous *superficial spreading melanomas.*

Vertical growth presents as a clinically nodular mucosal mass that may arise rapidly within a polychromatic, irregularly shaped macule with ill-defined borders. *Nodular* (i.e., invasive) *melanomas* [93, 105–107] may be brown-black, red-brown, bluish, purplish, grey, partially depigmented or combinations of all. Occasionally the masses are nonpigmented, in which case they are termed *amelanotic melanomas*. Pain, ulceration and a tendency to bleed are characteristic of nodular melanomas. The primary tumor mass may be flanked by so-called *satellite tumors*.

On histopathologic examination, immunohistochemistry analysis for expression of HMB45, MART-1, S100 and other antibodies that interact with proteins expressed by melanoma rather than melanin-associated antigens, [106, 109] can be helpful for confirming the melanocytic nature of tumors that are clinically and/or histologically amelanotic. Nodular oral melanomas demonstrate atypical melanocytes that proliferate with a vertical growth pattern, invading both in an upward direction through the superficial epithelial

strata, and downward into the underlying stroma (Fig. 17.27f). Attendant circumferential spread is also evident, accounting for the clinically macular features that immediately surround the nodule.

Management

Given the generally aggressive character and poor prognosis of oral mucosal melanomas (especially nodular types), therapeutic interventions have often proven less than effective. This is likely due to the many unknown differences among affected patients' molecular genetic profiles, and discrepancies possibly attributable to racial and/or individual immune responses to these neoplasms [109, 110]. Treatments have ranged from radical surgical resection with or without neck dissection, plus adjuvant radiation therapy, to systemic therapy using various cell cycle checkpoint inhibitors for tumors with specific mutations, and immunotherapy. The latter two approaches have been applied in patients with metastatic disease. The spectrum of mutations in melanomas is vast and is constantly evolving; this, in part partly explains the poor responses to selective checkpoint inhibitor therapeutics [105, 106, 109, 110].

References

1. Eisenberg E, Oreadi D. Differential diagnosis and management of oral mucosal lesions (chap. 24). In: Laskin DM, Carlson ER, editors. Clinician's handbook of oral and maxillofacial surgery. 2nd ed. Batavia: Quintessence; 2019. p. 442–3.
2. Eisenberg E, Krutchkoff DJ. The clinical-pathologic forum in oral pathology. J Dent Educ. 1983;47:552–4. PMID: 6577048.
3. Oral epithelium. Regional differences in the oral mucosa (chaps. 3 and 6). In: Squier C, Brogden KA, editors. Human oral mucosa: development, structure and function. Ames: Wiley; 2011. p. 19–57; 77–88.
4. Eisenberg E, Natarajan E, Formaker BK. Oral mucosa and mucosal sensation (chap. 9). In: Hand AR, Frank ME, editors. Fundamentals of oral histology and physiology. Ames: Wiley-Blackwell; 2014. p. 165–78.
5. Leukoedema. Developmental defects of the oral and maxillofacial region (chap. 1). In: Neville BW, Damm DD, Allen CM, Chi AC, editors. Oral and maxillofacial pathology. 4th ed. St Louis: Elsevier; 2016. p. 7, 8.
6. White sponge nevus. Dermatologic diseases (chap. 16). In: Neville BW, Damm DD, Allen CM, Chi AC, editors. Oral and maxillofacial pathology. 4th ed. St Louis: Elsevier; 2016. p. 691–2.
7. Woo SB, Lin D. Morsicatio mucosae oris—a chronic oral frictional keratosis, not a leukoplakia. J Oral Maxillofac Surg. 2009;67:140–6.
8. Mignogna MD, Fortuna G, Leuci S, et al. Frictional keratoses on the facial attached gingiva are rare clinical findings and do not belong to the category of leukoplakia. J Oral Maxillofac Surg. 2011;69(5):1367–74.
9. Linea alba and morsicatio mucosae oris (chronic mucosal chewing). Physical and chemical injuries. In: Neville BW, Damm DD, Allen CM, Chi AC, editors. Oral and maxillofacial pathology. 4th ed. St Louis: Elsevier; 2016. p. 259, 260.
10. Natarajan E, Woo SB. Benign alveolar ridge keratosis (oral lichen simplex chronicus): a distinct clinicopathologic entity. J Am Acad Dermatol. 2008;58(1):151–7.
11. Chi AC, Lambert PR III, Pan Y, et al. Is alveolar ridge keratosis a true leukoplakia? A clinicopathologic comparison of 2,153 lesions. J Am Dent Assoc. 2007;138(5):641–51.
12. Almazayad A, Li C-C, Woo S-B. Benign alveolar ridge keratosis: clinical and histopathological analysis of 167 cases. Head Neck Pathol. 2020;14:915–22. https://doi.org/10.1007/s12105-020-01151-1.
13. Saunders WH. Nicotine stomatitis of the palate. Ann Otol Rhinol Laryngol. 1958;67:618–27. https://doi.org/10.1177/000348945806700303. PMID: 13583891.
14. Ortiz GM, Pierce AM, Wilson DF. Palatal changes associated with reverse smoking in Filipino women. Oral Dis. 1996;2:232–7.
15. Behura SS, Masthan MK, Narayanasamy AB. Oral mucosal lesions associated with smokers and chewers—a case–control study in Chennai population. J Clin Diagn Res. 2015;9(7):Zc17-22.
16. Natarajan E, Eisenberg E. Contemporary concepts in the diagnosis of oral cancer and precancer. In: Lamster IB, editor. Dental clinics of North America. Philadelphia: Elsevier; 2011. p. 63–80. https://doi.org/10.1016/j.cden.2010.08.006.
17. Warnakulasuriya S, Kujan O, Aguirre-Urizar JM, Bagan JV, et al. Oral potentially malignant disorders: a consensus report from an international seminar on nomenclature and classification, convened by the WHO Collaborating Centre for Oral Cancer. Oral Dis. 2021;27:1862–80. https://doi.org/10.1111/odi.13704.
18. Leukoplakia. Epithelial pathology. In: Neville BW, Damm DD, Allen CM, Chi AC, editors. Oral and maxillofacial pathology. 4th ed. St Louis: Elsevier; 2016. p. 355–63.
19. Dost F, Lê Cao K, Ford PJ, et al. A retrospective analysis of clinical features of oral malignant and potentially malignant disorders with or without oral epithelial dysplasia. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;116:725–33.
20. Woo SB. Oral epithelial dysplasia and premalignancy. Head Neck Pathol. 2019;13(3):423–39. https://doi.org/10.1007/s12105-019-01020-6. Epub 2019 Mar 18. PMID: 30887394.
21. Speight PM. Update on oral epithelial dysplasia and progression to cancer. Head Neck Pathol. 2007;1:61–6. https://doi.org/10.1007/s12105-007-0014-5.
22. Dost F, Le Cao K, Ford PJ, et al. Malignant transformation of oral epithelial dysplasia. A real-world evaluation of histopathologic grading. Oral Sur Oral Med Oral Pathol Oral Radiol. 2014;117:343–52.
23. Müller S. Oral epithelial dysplasia, atypical verrucous lesions and oral potentially malignant disorders: focus on histopathology. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018;125:591–602.
24. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer. 1953;6:963–8. https://doi.org/10.1002/1097-0142(195309)6:5<963::AID-CNCR2820060515>3.0.CO;2-Q. PMID 13094644.
25. Chai H, Brown RE. Field effect in cancer-an update. Ann Clin Lab Sci. 2009;39:331–7.
26. Krutchkoff DJ, Eisenberg E, Anderson C. Dysplasia of oral mucosa: a unified approach to proper evaluation. Mod Pathol. 1991;4:113–9.
27. Gerardo G, Eduardo P, René P. Oral epithelial reactive atypia/dysplasia: an underestimated true atypia/dysplasia? Med Hypotheses. 2020;144:110217. https://doi.org/10.1016/j.mehy.2020.110217. Epub 2020 Aug 26. PMID: 33254524.
28. Muller S. Update from the 4th edition of the World Health Organization of head and neck tumours: tumours of the oral cav-

ity and mobile tongue. Head Neck Pathol. 2017;11:33–40. https://doi.org/10.1007/s12105-017-0792-3.
29. Ramos-García P, González-Moles MA, Mello FW, Bagan JV, Warnakulasuriya S. Malignant transformation of oral proliferative verrucous leukoplakia: a systematic review and meta-analysis. Oral Dis. 2021;27:1896–907. https://doi.org/10.1111/odi.13831.
30. Upadhyaya JD, Fitzpatrick SG, Islam MN, et al. Marginal linear gingival leukoplakia progressing to "ring around the collar"—an ominous sign of proliferative verrucous leukoplakia. J Periodontol. 2020;92:273. https://doi.org/10.1002/jper.19-0621. PMID: 32725623.
31. Thompson LDR, Fitzpatrick SG, Muller S, Eisenberg E, et al. Proliferative verrucous leukoplakia: an expert consensus guideline for standardized assessment and reporting. Head Neck Pathol. 2021;15:572–87. https://doi.org/10.1007/s12105-020-01262-9. Epub 2021 Jan 7.
32. Akrish S, Eskander-Hashoul L, Rachmiel A, Ben-Izhak O. Clinicopathologic analysis of verrucous hyperplasia, verrucous carcinoma and squamous cell carcinoma as part of the clinicopathologic spectrum of oral proliferative verrucous leukoplakia: a literature review and analysis. Pathol Res Pract. 2019;215(12):152670. https://doi.org/10.1016/j.prp.2019.152670. Epub 2019 Sep 25. PMID: 31630872.
33. Woo S-B, Grammer RL, Lerman MA. Keratosis of unknown significance and leukoplakia: a preliminary study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2014;118:713–24. https://doi.org/10.1016/j.oooo.2014.09.016.
34. Müller S. Frictional keratosis, contact keratosis and smokeless tobacco keratosis: features of reactive white lesions of the oral mucosa. Head Neck Pathol. 2019;13(1):16–24.
35. Mello FW, Miguel AFP, Dutra KL, Porporatti AL, Warnakulasuriya S, Guerra ENS, Rivero ERC. Prevalence of oral potentially malignant disorders: a systematic review and meta-analysis. J Oral Pathol Med. 2018;47:633–40. https://doi.org/10.1111/jop.12726. Epub 2018 Jun 6. PMID: 29738071.
36. Dancyger A, Heard V, Huang B, Suley C, Tang D, Ariyawardana A. Malignant transformation of actinic cheilitis: a systematic review of observational studies. J Investig Clin Dent. 2018;9(4):e12343. https://doi.org/10.1111/jicd.12343. Epub 2018 Jun 4. PMID: 29863311.
37. Trager MH, Farmer K, Ulrich C, Basset-Seguin N, Herms F, Geskin LJ, Bouaziz JD, Lebbé C, de Masson A, Bagot M, Dobos G. Actinic cheilitis: a systematic review of treatment options. J Eur Acad Dermatol Venereol. 2021;35(4):815–23. https://doi.org/10.1111/jdv.16995. Epub 2020 Dec 26. PMID: 33251620.
38. Resnick L, Herbst JS, Raab-Traub N. Oral hairy leukoplakia. J Am Acad Dermatol. 1990;22:1278–82. https://doi.org/10.1016/0190-9622(90)70174-g. PMID: 2163409.
39. Zunt SL, Tomich CE. Oral hairy leukoplakia. J Dermatol Surg Oncol. 1990;16:812–6. https://doi.org/10.1111/j.1524-4725.1990.tb01566.x. PMID: 2168906.
40. Flores-Hidalgo A, Lim SO, Curran AE, Padilla RJ, Murrah V. Considerations in the diagnosis of oral hairy leukoplakia—an institutional experience. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018;125:232–5. https://doi.org/10.1016/j.oooo.2017.10.017. Epub 2017 Nov 15. PMID: 29325854.
41. Darling MR, Alkhasawneh M, Mascarenhas W, Chirila A, Copete M. Oral hairy leukoplakia in patients with no evidence of immunosuppression. A case series and review of the literature. J Can Dent Assoc. 2018;84:i4. PMID: 31199724.
42. Lichen planus. Dermatologic diseases (chap. 16). In: Neville BW, Damm DD, Allen CA, Chi AC, editors. Oral and maxillofacial pathology. 4th ed. St Louis: Elsevier; 2016. p. 729–4.
43. Lichen planus. White lesions (chap. 3). In: Regezi JA, Sciubba JJ, Jordan RCK, editors. Oral pathology: clinical pathologic correlations. 7th ed. St Louis: Elsevier; 2017. p 90–5.
44. Eisenberg E, Oreadi D. Differential diagnosis and management of oral mucosal lesions (chap. 24). In: Laskin DM, Carlson ER, editors. Clinician's handbook of oral and maxillofacial surgery. 2nd ed. Batavia: Quintessence; 2019. p. 446–8.
45. Al-Hashimi I, Schifter M, Lockhart PB, Wray D, Brennan M, Migliorati CA, Axéll T, Bruce AJ, Carpenter W, Eisenberg E, Epstein JB, Holmstrup P, Jontell M, Lozada-Nur F, Nair R, Silverman B, Thongprasom K, Thornhill M, Warnakulasuriya S, van der Waal I. Oral lichen planus and Oral lichenoid lesions: diagnostic and therapeutic considerations Oral Surg Oral Med Oral Pathol Oral Radiol 2007;103 Suppl:S25.e1–12. https://doi.org/10.1016/j.tripleo.2006.11.001. Epub 2007 Jan 29. PMID: 17261375.
46. Hypersensitivity and autoimmune disorders. Diseases of the immune system (chap. 6). In: Kumar V, Abbas AK, Fausto N, Aster JC, editors. Robbins and Cotran, pathologic basis of disease. 8th ed. Philadelphia: Saunders/Elsevier; 2010. p. 197–257.
47. Cheng YS, Gould A, Kurago Z, Fantasia J, Muller S. Diagnosis of oral lichen planus: a position paper of the American Academy of Oral and Maxillofacial Pathology. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122:332–54.
48. Sciubba JJ. Autoimmune oral mucosal diseases: Clinical, etiologic, diagnostic, and treatment considerations. Dent Clin N Am. 2011;55:89–103.
49. Eisenberg E. Clinicopathologic patterns of oral lichenoid lesions. In: Gold L, editor. Oral maxillofacial clinics of North America, vol. 3. Philadelphia: WB Saunders; 1994. p. 445–63.
50. Krutchkoff DJ, Eisenberg E. Lichenoid dysplasia: a distict histopathologic entity. Oral Surg Oral Med Oral Pathol. 1985;60:308–15. https://doi.org/10.1016/0030-4220(85)90315-9. PMID: 3862044.
51. Eisenberg E, Krutchkoff DJ. Lichenoid lesions of oral mucosa. Diagnostic criteria and their importance in the alleged relationship to oral cancer. Oral Surg Oral Med Oral Pathol. 1992;73:699–704. https://doi.org/10.1016/0030-4220(92)90013-g. PMID: 1437039.
52. Müller S. Oral lichenoid lesions: distinguishing the benign from the deadly. Mod Pathol. 2017;30(s1):S54–67. https://doi.org/10.1038/modpathol.2016.121. PMID: 28060366
53. Shearston K, Fateh B, Tai S, Hove D, Farah CS. Oral lichenoid dysplasia and not oral lichen planus undergoes malignant transfortmation at high rates. J Oral Pathol Med. 2019;48:538–45. https://doi.org/10.1111/jop.12904. Epub 2019 Jun 22. PMID: 31172588.
54. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med. 2007;36(10):575–80. https://doi.org/10.1111/j.1600-0714.2007.00582.x.
55. Wetzel SL, Wollenberg J. Oral potentially malignant disorders. J Dent Clin North Am. 2020;64(1):25–37. https://doi.org/10.1016/j.cden.2019.08.004. PMID: 31735231.
56. Sanketh DS, Patil S, Swetha B. Oral lichen planus and epithelial dysplasia with lichenoid features: a review and discussion with special reference to diagnosis. J Investig Clin Dent. 2017;8 https://doi.org/10.1111/jicd.12233. Epub 2016 Jul 21. PMID: 27443699.
57. Yuan A, Woo SB. Adverse drug events in the oral cavity. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;119:35.
58. Graft-versus-host disease. Dermatologic diseases (chap. 16). In: Neville BW, Damm DD, Allen CA, Chi AC, editors. Oral and maxillofacial pathology. 4th ed. St Louis: Elsevier; 2016. p 736–9.
59. Margaix-Muñoz M, Bagán JV, Jiménez Y, Sarrión MG, Poveda-Roda R. Graft-versus host disease affecting oral cavity. A review. J Clin Exp Dent. 2015;7(1):e138–45. https://doi.org/10.4317/jced.51975. eCollection 2015 Feb. PMID: 25810826.
60. Shulman HM, Cardona DM, Greenson JK, Hingorani S, Horn T, Huber E, Kreft A, Longerich T, Morton T, Myerson D, Prieto VG, Rosenberg A, Treister N, Washington K, Ziemer M, Pavletic

SZ, Lee SJ, Flowers ME, Schultz KR, Jagasia M, Martin PJ, Vogelsang GB, Kleiner DE. NIH Consensus development project on criteria for clinical trials in chronic graft-versus-host disease: II. The 2014 Pathology Working Group Report. Biol Blood Marrow Transplant. 2015(21):589–603. https://doi.org/10.1016/j.bbmt.2014.12.031. Epub 2015 Jan 29. PMID: 2563977.
61. White lesions: lupus erythematosus. In: Regezi JA, Sciubba JJ, Jordan RCK, editors. Oral pathology: clinical pathologic correlations. 7th ed. St Louis: Elsevier; 2017. p. 95–8.
62. Lupus erythematosus. Dermatologic diseases (chap. 16). In: Neville BW, Damm DD, Allen CA, Chi AC, editor. Oral and maxillofacial pathology. 4th ed. St Louis: Elsevier; 2016. p. 740–744.
63. Systemic lupus erythematosus. Diseases of the immune system (chap. 6). In: Kumar V, Abbas AK, Fausto N, Aster JC, editors. Robbins and Cotran pathologic basis of disease. 8th ed. Philadelphia: Saunders/Elsevier; 2010. p. 213–21.
64. Rivas-Larrauri F, Yamazaki-Nakashimada MA. Systemic lupus erythematosus: is it one disease? Rheumatol Clin. 2016;12:274–81. https://doi.org/10.1016/j.reuma.2016.01.005. Epub 2016 Feb 26. PMID: 26922326.
65. Stojan G, Petri M. Epidemiology of systemic lupus erythematosus: an update. Curr Opin Rheumatol. 2018;30:144–50. https://doi.org/10.1097/BOR.0000000000000480. PMID: 29251660.
66. Brennan MT, Valerin MA, Napeñas JJ, Lockhart PB. Oral manifestations of patients with lupus erythematosus. Dent Clin N Am. 2005;49:127–41; ix. https://doi.org/10.1016/j.cden.2004.07.006. PMID: 15567365.
67. Dermatologic diseases. In: Neville BW, Damm DD, Allen CA, Chi AC, editors. Oral and maxillofacial pathology. 4th ed. St Louis: Elsevier; 2016. p. 726–8.
68. Assimakopoulos D, Patrikakos G, Fotika C, Elisaf M. Review: benign migratory glossitis or geographic tongue: an enigmatic oral lesion. Am J Med. 2002;113(9):751–5. https://doi.org/10.1016/s0002-9343(02)01379-7. PMID: 12517366.
69. Mangold AR, Torgerson RR, Rogers RS III. Diseases of the tongue. Clin Dermatol. 2016;34:458–69. https://doi.org/10.1016/j.clindermatol.2016.02.018. Epub 2016 Mar 8. PMID: 27343960.
70. González-Álvarez L, García-Pola MJ, Garcia-Martin JM. Geographic tongue: predisposing factors, diagnosis and treatment. A systematic review. Rev Clin Esp (Barc). 2018;218:481–8. https://doi.org/10.1016/j.rce.2018.05.006. Epub 2018 Jun 11. PMID: 29903400.
71. Reamy BV, Derby R, Bunt CW. Common tongue conditions in primary care. Am Fam Physician. 2010;81(5):627–34. PMID: 20187599.
72. Picciani BL, Domingos TA, Teixeira-Souza T, Santos Vde C, Gonzaga HF, Cardoso-Oliveira J, Gripp AC, Dias EP, Carneiro S. Geographic tongue and psoriasis: clinical, histopathological, immunohistochemical and genetic correlation-a literature review. An Bras Dermatol. 2016;91:410–21. https://doi.org/10.1590/abd1806-4841.20164288. PMID: 27579734.
73. Eisenberg E, Oreadi D. Differential diagnosis and management of oral mucosal lesions (chap. 24). In: Laskin DM, Carlson ER, editors. Clinician's handbook of oral and maxillofacial surgery. 2nd ed. Batavia: Quintessence; 2019. p. 448–9.
74. Candidiasis. White lesions (chap. 3). In: Regezi JA, Sciubba JJ, Jordan RCK, editors. Oral pathology: clinical pathologic correlations. 7th ed. St Louis: Elsevier; 2017. p. 98–102.
75. Hellstein JW, Marek CL. Candidiasis: red and white manifestations in the oral cavity. Head Neck Pathol. 2019;13:25–32. https://doi.org/10.1007/s12105-019-01004-6. Epub 2019 Jan 29. PMID: 30693459.
76. Lalla RV, Patton LL, Dongari-Bagtzoglou A. Oral candidiasis: pathogenesis, clinical presentation, diagnosis and treatment strategies. J Calif Dent Assoc. 2013;41:263–8. PMID: 23705242.
77. Millsop JW, Fazel N. Oral candidiasis. Clin Dermatol. 2016;34:487–94. https://doi.org/10.1016/j.clindermatol.2016.02.022. Epub 2016 Mar 2. PMID: 27343964.
78. Akpan A, Morgan R. Oral candidiasis. Postgrad Med J. 2002;78:455–9. https://doi.org/10.1136/pmj.78.922.455. PMID: 12185216.
79. Gendreau L, Loewy ZG. Epidemiology and etiology of denture stomatitis. J Prosthodont. 2011;20:20251–60. https://doi.org/10.1111/j.1532-849X.2011.00698.x. Epub 2011 Apr 4. PMID: 21463383.
80. Martorano-Fernandes L, Dornelas-Figueira LM, Marcello-Machado RM, Silva RB, Magno MB, Maia LC, Del Bel Cury AA. Oral candidiasis and denture stomatitis in diabetic patients: Systematic review and meta-analysis. Braz Oral Res. 2020;34:e113. https://doi.org/10.1590/1807-3107bor-. PMID: 32965459.
81. Yarborough A, Cooper L, Duqum I, Mendonça G, McGraw K, Stoner L. Evidence regarding the treatment of denture stomatitis. J Prosthodont. 2016;25(4):288–301. https://doi.org/10.1111/jopr.12454. Epub 2016 Apr 6. PMID: 27062660.
82. Corrêa PH, Nunes LC, Johann AC, Aguiar MC, Gomez RS, Mesquita RA. Prevalence of oral hemangioma, vascular malformation and varix in a Brazilian population. Braz Oral Res. 2007;21:40–5. https://doi.org/10.1590/s1806-83242007000100007. PMID: 17384854.
83. Lazos JP, Piemonte ED, Panico RL. Oral varix: a review. Gerodontology. 2015;3:82–9. https://doi.org/10.1111/ger.12074. Epub 2013 Sep 1. PMID: 23992044.
84. Developmental defects of the oral mucosa and maxillofacial region. In: Neville BW, Damm DD, Allen CA, Chi AC, editors. Oral and maxillofacial pathology. 4th ed. St Louis: Elsevier; 2016. p. 12–3.
85. Pernicious anemia; Iron deficiency anemia. Red-blue lesions (chap. 4). In: Regezi JA, Sciubba JJ, Jordan RCK, editors. Oral pathology: clinical pathologic correlations. 7th ed. St Louis: Elsevier; 2017. p. 118–9.
86. Chiang CP, Chang JY, Wang YP, Wu YH, Wu YC, Sun A. Atrophic glossitis: etiology, serum autoantibodies, anemia, hematinic deficiencies, hyperhomocysteinemia, and management. J Formos Med Assoc. 2020;119:774–80. https://doi.org/10.1016/j.jfma.2019.04.015. Epub 2019 May 8. PMID: 31076315.
87. Erythema multiforme. Ulcerative conditions (chap. 2). In: Regezi JA, Sciubba JJ, Jordan RCK, editors. Oral pathology: clinical pathologic correlations. 7th ed. St Louis: Elsevier; 2017. p. 40–3.
88. Erythema multiforme. Dermatologic diseases (chap. 16). In: Neville BW, Damm DD, Allen CA, Chi AC, editors. Oral and maxillofacial pathology. 4th ed. St Louis: Elsevier; 2016. p. 723–6.
89. Samim F, Auluck A, Zed C, Williams PM. Erythema multiforme: a review of epidemiology, pathogenesis, clinical features, and treatment. Dent Clin N Am. 2013;57:583–96. https://doi.org/10.1016/j.cden.2013.07.001. PMID: 24034067.
90. Sokumbi O, Wetter DA. Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist. Int J Dermatol. 2012;51:889–902. https://doi.org/10.1111/j.1365--4632.2011.05348.x. PMID: 22788803.
91. Ayangco L, Rogers RS III. Oral manifestations of erythema multiforme. Dermatol Clin. 2003;21:195–205. https://doi.org/10.1016/s0733-8635(02)00062-1. PMID: 12622281.
92. Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, Harr T. Current perspectives on Stevens-Johnson syndrome and toxic epidermal necrolysis. Clin Rev Allergy Immunol. 2018;54(1):147–76. https://doi.org/10.1007/s12016-017-8654-z. PMID: 29188475.
93. Alawi F. Pigmented lesions of the oral cavity: an update. Dent Clin N Am. 2013;57:699–710. https://doi.org/10.1016/j.cden.2013.07.00.

94. Rosebush MS, Briody AN, Cordell KG. Black and brown: non-neoplastic pigmentation of the oral mucosa. Head Neck Pathol. 2019;13:47–55. https://doi.org/10.1007/s12105-018-0980-9.
95. Eisenberg E, Oreadi D. Oral pigmented lesions. Differential diagnosis and management of oral mucosal lesions (chap. 24). In: Laskin DM, Carlson ER, editors. Clinician's handbook of oral and maxillofacial surgery. 2nd ed. Batavia: Quintessence; 2019. p. 466–71.
96. Drug-related discolorations of the oral mucosa. Physical and chemical injuries. In: Neville BW, Damm DD, Allen CA, Chi AC, editors. Oral and maxillofacial pathology. 4th ed. St Louis: Elsevier; 2016. p. 290–2.
97. Pigmented lesions. Non-melanocytic lesions (chap. 5). In: Regezi JA, Sciubba JJ, Jordan RCK, editors. Oral pathology: clinical pathologic correlations. 7th ed. St Louis: Elsevier; 2017. p 137–9.
98. Non-keratinocytes in the oral epithelium. Melanocytes and oral pigmentation. Oral epithelium (chap. 3). In: Squier C, Brogden KA, editors. Human oral mucosa: development, structure and function. Ames: Wiley; 2011. p. 41–6.
99. Eisenberg E, Natarajan E, Formaker BK. Non-keratinocytes. Melanocytes. Oral mucosa and mucosal sensation (chap. 9). In: Hand AR, Frank ME, editors. Fundamentals of oral histology and physiology. Ames: Wiley-Blackwell; 2014. p. 176–7.
100. Gondak RO, da Silva-Jorge R, Jorge J, Lopes MA, Vargas PA. Oral pigmented lesions. Clinicopathologic features and review of the literature. Med Oral Patol Oral Cir Bucal. 2012;17:e919–24. https://doi.org/10.4317/medoral.17679. PMID: 22549672.
101. Pigmented lesions. Melanocytic lesions (Benign) (chap. 5). In: Regezi JA, Sciubba JJ, Jordan RCK, editors. Oral pathology: clinical pathologic correlations. 7th ed. St Louis: Elsevier; 2017. p 127–3.
102. Oral melanotic macule (Focal melanosis), Melanoacanthoma, oral melanocytic nevi. Epithelial pathology (chap. 10). In: Neville BW, Damm DD, Allen CA, Chi AC, editors. Oral and maxillofacial pathology. 4th ed. St Louis: Elsevier; 2016. pp. 348–55.
103. Kiuru M, Tartar DM, Qi L, Chen D, Yu L, Konia T, McPherson JD, Murphy WJ, Fung MA. Improving classification of melanocytic nevi: association of BRAF V600E expression with distinct histomorphologic features. J Am Acad Dermatol. 2018;79:221–9. https://doi.org/10.1016/j.jaad.2018.03.052. Epub 2018 Apr 11. PMID: 29653212.
104. Damsky WE, Bosenberg M. Oncogene. Melanocytic nevi and melanoma: unraveling a complex relationship. J Am Acad Dermatol. 2017;36:5771–92. https://doi.org/10.1038/onc.2017.189. Epub 2017 Jun 12. PMID: 28604751.
105. Melanoma (malignant melanoma, melanocarcinoma). Epithelial pathology (chap. 10). In: Neville BW, Damm DD, Allen CA, Chi AC, editors. Oral and maxillofacial pathology. 4th ed. St Louis: Elsevier; 2016. p. 401–7.
106. Pigmented lesions. Melanoma (chap. 5). In: Regezi JA, Sciubba JJ, Jordan RCK, editors. Oral pathology: clinical pathologic correlations. 7th ed. St Louis: Elsevier; 2017. p 124–37.
107. Rawal YB, Dodson TB, Bal HS. Oral melanoma: relevance to the dental team. JADA. 2017;148:113–8. https://doi.org/10.1016/j.adaj.2016.10.005. PMID: 27836097.
108. Mao L, Qi Z, Zhang L, Guo J, Si L. Immunotherapy in acral and mucosal melanoma: current status and future directions. Front Immunol. 2021;12:680407. https://doi.org/10.3389/fimmu.2021.680407. eCollection 2021. PMID: 34149718.
109. Benevenuto de-Andrade B-A, Toral-Rizo VH, León JE, Contreras E, Carlos R, Delgado-Azañero W, Mosqueda-Taylor A, de-Almeida O-S. Primary oral melanoma: a histopathological and immunohistochemical study of 22 cases of Latin America. Med Oral Patol Oral Cir Bucal. 2012;17:e383–8. https://doi.org/10.4317/medoral.17588.
110. Green B, Elhamshary A, Gomez R, Rahimi S, Brennan PA. An update on the current management of head and neck mucosal melanoma. J Oral Pathol Med. 2017;46:475–9. https://doi.org/10.1111/jop.12526. Epub 2017 Jan 10. PMID: 27864904.

Ulcerations

18

Scott M. Peters

Introduction

An **ulceration**, by definition, is a lesion which lacks surface epithelium. Ulcerations involving the oral cavity are frequently detected on clinical examination. They may be acute or chronic, solitary, or multifocal, and variably painful. In some instances, they may represent oral manifestations of underlying systemic diseases. This chapter will review some of the more commonly encountered oral ulcerations and discuss their etiology and management.

Acute Oral Ulcerations

Aphthous Ulceration

An **aphthous ulcer**, colloquially referred to as a "canker sore," is one of the most commonly encountered oral lesions. Aphthous ulcerations may be seen in patients of any age, gender, and racial or ethnic background, although the majority of patients who report recurrent oral aphthae are young adults below the age of 30 years [1]. Although much investigation has been performed in an attempt to find the cause of aphthous ulcerations, no single triggering agent has been identified. Rather, there are likely a collection of factors which may predispose patients to developing aphthae, including (but not limited to) allergies, genetic factors, hormonal factors, hematologic abnormalities, vitamin or nutritional deficiencies, immunologic factors or infectious agents, stress, and trauma [1, 2]. In a large percentage of patients, the cause for their aphthous ulcerations is never identified. While the causes for oral aphthae are diverse, the lesions themselves are believed to be the result of T-cell mediated mucosal destruction, which leads to surface ulceration and inflammation [3].

S. M. Peters (✉)
Oral and Maxillofacial Pathology,
Geisinger Health System, Wilkes-Barre, PA, USA
e-mail: smp2140@cumc.columbia.edu

Aphthous ulcerations typically involve non-keratinized oral mucosal surfaces, such as the labial mucosa, buccal mucosa, soft palate, floor of mouth, and lateral or ventral aspects of the tongue. The ulcerations are often covered by a tan-gray pseudomembrane with a surrounding erythematous halo [1]. Oral aphthae are further subclassified based on their size and duration (Table 18.1). **Minor aphthous ulcerations**, also known as Mikulicz aphthae, measure between 3 and 10 mm in diameter, have a variable recurrence rate, and heal without scarring over a course of 1–2 weeks (Fig. 18.1). Minor aphthae are the most commonly encountered variant of oral aphthous ulcerations, representing approximately 80% of cases of oral aphthae [1, 2]. **Major aphthous ulcerations**, also referred to as Sutton disease or periadenitis mucosa necrotica recurrens, are larger and deeper than minor aphthae and take longer to heal. Most major aphthous ulcerations measure between 1 and 3 cm in diameter and require approximately 2–6 weeks to fully heal (Fig. 18.2). Due to their increased size and depth, scarring of the affected tissue may develop as a result of the healing process. Although any oral mucosal site may be affected, major aphthae show an increased predilection for the palate, tonsillar region, and labial mucosa [1, 2]. The last subcategory, **herpetiform aphthous ulcerations**, is named due to the resemblance of these lesions to recurrent intraoral herpetic ulcerations (see later in this chapter). Unlike recurrent herpetic lesions, however, the herpetiform version of oral aphthae tends to involve non-keratinized oral tissues. This variant of aphthous ulcerations demonstrates the greatest number of lesions and the most frequent recurrences; however, the individual lesions themselves are quite small, measuring only between 1 and 3 mm in size (Fig. 18.3). Herpetiform aphthae usually heal over a course of 7 to 10 days; however, recurrences are seen more frequently than in the minor and major variants [1, 2].

The term **recurrent aphthous stomatitis** is sometimes used to describe patients who frequently suffer from multiple bouts of oral aphthae. Patients may be described as having either **simple** or **complex aphthosis.** Simple aphthosis is defined as patients who develop only a few lesions which

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_18

Table 18.1 Summary of aphthous ulceration subcategorization

Category	Number	Size	Duration
Minor	Few	Less than 1 cm	1–2 weeks
Major	Few	1–3 cm	2–6 weeks
Herpetiform	Hundreds	Less than 3 mm	7–10 days but with frequent recurrences

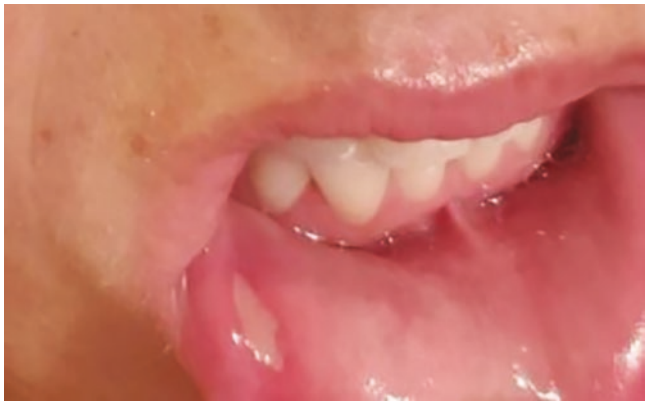


Fig. 18.1 Minor aphthous ulceration involving the lower labial mucosa

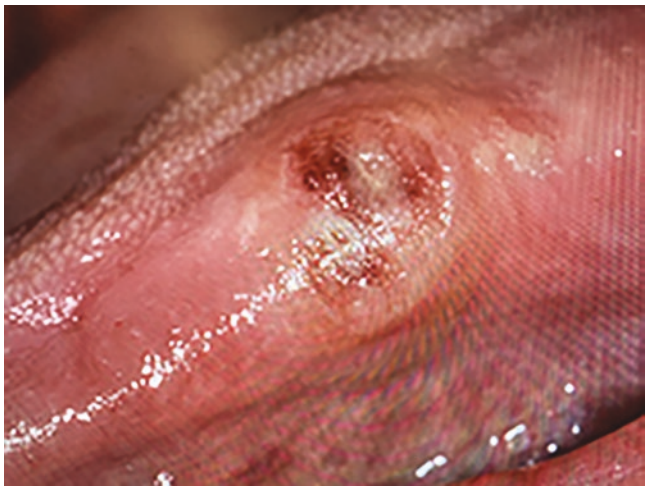


Fig. 18.2 Major aphthous ulceration involving the left lateral tongue. This patient's medical history was significant for Crohn's Disease (photograph courtesy of Dr. Michele Bergen)

heal in 1–2 weeks and recur infrequently. Complex aphthosis is characterized by multiple aphthae in which new lesions form almost as quickly as older lesions resolve [4].

Treatment of aphthous ulcerations is primarily palliative. Patients with minor aphthae are best treated with topical corticosteroid therapy. If multiple lesions are present, a Dexamethasone solution administered as a swish and spit is most effective [5]. If the lesion is solitary in nature, then a topical steroid cream such as Triamcinolone is more appropriate. Patients may also be advised to use these medications

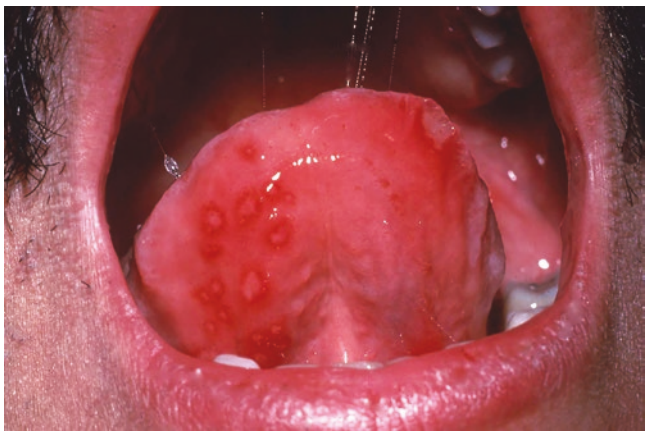


Fig. 18.3 Herpetiform aphthae involving the lateral and ventral aspect of the tongue (photograph courtesy of Dr. Elizabeth Philipone)

at the start of any recognizable prodromal symptoms in an attempt to abort ulcer development or shorten the course of the ulcer outbreak. Even without any treatment, minor and herpetiform aphthae will predictably heal over the course of several weeks. Due to their larger size, major aphthae will not respond as readily to topical corticosteroid treatment and often require either injectable corticosteroids or a short course of a systemic corticosteroid. An abundance of caution should be used when prescribing systemic corticosteroid therapy in patients with multifocal oral ulcerations, as this may have inadvertent negative consequences in patients with undiagnosed pemphigus vulgaris (see later in this chapter). In most cases, topical corticosteroid therapies are the best initial course of management. Other treatment modalities, such as laser ablation, chemical cautery, and non-steroidal medications, also exist [6].

In addition to palliative care of aphthous ulcerations, an attempt should be made to try to identify the triggering agent in a patient. In greater than 50% of patients with complex aphthosis, there is often an underlying systemic disease or condition that may be associated with the patient's oral lesions [4]. A listing of some of the more commonly diagnosed systemic diseases that may be associated with recurrent aphthous stomatitis is listed in Table 18.2. Some of these conditions are discussed in greater detail later in this chapter. The histologic features of an aphthous ulceration are non-specific. A biopsy of an oral aphthae will demonstrate a fibrinopurulent membrane and absence of surface epithelium; in the ulcer bed, acute and chronic inflammatory cells and granulation tissue formation will be observed (Fig. 18.4) [6]. Biopsy is not indicated to confirm the diagnosis of an aphthous ulceration, but may have value if trying to exclude other vesiculoerosive conditions from a differential diagnosis (see later in this chapter). Similarly, no laboratory tests will help provide a definitive diagnosis of an aphthous ulceration, but may shed light on possible underlying causes for a patient's lesions.

Herpetic Ulceration

Recurrent herpetic ulcerations are commonly encountered acute ulcerative processes which may involve the oral cavity. They represent a re-activation of **herpes simplex virus** (see Chap. 12), which typically remains latent in neural ganglia following an initial (often subclinical) infection. Recurrent herpetic ulcerations may be caused by a variety of factors, including (but not limited to) stress, environmental factors such as heat, wind, or cold, old age, pregnancy, ultraviolet light, dental treatment, systemic disease, respiratory tract infections, and menstruation [7, 8]. Unlike aphthous ulcerations, which tend to involve non-keratinized oral sites, herpetic ulcerations will affect keratinized tissues such as the hard palate and attached gingiva (Fig. 18.5). The lesions appear as clustered vesicles, each measuring approximately 1–3 mm in size [9]. They are acutely painful. Recurrent herpetic ulcerations are self-limiting and will resolve on their own over a course of 1–2 weeks. Patients should be instructed not to touch active lesions as this may lead to auto-inoculation of other body sites. Similarly, elective dental procedures should be delayed until the lesions resolve. Anti-viral therapies, such as Acyclovir, may be considered when a patient suffers from multiple recurrences, has an exacerbated erythema multiforme-like response to a recurrence (see later in this chapter), or when the condition is detected and diagnosed within the first 24 h of lesion onset [9]. In most cases, however, treatment is palliative and antiviral therapy is not indicated. Recurrent herpetic ulcerations represent the intraoral equivalent of a cold sore, or **herpes labialis** (see Chap. 12). The oral cavity may be host to a variety of lesions caused by either initial or recurrent infection with a large number of members of the **Human Herpes Virus** (HHV) family, of which herpes simplex virus is only one member. For a full listing of these different conditions, please refer to Chap. 12.

Table 18.2 Systemic conditions which may present with oral aphthous ulcerations

Bechet syndrome
Celiac disease
Cyclic neutropenia
IgA deficiency
Immunocompromised conditions
MAGIC syndrome
PFAPA syndrome
Reactive arthritis
Sweet syndrome
Vitamin and mineral deficiencies

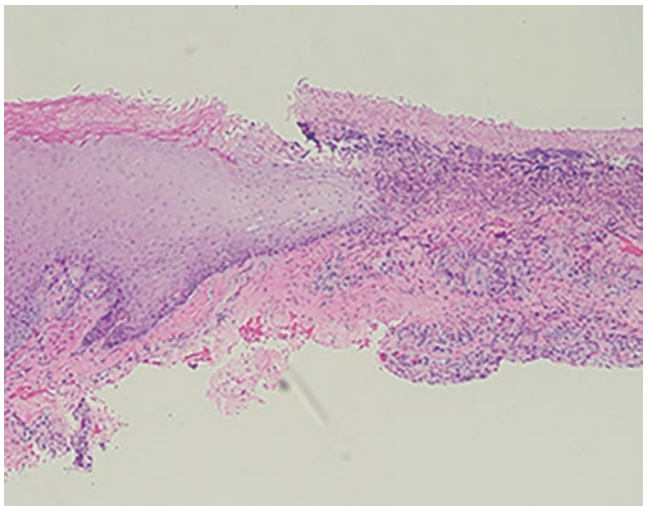


Fig. 18.4 Histologic examination of an aphthous ulceration demonstrates a loss of surface epithelium. Collections of inflammatory cells are seen in the superficial connective tissue layers

Erythema Multiforme

Erythema multiforme (EM) is a blistering, mucocutaneous disease of uncertain etiology. Although the exact pathogenesis is not fully understood, it is believed to represent an immunologically mediated hypersensitivity reaction. The majority of cases of EM occur in response to an infectious agent, most frequently herpes simplex virus or *Mycoplasma pneumoniae*. EM may also be the result of an offending medication, usually either an antibiotic or an analgesic [10]. In some cases, the cause for the patient's lesions remains unknown. EM is subclassified as **erythema multiforme**

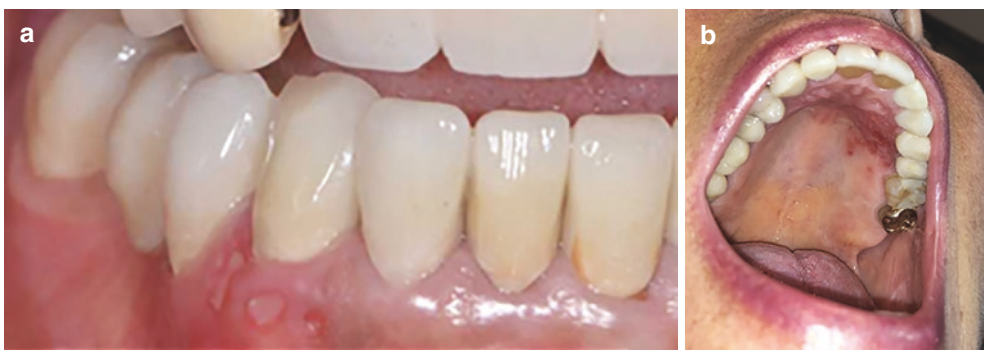


Fig. 18.5 Recurrent intraoral herpes. Small, clustered tan-gray ulcerated lesions involving the keratinized oral tissues, specifically the attached gingiva (**a**) and the hard palate (**b**)

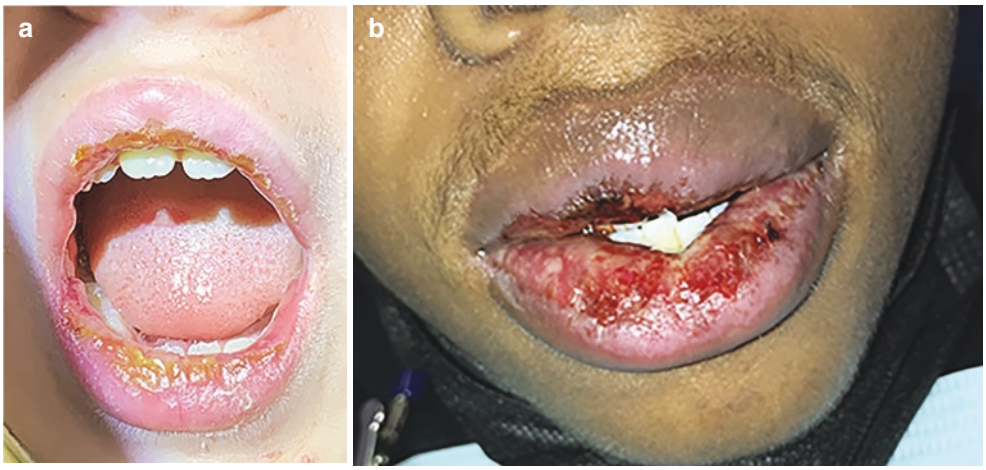


Fig. 18.6 (**a**, **b**) Crusted, hemorrhagic labial mucosal lesions observed in a patient with erythema multiforme ((**a**) courtesy of Dr. Khanh Trinh, (**b**) courtesy of Dr. Nicholas Saggese)

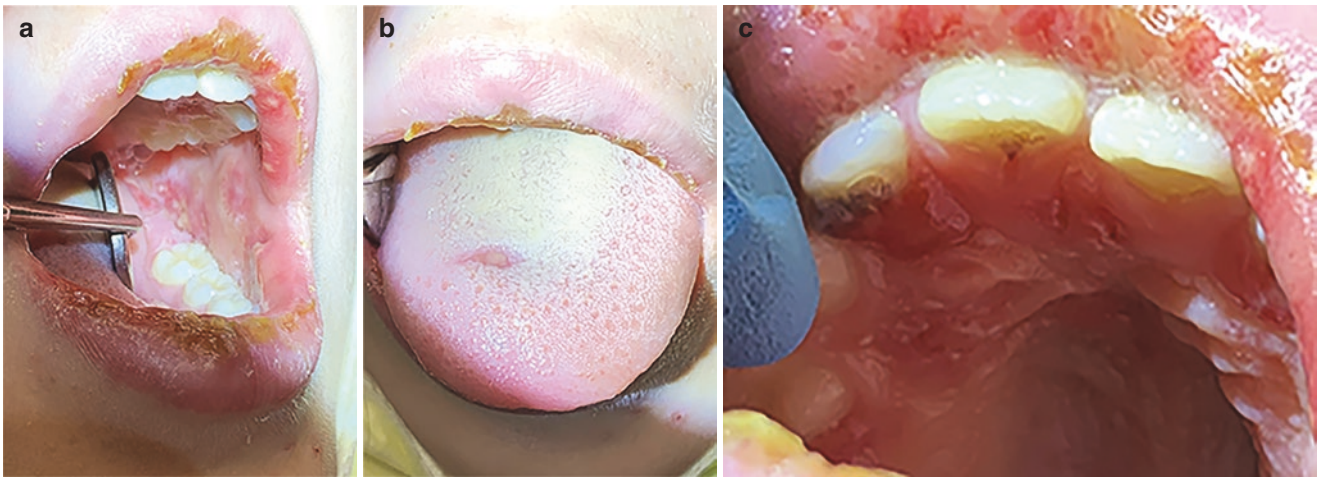


Fig. 18.7 Buccal mucosal (**a**), tongue (**b**), and gingival (**c**) lesions in a patient with erythema multiforme. This is the same patient as seen in Fig. 18.6a (photographs courtesy of Dr. Khanh Trinh)

minor or **erythema multiforme major** based on the amount of body sites involved. **Stevens-Johnson syndrome** and **toxic epidermal necrolysis**, once considered part of the EM-spectrum of lesions, are now categorized as distinct entities [11].

EM most commonly affects young adults with a peak incidence between the ages of 20–30 years. It has an acute onset, and the lesions may be preceded by a prodromal stage consisting of non-specific symptoms such as fever, malaise, headache, cough, and a sore throat [10]. The lesions of erythema multiforme are varied in appearance and distribution. When the oral cavity is affected, lesions first appear as erythematous patches which undergo epithelial necrosis and begin to slough, resulting in large, irregular tan-gray pseudomembranes. Hemorrhagic crusting of the lips may also be seen; these are often described clinically as "black, crusted lips" (Fig. 18.6). The oral lesions more commonly involve the buccal mucosa, labial mucosa, and the tongue (Fig. 18.7). Although the palate and gingiva may be affected, these sites are often spared [12, 13]. When the skin is involved, lesions will have varied appearances but the hallmark feature is the so-called "targetoid" or "bullseye" lesion. These lesions appear as concentric rings of erythema with central zones of ulceration and tissue necrosis [14].

The distinction between EM Minor and EM Major is based on number of mucosal sites involved. In patients with EM Major, widespread skin lesions along with lesions involving two or more mucosal sites must be documented. Mucosal sites that may be affected by EM include oral, genitourinary, respiratory, and conjunctival [10]. Of these, oral involvement is seen most frequently. Severe ocular involvement may result in adhesions similar to those seen in mucosal membrane pemphigoid (see later in this chapter).

EM is a self-limiting condition and the majority of treatment is palliative in nature. Most cases of EM will resolve over a period of 2–6 weeks. In patients whose lesions resulted from a hypersensitivity reaction to medication, the offending agent should be identified and withdrawn. Patients who

develop EM as a result of recurrent herpes simplex infection may benefit from long-term Acyclovir therapy [9, 10, 14]. Due to the discomfort associated with the oral lesions, patients may be unable to maintain adequate nutrition and may require intravenous rehydration. Topical anesthetics, such as viscous lidocaine solutions, may also be helpful in reducing the pain associated with the oral lesions. Although steroid therapy in patients with EM has been considered controversial in the past, most patients with EM minor or major will benefit from a topical steroid solution, such as dexamethasone, or a short course of a systemic steroid therapy [14]. Diagnosis of EM is made clinically and if these lesions are biopsied, the microscopic findings are non-specific. In patients with lesions resembling EM but of chronic duration, conditions such as pemphigus vulgaris (see later in this chapter) and paraneoplastic pemphigus should be considered.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Previously considered to represent extreme manifestations of EM, **Stevens-Johnson syndrome** (SJS) and **toxic epidermal necrolysis** (TEN) are now considered distinct entities. Most cases of SJS and TEN (also referred to as Lyell Disease) are the result of an adverse reaction to an offending medication [11]. The primary distinction between SJS and TEN is the degree of skin involvement. In patients with SJS, less than 10% of body surfaces are affected. In TEN, greater than 30% of sites are affected. Patients are said to have overlapping features of SJS and TEN when between 10 and 30% of the body surface is involved [15]. Patients with SJS and TEN will have a prodromal stage similar to that observed in EM, after which skin and mucosal involvement will develop. The skin lesions begin as erythematous patches which subsequently form large blisters and surface ulcerations. Oral lesions will appear similarly to their EM counterparts.

Due to the degree of skin involvement, patients with SJS and TEN are often treated in the burn units of hospitals. They are at increased risk for both dehydration and infection, and corticosteroid treatment is often contraindicated. Treatment involves removal of the offending medication and palliative therapies [11, 15].

Necrotizing Sialometaplasia

Necrotizing sialometaplasia is an acute, locally destructive inflammatory process of the minor salivary glands. It is believed to occur as a result of local ischemia and infarction of the salivary gland tissue [16]. Approximately 75% of cases of necrotizing sialometaplasia involve the palate, with the hard palate being the most commonly affected site. The most frequently reported cause of necrotizing sialometaplasia is local anesthetic (dental) injections. Other causes include trauma, denture irritation, upper respiratory infections, surgery, adjacent tumors, and bulimia. It is theorized that these conditions restrict the blood supply to the affected minor salivary glands, which then leads to ischemia and tissue necrosis [16, 17].

Necrotizing sialometaplasia initially presents as a non-ulcerated swelling of the affected tissue. In most cases, there is accompanying pain or paresthesia. Over the course of the following 2–3 weeks, the necrotic tissue at the site of the swelling will slough off, leaving an ulcerated defect. Patients will often report that a piece of their palate "fell out." At this stage, the lesion also becomes relatively painless [16].

Necrotizing sialometaplasia is an acute, self-limiting process that will resolve over a period of weeks. The challenge with necrotizing sialometaplasia is that it clinically and microscopically resembles malignant lesions, and diagnosis can be difficult in the absence of a strong clinical suspicion. From a clinical perspective, when necrotizing sialometaplasia appears as a swelling in its early stages, it may resemble a variety of mesenchymal tumors, salivary gland tumors, and lymphomas which may also present as palatal swellings. In its later ulcerated stages, necrotizing sialometaplasia resembles squamous cell carcinoma and a variety of infectious entities, such as gumma, deep fungal ulcerations, and oral lesions of tuberculosis [18]. Microscopically, necrotizing sialometaplasia will demonstrate necrosis of the minor salivary gland lobules and squamous metaplasia of the ducts; this latter change can rarely be misinterpreted as squamous cell carcinoma. A thorough clinical history, including detailing any recent dental work which may have occurred prior to formation of the lesion, can be helpful when trying to arrive at a diagnosis. Biopsy may not always be indicated if there is strong reason to suspect a diagnosis of necrotizing sialometaplasia; however, patients must be kept on close clinical follow-up. Furthermore, a tissue biopsy should be performed if a suspected necrotizing sialometaplasia lesion fails to resolve over the course of a few weeks [16, 19].

Chronic Oral Ulcerations

Traumatic Ulcerations and TUGSE

Traumatic ulcerations may be either acute or chronic in nature. They are the result of irritation of the oral mucosa which leads to a disruption of the surface epithelium. The clinical appearance of a traumatic ulceration is similar to that of an aphthous ulceration. The majority of cases involve the tongue, lips, or buccal mucosa. Unlike aphthous ulcerations, keratinized mucosa such as the hard palate and gingiva may also be affected. In cases of longer-standing or chronically

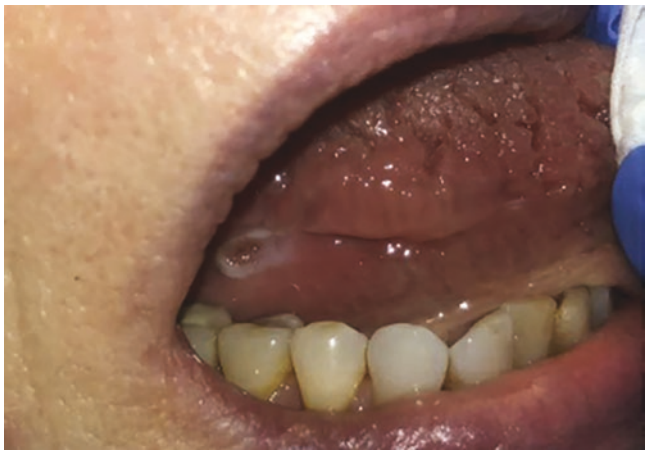


Fig. 18.8 Traumatic ulceration of the right ventro-lateral tongue

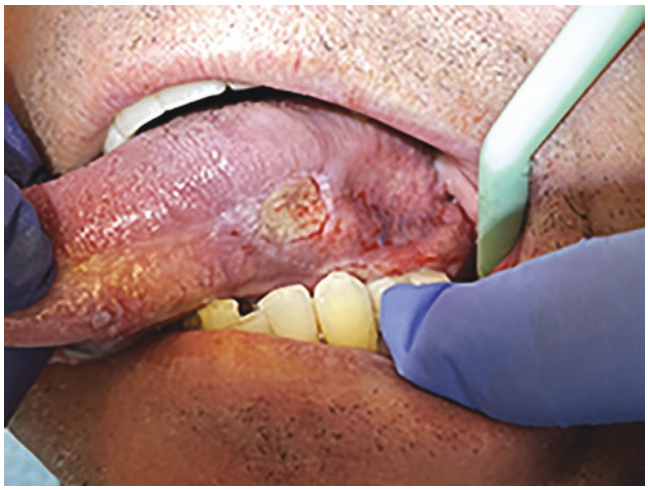


Fig. 18.9 Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE) of the left lateral tongue (photograph courtesy of Dr. Jared Miller)

irritated traumatic ulcerations, the mucosa surrounding the central ulcerative zone will be firm, rolled, and hyperkeratotic (Fig. 18.8). The microscopic appearance of a traumatic ulceration is also similar to that of oral aphthae [6].

Traumatic ulcerative granuloma with stromal eosinophilia, or **TUGSE**, is a type of chronic traumatic ulceration with a unique histologic appearance and behavior profile. Clinically, most cases of TUGSE have been reported on the tongue, but other oral sites may also be affected [20] (Fig. 18.9). Unlike most traumatic ulcerations, TUGSEs can take several months to resolve and in some instances may develop an exophytic component due to the proliferation of granulation tissue. Due to the clinical appearance of a slowly healing ulcerative lesion, squamous cell carcinoma is often included on the differential diagnosis for TUGSE lesions. Microscopic examination of a TUGSE will show a pseudoinvasive inflammatory reaction which often extends to and dissects through underlying skeletal muscle. The inflammatory infiltrate is mixed, but significant for the presence of abundant eosinophils [21].

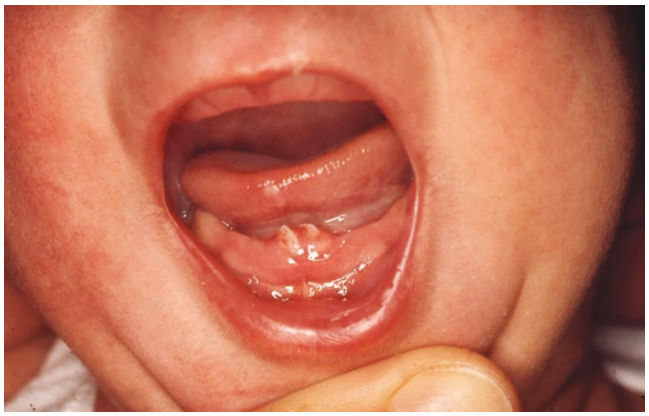


Fig. 18.10 Riga Fede Disease. An ulceration of the ventral tongue associated with natal teeth (courtesy of Dr. Elizabeth Philipone)

Treatment of traumatic ulcerations involves identifying and removing the offending irritant. In most cases, this involves smoothing an adjacent sharp tooth cusp or denture flange. Topical corticosteroids may also be prescribed in an attempt to promote healing of the lesion; however, if the cause of irritation is not removed, then the ulcer may recur [6]. TUGSEs may not be clearly associated with any source of irritation and often do not respond to topical corticosteroid therapy. Rather, definitive treatment of a TUGSE is typically achieved via intralesional corticosteroid injections or surgical excision. In some cases, TUGSEs have been shown to resolve following incisional biopsy performed for diagnostic purposes. The etiology as to why this occurs is unclear, but one hypothesis is that the surgical procedure helps increase vascular supply to the affected tissues [22].

Of note, there are other conditions which present with lesions that resemble TUGSEs clinically and microscopically. **Riga-Fede disease** typically occurs between 1 week and 1 year of age and is caused by chronic irritation of the anterior ventral surface of the tongue by natal teeth. The lesion appears as a long-standing ulceration of the ventral tongue which demonstrates features of TUGSE microscopically [23] (Fig. 18.10). Although extraction of the natal teeth would remove the source of irritation, these teeth represent the child's primary dentition in the area and they should be retained if possible. Alternative treatments include shaving down the sharp incisal edges of these teeth or cushioning them with a protective barrier.

EBV Mucocutaneous Ulcerations

Epstein-Barr virus (EBV), a member of the human herpesvirus family and also known as HHV-4, is the etiologic agent for a dizzying number of neoplastic, reactive, and infectious

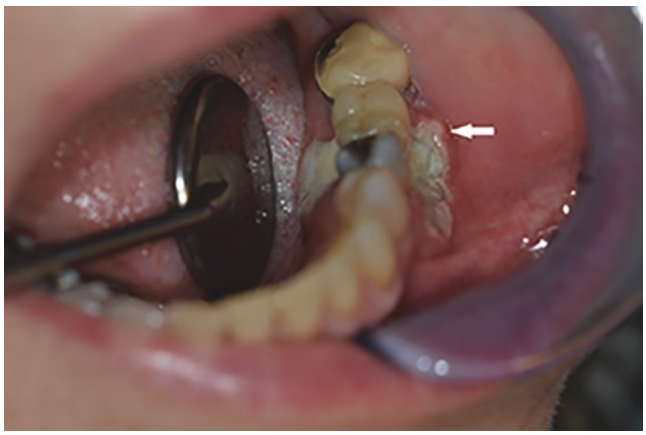


Fig. 18.11 EBV mucocutaneous ulceration. The patient's medical history was significant for recent single lung transplant (photograph courtesy of Dr. Michael McKenzie)

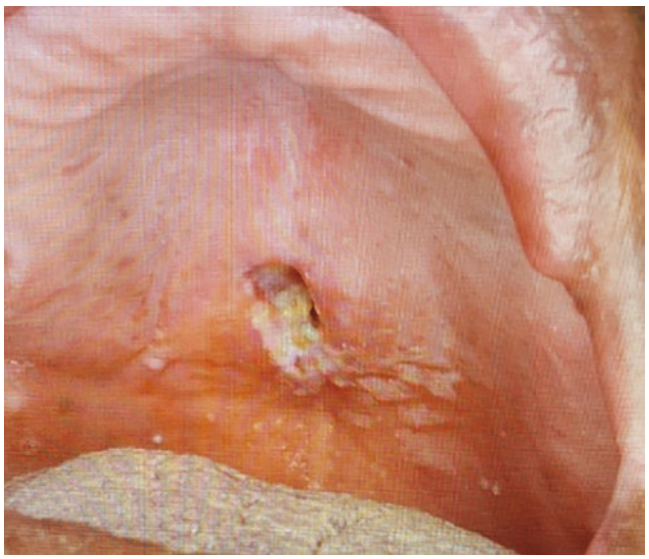


Fig. 18.12 Gumma of tertiary syphilis presenting as an ulcerated lesion of the palate (photograph courtesy of Dr. Jose Liens)

pathologies. A full listing of some of the more commonly identified EBV-associated diseases can be found in Chap. 12. This section will focus on the **EBV-associated mucocutaneous ulceration (EBVMCU)** which may present as a chronic ulcerative lesion of the oral cavity.

EBVMCUs present as non-healing chronic ulcerations of the oral mucosa, skin, or gastrointestinal tract. When the oral cavity is affected, the tongue and the tonsillar region are the most commonly involved locations. EBVMCUs occur in patients who are on immunosuppressive medications for autoimmune diseases, in post-organ transplant patients, in patients with immunosuppression due to chronic disease (HIV+ individuals), and in patients in the eighth decade of life or older (age related immune senescence). The lesions form as a result of reactivation of latent EBV infection in the setting of the aforementioned immune suppression. They appear as tan-gray ulcerations, often with overlying fibrinopurulent membranes (Fig. 18.11). Treatment requires alteration of the patient's immunosuppressive therapy regimen or management of the patient's underlying immunocompromised status [24].

Gumma

A **gumma** is an area of granulomatous inflammation that is a characteristic feature of **tertiary syphilis**. Syphilis is a bacterial infection caused by the spirochete organism ***Treponema pallidum*****.** Syphilis infection occurs in three stages: primary, secondary, and tertiary, with a period of latency ranging from months to years in between secondary and tertiary syphilis [25]. A full discussion of the clinical manifestations of syphilis is beyond the scope of this chapter; rather, this section will focus on the oral ulcerations that tertiary syphilis may cause.

Gummas appear as indurated, nodular, or ulcerated lesions which cause extensive tissue destruction. They may involve the skin, mucosa, soft tissue, bones, and internal organs. Oral lesions typically involve the palate or the tongue (Fig. 18.12). When the palate is affected, patients will present with a chronic ulceration which perforates through and communicates with the nasal cavity [26]. Tongue involvement by multiple gummas will produce a lobular pattern referred to as **interstitial glossitis**.

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is a malignant neoplasm of epithelial origin. It accounts for greater than 90% of oral malignancies. When combined with oropharyngeal carcinoma, oral cancer represents the sixth most common cancer worldwide, with approximately half a million new cases diagnosed annually [27]. The clinical appearance of oral SCC is variable, and a full discussion of all of the different oral manifestations of SCC is beyond the scope of this chapter.

The relevance of oral SCC to this section on chronic ulcerations is that one form which oral cancer may take is that of a non-healing ulcerative lesion. As a general rule, any isolated oral ulcer which fails to resolve after a course of 2 weeks should be biopsied to rule out oral SCC. Ulcerated lesions of SCC are often hard or indurated on palpation and may have surrounding areas of leukoplakia, erythroplakia, or erythroleukoplakia [28] (Fig. 18.13). When biopsying an ulcer to rule out possible oral cancer, it is important to sample the edge of the lesion rather than the center. Biopsying

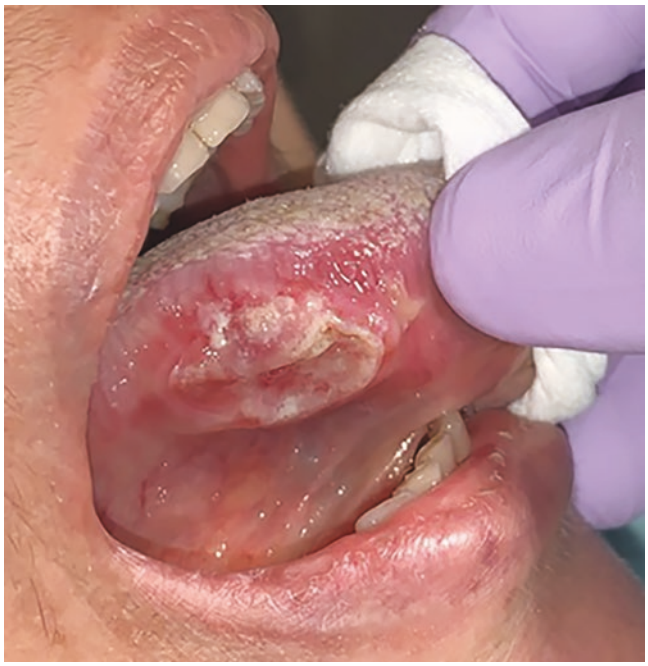


Fig. 18.13 Squamous cell carcinoma presenting as an ulcerated lesion of the right lateral tongue (photograph courtesy of Dr. Michael Forman)

the center of the ulcer will result in a non-specific diagnosis of ulceration and granulation tissue formation, as the central zone of an ulcer lacks any surface epithelium required for diagnosis. The edge of an ulcerated lesion will show the interface zone between ulcer and adjacent tissue, which is typically of higher diagnostic quality.

Deep Fungal Ulcerations

Systemic fungal infections are infrequently seen in the oral cavity. When they occur, they often appear as poorly healing ulcerated lesions which may clinically resemble squamous cell carcinoma or traumatic ulcerations (Fig. 18.14). Different fungal organisms have distinct geographic or host predilections which may help when trying to arrive at a diagnosis. For a more comprehensive listing of the different systemic fungal infections that can occur in the oral cavity, please refer to Chap. 12.

Tuberculosis

Tuberculosis (TB) is a chronic infectious disease caused by the bacteria *Mycobacterium tuberculosis*. An estimated 2 billion individuals worldwide are infected with TB, and there are approximately eight million new cases of infection globally every year. The majority of patients infected with TB do not manifest signs or systems of active disease [29].

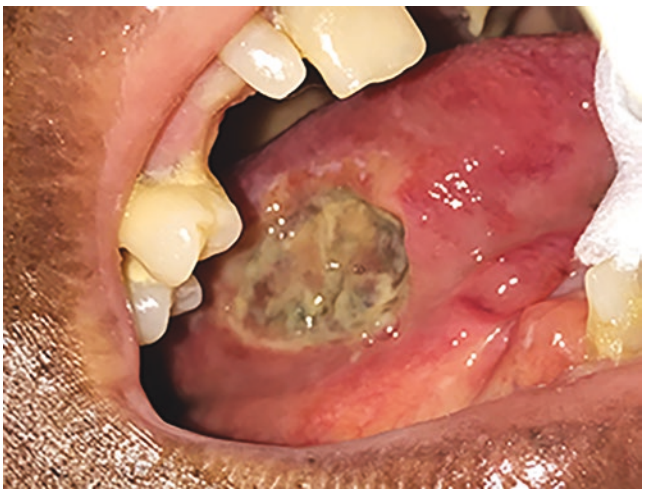


Fig. 18.14 Deep fungal ulceration. A large, tan-gray ulceration of the lateral tongue in a patient with poorly controlled Diabetes Mellitus. Biopsy showed fungal organisms belonging to the Mucor genera

Initial infection with TB results in **primary tuberculosis**. Primary TB occurs in previously unexposed individuals and almost always involves the lungs. Patients may present with a fibrocalcified lung nodule at the initial site of involvement; however, other manifestations of TB are rarely seen at this time. In the overwhelming majority of patients, TB will remain latent following this primary stage of infection. In a small percentage, typically those who are immunosuppressed, TB will reactivate; this reactivation is known as **secondary tuberculosis**. Secondary TB will have extrapulmonary involvement [29, 30].

Oral manifestations of TB are exceedingly rare and are seen as a feature of secondary TB. The most common presentation is chronic ulcerations or swelling of the oral mucosa. Chronic ulcerations of the tongue are seen most frequently, although the gingiva, labial mucosa, buccal mucosa, and palatal mucosa may also be affected [31]. TB should be included in the differential diagnosis of chronic oral ulcerations in the appropriate clinical context.

Drug-Induced Midline Defects

Patients who use recreational drugs may develop significant orofacial complications; one of the most frequently encountered is a **drug induced midline defect** (DIMD). DIMDs are typically seen in patients who abuse cocaine. Cocaine is associated with sympathetic mediated vasoconstriction that can cause local ischemia and infarction. When cocaine is snorted, patients will develop extensive necrosis of the palate which leads to ulceration and perforation (Fig. 18.15). The hard palate is more commonly affected than the soft palate, and patients will demonstrate an oral-antral communication [32].

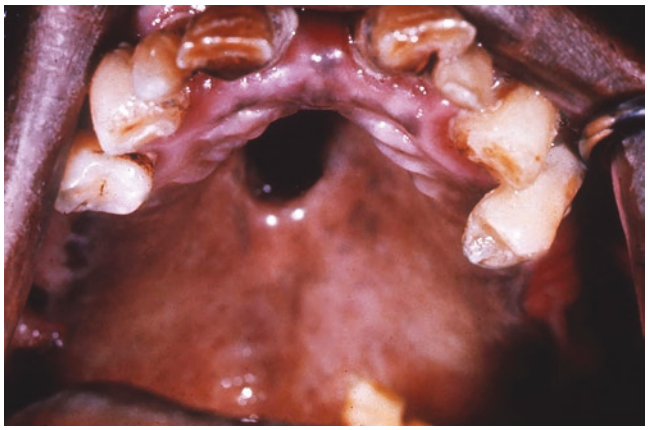


Fig. 18.15 Drug induced midline defect in a cocaine abuser (courtesy of Dr. Elizabeth Philipone)

Chronic Vesiculo-Erosive Diseases

A chronic vesiculo-erosive disease is a general term used to describe a number of conditions which present with diffuse and painful oral lesions. They tend to interfere with a patient's quality of life and can affect their ability to eat, drink, and speak. Patients will present with inflamed, erosive, and peeling oral lesions which are sometimes referred to as **desquamative**. Many of the chronic vesiculo-erosive diseases that manifest in the oral cavity are manifestations of autoimmune or autoimmune-like conditions. The three most frequently encountered chronic vesiculo-erosive lesions of the oral cavity are **lichen planus**, **mucosal membrane pemphigoid**, and **pemphigus vulgaris** [33]. These three entities account for approximately 90% of the chronic vesiculo-erosive lesions encountered in the mouth, and they will be the focus of the following sections.

Lichen Planus

Lichen planus is a chronic mucocutaneous disorder of unclear etiology. It is often categorized as an autoimmune disease, although the exact mechanism remains unknown. It has been theorized that lichen planus results from aberrant activation of CD4+ T-lymphocytes, which subsequently leads to an inflammatory response and the characteristic clinical manifestations of the disease. It is most often seen in middle-aged adults with a slight female predilection reported [34]. Lichen planus may involve the oral mucosa, genital mucosa, and/or the skin. The incidence of cutaneous lichen planus in the population has been reported to be approximately 1%. The incidence rate of oral lichen planus varies, but is generally accepted to be in the range of 0.1 to 2%. Approximately one quarter of patients with oral lichen planus may develop a cutaneous component to their disease [34]. This section will focus primarily on the oral manifestations of lichen planus.

Oral lichen planus may be broadly divided into two categories: **reticular** and **erosive**. Reticular lichen planus is seen more commonly than erosive lichen planus. Lesions are white in color and often demonstrate a lace-like pattern which is referred to as **Wickham Striae** [34, 35] (Fig. 18.16). In some areas, such as the dorsal aspect of the tongue, these white lesions appear thicker and more plaque-like in quality (Fig. 18.17). Patients with reticular lichen planus are often asymptomatic, although they may endorse a rough feeling of the affected mucosa. Erosive lichen planus is seen less frequently than reticular lichen planus, but it is often painful. Patients will frequently describe discomfort which they qualify as itching, burning, or stinging. These symptoms tend to be exacerbated by stress and certain types of foods and beverages (acidic, spicy, citrus-based). Lesions of erosive lichen planus are red and white in color; the red areas are described as erosive or erythematous and they may demonstrate varying degrees of prominence [35, 36] (Fig. 18.18). The white component of erosive lichen planus will often show a lace-like pattern similar to that seen in reticular lichen planus, although it may be more subtle to detect. Patients may also have an ulcerative component of erosive lichen planus which appears as shallow ulcerations with tan-gray pseudomembranes (Fig. 18.19). Any oral mucosal site may be affected by lichen planus, with the buccal mucosa, the gingiva, the palate, and the tongue most frequently involved. Oral lichen planus, both reticular and erosive forms, tends to be chronic, bilateral, and/or multifocal. The lesions of lichen planus will wax and wane but rarely completely disappear. The presence of a solitary lesion is also unusual for a diagnosis of lichen planus [35].

The diagnosis of lichen planus is confirmed via biopsy. On microscopic examination, there is a band-like infiltrate of lymphocytes seen subjacent to the epithelium in the superficial connective tissue (Fig. 18.20). Liquefactive degeneration of the basement membrane is observed, and exocytosis of lymphocytes into the epithelium is noted. The epithelium will demonstrate saw-tooth rete ridges, and degenerated keratinocytes referred to as **Civatte** or **colloid bodies** are seen [35, 37].

Lichen planus is primarily treated with topical corticosteroids. Steroid therapy is only indicated in patients with symptomatic lichen planus [38]. In those who are asymptomatic, no treatment other than continued follow-up is recommended. Patients should be informed of the association between oral lichen planus and oral squamous cell carcinoma. Although the exact nature of this association remains a topic of debate, there has been a reported 1–2% increased risk of developing oral squamous cell carcinoma in the setting of lichen planus [39–41] (Fig. 18.21). Patients should be kept on continued, long-term follow-up by a dentist and/or a dental specialist.

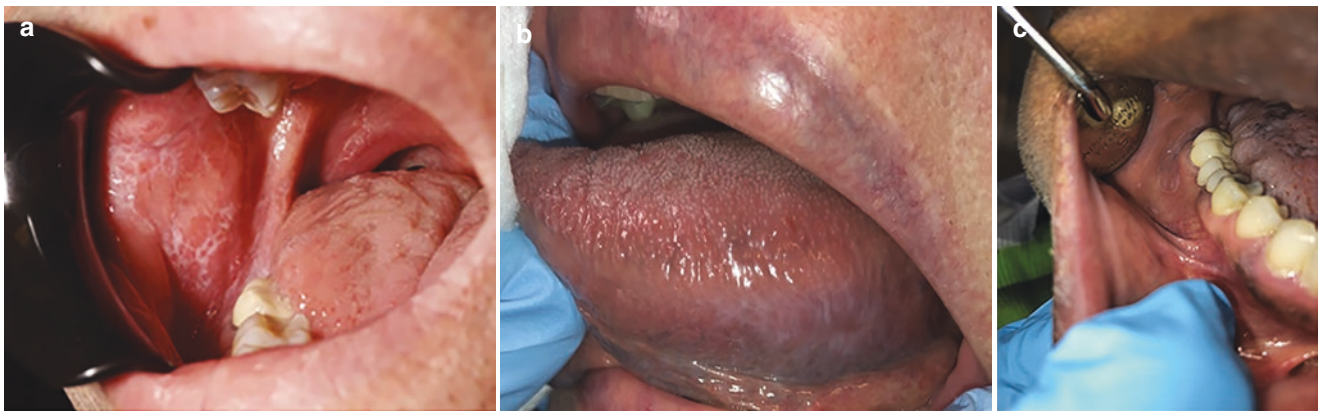
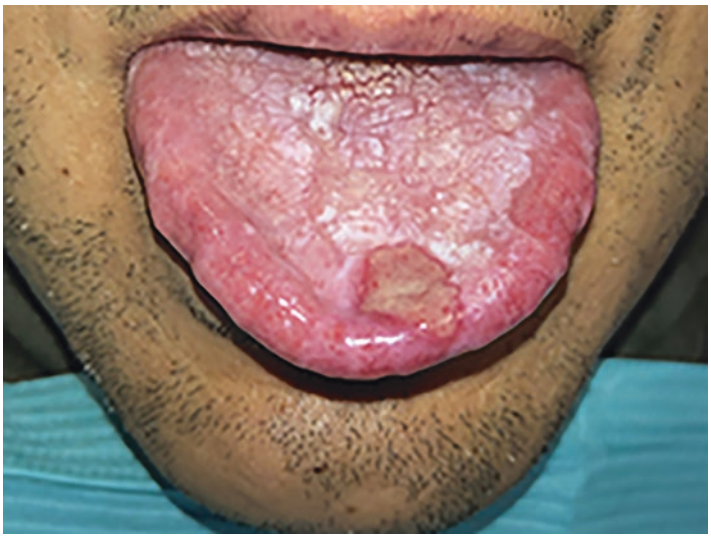


Fig. 18.16 White, lace-like lesions of reticular lichen planus involving the right buccal mucosa (**a**), the left lateral tongue (**b**), and the right retromolar region (**c**). (Panel A courtesy of Dr. Tim Kunkle)

Fig. 18.17 Plaque-like appearance of lichen planus on the dorsal aspect of the tongue. This patient also has an ulcerative component of lichen planus involving the anterior aspect of the tongue



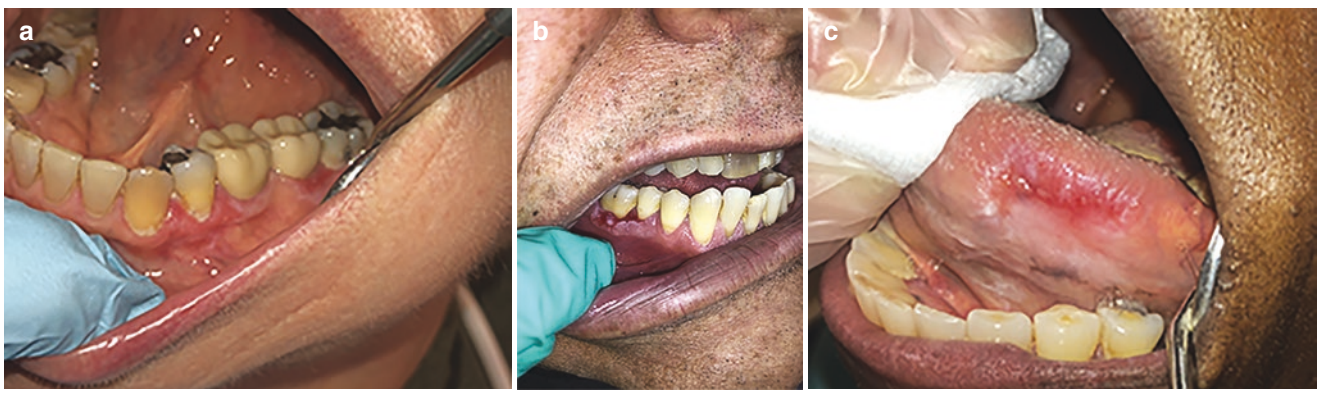


Fig. 18.18 Erosive lichen planus involving the left mandibular facial gingiva (**a**), the right mandibular facial gingiva (**b**), and the left lateral tongue (**c**). (Panel B courtesy of Dr. Garrick Alex)

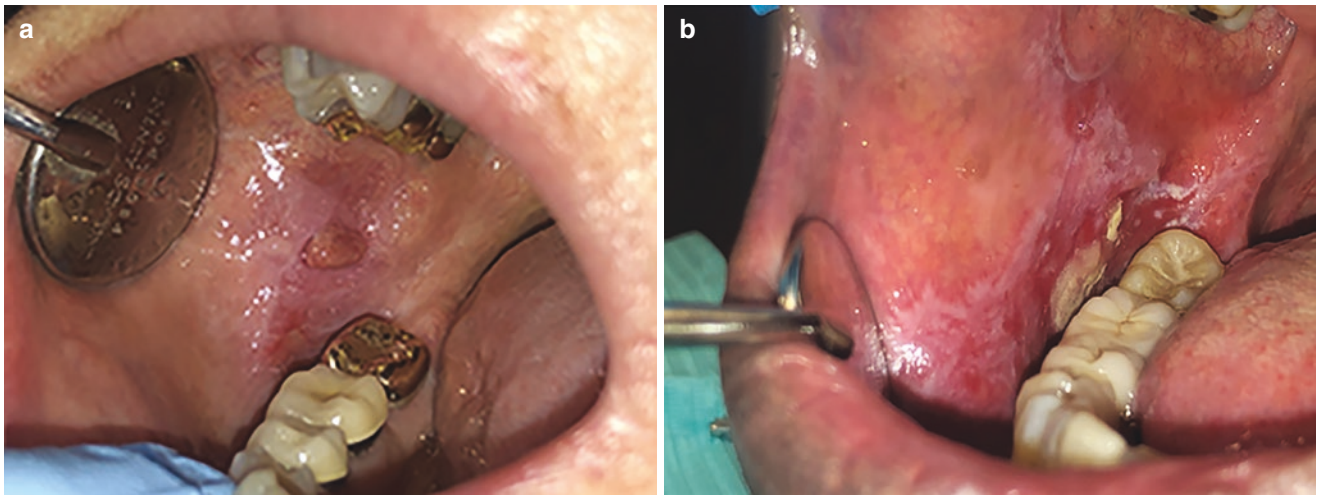


Fig. 18.19 (**a**, **b**) Erosive lichen planus with a prominent ulcerative component

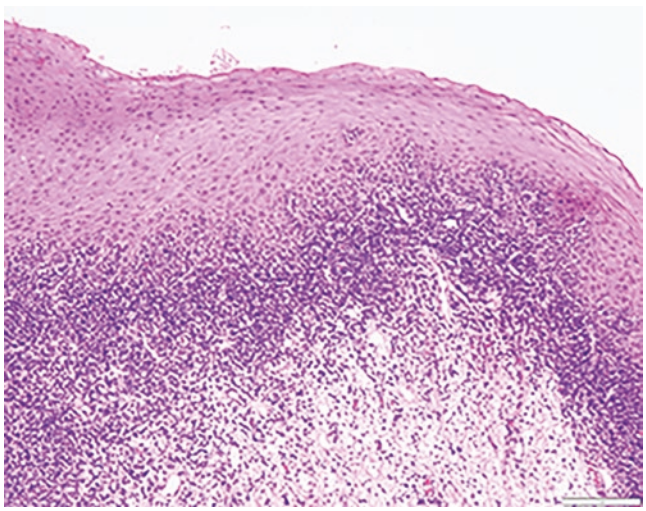


Fig. 18.20 Microscopic appearance of lichen planus demonstrating a dense band of lymphocytes in the superficial connective tissue subjacent to the epithelium

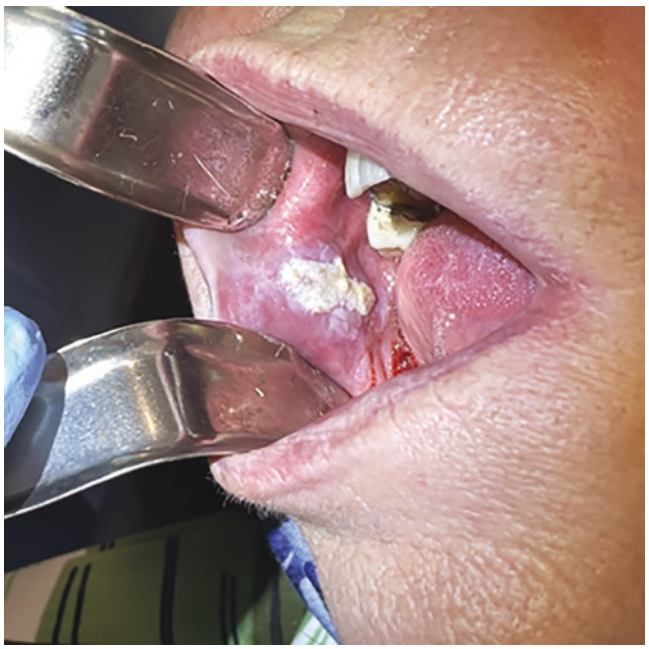


Fig. 18.21 Squamous cell carcinoma arising on the right buccal mucosa in a patient with lichen planus (photograph courtesy of Dr. Jared Miller)

Mucosal Membrane Pemphigoid

Mucous membrane pemphigoid (MMP), also known as cicatricial pemphigoid, is a chronic autoimmune disease of unclear etiology. It results from autoantibody production which targets hemidesmosomes and causes a subepithelial separation. Clinically, this results in the formation of vesicles or bullae which then rupture leading to ulceration and erythema [42]. Similar to oral lichen planus, MMP is seen most commonly in middle-aged females, and also is considered to be a mucocutaneous disease.

The intraoral presentation of MMP is comparable to that of erosive lichen planus. **Desquamative gingivitis** is a frequent finding; in many cases, the lesions of MMP are limited to the gingiva. Involvement of non-gingival sites may still be seen, and this does not exclude a diagnosis of MMP. Although blister formation may be seen, intraoral bullae will often rupture quickly, leading to the formation of mucosal erythema and ulceration (Fig. 18.22). MMP has a positive **Nikolsky sign**, meaning that firm pressure applied on clinically normal tissue can induce blister formation. Due to the hemidesmosomal destruction seen in MMP, patients will experience sloughing of the oral epithelium. Patients will often experience significant pain and bleeding in association with the lesions [42, 43].

The diagnosis of MMP is confirmed via biopsy. On microscopic examination, there is a neat separation

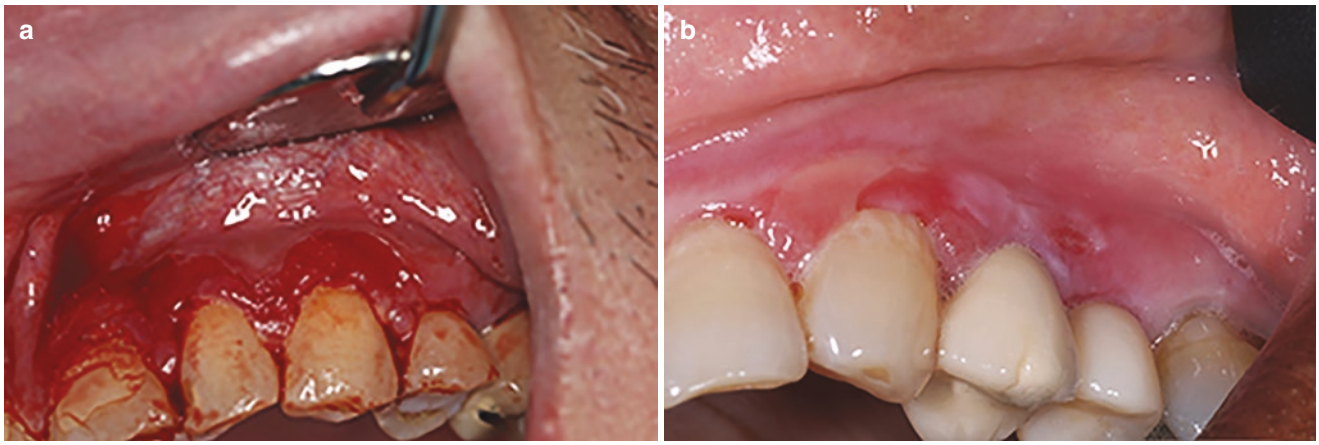


Fig. 18.22 (**a**, **b**) Gingival lesions of mucosal membrane pemphigoid (photographs courtesy of Dr. David Moisa)

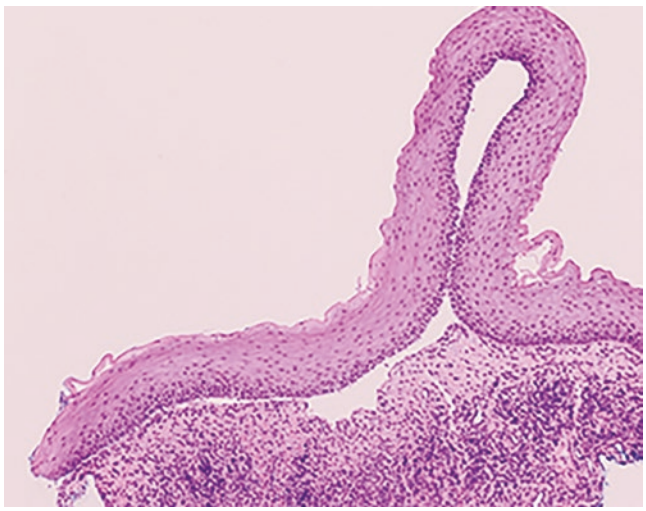


Fig. 18.23 Microscopic appearance of mucosal membrane pemphigoid demonstrating a separation between the epithelium and connective tissue

between the epithelium and the underlying connective tissue [44] (Fig. 18.23). Biopsy of these lesions can be quite challenging, because the epithelium will easily peel away from the underlying connective tissue and can be lost during the surgical procedure. **Direct immunofluorescence** (DIF) testing is often used as additional diagnostic confirmation. On DIF, MMP shows a linear, band-like proliferation of immunoglobulins and complement at the basement membrane zone [44].

MMP may be treated with topical corticosteroids or immunomodulatory agents (Tacrolimus), and/or short courses of systemic steroid therapies [44]. Patients diagnosed with MMP should also be referred to dermatology and ophthalmology to assess for the presence of skin and ocular lesions, respectively. With regard to the latter, approximately one quarter of patients will develop lesions of the eye which may lead to blindness if untreated. The initial ocular lesion is an adhesion which develops between the bulbar and the palpebral conjunctiva and is known as a **symblepharon**. These adhesions will cause the eye to scar and rotate inward (**entropion**). This, in turn, leads to the eyelashes irritating the cornea and globe (**trichiasis**), resulting in corneal keratin production and blindness [45].

Pemphigus Vulgaris

Pemphigus Vulgaris (PV) is a severe, progressive autoimmune disease caused by autoantibodies directed against intraepithelial desmosomes. The resulting intraepithelial clefting, termed **acantholysis**, produces the clinical lesions of PV, which appear as vesicles and bullae involving the skin and the mucosa [46]. Because the microscopic separation in PV occurs more superficially when compared to MMP, the blisters that result are more prone to rupture and ulceration. PV is also seen most often in middle-aged adults, with no clear gender predilection. PV occurs with higher frequency in patients of Mediterranean, Ashkenazi Jewish, and South Asian descent. It is seen infrequently in the general population, with a reported incidence of approximately one in five million [46, 47].

Oral lesions of PV present as fragile vesicles which quickly rupture, resulting in ulcerations with surrounding erythema. The ulcers of PV can be quite large in size, and some authors have described them as having "irregular, ragged" borders (Fig. 18.24). Any oral site may be involved, and similar to both lichen planus and MMP, the presentation of PV is often bilateral and/or multifocal. As with MMP, PV is a Nikolsky positive process [46]. The oral lesions of PV often precede the development of cutaneous manifestations, in some cases by almost 1 year.

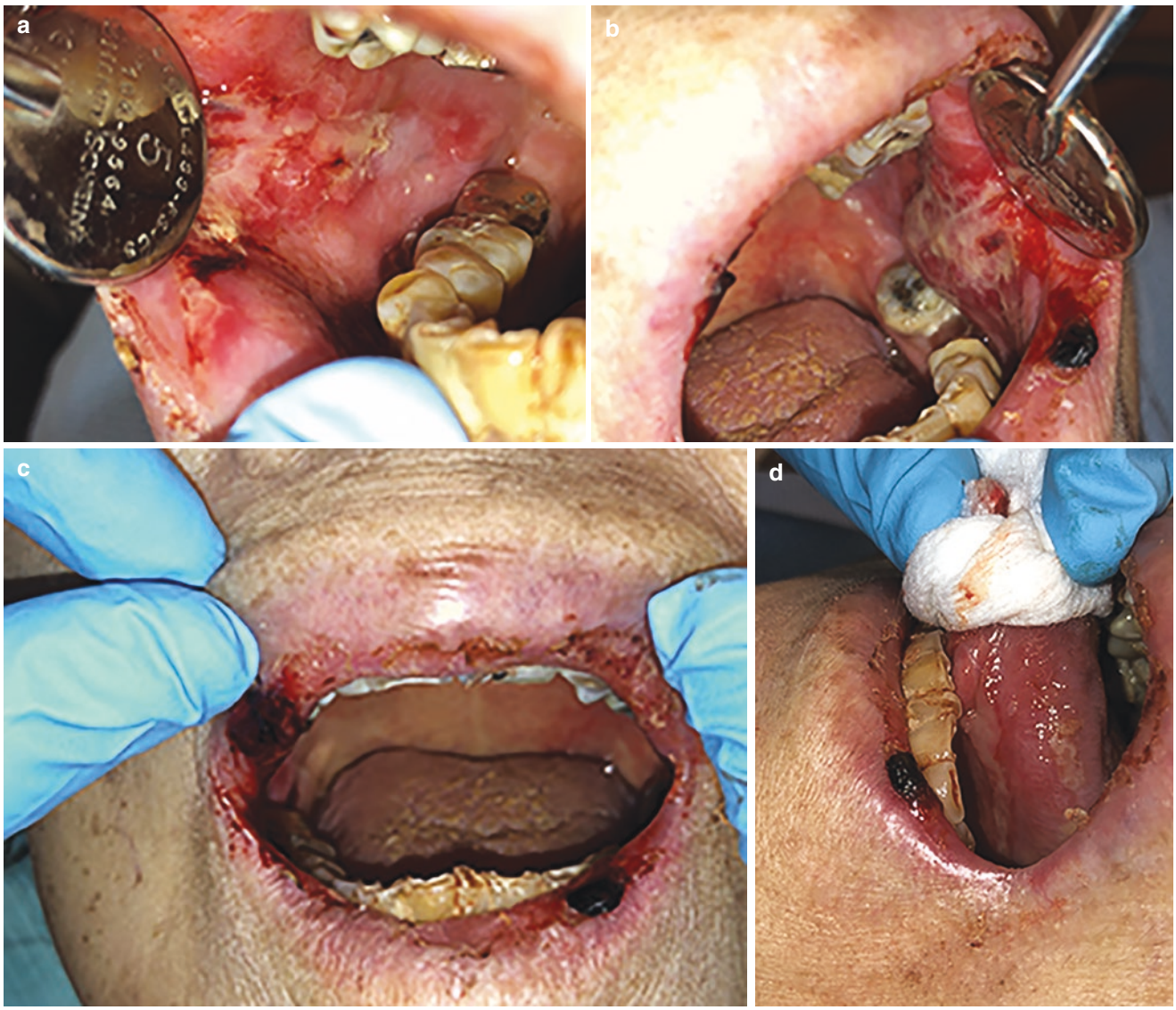


Fig. 18.24 Right buccal mucosal (**a**), left buccal mucosal (**b**), labial (**c**), and lateral tongue (**d**) lesions in a patient with pemphigus vulgaris

They are also frequently slower to resolve than the skin lesions. In extreme cases, patients with chronic, undiagnosed PV may present with weight loss because the lesions may interfere with the ability to maintain proper nutrition. Mortality from PV has been infrequently reported [48].

Microscopic examination of PV demonstrates an intraepithelial separation or cleft. In oral lesions, this separation occurs in the lower third of the epithelium near the level of the basement membrane (Fig. 18.25). Free-floating, rounded epithelial cells are seen within the cleft. These cells are referred to as **Tzanck cells**. Tzanck cells are not specific for PV, but rather may be seen in any acantholytic process, including herpes infection and Darier disease, among others. DIF testing is often required for additional diagnostic confirmation of PV. The DIF pattern of PV is often described as "chicken wire" or "fishnet" and it demonstrates antibodies and complement in the intercellular spaces between the epithelial cells. Patients with PV require strict dosing with systemic steroidal or intravenous nonsteroidal therapies [49, 50].

Oral Ulcerations as a Manifestation of Systemic Disease

There are a variety of systemic diseases which may manifest with oral ulcerations. Some of these have already been discussed earlier in this chapter or in other sections of this text. This final portion of the chapter will review additional examples of systemic diseases which may present with oral lesions.

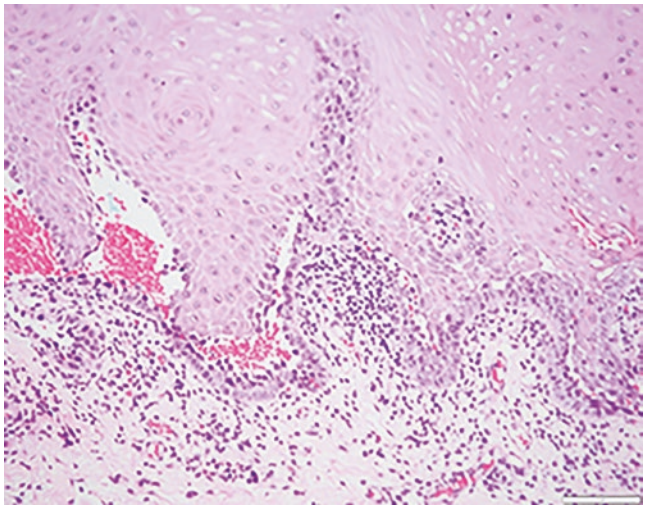


Fig. 18.25 Microscopic appearance of pemphigus vulgaris demonstrating an intraepithelial cleft

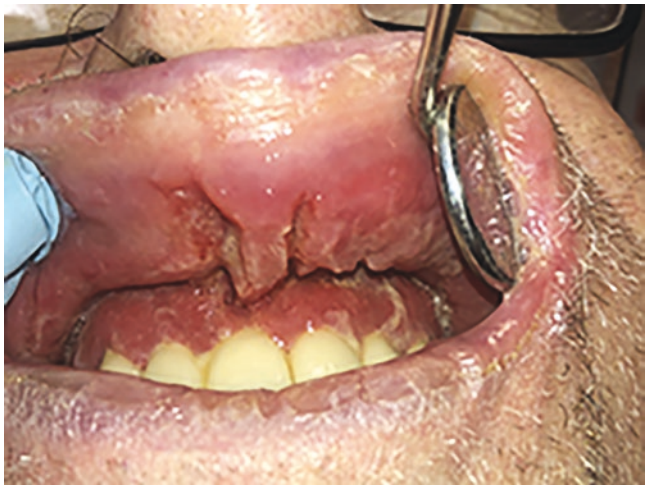


Fig. 18.26 "Cobblestone" mucosa in a patient with Crohn's disease

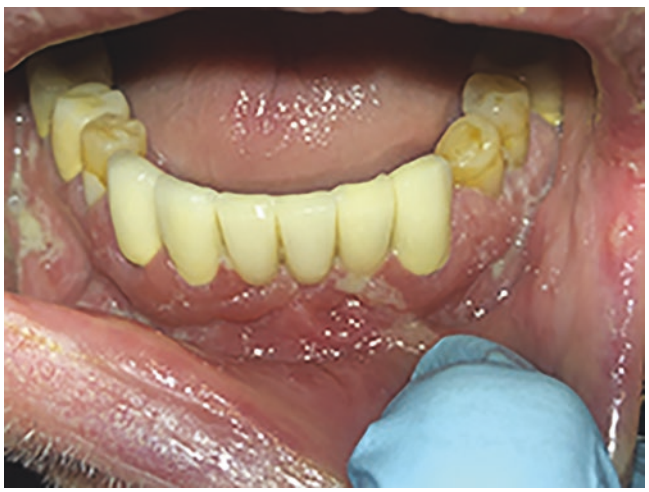


Fig. 18.27 Linear ulceration of Crohn's disease. This is the same patient as Fig. 18.27

Crohn's Disease and Ulcerative Colitis

Crohn's disease is a chronic inflammatory bowel disorder that can affect any portion of the gastrointestinal tract. The terminal ileum and the colon are most commonly involved, and the rectum is often spared [51]. A slight female predilection has been reported and the typical age of onset around 15–40 years. It is most commonly found in white and Ashkenazi Jewish populations [52, 53]. Patients often present with right-lower quadrant abdominal pain, diarrhea, and constitutional symptoms such as fatigue, weight loss, and fever [54].

Extra-intestinal manifestations are common in Crohn's disease, presenting in roughly one-third of patients [55]. These manifestations may develop in almost any area of the body with the eyes, skin, and joints commonly affected [56]. Oral manifestations of Crohn's disease present in several ways, and have been found to precede gastrointestinal findings in roughly 30% of cases. Oral manifestations are more common in the pediatric-aged population. As the disease progresses, serpiginous depressed ulcerations that separate elevated islands of healthy tissue can develop along the gastrointestinal tract, including the oral mucosa, giving it a "cobblestone" appearance (Fig. 18.26). Aphthous stomatitis may be seen in 20–30% of patients with Crohn's disease. Other oral findings of Crohn's disease may include the development of linear granulomatous-appear ulcerations with hyperplastic margins. These linear ulcerations are most commonly found in the buccal vestibule [56] (Fig. 18.27).

Histologically, Crohn's disease manifests with patchy transmural inflammation interspersed with areas of normal bowel wall. Lymphoid aggregates with noncaseating granulomas are a microscopic hallmark of the disease, and are often accompanied by the distortion of normal mucosal architecture and Paneth cell metaplasia [57]. Microscopic examination of the oral lesions will show a similar pattern of inflammation. Biopsy of the oral linear ulcerations of Crohn's disease reveals chronic inflammatory cell infiltration, with isolated areas of noncaseating granulomas and lymphocytes.

Definitive treatment of Crohn's disease and its oral manifestations is determined by location, activity, and severity. Controlling colonic disease is the first and most important step in treating oral lesions.

Ulcerative colitis is another example of a chronic inflammatory bowel disorder. Unlike Crohn's disease, ulcerative colitis primarily affects the rectum and colon and spares the rest of the gastrointestinal tract. Patients will present with similar symptoms when compared to those with Crohn's disease, including weight loss, malnutrition, and diarrhea.

While Crohn's disease will present with noncaseating granulomatous inflammation on microscopy, histologic examination of the mucosa affected by ulcerative colitis demonstrates generalized and non-specific mucosal inflammation [6].

Oral manifestations of ulcerative colitis are seen far less commonly when compared to Crohn's disease. The primary oral finding in patients with ulcerative colitis is **pyostomatitis vegetans**. Pyostomatitis vegetans appears as yellowish, serpentine or "snail track" ulcerations most frequently involving the soft palate, buccal and labial mucosa, and ventral tongue. Similar lesions may also be seen in patients with Crohn's disease [58, 59].

Similar to Crohn's disease, management of the oral manifestations of ulcerative colitis involves definitive treatment of the patient's underlying gastrointestinal condition.

Behçet Syndrome

Behçet syndrome is a chronic, inflammatory, relapsing disorder of uncertain etiology. The prevalence of Behçet syndrome in the Middle East and far-east Asia is markedly higher than in the United States and Europe—hence the name of "Silk Road disease." Behçet syndrome most frequently has an age of onset around 30–40 years of age. Young males tend to have a more severe course of Behçet syndrome [60, 61].

Behçet syndrome is a multisystem vasculitis with variable clinical manifestations. Oral and genital aphthae and ocular involvement are characteristic of the disorder, although many additional organ systems can be affected. Oral ulcerations are typically the first and most frequent symptom in Behçet syndrome, with minor aphthous ulcers (<10 mm in diameter) being the most common type [60]. The minor aphthous ulcers commonly affect non-keratinized mucosa, and are generally pale in color with a surrounding erythematous border [62]. Major aphthous ulcers (>10 mm in diameter) can occasionally be present involving the soft palate and oropharynx, and may cause scarring (Fig. 18.28). Oral ulcerations in Behçet syndrome can commonly be confused with recurrent aphthous stomatitis; however, in Behçet syndrome the aphthae are usually more painful and frequent. The oral ulcerations can continue to develop for many years despite apparent resolution of other systemic manifestations. Menstruation, local trauma, food, and tobacco cessation have all been found to be triggering factors for the development of these aphthous-like ulcers [60, 61].

Gastrointestinal involvement in Behçet syndrome can mimic a presentation similar to Crohn's disease, with such symptoms as abdominal pain and diarrhea. Similarly, the terminal ileum is most commonly affected, although the ulcers present in Behçet syndrome are often round or oval, unlike the long longitudinal ulcers in Crohn's disease. Skip lesions, or non-contiguous areas of inflammation, can be present in both Behçet syndrome and Crohn's disease. Patients with Behçet syndrome will also report severe gastrointestinal symptoms 10–15% of the time [60, 63].

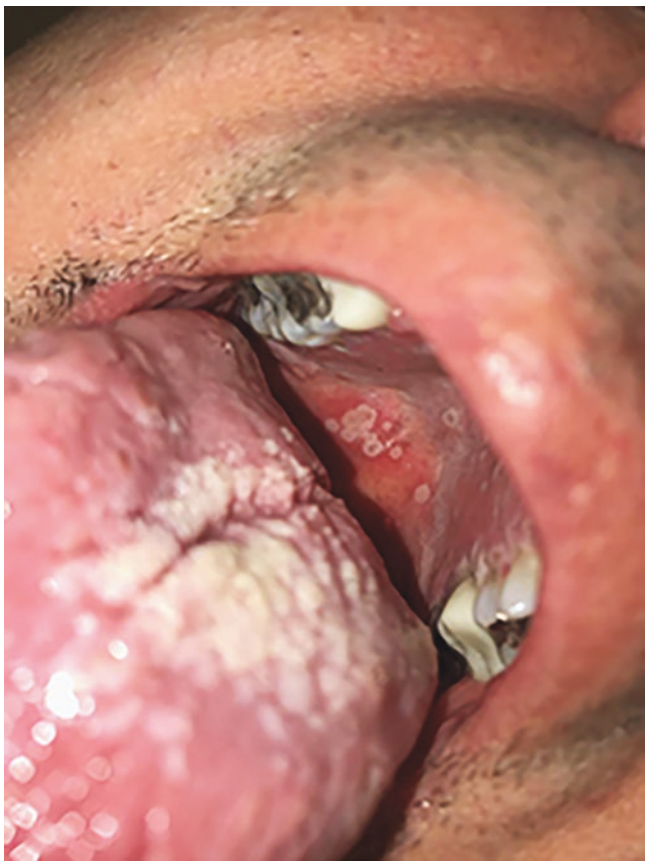


Fig. 18.28 Aphthous-like ulcerations involving the palate in a patient with Behçet syndrome

Diagnosis of Behçet syndrome is based on a constellation of clinical criteria agreed upon by the Bechet International Study Group. There are no diagnostic laboratory tests, and biopsy of the oral ulcerations will always yield non-specific microscopic findings. Treatment is based on an individual patient's disease severity and progression [60].

Granulomatosis with Polyangiitis (Wegner's Granulomatosis)

Granulomatosis with polyangiitis, previously referred to as Wegner's Granulomatosis, is a chronic disorder of uncertain etiology. It is most often characterized by necrotizing granulomatous lesions of the respiratory tract, necrotizing glomerulonephritis, and systemic vasculitis primarily involving small arteries and veins. It most frequently presents in adults, with no reported sex predilection. The spectrum of clinical findings in patients with granulomatosis with polyangiitis

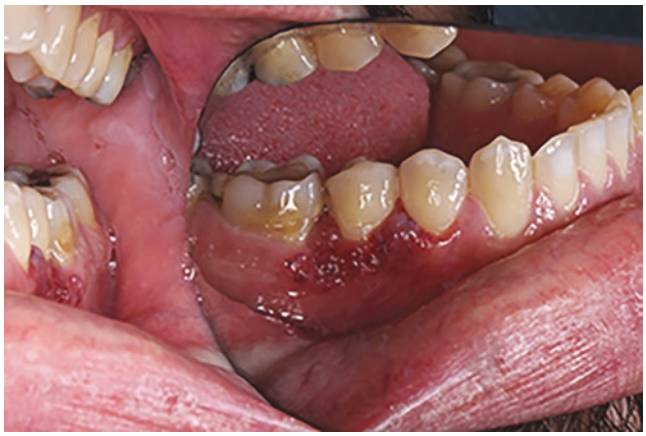


Fig. 18.29 Strawberry gingivitis in a patient with granulomatous with polyangiitis (courtesy of Dr. Elizabeth Philipone)

varies based on the extent of disease involvement. In generalized cases, patients will present with involvement of the upper and lower respiratory tract, followed by renal involvement. In limited forms of the disease, clinical manifestations are limited to the respiratory tract without significant renal complications. A superficial form of granulomatosis with polyangiitis will demonstrate lesions of the skin and mucosa, with less involvement of internal organs [64].

The most characteristic oral manifestation of granulomatosis with polyangiitis is **strawberry gingivitis**. The affected gingiva appears florid with granular hyperplasia and numerous short, red, bulbous projections resembling the surface of a strawberry (Fig. 18.29). Strawberry gingivitis is considered an early manifestation of granulomatosis with polyangiitis, and often precedes the development of renal lesions [65]. Patients with later stages of disease will develop chronic oral ulcerations, which are typically non-specific in appearance and slowly-healing [66].

Diagnosis of granulomatosis with polyangiitis requires a combination of the clinical presentation and microscopic findings of necrotizing and granulomatous vasculitis. Laboratory markers for PR3-ANCA (c-ANCA) and MPO-ANCA (p-ANCA) are also helpful when evaluating a patient for granulomatosis with polyangiitis. Treatment of the oral manifestations is based on the management of the patient's underlying disease [64].

Celiac Disease

Celiac disease is an autoimmune disease associated with gluten sensitivity. In patients with celiac disease, gluten consumption will result in damage to the small intestine. Specifically, there is destruction of the villus structures which are necessary for nutrient absorption. Common symptoms of celiac disease include weight loss, gastrointestinal upset including cramping, bloating, diarrhea, and/or constipation, fatigue, and joint pain. Oral manifestations include **recurrent aphthous stomatitis** and enamel loss. Celiac disease should be considered in the differential diagnosis of a younger individual presenting with gastrointestinal symptoms and recurrent aphthous ulcerations.

Cyclic Neutropenia

Cyclic neutropenia is a rare hematologic disorder characterized by regular periodic reductions in a patient's neutrophil counts. These reductions typically occur over an approximately 21-day cycle. The cause is believed to be a mutation in the neutrophil elastase gene, or ELA-2. The signs and symptoms of cyclic neutropenia vary based on a patient's neutrophil count. When it is at its lowest during the 21-day cycle, patients will present with multiple oral ulcerations resembling aphthae. Patients will also have advanced periodontal disease due to generalized bone loss and gingival recession [67].

PFAPA Syndrome

PFAPA syndrome is an abbreviation for **periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis**. Patients with PFAPA syndrome will have recurrent episodes of the aforementioned clinical findings. It is a disease of early childhood, with most cases occurring between the ages of 2 and 5 years old. The etiology of PFAPA syndrome is unknown, and it is considered a diagnosis of exclusion. Treatment is palliative in nature. In most patients, the syndrome resolves on its own after early adolescence [68].

MAGIC Syndrome

MAGIC syndrome is an abbreviation for **mouth and genital ulcerations with inflamed cartilage**. It is a rare autoimmune disease that shares some clinical features of Behçet syndrome and relapsing polychondritis. The cause is unknown. The oral ulcerations of MAGIC syndrome clinically resemble aphthae [69].

Summary

Evaluation of oral ulcerations is a challenging, albeit important, aspect of patient care. Knowledge of the different conditions which may present with oral mucosal disease can help the provider when establishing a differential or a definitive diagnosis.

References

1. Scully C, Porter S. Oral mucosal disease: recurrent aphthous stomatitis. Br J Oral Oralmaxillofac Surg. 2008;46:198–206.
2. Baccaglini L, Lalla RV, Bruce AJ, et al. Urban legends: recurrent aphthous stomatitis. Oral Dis. 2011;17:755–70.
3. Pederson A, Hougen HP, Kenrad B. T-lymphocyte subsets in oral mucosa of patients with recurrent aphthous ulceration. J Oral Pathol Med. 1992;21:176–80.
4. Rogers RS. Complex aphthosis. Adv Exp Med Biol. 2003;528:311–6.
5. Liu C, Zhou Z, Liu G, et al. Efficacy and safety of dexamethasone ointment on recurrent aphthous ulceration. Am J Med. 2012;125:292–301.
6. Neville BW, Damm DD, Allen CM, et al. Oral and maxillofacial pathology. 4th ed. St. Louis, MO: Elsevier; 2016.
7. Usatine RP, Tinitigan R. Nongenital herpes simplex virus. Am Fam Physician. 2010;82:1075–82.
8. Woo SB, Challacombe SJ. Management of recurrent oral herpes simplex infections. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;103(1):S12.e1-18.
9. Raborn GW, Grace MGA. Recurrent herpes simplex labialis: selected therapeutic options. J Can Dent Assoc. 2003;69:498–503.
10. Samim F, Auluck A, Zed C, et al. Erythema multiforme: a review of the epidemiology, pathogenesis, clinical features, and treatment. Dent Clin N Am. 2013;57:583–96.
11. Williams PM, Conklin RJ. Erythema multiforme: a review and contrast from Stevens-Johnson syndrome/toxic epidermal necrolysis. Dent Clin N Am. 2005;49:67–76.
12. Ayangco L, Rogers RS. Oral manifestations of erythema multiforme. Dermatol Clin. 2003;21:195–205.
13. Farthing P, Bagan JV, Scully C. Erythema multiforme. Oral Dis. 2005;11:261–7.
14. Sokumbi O, Wetter DA. Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist. Int J Dermatol. 2012;51:889–902.
15. Gerull R, Nelle M, Schaible T. Toxic epidermal necrolysis and Stevens-Johnson syndrome: a review. Crit Care Med. 2011;39:1521–32.
16. Brannon RB, Fowler CB, Hartman KS. Necrotizing sialometaplasia: a clinicopathologic study of sixty-nine cases and review of the literature. Oral Surg Oral Med Oral Pathol. 1991;72:317–25.
17. Kaplan I, Alterman M, Kleinman S, et al. The clinical, histologic, and treatment spectrum in necrotizing sialometaplasia. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;114:577–85.
18. Abrams AM, Melrose RJ, Howell FV. Necrotizing sialometaplasia: a disease simulating malignancy. Cancer. 1973;32:130–5.
19. Carlson DL. Necrotizing sialometaplasia: a practical approach to the diagnosis. Arch Pathol Lab Med. 2009;133:692–8.
20. Bhaskar SN, Lilly GE. Traumatic granuloma of the tongue (human and experimental). Oral Surg Oral Med Oral Pathol. 1964;18:206–18.
21. El-Mofty SK, Swanson PE, Wick MR, et al. Eosinophilic ulcer of the oral mucosa: report of 39 new cases with immunohistochemical observations. Oral Surg Oral Med Oral Pathol. 1993;75:716–22.
22. Chatzistamou I, Doussis-Anagnostopoulou I, Georgiou G, et al. Traumatic ulcerative granuloma with stromal eosinophilia: report of a case and literature review. J Oral Maxillofac Surg. 2012;70:349–53.
23. Padmanabhan MY, Pandey RK, Aparna R, et al. Neonatal sublingual traumatic ulceration—case report & review of the literature. Dent Traumatol. 2010;26:490–5.
24. Will BM, Peters SM, Eisig SB, et al. Gingival ulceration in a 63-year-old lung transplant recipient. Oral Surg Oral Med Oral Pathol Oral Radiol. 2019;127(5):364–71.
25. Little JW. Syphilis: an update. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;100:3–9.
26. Vinals-Iglesias H, Chimentos-Kustner E. The reappearance of a forgotten disease of the oral cavity: syphilis. Med Oral Patol Oral Cir Bucal. 2009;14:e416–20.
27. Bsoul SA, Huber MA, Terezhalmy GT. Squamous cell carcinoma of the oral tissues: a comprehensive review for oral healthcare providers. J Contemp Dent Pract. 2005;6:1–16.
28. Bouquot JE. Common oral lesions found during a mass screening examination. J Am Dent Assoc. 1986;112:50–7.
29. Centers for disease control and prevention. Trends in tuberculosis—United States, 2012. MMWR Morb Mortal Wkly Rep. 2012;62:201–5.
30. Rinaggio J. Tuberculosis. Dent Clin N Am. 2003;47:449–65.
31. Andrade NN, Mhatre TS. Orofacial tuberculosis—a 16 year experience with 46 cases. J Oral Maxillofac Surg. 2012;70:e12–22.
32. Silvestre FJ, Perez-Hervera A, Puente-Sandoval A, et al. Hard palate perforation in cocaine abusers: a systematic review. Clin Oral Investig. 2010;14:621–8.
33. Rogers RS, Sheridan PJ, Nightingale SH. Desquamative gingivitis: clinical, histopathologic, immunopathologic, and therapeutic observations. J Am Acad Dermatol. 1982;7(6):729–35.
34. Lavanya N, Jayanthi P, Rao UK, Ranganathan K. Oral lichen planus: an update on pathogenesis and treatment. J Oral Maxillofac Pathol. 2011;15(2):127–32.
35. Cheng YL, Gould A, Kurago Z, Fantasia J, Muller S. Diagnosis of oral lichen planus: a position paper of the American Academy of Oral and maxillofacial pathology. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122:332–54.
36. Ingafou M, Leao JC, Porter SR, et al. Oral lichen planus: a retrospective study of 690 British patients. Oral Dis. 2006;12:463–8.
37. Kalmar JR. Diagnosis and management of oral lichen planus. J Calif Dent Assoc. 2007;35:405–12.
38. Lodi G, Carrozzo M, Furness S, et al. Interventions for treating oral lichen planus: a systematic review. Br J Dermatol. 2012;166:938–47.
39. Van der Meij EH, Mast H, van der Waal I. The possible premalignant character of oral lichen planus and oral lichenoid lesions: a prospective follow-up study of 192 patients. Oral Oncol. 2007;43:742–8.
40. Muller S. Oral lichenoid lesions: distinguishing the benign from the deadly. Mod Pathol. 2017;30:S54–67.
41. Fitzpatrick SG, Hirsch SA, Gordon SC. The malignant transformation of oral lichen planus and oral lichenoid lesions: a systematic review. J Am Dent Assoc. 2014;145(1):45–6.
42. Bagan J, Muzio LL, Scully C. Mucous membrane pemphigoid. Oral Dis. 2005;11:197–218.
43. Darling MR, Daley T. Blistering mucocutaneous diseases of the oral mucosa—a review: part 1. Mucous membrane pemphigoid. J Can Dent Assoc. 2005;71:851–4.
44. Chan LS, Ahmed AR, Anhalt GJ, et al. The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. Arch Dermatol. 2002;138:370–9.
45. Kirzhner M, Jakobiec FA. Ocular cicatricial pemphigoid: a review of clinical features, immunopathology, differential diagnosis, and current management. Semin Ophthalmol. 2011;26:270–7.
46. Black M, Mignogna MD, Scully C. Pemphigus vulgaris. Oral Dis. 2005;11:119–30.
47. Darling MR, Daley T. Blistering mucocutaneous diseases of the oral mucosa—a review: part 2. Pemphigus vulgaris. J Can Dent Assoc. 2006;72:63–6.
48. Tsuruta D, Ishii N, Hashimoto T. Diagnosis and treatment of pemphigus. Immunotherapy. 2012;4:735–45.

49. Pohla-Gubo G, Hintner H. Direct and indirect immunofluorescence for the diagnosis of bullous autoimmune diseases. Dermatol Clin. 2011;29:365–72.
50. Strowd LC, Taylor SL, Jorizzo JL, et al. Therapeutic ladder for pemphigus vulgaris: emphasis on achieving complete remission. J Am Acad Dermatol. 2011;64:490–4.
51. Goulart RA, Barbalho SM, Gasparini RG, et al. Facing terminal ileitis: going beyond Crohn's disease. Gastroenterology Res. 2016;9(1):1–9.
52. Cosnes J, Gower-Rousseau C, Seksik P, et al. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology. 2011;140(6):1785–94.
53. Santos MPC, Gomes C, Torres J. Familial and ethnic risk in inflammatory bowel disease. Ann Gastroenterol. 2018;31(1): 14–23.
54. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical guideline: management of Crohn's disease in adults [published correction appears in Am J Gastroenterol. 2018 Jul;113(7):1101]. Am J Gastroenterol. 2018;113(4):481–517.
55. Lankarani KB, Sivandzadeh GR, Hassanpour S. Oral manifestation in inflammatory bowel disease: a review. World J Gastroenterol. 2013;19(46):8571–9.
56. Eckel A, Lee D, Deutsch G, et al. Oral manifestations as the first presenting sign of Crohn's disease in a pediatric patient. J Clin Exp Dent. 2017;9(7):e934–8.
57. Kalla R, Ventham NT, Satsangi J, et al. Crohn's disease. BMJ. 2014;349:g6670.
58. Markiewicz M, Suresh L, Margarone J, et al. Pyostomatitis vegetans: a clinical marker of silent ulcerative colitis. J Oral Maxillofac Surg. 2007;65:346–8.
59. Ayangco L, Rogers RS, Sheridan PJ. Pyostomatitis vegetans as an early sign of reactivation of Crohn's disease: a case report. J Periodontol. 2002;73:1512–6.
60. Yazici H, Seyahi E, Hatemi G, et al. Behçet syndrome: a contemporary view [published correction appears in Nat Rev Rheumatol. 2018 Jan 24;14 (2):119]. Nat Rev Rheumatol. 2018;14(2):107–19.
61. Bulur I, Onder M. Behçet disease: new aspects. Clin Dermatol. 2017;35(5):421–34.
62. Taylor J, Glenny AM, Walsh T, et al. Interventions for the management of oral ulcers in Behçet's disease. Cochrane Database Syst Rev. 2014;2014(9):CD011018.
63. Valenti S, Gallizzi R, De Vivo D, et al. Intestinal Behçet and Crohn's disease: two sides of the same coin. Pediatr Rheumatol Online J. 2017;15(1):33.
64. Weeda LW Jr, Coffey SA. Wegener's granulomatosis. Oral Maxillofac Surg Clin North Am. 2008;20:643–9.
65. Knight JM, Hayduk MJ, Summerlin DJ, et al. "Strawberry" gingival hyperplasia: a pathognomonic mucocutaneous finding in Wegener's granulomatosis. Arch Dermatol. 2000;136:171–3.
66. Stewart C, Cohen D, Bhattacharyya I, et al. Oral manifestations of Wegener's granulomatosis: a report of three cases and a literature review. J Am Dent Assoc. 2007;138:338–48.
67. Baer PN, Iacono VJ. Cyclic neutropenia: report of a case with a 15-year follow-up. Periodontal Clin Investig. 1994;16:14–9.
68. Vanoni F, Theodoropoulou K, Hofer M. PFAPA syndrome: a review on treatment and outcome. Pediatr Rheumatol Online J. 2016;14(1):38.
69. Orme RL, Nordlund JJ, Barich L, et al. The MAGIC syndrome (mouth and genital ulcers with inflamed cartilage). Arch Dermatol. 1990;126(7):940–4.

Oral and Oropharyngeal Cancer

19

Easwar Natarajan

Introduction

The head and neck region is among the most complex anatomical areas of the human body. It hosts a variety of tissue types that serve a range of functions: digestive, respiratory, immune, communication, and sensory. The head and neck region is also host to a broad spectrum of pathological conditions, including cancer. Cancers of the H&N range from those that arise from the mucosal membranes (mucosal squamous carcinomas) to non-squamous cancers that derive from regional salivary glands, respiratory structures, mucous glands, bone, other mesenchymal tissue, lymphoid and hematopoietic tissue. Clinicians looking to detect and diagnose cancers in this region must understand the anatomical and functional complexity and approach clinical assessment with discipline. Above all, they must understand the pathogenesis of the disease and be informed of the latest developments relative to head and neck cancer risk factors, detection, diagnosis, staging, treatment, and prognosis to best educate and guide their patient management.

Cancers of the head and neck (H&N) contribute significantly to the worldwide burden. The term "head and neck cancer" encompasses cancers of the nasal cavity, paranasal sinuses, hypopharynx, larynx, trachea, parapharyngeal space, salivary glands, maxillofacial skeleton, the oral cavity, and the oropharynx. When thus combined, cancers of the H&N cancer rank as the eighth most common cancer [1] (see Fig. 19.1. GLOBOCAN Cancer Incidence 2020). Among developing countries, H&N cancer ranks third and is the fifth most common cancer in men worldwide (https://gco.iarc.fr/today/home). Global variations in the incidence and anatomic distribution relate to locoregional risk factors. The traditional risk factors, tobacco, betel quid, and the synergistic use of alcohol, still contribute to the cancer burden. An emerging risk factor is high-risk human papillomavirus (HR-HPV); this has contributed significantly to the rising incidence of cancers in the H&N region, even as cancers associated with tobacco and alcohol have remained steady or declined (in specific oral sites). It is important to note that tobacco and alcohol remain significant risk factors in developing countries. Other recognized risk factors include betel quid use, smokeless tobacco products, Epstein–Barr virus, ultraviolet light exposure, and diet.

Despite there being a wide array of cancers that affect the H&N, squamous cell carcinoma (SCC) arising from the mucosal lining is the most commonly diagnosed malignant neoplasm in this region. Of the H&N sites, SCC of the oral cavity and oropharynx comprises the majority of cancers arising in this region, accounting for >90% of all malignancies. In the USA, in 2022, it is estimated that there will be 54,000 new cases of oral and oropharyngeal cancer and an estimated 11,230 deaths resulting from this disease; this is an increase from the previous year's estimate. The incidence of oral cavity SCC (OC-SCC), associated with traditional risk factors like tobacco and alcohol use, has remained steady and increased slightly over 20 years (1.6 cases in 2000 to 1.8 cases/100,000 in 2020). In contrast, there has been a dramatic increase in oropharyngeal cancer (1.8 cases/100,000 in 2000 to 2.9 cases/100,000 in 2020) (Fig. 19.2a). This rise in the incidence of oropharyngeal SCC (OP-SCC) is primarily the result of non-traditional risk factors, namely high-risk human papillomavirus. Regardless of their risk factors, oral and oropharyngeal cancers carry a significant risk of mortality and morbidity, representing a serious health problem. Clinicians assessing patients must understand the differences between oral and oropharyngeal SCCs. They must acknowledge that current evidence shows that SCCs at these two sites are distinct and represent two unique disease entities, each with different etiopathogenesis, treatment, and prognostic outcomes. This chapter presents the latest evidence relative

E. Natarajan (✉)
Section of Oral and Maxillofacial Pathology, School of Dental Medicine, University of Connecticut, Farmington, CT, USA
e-mail: natarajan@uchc.edu

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_19

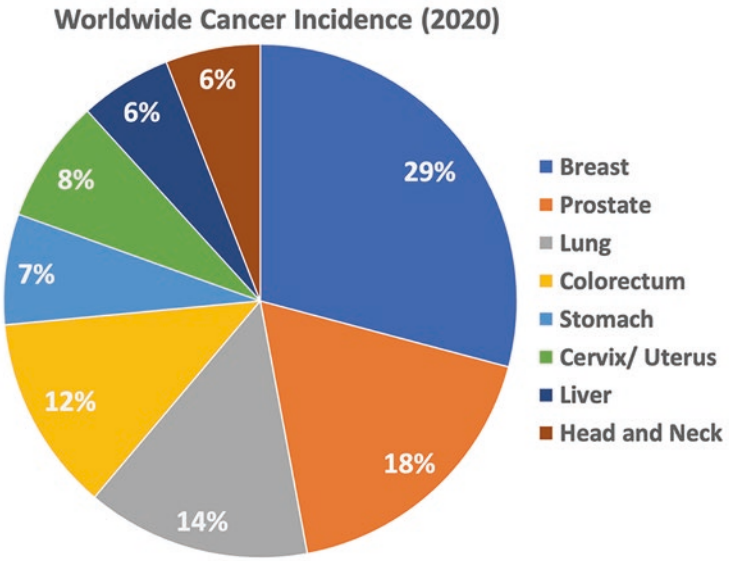


Fig. 19.1 Worldwide cancer incidence (GLOBOCAN/IARC 2020). Head and neck cancers account for 6% of the global cancer burden and are the 8th most common cancer when oral cavity, oropharynx, nasal cavity, paranasal sinuses, hypopharynx, larynx, trachea, parapharyngeal space, salivary glands, and the maxillofacial skeleton are combined. It is essential to consider each anatomical site independently owing to differences in risk factors, pathogenesis, and types of cancers unique to each anatomic site

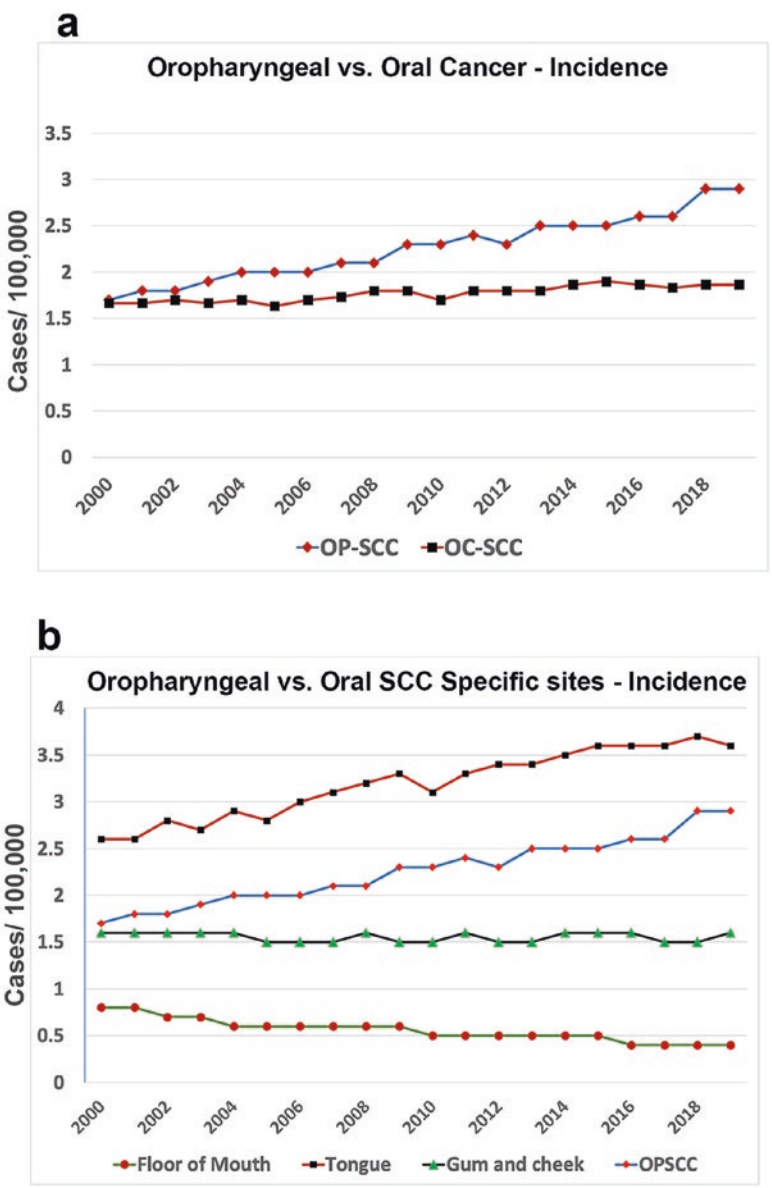


Fig. 19.2 Oral and oropharyngeal cancer (SCC) age-adjusted incidence rate, 2000–2019. All races, all ages, all stages (Source: NCI SEER data). (**a**) Oropharyngeal vs. oral SCC incidence rate (cases/100,000). The incidence of oral cavity SCC (OC-SCC) has remained steady with a minor increase (1.6–1.8 cases/100,000 from 2000 to 2019). In contrast, there has been a dramatic increase in oropharyngeal cancer (1.8 cases to 2.9 cases/100,000 from 2000 to 2019). (**b**) Oropharyngeal vs. oral SCC by specific site (tongue, floor of mouth, gum, and other sites). With age-adjusted incidence (AAI) for oral SCC broken down by site, there is an increase in the AAI of tongue SCC at 3.6 cases/100,000 and a decrease in the AAI of floor-of-mouth SCCs at 0.4 cases/100,000. The AAI for gum and cheek SCC has remained steady at 1.6 cases/100,000 from 2000 to 2019. The increase in tongue SCC AAI is unrelated to HR-HPV infection or oropharyngeal SCC

to the incidence, associated risk factors, pathogenesis, evaluation of relevant precursor lesions, clinical and pathological presentation, clinical assessment, management, and prognosis of OC-SCC and OP-SCC. To conclude, this chapter will address commonly asked clinical questions that come with daily practice. The responses and accompanying discussion should help with evidence-based clinical decision-making and patient education.

The Oral Cavity and the Oropharynx: Anatomical Considerations

The oral cavity and oropharynx are anatomically separate regions with different embryological derivation. There are regions where the mucosal lining (stratified squamous epithelium) of the oral cavity and oropharynx is contiguous. This poses a challenge in clearly delineating the boundary between the oral cavity lining and the oropharynx.

Oral Cavity

The oral cavity is ectodermally derived. The oral cavity proper begins anteriorly where the labial mucosa begins; the skin and vermilion borders of the external lips are dry tissues and hence not considered part of the oral cavity. Demarcated anteriorly by the junction of the vermilion and labial mucosa, the oral cavity extends posteriorly. It is bound laterally by the buccal mucosa, inferiorly by the floor of the mouth and ventral tongue, superiorly by the hard palate, and posteriorly by the anterior portion of the soft palate (~0.5 cm posterior to the hard-soft palatal junction). The maxillary and mandibular ridges and teeth subdivide the oral cavity internally into the outer oral vestibule (the region between the cheek and teeth) and the inner "chamber" containing the movable tongue. The oral cavity is roughly subdivided into the mobile tongue, floor of the mouth, cheek/buccal mucosa and outer vestibular tissue, alveolar ridge, and palate.

- The mobile portion or body of the tongue belongs in the oral cavity. It is demarcated posteriorly by the V-shaped groove (terminal sulcus) on the dorsal tongue bounded posteriorly by the circumvallate papillae. At the apical convergence and most posterior point of the terminal sulcus is the foramen cecum, which forms the anterior portion of the base of the tongue (the anterior boundary of the oropharynx). The body of the tongue is divided into the dorsal tongue which is naturally rough surfaced with filiform and fungiform papillae, the lateral border of the tongue, and the ventral (undersurface) surface of the tongue. The latter two surfaces are typically smooth and surfaced by thin, moveable, non-papillated, and pink mucosal tissue.
- The floor of the mouth forms the inferior investing tissue of the oral cavity and is a U-shaped area between the lateral-ventral tongue and the lingual portion of the gingival of the lower alveolar ridge. Dorsally, it extends to the left and right tonsillar areas. Lingual tonsillar tissue may be evident in some patients at the posterior-most junction of the floor of the mouth and ventral-lateral tongue.
- The buccal mucosa is the internal lining of the cheek. It begins at the labial mucosa anteriorly and extends posteriorly to the retromolar pad. The upper and lower borders extend to the maxillary and mandibular vestibule and alveolar mucosa (the unattached facial portion below the gingiva).
- The alveolar ridge mucosal tissues are considered attached tissues in that they are bound to the underlying periosteum of the jawbones. In the mandible, it extends to the retromolar pad regions bilaterally and bordered medially by the floor of the mouth. In the maxilla, the alveolar ridge mucosa is bound laterally by the buccal mucosa. Medially, it blends into the attached mucosal tissue of the hard palate. Laterally, the alveolar ridge is bound by the buccal mucosa.
- The oral palate is comprised of the hard palate anteriorly and includes ~0.5 cm of the soft palate (anterior portion). The hard palate is surfaced by attached (bound to the underlying periosteum), heavily keratinized mucosal tissue; also referred to as masticatory mucosa. Anteriorly the hard palate begins just behind the upper central incisors and extends posteriorly to the junction of the hard and soft palate. The hard palate is subdivided into regions distinguished from one another by their respective submucosal contents. The palatal zone lying anterior and lateral to the midline palatal raphe contains adipose tissue and is designated as the "fatty zone." The zone posterior to and lateral to the palatal raphe extending into the soft palatal region is the glandular zone (submucosal glands). The glandular zone is the most common location for both benign and malignant intraoral salivary gland neoplasms. A narrow ribbon of (~0.5 cm in width) soft palatal mucosa just posterior to the hard-soft palatal junction forms the oral portion of the soft palate and forms the boundary between oral cavity and oropharynx.

Oropharynx

The pharynx is endodermally derived and is divided into three functional and structural regions: the oropharynx, nasopharynx, and the hypopharynx. The oropharynx is located between the nasopharynx cranially and the hypopharynx caudally. The oropharynx can be further subdivided into the posterior pharyngeal wall, tonsils and tonsillar pillars/fossae, base of the tongue, and the posterior soft palate (with the uvula). All oropharyngeal regions are rich in tonsillar/lymphoid tissue and are part of the Waldeyer's ring. In the region of the tonsils, tongue, and soft palate, the oropharynx is contiguous with the lining of the oral cavity.

- The pharyngeal wall is the posterior-most surface visible when the tongue is depressed. It is bounded superiorly at the level of the soft palate and inferiorly at the level of the vallecula. This region often contains tonsillar tissue aggregates (lymphoid tissue).

- The tonsillar area is visible on oral examination and is best visualized by depressing the dorsal tongue and asking the patient to say "Aah." It is bordered anteriorly by the anterior and posterior tonsillar faucial pillars and glossopalatine sulcus. Superiorly, the tonsillar area is bounded by the inferior and posterior portion of the soft palate and uvula. The palatine tonsils and lingual tonsils complete the continuum.
- The base of the tongue is the posterior-most portion of the tongue and is barely visible on intraoral examination with a tongue-blade or dental examination mirror. Anteriorly, it is bounded by the circumvallate papillae; this junction separates the posterior one-third of the non-mobile tongue from the anterior two-thirds mobile tongue. Posteriorly, the base of the tongue ends at the base of the epiglottis. Laterally, it is bound by the glossopalatine sulci, the lingual tonsils (anterio-superiorly), palatine tonsils (superiorly), and the faucial pillars.

Oral Cavity and Oropharynx: Histological and Ultrastructural Considerations

All oral and oropharyngeal mucosal membranes are invested by stratified squamous epithelium. Depending on the specific location, the surfaces are either keratinized, lightly or non-keratinized, exhibit apical specialization (dorsal tongue papillae), or exhibit a specialized *reticulated stratified squamous epithelium* (seen in the oropharyngeal tonsillar regions). Similar to all epithelia, oral and oropharyngeal mucosal membranes rest on a complex fishnet like basement membrane composed of collagen IV and other adhesive basement membrane proteins (entactin, nidogen, laminins). The basal-most epithelial cells are tethered down to the basement membrane by hemidesmosomes (integrins, BP180, BP230, laminin 332). The collagen IV framework is bound down to the lamina propria by anchoring collagen VII fibrils. Keratinocytes, the cells that serve as the functional units of all squamous epithelia, form a meshwork of interconnected cells that comprise the labile (proliferative) stratified squamous epithelium. The primary role of a keratinocyte is to proliferate and ascend from its origin in the basal-most stratum (basal cell layer) to the epithelial surface. As they ascend through the epithelial strata, keratinocytes are genetically programmed to differentiate, mature, undergo natural death (regulated apoptosis), and finally leave a protective protein product, keratin, on the epithelial surface. This facilitates the formation of a continually renewable barrier that serves several functions: *innate immune protection, abrasion resistance, insulation, and impermeability*. Homeostatic mechanisms within the basal and suprabasal epithelial layers are tightly regulated by a series of genes that play critical roles in controlling stem-cell renewal and cell-cycle progression. Progression through the cell cycle (proliferation) and cell survival is dependent on a combination of growth factors, growth suppressors, telomere length, nutrition (vascular supply) and is regulated by checkpoint genes (e.g., p53, Rb), programmed cell death (apoptosis), local immune surveillance, and other local environmental factors. In addition, the components of the basement membrane, the structure that provides a natural barrier (physical and charge-based) between the epithelium and the underlying superficial submucosa (lamina propria), are maintained in a state of equilibrium by constant remodeling (protease and antiprotease activity). Any lasting change (e.g., acquired genetic defects, dysregulated immune function, chronic infection) that disturbs the local equilibrium has the potential to disrupt this carefully regulated microenvironment. These are the often irreversible changes resulting in uncontrolled keratinocyte proliferation and/or loss of epithelium-basement membrane relationship observed in oral and oropharyngeal carcinogenesis.

1. *Oral mucosa:* Regardless of location, the stratified squamous epithelium of the oral mucosa is defined by the presence of a *continuous basement membrane* barrier. As described above, the basal keratinocytes form a continuous adherent, and largely impermeable barrier along the stratum basale; they are anchored to the basement membrane by hemidesmosomes. This forms a foundation upon which epithelial cell renewal can progress apically. Basal and spinous cells adhere to each other through desmosomes (desmogleins and desmoplakins). The masticatory mucosa investing the attached gingiva, hard palate, alveolar ridge, and the retromolar pad are heavily keratinized (orthokeratinized; prominent granular layer) given the physical functional demands placed on them (abrasion and mastication) (Fig. 19.3b, d). The movable/lining/unattached mucosal surfaces of the floor of the mouth (FOM), ventral tongue, lateral-ventral tongue, buccal mucosa, vestibules, alveolar mucosa, labial mucosa, and anterior soft palate are technically "non-keratinized" (Fig. 19.3a, c); the apical domain/stratum superficiale contains a very thin [1, 2] layer of lightly keratinized squamous cells. These tissues are elastic. The buccal mucosa and labial mucosal surfaces are relatively thick (prominent stratum spinosum) (Fig. 19.3a), whereas the ventral tongue, FOM, anterior soft palate, and vestibules are thin (delicate stratum spinosum) (Fig. 19.3c). The dorsal tongue is specialized and is surfaced by thousands of papillae; parakeratinized filiform (hair/finger like), fungiform (small button-like/mushroom-like), and circumvallate papillae (along the terminal sulcus).

   The epithelial–stromal interface facilitates adhesion and resistance to shear. The epithelial invaginations and

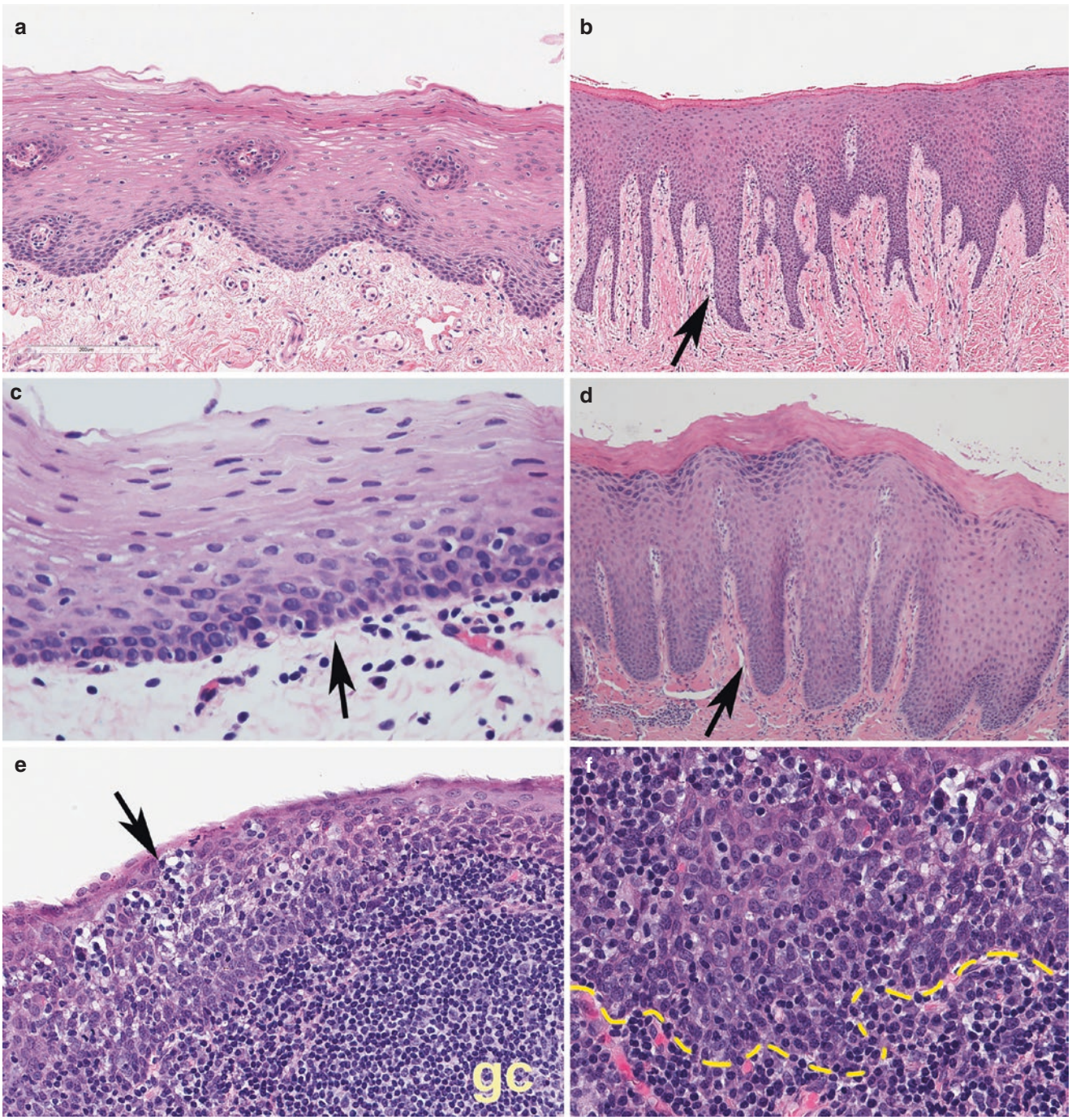


Fig. 19.3 Histological features of normal oral and oropharyngeal mucosa. Variations of stratified squamous epithelium. (**a**) Buccal mucosa or lateral tongue. Non-keratinized or lightly keratinized stratified squamous epithelium characteristic of unattached oral mucosa. The epithelial–stromal interface is slightly undulating with a normal maturation from basal (single layer) to spinous to superficial layers (differentiation). (**b**) Gingival mucosa. Parakeratinized stratified squamous epithelium characteristic of attached mucosa. The epithelial-stromal interface is jagged with tapered *rete pegs* (black arrow); normal maturation. (**c**) Floor of mouth, ventral tongue, or soft palate. Non-keratinized stratified squamous epithelium. The epithelial–stromal interface is relatively flat and continuous. Note the lack of *rete pegs* (black arrow). The epithelium exhibits normal maturation. (**d**) Hard palatal mucosa. Orthokeratinized (prominent granular layer) stratified squamous epithelium characteristic of attached mucosa. The epithelial–stromal interface is jagged with tapered *rete pegs* (black arrow; normal maturation). (**e**) Tonsillar crypt mucosa. Reticulated stratified squamous epithelium or lymphoepithelium. Non-keratinized stratified squamous epithelium. Note that the epithelial–stromal interface is indiscernible. Lymphocytes from normal lymphoid tissue (gc = germinal center) are seen percolating up into the superficial epithelial layers (black arrow). This is a normal feature. (**f**) Reticulated stratified squamous epithelium/lymphoepithelium. The epithelial–stromal interface and basal cell population are obscured by lymphoid tissue in the region. On ultrastructural examination (electron microscopy), the basement membrane is discontinuous (as shown with the dashed yellow lines). Note normal lymphocytes percolating among the spinous cell layers

reciprocal upward projections of the lamina propria (akin to the papillary dermis on the skin) resemble the adhesive qualities of a hook-and-loop structure, increase the attachment surface area, and facilitate mechanical abrasion resistance. These structures, observed on histological preparations, are referred to as *rete pegs or rete processes.* As seen on thick skin surfaces (palm/soles), the masticatory surfaces and buccal mucosa exhibit prominent *rete pegs* with a prominent, pencil tip-like taper toward the basal domain (Fig. 19.3b, d). The thicker buccal and labial mucosal surfaces exhibit *rete pegs* that are more undulating and wave-like (Fig. 19.3a). The epithelial–stromal interface seen along the FOM, ventral tongue, vestibules, and soft palate tends to be relatively flat or gently undulating (Fig. 19.3c). The histological differences seen in each oral location helps pathologists better evaluate oral epithelial specimens for deviations from normal epithelial maturation.

2. *Oropharyngeal mucosa:* The presence of subepithelial lymphoid/tonsillar tissue and submucosal mucous glands makes the oropharyngeal surface intermittently smooth and nodular. The palatine tonsils and tongue base contain numerous epithelial lined surface invaginations or crypts. The tonsils include around 20–30 crypts, which may extend their full depth, whereas the tongue base crypts tend to be shallower and less convoluted. The oropharyngeal mucosa is lined by non-keratinized or lightly parakeratinized stratified squamous epithelium. It is usually around 15–20 cell layers thick. The oropharyngeal epithelium exposed to the pharyngeal lumen is similar to the oral epithelium in that the basal layers and basement membrane exhibit a degree of continuity. In contrast, the stratified squamous epithelium that lines tonsillar crypts shows significantly different morphological, structural, and functional differences. The crypt epithelium is composed of *reticulated stratified squamous epithelium or lymphoepithelium* (Fig. 19.3e). The epithelium in this area is around 8–10 layers thick and is naturally attenuated with a discontinuous basement membrane (Fig. 19.3f). The spinous cells within the reticulated epithelium maintain desmosomal attachments, albeit in a loose networked/sieve-like arrangement. This sieve-like arrangement is a highly specialized adaptation that allows for transepithelial transport of antigens to the underlying lymphoid tissue; native lymphocytes percolate among the spinous epithelial cells to interact and sense antigens. The infiltration of native lymphocytes and neutrophils often obscures the presence of epithelium on H&E-stained specimens (Fig. 19.3e, f). The frequent interruptions within the epithelium and the intraepithelial capillaries render much of the epithelium, the epithelial–stromal interface, and the underlying vascular lamina propria indiscernible. This specialized feature of *reticulated stratified squamous epithelium* facilitates adaptive immune education, is tightly regulated by regulatory T-lymphocytes (that suppress/regulate immune responses). It creates an immune-privileged environment (strong lymphoepithelial expression of programmed death-ligand PD-L1 that suppresses T-cell responses). This naturally attenuated and discontinuous epithelium inadvertently forms a direct path to vulnerable and proliferative basal epithelial cells. Thus, the *reticulated stratified squamous epithelium* inadvertently aids and abets pathogens like high-risk HPV and facilitates a portal of entry to the basal epithelial cells in the oropharyngeal mucosa.

What Is Squamous Cell Carcinoma?

Squamous cell carcinoma (SCC) is a malignant neoplasm that originates from a stratified squamous epithelium. As with all neoplastic processes, it is a disease of genetic deregulation. SCCs result from a protracted sequence of events that results in abnormal proliferation of stratified squamous epithelial lined surfaces, followed by the invasion of neoplastic epithelium into surrounding structures and its potential distant spread. SCCs are among the most common malignant neoplasms to affect any organ surfaced by stratified squamous epithelium: oral cavity, oropharynx, skin, esophagus, cervix (ectocervix-uterine lining), upper conducting respiratory tract (epiglottis, larynx, trachea, bronchi), anorectal tissues, vagina, penis, and occasional intraosseous examples.

Where and How Do Squamous Cell Carcinomas Arise at the Tissue and Cellular Level? What Is the Epicenter?

The primary focus and epicenter of squamous cell carcinogenesis is the *basal epithelial cell* or the stem cells that constitute the basal layer of a labile stratified squamous epithelium. In a normal stratified squamous epithelium, the basal and occasional suprabasal epithelial cells are the only cells with proliferative capacity. Basal-most keratinocytes originate from a small population of stem cells concentrated around the apices of a papillary lamina propria. When stem cells divide, one daughter cell remains in the region with stem-cell characteristics, while the other cell moves toward the rete peg tip to form committed *transit amplifying cells (TACs).* The highly proliferative TACs, restricted to one to two basal layers, undergo a cycle of mitotic division before progressing to terminal differentiation (transcribing a series of cytokeratins) up to the stratum

superficiale. Disruption to this tightly ordered, genetically programmed, homeostatic sequence of basal cell renewal and differentiation has the potential to tip the scales toward abnormal proliferation. Labile epithelial cells are susceptible to various disruptions daily: DNA damage, abnormal growth factor or receptor activity, insufficient nutrition, gene defects during mitotic division, etc. Fortunately, checkpoint, regulatory quality control, and repair mechanisms are often ready to address "deviant" cells. Consequently, most of all cell-proliferative/differentiation defects do not progress to carcinoma. A basal cell or TAC must acquire several cumulative genetic defects to become a "successful" neoplasm.

At a cellular level, with an intact basement membrane, an abnormally proliferative stratum basale tends to pile upward and push the basal lamina downward. This can result in abnormal thickening of a stratified squamous epithelium; synonymous with precancerous change or a "precursor" lesion. With cumulative defects, a still-proliferative abnormal basal cell may develop the ability to destroy the basement membrane barrier and infiltrate the underlying lamina propria and stromal tissue. The definition of a squamous cell carcinoma is the point at which a deviant, proliferative basal epithelial cell loses polarity, defies homeostatic squamous differentiation, and infiltrates the basement membrane barrier to enter the loose connective tissue. From this point on, an infiltrative, neoplastic squamous cell has the potential to invade the deeper stromal tissues, enter local lymphatic channels or blood vessels, and potentially metastasize to distant sites.

Epithelial Carcinogenesis: The Result of a Multistep Genetic Deregulatory Process

Epithelial cells must acquire several genetic defects to proliferate, survive, overcome regulatory checkpoints, infiltrate, and transform into a "successful" cancer cell. As described in several cancer-progression models, neoplastic epithelial cells exhibit the "Hallmarks of Cancer" [2] (Table 19.1). The sequential inactivation (loss of function/LOF) of tumor suppressor gene activity and autonomous activation (gain of function/GOF) of oncogenes results in abnormal clonal cell proliferation and survival. Studies show that SCCs (regardless of location) result from a similar protracted sequence of events that recur over many years. This finding is consistent with epidemiologic data that SCC is a disease that affects adults primarily. Several cancer-progression models that focus on a few commonly affected signaling pathways and genes have been proposed. Among these, there are several reproducible *types* of molecular alterations (affecting a variety of genes) characterized that appear consistently across SCCs:

Table 19.1 Epithelial carcinogenesis: pathogenetic mechanisms

Acquired genetic defect	Gain of function/loss of function/ altered function
1. Self-sufficiency in growth signals	1. Autocrine signaling (e.g., GOF of EGF, TGFb). Ligand independent receptor activation (EGFR)
2. Insensitivity to antigrowth signals	2. LOF/altered function of tumor suppressors (e.g., p53, Rb, p16, p21)
3. Acquired capability to evade apoptosis	3. GOF of anti-apoptotic genes (MDM2); LOF of p53; survival
4. Limitless replicative potential	4. Telomere lengthening (GOF of telomerase activity)
5. Sustained angiogenesis, stromal support	5. GOF of angiogenic signals (e.g., VEGF, PDGF, bFGF)
6. Evasion of immune surveillance	6. Suppression of dendritic cells, T-reg cell dysregulation (PD-L1/ PD-1), resident T-lymphocyte suppression
7. Tissue invasion and metastasis: (a) Independence from cell–cell interaction (lack of cell adhesion) (b) Degrade basement membrane and extracellular connective tissue matrix (c) Migration and locomotion (stromal infiltration) (d) Vascular/lymphatic dissemination and homing of tumor cells (e) Survival in a "foreign" environment with altered metabolism	7. Tissue invasion and metastasis: (a) Dyshesion, altered function of e-cadherins, keratins, survival in suspension, LOF of apoptotic mechanisms (b) GOF of proteolytic enzyme activity (e.g., collagenases, MMPs, elastases) or LOF of antiproteases (TIMPs) (c) Abnormal protein folding, abnormal extracellular matrix protein (e.g. integrins, laminins, collagens) (d) Migrate and home to vascular channels (chemokinesis); cell surface markers enabling entry into vascular channels (e) Survive mechanical shear stress; altered metabolism (switch from oxidative phosphorylation to glycolysis)

GOF gain of function, *LOF* loss of function, *EGF/EGFR* epidermal growth factor/receptor, *TGF* transforming growth factor, *VEGF* vascular endothelial growth factor, *PDGF* platelet derived growth factor, *MMP* matrix metalloprotease, *TIMP* tissue inhibitor of matrix metalloprotease, *bFGF* basic fibroblast growth factor

- *Loss of heterozygosity (LOH):* Loss of heterozygosity occurs when portions of chromosomal material are lost. This typically occurs when an individual has one intact/functional allele, and the loss of the remaining functional chromosome locus is lost. This may result from an inherited or acquired defective allele that is susceptible to LOH in the setting of specific risk factor exposure. Numerous SCC studies [3] have documented LOH defects in the regions coding for tumor suppressor genes, especially in the setting of tobacco use. LOH on chromosome loci 9p (CDKN2A; p16INK4a, p14ARF) and 3p (several candidate tumor suppressor genes) are common in oral precan-

cerous lesions and SCC. LOH defects are not consistently observed in HR-HPV positive (HR-HPV +) associated oropharyngeal cancers.

- *Copy number alterations (CNA):* Copy number alterations are a type of genetic defect where segments of a genome are either gained or lost during neoplastic progression. Copy number gains have been observed affecting chromosomes 3q, 5p, 16p, 17q, 11q. Reproducible losses have been observed in chromosomes 2q, 3p, 4p, 9p, 11q, and 18q [4–10]. HR-HPV positive oropharyngeal cancers and colorectal cancers exhibit 14q32 and 11q copy number losses [11].
- *Hypermethylation:* Abnormal methylation of gene promoter regions has been a long-documented finding in epithelial neoplasms. Hypermethylation of cell-cycle control gene promoter regions like the CDKN2A locus (p16, p14) is common in tobacco and alcohol oral precancerous and SCC lesions. Hypermethylation of critical DNA repair, apoptosis, angiogenesis genes results in gene silencing (this does not require mutations or specific gene deletions). Hypermethylation and resulting gene silencing is considered to be an early event in SCC. Differences in methylation patterns are observed in patients with tobacco-associated oral SCC versus those with HR-HPV associated oropharyngeal SCC.
- *DNA mutations:* Large-scale genome sequencing studies have demonstrated consistently occurring mutations affecting critical tumor suppressor genes—TP53 (p53), CDKN2A (p16INK4a and p14ARF), and oncogenes—PIK3CA, supporting their role as drivers in SCC development. Of these, TP53 was the most frequently mutated gene; p53 plays a central role in DNA repair mechanisms and apoptosis. Consequently, LOF of p53 promotes cell survival and proliferation (loss of regulation at both the G1-S and G2-M cell-cycle checkpoints). p53 LOF is observed in both tobacco-associated oral SCC (via deletion), whereas HR-HPV positive tumors exhibit intact TP53 loci with LOF caused by p53 protein degradation (no mutations). The mutations observed in HPV-negative and HPV-positive tumors are different. Tobacco-associated, HPV-negative SCCs demonstrated mutations in CCND1 (cyclin D1-GOF), PIK3CA (PIK3-GOF), EGFR (ligand independent EGF activation-GOF), and FGF1 amplification (bFGF-GOF), and deletions in CDKN2A (p16INK4a LOF). In contrast, HR-HPV-positive oropharyngeal SCC demonstrated amplification of PIK3CA and FGF43 mutations with a few deletions/mutations affecting tumor suppressor genes.
- *Changes in RNA molecule expression:* Micro-RNA (miRNA) and messenger-RNA (mRNA) defects have been documented affecting critical tumor suppressor and proliferative signaling pathways. For instance, HR-HPV positive oropharyngeal SCC miRNA profiles resemble those of cervical HR-HPV positive SCCs.

In summary, and as will be expounded on in the following sections, the specific genetic defects/alterations observed in tobacco-associated oral SCCs and HR-HPV positive oropharyngeal SCCs differ. Regardless, these observed molecular changes are cumulative and consistent with malignant neoplasms affecting any system—a multistep genetic deregulatory process.

Oral and Oropharyngeal Squamous Cell Carcinoma: Epidemiology

As described above, the oral cavity and oropharynx are two distinct anatomical sites with significantly different embryological origins, functional, and ultrastructural features. A review of statistical data and literature on oral and oropharyngeal cancers can be challenging. These tumors are frequently reported in aggregate and are combined with cancer-data reporting on other pharyngeal and upper aerodigestive tract tumors. This may not allow for distinction (clinical, pathogenesis, risk factors) between oral and oropharyngeal cancer and is the root cause of confusion among clinicians and patients alike. The updated GLOBOCAN database reports lip and oral cavity cancers together and has recognized the oropharynx as a distinct site. The latest GLOBOCAN database correctly separates tumors of the nasopharynx and hypopharynx from those of the oral cavity and oropharynx (https://gco.iarc.fr/today/home). The American National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database pools the oral cavity and pharynx into a large category. This category is broken down into lip; tongue; floor of mouth; gum and other mouth; oropharynx and tonsil; salivary gland. The tongue includes the mobile tongue (body) and the base of the tongue/lingual tonsils, the latter of which should correctly be categorized as the oropharynx. The SEER database reports the "oropharynx and tonsils" as distinct subsites, although the tonsils are part of the oropharynx. Also, this database lists the lip as part of the oral cavity; included in this are cancers of the vermilion border of the lip which should be rightly categorized with non-melanoma skin cancers related to UV-radiation; this chapter does not discuss squamous cell carcinoma of the lip vermilion which is a result of chronic UV-exposure and with markedly better prognosis. Salivary gland cancers, although extremely rare and with different risk profiles, are included in this category. A review of epidemiological literature may result in further confusion as some authors use the term "oral" to refer to both oral and oropharyngeal cancers; some use the term head and neck cancer to report on oral and oropharyngeal cancers, while others report separately on oral and oropharyngeal cancers. As laid out in previous sections, the current evidence supports that oral cavity and oropharyngeal cancers are very different diseases that happen to share a name, "squamous cell carcinoma."

They are distinct with differing etiopathogenesis, clinical features, microscopic and diagnostic features, management approach, and prognosis. This chapter will separate squamous cell carcinoma of the oral cavity (OC-SCC) from squamous cell carcinoma of the oropharyngeal tissues (OP-SCC).

According to the 2020 GLOBOCAN estimates, there were 377,713 new cases of lip and oral cavity cancer with an age-standardized rate (ASR-W) of 4.1/100,000 with a corresponding mortality ASR-W of 1.9/100,000. The ASR-W for lip/oral cavity cancer is highest in the South-Central Asia region (including the Indian subcontinent region) at 9.0/100,000 with a mortality ASR-W of 5.1/100,000; this is likely attributable to differences in risk-factor profiles, diet, and types of betel nut/tobacco products used in this region. A fundamental flaw in this report, as described above, is the inclusion of lip cancers with OC-SCC. Worldwide, in 2020, there were 98,412 new cases of oropharyngeal cancer with an ASR-W of 1.1/100,000 and a corresponding mortality ASR-W of 0.51/100,000. The ASR-W for oropharyngeal cancer is highest in three western hemispheric regions, Western and Northern Europe (2.8/100,000 and 2.6/100,000) and North America (2.4/100,000); the corresponding mortality ASR-W rates are 1.0, 0.72, and 0.52/100,000, respectively. The above data, imperfections accounted for, reflects what clinicians in their respective global regions encounter every day.

In the USA, the National Cancer Institute's SEER database estimates that, in 2022, there will be 54,000 new cases of oral cavity and pharynx cancer (constitutes 2.8% of all cancers) and 11,230 deaths from these tumors. The median age at diagnosis is 64 years; oral cavity and pharyngeal cancer is most frequently diagnosed among people aged 55–64 years (31% of all new cases). The SEER*Explorer application (https://seer.cancer.gov) allows one to parse through incidence-rate data of cancers that affect specific oral (tongue, gum and other oral, floor of the mouth, and lip) and oropharyngeal sites (oropharynx and tonsils). With all oral sites combined, the age-adjusted incidence in the USA (AAI-US) for oral cancer is 1.9 cases/100,000, whereas the AAI-US for oropharyngeal cancer is 2.9 cases/100,000. As seen in Fig. 19.1a, there has been a dramatic rise (AAI-US 1.7–2.9) in the incidence of oropharyngeal cancer over 20 years compared to the combined incidence of oral cavity cancers (AAI-US 1.7–1.9) during the same time. The annual percentage change in the United States (APC-US) for oropharyngeal cancers was +2.8 from 1996 to 2019.

When the SEER*Explorer data on oral cavity cancers from 2000 to 2019 is broken down by subsite, an interesting trend emerges (Fig. 19.2b). Taken separately, the AAI-US for tongue cancer is 3.6 cases/100,000, with an APC-US increase of +2.2 from 1998 to 2019. The AAI-US for gum and other mouth sites (cheek, retromolar pad) has remained steady at 1.6 cases/100,000 with an APC-US of +1.4 from 2007 to 2019 (following a decreased APC-US −1.9 from 1985 to 2007). The AAI-US for floor of mouth is 0.4 cases/100,000 with an APC-US net decrease of −3.7 from 1983 to 2019.

Two trends that emerge from a survey of the GLOBOCAN and SEER data.

- There has been a dramatic and sustained increase (since the mid-1990s) in the incidence of oropharyngeal cancer around the world, specifically in North America, Europe, and Australia, which is attributable primarily to HR-HPV as the major etiologic factor (Fig. 19.2a).
- Although the overall incidence of oral cavity cancer (combined sites) is lower than that of oropharyngeal cancers (AAI-US 1.9 oral vs. 2.9 oropharyngeal cases/100,000), there is a steady increase in the incidence of tongue cancer (AAI-US 3.6 tongue vs. 1.9 oral combined cases/100,000) (Fig. 19.2a, b). The lower AAI-US average for all oral sites combined is attributable to a steady decline in floor of mouth cancers. The underlying cause for this increase in tongue cancers is unclear. This increase was initially attributed to the combination of base of tongue cancers (HR-HPV positive) with mobile/body of the tongue (HR-HPV-negative). However, the vast majority of tongue cancers examined thus far have been negative for HR-HPV [12–22]. In a pooled analysis of case-control studies by the International Head and Neck Cancer Epidemiology Consortium, adults aged 45 years and younger exhibited a higher proportion of oral tongue cancers than those older than 45. In the same study, the association of smoking and drinking with tongue cancer was weaker in young adults compared with older adults [23]. Clinicians must recognize this worrisome trend and adapt their clinical assessment of patients (routine oral examination and screening regardless of a patient's documented traditional risk factors, i.e., tobacco, alcohol).

Oral and Oropharyngeal Cancer: Risk Factors

The genetic defects and deregulation leading to cancers may be spontaneous in some individuals. In a small subset of patients, neoplasms result from inherited mutations/defects of genes involved in DNA repair or cell regulation function. The vast majority of cancers are acquired and are associated with predisposing or etiologic risk factors. Classic carcinogenesis experiments show the importance of risk factors and break them down into initiators or promoters that either inaugurate or advance permanent DNA damage or cellular dysfunction. Carcinogenic agents can inflict genetic damage, which lies at the heart of carcinogenesis. There are three broad classes of carcinogenic agents: (1) chemicals, (2) microbial products, and (3) radiation. Each of the following risk factors may act alone or in synchrony with one another

to sequentially produce the multiple genetic abnormalities characteristic of cancerous cells.

Tobacco

Tobacco, the most common exogenous cause of human cancers, is a significant risk factor for upper and lower aerodigestive tract cancers. Worldwide, it is estimated that cigarette-smoking and the use of tobacco account for over 8 million deaths from cancer and other tobacco-associated illnesses (cardiovascular disease, cancers, chronic respiratory illnesses). Tobacco use accounts for 90% of lung cancers, ~60% of bladder cancers, 65% of esophageal cancers (upper third), and ~85% of OC-SCCs, and is still a significant risk factor for OP-SCC. The International Agency for Research on Cancer classified tobacco smoking as a group 1 carcinogen for carcinogenesis in each of the above anatomic sites.

Numerous independent investigations have confirmed a link between OC-SCC, OP-SCC, and tobacco smoking, including case-control and cohort studies [24–27]. The proportion of smokers among patients with OC-SCC is nearly three times greater than the general population. In addition, studies show that the risk for a second primary carcinoma of the oral cavity/aerodigestive tract is ~2 to 6 times greater in patients with a smoking history. Although tobacco use has been declining or stabilizing in many high-income countries, it has increased in many low-income and middle-income countries. An analytical study noted a relative risk of 3.43 for OC-SCC and 6.76 for OP-SCC among current tobacco smokers compared with non-smokers [28]. Smoking-associated risk is dose-dependent and correlates with daily or cumulative cigarette consumption. For patients who quit smoking, the risk for OC-SCC or OP-SCC declines over time and may approach that of non-smokers 10–15 years after cessation [29]. Other studies show that the risk of developing OC-SCC does not necessarily diminish after smoking cessation [26, 30, 31].

Cigarette smoking is the most common form of tobacco used worldwide. Other forms of combustible/smoked tobacco products include cigars, pipes, bidis (tobacco hand-rolled in a tendu leaf), hookahs (water pipe), and kretek (clove cigarettes). The number of potentially noxious chemicals in tobacco smoke is vast. Some constituents include tar, polycyclic aromatic hydrocarbons, benzopyrenes, and nitrosamines, which are carcinogenic (in animal and in vitro human studies). Organ-specific carcinogens that contribute to OC-SCC and OP-SCC include polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines (TSNA-NNK and N'-nitrosonornicotine), and ^{210}Polonium. These carcinogenic agents are implicated in causing DNA adduct formation, permanent DNA damage, gene and/or promoter deletion/mutations/hypermethylation defects. Carcinogens from smoking that are released into the saliva tend to pool in the low-lying areas of the mouth and could account for the frequent occurrence of oral SCC along the lateral-ventral tongue and floor of the mouth [32, 33].

Smokeless tobacco products (wet snuff, dry snuff, and chewing tobacco) also pose a risk for developing OC-SCC. The risk of developing OC-SCC appears to be higher with dry snuff products and is attributable to the same TSNA's seen in cigarette smoke. The use of smokeless chewing tobacco combined with betel nut is prevalent in parts of South-East and South-Central Asia, accounting for the vast majority of tobacco + betel nut-associated OC-SCCs. The mode of delivery of tobacco products accounts for striking variations in the oral sites and incidence affected. These patients' tumors tend to occur more often in the vestibular, gingival, and buccal mucosae due to the placement of non-combustible carcinogenic substances in direct and prolonged contact with these areas. Swedish snuff (snus) has been reported as a "safer alternative" to smoking and promoted as a potential smoking cessation tool. It is reported that Swedish snus has lower levels of TSNAs, potentially justifying its use. Nevertheless, using snus as a truly "safer alternative" to smoking requires further investigation. Studies from the USA and around the world tell a different story. With the general upswing in snuff dipping and tobacco chewing, especially in the Southeastern United States, the incidence of oral SCC is higher than expected, especially in women [34]. A case-control study of 255 women in North Carolina showed a 50-fold increased risk for SCC of the gingiva and buccal mucosa in long-term snuff dippers [35]. The influence of smokeless tobacco on carcinogenesis seems to be associated with long-term use. Although studies often present conflicting opinions about smokeless tobacco, different risks are associated with different brands and products [36, 37]. These differences are attributable to the presence/absence of additives, flavoring agents, and modifiers that enhance the carcinogenic potential of smokeless tobacco.

Tobacco smoking (past or present) remains the most consistent risk factor for OC-SCC and is still considered a significant risk factor for OP-SCC in the USA. Even with substantial epidemiological shifts resulting from increased incidence of HPV-associated oropharyngeal cancers, any history of tobacco use (past or present; smoking/smokeless) must be viewed as either an independent or a synergistic risk factor for both OC-SCC and OP-SCC.

Alcohol

Alcohol is a well-recognized risk factor for several malignant neoplastic diseases, including OC-SCC and OP-SCC. It is recognized as a potent promoter of carcinogenesis. Ethanol is oxidized to acetaldehyde by acetaldehyde-dehy-

drogenase and further breakdown by CYP2E1, releasing reactive oxygen species that have the potential to disrupt cell membranes and cause chromatin defects. Although investigations that attempt to implicate alcohol alone as the primary causative agent of OC-SCC and OP-SCC have yielded conflicting results [30, 32], the correlation of alcohol with increased risk for OC-SCC and OP-SCC is indisputable. After adjusting for smoking and other variables, most studies in the USA, Europe, and Asia report an increased risk for OC-SCC and OP-SCC in association with heavy alcohol consumption (defined as >60 g/day or >4–7 drinks/week). Meta-analyses estimate that the relative risk for H&N SCC is 1.3 for 10 g of ethanol per day compared with 13.0 for 125 g of ethanol per day, with higher risk estimates for OP-SCC than for OC-SCC [38].

The major clinical significance of alcohol consumption seems to be its ability to potentiate the carcinogenic effect of tobacco. The effect is at least additive and may be multiplicative in individuals with heavy alcohol consumption or at sites with the highest levels of alcohol exposure. Although the underlying mechanisms for this association are poorly understood, some proposed mechanisms include (a) dehydration effects of alcohol render the mucosa more susceptible to the carcinogens in tobacco. (b) Alcohol activates carcinogens present in tobacco by a cytochrome p450-2E1–dependent toxin metabolism mechanism. (c) Release of free radicals in the mucosa from local and hepatic alcohol metabolism results in mutagenesis. Therefore, although alcohol is recognized as a potent contributory/independent risk factor for OC-SCC and OP-SCC when consumed in large quantities and in frequently in combination with tobacco smoking.

Betel Quid and Related Products

Areca nut and betel quid (paan) is a commonly used product in South-East, South-Central Asia, and the Indian subcontinent region. Betel quid consists of a betel leaf wrapped around a mixture of slaked lime, areca nut pieces, tobacco, sweeteners, and spices. Regional variations include "mawa," "khaini," and "zarda." Also used is gutka (paan masala), a dry areca nut product coated with chemicals with/without tobacco; this product, in particular is associated with a specific clinical oral precancerous lesion—*oral submucous fibrosis*. Betel quid and related tobacco products are proven carcinogens and account for the high incidence of OC-SCC in the above regions. Several large-scale studies and systematic reviews have reported an odds-ratio for developing OC-SCC of 7–8 in individuals using betel quid with tobacco and an odds-ratio of 3–6 among individuals who used betel quid without tobacco [39–41]. The OC-SCC risk is exceptionally high among individuals who smoke, drink alcohol, chew betel quid, and/or use gutka (odds-ratio of 40). These habits and products are prevalent and typically used in South-East Asia and the Indian subcontinent; this explains the high incidence of OC-SCC [1].

Human Papillomavirus

Human papillomaviruses (HPVs) are small epitheliotropic DNA viruses with more than 200 characterized strains that infect cutaneous and mucosal surfaces. The overwhelming majority of HPV strains are known to cause benign epithelial neoplasms (viral warts) of cutaneous and mucosal surfaces (verruca vulgaris, squamous papilloma, etc.). It has long been known that selected "high-risk" strains of HPV (HPV 16, 18, 33, and others) are carcinogenic and have been associated with squamous cell carcinoma of the ectocervix. Over the past three decades, there has been accumulating evidence from epidemiologic, clinicopathological, and molecular studies that have established HPV as a major etiological factor in a subset of H&N cancers; particularly in the oropharynx (involving the tonsillar tissues). In 2007, the International Agency for Research on Cancer (IARC), acknowledging this significant epidemiological shift, classified HPV16 as "oncogenic to several cancer sites": cervix, oropharynx, and anogenital (vulva, penis, anus, vagina). This has coincided with a steady increase in the global burden of oropharyngeal SCC attributable to HPV16 (approximately 92–95%). The growth in HPV16 related OP-SCC is predicted to surpass HPV-related cervical cancer in some developed countries. In contrast, there has been a steady decline (all oral and oropharyngeal sites) in tobacco-related SCC. Only a small proportion of OC-SCC appears to be caused by HPV.

What Is Human Papillomavirus? How Does It Cause Infection?

Human papillomaviruses are small, icosahedral non-enveloped circular double-stranded DNA viruses. They are classified into five categories: (1) alpha mucocutaneous; (2) beta cutaneous; (3) gamma cutaneous; (4) mu cutaneous; (5) nu cutaneous. The alpha family is the most common and clinically significant and further sub-classified into [42–44]:

- *Alpha low-risk cutaneous* (LR-HPVcuta: HPV strains 2, 3, 10, 21, etc.): implicated in the formation of benign cutaneous warts. Verruca vulgaris, verruca plana, and others
- *Alpha low-risk mucosal* (LR-HPV: HPV6, 7, 11, 13, 32): implicated in the formation of benign oral and mucosal viral warts (verruca vulgaris; squamous papillomas)
- *Alpha high-risk mucosal* (HR-HPV: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59): implicated in the malignant epithelial neoplasms. Squamous cell carcinomas of the oropharynx, cervix, anogenital mucosae

Given the disproportionately high disease burden associated with alphaviruses (LR-HPV and HR-HPV), the HPV disease mechanisms discussed below will focus on the alpha family; it is also the best studied and characterized. As an obligate intracellular parasite, HPV depends on a host's replicative machinery and protein transcription "factory." The cells best suited to HPV's viral transcription needs are proliferative and differentiating keratinocytes in stratified squamous epithelia; HPV is bound to the keratinocyte life-cycle from basal to spinous to superficial layers. Hence, the *basal epithelial cells of stratified squamous epithelium* serve as the host cell of choice and the "portal of entry." A successful human papillomavirus "hijacks" a host epithelial cell to transcribe its proteins and in the process promotes unregulated epithelial proliferation. The virus harnesses the epithelial proliferation machinery, the cell cycle, to achieve its evolutionary end-goal: replicate, assemble millions of viral capsids, infect another host cell, and go on a repeat cycle. To understand HPV pathogenesis, one needs to appreciate HPV's structure and function. The 8kb HPV DNA genome is organized into three major regions: (1) an upstream regulatory region (URR) that initiates replication and includes transcription factor-binding sites and controls gene expression; (2) an early region, encoding for six viral genes (E1, E2, E4, E5, E6, and E7). Each of these early (E-genes) serves a specific function that enables the virus to incorporate itself in the host, evade host-immune mechanisms, stabilize growth factor signaling, transcribe viral proteins, promote viral replication, and transform the host cell. (3) A late region that encodes for the L1 and L2 capsid proteins, which self-assemble to yield a virion. The main functions of important genes on the HPV genome are summarized in Fig. 19.4.

Generally, HPV resists inactivation and can be transmitted on fomites such as surfaces of countertops, furniture, floors, and towels. HPV can be transmitted and/or acquired (1) by direct contact through small breaks in the skin or mucosa, (2) during sexual intercourse—through small breaks/microwounds in the ectocervical mucosa and the metaplastic transformation zone, or (3) while an infant is passing through an infected birth canal. During transmission, the virus accesses the basement membrane proteins through breaks in the stratified squamous epithelium (microwounds, abrasions). The pentameric L1 capsid protein facilitates attachment to heparan sulfate proteoglycans, laminin-332, and α6-integrin in the hemidesmosome complex (Fig. 19.4). HPV is then assumed into the basal epithelial cell through the "basal domain" through an uptake receptor complex and into endosomal vesicles. At this stage, the L2 capsid protein undergoes a conformational change, transforms into a hook-like structure, adheres to the retromer complex and dynein on microtubules, and migrates (ziplines) to the perinuclear trans-Golgi complex. The virus core remains in the trans-Golgi network (TGN) complex until the basal cell goes through one more cycle of mitosis prior to binding to host epithelial cell DNA and driving viral gene expression and protein transcription. This rapid cycle of events and the endosomal uptake allow HPV to avoid and evade cytosolic immune-sensors. This explains why there is little to no innate immune-response to HPV infection. At this juncture, host immune-intervention via TNF-alpha and interleukin-1 has the potential to downregulate HPV early gene activity. It has been demonstrated in patients with HPV infection that the majority of infected individuals mount an immune-response and clear the initial infection; ~10% develop persistent infection, and only 5–10 per 100,000 progress to recognizable viral changes. Persistent viral infection with high-risk subtypes is a central etiological factor in the development of OP-SCC, anogenital, and cervical cancers. The initial HPV infection in the basal layer affects two populations: (i) basal cells and (ii) the transit amplifying cell (TAC) reservoir. It is in the TAC population that the virus establishes itself as a low copy extrachromosomal plasmid (independent of the cell-cycle). It serves as a reservoir for future phenotypic manifestation of HPV infection (viral warts or carcinoma).

How Does HPV Cause Neoplasia (Benign and Malignant)?

The process of HPV-related oncogenesis is a function and consequence of its early genes (Fig. 19.4). The late genes are involved in facilitating virion assembly, capsid formation, and transmissibility. The steps in the HPV oncogenesis life-cycle are described below:

- HPV remains sequestered within the TGN until the basal stem cells go from prophase to pro-metaphase.
- Shortly thereafter, HPV enters the host nucleus and binds to host DNA to initiate early viral transcription mediated by E1 and E2.
- At this stage, E6 and E7 regulatory proteins briefly dysregulate the basal epithelial cell-cycle (degradation of Rb and p53) to push the cell through the G1-S and G2-M checkpoints (Fig. 19.4; function of E6, E7). This facilitates the incoming virus's first goal to carry out its genome's initial replication. Despite their designation as oncoproteins, E6 and E7 expression is essential for the normal replicative HPV life-cycle, even in benign LR-HPV mediated lesions. Together, E6 and E7 enable HPV to reach the second, productive phase of viral genome replication in cells in the suprabasal and spinous epithelial cells.
- E6 and E7 modify the cellular environment to allow viral genome amplification, mainly by driving S-phase re-entry in the upper epithelial layers. In HR-HPV, E6 and E7 also drive cell proliferation in the basal and suprabasal layers. By contrast, E6 and E7 activity is subdued in the basal and suprabasal layers (playing a role in the higher spinous

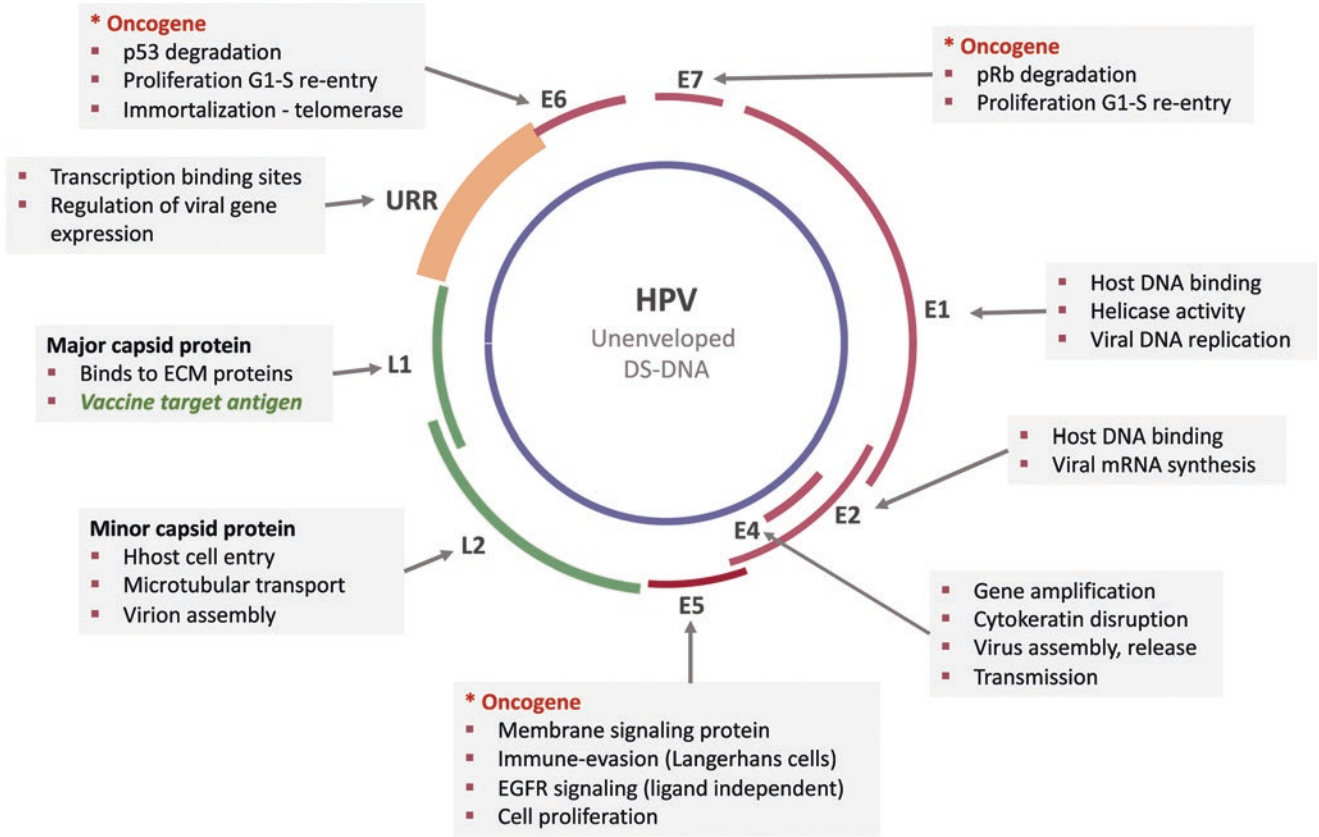


Fig. 19.4 Human papillomavirus genome. Functions and characteristics of the HPV alphavirus family genome. The three main regions are the upstream regulatory region (URR), the early regions that encode for the 6 early genes (E1, E2, E4, E5, E6, and E7), and the late region that encodes for the 2 capsid proteins (L1 and L2). E1 and E2 promote viral replication and genome amplification. E6, E7, and E5 exhibit oncogenic characteristics

layers). This functional difference in E6 and E7 activity, and the specific location they occur within the basal and suprabasal epithelium is a major determinant of HPV disease pathogenicity. *The specific role of E6 and E7 in HR-HPV carcinogenesis is discussed in the following section*.

– E5 contributes to viral genome amplification by stabilizing the epidermal growth factor (EGFR) in a ligand independent manner (Fig. 19.4). This enhances the mitogen-activated protein kinase pathway (MAPK). E5 also activates ERK1/2 and p38 independently of the EGFR. Furthermore, E5, in long-term HPV infection, progressively reduces the number of dendritic/Langerhans cells within the stratum spinosum, further impairing immune-detection.
– The E4 protein assembles into amyloid fibrils, disrupts keratin structure, and disrupts the normal assembly of the stratum superficiale and corneum. E4 also plays a role in virus assembly, release, and further transmission to other cells.
– Following viral genome amplification and capsid protein synthesis, virion formation occurs in the nucleus. Capsid protein is delayed until the cells reach the superficial spinous or granular layers. L2 protein is synthesized prior to L1 and is imported into the nucleus. L1 proteins self-assemble into pentameric capsomeres in the cytoplasm and transported into the nucleus (Fig. 19.4). Post-synthesis, viral genomes are located to preassembled capsid pentamers L1 and L2 interact; L2 is incorporated and folded into the assembling virus particles; L2 plays a role in efficient DNA packaging and final virion assembly. Fully formed virions are released along with dead squamous epithelial cells that are now shed from the epithelial surface. Free virions can survive on fomites and in the environment; they also have the potential to reinfect cells at sites adjacent to where they are shed; this accounts for patients often having more than one or two warts in a particular location.

What Role Do Early Viral Genes E6 and E7 Play in HPV Carcinogenesis?

HPV E6 and E7 early proteins play a central role in HPV-related OP-SCC, cervical, and anogenital carcinomas. Hence

E6 and E7 are designated as oncogenes (Fig. 19.4; E6 and E7 are oncogenes). Specifically, E6 and E7 disrupt the normal homeostatic regulation of the epithelial cell-cycle.

- *E7 binds to pRb* (a critical tumor suppressor and master regulator of the G1-S cell-cycle checkpoint) *and inhibits its normal function*. E7 binds + releases or degrades Rb (and other pocket proteins p107 and p130) from a transcription repression complex. E2F is thus free to activate cell-cycle promoting genes such as cyclin A and E, thus tipping the cell over the G1-S checkpoint. E7 also interacts and abrogates E2F inhibitory transcriptional complex activity leading to increased activity of growth-related genes.
- Normal cells respond to unregulated cell proliferation by inducing apoptosis. Therefore, HPVE7-mediated proliferation might be expected to induce apoptosis. To counter this, HR-HPV expresses E6 protein early. *E6 binds p53* (a key regulator of apoptosis) *and targets it for degradation*; it impairs p53 function by inducing conformation change. Further, HR-HPV E6 proteins abrogate p53 function by inhibiting p53 transcriptional activity. Finally, E6 can sequester p53 in the cytoplasm preventing it from carrying out its nuclear transcription functions.
- Together, E6 and E7 inhibit cytokines like TNF-alpha, TGF-beta, and interferons, altering cytokine signaling and impairing innate and adaptive immune responses.
- E6 and E7 deregulation and overexpression in HR-HPV strains promote episomal silencing of E1 and E2, which results in a non-productive viral infection and sustained genetic deregulation.
- E7 activation results in the release of p16INK4a from the inhibitory activity of the pRb/E2F complex, resulting in p16INK4a overexpression. This allows epithelial cells to escape oncogene-induced senescence. p16INK4a overexpression is critical for cell survival in HR-HPV associated SCC. This makes p16INK4a immunoexpression an acceptable surrogate marker of transcriptionally active HR-HPV OP-SCC.

The accumulation of additional genetic or epigenetic alterations is required for eventual neoplastic transformation, tumor progression, infiltration, and survival. The cumulative defects leading up to invasion and metastatic disease observed in HR-HPV associated OP-SCC are no different than those seen in OC-SCCs.

What Is the Fundamental Difference Between HPV Pathogenesis in Warts and HPV-Related SCC?

The fundamental difference between viral warts and HPV-related SCC (all locations) is the presence of a productive viral infection cycle during the formation of warts (benign epithelial neoplasms) compared to a non-productive viral cycle (no viral capsid release) noted in HPV-related SCCs. The other critical difference is that benign viral warts do not cause or progress to HPV-related SCC as the specific viral strains are very different: LR-HPV vs. HR-HPV.

Viral warts (cutaneous or mucosal) are caused by low-risk strains (LR) of HPV (alpha, beta, gamma, mu, nu). They are benign epithelial neoplasms caused by virally driven, clonal epithelial proliferation. In the oral and oropharyngeal region, HPV6 and 11 account for the majority of mucosal warts (verruca vulgaris, squamous papilloma, condyloma acuminatum). HPV6 and 11 are alphaviruses and share early pathogenetic mechanisms common to all viruses in the family (high and low risk). Upon entry into the TGN, LR-HPV strains through E1, E2, E6, and E7 gene function promote an initial phase of genome amplification and the establishment of a low copy number in infected basal stem cells. What follows is the orderly expression of E1, E2, E4, E5 and late spinous layer expression of E6, E7, and resulting clonal epithelial proliferation. Viral capsid protein assembly proceeds in order, with virions released at the epithelial surface. This productive viral life-cycle accounts for the infectious nature of benign warts. By contrast, in HR-HPV related carcinogenesis, late gene expression is retarded. All the order of events described with warts remains the same. The production of infectious virions is restricted to smaller numbers and is eventually shut down. HR-HPV strains demonstrate elevated and dysregulated levels of E6/E7 (oncogene) expression. Integration of HPV DNA into the host cell genome is facilitated by deregulated E6/E7 expression; in HR-HPV strains [16, 18], this integration often disrupts the E1/E2 region resulting in E1 and E2 episomal silencing. This results in protracted and sustained disruption of critical cell-cycle regulatory mechanisms. Eventually, the productive virus cycle is no longer supported, and viral episomes are lost—this is the definition of a "non-productive" viral infection—there are no viral capsids being released at the epithelial surface.

Determining the HR-HPV attributable fraction of OP-SCC and OC-SCC can be challenging given the wide array of methods used to test for and determine HPV causality. Testing for the mere presence of HR-HPV DNA in OP-SCC and OC-SCC is an inconsistent and low-value testing approach. Many large-scale studies report the presence of HR-HPV DNA without concurrently evaluating for the biomarkers of HPV carcinogenesis: E6 and E7 mRNA or the presence of p16 overexpression. This approach fails to distinguish between truly carcinogenic HPV infection and "passenger" HPV infection (the presence of transcriptionally inactive/latent HR-HPV). Despite these limita-

tions, and with corrections, a meta-analysis of studies reported worldwide from 1990 to 2004 estimated the HR-HPV attributable fraction for OP-SCC to be around 65% and ~5 to 7% for OC-SCC. North American studies evaluating for the presence of transcriptionally active HR-HPV (as measured by quantitative RT-PCR or in situ hybridization for HR-HPV E6 or E7 mRNA) report a 0–4% presence in OC-SCC.

Molecular evidence in support of HR-HPV OP-SCC includes the following: (1) Transcriptionally active HPV16 is present in 90% of HPV-related OP-SCC; (2) HPV16 DNA is present in high copy numbers in HPV-related OP-SCC; (3) in situ hybridization testing demonstrates intranuclear localization of HR-HPV16 in OP-SCC; (4) HPV16 genomic DNA is integrated into OP-SCC cells with active transcription of E6 and E7 viral oncoproteins.

Molecular Differences in SCC: HPV-Related vs. Tobacco Associated

It is essential to distinguish the significant molecular differences between HPV-related SCC and HPV-negative (tobacco and alcohol-related) SCCs of the head and neck region (Table 19.4). Tobacco-associated, HPV-negative head and neck SCCs demonstrate frequent irreversible LOF in chromosomes 3p, 9p, and 17p (deletion; promoter hypermethylation; silencing). In particular, the function of tumor suppressor proteins p53 (TP53) located on chromosome 17p and p16INK4a related to the CDKN2A locus on chromosome 9p21 is lost early, and often, in tobacco/alcohol-associated HPV-negative head and neck SCCs; this results in early cell-cycle dysregulation and significant genomic instability. Thus, when tested for protein expression, HPV-negative SCCs express little to no p16 or p53. In contrast, HPV-related OP-SCC lacks chromosomal loss, gene deletions, and promoter hypermethylation defects. The cellular dysregulation and proliferation seen in HPV-related OP-SCCs result from decreased function of wild-type tumor suppressor proteins p53 and pRb. The respective genes are intact and do not harbor demonstrable defects. The function of p53 protein is compromised (post-translation) resulting from its degradation and inactivation by HPV early protein E6. The retinoblastoma protein pRb is bound by E7 (allowing E2F mediated transcription at the G1-S checkpoint). Consequently, p16INK4a expression is upregulated but is largely non-functional. Therefore, as described above, HR-HPV related disruption of wild-type tumor suppressor proteins results in disruption of the cell cycle at the G1-S and G2-M checkpoints resulting in epithelial cell survival, proliferation, and immortalization.

Therefore, HPV-negative (tobacco/alcohol-related) SCCs and HR-HPV-related head and neck SCCs are two pathogenetically distinct disease entities that share a last name: squamous cell carcinoma (Table 19.4).

Radiation

Exposure to ionizing radiation is a well-recognized risk factor for non-melanoma skin cancers (basal cell carcinomas and SCCs). Ultraviolet (UV) radiation is known to cause DNA damage and mutations in critical DNA repair mechanisms (p53, p14; GOF of MDM2) and is a known risk factor for actinic cheilitis (precancer) and SCC of the vermilion and skin of the lip. However, there is no association between exposure to ionizing radiation and the development of OC-SCC or OP-SCC. Therefore, it is important to exclude SCCs of the lip in our discussion of OC-SCC and OP-SCC. Hence, the inclusion of Lip-SCC in the GLOBOCAN data tends to skew the incidence of "oral SCC" upward. Furthermore, therapeutic radiation of the head and neck does not seem to induce second primary OC-SCC or OP-SCC.

Clinical Considerations: Oral and Oropharyngeal Cancer

Introduction

A variety of cancers occur in the upper aerodigestive tract: those that arise from the mucosal membranes (mucosal squamous carcinomas) and a range of non-squamous cancers that derive from other tissues. Given that squamous cell carcinomas account for the vast majority of cancers involving the oral cavity and oropharynx, this section will focus entirely on the salient clinical and pathological features, diagnostic approach, and management principles of squamous cell carcinomas. Discussing the vast array of other cancers that affect the oral and oropharyngeal region is beyond the scope of this chapter.

As defined above, squamous cell carcinoma (SCC) is a malignant neoplasm that originates from stratified squamous epithelium. It is a disease of genetic deregulation that results from a protracted sequence of events that results initially in abnormal proliferation and maturational dysregulation, followed by neoplastic infiltration into the surrounding structures. Before the emergence of a frank SCC, there are typically clinically and pathologically visible mucosal alterations that correlate with the multistep genetic deregulation (Fig. 19.5). These changes allow clinicians to screen and detect early precursor or precancerous findings to properly monitor, manage, and potentially prevent further carcinogenic devolution. Familiarity with the profile of patients who present with either oral or oropharyngeal cancers, their respective associated risk factors, salient clinical features, and their respective precursor lesions will enable clinicians to assess and evaluate their patients for these common upper aerodigestive tract cancers.

The first section below is devoted to the clinical and microscopic features of oral epithelial dysplasia (OED), the precursor lesion for oral squamous cell carcinoma, and guidelines for management. This is followed by a discussion on the clinical features (patient profile, location, and appearance) of oral squamous cell carcinoma (OC-SCC). The second section will discuss the typical clinical features of oropharyngeal squamous cell carcinoma (OP-SCC), emphasizing high-risk-HPV (HR-HPV) related OP-SCC. Differences in the classic patient profile, potential precursor findings, approach to diagnosis, management, and prognosis will be highlighted (Table 19.4).

Oral Cavity Squamous Cell Carcinoma and Precursor Lesions

Oral Precursor/Premalignant Lesions: Terminology

Precursor lesions for oral squamous cell carcinomas have been studied and reported on extensively. Oral precursor lesions are classified and diagnosed as *epithelial dysplasia* based on microscopic evaluation. Oral epithelial dysplasia (OED) is diagnosed based on a spectrum of intraepithelial architectural and cytological epithelial changes caused by an accumulation of genetic mutations. The clinical presentation of oral precursor lesions is diverse. The clinical correlation with risk of transformation is well documented and enables clinicians to evaluate findings. However, the widely characterized clinical and histological features have led to a proliferation of descriptive (clinical and microscopic) terms. Experts reporting on oral precursor lesions often focus on microscopic and clinical nuances. This is important to anatomic or oral pathologists (with clinical and surgical pathology expertise) trying to discern between benign and potentially dysplastic changes. Unfortunately, this has often led to an over-proliferation of terminology ("*nomenclaturitis*"), confusing clinicians and patients who look to understand and navigate through a detected abnormal finding. There is also a lack of consistency in the clinical and pathological application of these terms. Commonly used (and misused) clinical and microscopic terms that appear in the literature are listed in Tables 19.2 and 19.3. The following sections on clinical features of oral precursor lesions will use simple clinical descriptive terms (*white, red, patch, plaque, nodule, ulcer, heterogeneous, erosion, corrugated, leathery etc.*). They will refer to all precursor oral lesions (microscopically diagnosed) as oral epithelial dysplasia (OED) (Table 19.3).

Table 19.2 Oral precursor lesions—commonly used clinical terminology

Term	Definition and application
I. Clinical descriptive/terms/adjectives	
Plaque	A flattened patch of mucosa that is slightly raised from the surrounding normal mucosa
Macule	A flat, distinctly discolored/abnormally colored mucosal change
Leathery	A rough surfaced appearance—resembling the texture of full grain leather
Pebbly	The appearance of small pink or white raised dots on a red background—resembles pale (small) cobblestones on a red background
Speckled	Heterogeneous with alternating red and white changes
Verrucous	An adjective describing the corrugated/papillary/rough surface mucosal changes—resembles the surface of a wart or a shag rug
Nodular	A raised mass/bump/tumor
Leukoplakia	Leukoplakia is a non-wipeable white patch/plaque that is a strictly clinical descriptive term. It is NOT synonymous with epithelial dysplasia – *Over the years, the term leukoplakia has been defined and redefined and unfortunately misused synonymously with precancerous change. This has generated much confusion* – *The current definition is "a white non-wipeable patch of questionable risk, having excluded known diseases that carry no increased risk for cancer"* – *Once a histological diagnosis is available, the term leukoplakia must be dispensed with*
Erythroplakia	A strictly clinical term used to describe a red, hyperemic patch on the oral mucosa. Often correlates with areas of mucosal erosion or ulceration
Erythroleukoplakia	A strictly clinical term used to describe a combination of *leukoplakia* and *erythroplakia.* Alternating areas of red and white patches/"speckled"/heterogeneous
Proliferative verrucous leukoplakia (PVL)	A strictly clinical description for a specific presentation of *multifocal* white non-wipeable white plaques that often exhibit foci of verrucous surface changes. This clinical presentation is seen often in elderly women and men, non-smokers, and presents on unconventional sites: gingiva, buccal mucosa, in multiple oral locations – *Biopsies of lesions clinically described as PVL are diagnosed as epithelial atypia, verrucous hyperplasia, oral epithelial dysplasia, squamous cell carcinoma, or verrucous carcinoma*

Oral Epithelial Dysplasia: Clinical Presentation

Before looking for suspicious oral findings, it is essential that we review the important elements of an oral examination. Clinicians looking to conduct a thorough oral exam require nothing more than good lighting, an oral examination mirror (single use/stainless steel), and gauze sponges. When looking for mucosal abnormalities, it is essential to dry the oral mucosal tissues, especially the floor of the mouth, ven-

Table 19.3 Oral precursor lesions: commonly used microscopic terminology

Term	Definition and application
II. Microscopic	
Hyperplasia	An increase in number of cells resulting from proliferation of cells – *Basal cell hyperplasia refers to changes seen in precursor lesions/OED correlating with abnormal numbers of basal/suprabasal cells* – *Most epithelial hyperplasia is benign and a result of increased numbers and thickness of the stratum spinosum/spinous layers*
Acanthosis	An increase in the number of cells in the stratum spinosum
Dyskeratosis	Premature intracytoplasmic keratinization; this is often indicative of dysregulation in the differentiation of stratified squamous epithelium – *This can be a feature seen in some oral precursor lesions or carcinoma but is not specific to or pathognomonic for neoplastic progression*
Rete peg/Rete ridge	Epithelial invaginations and reciprocal upward projections of the lamina propria *Resemble a hook-and-loop structure* *Rete pegs promote adhesion, increase attachment surface area, and facilitate abrasion resistance*
Atypia	Abnormal cytological or architectural features *The term "epithelial atypia" may be used in a diagnosis. It may represent:* – *reactive change at ulcer margins, viral cytological change, epithelial reaction to friction/inflammation* – *incipient or evolving epithelial dysplasia*
Epithelial dysplasia	A specific microscopic diagnosis is used to indicate potentially malignant behavior *Pathologists assess the architecture and cytological features using specific diagnostic criteria* *The grade of epithelial dysplasia (low, moderate, high) is an inconsistent predictor of progression to carcinoma*
Carcinoma in situ	Epithelial dysplasia exhibiting top-to-bottom architectural and cytological abnormality
Verrucous	Corrugated surface texture with prominent spires, ridges, and furrows of keratin (ortho or para) Wart-like surface; exophytic and endophytic epithelial architecture

tral, and lateral tongue**.** Gauze sponges (2 × 2 cm) are used to dry mucosae, determine whether a discovered white area is wipeable (or not), and help the clinician hold the tongue. Another helpful tool in evaluating patients is a camera that can capture intraoral photographs (a good DSLR or mirrorless camera with a macro lens and ring flash attachment).

Where in the Oral Cavity Does Epithelial Dysplasia Occur Most Commonly?

Knowing the most likely where precursor lesions/oral epithelial dysplasia (OED) occurs is vital. In the USA, the vast majority of OED lesions are discovered in the following areas: (1) lateral tongue; (2) ventral tongue; (3) floor of the mouth; (4) anterior soft palate. These sites are lightly or non-keratinized and are lined by unattached mucosal tissues. It is thought that the thinness of these areas allows carcinogens from cigarette smoke to accumulate and penetrate into the basal epithelial region. In South-Central, South-East Asia, and the Middle-East, where betel quid/chewing tobacco/paan use is common, or in patients who use smokeless tobacco products, OED lesions occur more often in the oral vestibular, gingival, and buccal mucosa. This results from the placement of noncombustible carcinogenic substances directly in these areas.

What Is the Typical Clinical Appearance of an OED Lesion?

Epithelial dysplasia results from cumulative genetic deregulation that results primarily in disruption of basal cell homeostasis and abnormal intraepithelial proliferation that may or may not be accompanied by increased keratinization (hyperkeratosis). Intraorally, this translates to a thickening of the mucosal tissues—this blocks light from reflecting off blood vessels in the superficial lamina propria. The clinical correlate is a non-wipeable white/pale macule/plaque (patch). Commonly used clinical terms used in describing oral precursor lesions are listed in Table 19.2. The non-wipeable white plaques associated with OED are typically not associated with obvious sources of irritation/friction (e.g., sharp tooth cusp/restoration/prosthesis; parafunctional habit—tongue/cheek chewing). Clinicians must rule out the latter as a source of irritational hyperplasia. Also, the findings are typically painless, asymptomatic, and often incidentally discovered (during a routine oral hygiene visit, a routine physical examination, or a dentist visit).

As depicted in Fig. 19.5, incipient precursor lesions may not present with any clinically detectable white macular or plaque-like change. When an as yet undefined threshold of genetic defects is reached, the "subtle" goes into "obvious" territory. The earliest detectable changes are often diffuse, milky white, or pale macules (whitish, flat discoloration) (Fig. 19.6a) or leathery/ wrinkly/ textured non-wipeable plaques (Fig. 19.6b). Lesion borders are often diffuse, indiscernible, and blend into the surrounding "normal" appearing mucosa (Fig. 19.6a; posterior ventral tongue). The white changes can range from homogeneous (uniformly white) to varying textured changes: thicker and bright white (see arrow in Fig. 19.6c), corrugated/verrucous. As the epithelium thickens, the mucosa appears more textured and whiter—these are changes one can observe and document from clinical visit to visit, especially with high-quality photographs.

As genetic regulation devolves, OED lesions evolve and develop heterogeneous qualities. Foci with an abundance of neoangiogenesis accompanying unregulated epithelial proliferation make previously white patches appear red, adding

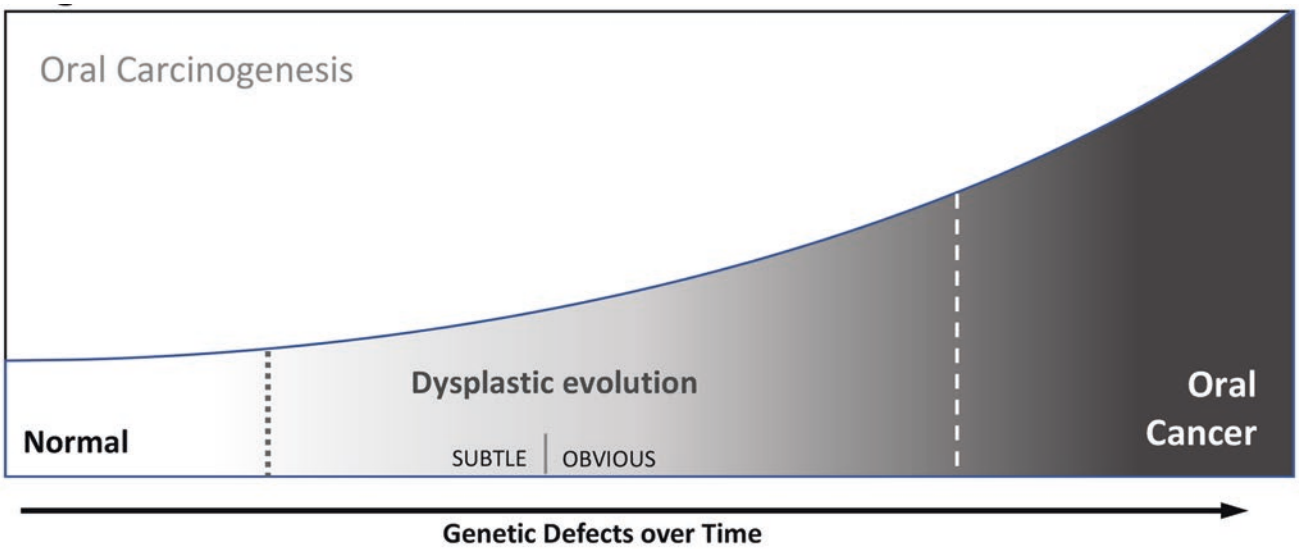
a "speckled" appearance (Fig. 19.6e, f). Areas of redness may also correspond to areas where the surface epithelium is thinner, i.e., eroded/atrophic. These red areas are often depressed relative to the surrounding white changes—this is a harbinger of potential invasion, warrants a closer look, and is prioritized for biopsies. Microscopically, foci or patches of redness occasionally correspond to micro-breaches in the basement membrane and early invasion. Similarly, the presence or development of an ulcer (complete break in the mucosa) is highly suspicious for invasion (Fig. 19.6e, f). The development of tissue firmness/hardness is a sign of an underlying stromal desmoplastic response, highly suggestive of tumor infiltration into the lamina propria. The following mucosal changes noted in oral cancer-prone locations (floor

Table 19.4 HPV-negative oral SCC vs. HR-HPV-positive oropharyngeal squamous cell carcinoma

	Oral cavity SCC: HPV-negative	Oropharyngeal SCC: HR-HPV associated
Risk factor	Tobacco and alcohol	HR-HPV; oral sex or numerous partners
Patient profile	Older; average age >50 years; longtime tobacco use	Younger; 35–50 years; higher socioeconomic status; educated
Incidence trend	All oral sites stable to declining; tongue increasing (non-tobacco)	Increasing; +2.8 annual percentage change
Anatomical location	Oral cavity—tongue, floor of mouth, gum, cheek	Oropharynx: base of tongue, tonsillar fauces, palate, pharyngeal wall
Epithelial ultrastructure	Stratified squamous epithelium; continuous basement membrane	Reticulated stratified epithelium/lymphoepithelium; discontinuous basement membrane; lymphoid tissue
Clinical precursor lesions	Yes. Oral epithelial dysplasia; white and red plaques	No identifiable precursor lesions
Clinical presentation (typical)	Ulcerated oral mucosal mass; speckled; pebbly appearance Red and white surrounding patches (OED) Indurated on palpation Symptoms: pain, paresthesia	Cervical lymph node swelling Dysphagia Hoarseness Symptoms: incidentally discovered mass
Diagnostic approach	Definitive incisional or excisional biopsy Scalpel or punch biopsy	Fine needle aspirate cytology + p16 immunoexpression Laryngoscopy/nasopharyngoscopy + biopsy Advanced imaging: CT/MRI/ultrasound
Histopathological features	Ulcerated nodule; hyperkeratosis; infiltrating keratinizing squamous cell carcinoma; surface epithelium exhibits maturational disturbance	Basaloid appearing, non-keratinizing squamous cell carcinoma Cystic degeneration and central necrotic change
p16 immunoexpression profile	Negative resulting from deletion/ hypermethylation or LOH	Strong nuclear and cytoplasmic expression
Biology and genetic alterations	Multiple acquired, often irreversible, genetic alterations chromosomal loss; gene deletions and mutations; hypermethylation defects; loss of heterozygosity	Few permanent genetic alterations Does not exhibit chromosomal loss; no gene deletions and mutations; no loss of heterozygosity
(a) *p53* (b) *p16* (c) *pRb* (d) *EGFR*	(a) Gene deletion—frequently seen (b) Gene deletion; promoter hypermethylation—frequently seen (c) Intact; rare deregulation (d) Gain of function of gene and protein transcription	(a) Gene intact—protein impaired by HPV E6 mediated degradation (b) Overexpression resulting from HPV E7 abrogation of Rb (c) Gene intact—Rb protein impaired by HPV E7 mediated abrogation (d) Activated—ligand independent activation mediated by HPV E5
Metastasis	Frequent distant metastases with poor outcomes	Frequent nodal spread; rare distant metastasis; good outcomes
Treatment outcomes	Worse overall survival and progression free survival	Good overall survival and progression free survival
Prevention strategies	Smoking cessation and alcohol cessation	HPV vaccination—Gardasil 4-valent and Gardasil 9-valent

Salient differences in risk factors, patient profile, clinical presentation, tissue ultrastructure, disease mechanisms, treatment, outcomes, and prevention strategies

Fig. 19.5 Oral cancer is a disease of cumulative genetic deregulation with clinical, microscopic, and genetic correlates. Note that the underlying genetic defects do not show up as obvious clinical and histopathologic phenotypic changes until later in the process. (1) Clinically visible changes. Features noted during the progression from normal to early/ incipient dysplastic change to oral epithelial dysplasia to oral SCC. (2) Histopathological features. Microscopic architectural and cytological maturational changes observed progression from normal to oral epithelial dysplasia to oral SCC. (3) Acquired genetic defects. Cumulative genetic defects that correlate with microscopic and clinical findings (refer to Table 19.1 for details)



NORMAL	DYSPLASTIC EVOLUTION		SQUAMOUS CELL CARCINOMA
	EARLY	LATE	
1. Clinical appearance / signs & symptoms			
Normal Oral Mucosa	**No detectable changes** **Or** **Subtle mucosal changes** - white, leathery textured plaques	**White non-wipeable plaque** - Diffuse, homogenous - Milky, leathery texture **Heterogeneous, red/ white plaque** - Pebbly texture, erosion, erythema - Ulceration, nodularity, discomfort - Verrucous surface texture - Increase in size > 200 sq. mm.	**MASS/ TUMOR/ NODULE** **White/ Red/ Heterogeneous plaques** Ulceration Pain/paresthesia Induration Lymphadenopathy Tooth mobility Metastatic Disease
2. Histopathological Features			
Normal Mucosal Architecture: - Cellular differentiation & keratinization - 1 to 2 basal epithelial cells - Normal cytological features	**Normal → Atypia:** - Normal mucosal architecture - Subtle mucosal architectural changes or cytological abnormalities (ATYPIA)	**Intraepithelial Dysplasia:** - Hyperkeratosis - Bulbous, droplet-like rete pegs - Basal cell hyperplasia/ crowding - Dyskeratosis (premature keratin) - Hyperchromatism - ↑ N/C ratio - Pleomorphism - Ulceration/ erosion - Lymphocytes at stromal interface - **INTACT BASEMENT MEMBRANE**	**All features of Dysplasia** **PLUS** - Invasion through basement membrane - Ulceration - Infiltration of stroma - Invasive nests in muscle/deep tissues - Keratin pearls - Lymphocytes - Invasion of bone/lymph nodes etc.
3. Pathogenetic Correlation			
Normal Homeostasis: - Regulation of growth / Apoptosis - Normal keratinocyte differentiation - Regulated local immune surveillance	**Acquired genetic mutations (Gain / Loss / Altered Function) of key mechanisms that regulate local homeostasis:** A. Self-sufficiency in growth signals (GOF) B. Insensitivity to antigrowth signals (LOF) C. Acquired capability to evade apoptosis (GOF) D. Limitless replicative potential (GOF) E. Sustained angiogenesis, stromal support (GOF)		**A,B,C,D, & E** **PLUS** **Tissue invasion and metastasis:** - Cell-cell dyshesion (GOF) - Ability to degrade basement membrane & extracellular matrix (GOF) - Evade immune surveillance - Cell migration (GOF) - Homing of tumor cells (GOF) - Vascular dissemination (GOF)

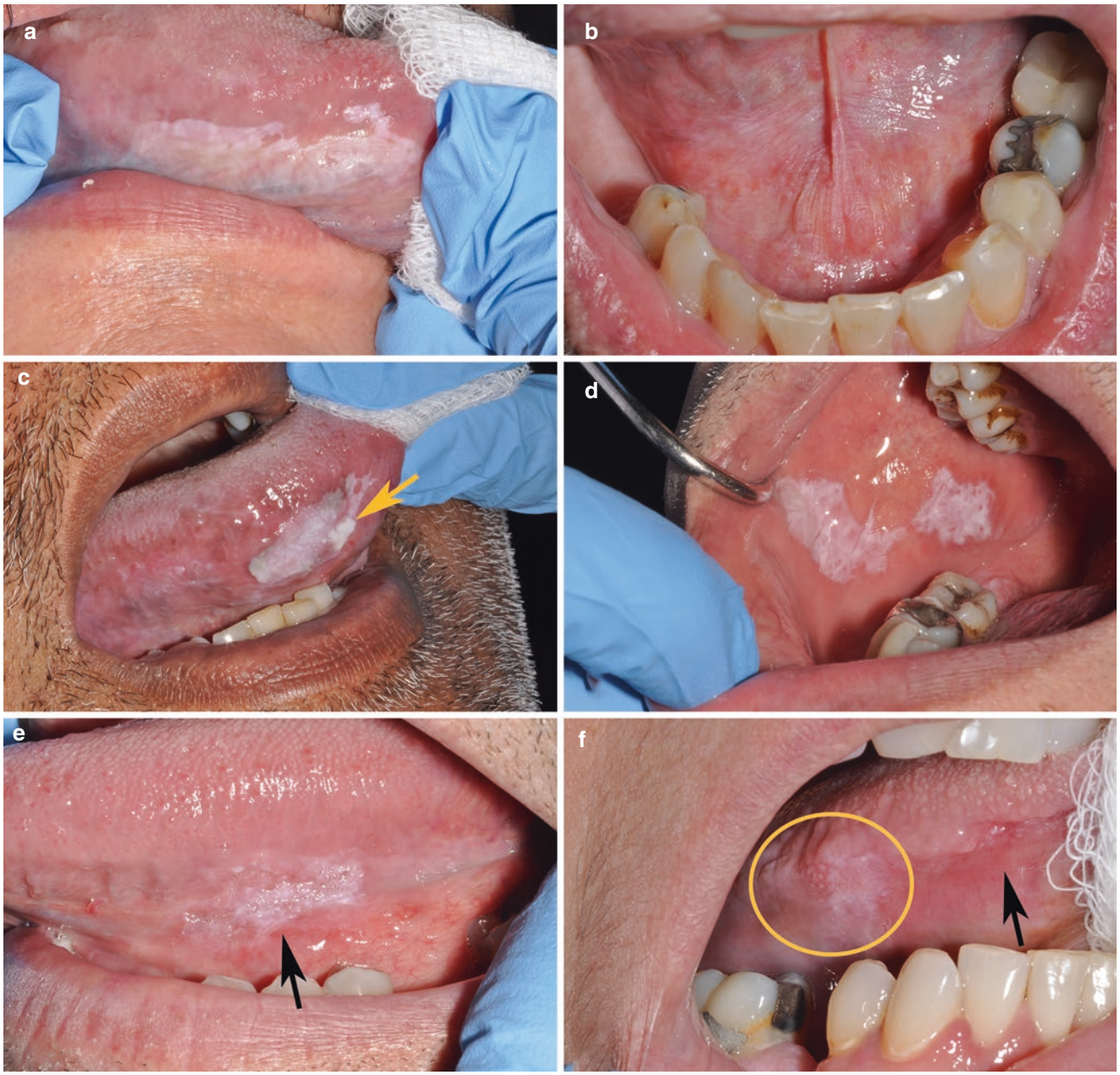


Fig. 19.6 Clinical features of oral epithelial dysplasia (OED). (**a**) Right lateral-ventral tongue OED. White non-wipeable white plaque with thicker, leathery changes toward the anterior–superior portion of the tongue; note the homogeneous white appearance and diffuse nature of the finding as it blends into "normal" ventral tongue. (**b**) Floor of mouth OED. Subtle white, leathery texture of the floor of the mouth bilaterally. Note that the floor of the mouth was dried with gauze sponges to reveal these early findings. (**c**) Right ventral tongue OED. A thick, leathery white patch toward the anterior ventral tongue; note the heterogeneity—thick white (black arrow) plaque toward the anterior and blending, diffuse white changes extending posteriorly. (**d**) Right buccal mucosa OED. Two white non-wipeable patches surrounded by erythematous borders and intervening regions of heterogeneity. (**e**) Left ventral tongue OED with clinically suspicious findings. Diffuse white plaque on the ventral tongue with central areas of "pebbly change" (black arrow) and focal ulceration; targeted biopsies revealed OC-SCC. (**f**) Right ventral tongue OED with OC-SCC. Patient with history of OED presented with two suspicious findings. Pebbly changes with white and red speckled appearance diagnosed with OC-SCC on biopsy (yellow circle). Targeted biopsy of the anterior area (black arrow) revealed microinvasive OC-SCC

of mouth, ventral tongue, lateral tongue, soft palate) are highly suspicious for invasive OC-SCC: (1) large homogeneous red patches surrounded by white changes (Fig. 19.10c); (2) heterogeneous, alternating areas of red and white plaques (Figs. 19.6f and 19.9a, b); (3) ulceration/erosion/loss of continuity (Figs. 19.6e, f, 19.9, and 19.10); (4) pebbly textural change (Fig. 19.6e, f)—the pebbles are "islets"/pink-white papules of normal epithelium surrounded by "seas" of

eroded/micro-ulcerated foci; (5) firmness/hardness/induration on palpation is an ominous sign—it correlates with a desmoplastic stromal response to invasive carcinoma; (6) lesions >200 mm^2 and increase in size from visit-to-visit; (7) patients reporting symptoms of burning, pain, tingling associated with a heterogeneous red and white patch [45, 46].

Patients with a history of betel quid, paan, areca nut, and gutka can potentially develop the clinical signs of *oral submucous fibrosis*. Patients present with progressively reduced mouth opening (reduced interincisal opening), sensitivity to hot/acidic/spicy foods, and pale/white/red changes in the right and left buccal vestibules and gingivae. The most notable finding, in addition to white leather patches, is the presence of circumoral and buccal mucosal submucosal fibrous bands. The vertical bands that run from the upper to lower buccal vestibules feel like guitar strings. When biopsied, the white patches often show epithelial atypia or OED along with prominent submucous fibrosis. Submucous fibrosis with continued product use is associated with a high malignant transformation risk.

A subset of patients present with the so-called *proliferative verrucous leukoplakia* (PVL). Patients with this clinical pattern are typically elderly, often female, and report none of the typical risk factors (tobacco, alcohol). Rather than a specific diagnostic entity, this is a peculiar clinical-pathological presentation with widespread, painless, *multifocal*, corrugated, white and red plaques involving multiple oral sites. The oral locations typically affected are the buccal mucosa, attached and marginal gingiva, and tongue; the white gingival changes often encircle teeth, involve the interdental papillae, and gingival col region. The white changes are often described as corrugated/verrucous/wart-like; not all areas appear warty or rough. This clinical presentation is associated with exceptionally high carcinomatous transformation risk [47–50]. Biopsies obtained from the so-called PVL lesions demonstrate OED, OC-SCC, or verrucous carcinoma (discussed below).

Patients who present with non-wipeable white and/or white + red oral mucosal plaques must be assessed thoroughly and with discipline. Local factors such as friction, trauma, or obviously recognizable clinical causes must be ruled out. If said lesions are present in cancer-prone locations and associated with potential risk factors, a biopsy or multiple biopsies (as described below) must be obtained to rule out potential oral epithelial dysplasia or infiltrating OC-SCC. Biopsies for assessment of OED are ideally incisional surgical biopsies or punch biopsies. The sample must extend into the tissue several millimeters and capture portions of the epithelial–stromal interface and connective tissue. These definitive tissue samples contain full-thickness epithelium and capture the underlying stromal tissue. This allows pathologists to adequately evaluate epithelial architecture from the basal-spinous-superficial layers and assess the epithelial–stromal interface at the basement membrane zone.

Table 19.5 Oral epithelial dysplasia: diagnostic

Architectural features	Cytological features
• Abnormal surface keratinization	• Basal cell regimentation/ parallel arrangement
• Bulbous/drop-shaped rete pegs/ridges	• Loss of basal cell polarity
• Abnormal epithelial–stromal interface pattern (*site specific*)	• Nuclear hyperchromasia
• Irregular epithelial stratification	• Nuclear enlargement
• Dyskeratosis/premature cytoplasmic keratinization	• Increased number and size of nuclei (upper strata)
• Loss of basal cell polarity	• Pleomorphism—variation in cell shape + size
• Basal and suprabasal hyperchromasia	• Atypical mitoses
• Basal cell crowding and budding	
• Verrucous	

Oral Epithelial Dysplasia is a precursor lesion that has the potential to progress to oral squamous cell carcinoma. It is a diagnosis made using a combination of architectural and cytological features

Oral Epithelial Dysplasia: Microscopic Features

The first step in evaluating for OED is recognizing the variations in stratified squamous epithelial morphology in different oral mucosal sites. As described in the section on oral mucosal histology and ultrastructure, the epithelial–stromal interface, the presence or absence of surface keratinization, and *rete peg* (if present) morphology vary depending on the specific site. Therefore, it is essential to know the specific oral mucosal site when evaluating biopsies for OED. The second challenge faced by some pathologists evaluating oral mucosal biopsies for OED has been the influence of terminology and concepts applied in diagnosing HPV-related intraepithelial neoplasia of the uterine cervix. For instance, the concept of intraepithelial neoplasia, grading dysplasia by epithelial thickness, and applying HR-HPV related pathophysiology to the oral stratified epithelium is flawed—it does not correlate with the behavior and progression of OC-SCC.

What Are the Microscopic Features of Oral Epithelial Dysplasia?

Oral epithelial dysplasia is diagnosed based on a low-to-intermediate magnification evaluation of epithelial architecture and intermediate-to-high magnification assessment of cytological changes noted in the basal and suprabasal regions. The list of architectural and cytological features as laid out in the WHO classification is shown in Table 19.5. Some of the diagnostic criteria, taken in isolation, may be features of benign processes; arriving at a diagnosis of OED requires clinical context, a trained eye, and consistent appli-

cation of a combination of architectural and cytological characteristics. This last fact accounts for interoperator diagnostic variability [51, 52]; both studies in consistently diagnosing OED. Pathologists evaluating for OED must begin by assessing the architectural make-up of the basal and suprabasal regions, *the proliferative compartment of stratified squamous epithelium*. The earliest changes noted in OED are often a loss of basal cell polarity, cellular hyperchromasia, nuclear + nucleolar enlargement, and cellular crowding. This reflects chromosomal instability, potential aneuploidy, and proliferation. Basal cells are typically cuboidal. The loss of basal cell polarity results in cells taking on a columnar cytoplasmic profile. Basal cell nuclei are elongated and exhibit regimentation (Fig. 19.7a-f). With increased proliferation in the proliferative compartment (basal 1/3rd), there tends to be cellular crowding—this tends to push the basement membrane downward and the spinous cells upward. The downward growth changes the structure of the whole epithelium. This is seen at low-medium magnification as bulbous/drop-shaped rete pegs/ridges (Fig. 19.7b-f). This tear-drop-shaped morphology (Fig. 19.7b) is especially notable in specimens obtained from otherwise thin oral mucous membranes (e.g., floor of the mouth, ventral tongue, soft palate, and lateral-ventral tongue). On the gingival tissues, the bulbous architectural changes are distinct compared to normally tapered *rete pegs*. Normal stratification and differentiation patterns may be disrupted: early keratinization, keratin pearl formation, and/or single-cell intracytoplasmic hyperkeratinization are observed (dyskeratosis) (Fig. 19.7e). The loss of keratinization in a previously white plaque corresponds to clinical redness or a "speckled" patch. This finding is often a sign of devolution and warrants a closer look (Fig. 19.7f). Abnormal cellular proliferation from the basal region may progress upward through the strata and potentially to the stratum superficiale; this is often accompanied by enlarged and round nuclear forms, altered N:C ratio, and lack of keratinization and nuclear condensation. This feature of upward (toward the apical domain) cellular and architectural change (divided in thirds) formed the basis for dysplasia grading systems in the cervix and other locations. As discussed later, a "thirds-based" dysplasia grading system (mild, moderate, severe grade) has been shown to be an inconsistent marker of progression and predictor of clinical behavior. A verrucous surface morphology with hyperkeratosis, papillary and corrugated surface change, endophytic (inward growth of *rete pegs),* or exophytic (outward growth of the apical layers) are worrisome signs. Another sign of significant cellular dysregulation is the presence of dyshesion resulting in acantholysis (separation between the spinous cells). The latter is often an indicator of potential microinvasion beyond the basement membrane—at a cellular level, it corresponds to potentially malignant epithelial cells being able to survive independent of anchoring proteins and thus evading apoptosis (akin to the in vitro concept of anoikis). It is not uncommon to find a robust cell-mediated lymphocytic infiltrate at the dysplasia-lamina propria interface (Fig. 19.7c–e). This is the result of immune-surveillance mechanisms. The above features, in various combinations, are the typical hallmarks of OED.

Does One Have to Grade Oral Epithelial Dysplasia? What Is the Significance of Grade?

Microscopic grading of epithelial dysplasia has been in practice for decades and adopted the cervical intraepithelial neoplasia model of thirds. The original reason for grading was to report on the thickness of the epithelial maturation disturbance and use it to correlate clinical progression toward carcinoma. Grading has historically been justified as a means to predict the probability of malignant transformation. Unfortunately, the literature on grading tells a different story: it has poor standardization and reproducibility.

The third method of evaluating OED has been used for decades. It assesses the degree of architectural and cytological disarray by thirds of the epithelium: the lower 1/3 or proliferative compartment; the middle 1/3 and spinous cell section; and the upper 1/3rd or superficial cell section. Pathologists characterize OED lesions as mild (changes involving only the lower 1/3), moderate (changes involving the lower and middle 1/3, i.e., the lower 2/3rd of the epithelium), or severe (carcinoma in situ; changes involving the full thickness of the epithelium a.k.a. top-to-bottom) in histopathologic degree depending on the extent of architectural, cellular, and maturational abnormality observed from the basal cell layer inferiorly, to the epithelial surface superiorly. This method may apply in the cervix but does not apply to OED, given that oral surfaces are variably keratinized and, importantly, not involved with HR-HPV related pathogenesis. This approach also fails to acknowledge that THE epicenter for OED is the basal and suprabasal proliferative compartment. With a basic understanding of epithelial carcinogenesis, one understands that there is no requirement or biological rule for a genetically altered cell OED cell to travel up to the full thickness of the epithelium before accumulating the necessary defects to break through the basement membrane barriers. In daily practice, given time and adequate genetic deregulation, a "mild" OED can transform and infiltrate through the basement membrane barriers. Furthermore, a critical flaw in OED grading is its lack of reproducibility between providers and labs. Additionally, the grade of dysplasia does not provide a surgeon with scientifically justifiable and actionable information—the addition of adjectives like "mild" or "moderate" may lull a clinician into a false sense of comfort. A "severe" OED diagnosis sounds severe and may force a surgeon into an aggressive treatment plan.

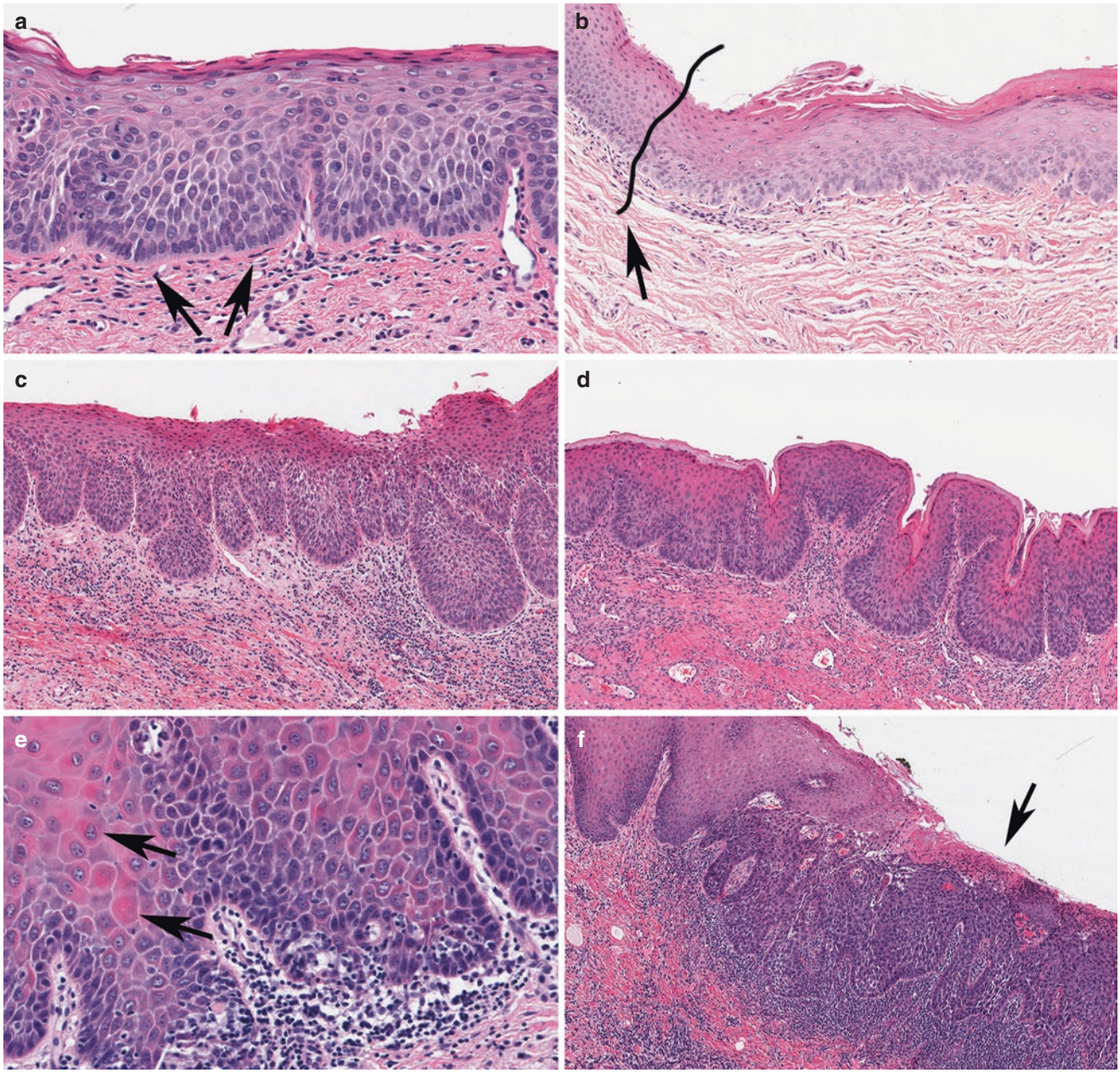


Fig. 19.7 Histopathological features of oral epithelial dysplasia (OED). OED is diagnosed based on a combination of architectural and cytological criteria (see Table 19.5). The epithelial–stromal interface and architecture is altered but the basement membrane zone is intact. (**a**) Floor of mouth OED; basal cell regimentation. The epithelial–stromal interface is altered—bulbous *rete pegs*. Basal cells exhibit hyperchromasia (darker), loss of polarity—regimented (black arrows show cells in parallel); basal + suprabasal crowding; mitoses; superficial parakeratosis. (**b**) Ventral tongue OED; hyperkeratosis and tear-drop *rete pegs.* Note the change at the junction between "normal" and altered epithelium (black line). The epithelium shows surface hyperkeratosis, basal cell crowding, tear drop-shaped *rete pegs*. The epithelial–stromal interface is not flat. (**c**, **d**) Lateral tongue and ventral tongue OED. Note the surface hyperkeratosis, epithelial thickening, prominently endophytic and bulbous *rete pegs*. Basal cell crowding, hyperchromasia. Chronic inflammatory aggregates are noted at the epithelial–stromal interface. The surface in image (**d**) appears irregular and likely corresponds with a corrugated surface clinically. (**e**) OED, premature keratinization (dyskeratosis). Note the bright pink intracytoplasmic premature keratinization in the spinous layers. (**f**) Buccal mucosa OED, surface ulceration. Biopsy obtained from an area described as a red, ulcerated patch (erythroplakia). Prominent maturational disarray noted in the epithelium beneath the noted ulcer (black arrow)

Some of the OED grading systems currently in use are:

- *WHO system*: mild, moderate, and severe (including carcinoma in situ). This is the most widely used system for OED grading.
- *Binary system:* low-grade and high-grade. This is a purportedly clinically actionable grading system that follows grading of dysplasia in other upper aerodigestive locations. Surgical excision or laser ablation is recommended for high-grade lesions, while low-grade lesions are monitored.
- Others include the Ljubljana, Japanese Society of Oral Pathology system

Each grading system includes morphological, architectural, and cytological diagnostic criteria. Grading systems are designed to help pathologists recognize and diagnose OED consistently. While the criteria for dysplasia are applied consistently and work well, the grading systems are not reproducible in large-scale interoperator studies. Most importantly, the grades of dysplasia have not consistently predicted the risk of progression or transformation to OC-SCC and hence are clinically unreliable.

Therefore, irrespective of degree, a diagnosis of OED should alert a clinician that there is a recognized risk for progression to carcinoma. Management, surgical or conservative monitoring, must be tailored to a particular patient's clinical findings acknowledging the risk of progression. The author believes that oral epithelial dysplasia should be diagnosed as "oral epithelial dysplasia" with no mention of grade. Clinicians may be informed of the specific grade (thirds or binary) in a comment (describing the diagnostic criteria used to make the final assessment); they must be reminded that grade is not a consistent predictor of progression to OC-SCC. Patients diagnosed with epithelial dysplasia must be appropriately educated about the genetic basis of the disease and must be monitored/managed in an ongoing, indefinite manner.

Oral Epithelial Dysplasia: Management and Prognosis

The diagnosis of oral epithelial dysplasia is significant and constitutes a risk for progression to squamous cell carcinoma. There has been extensive research looking into best clinical practices [46, 53–55] and in identifying predictive biomarkers. The grade of OED is not a consistent predictor [45, 46]. Immunohistochemical expression of various proteins, LOH of specific tumor suppressor genes, and amplification/overexpression of oncogenes have been reported with inconsistent results.

Biomarkers that appear consistently in research studies are: (1) podoplanin immunohistochemical expression indicates an increased relative risk (8.7%) of transformation; (2) LOH at 3p14 and 3p21 (hMLH1-DNA mismatch repair function and fHIT); (3) LOH at 9p (p16INK4a and p19) is associated with a 22-fold relative risk for malignant transformation over lesions without LOH in these loci (3); (4) aneuploidy studies have demonstrated a 38% positive predictive value; (5) EGFR amplification [56–63].

While these results show promise, to date, there are no clinically applicable biomarkers that consistently predict which OED lesions are at highest risk of progression to OC-SCC. These predictive biomarkers need to be studied further, assays standardized, and reported on through large-scale multicenter research studies. Until then, clinicians managing patients diagnosed with OED approach them as follows:

- *Patient education:* Patients diagnosed with OED, irrespective of histopathological grade, must be educated about the potentially cancerous nature of the lesion and the underlying acquired genetic deregulatory basis of the disease. From the outset, given the lack of genetic biomarkers that predict progression to OC-SCC, clinicians must strongly emphasize the need for continued clinical monitoring at regular intervals. Patients must also be educated about the "field effect" of genetic change likely present in normal-appearing oral mucosal tissues surrounding the clinically detectable white plaque [64, 65]. Patients may be offered surgical management options, including excision of visible lesions. However, clinicians must advise patients that excision of all clinically abnormal tissue will neither eliminate nor predictably "cure" a disease characterized by underlying genetic deregulation, further emphasizing the need for ongoing clinical vigilance.
- *Surgical treatment/excision:* Surgical excision provides a sample for accurate diagnosis and detection of OC-SCC. Complete surgical excision of all clinically visible areas in extensive OED lesions can pose a surgical and clinical challenge. In this clinical scenario, targeted excision is recommended. Complete surgical excision is recommended for small dysplastic lesions measuring < 200 sq. mm. in area followed by clinical follow-up at defined 3–6 months intervals. For large and extensive dysplastic lesions measuring >200 mm^2, or for lesions that are heterogeneous (red/white/speckled/ulcerated/eroded), multiple biopsies are recommended from the outset. In these patients, clinicians may elect to follow a conservative and selective approach. One recommendation based on findings in the literature includes complete surgical excision of clinically "suspicious" areas followed by indefinite follow-up. *Clinically "suspicious" findings that warrant full surgical excision include areas within a white plaque that exhibit the following features*:

  - Increase in size >200 mm² between clinical visits
  - Color: erythema, variegation of color, change in color between visits
  - Surface texture: ulceration, pebbly (red + white), verrucous, nodular, ulceration, induration (palpation) or changes between visits
  - Patient symptoms: discomfort, pain, paresthesia, increase in size
  - Methods used for surgery include conventional excision by cold steel (blade) and laser excision methods. Laser surgical methods are becoming more commonplace as they reduce adjacent tissue damage and produce less postoperative discomfort and swelling. There is reportedly less scarring compared to scalpel excision. Regardless of the surgical approach, it is essential to recognize that post-surgical recurrence rates of OED are high (1.2–10%). The author believes that the term "recurrence" in this setting does not fully address the genetic deregulatory nature of OED and oral carcinogenesis. It is essential to acknowledge that surgically excising an OED lesion only addresses the clinically visible finding and does not "remove" the genetically abnormal and phenotypically normal-appearing surrounding mucosa that harbors the same genetic changes. This final point is essential for all clinicians—physicians, dentists, surgeons, and pathologists—to understand. It forms the basis for patient education and indefinite clinical monitoring.
- *Clinical monitoring and intervention:* Ongoing and indefinite clinical follow-up must be emphasized at every patient visit, given the genetic basis of epithelial dysplasia and squamous cell carcinoma. This conservative approach aims to reduce the risk of transformation to OC-SCC, detect clinically suspicious findings, and reduce morbidity. A logical first step during monitoring and intervention visits is to address patient-risk factors. Smoking cessation and reduction of alcohol intake are beneficial. Patients diagnosed with OED must be monitored following a defined schedule (every 3–6 months)—a clinician can examine these patients and alternate with a dentist/oral hygiene team every 6 months. At these visits, it is important to evaluate the lesion for the presence/absence of the clinically suspicious findings described above. Baseline photographic documentation of the lesion (at the initial visit), original biopsy site, and the surrounding tissues is strongly recommended. Photographs obtained at follow-up visits allow for comparison and evaluation of progression. If a clinically suspicious finding is detected at these monitoring visits, selective biopsies/re-biopsies or targeted excision is recommended. If multiple evolutionary changes are noted, then multiple biopsies are recommended.

Oral Squamous Cell Carcinoma: Clinical Features

Who Develops Oral Cavity Squamous Cell Carcinomas?

OC-SCC results from a protracted accumulation of genetic defects with or without a history of underlying risk factors. Therefore, OC-SCC is a disease in individuals 45 years or older; it is less common in younger persons (Fig. 19.8). This is in contrast to OP-SCC, which appears to have a predilection for younger individuals with few or none of the classic risk factors associated with OC-SCC (tobacco, alcohol). An unusual and relatively recent trend has been an increased incidence of OC-SCC involving the tongue in adults, especially females, aged 20–44. These OC-SCCs are HR-HPV negative [12–22]. Epidemiological studies have not disclosed a significant association with specific risk factors. It is thought that these individuals may have an, as yet uncharacterized, increased genetic susceptibility.

Where Do Oral Squamous Cell Carcinomas Occur?

In the USA, the most common location for OC-SCC is the tongue. Tongue SCCs account for ~50% of all intraoral cancers. The cancer-prone locations of the tongue include the lateral and ventral surfaces of the tongue. OC-SCC of the dorsal tongue is extremely rare, and as such the dorsum is not considered a cancer-prone location. The so-called OC-SCC prone sites (with the exception of the gingiva) are lightly keratinized or non-keratinized, and thinner than the surrounding tissues. Consequently, examination of the ventral tongue, lateral tongue, and floor of the mouth should be a routine part of all physical examinations. Although reduced smoking has resulted in declines in OC-SCC of the floor of the mouth, tongue SCC incidence has increased over 20 years. As described in the section on OC-SCC epidemiology, there is a significant increase in the age-adjusted incidence of OC-SCC of the tongue (3.6 cases/100,000) with an APC-US increase of +2.2 from 1998 to 2019 (Fig. 19.2b). Tongue SCCs are typically ulcerated (Fig. 19.9a, b), deeply invasive and account for the majority of metastatic OC-SCCs: 30% for T1, 40% T2, and 75% of T3 tumors are metastatic.

The next most common location for OC-SCC is the floor of the mouth (Fig. 19.9c). It represents ~20% of all OC-SCCs. Involvement and infiltration along salivary ducts are common in this location. FOM SCCs are staged similarly to that of the tongue: T1, T2, and T3 according to size and T4 when it infiltrates the surrounding structures (Figs. 19.10c and 19.12a-c). A horizontally spreading FOM SCC is considered a T4 tumor.

In the USA, the cheek and gingiva (listed by SEER as gum and other sites) account for 8–13% of all OC-SCCs, respectively. SCCs of the cheek spread diffusely into the underlying tissues, do not cause symptoms initially, and may appear more crateriform than mass-like given their infiltra-

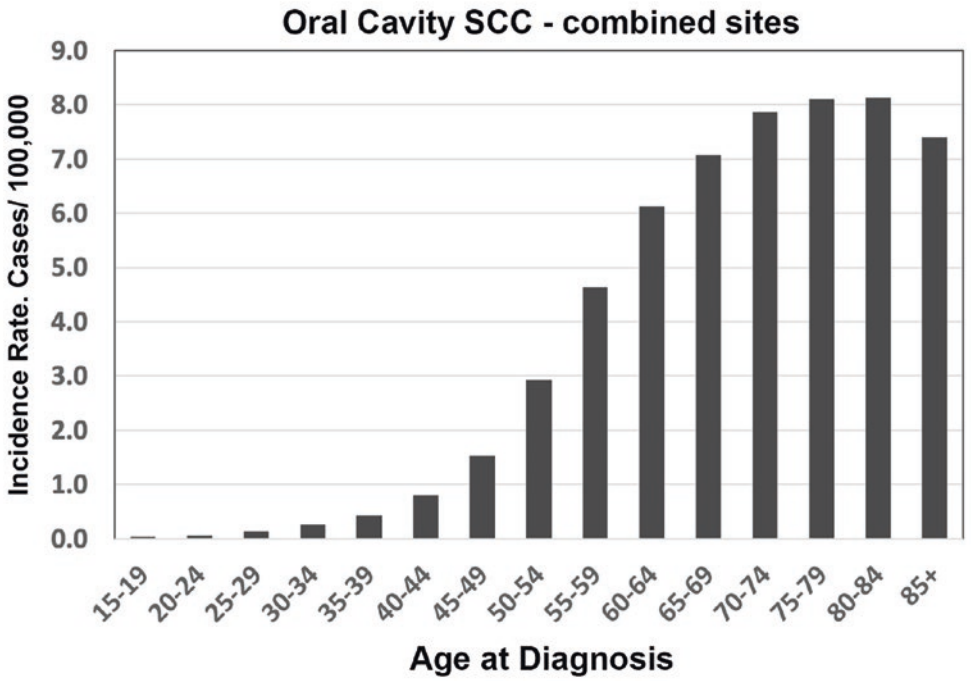


Fig. 19.8 Oral SCC is a disease of age. Incidence of OC-SCC (all oral sites combined) in the USA, 2000–2019 (NCI, SEER database) by age group. Rate reported in cases/100,000

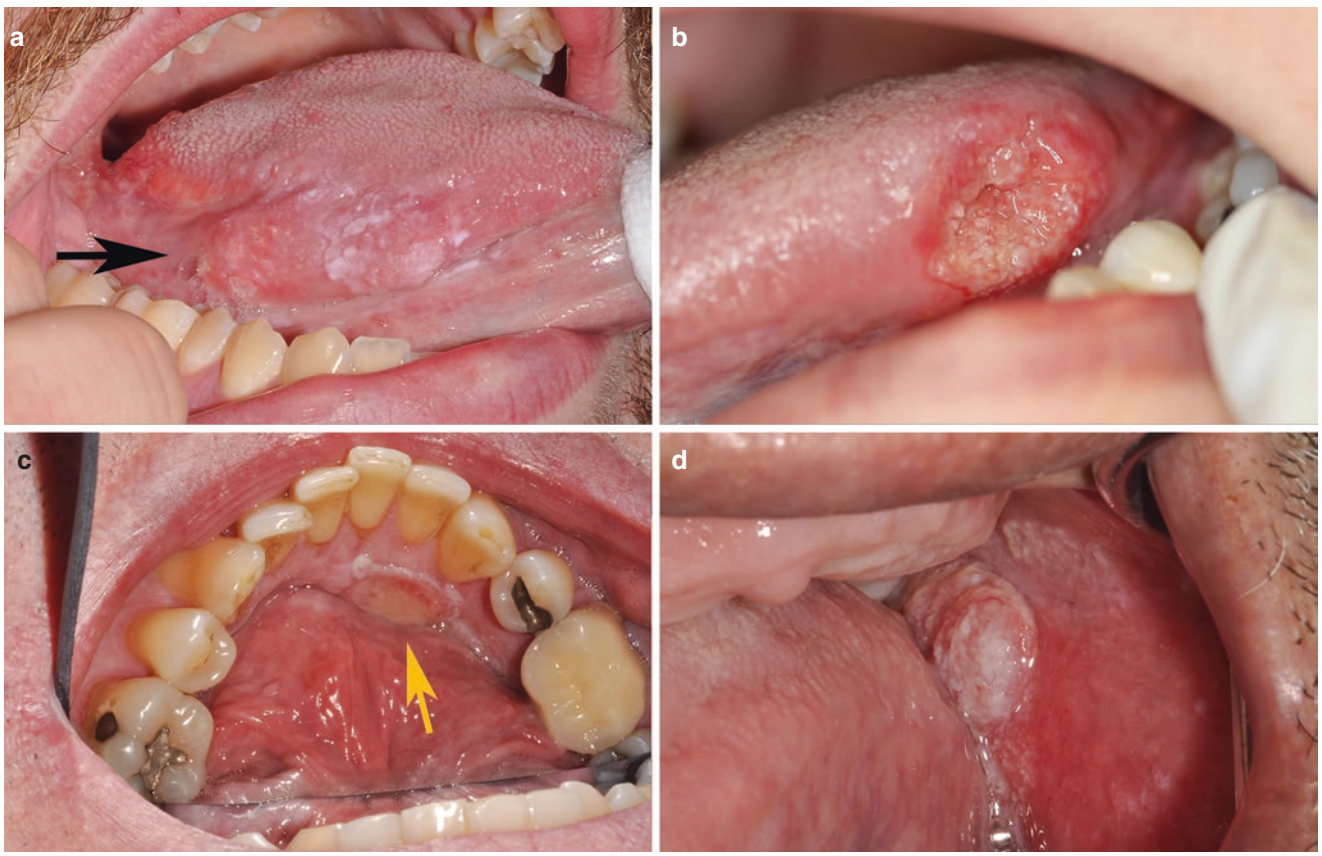


Fig. 19.9 Clinical features of oral SCC-1 (OC-SCC). (**a**) OC-SCC, right ventral tongue. An ulcerated, indurated (on palpation) mass of the posterior ventral tongue (black arrow). Note the heterogeneous appearance and the white, verrucous/corrugated appearing white plaque toward the anterior tongue. (**b**) OC-SCC, left lateral tongue. Erythematous, heterogeneous appearing ulcerated mass with central yellowish necrotic debris. The patient was a young woman with a non-healing ulcer of the tongue of 8 months duration (no local trauma). (**c**) OC-SCC, anterior floor of the mouth. Ulcerated red and white mass (yellow arrow). The patient had a history of extensive right and left ventral tongue OED that was previously excised. This finding was brought to the dentist's attention at a follow-up visit. (**d**) OC-SCC, left posterior buccal mucosa. White and red, pebbly surfaced, ulcerated, indurated (palpation) mass surrounded by erythema. The patient had OED of the buccal mucosa and was the recipient of a recent solid organ transplant; OC-SCC developed 3 months post-transplant. *Note: Immunocompromised patients have an elevated risk of SCC transformation*

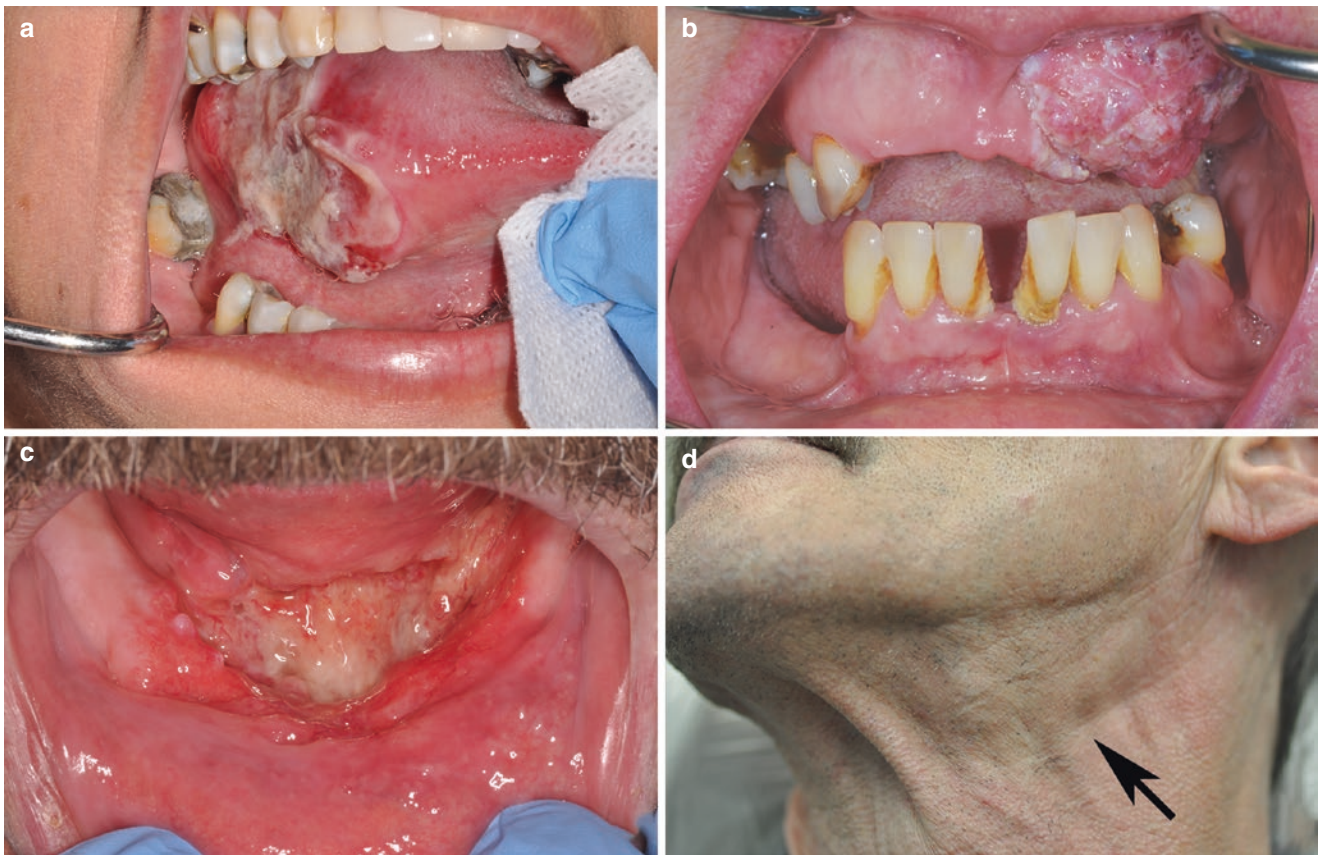


Fig. 19.10 Clinical features of oral SCC-2 (OC-SCC). (**a**) OC-SCC, right lateral-ventral tongue, HPV16 associated. Example of the rare HPV-positive OC-SCC arising in the setting of HIV/AIDS. The patient had CD4+ T-cell counts <50. (**b**) OC-SCC, left maxillary alveolar ridge. Note the corrugated, verrucous, ulcerated mass on the left maxillary ridge. This arose in the setting of previous OED with verrucous surface features. (**c**, **d**) Late-stage OC-SCC, anterior floor of the mouth with locoregional lymph node spread. The patient presented with a non-healing ulceration of 10 months duration beneath his lower denture (unable to wear it). The anterior floor of the mouth was indurated, tender, and demonstrated white plaques on the left ventral tongue. The patient presented with swollen lymph nodes (black arrow)

tion into the muscle and buccal fat pad (Fig. 19.9d). The tumor may extend into the maxillary or mandibular bone. OC-SCCs of the alveolar ridge and gingival surfaces are typically ulcerating, exophytic, and frequently exhibit a papillary/corrugated surface texture (Fig. 19.10b). Gingival SCCs tend to infiltrate the surrounding bone, invade the periodontal ligament, and cause tooth mobility. Radiographic examination will show ill-defined borders and lytic radiolucent change in the alveolar bone. Maxillary tumors have the potential to penetrate through the bone into the maxillary sinus and paranasal cavities. Mandibular SCCs have the potential to cause perineural and intraneural infiltration and associated paresthesia (Fig. 19.12a–c).

What Is the Typical Clinical Appearance of Oral Cavity Squamous Cell Carcinoma?

The most common clinical presentation of OC-SCC is as a solitary, progressive, ulcerated/eroded mass on a typical cancer-prone location (i.e., ventral tongue, lateral tongue, floor of the mouth, anterior soft palate, etc.) and in locations in contact with tobacco and tobacco products (i.e., gum, buccal vestibules) (Figs. 19.9 and 19.10). The mass is typically red, white, or red and white, with a non-homogeneous surface topography (i.e., corrugated, verrucous, pebbly, or nodular) (Figs. 19.9 and 19.10). As described in the section on dysplasia, the presence of "pebbly" surface findings is highly suggestive of and often correlates with foci of tumor infiltration. The ulcerated surface is typically heaped up and may have rolled hard borders; the center may have yellow-white necrotic, fibrinopurulent, and/or keratotic debris (Figs. 19.9b and 19.10b, c). Patients are often aware of a "sore," "lump," or "non-healing wound" (ulcer) in these locations for several weeks or months and may report progressive growth. The ulcerated mass is often painless, but in some patients can present with symptoms of pain (varying degree of severity) and paresthesia (numbness, tingling, burning). The growth rate of the mass/ulcer is variable but relatively rapid when compared to benign processes. On palpation, the mass feels indurated (hard) due to peritumor desmoplastic stromal tissue deposition. Depending on the location, the mass has the

potential to tether down the affected tissues due to tumor infiltration and desmoplastic scarring. OC-SCC masses are typically surfaced by and surrounded by white plaques microscopically diagnosable as oral epithelial dysplasia. In addition to orally visible changes, patients with OC-SCC may present with invasion into the surrounding jaw bone, skeletal structures, and potential metastatic spread to the locoregional lymph node system. When the latter occurs, patients may present with palpable regional lymphadenopathy; as with the tumor, these nodes are typically indurated and tethered/matted to adjacent tissues.

Oral Squamous Cell Carcinoma: Microscopic Features

An ideal biopsy or specimen of an ulcerated oral mucosal mass suspicious for OC-SCC must include some surrounding intact mucosal tissue. Obtaining a specimen from the middle of a necrotic ulcer is not optimal; it does not allow a pathologist to orient the specimen well enough to evaluate for depth of invasion relative to the overlying mucosal tissue. On microscopic examination, the specimen is frequently ulcerated. The marginal and overlying epithelium exhibits varying degrees of maturational irregularity, i.e., OED. The epithelial surface may show alternating areas of hyperkeratosis, hyperplasia, and/or atrophy. The rete pegs are bulbous, irregular in shape (endophytic), depth, and number. The hallmark of squamous cell carcinoma is defined by neoplastic squamous epithelium, arising in the basal region, infiltrating beyond the basement membrane, and the depth of rete pegs into underlying lamina propria (Fig. 19.11a, b). This is often accompanied by a cellular myofibroblastic stromal response (desmoplasia—corresponds to tissue induration) and chronic inflammatory infiltrate (Fig. 19.11b). Evaluation of early invasion may be hampered by tissue orientation, especially in small biopsy specimens. The earliest invasive changes may be subtle: nests, strands, or individual squamous epithelial nests that go just beyond the basal lamina region. Violation of the basement membrane allows migratory and dyscohesive neoplastic cells to access vasculature and lymphatic channels. Tumor cells can infiltrate the submucosa, skeletal muscle bundles, and nerve trunks. Necrotic foci, vascular ectasia, and hemorrhage are frequently observed. Cytologically, tumor cells exhibit nuclear enlargement, hyperchromatism, increased N:C ratio, nuclear pleomorphism, dyskeratosis (i.e., individual cell keratinization), acantholysis, apoptosis, and increased mitotic activity. Conventional OC-SCCs can be graded as well-differentiated, moderately differentiated, or poorly differentiated, depending on the degree of keratinization and recognizable squamous epithelial characteristics. Keratin pearl formation (Fig. 19.11b), pink cytoplasm, dyskeratosis, prominent intercellular bridges, and squamous forms are seen in well-differentiated SCCs. Well differentiated tumors tend to invade in large islands, whereas less well-differentiated tumors exhibit jagged, streaming nests and smaller islands. It is important to note that tumor grade does not necessarily correlate well with prognosis. Still, tumor grade is part of an overall synoptic pathology report—it is among one of the several criteria that contribute to pathological staging (pTNM). Poorly differentiated OC-SCC lacks or demonstrates very little squamous differentiation. Immunohistochemical analysis may be required in these settings. OC-SCCs typically express AE1/AE3 (pancytokeratin), CK5/6, and p63.

Oral Squamous Cell Carcinoma: Management and Prognosis

On being diagnosed with OC-SCC, the patient is staged to determine the size and extent of the primary tumor (T), assess locoregional lymph node spread (N), and evaluate for distant metastatic spread (M). Staging provides a common language for providers to effectively communicate about a patient's cancer and arrive at actionable, collaborative treatment plans. Currently, clinicians use the 8th Edition of the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) staging system (AJCC8) for both oral and oropharyngeal cancers. The latest edition incorporates changes based on the latest evidence and understanding of the clinical and biological behavior of OC-SCC and OP-SCC and their outcomes. Applying the latest staging system to OC-SCC and HR-HPV-related OP-SCC is critical given that they are diseases with distinct risk factors, require different treatment modalities, and have differing outcomes. As discussed earlier, the vast majority of OC-SCCs are not associated with HR-HPV (p16-negative; HPV-negative). Hence, AJCC8 separates OC-SCC staging from OP-SCCs that are p16-positive and HR-HPV positive.

An initial assessment is made by visual examination (transorally or using a scope). Imaging studies are used in most circumstances to assess the size and extent of OC-SCC. The most commonly utilized study is computed tomography (CT) with intravenous contrast. This study allows for assessment of the extent of primary tumors, identification of tumor involvement of the mandible, maxilla, surrounding soft tissues, and evaluation of locoregional lymphadenopathy. In selected circumstances, other imaging studies such as magnetic resonance imaging (MRI) or positron emission tomography (PET) combined with CT may be used. For patients at risk for distant metastasis, CT of the chest as well as a full-body CT/PET may be indicated. The AJCC8 for OC-SCC was modified from the 7th edition. The main modifications in AJCC8 are the inclusion of depth of invasion (DOI) of the primary tumor in the T category and extranodal extension (ENE) in the N category.

Most stage I OC-SCCs are less than 2 cm in size and do not involve deep tissues. These superficial OC-SCC tumors may not be evident on imaging studies. OC-SCCs that are larger than 2 cm have the potential to infiltrate adjacent soft

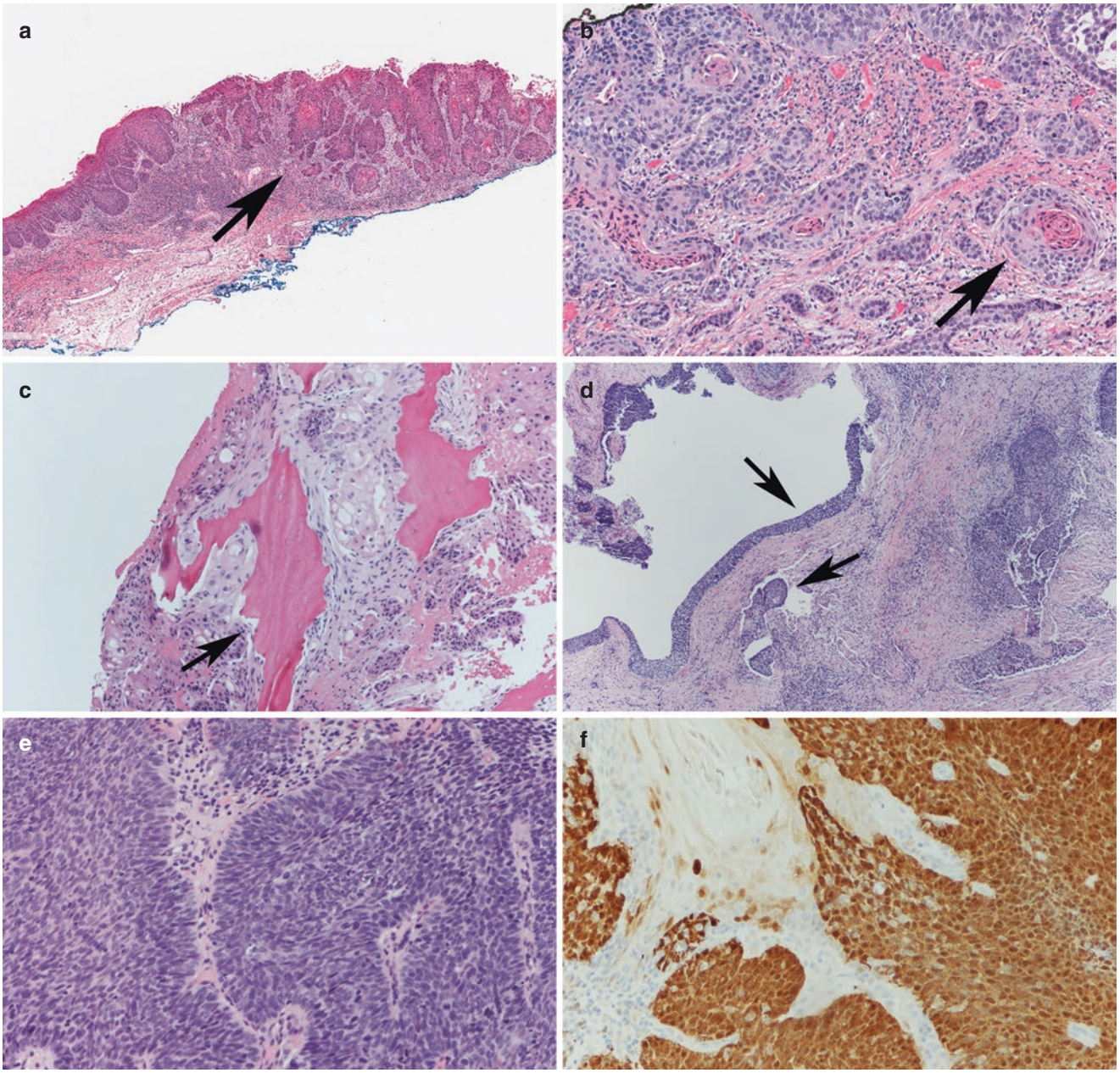


Fig. 19.11. Histopathological features of oral (OC-SCC) and oropharyngeal SCC (OP-SCC) (OED). Squamous cell carcinoma is diagnosed when proliferative, neoplastic squamous epithelial nests are seen breaching the basement membrane zone and infiltrating the underlying stromal tissue (see pathogenesis Fig. 19.5). Note the differences between OC-SCC (**a**–**c**) (p16 IHC negative) and OP-SCC (**d**–**f**). (**a**) OC-SCC, low magnification. Nests of neoplastic squamous epithelial cells infiltrating the stroma (black arrow). The surface is ulcerated and atrophic. The surrounding epithelium exhibits notable OED (left of the arrow). (**b**) OC-SCC, intermediate magnification. Well-differentiated, infiltrative neoplastic epithelium with keratin pearl formation (arrow); cellular pleomorphism, inflammatory infiltrates, and stromal response. (**c**) OC-SCC in bone, intermediate magnification. Neoplastic epithelium infiltrating bone trabeculae; note tumor abutting bone causing widespread concave bone defects (arrow). (**d**) OP-SCC, tonsil, low magnification. OP-SCCs typically exhibit a cyst-like configuration and early invasion (arrows). Tumor nests are typically basaloid (deep blue) and efface the surrounding lymphoid architecture. (**e**) OP-SCC, high-magnification. Basaloid neoplastic epithelial sheets with minimal keratinization/dyskeratosis; no keratin pearl formation noted. (**f**) OP-SCC, p16 immunohistochemical expression. Characteristic p16 overexpression in tumor cells with nuclear and cytoplasmic staining (brown)

tissue structures and present with lymph node metastasis. Imaging with PET/CT or MRI (for soft tissue invasion) helps in this regard.

The general treatment approach to OC-SCC can be divided into management of early stage, defined as stage I or II, and late stage, defined as stage III or IV disease. For early-stage disease, surgery remains the mainstay for treatment. For late-stage disease, surgery with adjuvant therapy is the preferred treatment for resectable disease. Adjuvant therapy may involve radiation therapy or adjuvant chemotherapy and

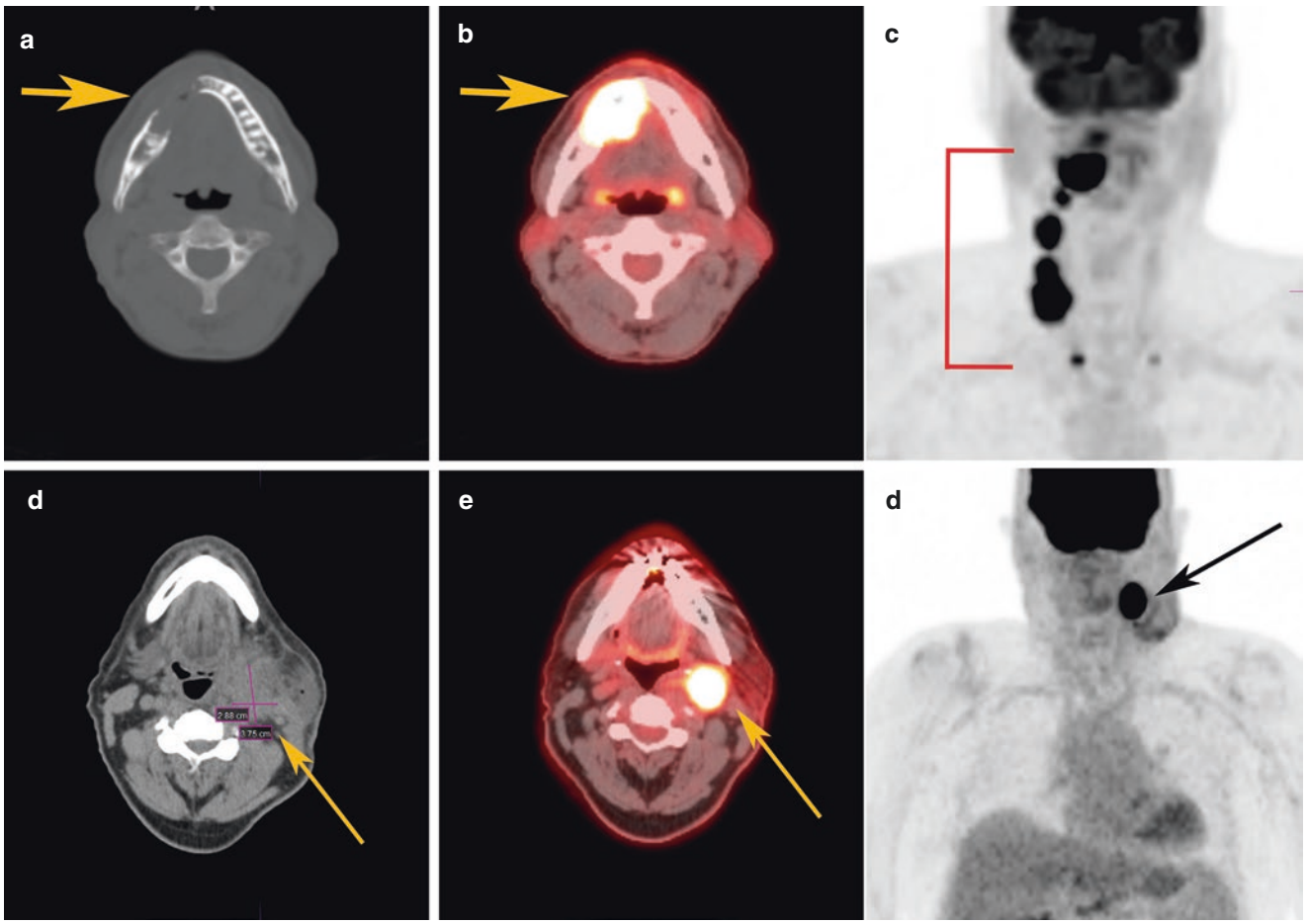


Fig. 19.12 OC-SCC and OP-SCC staging. Advanced imaging (CT/PET). Patients with OC-SCC and OP-SCC undergo clinical staging to evaluate for extent of locoregional (N:nodal) and distant metastatic disease. They undergo advanced imaging with contrast-enhanced computed tomography (CT) and positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG). CT/PET fusion studies from patients with OC-SCC (**a**–**c**) and OP-SCC (**d**–**f**) are shown. (**a**–**c**) OC-SCC, floor of mouth primary, mandibular invasion, and advanced-stage disease. CT/PET image demonstrates lytic mandibular destruction. The primary FOM tumor and infiltrating mandibular component show FDG uptake demonstrating the extent of disease activity. Image (**c**) demonstrates a coronal view of FDG uptake; it highlights OC-SCC of the FOM and mandible involving multiple cervical lymph nodes (starting with level 1B) to the subclavicular region (level 7) (red bounding box). (**d**–**f**) OP-SCC, cervical lymph node involvement as primary clinical presentation. The patient presented with a painless cervical node swelling with no visually detectable oropharyngeal mucosal changes. CT/PET images demonstrate cervical lymph node involvement. FNA samples obtained from the node revealed p16 IHC+ epithelial cells consistent with HR-HPV associated OP-SCC. A small primary focus was detected in the base of tongue region

radiation therapy for high-risk disease. The details of site-specific surgery/radiation/chemotherapeutic treatment of OC-SCC are beyond the scope of this chapter. With the exception of superficial OC-SCCs, management of cervical lymph nodes must be considered in all patients. Patients presenting with locoregional lymph node involvement may require a comprehensive neck dissection followed by adjuvant radiation therapy (Figs. 19.10c, d and 19.12a-c). The nodes most commonly involved in OC-SCC are at the submandibular level (level I), upper cervical (levels II and III).

The extent and impact of OC-SCC treatment (surgery, radiation, chemotherapy) on patient quality of life is defined by the tumor size, depth, location, and spread. It is important to note that even small, early-stage tumors in a critical oral site (high function places) can result in significant morbidity. Advanced, late-stage OC-SCC patients present a unique challenge. Regardless of early or late stages, it is essential to approach OC-SCC treatment with a multidisciplinary team to develop individualized treatment plans. Multidisciplinary teams comprised of surgeons, radiation oncologists, medical oncologists, reconstructive surgeons, speech pathology, dietitians, dentists, nurses, social workers, and others help weigh the risks and benefits of surgical and/or non-surgical modalities.

For OC-SCC, the average 5-year relative survival rate (5RSrate) for patients for all oral sites and all stages is 61%. For patients with localized disease (early stage) at the time of diagnosis, the 5RSrate is 80.7%; regional disease (nodal

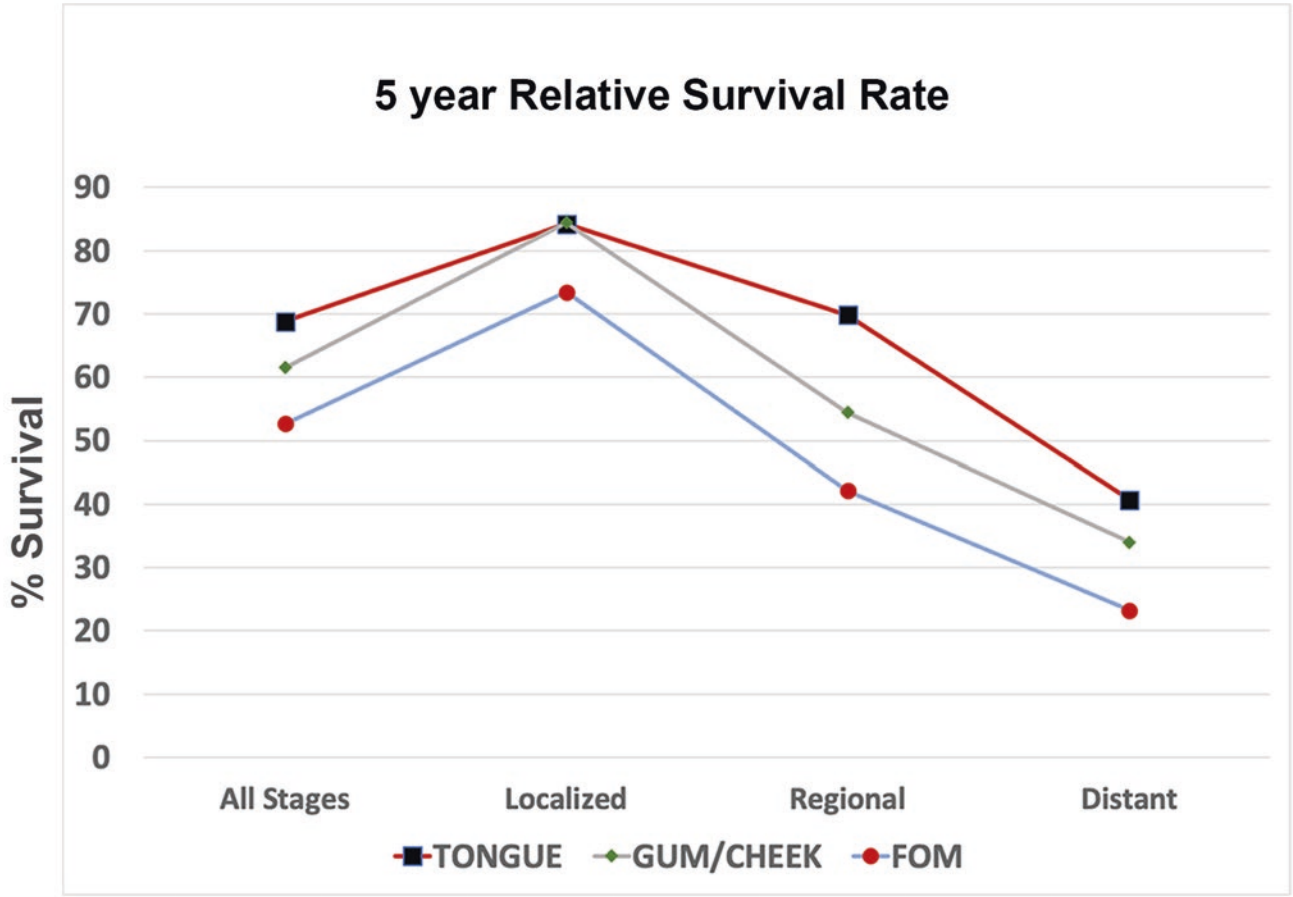


Fig. 19.13 OC-SCC 5-year relative survival rate. Early diagnosis is key in the prognosis and outcomes related to oral cavity SCC. Patients diagnosed with minimal to local disease (regardless of specific oral site) tend to have a significantly better prognosis than those with regional or distant metastatic disease over a 5-year period

spread) 5RSrate is 55.4%; distant metastatic disease (late-stage) 5RSrate is 32.6%. The 5RSrate for specific oral sites is shown in Fig. 19.13.

Ongoing and indefinite clinical follow-up is crucial for surveillance of possible recurrence of the development of a second primary malignancy. The risk of a second primary head and neck cancer in patients with a history of tobacco use is roughly 3–5% [64–67], justifying the need for continued observation. The recommended schedule for patients to consult with their surgeon/oncologist is every 3–4 months for the first 2 years and every 6 months until 5 years, and annually after 5 years [53, 55, 64, 65]. This is in addition to their routine annual physician visits and exams with their dentist/oral hygiene every 6 months. As with OED, it is important to evaluate for the presence of non-wipeable white plaques in and around the site (and at other oral sites) and assess for the clinically suspicious findings described in the OED section above. Photographic documentation is always helpful and allows for comparison and potential recurrence of disease.

Survival is an important end result but so is quality of life following treatment. Patients treated for OC-SCC frequently experience xerostomia, mucositis, and potential speech deficit. Post-treatment dysphagia can be severe, resulting from hyposalivation or fibrosis. Patients may be susceptible to osteoradionecrosis if emergent dental needs are not addressed prior to radiotherapy. Taste may be affected, especially following radiotherapy. Patients who undergo large intraoral surgical procedures may require reconstructive surgery, dental rehabilitation, and potential free tissue transfers (free flaps) from extraoral sites to help address large intraoral defects.

Oral Squamous Cell Carcinoma Variants

There are several histopathological and clinical variants of OC-SCC: (1) verrucous carcinoma; (2) spindle cell carcinoma; (3) basaloid squamous cell carcinoma; (4) papillary squamous cell carcinoma; (5) adenosquamous carcinoma; (6) carcinoma cuniculatum. The clinical behavior of several of these SCC subtypes is similar to that of conventional OC-SCC with the exception of verrucous carcinoma, a distinct, low-grade variant of OC-SCC.

- *Oral verrucous carcinoma:* Verrucous carcinoma (VC) is a clinically low-grade variant of OC-SCC that has a prominent verrucous/corrugated and exaggerated, exophytic wart-like surface texture. It is a locally invasive and destructive process that does not metastasize. VC is typically seen in patients who are older, the majority of them being >55–60 years old. There is an equal distribution between men and women; some studies report a predilection for older women. Within the oral cavity, the majority of VCs present on the buccal mucosa and gingiva (in contrast with conventional OC-SCC). Although there had been speculation about an etiologic role for HPV in the development of VC, studies to date have concluded that HR-HPV is not of etiological significance [68, 69]. Exposure to smoked tobacco products, pipes, cigars seem to play a role but this is not substantiated.
- Clinically, the behavior of VC is indolent in that it spreads superficially, horizontally, and slowly. The early changes of VC are often described clinically as PVL (proliferative verrucous leukoplakia—the previously described clinical descriptive). The tumor presents as a papillary (shag rug-like appearance), non-ulcerating, exophytic soft tissue mass that is painless. It often occupies large surface areas; on the gingiva, VC can encroach on the interdental papillary regions and along the periodontium. If the tumor is close to the bone, it can result in erosion or saucerization of the bony cortices. The microscopic features of VC are distinct in that it is notably exophytic with large frond-like growths of epithelium and heavy surface keratinization. The epithelium is thrown in to exaggerated furrows and spires with keratin filling the furrows; candida colonization may be evident in these areas. The rete pegs are broad, blunted, and notably endophytic. The rete pegs encroach on the underlying stroma in a broad, pushing front as opposed to the infiltrative/nested invasion noted in conventional SCC. The tumor front can be observed pushing into muscle, bone, and submucosal tissue. At low and intermediate magnification, the basement membrane zone may appear intact. Cytological features are banal. The basal and suprabasal cells exhibit mild to no atypical cellular features. Mitoses are rare. There is often a healthy sprinkling of chronic inflammatory aggregates at the epithelial–stromal interface dominated by lymphocytes.
- Surgery is the most effective mode of treatment for VC [70, 71]. VCs are notorious for undergoing transformation to conventional OC-SCCs. Hence it is essential that post-treatment, patients with VC are monitored on a regular basis.

Oropharyngeal Squamous Cell Carcinoma

Oropharyngeal SCC: HR-HPV vs. Tobacco Pathogenesis

As discussed in the section on the epidemiology of head and neck cancer, there has been a steady increase in cancers of the oral cavity and pharynx; a SEER estimate of 54,000 cases in 2022. A big contributor to this number is pharyngeal cancer. The incidence of OP-SCC has risen sharply over the last several decades, due primarily to increased rates of HR-HPV associated disease. The annual percentage change in the USA for oropharyngeal cancers is +2.8 from 1996 to 2019, with an age-adjusted incidence (AAI-US) of 2.9 cases/100,000. This increase is alarming when one accounts for the decline in tobacco-associated oropharyngeal cancers in the USA; there was a 70% decline from 1988 to 2019. To put it in perspective, there has been >225% increase in the incidence of HR-HPV positive OP-SCC during this period. With tobacco-associated HPV-negative OP-SCCs on the decline, >85% of OP-SCCs in the USA and Europe are attributed to HR-HPV. The HR-HPV related OP-SCC burden is high enough that in the USA, OP-SCC has surpassed cervical cancer as the most common site of HPV-related cancer [72].

Differences in the molecular genetic profile of HR-HPV OP-SCC and HPV-negative OP-SCCs support two biologically distinct entities. In HPV-negative SCCs, there are early LOF, deletions, and methylation defects in genes located on chromosomes 9p21, 3p, and 17p (p16, fHIT, p53). In contrast, HR-HPV OP-SCC lacks chromosomal losses and exhibits the ability to produce wild-type p53 protein (but degraded and decreased by HPV E6), wild-type Rb protein (but abrogated by HPV E7), and an overexpression of p16 protein expression (non-functional but present). Significantly, this correlates with significant differences in clinical presentation.

With regard to the specific oncogenic HPV strains implicated, it is well established that cervical cancer is associated with a number of high-risk strains [16, 18, 31, 33, 35, 45, 51, 52, 58, 59]. By contrast, the distribution of HR-HPV strains involved in OP-SCC is different. A systematic review found that HPV16 transcriptional activity is present in 95.7% of HR-HPV OP-SCC compared to its presence in cervical SCC (61%). Therefore, HPV16 is the commonest genotype and accounts for 90% of OP-SCCs originating in the tonsillar region [73, 74]. A number of high-risk HPV strains have been identified associated with OP-SCC. However, a consistent finding in the literature is that HPV16 is present in 95% of HR-HPV associated OP-SCC.

The distinct clinical presentation of OP-SCC today is a direct result, as discussed previously, of the make-up of spe-

cific tissues involved, their respective ultrastructure, HR-HPV pathobiology, lymphoid tissue architecture, and drainage patterns. Given its preponderance and the current trend, the typical clinical presentation of HR-HPV associated OP-SCC will be emphasized in the following sections. The clinical presentation of HPV-negative (tobacco/alcohol-related) OP-SCC will also be presented.

Oropharyngeal SCC: Clinical Presentation

In order to evaluate and accurately diagnose patients with OP-SCC, it is important to know the typical patient profile, obtain a thorough clinical history, be knowledgeable of the boundaries of the oropharynx (and upper aerodigestive tract), conduct a good physical examination, and obtain appropriate imaging (Table 19.4).

Who Develops Oropharyngeal Squamous Cell Carcinomas?

Patients with HR-HPV associated OP-SCC have a distinct patient-risk profile. Compared to HPV-negative OP-SCC (tobacco-associated), patients with HR-HPV OP-SCC are more likely to be young, white, or non-Hispanic, of higher socioeconomic status, non-smokers, and non-drinkers (Table 19.4). Sexual history is strongly associated with HR-HPV positive SCCs. Studies show that there is a significant increase in HR-HPV OP-SCC with an increased number of lifetime sexual partners, including oral sex partners, any history of oral sex, earlier age at sexual debut, infrequent use of barrier devices during sex, and among men, a history of same-sex sexual contact [75, 76]. Patients with HR-HPV OP-SCC are younger and, on average 10 years younger than those with HPV-negative tumors. Patients aged 40–50 years had a 3.4-fold higher risk of developing HR-HPV OP-SCC compared to tobacco-associated OP-SCC. The typical patient with HR-HPV OP-SCC is in the 35–55 age bracket (contrasted with >50 years for HPV-negative SCC). It is evident that unlike HPV-negative SCCs (tobacco associated), which are considered a disease of age and cumulative genetic defects, HR-HPV OP-SCC is a disease of younger men and women with none of the classic chemical carcinogen risk factors (Table 19.4).

Where Do Oropharyngeal Squamous Cell Carcinomas Occur? Why?

The oropharynx is situated between the nasopharynx superiorly and the hypopharynx inferiorly. It is divided roughly into the following anatomic regions: base of the tongue, tonsil and tonsillar pillars (fossae), soft palate + uvula, and the posterior pharyngeal wall. As discussed previously, one must be familiar with the anatomic boundaries and the composition of the oropharynx. As described, the oropharynx is invested intermittently, especially in regions with abundant tonsillar tissue, by specialized epithelium. This endodermally derived *reticulated stratified squamous epithelium* or *lymphoepithelium* is particularly vulnerable to HR-HPV infection. Consequently, the vast majority of HR-HPV OP-SCC originates from the reticulated epithelium located in the proximal regions of the tonsil, base of tongue crypts, tonsillar fossae, tonsillar tissue within posterior palate, and posterior pharyngeal wall. This also accounts for the differences in the clinical presentation of HPV-negative vs. HPV-positive OP-SCC.

HR-HPV OP-SCCs originating in the base of the tongue arise within tonsillar mucosa and present as clinically small (barely visible) non-keratinizing primary tumors. HPV-negative tumors (tobacco associated) arising in this region may present with an ulcerated, red + white mass similar to OC-SCCs. Flexible fiberoptic nasopharyngoscopy and laryngoscopy may be required to examine this area, especially if the clinician is looking to determine a primary site in patients presenting with cervical nodal disease.

Similarly, HR-HPV OP-SCCs originating in the tonsillar region may present with little to no visible swelling. Tumors in this area may involve the faucial pillars, tonsillar area proper, and the soft palate. HPV-negative tumors tend to present with more readily visible masses.

Tumors arising on the pharyngeal wall usually have attained a large size before being discovered, as they are largely symptom free. Tumors may extend superiorly into the nasopharynx and posteriorly into the prevertebral fascia and inferiorly into the hypopharynx. Neck node metastasis is the most common clinical presentation.

The discontinuous nature of the *reticulated stratified squamous epithelium* and the absence of a "continuous" basement membrane in the tonsillar mucosal tissue render it susceptible to early invasion and tumor migration (Fig. 19.3e, f). This accounts for the typical clinical presentation of HR-HPV OP-SCC: small to barely visible tumor masses in the oropharyngeal lining, with the primary manifestation of disease being cervical lymph node swellings.

What Is the Typical Clinical Presentation of Oropharyngeal Squamous Cell Carcinoma?

The complex anatomy and general inaccessibility of the oropharynx do not lend itself to easy clinical examination. Hence, detecting and characterizing precursor lesions (as discussed with the oral cavity) is a challenge for several reasons: (1) HR-HPV related carcinogenesis in the oropharyngeal mucosa does not cause an upward "dysplastic" growth of epithelium. This is thought to be the result of a discontinuous basal region. The reticulated stratified epithelium lacks the degree of stratification; applying the morphological crite-

ria of epithelial dysplasia in this setting is not possible. (2) It is not possible to characterize HR-HPV infection in adjacent "normal epithelium" in the oropharyngeal region. (3) There are currently no models for HR-HPV associated precursor lesions [77]. (4) The discontinuous epithelium and the ready availability of lymphatic channels in the lymphoid tissue of the oropharynx lead to early invasion and lymph node spread.

The most common presentation of HR-HPV OP-SCC is a neck mass, a cervical lymph node, that may be asymptomatic and slow growing (Fig. 19.12d–f). The typical patient is a young man or woman discovering a neck mass while shaving, in the shower, or incidentally. Patients may report symptoms of sore throat or occasional dysphagia. The clinical presentation of OP-SCC can be easily confused with common benign conditions such as laryngopharyngeal reflux or lymphadenopathy from a local infection. The neck masses may feel cyst-like and trigger a diagnostic work-up that may involve a laryngoscopy or nasopharyngoscopy. On scoping, clinicians may find an irregular, erythematous mucosal change, potentially an ulcerated mass in the tonsillar or base of tongue region. Most HR-HPV OP-SCC primary lesions are either T1 or T2 (small primary tumor size). Given the propensity for early invasion and little in the way of precursor changes, there may be little to no observable mucosal changes in the oropharyngeal membranes.

Oropharyngeal SCC: Diagnosis, Cytological, and Microscopic Features

Patients presenting with enlarged cervical lymph nodes need to be evaluated for the presence of an active infectious etiology (upper respiratory tract infection or dental infection). Once these possibilities are ruled out and a thorough oral exam is performed, and if OP-SCC is suspected, then the patient may be referred to an otolaryngologist/head and neck surgeon or clinician who can evaluate the patient further. A first diagnostic step may involve advanced imaging: CT scan or MRI of the neck or an ultrasound. Although CTs and MRIs are the first lines of imaging, recent studies have shown the utility of a transcervical ultrasonography. Ultrasound imaging has been shown to be sensitive (not very specific) and revealed hypoechoic or isoechoic (cyst-like appearance) findings; notably, the ultrasound served as a helpful adjunct in guiding fine-needle aspiration (FNA) of the lymph node. FNA sampling of the cervical node is the standard first approach in establishing diagnosis; excisional biopsy of the neck mass is not recommended. Cytological samples from HR-HPV OP-SCC typically reveal basaloid squamous epithelial cells that exhibit prominent p16 immunoexpression. The immunocytochemical expression of p16 protein is considered a reliable surrogate marker for HR-HPV infection [78–81]. Cytological samples must exhibit diffuse nuclear and cytoplasmic staining of malignant cells. p16 immunoexpression is 97% sensitive. Epithelial cells expressing only cytoplasmic p16 immunostaining are non-diagnostic and are considered negative for HR-HPV. p16 expression in carcinomas of unknown primary of the cervical nodes is presumed to be HR-HPV OP-SCC [82–85] and triggers a work up to identify the primary site within the oropharynx.

Scoping the oropharyngeal region may reveal apparent mucosal abnormalities that trigger a biopsy. The microscopic features of HR-HPV OP-SCC are distinctively non-keratinizing. If the pharyngeal mucosa is captured in the biopsy, the overlying epithelium seldom exhibits epithelial dysplasia. Infiltrating nests of basaloid (hyperchromatic, small-dense nuclei) appearing squamous cell carcinoma arise from the tonsillar crypt epithelium and grow beneath the surface in nests, lobules, and forming pseudocystic structures with central areas of necrosis. Tumor nests are present among the lymphoid tissue (Fig. 19.11e). Cytologically, the tumor cells display a high N:C ratio and high apoptotic rate. Mitoses are noted. Keratinization is typically absent (Fig. 19.11e). Immunohistochemical analysis for p16 expression reveals diffuse immunoreactivity (nuclear and cytoplasmic staining) (Fig. 19.11f). p16 overexpression in HR-HPV OP-SCC is in contrast to OP-SCC or OC-SCCs associated with tobacco/conventional risk factors. p16 immunoexpression (IHC) to assess HR-HPV etiology is essential for all OP-SCCs as it plays a significant role in tumor staging, evaluation, and treatment planning. The AJCC8 recommends p16 IHC only as a surrogate for HPV status because p16 positivity does not capture the subset of OP-SCC patients who are p16-positive/HPV-negative; the latter group has a significantly lower 5-year overall survival than patients with p16-positive/HPV-positive OP-SCC (33% vs. 77%).

Once the diagnosis of HR-HPV OP-SCC is confirmed, all patients undergo multidisciplinary evaluation. Advanced imaging is obtained to evaluate the precise location of the primary tumor within the oropharynx and to assess the cervical nodal basin and the chest. The diagnostic imaging study of the neck should extend from the skull base to the thoracic inlet providing evaluation of the pharynx and nodes in a single study. Computed tomography with superimposed PET scans offers an efficient way to evaluate and appropriately stage a patient (Fig. 19.12d–f). Imaging of the chest generally consists of diagnostic-quality chest CT, although PET/CT may be considered in evaluating advanced-stage disease (stage III–IV) due to the increased risk of distant metastasis. MRIs may be used to assess the extent of local invasion and soft tissue spread.

Oropharyngeal SCC: Management and Prognosis

The HR-HPV OP-SCC Staging Guidelines Story: From 7th to 8th Edition

Staging systems are designed to be user-friendly and applied consistently across healthcare systems regardless

Table 19.6 UICC/AJCC 8th edition (2018) HR-HPV oropharyngeal cancer staging

Primary tumor (T)		Regional lymph nodes		
T	T *criteria*	N	N *criteria*	
T0	No primary identified	NX	Regional nodes cannot be assessed	
T1	Tumor <2 cm	N0	No regional lymph node metastases	
T2	Tumor >2 cm and <4 cm	N1	1 or more ipsilateral nodes; all <6 cm	
T3	Tumor >4 cm or extension on lingual surface of epiglottis	N2	Bilateral or contralateral nodes; all <6 cm	
T4	Advanced local disease *Tumor invades larynx, muscle of tongue, medial pterygoid, hard palate, mandible or beyond*	N3	Lymph nodes >6 cm	
Distant metastasis (M)				
M0	No distant metastasis	M1	Distant metastasis present	
Stage classifications and 5-year overall survival %				
T	N	M	Stage	5-year OS
T0, T1, or T2	N0 or N1	M0	I	88%
T0, T1, or T2	N2	M0	II	81%
T3	N0, N1, or N2	M0		
T0, T1, T2, T3, or T4	N3	M0	III	65%
T4	N0, N1, N2, or N3	M0		
Any T	Any N	M1	IV	48.7%

This staging system is used exclusively for HPV-associated squamous cell carcinoma of the oropharynx and is distinct from the staging system used for HPV-negative (typically tobacco/alcohol-associated) squamous cell carcinoma of the oropharynx

of geographic location. The TNM staging system in use for well over three decades is a unified system put together by the UICC and AJCC; the unified staging system has been revised numerous times, with its 7th edition released in 2009. Each new edition of the AJCC/UICC manual includes changes designed to improve the accuracy and usability of the system, taking into account changes in diagnostic approach and treatment outcomes. The 8th edition of the UICC/AJCC manual (AJCC8) now includes a new staging system exclusively for HR-HPV OP-SCC; it was published in 2017 and came into effect in January 2018 (Table 19.6).

It was evident in the literature that HR-HPV OP-SCC has a markedly better prognosis and overall survival rate. It became clear that the 7th edition of the AJCC cancer staging system was inadequate in stratifying disease risk and prognosis. A hallmark of HR-HPV OP-SCC patients is the presence of bulky neck lymph nodes (late N stage) and small primary tumors (low T stage). Based on the criteria set out in the 7th edition, up to 80% of patients were diagnosed with stage IV disease. Considering this, the ICON-S group proposed a revision to staging of HR-HPV OP-SCC taking into account HPV status (evaluated by p16 immunoexpression, HPV mRNA, or HPV-ISH) [86].

Multiple studies thereafter showed that the 7th edition did not fully capture patient prognosis and treatment outcomes—it was based on tobacco-associated OP-SCC (HPV-negative with poorer overall survival rates. There was an urgent need to revise the 7th edition and acknowledge the different disease that was HR-HPV OP-SCC [87].

The 8th edition evaluates OP-SCC based on HR-HPV status as determined by p16 immunohistochemical expression (p16 IHC+ve); as described above, >75% of tumor cells must show p16 IHC positivity (nuclear and cytoplasmic) (Table 19.6). The main changes to p16 IHC+ve OP-SCC in the 8th edition are:

- *Tumor category*: T*is (in situ)* is not included for p16. T4a and T4b are now unified into a single category (T4).
- *Node category*: Ipsilateral lymph nodes <6 cm are characterized as N1. Bilateral or contralateral nodes <6 cm are stage N2. Nodes >6 cm are N3.
- *Metastasis category*: Stage IV is used ONLY in patients who present with distant metastatic disease.

Patients diagnosed with HR-HPV OP-SCC confirmed by p16IHC+ve tests are imaged using PET/CT (see figure) and staged using the AJCC8 guidelines. This change from the 7th to 8th edition has been reviewed in multiple studies and validated accordingly. While it remains imperfect in some areas, application of the 8th edition guidelines has resulted in more accurate group discrimination, risk stratification, treatment planning, and prognostic outcomes. Among the weaknesses that need to be addressed is the method used to assess HPV-positivity.

Treatment: Pretreatment Evaluation

Patients diagnosed with OP-SCC are typically referred to a multidisciplinary cancer care team. Once patient staging is complete, patients undergo a thorough pretreatment evaluation to achieve the best treatment outcomes while minimizing morbidity. The pretreatment evaluation should include:

- *Nutritional and dietitian consultation*: Patients with HR-HPV OP-SCC have a worse prognosis if they are underweight and malnourished. Planning ahead for the morbidity associated with radiation/chemotherapy is essential. Nutritional supplements, caloric and protein supplementation, side effects of dysgeusia, and enteral nutrition must be discussed with patients and their families.
- *Dental evaluation*: Patients undergoing surgery and/or radiation must receive a complete dental evaluation. All emergent dental needs must be addressed (carious teeth restored, endodontic therapy completed, non-salvageable

teeth must be extracted). Preventive measures must be taken prior to initiation of radiotherapy to minimize the risk of osteoradionecrosis. Fluoride application and rinses may be required to prevent future dental caries risk.
- *Pain management specialists*: Patients may have pain related to their tumor and post-radiation/chemotherapy treatments. Pain specialists and support must be provided to patients to ensure adequate treatment compliance and nutrition.
- *Speech therapy*: Patients with OP-SCC have the potential to develop scar tissue, muscle atrophy, and speech impairment. Hyposalivation may cause difficulty with enunciation. Supportive measures are taken to address this.

Treatment: Surgery, Radiation, and Chemotherapy

The treatment of OP-SCC is based on the patient's HPV status (determined by p16 IHC+ve results or other accepted HPV testing modality).

Patients with early stage (I and II) HPV-negative (p16 IHC negative) OP-SCC are treated using previous conventions and guidelines using a combination of surgery and radiation (RT). Primary surgery or definitive RT can be used as single modalities; both yield similar rates of local control and survival. The morbidity associated with each treatment approach is an important factor in making a decision. Either modality should include management of both the primary tumor site within the oropharynx and also the at-risk cervical nodal basin. Treatment of the cervical nodes is required even for early-stage (clinically N0) disease due to the elevated risk for occult nodal metastasis associated with tumors of the oropharynx. Locoregionally advanced-stage HR-HPV negative OP-SCC requires multimodality therapy. This may include primary surgery followed by adjuvant RT, or concurrent chemoradiation. Induction chemotherapy is an attempt to minimize risk of distant metastasis in patients considered high risk due to high volume nodes or large primary tumors.

For patients with HR-HPV OP-SCC with stage I, T1-T2, node negative disease, the initial treatment is either minimally invasive surgery (transoral robotic or transoral laser microsurgery) or intensity-modulated RT (IMRT). Treatment options for patients with stage I or stage II, T1-T2, with a single node N1 disease include single-agent IMRT, definitive chemoradiation, or surgery (with or without adjuvant RT). For patients with locoregionally advanced disease (stages III), T3–T4 or any T stage with N3, chemoradiation (cisplatin) alone is recommended rather than "trimodality therapy" (surgery + adjuvant chemoradiation) as this approach is associated with organ preservation and excellent oncologic outcomes. Recent multicenter studies are underway exploring the concept of deintensification therapy for HR-HPV OP-SCC. The aim is to preserve superior oncologic outcomes while minimizing treatment-associated toxicity and morbidity. Deintensification involves RT and/or chemotherapy modulation: lower doses of adjuvant RT; induction chemotherapy to deescalate RT dosing; dose-reduced definitive RT alone; alternates to cisplatin.

Upon completion of therapy, patients must be monitored for recurrent or metastatic disease. The approach is similar to that described for OC-SCC—routine monitoring. Advanced imaging at 12-weeks post-treatment (PET/CT) for select patients is recommended. A big part of surveillance is educating and helping patients manage treatment-related toxicity and morbidity. Among the common long-term complications of head and neck cancer treatment (RT, surgery, and chemotherapy) include: (1) salivary gland damage and xerostomia; (2) rampant dental caries risk; (3) osteoradionecrosis and soft-tissue necrosis; (4) fibrosis and scar tissue formation; (5) dysphagia secondary to surgical disruption and/or RT; (6) dysphonia.

Oropharyngeal SCC: Prevention and Vaccination

An integral part of managing patients with OP-SCC is patient education. This often involves formal education strategies that include the patient and their families. These visits are opportunities to promote awareness of the association between HPV and cancer development, as well as other HR-HPV related cancers, and discuss patient concerns about HPV transmission to their sexual partners. Smoking and alcohol cessation education should be incorporated as they increase the combined risk of developing OP-SCC. Each patient visit, from the first to the last, is an opportunity to discuss the benefits of HPV vaccination for family members, especially young children.

The discovery of virus-like proteins (VLPs) from recombinant expression of HPV capsid protein L1 paved the way for vaccine development. L1 VLP proteins elicit titers of neutralizing antibodies that protect against viral challenges; the L1 VLP proteins formed the backbone for the first FDA-approved vaccine to prevent cervical cancer in 2006 [88]. The L1 VLPs are non-infectious and non-oncogenic and can be packaged and delivered for intramuscular injection. All current HPV vaccines are non-infectious, recombinant, and are prepared from purified L1 VLPs of various HPV strains. Multiple studies have shown that HPV vaccines have a high efficacy (close to 100%) in preventing cervical cancer. As discussed previously, HR-HPV is associated with a range of other cancers: cervical, anal, oropharyngeal, vaginal, penile, and vulvar cancers. LR-HPV causes cutaneous and mucosal warts. The first vaccine Gardasil® (2006 first-generation; 4-valent) vaccine protected against HR-HPV strains HPV16 and 18 as well as LR-HPV strains 6 and 11. Thus it protected against several cancers and the development of warts. There are three vaccines available that protect against a variety of strains, both low-risk and high-risk HPV strains:

1. Gardasil® 4-valent—targets HPV 6, 11, 16, 18
2. Cervarix® 2-valent—targets HPV 16, 18
3. Gardasil® 9-valent—targets HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.

They protect against the acquisition of HPV infection and development of subsequent HPV-associated disease. Currently, only the 9-valent vaccine is available in the USA. As of 2020, Gardasil® 9-valent is specifically approved for the prevention of cervical, oropharyngeal, vulvo-vaginal, and anal cancers, warts, and dysplastic lesions. The indications and schedules for administering HPV vaccines are as follows:

- Children: Routine HPV vaccination for all children at 11–12 years. The vaccine can be started at 9 years.
- *Two doses of HPV vaccine should be given at 0 and at 6–12 months*
- Adolescents and adults (13– 26 years): Catch-up vaccination for those who have not been vaccinated
- *Three doses of HPV vaccine should be given at 0, 1–2 (typically 2), and 6 months*
- Adults older than 27 years: Catch-up vaccination is not routinely recommended. Selected situations may apply (i.e., immunocompromised patients)
- *Three doses of HPV vaccine should be given at 0, 1–2, and 6 months*

The impact of HPV vaccination has been reported to be positive. Modeling studies [89, 90] suggest substantial reductions in cervical incidence in the next 2 decades. Similar modeling studies [88] have forecasted significant reductions (by prevention) of HR-HPV OP-SCC over the next 2–3 decades as the effects of childhood vaccination bear fruit. These findings forecast a continued shift in the landscape of OP-SCC as the current population ages.

Clinical and Patient Education Questions + Responses

1. What is the fundamental difference between oral and oropharyngeal cancer?

   Response: Oral cancer and oropharyngeal cancers are different from one another at many levels. They are fundamentally different diseases with different risk factors and resultant genetic profiles. Oral cancer is typically a disease of age, associated with the traditional risk factors tobacco and alcohol and has recognizable precursor lesions. Oropharyngeal cancer typically affects the tonsils and "throat." It is a disease of younger individuals, associated with high-risk HPV infection, and has a distinct clinical presentation.

Oral Cancer

1. Oral epithelial dysplasia is precancerous. Do all dysplastic lesions progress to oral cancer?

   Response: No. The majority of oral epithelial dysplasia does not progress to oral cancer. Currently, there are no biomarkers to predict which precancerous lesions are going to progress to cancer.
2. I have a patient with oral epithelial dysplasia. What conversation should I have with them? What clinical findings should one regard as "suspicious" for evolving cancer?

   Response: I would advise patients with oral epithelial dysplasia that they have an oral precursor or potentially malignant oral finding. The changes noted are the result of genetic deregulation or faults in their genes that have accumulated over a period of time. As we continue to monitor these patients, it is essential to educate them about findings that are regarded as "suspicious" for evolving cancer. Explain to patients that one should look out for "open sores," areas of redness, increase in size of the white changes that were diagnosed as dysplasia, bumpy surface changes, or changes in symptoms. If they see or experience any of these, have them contact you for evaluation.
3. In patients with extensive epithelial dysplasia, is the answer simply to monitor and follow-up?

   Response: There is no one single approach to managing extensive epithelial dysplasia. Evidence-based studies show that management should be tailored to patients. Those with clinically suspicious areas will likely require more aggressive surgical management compared to patients with homogeneous/milky-white changes. The latter patients may benefit from continued monitoring with photographic documentation.
4. What is leukoplakia? Should I use this term with patients? Why or why not?

   Response: Leukoplakia is a provisional clinical term that describes a non-wipeable white plaque that cannot be diagnosed on clinical grounds alone. While the term is useful to clinicians, it unfortunately creates much confusion and anxiety in patients. Far too often, leukoplakia is used erroneously as a synonym for precancerous change. Hence, it is recommended that this term not be used with patients.
5. My patient has a non-healing oral ulceration. How do I approach this clinical scenario?

   Response: Determine the duration of the non-healing ulcer and rule out local irritants that may have triggered the ulcer. If there is/are potential traumatic sources, they should be addressed (blunting sharp tooth surfaces or restorations). The patients should be recalled in 2–3 weeks. If the ulcer persists or shows no sign of healing, a biopsy should be considered.

6. What are typical clinical features of oral cancer?

   Response: Oral cancers typically present as lumps/masses/nodules on oral cancer-prone sites (tongue, floor of mouth, gum, cheek, etc.) that are ulcerated and surrounded by non-wipeable white plaques consistent with precancerous changes. The typical patient is someone older than 45 years and with a history of tobacco and/or alcohol use.

Oropharyngeal Cancer

1. The oral cavity is a different environment from the oropharynx (tonsils, base of tongue etc.). Explain.

   Response: The oral mucosa derives from ectoderm and is surfaced by a continuous epithelium. The oropharynx is rich in tonsillar tissue that is endodermally derived and comprised of a naturally reticulated epithelium. This renders the latter susceptible to high-risk HPV infection.
2. What is the typical clinical presentation of patients with HR-HPV associated oropharyngeal cancer?

   Response: The typical presentation of HR-HPV associated oropharyngeal cancer is a young man or woman presenting with an incidentally discovered swollen neck lymph node that is painless and growing. The patients generally do not have the traditional risk factors (tobacco use). FNA samples from the lymph node show p16 IHC+ve epithelial cells that trigger a work-up to identify the primary site within the oropharynx. There is typically no evidence of surface precursor changes as seen in the oral cavity.
3. Why do patients with oropharyngeal SCC present with early invasion and lymph node metastasis? What bearing does this have on a clinician's patient assessment?

   Response: HR-HPV oropharyngeal cancers arise within the depths of tonsillar crypts and in basal cells within a reticulated stratified squamous epithelium. With adequate genetic defects, these neoplastic cells do not face resistance from a naturally continuous basement membrane barrier. They infiltrate into the underlying lymphoid tonsillar tissue, access the lymphatics, and spread to local lymph nodes. Hence, clinicians assessing patients presenting with cervical lymph node swellings should consider with HR-HPV associated oropharyngeal cancer in their differential diagnosis.
4. My patient has an oral wart. Are they at risk of developing oropharyngeal SCC? Should I order tests to look for a specific type/strain of HPV?

   Response: Oral warts are benign epithelial neoplasms caused by low-risk strains (LR-HPV) HPV6 and 11. They are not related to either oral or HR-HPV (HPV16, HPV18) associated oropharyngeal cancer. The viral mechanisms leading up to either wart of oropharyngeal cancer are very different. Therefore, one does not have to be concerned about an oral wart transforming or predisposing to oropharyngeal cancer (or oral cancer). An exophytic (sticking above the surface) is a sign of benignity. Testing for specific strains of HPV is neither indicated nor required.
5. Do patients ever develop HR-HPV associated SCC of the oral mucosal tissues?

   Response: Yes. In a few selected clinical circumstances. HR-HPV associated SCC can be seen in the oral cavity in patients who are immunocompromised or immune-depleted (HIV infection; immunosuppression secondary to transplants). Studies show that <3 oral cavity squamous cell carcinomas are HR-HPV associated and they typically arise within ectopic tonsillar tissue or lingual tonsillar tissue toward the posterior ventral tongue.
6. What role do HPV vaccines have in preventing cancer?

   Response: The latest HPV vaccines (gardasil nine-valent or four-valent) afford protection against several HR-HPV and LR-HPV strains. Hence patients vaccinated for HPV against several HR-HPV related cancers: cervical, oropharyngeal, penile, vulvovaginal, anal. Additionally, patients are protected against developing benign warts caused by HPV6 and HPV 11. Multiple studies have shown the vaccines to be highly efficacious.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–74.
3. Zhang L, Poh CF, Williams M, Laronde DM, Berean K, Gardner PJ, et al. Loss of heterozygosity (LOH) profiles–validated risk predictors for progression to oral cancer. Cancer Prev Res. 2012;5(9):1081–9.
4. Chung CH, Guthrie VB, Masica DL, Tokheim C, Kang H, Richmon J, et al. Genomic alterations in head and neck squamous cell carcinoma determined by cancer gene-targeted sequencing. Ann Oncol. 2015;26(6):1216–23.
5. Peng CH, Liao CT, Peng SC, Chen YJ, Cheng AJ, Juang JL, et al. A novel molecular signature identified by systems genetics approach predicts prognosis in oral squamous cell carcinoma. PLoS One. 2011;6(8):e23452.
6. Pickering CR, Zhang J, Yoo SY, Bengtsson L, Moorthy S, Neskey DM, et al. Integrative genomic characterization of oral squamous cell carcinoma identifies frequent somatic drivers. Cancer Discov. 2013;3(7):770–81.
7. Ribeiro IP, Marques F, Caramelo F, Pereira J, Patricio M, Prazeres H, et al. Genetic gains and losses in oral squamous cell carcinoma: impact on clinical management. Cell Oncol. 2014;37(1):29–39.
8. Salahshourifar I, Vincent-Chong VK, Kallarakkal TG, Zain RB. Genomic DNA copy number alterations from precursor oral lesions to oral squamous cell carcinoma. Oral Oncol. 2014;50(5):404–12.

9. Seiwert TY, Zuo Z, Keck MK, Khattri A, Pedamallu CS, Stricker T, et al. Integrative and comparative genomic analysis of HPV-positive and HPV-negative head and neck squamous cell carcinomas. Clin Cancer Res. 2015;21(3):632–41.
10. Smeets SJ, Braakhuis BJ, Abbas S, Snijders PJ, Ylstra B, van de Wiel MA, et al. Genome-wide DNA copy number alterations in head and neck squamous cell carcinomas with or without oncogene-expressing human papillomavirus. Oncogene. 2006;25(17):2558–64.
11. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nat Rev Dis Primers. 2020;6(1):92.
12. Braakhuis BJ, Rietbergen MM, Buijze M, Snijders PJ, Bloemena E, Brakenhoff RH, et al. TP53 mutation and human papilloma virus status of oral squamous cell carcinomas in young adult patients. Oral Dis. 2014;20(6):602–8.
13. Bragelmann J, Dagogo-Jack I, El Dinali M, Stricker T, Brown CD, Zuo Z, et al. Oral cavity tumors in younger patients show a poor prognosis and do not contain viral RNA. Oral Oncol. 2013;49(6):525–33.
14. Chang AM, Kim SW, Duvvuri U, Johnson JT, Myers EN, Ferris RL, et al. Early squamous cell carcinoma of the oral tongue: comparing margins obtained from the glossectomy specimen to margins from the tumor bed. Oral Oncol. 2013;49(11):1077–82.
15. El-Mofty SK, Lu DW. Prevalence of human papillomavirus type 16 DNA in squamous cell carcinoma of the palatine tonsil, and not the oral cavity, in young patients: a distinct clinicopathologic and molecular disease entity. Am J Surg Pathol. 2003;27(11):1463–70.
16. Harris SL, Thorne LB, Seaman WT, Hayes DN, Couch ME, Kimple RJ. Association of p16(INK4a) overexpression with improved outcomes in young patients with squamous cell cancers of the oral tongue. Head Neck. 2011;33(11):1622–7.
17. Kabeya M, Furuta R, Kawabata K, Takahashi S, Ishikawa Y. Prevalence of human papillomavirus in mobile tongue cancer with particular reference to young patients. Cancer Sci. 2012;103(2):161–8.
18. Liang XH, Lewis J, Foote R, Smith D, Kademani D. Prevalence and significance of human papillomavirus in oral tongue cancer: the Mayo Clinic experience. J Oral Maxillofac Surg. 2008;66(9):1875–80.
19. O'Regan EM, Toner ME, Finn SP, Fan CY, Ring M, Hagmar B, et al. p16(INK4A) genetic and epigenetic profiles differ in relation to age and site in head and neck squamous cell carcinomas. Hum Pathol. 2008;39(3):452–8.
20. Poling JS, Ma XJ, Bui S, Luo Y, Li R, Koch WM, et al. Human papillomavirus (HPV) status of non-tobacco related squamous cell carcinomas of the lateral tongue. Oral Oncol. 2014;50(4):306–10.
21. Siebers TJ, Merkx MA, Slootweg PJ, Melchers WJ, van Cleef P, de Wilde PC. No high-risk HPV detected in SCC of the oral tongue in the absolute absence of tobacco and alcohol–a case study of seven patients. Oral Maxillofac Surg. 2008;12(4):185–8.
22. Tsimplaki E, Argyri E, Xesfyngi D, Daskalopoulou D, Stravopodis DJ, Panotopoulou E. Prevalence and expression of human papillomavirus in 53 patients with oral tongue squamous cell carcinoma. Anticancer Res. 2014;34(2):1021–5.
23. Toporcov TN, Znaor A, Zhang ZF, Yu GP, Winn DM, Wei Q, et al. Risk factors for head and neck cancer in young adults: a pooled analysis in the INHANCE consortium. Int J Epidemiol. 2015;44(1):169–85.
24. Brunnemann KD, Prokopczyk B, Djordjevic MV, Hoffmann D. Formation and analysis of tobacco-specific N-nitrosamines. Crit Rev Toxicol. 1996;26(2):121–37.
25. Hammond EC, Horn D. Smoking and death rates: report on forty-four months of follow-up of 187,783 men. 2. Death rates by cause. J Am Med Assoc. 1958;166(11):1294–308.
26. Morse DE, Katz RV, Pendrys DG, Holford TR, Krutchkoff DJ, Eisenberg E, et al. Smoking and drinking in relation to oral epithelial dysplasia. Cancer Epidemiol Biomark Prev. 1996;5(10):769–77.
27. Wynder EL, Bross IJ, Feldman RM. A study of the etiological factors in cancer of the mouth. Cancer. 1957;10(6):1300–23.
28. Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, et al. Tobacco smoking and cancer: a meta-analysis. Int J Cancer. 2008;122(1):155–64.
29. Chi AC, Day TA, Neville BW. Oral cavity and oropharyngeal squamous cell carcinoma–an update. CA Cancer J Clin. 2015;65(5):401–21.
30. Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, et al. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res. 1988;48(11):3282–7.
31. Schlecht NF, Franco EL, Pintos J, Kowalski LP. Effect of smoking cessation and tobacco type on the risk of cancers of the upper aerodigestive tract in Brazil. Epidemiology. 1999;10(4):412–8.
32. Mashberg A, Garfinkel L, Harris S. Alcohol as a primary risk factor in oral squamous carcinoma. CA Cancer J Clin. 1981;31(3):146–55.
33. Moore C, Catlin D. Anatomic origins and locations of oral cancer. Am J Surg. 1967;114(4):510–3.
34. Marwick C. Increasing use of chewing tobacco, especially among younger persons, alarms Surgeon General. JAMA. 1993;269(2):195.
35. Winn DM, Blot WJ, Shy CM, Pickle LW, Toledo A, Fraumeni JF Jr. Snuff dipping and oral cancer among women in the southern United States. N Engl J Med. 1981;304(13):745–9.
36. Brandwein-Gensler M, Hille JJ. Behind the cover: the Guthka story. Arch Otolaryngol Head Neck Surg. 2003;129(7):699–700.
37. Idris AM, Ibrahim SO, Vasstrand EN, Johannessen AC, Lillehaug JR, Magnusson B, et al. The Swedish snus and the Sudanese toombak: are they different? Oral Oncol. 1998;34(6):558–66.
38. IARC. Cancer of the oral cavity and pharynx. In: IARC Working Group on the evaluation of carcinogenic risks to humans. Paris: IARC Press; 2010. p. 237–329.
39. Guha N, Warnakulasuriya S, Vlaanderen J, Straif K. Betel quid chewing and the risk of oral and oropharyngeal cancers: a meta-analysis with implications for cancer control. Int J Cancer. 2014;135(6):1433–43.
40. Gupta B, Johnson NW. Systematic review and meta-analysis of association of smokeless tobacco and of betel quid without tobacco with incidence of oral cancer in South Asia and the Pacific. PLoS One. 2014;9(11):e113385.
41. Merchant AT, Pitiphat W. Total, direct, and indirect effects of paan on oral cancer. Cancer Causes Control. 2015;26(3):487–91.
42. Doorbar J. Host control of human papillomavirus infection and disease. Best Pract Res Clin Obstet Gynaecol. 2018;47:27–41.
43. Doorbar J, Egawa N, Griffin H, Kranjec C, Murakami I. Human papillomavirus molecular biology and disease association. Rev Med Virol. 2015;25(Suppl 1):2–23.
44. Egawa N, Egawa K, Griffin H, Doorbar J. Human papillomaviruses; epithelial tropisms, and the development of neoplasia. Viruses. 2015;7(7):3863–90.
45. Arnaoutakis D, Bishop J, Westra W, Califano JA. Recurrence patterns and management of oral cavity premalignant lesions. Oral Oncol. 2013;49(8):814–7.
46. Holmstrup P, Vedtofte P, Reibel J, Stoltze K. Long-term treatment outcome of oral premalignant lesions. Oral Oncol. 2006;42(5):461–74.
47. Hansen LS, Olson JA, Silverman S Jr. Proliferative verrucous leukoplakia. A long-term study of thirty patients. Oral Surg Oral Med Oral Pathol. 1985;60(3):285–98.
48. Silverman S Jr, Gorsky M. Proliferative verrucous leukoplakia: a follow-up study of 54 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997;84(2):154–7.

49. Suarez P, Batsakis JG, el-Naggar AK. Leukoplakia: still a gallimaufry or is progress being made? A review. Adv Anat Pathol. 1998;5(3):137–55.
50. Thompson LDR, Fitzpatrick SG, Muller S, Eisenberg E, Upadhyaya JD, Lingen MW, et al. Proliferative verrucous leukoplakia: an expert consensus guideline for standardized assessment and reporting. Head Neck Pathol. 2021;15(2):572–87.
51. Abbey LM, Kaugars GE, Gunsolley JC, Burns JC, Page DG, Svirsky JA, et al. The effect of clinical information on the histopathologic diagnosis of oral epithelial dysplasia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;85(1):74–7.
52. Abbey LM, Kaugars GE, Gunsolley JC, Burns JC, Page DG, Svirsky JA, et al. Intraexaminer and interexaminer reliability in the diagnosis of oral epithelial dysplasia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1995;80(2):188–91.
53. Ho MW, Field EA, Field JK, Risk JM, Rajlawat BP, Rogers SN, et al. Outcomes of oral squamous cell carcinoma arising from oral epithelial dysplasia: rationale for monitoring premalignant oral lesions in a multidisciplinary clinic. Br J Oral Maxillofac Surg. 2013;51(7):594–9.
54. Ho MW, Risk JM, Woolgar JA, Field EA, Field JK, Steele JC, et al. The clinical determinants of malignant transformation in oral epithelial dysplasia. Oral Oncol. 2012;48(10):969–76.
55. Field EA, McCarthy CE, Ho MW, Rajlawat BP, Holt D, Rogers SN, et al. The management of oral epithelial dysplasia: The Liverpool algorithm. Oral Oncol. 2015;51(10):883–7.
56. Partridge M, Emilion G, Pateromichelakis S, A'Hern R, Phillips E, Langdon J. Allelic imbalance at chromosomal loci implicated in the pathogenesis of oral precancer, cumulative loss and its relationship with progression to cancer. Oral Oncol. 1998;34(2):77–83.
57. Partridge M, Emilion G, Pateromichelakis S, Phillips E, Langdon J. Field cancerisation of the oral cavity: comparison of the spectrum of molecular alterations in cases presenting with both dysplastic and malignant lesions. Oral Oncol. 1997;33(5):332–7.
58. Lee JJ, Hong WK, Hittelman WN, Mao L, Lotan R, Shin DM, et al. Predicting cancer development in oral leukoplakia: ten years of translational research. Clin Cancer Res. 2000;6(5):1702–10.
59. Partridge M, Pateromichelakis S, Phillips E, Emilion GG, A'Hern RP, Langdon JD. A case-control study confirms that microsatellite assay can identify patients at risk of developing oral squamous cell carcinoma within a field of cancerization. Cancer Res. 2000;60(14):3893–8.
60. de Vicente JC, Rodrigo JP, Rodriguez-Santamarta T, Lequerica-Fernandez P, Allonca E, Garcia-Pedrero JM. Podoplanin expression in oral leukoplakia: tumorigenic role. Oral Oncol. 2013;49(6):598–603.
61. Mao L, Lee JS, Fan YH, Ro JY, Batsakis JG, Lippman S, et al. Frequent microsatellite alterations at chromosomes 9p21 and 3p14 in oral premalignant lesions and their value in cancer risk assessment. Nat Med. 1996;2(6):682–5.
62. Lippman SM, Hong WK. Molecular markers of the risk of oral cancer. N Engl J Med. 2001;344(17):1323–6.
63. Rosin MP, Cheng X, Poh C, Lam WL, Huang Y, Lovas J, et al. Use of allelic loss to predict malignant risk for low-grade oral epithelial dysplasia. Clin Cancer Res. 2000;6(2):357–62.
64. Califano J, van der Riet P, Westra W, Nawroz H, Clayman G, Piantadosi S, et al. Genetic progression model for head and neck cancer: implications for field cancerization. Cancer Res. 1996;56(11):2488–92.
65. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer. 1953;6(5):963–8.
66. Lippman SM, Hong WK. Second malignant tumors in head and neck squamous cell carcinoma: the overshadowing threat for patients with early-stage disease. Int J Radiat Oncol Biol Phys. 1989;17(3):691–4.
67. Natarajan E, Eisenberg E. Contemporary concepts in the diagnosis of oral cancer and precancer. Dent Clin N Am. 2011;55(1):63–88.
68. Odar K, Kocjan BJ, Hosnjak L, Gale N, Poljak M, Zidar N. Verrucous carcinoma of the head and neck - not a human papillomavirus-related tumour? J Cell Mol Med. 2014;18(4):635–45.
69. Patel KR, Chernock RD, Zhang TR, Wang X, El-Mofty SK, Lewis JS. Verrucous carcinomas of the head and neck, including those with associated squamous cell carcinoma, lack transcriptionally active high-risk human papillomavirus. Hum Pathol. 2013;44(11):2385–92.
70. Hagen P, Lyons GD, Haindel C. Verrucous carcinoma of the larynx: role of human papillomavirus, radiation, and surgery. Laryngoscope. 1993;103(3):253–7.
71. Slootweg PJ, Muller H. Verrucous hyperplasia or verrucous carcinoma. An analysis of 27 patients. J Maxillofac Surg. 1983;11(1):13–9.
72. Berman TA, Schiller JT. Human papillomavirus in cervical cancer and oropharyngeal cancer: One cause, two diseases. Cancer. 2017;123(12):2219–29.
73. St Guily JL, Clavel C, Okais C, Pretet JL, Beby-Defaux A, Agius G, et al. Human papillomavirus genotype distribution in tonsil cancers. Head Neck Oncol. 2011;3(1):6.
74. Woods R Sr, O'Regan EM, Kennedy S, Martin C, O'Leary JJ, Timon C. Role of human papillomavirus in oropharyngeal squamous cell carcinoma: a review. World J Clin Cases. 2014;2(6):172–93.
75. Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst. 2008;100(6):407–20.
76. Heck JE, Berthiller J, Vaccarella S, Winn DM, Smith EM, Shan'gina O, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Int J Epidemiol. 2010;39(1):166–81.
77. Palmer E, Newcombe RG, Green AC, Kelly C, Noel Gill O, Hall G, et al. Human papillomavirus infection is rare in nonmalignant tonsil tissue in the UK: implications for tonsil cancer precursor lesions. Int J Cancer. 2014;135(10):2437–43.
78. Chung CH, Zhang Q, Kong CS, Harris J, Fertig EJ, Harari PM, et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. J Clin Oncol. 2014;32(35):3930–8.
79. Dayyani F, Etzel CJ, Liu M, Ho CH, Lippman SM, Tsao AS. Meta-analysis of the impact of human papillomavirus (HPV) on cancer risk and overall survival in head and neck squamous cell carcinomas (HNSCC). Head Neck Oncol. 2010;2:15.
80. Tanaka TI, Alawi F. Human papillomavirus and oropharyngeal cancer. Dent Clin N Am. 2018;62(1):111–20.
81. Zur Hausen H. Papillomaviruses and cancer: from basic studies to clinical application. Nat Rev Cancer. 2002;2(5):342–50.
82. Begum S, Gillison ML, Nicol TL, Westra WH. Detection of human papillomavirus-16 in fine-needle aspirates to determine tumor origin in patients with metastatic squamous cell carcinoma of the head and neck. Clin Cancer Res. 2007;13(4):1186–91.
83. Golusinski P, Di Maio P, Pehlivan B, Colley S, Nankivell P, Kong A, et al. Evidence for the approach to the diagnostic evaluation of squamous cell carcinoma occult primary tumors of the head and neck. Oral Oncol. 2019;88:145–52.
84. Lechner M, Liu J, Masterson L, Fenton TR. HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management. Nat Rev Clin Oncol. 2022;19(5):306–27.
85. Zhang MQ, El-Mofty SK, Davila RM. Detection of human papillomavirus-related squamous cell carcinoma cytologically and by in situ hybridization in fine-needle aspiration biopsies of cervical metastasis: a tool for identifying the site of an occult head and neck primary. Cancer. 2008;114(2):118–23.

86. Taberna M, Mena M, Pavon MA, Alemany L, Gillison ML, Mesia R. Human papillomavirus-related oropharyngeal cancer. Ann Oncol. 2017;28(10):2386–98.
87. Machczynski P, Majchrzak E, Niewinski P, Marchlewska J, Golusinski W. A review of the 8th edition of the AJCC staging system for oropharyngeal cancer according to HPV status. Eur Arch Otorhinolaryngol. 2020;277(9):2407–12.
88. Zhang Y, Fakhry C, D'Souza G. Projected association of human papillomavirus vaccination with oropharynx cancer incidence in the US, 2020-2045. JAMA Oncol. 2021;7(10):e212907.
89. Burger EA, Smith MA, Killen J, Sy S, Simms KT, Canfell K, et al. Projected time to elimination of cervical cancer in the USA: a comparative modelling study. Lancet Public Health. 2020;5(4):e213–e22.
90. Laprise JF, Chesson HW, Markowitz LE, Drolet M, Martin D, Benard E, et al. Effectiveness and cost-effectiveness of human papillomavirus vaccination through age 45 years in the United States. Ann Intern Med. 2020;172(1):22–9.

Facial Pain

20

Keyur Naik and Elie M. Ferneini

Introduction

Facial or orofacial pain can be defined as non-odontogenic and non-malignant causes of pain in the face and oral cavity. These conditions are varied in their etiology and frequently present as diagnostic and therapeutic challenges to those practitioners who do not encounter these syndromes routinely. Incorrect diagnosis is common and leads to unnecessary therapy without treatment of the underlying cause. As such, an understanding of these conditions will help the clinician guide patients to the most appropriate treatment.

Orofacial pain syndromes are most commonly musculocutaneous or neurologic in origin. Despite that, many patients first present to their dentist as facial pain syndromes are frequently and incorrectly attributed to tooth-related, or odontogenic, causes. The diagnosis of caries, periapical and periodontal disease is routine for the skilled dentist with a clinical exam of the oral cavity and intraoral radiographs. However, lack of a clear odontogenic source should prompt a referral to a dental or medical specialist experienced with the treatment of orofacial pain.

Diagnosis and treatment of orofacial pain frequently require a multidisciplinary approach. Orofacial pain is a specialty of dentistry. Orofacial pain specialists are skilled at diagnosing facial pain processes that frequently have overlapping symptomatology. However, many academic institutions do not have orofacial pain programs or specialists. As such, oral and maxillofacial surgeons, otolaryngologists, and neurologists typically work in conjunction to treat these patients.

Facial pain syndromes are complex and would not be adequately discussed in detail within the confines of one book chapter. Headache, psychosomatic disorders, and sinonasal causes of facial pain that do not fall under the traditional scope of dental science will not be discussed. Given the title of this publication, this chapter will discuss the types of facial pain most frequently encountered by the dentist or dental specialist, the ways in which these conditions are diagnosed, and the manner in which they are treated.

Temporomandibular Joint Disorders

Temporomandibular joint disorders (TMD) affect between 5 and 20% of adults [1]. The ubiquity of orofacial pain attributed to the dysfunction of the temporomandibular joint has made TMD part of the standard lexicon in American culture. However, all TMDs are not synonymous. The temporomandibular joint (TMJ) is a diarthrodial joint. It is composed of the mandibular condyle, a glenoid fossa in which the condyle sits while the mandible is at rest, and an articular disc which translates with the condyle when the mandible is in function. The joint is also affected by the pull of the muscles of mastication, including the masseter, temporalis, and pterygoid muscles. Any part of the joint and the surrounding myofascial apparatus can cause dysfunction and result in pain. Treatments vary by cause. Therefore, accurate diagnosis of the offending component is crucial in alleviating orofacial pain caused my TMD.

Myofascial Pain Dysfunction

Temporomandibular disorder is most commonly caused by myofascial pain dysfunction (MPD) and accounts for 30–90% of patients who seek treatment for TMD [2]. In MPD, pain is not caused by the pathology of the articular aspects of the temporomandibular joint. Rather, the syndrome presents as a myalgia of a combination of surrounding supramandibular and inframandibular muscles. The causes of MPD are multifactorial. Parafunctional habits including

K. Naik (✉)
Department of Oral and Maxillofacial Surgery, New York University/Bellevue Hospital Center, NY, New York, USA
e-mail: keyur.naik@nyulangone.org

E. M. Ferneini
Division of Oral and Maxillofacial Surgery, University of Connecticut, Farmington, CT, USA

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_20

bruxing and clenching, chronic stress and significant life stressors, and sleep disturbances are all associated with MPD. Diagnosis of myofascial pain can be made by eliciting a clinical history and examination. Imaging is usually not helpful in making the diagnosis of MPD. The clinical history of illness should be performed in the standard manner with special attention paid to patient's past medical history and psychiatric history (depression, anxiety). Inquiring about a patient's parafunctional habits, new or chronic physical and emotional stressors, and sleep habits can lead a clinician to suspect MPD. On exam, tenderness on palpation of the supramandibular (temporalis) and inframandibular (masseter and lateral pterygoid) muscles of mastication is a common sign [3]. Additionally, patients may show evidence of their parafunctional habits through wear facets on their teeth and enlarged masseters.

Treatment of myofascial pain is usually conservative. Nonsteroidal anti-inflammatory drugs (NSAIDs) and warm compresses can help alleviate inflammation of the muscles of mastication. Additionally, muscle relaxants and occlusal guards can help prevent parafunctional habits. More recently, Botox has gained increasing popularity in the treatment of myofascial pain when injected into the masseter and temporalis. However, studies are mixed as to the efficacy of Botox and further studies are needed [4]. Most patients with MPD require long-term follow-up. Lack of appropriate care can eventually lead to damage to the joint itself. In the case of concomitant psychiatric disorders or significant emotional stressors, recruiting the help of a psychiatrist may be of significant benefit.

Internal Derangement of the TMJ

Internal derangement of the temporomandibular joint is described as the aberrant position of the articular disc, while the mandible is in function or at rest as a result of stressors to the joint [5]. The mispositioned disc will not only cause significant pain during function of the mandible while speaking and eating but can also limit the opening of the mouth. Causes of internal derangement are numerous but include trauma, parafunctional habits, and myofascial pain dysfunction. Diagnosis of internal derangement involves a clinical history, exam, and imaging. The patient interview should elicit much of the same information as when a clinician suspects MPD, but a facial trauma history is also critical. It is important to note that the trauma may have occurred many years prior to initial presentation. On exam, patients demonstrate limited opening and varying amounts of deviation on opening in addition to preauricular pain. Unlike MPD, palpable clicks and joint crepitus may be appreciated as the mouth opens and closes. When internal derangement is suspected, dynamic magnetic resonance imaging (MRI) should be obtained which allows for the assessment of articular disc position while the joint is in function n [6]. Imaging will assist the clinician in determining the type of internal derangement: disk displacement with reduction or disk displacement without reduction. Both forms involve the disc being in an aberrant (usually anterior position) at rest. However, in patients that demonstrate disk reduction, the condyle passes into the correct anatomical position in relation to the disc when in function. Being able to interpret the findings on clinical exam and on imaging takes significant skill and experience with TMD patients.

The treatment of internal derangement of the TMJ typically follows a step-wise ladder. Clinicians can start with conservative therapy, including NSAIDs, soft diet, and warm compresses, as described for MPD. Intraarticular injections with bupivacaine and triamcinolone suspension can also be used. Neither of these treatments will address the underlying pathology but may provide patients with symptomatic relief. When pain relief is not achieved with these measures, surgical treatment can be undertaken. Similar to other joints in the body, arthrocentesis can be performed to wash inflammatory debris from the joint space. Arthrocentesis allows for washout of inflammatory debris in the joint space. Additionally, injecting anesthetic agents such as Marcaine or platelet rich plasma into the superior joint space can be used as adjunct to the procedure. In refractory patients, open surgery can be undertaken. Discectomy or modified condylotomy can be undertaken to alter the shape of the joint. Surgical treatment has been shown to reduce symptoms in 77–94% of patients and improve function (mouth opening) in 50–60% of patients [7]. End-stage treatment involves removal of the native joint, including the condyle and disc, and replacement with a prosthetic joint [7].

Degenerative Joint Disease (DJD)

Like other joints, the temporomandibular joint can be subject to degenerative changes. Through the course of the disease, arthritis leads to the destruction of the articular disk and the mandibular condyle. Both osteoarthritis and forms of inflammatory arthritis can impact the function of the TMJ and cause pain. Non-inflammatory arthritis or osteoarthritis is a progressive condition caused by an imbalance of catabolic and anabolic processes. As catabolic processes predominate and inflammatory cytokines overwhelm the joint, a breakdown of the articular disk and the joint occurs [8]. Osteoarthritis can be incited by other processes such as internal derangement of the TMJ or facial trauma. Inflammatory arthritis conditions such as rheumatoid arthritis and juvenile rheumatoid arthritis cause joint destruction through chronic inflammation.

Treatments for DJD are dependent on the type of underlying conditions. Like other disorders of the TMJ, the initial treatment for osteoarthritis of the temporomandibular joint is conservative in nature. Ideally, these measures are taken before joint destruction becomes severe enough to warrant surgical management. In severe disease, surgical correction with arthroplasty or total joint replacement become the only solution. The treatments remain similar for inflammatory arthritis conditions, though disease-modifying drugs also play an important role in slowing disease progression [9].

Neurologic Disorders

A broad number of neurological syndromes can result in orofacial pain. Headache, in its various forms, is likely the most common. Patients affected by headaches typically do not present to their dentist or dental specialist for primary evaluation and are treated by their primary care physician or neurologist. For those reasons, headache will not be discussed in detail here. Neuropathic pain syndromes in the region of the head and neck are relatively uncommon but are evaluated and treated by orofacial pain specialists and oral and maxillofacial surgeons in conjunction with their medical colleagues. Neuropathies can be mistaken for other odontogenic and non-odontogenic causes of orofacial pain. A through clinical history is vital to diagnose these disorders as diagnostic testing can be limited in terms of availability and efficacy. Once again, treatment is a team-based approach to adequately treat these patients.

Trigeminal Neuralgia

Trigeminal neuralgia (TN), also called *tic doloureux*, is a neurological condition affecting the fifth cranial nerve. Patients typically experience sharp, shock-like pain that lasts a few seconds to a few minutes and travels in the distribution of the trigeminal nerve branches. The nerve has three branches: the ophthalmic (V1), the maxillary nerve (V2), and mandibular nerve (V3). Pain can not only affect any combination of nerve branches but also affect one side of the face during a given episode. In typical trigeminal neuralgia, pain episodes occur in clusters of attacks over the course of several hours. However, an atypical form of trigeminal neuralgia also exists. The pain differs in that it is longer lasting (on the order of hours), though it is less severe. The etiology of trigeminal neuralgia has not been fully elucidated. It is thought that demyelination of the nerve can affect the function of the nerve and aberrant pain signals result. Demyelination is thought to occur secondary to compression of the nerve by blood vessels as it exits in the brainstem or as a result of systemic demyelinating processes such as multiple sclerosis.

The diagnosis of trigeminal neuralgia relies greatly on the patient interview and the history of the illness [10] Descriptions of unilateral, shooting pain should raise concern for this diagnosis. However, there are other causes of facial pain that can mimic trigeminal neuralgia. Post-herpetic neuralgia, cluster headaches, and temporomandibular joint disorders all have features that overlap with trigeminal neuralgia. As such, TN can be seen as a diagnosis of exclusion. Evaluating a patient for these other potential causes of facial pain guides a clinician away from an incorrect diagnosis and unnecessary treatment. If trigeminal neuralgia is considered the likely diagnosis, imaging studies can aid the practitioner in evaluating whether the symptoms are a result of another process. MRI studies can demonstrate compression of the trigeminal nerve by blood vessels or intracranial masses. Intracerebral plaques would suggest multiple sclerosis. Identifying triggers for TN can be useful in guiding treatment of the disorder.

Treatment of trigeminal neuralgia involves both medical and surgical approaches. Anticonvulsants, either carbamazepine or oxcarbazepine, are effective in up to 90% of patients. Over time, up to 20% of patient become resistant to these therapies. Second-line medications including gabapentin and amitriptyline have shown some success in treating symptoms [11]. Despite being a pain syndrome, opioid and nonopioid pain medications have not been shown to reliably alleviate pain caused by TN. Surgical treatment should be considered in patients who fail medical management. Microvascular decompression (MVD) and stereotactic radiosurgery are the common surgical treatments for trigeminal neuralgia. Microvascular decompression involves mobilizing the superior cerebellar artery off the trigeminal nerve. Alternatively, stereotaxic radiosurgery utilizes gamma knife or proton beam therapy targeted at the root of the trigeminal nerve. MVD provides sustained relief in greater than 80% of patients but is more invasive that stereotactic radiotherapy which demonstrates improvement in approximately 50% of patients at the 3-year mark [12].

Glossopharyngeal Neuralgia

Glossopharyngeal neuralgia is a pain syndrome that affects the ninth cranial nerve. The condition shares many similarities with trigeminal neuralgia. Patients frequently experience short period of intense sharp pain. Unlike trigeminal neuralgia, the pain is distributed in the region of the posterior tongue and throat. The pain is sometimes triggered by eating, and patients frequently lose weight in order to avoid attacks. Irritation to the glossopharyngeal nerve is thought to be the cause. However, the actual cause of the irritation is rarely found. Infrequently, irritation by a blood vessel at the nerve's exit through the brainstem, a benign or malignant growth

within the skull base, or systemic disease such as multiple sclerosis is found to be the cause [13].

The diagnosis and treatment of glossopharyngeal neuralgia mimic that of trigeminal neuralgia. Diagnosis begins with eliciting a detailed history. Episodic sharp pain in the throat triggered by eating or swallowing should raise suspicion for glossopharyngeal neuralgia. As part of the clinical exam, a swab can be used to touch the back of the oropharynx to trigger an episode. Glossopharyngeal neuralgia can be quickly distinguished from trigeminal neuralgia based on the location of pain. Masses located in the hypopharynx, tonsillar fossa, and piriform sinus can produce similar pain symptoms and should be ruled out with magnetic resonance imaging (MRI). Treatment of glossopharyngeal neuralgia begins with medical management. Carbamazepine and oxcarbazepine are first-line medications in the treatment of this neuralgia. When medical management fails, surgical options such as microvascular decompression can effectively provide symptom relief. Microvascular decompression has been shown to have a 56% reduction in symptoms while stereotactic radiosurgery has a 67% reduction in symptoms. Stereotactic surgery is also a noninvasive procedure with lower morbidity than microvascular decompression [14]. Ultimately, shared decision making with patients and individual patient risk factors will guide choice of therapy.

Burning Mouth Syndrome

Burning mouth syndrome (BMS) describes burning, scalding symptoms in the mouth which have no other medical or dental cause. The pain is most commonly experienced on the tongue but can also affect the gingiva, palate, and lips. Unlike trigeminal and glossopharyngeal neuralgia, the pain is chronic, and while symptoms can remit, they are longer lasting. The burning sensation can also be associated with xerostomia, or dry mouth. The symptoms are most frequently triggered by stress and fatigue and can be temporarily relieved with eating. In fact, pain relief with eating is pathognomonic for the condition [15]. In most cases, the cause of burning mouth syndrome is unknown and are called primary. The literature is conflicted in cases where a cause can be identified. Some will term these cases as secondary BMS, though others believe that BMS is only diagnosed when no underlying cause can be found. There is a strong association between BMS and depression or anxiety.

The diagnosis of burning mouth syndrome is one of exclusion. Per the International Classification of Headache Disorders, three criteria are needed to make the diagnosis: daily pain in the oral cavity, normal appearing oral mucosa, and exclusion of other pain processes affecting the oral cavity [16]. There are no clinical exam findings or tests that will help confirm the diagnosis of BMS. Given the association between BMS and psychiatric conditions, psychiatric evaluation may prove useful when treating these patients. Treatment of BMS centers around patient reassurance and use of antidepressants. Newer studies have demonstrated the efficacy of alpha-lipoic acid, a naturally occurring antioxidant, in the treatment of burning mouth syndrome. Despite newer treatment modalities, many patients find only limited relief and long-term management is necessary [17].

Post-Herpetic Neuralgia

Post-herpetic neuralgia (PHN) is a form of neuropathic pain caused by reactivation of varicella zoster in the peripheral nervous system. Herpes zoster remains dormant in the dorsal root ganglia of peripheral nerves after an initial exposure to the virus. Stressors can result in reactivation of the virus and damage to neurons usually in a single dermatome. The pain symptoms usually come after the appearance of vesicles that appear in a dermatomal distribution, though pain can precede or occur without herpetic vesicles. The type of pain can be variable. Though most commonly described as burning, it is not uncommon for patients to describe the pain as shooting or electric. The pain or burning sensation that patients experience must last a minimum of 3 months to be considered post-herpetic neuralgia. Approximately 20% of patients who experience herpes zoster have pain at 3 months and 15% continue to have pain at the 2-year mark [18].

The diagnosis of post-herpetic neuralgia can be made without the use of lab tests or imaging. A detailed history should include the appearance of herpetic vesicles and investigate the distribution of pain symptoms. Clinical exam may demonstrate cutaneous scars in the distribution of the pain symptoms from the healing or healed herpetic vesicles contained within a single dermatome. Altered sensation, either hyperalgesia or hypoalgesia, to touch within the affected dermatome can be observed on exam. Treatment of postherpetic neuralgia centers around both treatment of an acute episode and prevention of future attacks. Acute symptoms are treated with both oral and topical medications. Lidocaine and capsaicin creams can be applied in the distribution of pain. Topical ointments are useful in patients with mild pain, but systemic oral medications should be considered in those with more severe symptoms. Oral medications, namely tricyclic antidepressants, are used in the treatment of PHN. Additionally, anticonvulsants such as gabapentin have been shown to reduce symptoms [19]. Vaccination against herpes zoster or shingles is recommended for all adults above the age of 60. Not only has it been shown to prevent the herpes zoster rash, but also to reduce the incidence of PHN. Preventive antiviral medications used after the onset of the herpetic rash have been studied but have not been shown to be effective [20].

Conclusion

This chapter details facial pain syndromes that are frequently seen by dentists and dental specialists, namely orofacial pain specialists. Most facial pain conditions are musculoskeletal or neurologic in nature. Diagnosis of these conditions can be challenging. These pain syndromes are frequently attributed to odontogenic disease given the proximity to or involvement of the oral cavity. Even when non-odontogenic causes are explored, overlapping symptoms can make these diseases difficult to distinguish. As such, facial pain syndromes are complex and typically require attention from a team of clinicians. The ability to effectively recognize, evaluate, diagnose, and treat facial pain helps patients find appropriate treatment in an efficient manner.

References

1. Slade GD. Epidemiology of temporomandibular joint disorders and related painful conditions. Mol Pain. 2014;10(Suppl 1):O16. Published 2014 Dec 15. https://doi.org/10.1186/1744-8069-10-S1-O16.
2. Wheeler AH. Myofascial pain disorders. Drugs. 2004;64:45–62. https://doi.org/10.2165/00003495-200464010-00004.
3. Gerwin RD. Diagnosis of myofascial pain syndrome. Phys Med Rehabil Clin N Am. 2014;25(2):341–55. https://doi.org/10.1016/j.pmr.2014.01.011.
4. Soares A, Andriolo RB, Atallah AN, da Silva EM. Botulinum toxin for myofascial pain syndromes in adults. Cochrane Database Syst Rev. 2012;4:CD007533. https://doi.org/10.1002/14651858.CD007533.pub2. Published 2012 Apr 18.
5. Young AL. Internal derangements of the temporomandibular joint: a review of the anatomy, diagnosis, and management. J Indian Prosthodont Soc. 2015;15(1):2–7. https://doi.org/10.4103/0972-4052.156998.
6. Schellhas KP. Internal derangement of the temporomandibular joint: radiologic staging with clinical, surgical, and pathologic correlation. Magn Reson Imaging. 1989;7(5):495–515. https://doi.org/10.1016/0730-725x(89)90404-9.
7. Trumpy IG, Lyberg T. Surgical treatment of internal derangement of the temporomandibular joint: long-term evaluation of three techniques. J Oral Maxillofac Surg. 1995;53(7):740–7. https://doi.org/10.1016/0278-2391(95)90321-6.
8. Tanaka E, Detamore MS, Mercuri LG. Degenerative disorders of the temporomandibular joint: etiology, diagnosis, and treatment. J Dent Res. 2008;87(4):296–307. https://doi.org/10.1177/154405910808700406.
9. Kalladka M, Quek S, Heir G, Eliav E, Mupparapu M, Viswanath A. Temporomandibular joint osteoarthritis: diagnosis and long-term conservative management: a topic review. J Indian Prosthodont Soc. 2014;14(1):6–15. https://doi.org/10.1007/s13191-013-0321-3.
10. Maarbjerg S, Di Stefano G, Bendtsen L, Cruccu G. Trigeminal neuralgia—diagnosis and treatment. Cephalalgia. 2017;37(7):648–57. https://doi.org/10.1177/0333102416687280.
11. Sindrup SH, Jensen TS. Pharmacotherapy of trigeminal neuralgia. Clin J Pain. 2002;18(1):22–7.
12. Bick SKB, Eskandar EN. Surgical treatment of trigeminal neuralgia. Neurosurg Clin N Am. 2017;28(3):429–38. https://doi.org/10.1016/j.nec.2017.02.009.
13. Singh PM, Kaur M, Trikha A. An uncommonly common: glossopharyngeal neuralgia. Ann Indian Acad Neurol. 2013;16(1):1–8. https://doi.org/10.4103/0972-2327.107662.
14. Lu VM, Goyal A, Graffeo CS, Perry A, Jonker BP, Link MJ. Glossopharyngeal neuralgia treatment outcomes after nerve section, microvascular decompression, or stereotactic radiosurgery: a systematic review and meta-analysis. World Neurosurg. 2018;120:572–582.e7. https://doi.org/10.1016/j.wneu.2018.09.042.
15. Aravindhan R, Vidyalakshmi S, Kumar MS, Satheesh C, Balasubramanium AM, Prasad VS. Burning mouth syndrome: a review on its diagnostic and therapeutic approach. J Pharm Bioallied Sci. 2014;6(Suppl 1):S21–5. https://doi.org/10.4103/0975-7406.137255.
16. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders. Cephalalgia. 2018;38(1):1–211. https://doi.org/10.1177/0333102417738202.
17. Liu YF, Kim Y, Yoo T, Han P, Inman JC. Burning mouth syndrome: a systematic review of treatments. Oral Dis. 2018;24(3):325–34. https://doi.org/10.1111/odi.12660.
18. Johnson RW, Rice ASC. Postherpetic neuralgia. N Engl J Med. 2014;371(16):1526–33. https://doi.org/10.1056/nejmcp1403062.
19. Lin CS, Lin YC, Lao HC, Chen CC. Interventional treatments for postherpetic neuralgia: a systematic review. Pain Physician. 2019;22(3):209–28.
20. Saguil A, Kane S, Mercado M, Lauters R. Herpes zoster and Postherpetic neuralgia: prevention and management. Am Fam Physician. 2017;96(10):656–63.

Oral Manifestations of Systemic Disease

21

Julie E. McNeish and Lee W. McNeish

Introduction

Despite the mouth and oropharynx being the beginning of the digestive and respiratory tracts, signs and symptoms within the oral cavity are often neglected or forgotten about in the setting of systemic disease. The oral manifestations of many systemic diseases can be highly variable and affect not only the dentition but also the soft and hard tissues of the jaws. At times, signs and symptoms in the oral cavity may be the first recognizable feature of systemic disease. Early recognition can aid in timely diagnosis. In other disease processes, the oral manifestations may be the most severe feature requiring treatment primarily aimed within the oral cavity. Proper treatment may require collaboration with a dentist, oral pathologist, or oral and maxillofacial surgeon.

Knowledge of how diseases may manifest in the oral environment allows for comprehensive surveillance and potentially prophylactic care, resulting in a significant increase in quality of life and overall improved quality of patient care [1].

Differing approaches to the description of the oral manifestations of systemic disease have been proposed, including anatomic, disease-specific, and drug approaches. This chapter will attempt to classify the different disease processes by organ system.

J. E. McNeish (✉)
Lee W. McNeish, DMD, PC Oral, Facial, and Implant Surgery, Waterbury, CT, USA

Department of Oral and Maxillofacial Surgery, University of Connecticut, Farmington, CT, USA

L. W. McNeish
Lee W. McNeish, DMD, PC Oral, Facial, and Implant Surgery, Waterbury, CT, USA
e-mail: drmcneish@drmcneish.com

Pulmonary Diseases

Wegner's (Granulomatosis with Polyangiitis, GPA)

Wegner's is a well-known syndrome, despite it being relatively uncommon. The etiology remains unknown. The classic clinical triad consists of necrotizing granulomatous inflammation of the upper or lower respiratory tract, necrotizing glomerulonephritis, and small-vessel necrotizing systemic vasculitis [2]. These symptoms can present during a wide range of ages. When identified early, the disease can be kept in its limited form of upper and lower respiratory involvement only [3]. When the disease extends to the kidneys, it is termed generalized Wegner's. At this stage, the patient's prognosis becomes poor.

Although oral presentations are not part of the classic triad, the initial presentation may be in the oral cavity. The most common finding, termed "strawberry gingivitis," is red, granular-looking gingiva with short, bulbous, and friable projections [2]. Classically, it is confined to the attached gingiva and most commonly affects the buccal gingiva. There can be multiple involved areas, which can progress to ulcerations. Underlying alveolar bone degradation can occur; therefore, patients may present with dental pain and mobility of their teeth in these areas [4].

Other oral manifestations include nonspecific oral ulcerations that can occur on any mucosal surface. These lesions typically present when the patient has already developed the generalized disease, as up to 60% of patients with oral ulcerations have renal involvement [4]. Facial manifestations may include purulent nasal drainage, epistaxis, and nasal ulceration. Nasal ulcerations can become significant enough to develop into palatal fistulas. Upon involvement of the sinuses, patients may present with subjective complaints of congestion or sinus-related tooth pain, despite the absence of odontogenic pathology. Rare, but reported findings have included labial mucosal nodules, facial paralysis, temporomandibular joint pain, poorly healing extraction sites, and enlargement of salivary glands.

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_21

Sarcoidosis

Sarcoidosis is a multisystem granulomatous disease that most commonly affects the lungs [5]. Sarcoidosis is most common in the developed world. It has a predilection for blacks, females, and classically presents in middle age [4]. The most commonly involved organs after the lungs are the lymph nodes, skin, eyes, and salivary glands. Less common sites of presentation are the heart, spleen, and kidneys. In almost all cases, lymphoid tissue is involved. Although approximately 20% of patients are diagnosed based on incidental findings identified on chest radiographs, symptomatic patients typically present acutely over days to weeks [4, 5]. Due to the disease's nonspecific predilection for an organ system, patients may present with variable symptoms.

Cutaneous manifestations can be found in up to 25% of patients and may include the lips, nose, ears, and face. The most common cutaneous lesion is termed lupus pernio, which is an indurated, violaceous lesion, or shiny nodules [6]. It is often a predictor of systemic sarcoidosis. Identification or suspicion of this lesion should warrant a workup for sarcoidosis.

Oral manifestations of sarcoidosis may be a critical component of the diagnosis. A recent literature review showed that of 45 reported cases of intramural sarcoidosis, oral lesions were the first manifestation of the disease for the majority of patients [3]. Oral presentations include firm, asymptomatic, submucosal masses that can range in color from normal mucosa to brown-red, violaceous, or white. These masses are typically found on the tongue or buccal mucosa but can also be present on the floor of the mouth, palate, and gingiva. Oral papules, erythematous, ulcerative, or granular textural changes to the oral soft tissues can be seen in patients with sarcoidosis. Both the major and minor salivary glands can become enlarged. Major salivary glands (parotid, submandibular, and sublingual) are involved in 6% of sarcoidosis cases [7]. When minor glands become enlarged, they can be confused with a mucocele. In both cases, a biopsy is critical to aid in diagnosis. Patients can present with intraosseous lesions, although this is uncommon in the skull, jaws, or facial bones.

When the oral manifestations of bilateral parotid enlargement and facial palsy present with anterior uveitis, this may indicate a rare presentation of sarcoidosis known as Heerfordt's syndrome. Often it is associated with a low-grade fever. The diagnosis is made by salivary gland biopsy.

Gastrointestinal Diseases

Crohn's Disease

Crohn's disease is a chronic idiopathic inflammatory bowel disease (IBD) characterized by skip lesions and transmural inflammation that affects the entire gastrointestinal tract [8]. The disease is often first identified in teenagers. The most common presenting symptoms include abdominal complaints such as diarrhea, pain, weight loss, nausea, and vomiting. Although the predominant involvement is in the gastrointestinal tract, involvement of the skin, oral mucosa, eyes, and joints is well documented [4].

There is a wide range of possible oral lesions seen in Crohn's patients, most of which are nonspecific and may be associated with other conditions. Approximately 30% of cases have oral lesions and it is thought that they may precede gastrointestinal lesions [4]. The appearance of these lesions can be variable and includes diffuse or nodular swelling of the oral and perioral tissues, cobblestone appearance of the mucosa, linear granulomatous-appearing ulcers of the buccal mucosa, and mucosal tags [3, 4]. It remains controversial if there is an increased prevalence of aphthous ulcers.

Patients often present with firm and palpable cervical lymph nodes, usually seen before the intestinal lesions [8]. Although rare, patients may display pyostomatitis vegetans, which is more commonly associated with ulcerative colitis.

Ulcerative Colitis

Ulcerative colitis is also a chronic immune-mediated inflammatory bowel disease, though it is characterized by continuous lesions of the colon and rectum [9]. Onset of symptoms typically occurs between 15 and 40 years of age and has an equal incidence in men and females. Patients classically present with intermittent diarrhea that is often bloody, rectal urgency, and tenesmus. The degree of symptoms may often be correlated to the extent of colonic involvement. Extraintestinal manifestations can also occur including osteoporosis, arthritis, primary sclerosing cholangitis, uveitis, pyoderma gangrenosum, deep venous thrombosis, and pulmonary embolism [10].

The most common oral manifestation of ulcerative colitis is pyostomatitis vegetans. The vast majority of IBD patients with pyostomatitis vegetans carry the diagnosis of ulcerative colitis versus Crohn's disease. Historically, it was thought to be associated with diseases such as pemphigus and pyodermatitis vegetans, though this has since been disproven [11].

Pyostomatitis vegetans clinically presents as numerous punctate pustular eruptions that are serpentine or linear on the labial and buccal mucosa, palate, and rarely on the ventral tongue and floor of the mouth. The pustules can mature to coalesce and ulcerate, although ulceration is not typically present. Subjective complaints can include pain and sensitivity, with large variability in the amount of discomfort. Symptoms can be acutely managed with corticosteroids. Eruptions can be decreased by improved control of the patient's IBD flares.

Gardner Syndrome (Familial Colorectal Polyposis)

Gardner syndrome, also known as familial adenomatous polyposis (FAP), is an autosomal dominant disorder that includes gastrointestinal polyps, osteomas, tumors, and epidermoid cysts [12].

Gardner syndrome is often identified based on the orofacial presentation. Common oral findings include impacted teeth, multiple supernumerary teeth, odontomas, and osteomas of the maxilla and mandible [12]. Most of these presentations are first observed as incidental findings on dental radiographs and sometimes clinically as a lack of exfoliation of the primary teeth, lack of eruption in the permanent dentition, or expansion of the jaws. Osteomas can grow large enough to cause facial asymmetry, which is most profound during puberty. Other than the physical findings, patients typically deny any subjective complaints.

These classically asymptomatic oral manifestations carry increased importance as they often present before the development of polyps. As these patients have an increased risk of colon cancer, early diagnosis can set up a timely and appropriate screening. Oral surgical management of these patients involves aiding eruption of the impacted teeth, biopsies of lesions to confirm etiology, and may include surgical intervention of osteomas to correct facial asymmetries [13].

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is an autosomal dominant genetic condition characterized by gastrointestinal polyps and mucocutaneous pigmentation [14]. This typically presents as melanotic macules of the hands, perioral skin, and oral mucosa, in conjunction with gastrointestinal hamartomatous polyps and a predisposition for affected individuals to develop various neoplasms [10, 11]. Polyps can be found anywhere in the gastrointestinal tract, though the majority are found in the small bowel and colon. Although uncommon, polyps may also be found in the gallbladder, bronchi, bladder, and ureter [14]. The malignant potential of the polyps is controversial as malignant transformation is rare. Reports have shown that gastrointestinal cancer developed in 9–14% of individuals by age 40 and 33–42% by age 60 [11, 14].

Orofacial manifestations of PJS are often the first presenting sign. In early childhood, patients develop macules around the oral, nasal, anal, and genital orifices, as well as the fingers, toes, and dorsal and volar aspects of the hands and feet. The presence of melanotic macules in PJS is found in 95% of patients. They can range in size from 1 to 4 mm and color from brown to blue-gray. These lesions can fade after puberty, though often the buccal mucosa lesions persist [11, 14].

Treatment for PJS is focused around regular surveillance for polyps with removal as necessary based on size and the corresponding risk of intussusception, bleeding, or concern for malignant transformation. If mucocutaneous pigmentation is esthetically undesirable to a patient, various laser treatments including intense pulsed light (IPL), q-switched ruby laser, and CO2 laser therapy are reported to improve their appearance [11].

Celiac Disease or Gluten Hypersensitivity

Celiac disease is an autoimmune disease that occurs in genetically predisposed people, whereby the ingestion of gluten leads to damage in the small intestine [15]. It is estimated to affect 1 in 100 people worldwide. An estimated 2.5 million Americans are undiagnosed and at risk for long-term health complications.

Patients can present with bullae or ulcerations known as dermatitis herpetiformis. This oral presentation can appear very similar to pemphigoid [15, 16]. For this reason, a biopsy is necessary to aid in the diagnosis and appropriate management. Initiation of a gluten-free diet is critical for more than just patient comfort as untreated disease can lead to type I diabetes mellitus, multiple sclerosis, anemia, osteoporosis, infertility, epilepsy, and migraines. In addition, people with celiac disease have a two times greater risk of developing coronary artery disease and a four times greater risk of developing small bowel cancers.

Endocrine Diseases

Hyperparathyroidism

Hyperparathyroidism is a condition due to the uncontrolled production of parathyroid hormone (PTH). Primary hyperparathyroidism is due to a malfunction of the parathyroid glands, whereas secondary hyperparathyroidism is due to end-stage renal disease (ESRD).

Primary hyperparathyroidism is more likely to manifest in the sixth or seventh decade of life and is three to four times more common in women than men. It is most commonly due to a single parathyroid adenoma. In diseases such as multiple endocrine neoplasia (MEN) Type I, more than one parathyroid is often affected. Rarely it may be due to parathyroid malignancy [17]. Secondary hyperparathyroidism is seen in patients with ESRD. When kidney disease manifests in the bone it is termed renal osteodystrophy.

Whether due to primary or secondary causes, early oral involvement is seen as an alteration of the trabecular bone pattern, which creates a “ground glass appearance.” As the disease process becomes more advanced, non-neoplastic

lesions called Brown tumors may be seen. Brown tumors are giant cell granulomas that are most commonly found in the mandible, clavicle, ribs, and pelvis [17, 18]. Named for the color seen during dissection, they occur in areas of rapid bone turnover. It has been speculated that there is a cycle of hemorrhage followed by infiltration of granulation tissue to displace the bone marrow, resulting in a unique color [3, 4]. Brown tumors are seen in 1.5–13% of patients with chronic renal failures [3, 4].

Both "ground glass" bone and Brown tumors are typically incidental findings found on dental imaging as these lesions are usually asymptomatic. In some cases, Brown tumors may be expansile and can cause symptoms if they put structures at risk or make a patient susceptible to a pathologic fracture. Acute treatment may require surgical removal of the tumor if the location and extent are affecting the dentition or putting critical structures at risk.

Hypoparathyroidism

Hypoparathyroidism is a far rarer condition of the parathyroid and is due to a lack of parathyroid hormone or the presence of the inactive form of the hormone. Most commonly, it is acquired and is the result of surgical removal or damage of the parathyroids. Less commonly, it is due to cancer, extensive radiation therapy to the neck, or as the sequelae of an autoimmune disorder.

There are rare cases of congenital hypoparathyroidism where the disease presents in the first months of life. There are also rare disorders including DiGeorge syndrome, Barakat syndrome, Kenney-Caffey disease, Sanjad-Sakati syndrome, and others that develop hypoparathyroidism.

There are not many oral or facial manifestations of hypoparathyroidism, but if it occurs in early life when teeth are developing patients may present with pitting enamel, enamel hypoplasia, cessation of root development, or failure of tooth eruption [19, 20].

Diabetes Mellitus

Diabetes mellitus is a well-known and increasingly prevalent metabolic disorder characterized by chronic hyperglycemia due to alterations in carbohydrate, protein, and lipid metabolism [21]. The drastic increase in the prevalence of diabetes is now being considered a global epidemic.

This section will not attempt to discuss the pathogenesis, multitude of clinical presentations and symptoms, and complications associated with diabetes. Diabetes can affect every organ in the body. It is well known that patients with diabetes have impaired polymorphonuclear leukocytes, bactericidal activity, T cells, and response to antigen challenge [22, 23]. The amount and severity of manifestations and complications associated with diabetes are generally proportional to a patient's glycemic control.

There are several oral manifestations including xerostomia and altered taste, hyperplasia of attached gingiva, and an increased incidence of periodontal disease [3, 21]. Diabetic patients are predisposed to poor healing and an increased risk of infections, which can correlate to increased dental infections. This is supported by the literature as patients have an increased prevalence of periapical pathology. Diabetes itself does not predispose patients to an increased risk of caries or candidiasis; however, patients often demonstrate a higher caries risk and a predisposition to candida infections due to decreased salivary secretions and xerostomia [3, 21]. A rare orofacial manifestation can be benign parotid hypertrophy, referred to as diabetic sialadenosis. It is typically seen in elderly patients and presents as irreversible diffuse, non-tender, bilateral enlargement of the parotid glands [3, 23].

Treatment of all diabetic patients should first be centered around establishing glycemic control and preventing future end-organ complications. As the main oral complications are periodontal disease and an increased incidence in periapical pathology, reinforcement of oral hygiene and regular dental visits are important.

Cushing's Syndrome

Cushing's syndrome is a disorder that results from chronic exposure to excess glucocorticoids. It is more commonly due to exogenous steroid use than from an endogenous source. Endogenous causes can be related to excess production of adrenocorticotropic hormone (ACTH), which is most commonly secondary to a pituitary adenoma termed Cushing's disease. Less common causes of ACTH overproduction are tumors that cause increased levels of corticotrophin-releasing hormone (CRH), including extra pituitary tumors, medullary thyroid carcinoma, neuroendocrine tumors, and pheochromocytoma. Endogenous causes can also be related to excess cortisol production from adrenal adenoma, adrenal carcinoma, macronodular or micronodular adrenal hyperplasia, and McCune-Albright syndrome [24, 25].

Cushing's syndrome should be considered when patients present with unusual or severe features such as hypertension in a healthy young adult, medication-resistant hypertension, osteoporosis, increased weight, or proximal muscle weakness. Other findings may include, but are not limited to headaches, delayed sexual development, violaceous striae, bruising, and acanthosis nigricans.

Orofacial manifestations include facial plethora due to fatty deposition that is often referred to as "moon facies" [3, 24]. Patients may present with variable facial acne and hirsutism.

Treatment depends on the etiology of the syndrome but may include surgery, radiotherapy, pharmaceuticals, or a combination of some of these measures.

Addison's Disease

Addison's disease, also known as primary adrenal insufficiency, is a disorder that occurs when the adrenal glands do not make adequate amounts of the hormones cortisol and aldosterone. It is most commonly due to autoimmune disease but can also be caused by tuberculosis, cancer, bleeding into the adrenals, genetic disorders, and some medications. It is a relatively rare disorder, most often presenting between the ages of 30 and 50, and is more common in women [26, 27].

Patients classically present with chronic fatigue, muscle weakness, loss of appetite, weight loss, and abdominal pain. Less common symptoms can include nausea, vomiting, diarrhea, hypoglycemia, hypotension, joint pain, irregular or lack of menstruation, and decreased libido. Patients may also present with mucocutaneous hyperpigmentation, known as "bronzing" [11]. This can be seen in areas of sun exposure and friction, recent scars, and the vermillion border of the lips [11, 28].

Oral manifestations include mucosal hyperpigmentation. It presents as either diffuse or patchy brown macular pigmentation on the buccal mucosa, gingiva, and tongue. Where the skin hyperpigmentation often presents as a later finding, oral pigmentation can be an early finding [11].

Early diagnosis will allow for early treatment with corticosteroid replacement therapy and result in a good prognosis. Without treatment, Addison's disease can be fatal.

Infectious Diseases

Human Immunodeficiency Virus (HIV)

Human immunodeficiency virus (HIV) is a well-known lentivirus that can progress to acquired immunodeficiency syndrome (AIDS). The pathogenesis, clinical features, and treatment regimens will not be discussed in this section.

Oral manifestations of HIV are often indicative of disease control and prognosis. Studies have shown that 70–90% of patients infected with HIV will develop at least one oral manifestation [29]. When any of these oral findings are seen there should be a low threshold to recommend HIV testing [11]. The most common oral manifestations are candida infections, melanotic hyperpigmentation, oral hairy leukoplakia, and Kaposi's sarcoma.

Oral candidiasis is the most common opportunistic infection seen in HIV [11]. All four forms can be seen: pseudomembranous, hyperplastic, erythematous, and angular cheilitis. Pseudomembranous candidiasis, or "thrush" is the most prevalent form. It presents as a wipeable whitish creamy curd-like plaque usually seen on the buccal mucosa and tongue. It can also be seen on the hard palate, soft palate, and oropharynx [29]. When the plaque is wiped away, the tissue underneath reveals erythematous, bleeding mucosa. Hyperplastic candidiasis is a white plaque that is more adherent and non-wipeable. It can be found on the buccal mucosa or the commissures of the oral mucosa. Erythematous candidiasis presents as flat red lesions seen on the dorsal tongue or palate. The last form of candidiasis is angular cheilitis, which presents as erythematous fissured patches at the commissures of the mouth. Acutely ill patients can be prescribed nystatin oral suspension, clotrimazole troches, or nystatin pastilles. For more severe cases, they may require systemic fluconazole. Since candida infections typically correlate to poor control, adequate anti-retroviral treatment typically results in the resolution of most candida infections and prevents future outbreaks.

Oral hairy leukoplakia is a non-wipeable white plaque due to Epstein Barr virus (EBV) that presents on the lateral border of the tongue. It is seen in 9–25% of HIV patients. It can be found unilaterally or bilaterally. Patients are typically asymptomatic, though can present with complaints of sensitivity and burning. It can be confused with the aforementioned hyperplastic candidiasis, but it will not resolve with antifungals. Patients may undergo surgical excision of the lesion although it can be successfully treated with acyclovir.

Kaposi's sarcoma (KS) is a malignant lesion that arises from vascular endothelium [11]. As HIV has become better managed and controlled, Kaposi's sarcoma has become a rare finding. Their importance remains, however, as these lesions can be the first indication of unknown HIV disease [13] and are often first identified in the mouth [11]. They appear initially as red lesions that mature into blue-purple lesions that can become ulcerated and papular. They are most commonly found on the attached gingiva, tongue, or palate [10]. Bone loss can occur, which may result in dental pain, tooth migration, or tooth mobility. The presence of Kaposi's sarcoma is a sign of worsening disease and is associated with an increased risk of mortality. All lesions in HIV should undergo a biopsy for definitive diagnosis. Treatment in the setting of KS is first to ensure adequate antiviral treatment is being given. The lesion can then be treated with surgical excision, intralesional or systemic chemotherapy, sclerotherapy, or radiation [11].

Rheumatologic, Dermatologic, and Skeletal Diseases

Sjogren's Syndrome

Sjogren's syndrome is a disorder that causes chronic inflammation of the salivary and lacrimal glands due to lymphocytic infiltration, leading to ocular and oral dryness. It is the

second most common autoimmune disease and the most common connective tissue disease [30]. It typically affects patients between 50 and 60 years of age and is ten times more likely to be found in women than men. Despite its prevalence, diagnosis can be difficult as patients present with a multitude of symptoms and clinical testing is difficult.

The chief complaint of patients with Sjogren's is xerostomia. Patients often report increased intake of fluids. The other common complaint is dry or gritty eyes. About 30–50% of patients present with extra-glandular involvement, which includes nonerosive polyarthritis, neuritis, skin manifestations of small vessel vasculitis, interstitial lung disease, and interstitial neuropathies [30].

Oral manifestations are paramount in Sjogren's syndrome as xerostomia is the most common subjective complaint and objective finding. Many of the other oral manifestations are secondary to low salivary volumes, such as dysphagia, dyspepsia, difficulty in eating and speaking, and an increased risk of caries. Patients may also present with a bald tongue or a cobblestone appearance of the tongue due to atrophy of the papilla, cracking, and fissuring of the tongue, and secondary erythema. These findings often correlate with increased sensitivity and pain. Patients also carry an increased risk of intraoral fungal infections, specifically candida.

Patients may also present with salivary gland enlargement due to inflammation. The parotid gland is most commonly affected. There has also been an increased risk of suppurative sialadenitis, which is also thought to be secondary to inflammation and resulting obstruction.

Sjogren's syndrome is a potentially malignant disorder. Patients are 44 times more likely to develop a primary lymphoma [13]. The most common lymphoma is a low-grade marginal zone lymphoma (MALT), but diffuse B cell lymphomas, as well as lymphoplasmacytic lymphoma, have also been seen [13].

Although complaints of dry eyes and mouth are a common complaint of the general public, the vast majority certainly do not carry a diagnosis of Sjogren's disease. Practitioners should have a low threshold to recommend a biopsy of the minor salivary glands in the lower lip, especially when there are signs and symptoms of potential extra glandular involvement [29]. Currently, there is no cure, but treatment is aimed at decreasing symptoms and improving the quality of life with artificial tear eye drops and saliva substitutes. Due to the increased risk of caries, oral hygiene and routine dental care should be recommended [10, 30, 31].

Kawasaki Disease

Kawasaki disease (KD) is one of the most common pediatric vasculitides. It affects 10 out of 100,000 children, typically under the age of five, with a strong predilection for males [18, 32]. The known trigger in 40% of these cases was a concurrent infection. Infections are bacterial or viral and can be local or systemic [33]. KD primarily affects medium-sized muscular vessels with the coronary arteries being the most severely affected.

Patients present similarly to inoculation with an infectious disease with the development of a rash, mucosal inflammation, and extremity changes [32]. Diagnosis is made when a child has a fever lasting 5 days or more in addition to four of the five diagnostic criteria. The criteria include bilateral conjunctival injection, a primarily truncal polymorphous exanthema, acute cervical lymphadenopathy, peripheral extremity edema or erythema, and oral mucosal changes.

The oral manifestations include injected or fissured lips, an injected pharynx, or a "strawberry tongue." [3, 32]. A "strawberry tongue" appears as an erythematous and edematous tongue that has sloughed the filiform papillae but has hypertrophic fungiform papillae. Other oral findings may be present such as oral vesicles or ulcers as well as tonsillar exudates; however, these are not correlated to KD but are likely the result of the concurrent infection.

Patients are admitted to the hospital and treated with IVIG and aspirin. Prompt identification and treatment are critical as therapy within the first 10 days reduces the incidence of coronary artery aneurysms by 70% [32]. KD remains the primary cause of acquired childhood heart disease in the United States [3, 32, 33].

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a well-known complex autoimmune disease that involves both immune complexes and other immune processes as a reaction to multiple autoantibodies. Its disease process waxes and wanes and carries a large range of manifestations that have many different effects on the quality of life.

Classically the first symptoms to present are constitutional, mucosal and cutaneous, and musculoskeletal signs. Any organ can become affected resulting in numerous processes including a photosensitive rash, arthritides, avascular necrosis, lupus nephritis, mesenteric vasculitis and thrombosis, pleuritis, valvular heart diseases, seizures, and cerebrovascular disease [34–36].

It is very common for patients to have oral manifestations. They are seen in 5–35% of people and are not infrequently the first sign of disease [10, 11, 35]. The most common lesions seen are white plaques and ulcerations that display a "sunray pattern" [2]. The "sunray pattern" clinically appears as a white plaque with central erythema and peripheral keratotic striae [35]. These lesions can be easily confused with lichen planus and therefore a biopsy is recommended [3, 10]. Granulomatous lesions are also observed and have a predilection for the palate versus the buccal mucosa and gingiva

[3, 13]. 70% of lupus patients are diagnosed with periodontitis [35]. Patients carry a higher risk for candida infections [36].

The management of SLE is complex and patients continue to carry a high risk of morbidity and mortality despite multiple treatment modalities. Supportive care remains important, which includes regular dental care and surveillance for lesions. If ulcerative plaques are observed they should be biopsied for definitive diagnosis.

Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is a common autoimmune disease for which the pathogenesis is still not well understood. With a 1% prevalence, it typically presents between the ages of 35 and 45 and is two times more likely in women than men. The disease is characterized by synovial inflammation and hyperplasia, autoantibody production, and cartilage and bony destruction. Systemic features associated with RA include fatigue, reduced cognitive function, anemia of chronic disease, lung inflammation and fibrosis, secondary Sjogren's syndrome, sarcopenia, and osteoporosis. Patients carry increased rates of myocardial infarction, cerebrovascular events, heart failure, and lymphoma [37].

The most common joints affected are the metacarpophalangeal and proximal interphalangeal joints of the hands followed by the metatarsophalangeal joints of the feet. Patients usually demonstrate early morning stiffness that improves as the day goes on. As many as 30% of patients develop rheumatoid nodules on the extensor aspect of their elbows.

The temporomandibular joints (TMJ) can be affected by RA in up to 40% of patients although there is a wide variety in the prevalence reported in the literature [3, 37]. The likelihood is correlated with the severity and duration of the disease. The most common signs and symptoms include joint pain, edema, crepitus, and trismus. Radiographs can demonstrate condylar head flattening and erosion, articular fossa erosion, and a decreased joint space [37]**.** Typically, the involvement is bilateral and is found later in the disease progression. Treatment of TMJ findings depends on the severity of the disease and the patient's symptoms. It can range from nonsurgical support including disease management, NSAIDS, heat, and diet modifications to bilateral total joint replacement. Patients who are diagnosed with RA that have any of the common symptoms or signs should be referred to an oral and maxillofacial surgeon or TMJ specialist for evaluation and treatment as indicated.

Pemphigus

Pemphigus is an autoimmune bullous disease mediated by IgG autoantibodies directed against desmogleins that result in acantholysis and intraepidermal blister formation [38]. There are three distinct forms: pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus. Patients most commonly present from 40 to 60 years old and are more commonly female. The incidence varies geographically and among countries; however, pemphigus vulgaris is typically the most common whereas paraneoplastic pemphigus is rare.

Pemphigus vulgaris (PV) is the most common immunobullous disease and is considered the mucosal-dominant type [8, 38]. About 95% of all cases present with oral manifestations that are most commonly superficial bullae that become painful, erosive ulcerations, and are found most commonly on the palatal, lingual, and buccal mucosa [13]. Although less common, erosive lesions can also be seen on the tongue and gingiva, which presents as desquamative gingivitis. Oral lesions are the first site affected in 50% of patients [11]. Other mucosal surfaces that can become affected include the laryngeal mucosa, nasopharynx, esophagus, conjunctiva, anus, and vagina [38]. Patients can develop cutaneous lesions on the upper trunk, axilla, groin, and surfaces that undergo mechanical friction, which elicits a response similar to the Nikolsky sign. Cutaneous lesions are also present as flaccid blisters that evolve into erosions.

Pemphigus foliaceus affects the skin only and therefore oral manifestations are not seen.

Paraneoplastic pemphigus (PNP) is consistent with pemphigus vulgaris but in the setting of systemic malignancy. The most common associated cancers are hematologic malignancies such as NHL, CLL, and Castleman's disease. Although less common, sarcomas, lung cancer, and oral squamous cell carcinoma have also been associated with PNP. The presentation is similar to pemphigus vulgaris, but the oral mucosal lesions are more commonly seen on the vermillion border of lips, labial mucosa, and lateral borders of the tongue [13, 38]. PNP mucosal lesions tend to involve the pharynx and larynx first [13]. Cutaneous lesions vary more than in PV and may present as the classic blisters and erosion but can also present as papules, erythema multiforme-like target lesions, lichenoid lesions, scales, and pustules [38]. Nail and periungual erosions and scaling are commonly seen as well.

Diagnosis for PV and PNP often relies on a biopsy of the oral lesions, where both histopathology and immunofluorescence are used. Therefore, awareness of a patient's oral complaints, acknowledgment of clinical findings, and prompt biopsy help establish an early diagnosis. PV has a wide variety in the severity of presentation, but disease control can often be achieved with early detection and long-term steroid therapy [11, 37]. PNP has a poor prognosis with a 5-year survival of 38% [37]. The treatment goal is to control disease activity. First-line therapy involves systemic corticosteroids that are tapered to the lowest minimal dose. When this is not successful, immunosuppressive agents are administered.

Pemphigoid

Pemphigoid is an autoimmune bullous disease mediated by IgG autoantibodies directed against hemidesmosomes that result in subepidermal blister formation [38]. The most common subtype is bullous pemphigoid, followed by mucous membrane pemphigoid, and epidermolysis bullosa acquisita. The disease commonly presents in patients 70 to 80 years of age and does not have a sex predilection.

Bullous pemphigoid (BP) presents predominantly on the abdomen and limb flexures as pruritic tense blisters that develop after crusting erythema. Oral manifestations are seen in 15% of patients and include bullae and ulcerations of palatal, buccal, or lingual mucosa. Similar to PV, patients can develop desquamative gingivitis [11, 38].

Mucous membrane pemphigoid (MMP) presents predominantly on the oral mucous membranes followed by the nasopharyngeal, laryngeal, esophageal, and genital mucosa [38].

Epidermolysis bullosa acquisita (EBA) is more similar to BP but instead presents on the extensor surface of extremities. Lesions consist of tense blisters that evolve into erosions that tend to leave scars and milia.

Similar to pemphigus, diagnosis of pemphigoid often relies on a biopsy that is sent for histopathology and immunofluorescence. The specimen may come from oral tissues. The treatment utilizes both systemic and topical corticosteroids to help prevent antibody production and decrease inflammation. In severe cases, immunosuppressants, plasmapheresis, and IVIG can be used [38].

Paget's Disease (Osteitis Deformans)

Paget's disease of the bone is a metabolic disorder of unknown etiology due to a defect in osteoclasts that results in disorganized bone turnover. It is the second most common metabolic disorder of the bone after osteoporosis [39]. There are two types based on the number of bones involved: monostotic and polyostotic. It typically presents in patients aged 55 years and older.

Most patients remain asymptomatic and are diagnosed by an incidental laboratory finding of increased alkaline phosphatase or an incidental radiographic finding. When patients have symptoms, they can include bone pain that worsens with movement, bony deformities, decreased hearing, nerve pain, and headache. Clinical findings can include long bone deformities causing gait changes, increased risk of fractures, an enlarged skull causing dizziness and vertigo, hearing loss, spinal stenosis or compression fractures, and nerve compression. Patients carry an increased risk of osteosarcomas, giant cell tumors, high output heart failure, aortic septum, and calcification of the interventricular septum which can progress to cause a complete atrioventricular block [39].Oral manifestations include incidental radiographic findings, which characteristically present as a "cotton wool" appearance. Patients may also present with increased spacing between their teeth as the bone increases in size. If a patient is edentulous, they may present with a denture that no longer fits due to increased bone [10]. Excision or alveoloplasty is not indicated due to the concern for developing osteomyelitis.

Most patients do not require treatment, but when needed bisphosphonates are the pharmaceutical therapy of choice.

Hematologic and Oncologic Diseases

Iron Deficiency Anemia and Plummer Vinson Syndrome

Iron deficiency anemia is the most common and most treatable cause of anemia worldwide. The primary etiology is due to blood loss, which most commonly is from menstruation and gastrointestinal bleeding. Other causes can be due to issues with iron absorption or an iron-poor diet. The incidence in the United States reflects this etiology, as only 1% are male, whereas 11% or more are females [40].

Patients may present with symptoms due to anemia or low iron. Common symptoms include fatigue, tachycardia or other arrhythmias, and cold intolerance. There are multiple possible oral manifestations including angular cheilitis, atrophic glossitis, mucosal pallor, and generalized atrophy of the oral mucosa [3]. Atrophic glossitis is the flattening and loss of both fungiform and filiform papillae. Due to the denuding of their tongue, patients often present with a subjective complaint of a burning sensation. Atrophic glossitis can sometimes appear similar to a variant of normal called "geographic tongue." It can be differentiated by observing the pattern, as atrophic glossitis stays the same while the geographic tongue will shift [10, 18].

Plummer-Vinson syndrome is a rare condition that has become even rarer in the setting of improvement in hygiene, improved nutrition, and vitamin supplementation. This syndrome has a classic triad of iron deficiency anemia, dysphagia, and cervical esophageal webs. It most commonly presents in middle-aged Caucasian females [41]. These patients may first present with pain on swallowing before developing dysphagia. Other than the oral manifestation found in iron deficiency anemia, there can be atrophy of the hypopharynx and esophagus, enlargement of the thyroid, and koilonychia nail formation [10, 11]. Prompt diagnosis is imperative as there is a 3–15% increase in the incidence of malignancies especially oral and esophageal cancers [41, 42].

There is no specific oral management in either case, but recommendations can be made to decrease the patient's symptoms. Good oral hygiene habits and the removal of irritants such as spicy food will decrease the sensitivity associated with

glossitis. Topical ointments such as thick emollient and sometimes antifungal or bacteria ointments can be used to decrease the symptoms associated with angular cheilitis.

Pernicious Anemia

Pernicious anemia is a complex multifactorial disorder that has hematologic, gastric, and immunologic origins. The most common cause is cobalamin (also known as vitamin B12) deficiency [43, 44]. It most commonly presents in patients older than 60 due to a decrease in intrinsic factor and acid. People who have an autoimmune disorder, dietary restrictions, have undergone bowel resection, or carry the diagnosis of IBD are also at increased risk and may develop pernicious anemia at a younger age.

Patients may present with symptoms of anemia as described in the previous section. They can also present with neurologic symptoms due to B12 deficiency such as tingling and numbness or even a loss of reflexes in the hands or feet. Gastric symptoms are also seen and include nausea, vomiting, reflux, bloating, constipation or diarrhea, and weight loss. Patients with pernicious anemia often present with a classic oral manifestation termed "magenta tongue." The findings include erythema and atrophy of the papillae on the dorsal tongue. As seen with other cases of glossitis, patients may present with pain and burning.

Pernicious anemia is well managed with oral or intravenous B12 supplementation when caught before causing heart or nerve damage.

Langerhans Cell Histiocytosis (LCH)

Langerhans cell histiocytosis is a disorder characterized by aberrant function and differentiation or proliferation of cells of the mononuclear phagocyte system [45]. LCH is more commonly diagnosed in children than adults. Annually, it affects 4.6 per one million children and 1–2 per one million adults, with a slight predilection for males. When it does present in adults it is typically in the fourth decade and at this point already has multisystem involvement. The disease is classified based on the site of lesions, the number of sites, and if a high-risk organ is involved. There is an association with other myeloproliferative neoplasms [46].

Granulomatous lesions may arise anywhere but have an affinity for bone, skin, the lungs, and the pituitary. Liver, spleen, and bone marrow involvement carry a poor prognosis. Patients may present with a wide variety of symptoms depending on the organs affected. The bony skeleton is the most affected system with the most common sites of involvement being the skull, spine, extremities, and pelvis. Bone lesions are seen in 80% of patients diagnosed with LCH.

Oral manifestations depend on the age of the patient. In children, alveolar bone loss occurs resulting in the premature loss of primary teeth. In the setting of a lack of caries, periodontal disease, and an undeveloped permanent dentition successor, this should raise suspicion for LCH [3]. There are a wider variety of oral manifestations seen in adults. Bone lesions that may occur in the mandible are described as lytic lesions without marginal sclerosis, with or without a periosteal reaction. Other common areas of the skull that are affected are the orbit and the temporal bone, more specifically the mastoid process [46, 47]. Patients may also present with large ulcerations with underlying exposed bone, oral ecchymoses, gingivitis, periodontitis, tooth rotation, and tooth loss.

Intraoral lesions should be biopsied for definitive diagnosis even in the setting of an already-known diagnosis of LCH. Treatment consists of multiple-agent chemotherapy. Historically, the prognosis for the disease has improved, although its success in high-risk disease is less than 50%, and about 50% of survivors have at least one permanent consequence [46].

Sickle Cell Disease

Sickle cell disease is a multisystem disorder mediated by hemolytic anemia and vaso-occlusion [11, 48]. Nearly every organ can be affected by vaso-occlusive events. Chronic complications are caused by large vessel vasculopathy and may result in cerebrovascular disease, pulmonary hypertension, priapism, and retinopathy. Chronic complications can also arise from progressive ischemic damage, which may result in renal failure, bone disease, liver damage, and hyposplenism, which carries a severe risk for illness and infection.

The most common oral manifestation, as with other anemias, is oral mucosal pallor and atrophy of the tongue papilla. Since hemolytic anemia can cause an increase in bilirubin, the oral mucosa can also be a generalized yellow color. This change is typically most prominent on the soft palate and lingual frenum. Dental findings may include delayed tooth eruption, changes in the composition of the dentin and enamel, as well as an increased caries risk [11, 49]. Vaso-occlusive events, although uncommon, can result in loss of sensation to the chin, lip, and teeth in the distribution of the inferior alveolar nerve. This is thought to be secondary to the occlusion of the supporting branches of the inferior alveolar nerve. Patients are at an increased risk for systemic osteomyelitis [11]. Although uncommon to have head and neck osteomyelitis, when it does occur it typically is in the posterior mandible. Incidental findings can be seen on radiographs including loss of alveolar bone height, generalized osteoporotic appearance, and radiopaque lesions. The radiopaque

lesions are thought to be secondary to areas of vaso-occlusive infarcts [11, 49].

No specific treatment or biopsy is indicated for the oral manifestations of sickle cell disease, but good oral hygiene and routine dental care should be enforced due to the increased risk of caries. Overall, clinical outcomes have improved due to early diagnosis and treatment with hydroxyurea [48].

Multiple Myeloma

Multiple myeloma is a systemic malignant disease of the blood characterized by the uncontrolled proliferation of monoclonal plasma cells in the bone marrow [50]. It accounts for about 1% of all cancers and about 10–15% of all hematologic malignancies. It is considered a single disease but in reality, is a collection of cryogenically distinct plasma cell malignancies. The onset of multiple myeloma classically occurs when a patient is 45 years or older. Multiple myeloma is diagnosed by the presence of one or more myeloma-defining events such as end-organ damage, hypercalcemia, renal insufficiency, anemia, or bone lesions, as well as 10% or more clonal plasma cells or a biopsy-proven plasmacytoma [51].

There is no classic presentation of multiple myeloma. Patients may present with complaints of bone pain, fatigue, and weight loss. Diagnostic workup reveals anemia of unknown origin in about 75% of patients and impaired renal function.

Multiple myeloma can have multiple oral manifestations, which can be the first sign of disease, although typically when oral lesions appear it is in the later stage of the disease [3, 52]. Approximately 30% of patients have been found to have oral lesions [17, 52]. Common manifestations include pain, swelling, numbness, mobility or migration of teeth, and soft tissue tumors [52]. Bony lesions present as osteolytic lesions of the jaws without definitive cortical margins. They are most commonly located in the mandible and may be described as "punched-out" areas. The most common location of involvement is the posterior mandible. These lesions can become extensive enough that they cause numbness, mobility of teeth, and even pathologic fractures. Oral manifestations are also present in the soft tissues including mucosal pallor due to anemia, soft tissue swellings at sites of gingival inflammation, and macroglossia due to amyloid deposits in the tongue [2, 52].

Early diagnosis may lead to a better outcome and therefore surveillance of the oral environment and routine dental radiographs for these findings is critical. The relative 5-year survival rate for patients diagnosed with multiple myeloma is about 45%. Survival has improved significantly in the last 15 years due to the advance in numerous regimens and stem cell transplantation.

Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma (NHL) represents 90% of all lymphomas and is defined as solid tumors of the immune system [53]. NHL presents most of the time in patients who are 60 years old or more with a roughly even distribution between men and women. Increased risks of developing NHL include immunosuppression from HIV, chemotherapy, immunodeficiency syndromes, and autoimmune diseases. For example, Sjogren's patients are 44 times more likely to develop a primary lymphoma, which is most commonly located in the parotid [10].

Non-Hodgkin lymphoma has multiple histologic presentations and therefore a varied clinical presentation, which can make diagnosis very difficult. Typically, presentation depends on the site of involvement, lymphoma subtype, and whether B cell symptoms are present [53]. Two-thirds of patients present with asymptomatic lymphadenopathy, whereas the other third often present with B cell symptoms including weight loss, night sweats, or fever [53, 54]. Extranodal lymphomas make up only 24% of lymphomas [11].

Non-Hodgkin lymphoma of the orofacial regions is very uncommon but has been seen in both the bone and soft tissue. Sites have included the tongue, gingiva, hard palate, maxilla, mandible, Waldeyer's ring, as well as the palatine and lingual tonsils [55]. Typically, these lesions present as an asymptomatic mass with intact or ulcerated mucosa [13, 55]. If there is bony involvement, patients may present with mobile teeth or paresthesia as it effaces the bone [13].

Intraoral lesions whether a mass, ulcer, or bony lesion should be evaluated by a specialist and undergo biopsy. Timely diagnosis is imperative as there are many effective and curative therapies for certain subtypes.

Leukemia

Leukemias are a group of malignant disorders of the blood and bone marrow. They are classified by the progenitor cell involved and whether the disease follows an acute or chronic course. Acute leukemias are most commonly seen in children, adolescents, and young adults [56, 57]. Common symptoms displayed by patients with leukemia include fever, chills, fatigue or weakness, frequent infections, weight loss, lymphadenopathy, splenomegaly, or hepatomegaly. Specific signs and symptoms depend on the type of leukemia.

Oral manifestations are relatively common findings in patients diagnosed with leukemia but are more prevalent in the acute and myeloid types [58]. As patients with leukemia are anemic, mucosal pallor may be present. Patients are

often thrombocytopenic and therefore may demonstrate multiple petechiae—typically found on the hard and soft palate, tongue, or lips. Although less common, ecchymoses of the oral tissues may also be seen [3, 58]. When thrombocytopenia is severe, spontaneous gingival bleeding can occur. Ulcerations are also found more frequently and are thought to be due to neutropenia versus direct malignant infiltration [58]. About 10% of cases show signs of leukemic infiltrate that presents as generalized hyperplasia of the gingiva. Gingiva will appear boggy, edematous, and erythematous [3]. Rarely in patients diagnosed with acute myeloid leukemia (AML), patients may develop oral extramedullary myeloid sarcomas which present as solitary masses.

Intraoral lesions whether a mass or ulcer should be evaluated by a specialist and undergo biopsy for definitive diagnosis.

Malignancy

Malignant lung diseases such as small cell carcinoma and bronchogenic carcinoma can be associated with oral pigmentation, with as high as 25% of patients developing pigmentation of the lateral soft palate [3]. Although the most common site is the soft palate, it can be seen anywhere on the oral mucosa. Lesions can range from a single macule to multiple lesions.

Metastatic Disease

Nonhematopoietic neoplasms rarely metastasize to the oral cavity, representing only 1% of oral malignant lesions. The majority of metastases come from primary sites such as the breast, kidney, prostate, colon, and lung [10]. The lesions are more common in the bone than in the soft tissues [3]. The most common location is adjacent to the molar teeth. Initially, bony metastases may be asymptomatic. As the lesions spread, they may cause expansion, pain, and paresthesia. When the lesion spreads to involve the alveolar bone, the teeth nearby may become symptomatic or mobile. Metastases of the soft tissue typically appear as hyperplastic lesions with or without ulceration.

Summary

Many systemic diseases have oral manifestations, and in fact may be the first presentation of a disease. Close attention to an oral examination can lead to early detection and diagnosis. Additionally, the oral manifestations may help in assessing systemic treatment modalities.

References

1. Lockhart PB, Hong CH, van Diermen DE. The influence of systemic diseases on the diagnosis of oral diseases: a problem-based approach. Dent Clin N Am. 2011;55(1):15–28. https://doi.org/10.1016/j.cden.2010.08.003.
2. Lamprecht P, Gross WL. Wegener's granulomatosis. Herz. 2004;29(1):47–56. https://doi.org/10.1007/s00059-004-2525-0.
3. Islam NM, Bhattacharyya I, Cohen DM. Common oral manifestations of systemic disease. Otolaryngol Clin N Am. 2011;44(1):161–82, vi. https://doi.org/10.1016/j.otc.2010.09.006.
4. Neville D, Allen B. Oral and maxillofacial pathology. 3rd ed. Philadelphia, PA: Saunders; 2009.
5. Llanos O, Hamzeh N. Sarcoidosis. Med Clin North Am. 2019;103(3):527–34. https://doi.org/10.1016/j.mcna.2018.12.011. Epub 2019 Feb 21.
6. Redissi A, Penmetsa GK, Litaiem N. Lupus Pernio. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2021.
7. James DG, Sharma OP. Parotid gland sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2000;17(1):27–32.
8. Feuerstein JD, Cheifetz AS. Crohn disease: epidemiology, diagnosis, and management. Mayo Clin Proc. 2017;92(7):1088–103. https://doi.org/10.1016/j.mayocp.2017.04.010. Epub 2017 Jun 7.
9. Adams SM, Bornemann PH. Ulcerative colitis. Am Fam Physician. 2013;87(10):699–705.
10. Colitis Add-Langan RC, Gotsch PB, Krafczyk MA, Skillinge DD. Ulcerative colitis: diagnosis and treatment. Am Fam Physician. 2007;76(9):1323–30. Erratum in: Am Fam Physician. 2008 Apr 15;77(8):1079.
11. Parks ET, Lancaster H. Oral manifestations of systemic disease. Dermatol Clin. 2003;21(1):171–82. https://doi.org/10.1016/s0733-8635(02)00066-9, viii.
12. Bhalla N, Nudell Y, Thakkar J, Dym H. Oral manifestation of systemic diseases. Dent Clin N Am. 2020;64(1):191–207. https://doi.org/10.1016/j.cden.2019.08.016; Epub 2019 Oct 22.
13. Digman SW, Abramowicz S. Pediatric dentoalveolar surgery. Dent Clin N Am. 2012;56(1):183–207. https://doi.org/10.1016/j.cden.2011.09.002; ix.
14. Beggs AD, Latchford AR, HFA V, et al. Peutz–Jeghers syndrome: a systematic review and recommendations for management. Gut. 2010;59:975–86.
15. https://celiac.org/about-celiac-disease/what-is-celiac-disease/.
16. Porter SR, Mercadante V, Fedele S. Oral manifestations of systemic disease. Br Dent J. 2017;223(9):683–91. https://doi.org/10.1038/sj.bdj.2017.884.
17. Bilezikian JP. Primary hyperparathyroidism. In: De Groot LJ, Chrousos G, Dungan K, et al., editors. Diseases of bone and mineral metabolism. South Dartmouth, MA: MDTEXT.COM, Inc; 2017. p. 2000–18. https://www.ncbi.nlm.nih.gov/books/NBK278923/. Accessed 6 June 2018.
18. Bradley G, Magalhaes MA. Oral manifestation of systemic diseases-a perspective from an oral pathology diagnostic service. Oral Dis. 2018;24(1–2):219–23. https://doi.org/10.1111/odi.12751.
19. Walls AW, Soames JV. Dental manifestations of autoimmune hypoparathyroidism. Oral Surg Oral Med Oral Pathol. 1993;75(4):452–4. https://doi.org/10.1016/0030-4220(93)90169-5. Erratum in: Oral Surg Oral Med Oral Pathol 1993 Jun;75(6):779.
20. Kelly A, Pomarico L, de Souza IP. Cessation of dental development in a child with idiopathic hypoparathyroidism: a 5-year follow-up. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;107(5):673–7. https://doi.org/10.1016/j.tripleo.2008.11.017. Epub 2009 Feb 8.
21. Mauri-Obradors E, Estrugo-Devesa A, Jané-Salas E, Viñas M, López-López J. Oral manifestations of diabetes mellitus. A systematic review. Med Oral Patol Oral Cir Bucal. 2017;22(5):e 586–94. https://doi.org/10.4317/medoral.21655. PMID: 28809366; PMCID: PMC5694181.

22. Duncan BB, Schmidt MI, Pankow JS, Ballantyne CM, Couper D, Vigo A. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. Diabetes. 2003;52:1799–805.
23. Kudiyirickal MG, Pappachan JM. Diabetes mellitus and oral health. Endocrine. 2015;49(1):27–34. https://doi.org/10.1007/s12020-014-0496-3. Epub 2014 Dec 9.
24. Lacroix A, Feelders RA, Stratakis CA, Nieman LK. Cushing's syndrome. Lancet. 2015;386(9996):913–27. https://doi.org/10.1016/S0140-6736(14)61375-1. Epub 2015 May 21.
25. Raff H, Carroll T. Cushing's syndrome: from physiological principles to diagnosis and clinical care. J Physiol. 2015;593(3):493–506. https://doi.org/10.1113/jphysiol.2014.282871. Epub 2015 Jan 5. PMID: 25480800; PMCID: PMC4324701.
26. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(2):364–9.
27. Chabre O, Goichot B, Zenaty D, Bertherat J. Group 1. Epidemiology of primary and secondary adrenal insufficiency: prevalence and incidence, acute adrenal insufficiency, long-term morbidity and mortality. Ann Endocrinol (Paris). 2017;78(6):490–4.
28. Nieman LK, Chanco Turner ML. Addison's disease. Clin Dermatol. 2006;24(4):276–80. https://doi.org/10.1016/j.clindermatol.2006.04.006.
29. Millsop JW, Fazel N. Oral candidiasis. Clin Dermatol. 2016;34(4):487–94. https://doi.org/10.1016/j.clindermatol.2016.02.022. Epub 2016 Mar 2.
30. Witte T. Sjögren-Syndrom [Sjögren's syndrome]. Z Rheumatol. 2019;78(6):511–7. https://doi.org/10.1007/s00393-019-0625-8.
31. Chen X, Wu H, Wei W. Advances in the diagnosis and treatment of Sjogren's syndrome. Clin Rheumatol. 2018;37(7):1743–9. https://doi.org/10.1007/s10067-018-4153-8. Epub 2018 May 26
32. Sundel RP. Kawasaki disease. Rheum Dis Clin N Am. 2015;41(1):63–73, viii. https://doi.org/10.1016/j.rdc.2014.09.010.
33. Benseler SM, McCrindle BW, Silverman ED, Tyrrell PN, Wong J, Yeung RS. Infections and Kawasaki disease: implications for coronary artery outcome. Pediatrics. 2005;116(6):e760–6. https://doi.org/10.1542/peds.2005-0559.
34. Basta F, Fasola F, Triantafyllias K, Schwarting A. Systemic lupus erythematosus (SLE) therapy: the old and the new. Rheumatol Ther. 2020;7(3):433–46. https://doi.org/10.1007/s40744-020-00212-9. Epub 2020 Jun 2. PMID: 32488652; PMCID: PMC7410873.
35. Gualtierotti R, Marzano AV, Spadari F, Cugno M. Main Oral manifestations in immune-mediated and inflammatory rheumatic diseases. J Clin Med. 2018;8(1):21. https://doi.org/10.3390/jcm8010021. PMID: 30585183; PMCID: PMC6351952.
36. Fortuna G, Brennan MT. Systemic lupus erythematosus: epidemiology, pathophysiology, manifestations, and management. Dent Clin N Am. 2013;57(4):631–55. https://doi.org/10.1016/j.cden.2013.06.003.
37. Bessa-Nogueira RV, Vasconcelos BC, Duarte AP, Góes PS, Bezerra TP. Targeted assessment of the temporomandibular joint in patients with rheumatoid arthritis. J Oral Maxillofac Surg. 2008;66(9):1804–11. https://doi.org/10.1016/j.joms.2007.08.037.
38. Ohzono A, Sogame R, Li X, Teye K, Tsuchisaka A, Numata S, Koga H, Kawakami T, Tsuruta D, Ishii N, Hashimoto T. Clinical and immunological findings in 104 cases of paraneoplastic pemphigus. Br J Dermatol. 2015;173:1447–52.
39. Kravets I. Paget's disease of bone: diagnosis and treatment. Am J Med. 2018;131(11):1298–303. https://doi.org/10.1016/j.amjmed.2018.04.028. Epub 2018 May 10.
40. DeLoughery TG. Iron deficiency anemia. Med Clin North Am. 2017;101(2):319–32. https://doi.org/10.1016/j.mcna.2016.09.004. Epub 2016 Dec 8.
41. Lo KB, Albano J, Sandhu N, Candelario N. Plummer-vinson syndrome: improving outcomes with a multidisciplinary approach. J Multidiscip Healthc. 2019;12:471–7. https://doi.org/10.2147/JMDH.S180410. PMID: 31417270; PMCID: PMC6593774.
42. Zimmer V, Buecker A, Lammert F. Sideropenic dysphagia. Gastroenterology. 2009;137(6):e1–2. https://doi.org/10.1053/j.gastro.2009.03.051. Epub 2009 Oct 29.
43. Tun AM, Thein KZ, Myint ZW, Oo TH. Pernicious anemia: fundamental and practical aspects in diagnosis. Cardiovasc Hematol Agents Med Chem. 2017;15(1):17–22. https://doi.org/10.2174/1871525715666170203114632. PMID: 28164751.
44. Oo TH. Diagnostic difficulties in pernicious anemia. Discov Med. 2019;28(155):247–53. PMID: 32053765.
45. Allen CE, Merad M, McClain KL. Langerhans-cell histiocytosis. N Engl J Med. 2018;379(9):856–68. https://doi.org/10.1056/NEJMra1607548. PMID: 30157397; PMCID: PMC6334777.
46. Rodriguez-Galindo C, Allen CE. Langerhans cell histiocytosis. Blood. 2020;135(16):1319–31. https://doi.org/10.1182/blood.2019000934. PMID: 32106306.
47. Luz J, Zweifel D, Hüllner M, Bühler M, Rücker M, Stadlinger B. Oral manifestation of Langerhans cell histiocytosis: a case report. BMC Oral Health. 2018;18(1):106. https://doi.org/10.1186/s12903-018-0568-5. PMID: 29884166; PMCID: PMC5994067.
48. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. N Engl J Med. 2017;376(16):1561–73. https://doi.org/10.1056/NEJMra1510865. PMID: 28423290.
49. Acharya S. Oral and dental considerations in management of sickle cell anemia. Int J Clin Pediatr Dent. 2015;8(2):141–4. https://doi.org/10.5005/jp-journals-10005-1301.
50. Gerecke C, Fuhrmann S, Strifler S, Schmidt-Hieber M, Einsele H, Knop S. The diagnosis and treatment of multiple myeloma. Dtsch Arztebl Int. 2016;113(27–28):470–6. https://doi.org/10.3238/arztebl.2016.0470. PMID: 27476706; PMCID: PMC4973001.
51. Rajkumar SV. Multiple myeloma: every year a new standard? Hematol Oncol. 2019;37(Suppl 1(Suppl 1)):62–5. https://doi.org/10.1002/hon.2586. PMID: 31187526; PMCID: PMC6570407.
52. Epstein JB, Voss NJ, Stevenson-Moore P. Maxillofacial manifestations of multiple myeloma. An unusual case and review of the literature. Oral Surg Oral Med Oral Pathol. 1984;57(3):267–71. https://doi.org/10.1016/0030-4220(84)90182-8; PMID: 6369219.
53. Shankland KR, Armitage JO, Hancock BW. Non-Hodgkin lymphoma. Lancet. 2012;380(9844):848–57. https://doi.org/10.1016/S0140-6736(12)60605-9. Epub 2012 Jul 25. PMID: 22835603.
54. Narayanan S, Savage KJ. Staging and prognostic factors. In: Armitage JO, Mauch PM, Harris NL, Coiffier B, Dalla-Favera R, editors. Non-hodgkin lymphomas. 2nd ed. Philadelphia, PA: Wolters Kluwer and Lippincott Williams and Wilkins; 2010. p. 149–71.
55. Abdelwahed Hussein MR. Non-Hodgkin's lymphoma of the oral cavity and maxillofacial region: a pathologist viewpoint. Expert Rev Hematol. 2018;11(9):737–48. https://doi.org/10.1080/17474086.2018.1506326. Epub 2018 Aug 21. PMID: 30058399.
56. Juliusson G, Hough R. Leukemia. Prog Tumor Res. 2016;43:87–100. https://doi.org/10.1159/000447076. Epub 2016 Sep 5. PMID: 27595359.
57. Lohi O, Kanerva J, Taskinen M, Harila-Saari A, Rounioja S, Jahnukainen K, Lähteenmäki P, Vettenranta K. Lapsuusiän leukemia [Childhood leukemia]. Duodecim. 2013;129(9):939–46. PMID: 23786106.
58. Schlosser BJ, Pirigyi M, Mirowski GW. Oral manifestations of hematologic and nutritional diseases. Otolaryngol Clin North Am. 2011;44(1):183–203, Vii.

Xerostomia

22

Michael T. Goupil and Tyler J. Thomas

Introduction

Xerostomia is taken from the ancient Greek—xērós meaning dry and stóma meaning mouth. Hence the patient complaint of "my mouth feels dry." Xerostomia or "dry mouth" is a subjective feeling of oral dryness as opposed to salivary gland hypofunction which is an objective finding that is measured by a decreased salivary flow [1]. These two conditions are not necessarily related. Patients may have one without the other, but more commonly have both together.

Although the patient may present with a variety of symptoms, the primary complaint is usually of a dry mouth and difficulty eating. Patients are often at severe risk for dental caries and oral infections. Xerostomia has a significant effect on a patient's quality of life. A detailed health history should provide the underlying cause of the xerostomia which can aid in developing a treatment strategy.

There is usually no cure and the treatment for this complaint can prove to be a real challenge to any healthcare provider. Patients need to be cognizant that the treatment goal is partial relief of symptoms, improvement of quality of life, and protection of any remaining dentition.

Etiology

The primary component of saliva is water, but it also contains important proteins and electrolytes (see Chap. 6). Saliva is important for taste, speech, swallowing, and the prevention of dental caries. Due to its gastric acid buffering and antimicrobial properties, saliva protects the dentition and mucous membranes of the upper digestive tract [2]. A decrease in salivary production and flow produces the symptoms and signs of xerostomia.

M. T. Goupil (✉) · T. J. Thomas
Carmel, IN, USA

Xerostomia has a prevalence estimation of between 13% and 63% depending on the population surveyed. It appears to occur more often in women, an older population, and individuals in long-term-care facilities [3]. It is a common complaint of approximately half of the elderly and approximately 20% of young adults [1].

The most common causes of xerostomia are medication side effects, autoimmune diseases, especially Sjögren's syndrome, and head and neck radiation. The frequency seen in the elderly may be related to salivary gland hypofunction, polypharmacy, or dehydration. Anxiety and depression have also been linked to xerostomia [4] and the dry mouth will be further aggravated by any medications used to treat these mental health conditions.

The most common drugs associated with xerostomia are the tricyclic antidepressants and cardiovascular medications (see Table 22.1). Approximately 400 hundred drugs have been noted to have dry mouth as a side effect [5]. Xerostomia symptoms usually will manifest in the early phase of medication use (within a few weeks) [6]. Medications that are not usually associated with xerostomia may elicit a drug–drug xerostomic reaction. This is especially a problem in the polypharmacy elderly patient [7].

Head and neck cancer is the sixth most common cancer worldwide. Most if not all of the salivary glands are within the radiation port. There is a 50–60% decrease of salivary function within the first week of radiation treatment. The final result is that 64% of long-term head and neck cancer survivors have moderate to severe xerostomia [8]. An additional complication of head and neck radiation is a change in the oral microflora.

Although any of the autoimmune diseases may be associated with xerostomia, Sjögren's syndrome (SS) is the most common. It is the second most common of the autoimmune diseases [9]. SS is limited to the salivary glands of the oral cavity and the lacrimal glands of the eye. It is attributed to a lymphocytic infiltrate within the glands resulting in a decrease of secretory acini.(2] Sjögren, a Danish ophthalmologist, first described this syndrome as keratoconjuncti-

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_22

Table 22.1 Partial listing of commonly prescribed medications implicated in the cause of medication-induced xerostomia. Adapted from Guggenheimer, J and Moore PA. Xerostomia: Etiology, recognition, and treatment. JADA. 2003, 134:61–69

Commonly prescribed medications with xerostomia effects		
Drug class	Generic name	Trade name
Antidepressants	Amitriptyline	(generic)
Tricyclic antidepressants	Desipramine	Norpramine
Selective serotonin reuptake inhibitors	Citalopram	Celexa
	Fluoxetine	Prozac
	Paroxetine	Paxil
	Sertraline	Zoloft
	Venlafaxine	Effexor
Monoamine oxidase inhibitors	Pimozide	Orap
Heterocyclic antidepressants	Imipramine	Tofranil
Atypical antidepressants	Haloperidol	Haldol
	Mirtazapine	Remeron
	Phenelzine	Nardil
	Bupropion	Wellbutrin
	Nefazodone	Serzone
	Olanzapine	Zyprexa
Analgesics agents	Codeine	(generic)
CNS/opioids	Meperidine	Demerol
NSAIDS	Methadone	Dolophine
	Pentazocine	Talwin
	Tramadol	Ultram
	Diflunisal	Dolobid
	Ibuprofen	Advil, Motrin
	Naproxen	Aleve, Naprosyn
	Piroxicam	Feldene
Antihypertensive agents	Captopril	Capoten
	Clonidine	Catapres
	Enalapril	Vasotec
	Guanfacine	Tenex
	Lisinopril	Zestril
	Methyldopa	Aldomet
Diuretic agents	Chlorothiazide	Diuril
	Furosemide	Lasix
	Hydrochlorothiazide	Dyazide
Sedative/hypnotics	Alprazolam	Xanax
	Diazepam	Valium
	Flurazepam	Dalmane
	Temazepam	Restoril
	Triazolam	Halcion
Anticholinergic agents	Atropine	Lomotil
	Belladonna	Donnatal
	Benztropine	Cogentin
	Oxybutynin	Ditropan
Antihistamines	Astemizole	Hismanal
	Brompheniramine	Dimetane-DX
	Chlorpheniramine	Chlor-Trimeton
	Diphenhydramine	Benadryl, Dramamine
	Loratadine	Claritin
	Meclizine	Antivert
Muscle relaxant agents	Cyclobenzaprine	Flexeril
	Orphenadrine	Norflex
	Tizanidine	Zanaflex
This is a partial listing of medications that should be considered in evaluating xerostomia		

vitis sicca in 1933. Primary SS has a population prevalence of ~0.5% and has a female predilection [10]. When SS is associated with another autoimmune disease (Secondary SS), its prevalence increases [11].

Diagnosis

The majority of saliva (90%) is produced by the three paired major salivary glands—parotid, submandibular (submaxillary), and the sublingual. The remaining saliva is derived from the hundreds of minor glands found throughout the oro-pharynx. Together these glands produce 0.5–1.5 liters of saliva per day. Daily unstimulated salivary flow is 0.3–0.4 mL/min while stimulated flow (i.e., eating or anticipation of eating) increases to 3–4 mL/min. Saliva consistency and composition is based on the function requirements (i.e., wetting, buffering, digestion, and which gland is producing the saliva). Saliva may be watery or thick and ropey and its consistency is determined by both quantity (how much) and quality (how effective). The minor salivary glands, because of their high protein content contribute significantly to the lubrication of the oral mucosa [12].

When a patient presents with the complaint of "my mouth is dry," you should ask the following questions:

- Do you have difficulty swallowing?
- Do you have altered taste or does your food have no flavor?
- Do you take frequent sips of water when you eat?
- Do you ever have a burning sensation in your mouth?
- Have you ever noticed that your eyes seem to be dry also?
- Do you find yourself needing to get up at night to get a drink of water?

A detailed history is required. Of particular note are current medications, a history of head and neck radiation, and evidence of any underlying autoimmune disease, diabetes mellitus, renal failure, and/or graft-host disease. Since depression and anxiety can also elicit symptoms of xerostomia, a mental health review is also indicated.

An oral exam may demonstrate cracked lips, a red fissured tongue, and dry mucous membranes. In addition, patients will demonstrate an increased caries (tooth decay) rate especially along the cervical aspect of the teeth (along the gingival margin) (see Fig. 22.1a, b). Xerostomia patients are also prone to fungal disease and vulnerable areas should be tested for a Candida infection. As Sjögren's syndrome is a common cause of xerostomia, lacrimal gland function should also be assessed.

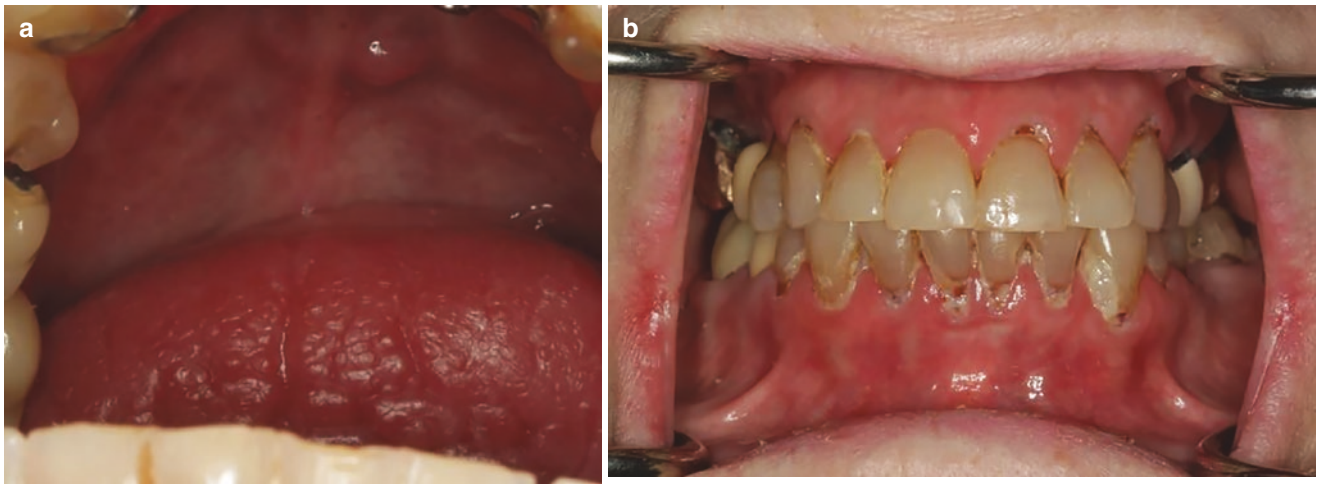


Fig. 22.1 Intraoral photos demonstrating (**a**) dry fissured tongue and (**b**) cervical caries and dry, inflamed mucosa. (Photos courtesy of Dr. Tyler Thomas, Carmel Indiana)

Note whether the patient is carrying a water bottle or other beverage and is frequently sipping from it during the interview.

Ideally, an assessment of salivary flow should be conducted. Simple palpating and milking of the glands can determine whether the glands are producing saliva and, also, allow analysis of the consistency of the saliva produced. This can indicate the potential of an infection or sialolith. Allow the patient to drool, not spit, into a container for a fixed period of time 4 or 10 min. This collection should be unstimulated and can determine the flow rate of total saliva production. A potential problem, especially if any spitting occurred, is the presence or air bubbles (frothy sputum) which will overestimate the amount of saliva produced.

An alternative method for determining saliva flow rate is a modified Schirmer test described by Kumar [13]. Pooled saliva is removed by having the patient swallow and then placing the tongue on the roof of the mouth. The test strip is held vertically on either side of the lingual frenum and held in place for 3 min. The control group (no evidence of salivary gland hypofunction) measured 31.0 ± 5.4 as opposed to the test group on tricyclic antidepressants (13.7 ± 10.08) and the test group on SSRIs (19.86 ± 8.95). This test is primarily evaluating submandibular and sublingual gland function. This objective test could be useful in determining the success of pharmacological treatment plans.

Salivary gland biopsy is indicated when there is a high suspicion of an autoimmune disease component such as Sjögren's syndrome. The classically described biopsy site is the minor salivary glands of the lip. In the author's [MG] experience, biopsy of the tail of the parotid gland is safe, easy, and more productive. In patients with Sjögren's syndrome, the labial salivary glands may be difficult to locate. The biopsy microscopic analysis reveals the formation of periductal lymphocytic infiltrates within the salivary tissue and is classic for Sjögren's syndrome and may be used to stage the disease process.

Sequalae

The consequence of xerostomia has a significant impact on the quality of life whether or not salivary gland hypofunction is the cause. The feeling of dry mouth is upsetting for most individuals and may affect their ability to speak and eat [14]. When the cause of xerostomia is hypofunction of the salivary glands, the sequalae become more significant.

Difficulty in eating or swallowing and taste alteration can have a marked effect on the patient's food choices and nutritional status. Saliva lubrication is required for taste and for the oral manipulation of a food bolus aiding its movement into and through the esophagus. The ability to eat is complicated further if the patient wears a prosthesis (maxillary and/or mandibular denture) [9]. The surface wetting of the maxillary and/mandibular ridges is mandatory for functional adhesion of removable prostheses and patients experiencing xerostomia may complain of poor fitting dentures.

Inability to wear dentures coupled with difficulty in eating and talking can lead to increased isolation by a vulnerable geriatric population. This may extenuate mental health issues of depression and anxiety. This in turn may lead to an increase in psychiatric medications further accentuating salivary gland hypofunction, resulting in an ever-increasing downward spiral.

One of the functions of saliva is to act as a gastric acid buffering agent for the oral cavity and the esophagus. With xerostomia, this lack of buffering capacity leads to demineralization of the dentition. Lack of saliva also reduces the oral cavity's ability to cleanse itself resulting in food particles adhering to the teeth. An acidic environment, a change in the oral microflora, and adherent food debris (generally high in sugar) all result in rampant and highly destructive dental caries. Difficulty in maintaining good oral health can lead to

increased tooth loss and the need for dental prostheses. This is only further complicated by the fact that xerostomia often affects the older population, a group that may have difficulty in cleaning their teeth and maintaining their oral health due to decreased eyesight, osteoporosis, and arthritis. As noted above, the need for removable prostheses has a negative effect on the patient's nutritional status.

Treatment Options

1. Because of the increased caries risk, dental care must be enhanced. More frequent dental visits, dental cleanings, and the addition of topical fluoride agents should be instituted regardless of the cause of any decrease of salivary function.
2. All of the patient's prescribed and over-the-counter medications should be reviewed. If possible, any medications with xerostomia side-effects should be eliminated. When this is not possible, substituting other medications should be considered. Wolf's review on xerostomia-inducing medications is a helpful guide in determining whether a patient's medications are having a negative effect. Keep in mind that drug–drug interactions may be the causative problem [7].
3. Salivary gland stimulants may prove effective if there are active secretory cells. Probably the most common mechanical stimulant is sugarless gum or citric acid based sugarless candies. Other options available include electrostimulation and acupuncture [15].
4. Sialagogues can be effective if there is residual salivary gland function. The best known of these is pilocarpine. It is a parasympathetic drug that works by stimulating the cholinergic receptors of exocrine glands. It should be used with caution or avoided in patients with glaucoma, asthma, chronic obstructive pulmonary disease (COPD), or cardiovascular disease. When pilocarpine cannot be taken systemically because of its adverse-effect profile, it could be use topically on the oral mucosa to activate the minor salivary glands [7]. Cevimeline is a parasympathetic and muscarinic agonist that acts specifically at the M3 receptor sites and has lower adverse side effects [5].
5. Wetting agents/saliva substitutes cannot replicate natural saliva and have mixed results depending on the needs of the patients and their expectations. These agents are available as liquid rinses, oil sprays, and topical gels. Patients will need to try several products and will likely find certain agents provide better relief depending on the situation—eating, talking, sleeping. Patients with removable protheses will be the most challenging group as saliva is a requisite for good denture adhesion.

Table 22.2 Treatment options for xerostomia. Adapted from Lysik, D et al. Artificial saliva: Challenges and future perspectives for the treatment of xerostomia. Int J Mol Sci. 2019, 3199; doi:10.3390/ijms20133199

Therapeutic options for xerostomia		
Endogenous (enhance or replace salivary gland function)	Pharmacological Mechanical Genetic	Change prescribed medications when possible Pilocarpine 4% ophthalmic solution: 2–4 drops in 1–2 teaspoons of water up to QID; swish and swallow Pilocarpine 5 and 7.5 mg tabs: 1 tab TID (use with caution in cardiac patients) Cevimeline 30 mg capsules: 1 cap BID-TID Bethanechol Sugarless chewing gum—with xylitol or sorbitol Citric acid tablets or sugarless candies
Exogenous (topical application of saliva substitutes to replace lost or enhance existing function)	Drinking water Moisturizing agents Saliva substitutes	Frequent sips of water especially during meals Sugarless beverages; avoid coffee and alcohol as they are drying agents Look for products containing xylitol carboxymethylcellulose or hydroxyethyl cellulose as lubricants/coating agents
Patients should be offered a variety of treatment modalities. The objective is palliation of the effects		

Patients should be offered a selection of treatment options (see Tables 22.2 and 22.3). Effectiveness may be influenced by lifestyle or different problems depending on the situation. For example, patients with a need to talk may find sprays more effective as they act quickly but may not last as long as topically applied gels [16].

For patients who are interested in alternative or integrative medicine options, there are a few natural remedies that might prove useful. Slipper elm is a jelly-like herb that may help retain moisture by coating the oral mucosa. Holding a few spoonful of sesame or coconut oil in the mouth for a few minutes may also provide some relief for irritated tissues [17].

Table 22.3 Treatment options by product name and manufacturer. This is a partial list of available products

Xerostomia treatment products
Chewing gum/candy
Basic bites neutralizing chews (Ortek)
Biotene lozenges (Biotene)
Xylitol gum (epic, orbit)
Sprays
3 M xerostomia relief spray (3 M)
All day dry mouth spray (elevate)
Lubricity dry mouth spray (lubricity)
Mouthkote (Parnell)
Oasis mouth spray (GlaxoSmithKline)
Stoppers4 dry mouth (Woodridge)
Salivea spray (Laclede)
Biotene moisturizing spray (Biotene)
Gels
GC America dry mouth gel (GC America)
Oral balance moisturizing gel (Laclede)
Biotene Oralbalance moisturizing gel
Mouthwash
Oasis mouth wash (GlaxoSmithKline)
Oral balance moisturizing gel (Laclede)

Summary

Xerostomia or "dry mouth" is a very common complaint among the elderly, patients taking antihypertensive and psychiatric medications, and those individuals who have received head and neck radiation. This condition has a significant influence on quality of life as chewing, swallowing, and speaking are directly affected. These problems are further aggravated by dental decay and the lack of stability of dental prostheses. Both the patient and dentist are challenged to keep rampant dental caries under control.

When the hyposalivation is secondary to medication, a change of the offending medication(s) make improve the situation. Otherwise treating this condition can prove to be challenging to the healthcare provider. A variety of sialagogues, artificial saliva products, and wetting agents are available that through trial-and-error may prove helpful for compliant patients with realistic goals.

References

1. Mortazavi H, Baharvard M, Movahhedian A, Mohammadi M, Khodadoustan A. Xerostomia due to systemic disease: a review of 20 conditions and mechanisms. Ann Med Health Sci Res. 2014;44(4):503–10.
2. Guggenheimer J, Moore PA. Xerostomia: etiology, recognition and treatment. JADA. 2003;134:61–9.
3. Delli K, Spijkervet FKL, Kroese FGM, et al. Xerostomia. Monogr Oral Sci. 2014;24:109–25. https://doi.org/10.1159/000358792.
4. Wiener RC, et al. Hyposalivation and xerostomia in dentate older adults. JADA. 2010;141:279–84.
5. Eveson JW. Xerostomia. Periodontology. 2000;2008(48):85–91.
6. Aliko A, et al. World workshop on oral medicine VI: clinical implications of medication-induced salivary gland dysfunction. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;120(2):185–206.
7. Wolf A, et al. A guide to medications inducing salivary gland dysfunction, xerostomia, and subjective sialorrhea: a systemic review sponsored by the world workshop on Oral medicine VI. Drugs R D. 2017;17:1–28. https://doi.org/10.1007/s40268-016-0153-9.
8. Dirix P, Nuyts S, Van den Bogaert W. Radiation-induced xerostomia in patients with head and neck cancer. Cancer. 2006;107(11):2525–34.
9. Donaldson M, Epstein J, Villines D. Managing the care of patients with Sjögren's syndrome and dry mouth: comorbidities, medication use and dental care considerations. JADA. 2014;145(12):1240–7.
10. Fox R. Sjögren's syndrome. Lancet. 2005;366:321.
11. Patel R, Shahane A. The epidemiology of Sjögren's syndrome. Clin Epidemiol. 2014;6:247–55.
12. Iorgulescu G. Saliva between normal and pathological, important factors in determining systemic and oral health. J Med Life. 2009;2(3):303–7.
13. Kumar NN, Panchaksarappa MG, Annigeri RG. Modified schemer test-a screening tool for xerostomia among subjects on antidepressants. Arch Oral Biol. 2014;59:829–34.
14. Van der Reijden WA, Vissink A, Veerman ECI, Nieuw Amerongen AV. Treatment of oral dryness related complaints (xerostomia) in Sjögren's syndrome. Ann Rheum Dis. 1999;58:465–73.
15. Lysik D, Niemirowicz-Laskowska K, Bucki R, Tokajuk G, Mysikowska J. Artificial saliva: challenges and future perspectives for the treatment of xerostomia. Int J Mol Sci. 2019;20:3199. https://doi.org/10.3390/ijms20133199.
16. Momm F, Volegova-Neher NJ, Shulte-Möonting J, Guttenberger R. Different saliva-substitutes for treatment of xerostomia following radiotherapy. Strahlenther Onkol. 2005;181:231–6. https://doi.org/10.1007/s00066-005-1333-7.
17. Peirce A. Five natural remedies for dry mouth. News & Information/In the News September 21 2016.

Part IV

Head and Neck Trauma

Elie M. Ferneini

Fractured and Avulsed Teeth

23

Brian Quinn and Steven Halepas

Introduction

Traumatic dental injuries (TDIs) are very common and a prevalent chief complaint in dentists' offices, urgent care facilities, pediatricians, and emergency rooms. TDIs occur in a third of all toddlers and one-fifth of adolescents/adults [1, 2]. Falls, recreational sports, traffic accidents, and physical violence account for most cases of tooth fractures and luxations [3, 4]. Additionally, these injuries are not uncommon in hospitals. Iatrogenic dental injuries, particularly during intubation, have been reported to account for 0.04–12% of all dental injuries [4, 5]. TDIs can be classified into two main categories: fractures and luxations [6]. Tooth luxation is when a force disrupts the tissues, ligaments, and bone that hold a tooth in the mouth. Severe luxation injuries may disrupt the neurovascular supply to the tooth, while severe fractures of the tooth may expose the dentin (the middle layer of the tooth) and the pulp (the most inner layer of a tooth) to the oral flora. These TDIs can result in infarction of the tooth, bacterial infiltration of the pulp, subsequent infection, inflammation, and necrosis [7–9]. Eventually, more severe medical issues may follow. Prompt diagnosis and treatment are critical to minimizing these unfavorable outcomes and maximizing the longevity of the tooth [10, 11]. However, medical providers are often unaware of how to recognize and direct treatment for these injuries [1, 7]. Therefore, it is essential for medical providers to stay up-to-date on the current guidelines for diagnosing and treating TDIs.

B. Quinn
College of Dental Medicine, Columbia University, New York, NY, USA

S. Halepas (✉)
Division of Oral and Maxillofacial Surgery, NewYork-Presbyterian/Columbia University Irving Medical Center, New York, NY, USA
e-mail: sh3808@cumc.columbia.edu

Although many traumatic dental injuries are urgent matters, it is vital to assess the patient for more critical injuries such as trauma to the head and neck as well as possible aspiration of teeth [7]. After having cleared the patient of more severe injuries, it is important to identify the dental traumas requiring immediate treatment, including avulsions, extrusive luxations, lateral luxations, alveolar fractures, and displaced root fractures [7, 12].

Tooth Anatomy

As a brief overview, the crown of the tooth has three identifiable layers. The enamel is the outer most layer, followed by the dentin surrounding the pulp. The pulp houses the neurovascular bundle that enters the apex of the root and supplies sensation and nutrients to the tooth. The periodontal ligament (PDL) is a complex structure made mostly of collagen connecting the cementum of the root to the alveolar bone (see Fig. 23.1).

Before explaining treatment, it is important to discuss terminology to allow for the correct diagnosis. Luxation is often classified based on the degree and the direction of displacement of the tooth. These injuries include concussions, subluxations, extrusive luxations, lateral luxations, intrusive luxations, and avulsions. Concussion injuries present with no displacement of the tooth and no increased mobility. Subluxations do not result in displacement of the tooth. However, they are distinguishable from concussions because of the increased mobility of the tooth. Extrusive luxation (extrusion) involves displacement of the tooth in the outward direction. Lateral luxations involve displacement of the tooth in any lateral direction other than the axial direction. Because the socket does not accommodate this movement, lateral luxations are often associated with a fracture of the alveolar bone [12]. Intrusive luxations are an inward displacement of the teeth. Avulsions are classified as the complete removal of the tooth from the socket (see Fig. 23.2).

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_23

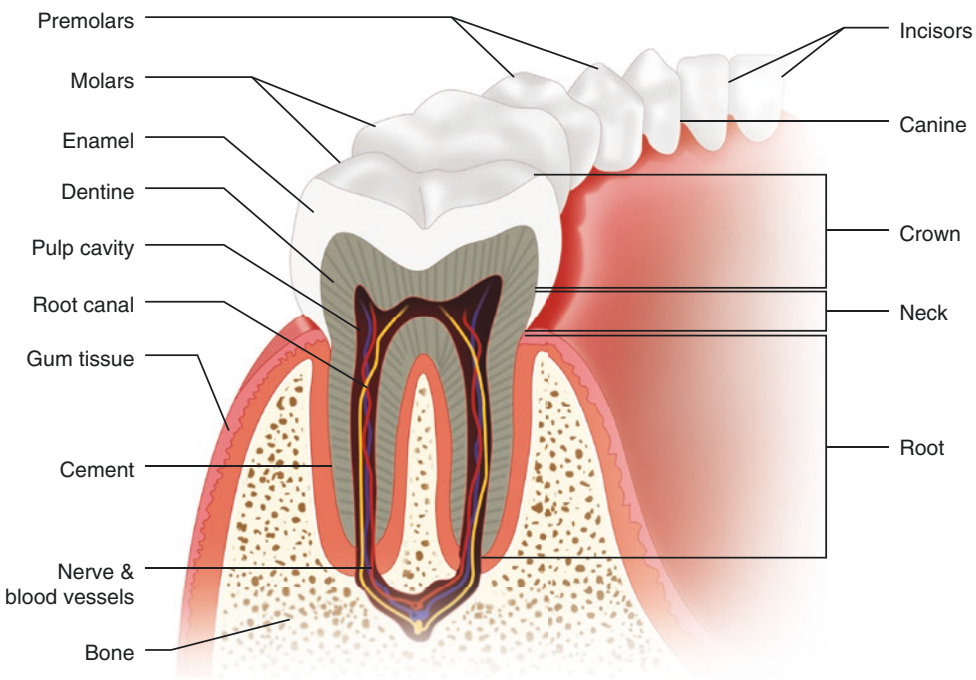


Fig. 23.1 Tooth anatomy

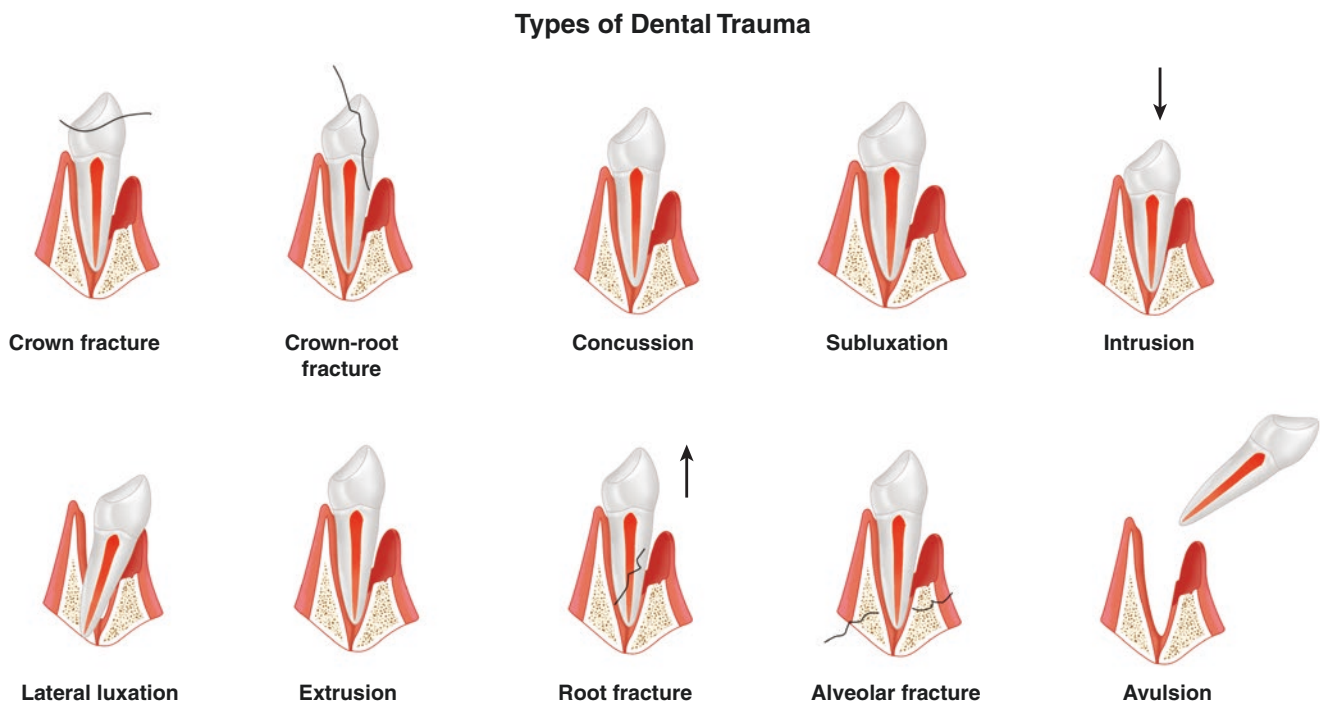


Fig. 23.2 Types of dental trauma

Avulsions

Avulsions are the most severe category of luxation injuries and require immediate action. Unfortunately, avulsions are not uncommon, accounting for 0.5–16% of all dental injuries [13–15]. These injuries expose the periodontal ligament to the oral cavity and disrupt the blood supply to the tooth's pulp leading to ischemia [16]. In the case of an avulsed tooth, the ideal treatment is immediate reimplantation. The patient's bloody socket is definitively the best media to store the avulsed tooth [7]. The International Association for Dental Traumatology (IADT) recommends picking the tooth up by the crown to avoid touching the root of the tooth, rinsing the tooth with ~~or~~ the patient's saliva, Hanks' Balanced Salt

Solution, normal saline solution, or milk; and immediately reimplanting the tooth into the patient's socket in the proper anatomical position. The patient should be encouraged to bite down on gauze or a napkin to keep the tooth in place [10, 17]. If the tooth cannot be reimplanted immediately, it may be temporarily stored in a physiological solution to preserve the periodontal ligament and to prevent dehydration of the root. However, it is important to understand that the longer an avulsed tooth is outside the socket, the poorer the long-term prognosis. In a recent systematic review of the current literature, milk, preferably chilled and with a low-fat content, is the most cited storage media based on its quick availability. It contains nutrients that help to maintain periodontal ligament cell viability. It also has an ideal pH between 6.5 and 7.2. The periodontal ligament cells will survive between 2 and 6 h in milk. These results may be skewed as many of the older studies in the literature utilized milk. Hank's Balanced Salt Solution (HBSS) is the preferred media followed by milk, the patient's saliva, a saline solution, or water if no other media is available [17, 18]. Khinda et al. wrote in a recent literature review: "Lekic et al. demonstrated that milk was as effective as HBSS for storing avulsed teeth for up to 1 h and superior to saline, saliva or water. At a cellular level, milk is ranked equal to HBSS as a storage medium although it loses its effectiveness after 2 h" [19, 20]. Regardless of the media, the most important factor is time until reimplantation.

Luxation

Luxation injuries may not be as easily diagnosable as avulsions. When this is the case, several tests, such as percussion and sensibility tests, are useful to gain insight into the extent of the injury. Percussion tests are helpful in determining the extent of injury to the periodontal ligament which contain receptors capable of localizing pain [21, 22]. These tests are usually performed by tapping the tooth's surface with the blunted end of a dental instrument such as a dental mirror. Percussion tests are also useful because luxation injuries will produce different sounds depending on what the tooth is contacting. A highly mobile tooth, such as an extrusive luxation, will feel "soft" on a percussion test. A tooth in contact with alveolar bone, such as a lateral or intrusive luxation, may produce a ringing sound when percussed [7, 10]. Keep in mind that luxated and fractured teeth may be very sensitive, so before performing a percussion test with an instrument, it is important to first gently tap or move the tooth to assess the pain. Sensibility tests are an indirect test of pulp vitality. They test the nerve supply of the tooth to infer the health of the pulp [23]. There are several sensibility tests, but the most commonly performed sensibility test is the cold test [24]. In this test, a cold source such as an ice cube or a refrigerant spray on a cotton pellet is applied to a control tooth. The patient is instructed to raise their hand if a sensation is perceived. After the control tooth, the injured tooth is tested. A positive response equal to the control indicates that the pulp is healthy. A negative test suggests that the nerve supply and possibly the blood supply to the pulp is injured. However, false negatives are not uncommon, and this is not a conclusive test [10, 25]. Despite its limitations, sensibility testing has shown to be a good predictor of long-term outcome, and the IADT recommends sensibility testing as soon as practical after a TDI to establish a baseline [10, 23, 26].

An important first step in any luxation injury that has resulted in the displacement of the tooth is to reposition the tooth back to its anatomical position. Because this is often painful for the patient, it may need to be performed under local anesthesia. Generally, any tooth that has been displaced or is mobile will require splinting to stabilize the tooth and promote healing. Splints must be flexible to allow normal physiological movement of the tooth. Orthodontic brackets or wire splints are preferred [7, 10]. The provider can use resin bonding and 24-gauge wire to splint the luxated tooth to the adjacent stable teeth. In order to get good stability, it is often necessary to span at least 2 teeth on either side of the luxated tooth/teeth. The duration of splinting will depend on the type and the extent of luxation injury. If the tooth is displaced, but there is no fracturing of the root or the alveolar bone, it is recommended to splint for 1–2 weeks. If there are fractures to the root or the alveolar bone, it is recommended to splint the tooth from 3–5 weeks [7, 10]. If the alveolar bone itself is fractured, the practitioner may need to utilize an Erich arch bar to provide the necessary stability.

Concussions, the least severe type of luxation injuries, do not damage the neurovascular supply of the tooth and do minor damage to the periodontal ligament. These types of injuries do not require immediate treatment; however, the IADT recommends monitoring the condition of the pulp for at least a year [12]. Subluxations do not result in displacement of the tooth but may be distinguished from a concussion because of the increased mobility of the tooth. Normally the injury does not require treatment [10]. If the tooth is excessively mobile, it may require splinting for stabilization (Fig. 23.3). These injuries may or may not result in damage to the pulp, which is why follow-up and monitoring by a dentist is important. Extrusive luxations involve the outward or incisal displacement of the tooth. Treatment of this injury involves pushing the tooth back into the socket into its proper anatomical position. Typically, this is done under local anesthesia. After the tooth is repositioned, the IADT recommends splinting the tooth for 2 weeks if there is no bone fracture and for 4 weeks if there is a fracture of the bone [10]. The direction of displacement of lateral luxations often results in a fracture of the alveolar bone around the socket. This fracture may lead to the tooth being immobile and "locked"

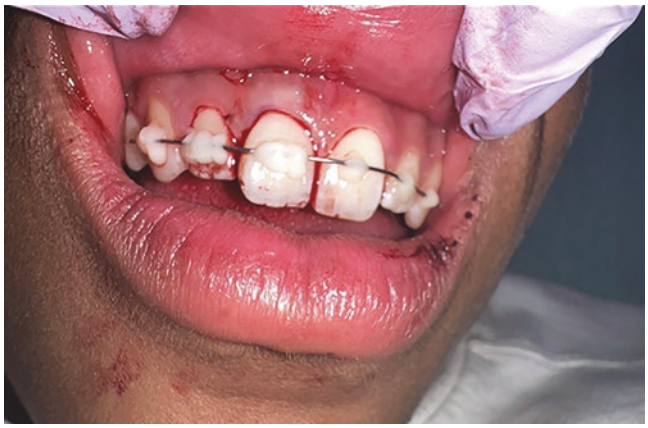


Fig. 23.3 Clinical photo of splinting

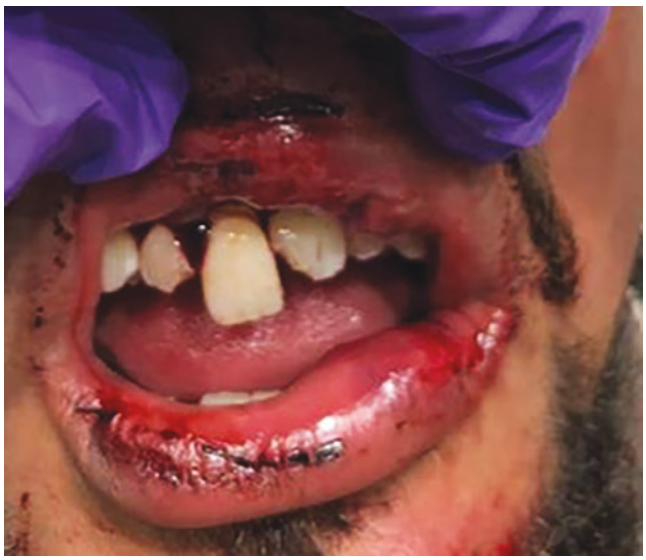


Fig. 23.4 Clinical photo of tooth luxation

into place (see Fig. 23.4). To return the tooth to anatomical position, the IADT suggests palpating the gingiva to feel for the apex of the root of the tooth. They recommend pushing the root downwards to mobilize the tooth, then using another finger to push it back into its socket. Usually, lateral luxations require a longer splinting period of around 4 weeks because of the associated fracture. Intrusive luxations result in an immobile tooth and do not require an immediate repositioning of the tooth. Typically, the tooth is allowed to re-erupt. The IADT recommends that teeth that have not re-erupted within 4 weeks be orthodontically or surgically repositioned [10]. After the initial treatment, follow-up is critical for a favorable long-term outcome. This follow-up usually includes radiographic evaluations and may consist of further treatment. Pulpal damage with a lack of monitoring could result in pulp necrosis, infection, and eventual tooth loss.

Tooth Fractures

As with luxation injuries, it is crucial to identify and communicate the severity of the fracture and the tissues involved when encountering a patient with a fractured tooth. Many classification systems to describe dental trauma exist, but the Ellis and the Andreasen classification systems are the most commonly used [27]. A strength of the Ellis classification is its simplicity, which makes it particularly useful in emergency medicine [28]. The Ellis system is outlined below, but a more detailed overview of the Ellis and the Andreasen systems may be found in *An Overview of Classification of Dental Trauma* by Pagadala et al. [29].

The Ellis classification system describes nine classes of tooth injury (see Fig. 23.5). To describe fractures, we will focus on the first three. Ellis class I fractures are fractures through the enamel, while Ellis class II fractures involve the enamel and the underlying dentin. Ellis class III fractures involve all three tissue layers of the crown: the enamel, the dentin, and the pulp. As a sidenote, infractions are similar to Ellis class I fractures but are less severe. They are incomplete enamel fractures and do not result in enamel loss. Infractions do not fall within any of these three Ellis classes, but it is useful to be able to distinguish infractions from more serious fractures.

Ellis class I fractures are distinguishable from class II because there is no color change. Additionally, because the enamel is not innervated, the tooth will not be tender to the touch unless there are additional injuries to the tooth. If the tooth appears to have a class I fracture but is sensitive to the touch, it must be investigated for a luxation injury or a root fracture [12]. Ellis class II fractures will typically present with a yellowish color, indicating that the dentin is exposed. The patient's tooth may or may not be sensitive to touch and to the air. As with Ellis class I fractures, if the tooth is sensitive, it should be investigated for a luxation injury or a root fracture. Ellis class III fractures will be distinct from the other two classes because of the pulp's visible pink or red color. The pulp is highly innervated and vascular. Therefore, a fracture involving the pulp will result in high sensitivity. In severe cases, blood may exude from the pulp [12, 29].

A primary goal of early treatment of dental fractures is to prevent bacteria from entering the dentin tubules or the pulp. Although it is widely believed that early treatment will limit the risk of bacterial infiltration and result in better long-term outcomes, there is limited evidence supporting specific treatment guidelines regarding the timing of treatment [8]. A common recommendation is to treat Ellis class III fractures within 24 h [7, 8]. Although Ellis class II fractures are not as time-sensitive as class III fractures, it is still important to cover the exposed dentin quickly to limit exposure time to the oral flora [7].

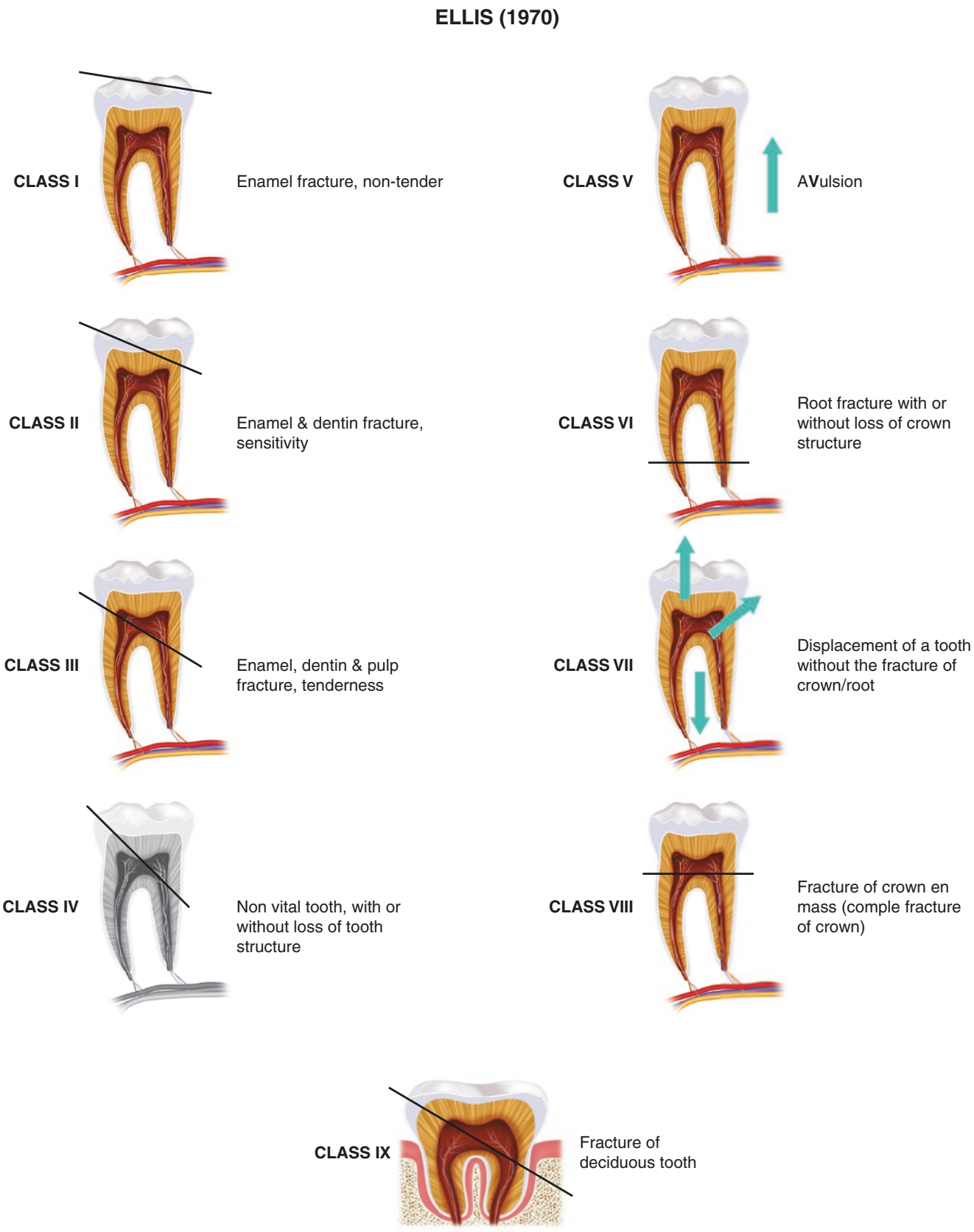


Fig. 23.5 Ellis classification

For Ellis class I and class II fractures, reattachment of the tooth fragment is often the best treatment option. Reattachment provides the patient with an excellent long-term prognosis and a good functional and aesthetic outcome. For these reasons, it is important to hold on to the tooth fragment and store it in saline or water [7]. If the tooth fragment is unavailable or cannot be re-bonded to the tooth, the dentist may restore the tooth with a composite resin [10, 12]. For Ellis class III fractures in young patients with immature roots, the preferred treatment is a partial pulpotomy or pulp capping, which will preserve the pulp and allow for further root development [10]. After treating the pulp, the tooth fragment may be re-bonded onto the tooth if it is available. For all three fracture classes, regular follow-up with a dental specialist is crucial to monitor the tooth's health. The International Association of Dental Traumatology (IADT) recommends follow-ups 6–8 weeks after treatment and 1 year after injury for class I and class II fractures, and additional check-ups 3 and 6 months after treatment for class III fractures [10].

Summary

The goal of this chapter is to help the medical provider recognize, diagnose, and arrange appropriate treatment for the patient. In luxated teeth, where the tooth is visibly displaced, it is best to reposition the tooth with gauze and digital pressure to the tooth's natural position and splint with wire and bonding agent. With avulsed adult teeth, it is best to quickly rinse the tooth of any debris with a medium and then reimplant the tooth into the socket and splint with wire. If more substantial trauma has occurred to the alveolar bone, then a larger bracket may be needed to provide stability. Primary (baby) teeth are never reimplanted due to the risk of damaging the developing adult tooth underneath. For tooth fractures that just involve the crown, it is important to save the tooth fragments and have the patient follow-up with their dentist as soon as possible. If the fracture is of the root, the tooth likely cannot be saved, but it is important to have the patient follow-up with a dentist to have the root removed before an infection occurs.

References

1. Lam R. Epidemiology and outcomes of traumatic dental injuries: a review of the literature. Aust Dent J. 2016;61(S1):4–20.
2. Andersson L. Epidemiology of traumatic dental injuries. J Endod. 2013;39(3 Suppl):S2–5.
3. Hecova H, Tzigkounakis V, Merglova V, Netolicky J. A retrospective study of 889 injured permanent teeth. Dent Traumatol. 2010;26(6):466–75.
4. Zaleckiene V, Peciuliene V, Brukiene V, Drukteinis S. Traumatic dental injuries: etiology, prevalence and possible outcomes. Stomatologija. 2014;16(1):7–14.
5. Chadwick RG, Lindsay SM. Dental injuries during general anaesthesia. Br Dent J. 1996;180(7):255–8.
6. Sigurdsson A. The treatment of traumatic dental injuries. 2019.
7. Moule A, Cohenca N. Emergency assessment and treatment planning for traumatic dental injuries. Aust Dent J. 2016;61(S1):21–38.
8. Andreasen JO, Andreasen FM, Skeie A, Hjørting-Hansen E, Schwartz O. Effect of treatment delay upon pulp and periodontal healing of traumatic dental injuries—a review article. Dent Traumatol. 2002;18(3):116–28.
9. Love RM, Jenkinson HF. Invasion of dentinal tubules by oral bacteria. Crit Rev Oral Biol Med. 2002;13(2):171–83.
10. Bourguignon C, Cohenca N, Lauridsen E, Flores MT, O'Connell AC, Day PF, et al. International Association of Dental Traumatology guidelines for the management of traumatic dental injuries: 1 Fractures and luxations. Dent Traumatol. 2020;36(4):314–30.
11. Petrovic B, Marković D, Peric T, Blagojevic D. Factors related to treatment and outcomes of avulsed teeth. Dent Traumatol. 2010;26(1):52–9.
12. Diangelis AJ, Andreasen JO, Ebeleseder KA, Kenny DJ, Trope M, Sigurdsson A, et al. International Association of Dental Traumatology guidelines for the management of traumatic dental injuries: 1. Fractures and luxations of permanent teeth. Dent Traumatol. 2012;28(1):2–12.
13. Fouad AF, Abbott PV, Tsilingaridis G, Cohenca N, Lauridsen E, Bourguignon C, et al. International Association of Dental Traumatology guidelines for the management of traumatic dental injuries: 2 avulsion of permanent teeth. Dent Traumatol. 2020;36(4):331–42.
14. Glendor U, Halling A, Andersson L, Eilert-Petersson E. Incidence of traumatic tooth injuries in children and adolescents in the county of Västmanland, Sweden. Swed Dent J. 1996;20(1–2):15–28.
15. Andreasen J, Andreasen F, Andersson L. Textbook and color atlas of traumatic injuries to the teeth. Stomatol Edu J. 2019;6:279.
16. Bustamante-Hernández N, Amengual-Lorenzo J, Fernández-Estevan L, Zubizarreta-Macho A, Martinho da Costa C-G, Agustín-Panadero R. What can we do with a dental avulsion? A multidisciplinary clinical protocol. J Clin Exp Dent. 2020;12(10):e991–e8.
17. Adnan S, Lone MM, Khan FR, Hussain SM, Nagi SE. Which is the most recommended medium for the storage and transport of avulsed teeth? A systematic review. Dent Traumatol. 2018;34(2):59–70.
18. Blomlöf L. Milk and saliva as possible storage media for traumatically exarticulated teeth prior to replantation. Swed Dent J Suppl. 1981;8:1–26.
19. Lekic PC, Kenny DJ, Barrett EJ. The influence of storage conditions on the clonogenic capacity of periodontal ligament cells: implications for tooth replantation. Int Endod J. 1998;31(2):137–40.
20. Is Khinda V, Kaur G, Brar SG, Kallar S, Khurana H. Clinical and practical implications of storage media used for tooth avulsion. Int J Clin Pediatr Dent. 2017;10(2):158–65.
21. Mortazavi H, Baharvand M. Review of common conditions associated with periodontal ligament widening. Imaging Sci Dent. 2016;46(4):229–37.
22. Kaku M, Yamauchi M. Mechano-regulation of collagen biosynthesis in periodontal ligament. J Prosthodont Res. 2014;58(4):193–207.
23. Alghaithy RA, Qualtrough AJE. Pulp sensibility and vitality tests for diagnosing pulpal health in permanent teeth: a critical review. Int Endod J. 2017;50(2):135–42.
24. Chen E, Abbott PV. Dental pulp testing: a review. Int J Dent. 2009;2009:365785.
25. Battista P, Pantera E. Principles of endodontic diagnosis. Decisions Dent. 2020;6(9–10):2–3.

26. Bastos JV, Goulart EM, de Souza Côrtes MI. Pulpal response to sensibility tests after traumatic dental injuries in permanent teeth. Dent Traumatol. 2014;30(3):188–92.
27. Feliciano KMPC, Caldas Jr AF. A systematic review of the diagnostic classifications of traumatic dental injuries. Dent Traumatol. 2006;22(2):71–6.
28. Vinson DR. The Ellis fracture: an anachronistic eponym in dentistry. Ann Emerg Med. 1999;33(5):599–600.
29. Pagadala S, Tadikonda D. An overview of classification of dental trauma. IAIM. 2015;2(9):157–64.

Mandibular Trauma

24

Gregory Scott Biron

Anatomy

The mandible is a U-shaped bone that makes up the lower one-third of the face. Superiorly, the mandibular condyle articulates with the temporal bone at the glenoid fossa to form the temporomandibular joint [1]. The temporomandibular joint is diarthrodial, meaning it has two motions: horizontal rotation and forward translation as the mouth opens [1]. There is a cartilaginous disc that lies between the condylar head and the glenoid fossa that moves with the mandible as it functions to act as a cushion [1]. Sensation of the mandible, lower teeth, gingiva, and skin arise from the inferior alveolar nerve, which is a branch of the trigeminal nerve (cranial nerve V) [1]. The inferior alveolar nerve enters the mandible on the medial surface of the mandibular ramus, travels within the mandibular canal, and exits the mandible at the mental foramen in the lateral surface of the mandible near the premolar teeth [2]. The blood supply to the mandible is via the inferior alveolar artery from the external carotid artery, as well as from muscle attachments [1]. The muscles that attach directly to the mandible are the muscles of mastication and suprahyoid muscle groups [1]. The teeth are housed in bone called the alveolar ridge which sits above the basal mandibular bone [1]. Occlusion is the term that is used to describe how the cusps of the upper and lower teeth fit together.

Epidemiology

The mandible is a frequently fractured facial bone just behind nasal bones [3]. In the United States, men in the age group of 18–24 are most likely to fracture their mandible [3, 4]. The most common etiology of mandible fractures is assault (42%), motor vehicle accident (31%) and falls (15%) as demonstrated in Fig. 24.1 [4]. With an aging population, most mandible fractures in the elderly are caused by falls and the majority are women. The fractures listed in decreasing frequency are symphysis (19.2%), body (18.1%), angle (16.2%), condyle (14.8%), subcondylar (12.6%), ramus (11.3%), alveolus (4.5%), and coronoid (3.3%) as demonstrated in Fig. 24.2 [4].

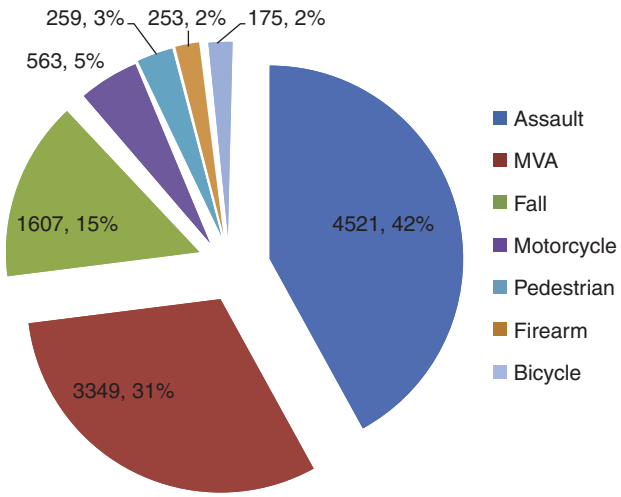


Fig. 24.1 Mechanism of injury for mandible fractures (3. Permission obtained 4/6/21)

Initial Evaluation

When evaluating a patient with a mandible fracture, it is important to remember the Advanced Trauma Life Support (ATLS) primary survey protocol as depicted in Table 24.1. Ensuring a patent airway is the first step in the algorithm and may become compromised secondary to blood, teeth, or other foreign bodies in the pharynx. If the patient is unable to protect their airway from bleeding or altered level of consciousness, an endotracheal tube should be placed. There is a fracture pattern called a "flail mandible"

G. S. Biron (✉)
Exeter Dental Implant and Oral Surgery, Exeter, NH, USA
e-mail: biron@oralsurgeryexeter.com

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_24

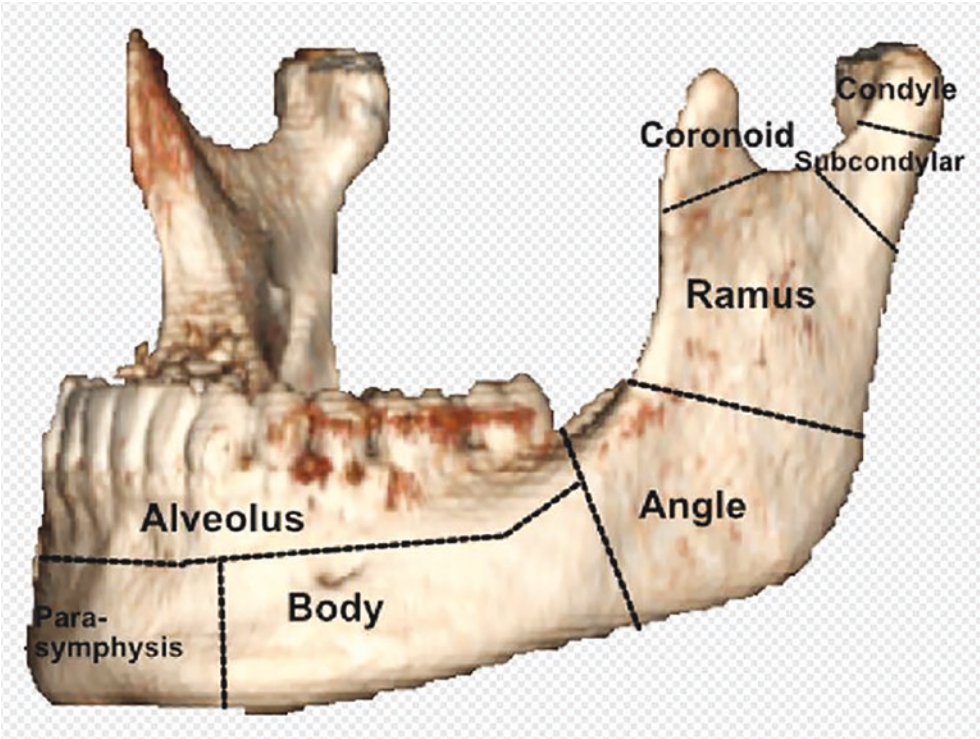


Fig. 24.2 Anatomic regions of the mandible

Table 24.1 ATLS primary survey [5]

A	Airway maintenance with cervical spine protection
B	Breathing and ventilation
C	Circulation with hemorrhage control
D	Disability—Neurologic status
E	Exposure, environmental control: Undressing the patient but preventing hypothermia

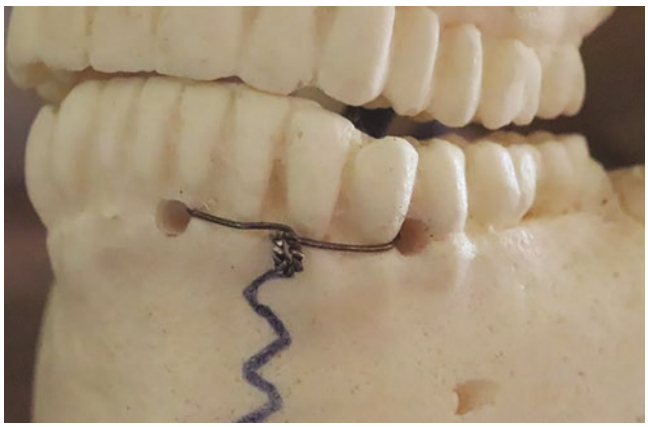


Fig. 24.3 Bridle wire placed to reduce the displaced fracture segments

caused by bilateral parasymphysis fractures, which has potential to cause airway embarrassment due to posterior displacement of glottic structures that normally attach to the symphysis of the mandible. In the case of a flail mandible, a "bridle wire" (26 gauge wire) can be passed between teeth adjacent to the fracture sites to stabilize the mobile segments as shown in Fig. 24.3. After the patient is stabilized and the primary survey is completed, secondary survey may be done.

Clinical Examination

The secondary survey of ATLS involves more thorough information gathering such as patient history and physical examination. Important information to obtain from the patient history is timing of the trauma, mechanism of the trauma, other injuries sustained, and medical comorbidities. There are many physical examination signs and symptoms that can assist in the diagnosis of a mandible fracture. Most important is a change in the occlusion or bite. The patient may state that their teeth do not come together properly, which can be demonstrated by an occlusal step (change in plane of occlusion), unilateral open bite or premature bite,

or an unstable bite pattern. Other signs of mandible fracture include tears in the gingiva at the site of the fracture, paresthesia in the trigeminal V3 distribution, mobile bone segments, floor of mouth and/or buccal sulcus hematoma, facial lacerations, and pain. If a mandible fracture is suspected, radiographic imaging should be obtained to confirm.

Imaging

If a mandible fracture is suspected based on clinical examination, a plain radiograph such as orthopantomogram, posteroanterior (PA), oblique, and lateral views are reasonable screening images [6]. Maxillofacial computed tomography (CT) imaging has many advantages including lack of overlap of anatomic structures, greater detail via 3-dimensional images, and better visualization of the TMJ space. Other indications for CT are imaging of unstable patients, when a mandible fracture is suspected despite a negative radiograph, or if operative intervention is planned for mandible fracture repair [6]. Technology now allows for CT-guided virtual surgical planning sessions to create ideal fracture reduction as well as print 3D models [7]. A custom reconstruction plate can be milled or a plate can be pre-bent by hand using a 3D printed model to save time in the operating room [7]. MRI does have its place in mandibular trauma when evaluating soft tissue such as the temporomandibular disc in the case of intracapsular condyle fractures [6].

Classification

There are several different ways that a mandible fracture can be classified. The first is by anatomic location as depicted in Fig. 24.2. Another term to describe a mandible fracture is open vs. closed. An open fracture is exposed to the oral cavity through a tear in the oral mucosa or if the fracture passes through a tooth socket. Conversely, a closed fracture is not exposed to the oral cavity which is common with fractures of the ramus, subcondylar, and condylar regions. A simple fracture has large bony segments whereas a comminuted fracture has many small fragments of bone. A fracture can be nondisplaced where the bone is broken but the segments are in the correct orientation vs. displaced where the segments are out of place [6]. A fracture can be dislocated if the condyle of the mandible is no longer within the glenoid fossa. If the fracture is secondarily caused by another process (i.e., osteomyelitis, cyst, tumor), this is termed as a pathologic fracture as shown in Fig. 24.4 [6].

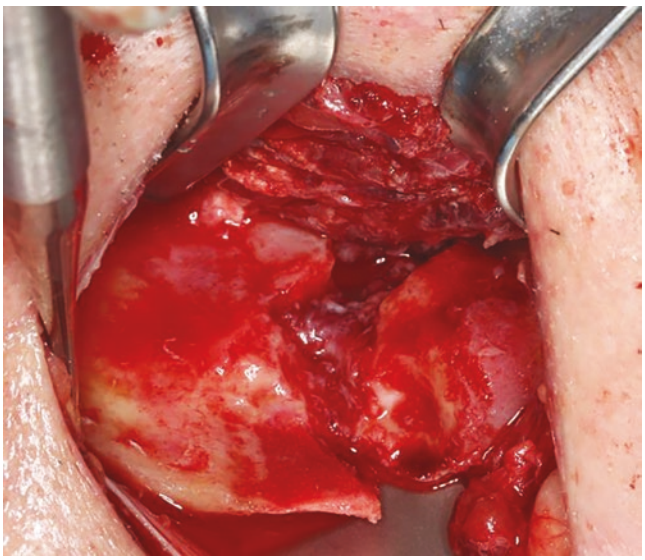


Fig. 24.4 Pathologic fracture of right mandibular angle secondary to osteomyelitis

Related Trauma

A force great enough to fracture a mandible should raise concern for injury to adjacent anatomic structures. Blunt trauma, such as a motor vehicle accident or assault, can injure the great vessels in the neck such as the carotid and vertebral arteries and have the potential to cause a stroke or death [8]. This is called blunt cerebrovascular injury (BCVI) and it is diagnosed via a neck CT angiogram [8]. Screening tools such as the Denver Criteria are used to identify the risk of BCVI as listed in Table 24.2. A systematic review by Gregory Kelts et al. found mandible fractures to be the most frequently associated craniomaxillofacial fracture associated with BCVI [8]. In a recent study by the Journal of Oral & Maxillofacial Surgery, it was noted that around 4.4% of patients with mandible fractures also suffer from a cervical spine injury [9]. For this reason, it is very important to immobilize the cervical spine during the primary survey when a patient presents with facial trauma. A high percentage of patients sustaining mandible fractures report loss of consciousness or some level of amnesia surrounding the trauma that may need to be worked up prior to discharge [10]. Other injuries to rule out in the patient with a mandible fracture are ocular injuries, facial lacerations, extremity injuries, abdominal and thoracic injuries [3].

Table 24.2 Denver criteria screening tool for BCVI (G)

Signs/symptoms of BCVI	Risk factors for BCVI
Arterial hemorrhage from neck/nose/mouth	High energy transfer mechanisms
Cervical bruit in patient <50 years old	LeFort II or III fractures
Expanding cervical hematoma	Mandible fracture
Focal neurologic defect	Complex skull fracture/basilar skull fracture/occipital condyle fracture
Neurologic defect inconsistent with head CT findings	Closed head injury with GCS <6
Stroke on CT or MRI	Cervical spine fracture, subluxation, or ligamentous injury at any level
	Near hanging with anoxic brain injury
	Clothesline type injury or seat belt abrasion with significant swelling, pain, or altered mental status
	Traumatic brain injury with thoracic injuries
	Scalp degloving
	Blunt cardiac rupture
	Upper rib fractures

Medical Management

Not every mandible fracture requires operative intervention or even a hospital admission, but this decision should be made by the specialist that ultimately will be managing the fracture. If the fracture is open, meaning it is exposed to the oral cavity, the patient should be placed on antibiotics that cover the oral flora such as gram-positive cocci, gram-negative bacilli, and HACEK organisms (Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella), most of which are facultative and obligate anaerobes [11]. Common antibiotics used are Penicillin and Clindamycin due to their broad coverage of the oral flora bacteria. Fractures that are not appropriately treated with antibiotics are at risk for infection and nonunion, which is a non-healing fracture. Selected cases such as greenstick fractures or high condylar/subcondylar fractures may be treated with a nonoperative strict liquid diet for 6 weeks at the surgeon's discretion.

Closed Treatment

The definitive management of the mandible fracture depends on the anatomic location as well as other factors such as existing dentition, patient preference, and severity of the fracture. Many mandible fractures are amenable to closed treatment with maxillomandibular fixation (wiring the jaws shut). This type of treatment requires a stable and reproducible dentition as well as a reliable patient who will comply with instructions. Maxillomandibular fixation can be achieved by interdental wiring via traditional Erich arch bars (Fig. 24.5), hybrid arch bars (combination of screws and arch bar), or bone screws. The advantages of closed treatment include less invasive procedure, less chance of infection, and preservation of the blood supply to the bone. Maxillomandibular fixation is not appropriate for patients with a seizure disorder, alcohol or substance abuse, unstable psychiatric conditions, or patients unwilling to comply with instructions. It is best to avoid maxillomandibular fixation if the fracture involves the condyle as this can lead to ankylosis of the joint.

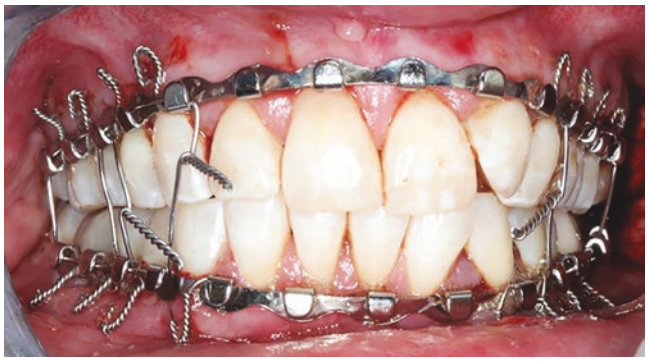


Fig. 24.5 Maxillomandibular fixation with traditional Erich arch bars

Open Treatment

Many fractures are treated with open reduction and internal fixation (ORIF) particularly if the fracture is displaced or the patient is not amenable to maxillomandibular fixation as discussed earlier. There are several advantages of ORIF over maxillomandibular fixation including early function of the mandible, rigid fixation, and treatment of the noncompliant patient. Open reduction is more invasive, which can lead to higher rates of postoperative infection, hardware failure, wound dehiscence, nonunion, or malunion. These complication rates are significantly higher in smokers and patients with systemic comorbidities [12]. Examples of treatment with ORIF are demonstrated in Figs. 24.6, 24.7, and 24.8.

Edentulous elderly patients may suffer from an atrophic mandible fracture as the mandible becomes thin and frail after teeth are lost [13]. Although there is much controversy surrounding the treatment of atrophic mandible fractures, most would agree that a reconstruction bar is necessary [13]. Treatment of mandibular condyle fractures varies widely, although studies have demonstrated improved results in terms of incisal opening and function in patients treated with open reduction rather than closed [14].

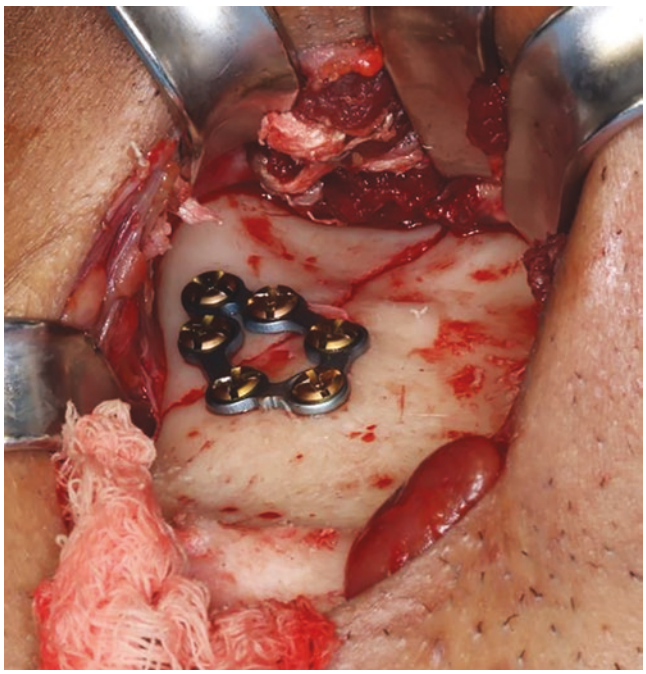


Fig. 24.6 ORIF right subcondylar fracture

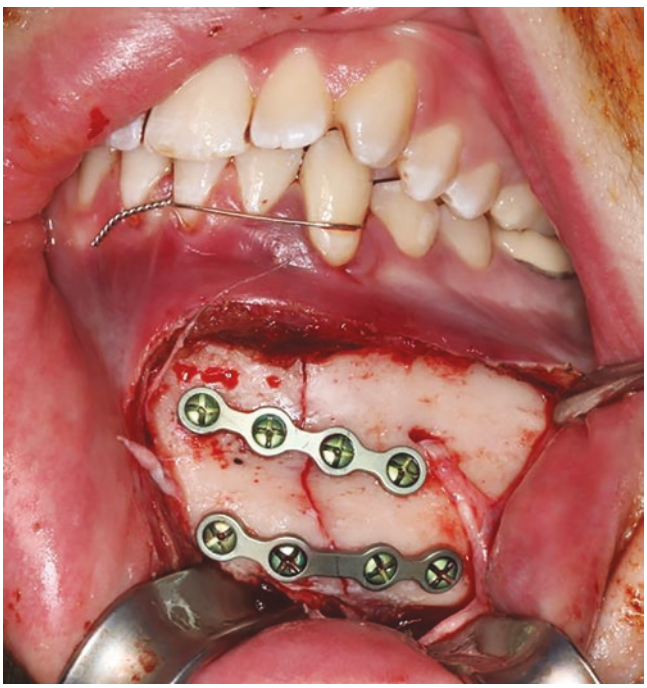


Fig. 24.7 ORIF left parasymphysis fracture

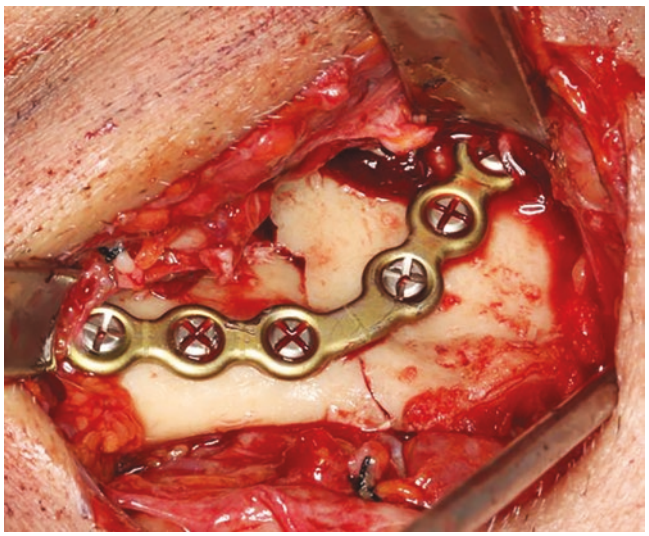


Fig. 24.8 ORIF left angle fracture

Complications

The key to prevention of postoperative complications is good patient selection. Although open reduction may be the favored treatment, patient risk factors may favor a nonsurgical approach. A noncompliant patient has been shown to be the leading cause of complications following a mandible fracture repair [15]. Other risk factors include teeth in the line of the fracture, history of depression, left mandibular angle fractures, and possibly even assault and incarceration [15]. Although there is no clear-cut timeline for definitive fracture repair, early is always preferred, as the risk of infection and nonunion may increase after 72 h [16].

Transfer

The patient with a mandible fracture should be evaluated by a specialist that will be definitively managing the fracture, such as an Oral & Maxillofacial Surgeon, Otolaryngologist, or Plastic Surgeon. If there is significant blunt injury, consider a workup by the general surgery trauma team to evaluate for related injuries such as cervical spine injury or BCVI. If the patient is unable to be evaluated by a specialist, the patient should be given clear instructions to follow up as an outpatient in a timely manner and be prescribed appropriate antibiotics if indicated.

References

1. Heath S, Doyle J. Management of mandible fractures. Plast Reconstr Surg. 2006;117:48–60.
2. Kademani D, Tiwana PS. Atlas of oral & maxillofacial surgery. In: Atlas of oral & maxillofacial surgery. St. Louis, MO: Elsevier Saunders; 2016. p. 35–49.
3. Olson RA, Fonseca RJ, Zeitler DL, Osbon DB. Fractures of the mandible: a review of 580 cases. J Oral Maxillofac Surg. 1982;40:23–8.
4. Afrooz P, Bykowski M. The epidemiology of mandible fractures in the United States part 1: a review of 13,142 cases from the US National Trauma Data Bank. J Oral Maxillofac Surg. 2015;73:2361–6.
5. Fonseca RJ. Initial assessment and intensive care of the trauma patient. In: Oral and maxillofacial trauma. St. Louis, MO: Elsevier/Saunders; 2013. p. 48–76.
6. Naeem A, Gemal H. Imaging in traumatic mandibular fractures. Quant Imaging Med Surg. 2017;7:469–79.
7. Marschall JS, Dutra V, Flint RL, Kushner GM, Alpert B, Scarfe W, Azevedo B. In-house digital workflow for the Management of Acute Mandible Fractures. J Oral Maxillofac Surg. 2019;77:2084.e1. https://doi.org/10.1016/j.joms.2019.05.027.
8. Kelts G, Maturo S. Blunt cerebrovascular injury following craniomaxillofacial fractures: a systematic review. Laryngoscope. 2017;127:79–86.
9. Brasileiro BF, Ferreira da Silva LC. Risk factors for cervical spine injury in patients with mandibular fractures. J Oral Maxillofac Surg. 2019;77(6):1099.
10. Hung YC, Montazem A, Costello MA. The correlation between mandible fractures and loss of consciousness. J Oral Maxillofac Surg. 2004;62:938–42.
11. Geddes AE, Burlew CC, Wagenaar AE, Biffl WL, Johnson JL, Pieracci FM, et al. Expanded screening criteria for blunt cerebrovascular injury: a bigger impact than anticipated. Am J Surg. 2016;212(6):1167–74.
12. Gutta R, Tracy K, Johnson C, James LE, Krishnan DG, Marciani RD. Outcomes of mandible fracture treatment at an academic tertiary hospital: a 5-year analysis. J Oral Maxillofac Surg. 2014;72(3):550–8.
13. Rocha A, Celia de Aguiar S. Fracture of the atrophic mandible: case series and critical review. J Oral Maxillofac Surg. 2011;69:1430–5.
14. Schneider M, Erasmus F, Gerlach KL, Kuhlisch E, Loukota RA, Rasse M, Schubert J, Terheyden H, Eckelt U. Open reduction and internal fixation versus closed treatment and Mandibulomaxillary fixation of fractures of the mandibular condylar process: a randomized, prospective, multicenter study with special evaluation of fracture level. J Oral Maxillofac Surg. 2008;66:2537–44.
15. Christensen BJ, Mercante DE, Neary JP, King BJ. Risk factors for severe complications of operative mandibular fractures. J Oral Maxillofac Surg. 2017;75:787.e1. https://doi.org/10.1016/j.joms.2016.12.003.
16. Lucca M, Shastri K, McKenzie W, Kraus J, Finkelman M, Wein R. Comparison of treatment outcomes associated with early versus late treatment of mandible fractures: a retrospective chart review and analysis. J Oral Maxillofac Surg. 2010;68:2484–8.

Midface Trauma

25

Jessica S. Lee

Globally, trauma is the leading cause of death, and more than three million maxillofacial injuries occur in the United States each year [1]. Of these, more than 50% of patients with maxillofacial injuries also sustain multisystem injuries, as well. As such, trauma patients require evaluation and management through a multidisciplinary approach and medical professionals of all disciplines will likely be involved in the care of these patients during their training or practice and should possess basic knowledge in the evaluation, diagnosis, and management of these patients. This chapter will focus on the initial evaluation and postoperative management of midface maxillofacial trauma for clinicians who, although not directly involved in the surgical management of these injuries, are directly involved in the overall care of these patients.

Anatomy

The midface spans from the cranial base to the maxillary teeth. The midface of the facial skeleton includes the orbits, globes, muscles of mastication and facial expression, and the maxillary dentition. Further, the midface consists of the structures responsible for many of the senses including vision, olfactory, and auditory functions, and houses sections of the respiratory and digestive tracts. The bones of the midface include the zygomatic, nasal, sphenoid, ethmoid, palatine bones and the maxilla. These bones create horizontal and vertical buttresses (Fig. 25.1): pillars that support and protect vital structures from injury [2–4]. The horizontal buttresses include the maxillary alveolus (tooth-bearing portion of the maxilla), zygomas, supraorbital rims/frontal bandeau, and the infraorbital rims. The stronger, vertical buttresses include the pterygomaxillary (posterior), zygomaticomaxillary (lateral), and nasomaxillary (medial) buttresses. Areas of thinner bone between the horizontal and vertical buttresses create areas of anatomic weakness which result in a predictable fracture pattern.

Initial Examination

Initial examination of a trauma patient is accomplished by the principles outlined in Advanced Trauma Life Support (ATLS), the gold standard in the diagnosis and management of a trauma patient (Fonseca Trauma). Completion of ATLS in the setting of maxillofacial trauma should provide special attention to the airway and cervical spine. Although evaluation of the maxillofacial skeleton is typically a component of the secondary ATLS survey, severe maxillofacial injuries can contribute to significant morbidity (e.g., loss of vision) and mortality (e.g., loss of patent airway) and should be evaluated in a timely and systematic fashion. Significant hemorrhage within the aerodigestive tract should be controlled with compressive measures or ligation of visible vessels but care should be taken when packing dressings or balloon catheters in patients with severe midface and/or panfacial injuries as the cranial base can be perforated and injury to the brain or orbital contents may occur [1]. A severely comminuted or displaced mandibular fracture may result in posterior displacement of the mandible and tongue base, leading to upper airway obstruction especially in the supine position.

Once ATLS has been completed and the patient has been stabilized, a thorough history and maxillofacial exam should be completed as part of the secondary survey. It is often difficult to obtain a history from the trauma patient due to unconsciousness or drug intoxication and must be gathered from prehospital personnel (e.g., Emergency Medical Services, witnesses at the scene of injury) or the

J. S. Lee (✉)
Department of Otolaryngology, Division of Oral & Maxillofacial Surgery, Icahn School of Medicine, Mount Sinai Health System, New York, NY, USA

Northeast Facial & Oral Surgery Specialists, Florham Park, NJ, USA
e-mail: drlee@nefoss.com

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_25

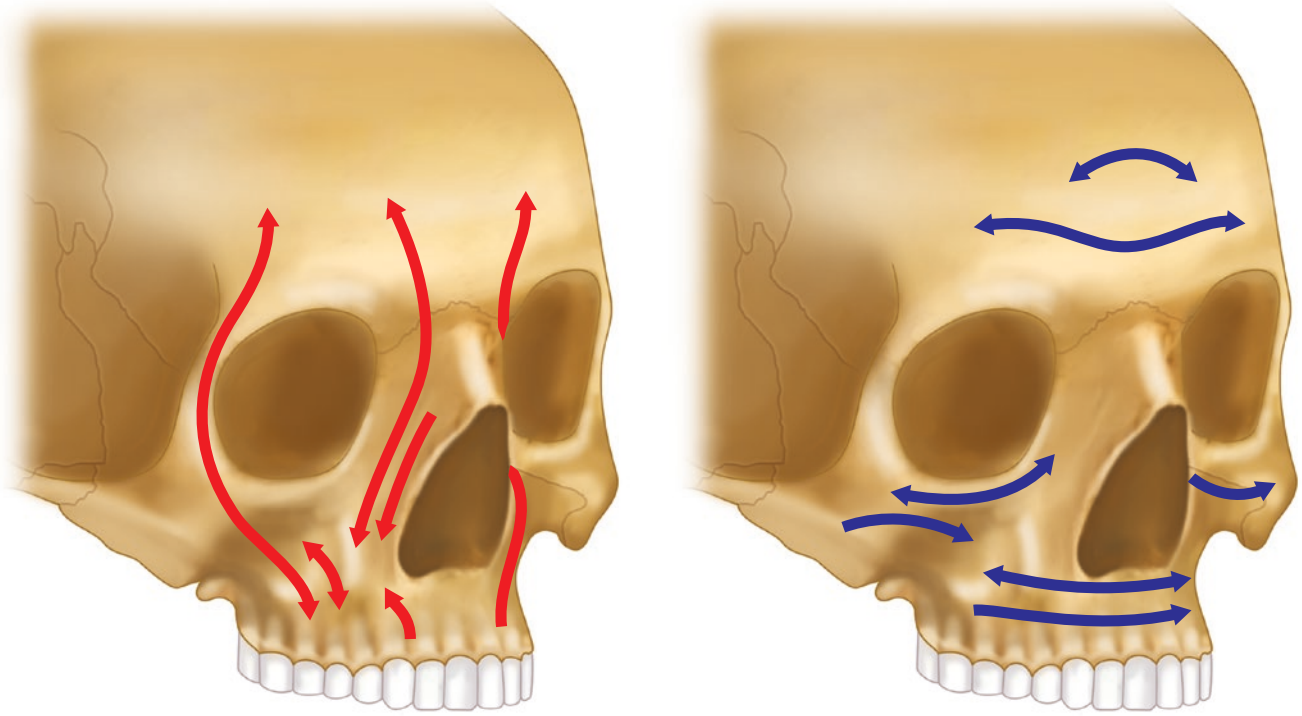


Fig. 25.1 Horizontal and vertical buttresses of the maxillofacial skeleton

family of the patient. The history, too, should be obtained in a systematic manner and the mnemonic "AMPLE" or others can be used to aid in this information gathering [5]:

Allergies.
Medications.
Pregnancy, **p**revious illnesses.
Last meal.
Events or **e**nvironment related to and leading to the trauma.

The patient's pregnancy status or time of last meal will have implications on how and when the patient can be managed safely from a surgical and anesthetic perspective. The mechanism of injury can also provide the medical team information on the types of injuries suspected [6]. For instance, a decelerating injury (e.g., a restrained passenger in a motor vehicle accident) should raise the suspicion for life-threatening conditions caused by shearing forces (e.g., lung or aortic injuries) [5]. The mechanism of injury to the maxillofacial skeleton should also raise suspicion for specific maxillofacial trauma; for example, blunt trauma to the midface resulting in a Le Fort I fracture [6].

Review of Systems

In an awake and alert trauma patient, a review of systems (ROS) should be completed as it will direct the provider's attention to the site of injury. For each patient, a full ROS should be performed and the method in which this should be completed can be found in many other resources and is beyond the scope of this chapter. Patients with maxillofacial trauma may report blurry or double vision, which may be secondary to an orbital injury and should be assessed urgently and in consultation with ophthalmology. Rhinorrhea or otorrhea reported by the patient may be a sign of skull base fracture and may suggest an intracranial injury for which urgent neurosurgical consultation may be required. Malocclusion reported by the patient should prompt evaluation of the maxilla, mandible, and/or supporting tooth structures to rule out a fracture.

Clinical Examination

As with the history and review of systems, the clinical exam of the maxillofacial trauma patient should be completed in a consistent and efficient manner. There are many methods for completing a maxillofacial exam. However, it is often more important to be consistent and thorough in the way in which a clinician completes the exam than the specific technique he or she chooses. A "top down" or "bottom up" approach will allow the examiner to complete the clinical exam in a systematic manner to ensure consistency and decrease the likelihood of a missed injury. Reviewing the comprehensive maxillofacial exam from the scalp to the clavicles is beyond the scope of this book and, therefore, this chapter will focus on examination of the midface in a "bottom up" manner.

Beginning with the most superficial structures, the soft tissue should be examined for any abrasions, laceration, edema, or ecchymosis. A laceration may be associated with an underlying fracture and/or foreign body impaction, therefore, there should be a high suspicion of an associated injury. Bimanual palpation beginning at the level of the maxillary dentition should be completed to assess for bony step-offs, crepitus, mobility, or tenderness to palpation. The exam should move through the remainder of the midface superiorly to the level of the supraorbital rims.

Evaluation of the maxilla can be first achieved by the patient's subjective report of malocclusion. Malocclusion can be a sign of a maxillary (e.g., Le Fort, palatal), mandibular, alveolar, or odontogenic fracture, or any combination of the above. Bimanual palpation of the maxilla by placing the clinician's thumb and index finger on the facial and palatal aspects of the premaxilla, respectively, can evaluate for a Le Fort fracture. These fractures are often associated with intraoral clinical findings such as lacerations, gingival bleeding/ecchymosis, or tenderness to palpation; therefore, any of these clinical findings should raise a suspicion for an underlying fracture. The zygomas should be examined for asymmetry, under projection, or mobility.

Intraoral dental appliances may be present when examining the patient and all removable appliances, such as complete or partial dentures, should be removed to ensure a thorough examination.

Ocular injuries are commonly associated with midface trauma and, therefore, an ocular exam is a crucial part of the midface exam. An ocular exam should consist of assessing the globes for proptosis, periorbital edema, or ecchymosis or any penetrating injury to the globe, which should raise a suspicion for an ocular injury. The extraocular muscles should be examined for asymmetric, restricted movement or entrapment of the globe. Visual acuity can be assessed with a Snellen chart and pupillary light reflexes should be tested. A consultation for an ophthalmologist may be indicated for severe ocular trauma.

Lacerations to the eyelid margins may result in injury to the lacrimal duct apparatus, which is responsible for the production and drainage of tears and should warrant ophthalmological consultation and evaluation. The medial canthus should be examined for stability by measuring the intercanthal distance and by bimanual palpation and traction test (e.g., bowstring test).

The nose should be examined for lacerations, abrasions, or deviation of the nasal dorsum and/or nasal septum. The nasal septum should be examined intranasally for perforations or hematoma formation, which should be drained expeditiously to prevent ischemia to the cartilaginous septum.

Imaging

Suspicion for midface trauma should be confirmed or ruled out by radiologic examination. Computed tomography (CT) imaging is the imaging modality of choice and remains the standard of care when assessing patients who have sustained maxillofacial injuries. There is less of a role for plain radiography given the excellent detection of fractures and patterns of facial injury provided by CT imaging, especially when the images are formatted with thin cuts of 1 mm or less. The provider should be aware that cuts of 5 mm or more may result in missed facial injuries.

CT images can be reformatted in 3-dimensional reconstruction and can aid in diagnosing and treatment planning multiple, complex fractures. Reformatting CT imaging to 3D CT may introduce radiographic artifacts and should be evaluated in conjunction with conventional CT imaging to decrease the likelihood of a missed injury.

Magnetic resonance imaging (MRI) is less commonly obtained and is typically used as an adjunctive imaging modality when assessing for soft tissue and/or cranial nerve trauma or a concomitant intracranial or cervical spine injury. Additional adjunctive modalities such as a CT angiogram (CTA) may be considered when major vessel injury is suspected.

Fractures

Le Fort Fractures

In 1901, French surgeon René Le Fort developed and published a classification system for midface fractures, which remains the most widely recognized midface fracture classification system today. Le Fort fractures consist of three fracture patterns which René Le Fort observed when blunt trauma was applied to the midface of cadavers, which generally occurred over three "lines" of weakness: across the midface (Le Fort I), circumscribing the midface (Le Fort II) and a line just below the cranial cavity (Le Fort III) (Fig. 25.2).

Anatomy

Le Fort fractures typically involve several bones including the maxilla, zygomas, nasal bones, palatine bones, pterygoid plates of the sphenoid, ethmoid, and vomer. The blood supply to the midface is predominantly supplied by the internal maxillary artery, which is a branch of the external carotid artery, and partially by the ophthalmic, anterior, and posterior ethmoid arteries via the internal carotid artery.

Neurosensory innervation is supplied by the second (maxillary) division of the trigeminal nerve (CN V_2), which exits the infraorbital foramen of the maxilla to supply the lateral nasal, superior labial, inferior palpebral

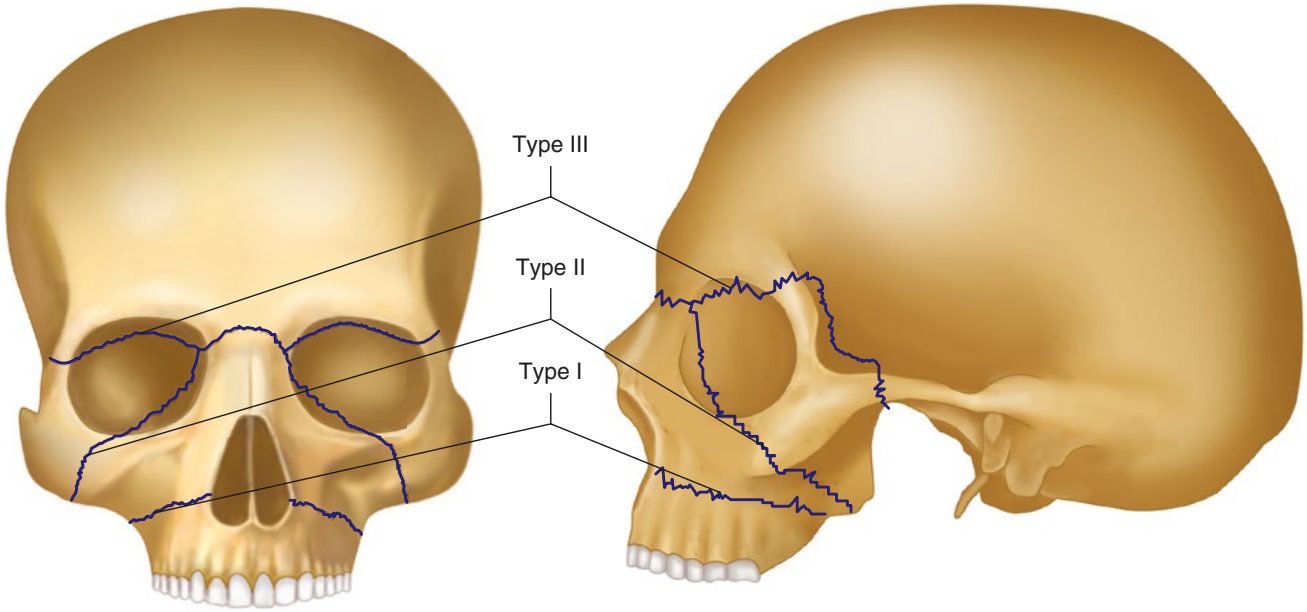


Fig. 25.2 Le Fort fractures

regions in addition to the labial mucosa, maxillary gingiva, and dentition intraorally. Neuromotor innership is supplied by the facial nerve (CN VII), predominantly by the temporal, zygomatic, and buccal branches.

Classification

A Le Fort I fracture is a horizontal fracture superior to the maxillary dentition extending from the pyriform aperture of the nasal fossae anteriorly to the pterygoid plates posteriorly. A Le Fort I fracture separates the dentition and palate from the maxilla superiorly.

A Le Fort II fracture is a pyramidal fracture extending from the pterygoid plates posteriorly through the zygomaticomaxillary suture, infraorbital rims, and terminates at the nasofrontal suture. The lateral orbits and zygomas are typically intact but Le Fort II fractures are more likely to be associated with intracranial injuries and increased mortality [7].

Le Fort III fractures are complete craniofacial disjunctions where the entire midface is separated from the cranial vault via fractures through the pterygoid plates posteriorly, zygomatic arches laterally, zygomaticofrontal sutures, medial and lateral orbital walls, and nasofrontal suture superiorly. As with Le Fort II fractures, Le Fort III fractures are also associated with a higher incidence of intracranial injuries.

Palatal fractures may also be present with Le Fort fractures, which will likely contribute to malocclusion and independent mobility of the hemimaxillae bilaterally.

Diagnosis

As previously discussed, a thorough and systematic approach to clinical and radiologic exam will help correctly identify and diagnose midface traumatic injuries. On clinical exam, malocclusion and maxillary mobility will likely be omnipresent in Le Fort I, II, and III fractures. Radiographically, fractures of the pterygoid plates are also an omnipresent finding in these patients. Patients may often present with multiple Le Fort fracture patterns, including unilateral or a combination.

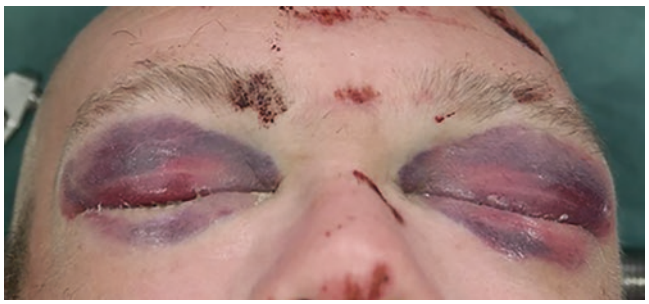


Fig. 25.3 A frontal photograph of a patient who sustained a base of skull fracture demonstrating "raccoon eyes"

Patients with a Le Fort I fracture will almost always present with malocclusion, most likely with an anterior open bite, mobility of the maxilla, ecchymosis of the maxillary buccal vestibule, and pain on occlusion. Palatal ecchymosis (Guerin's sign) is indicative of a palatal fracture.

Patients with a Le Fort II fracture may present with bilateral periorbital edema and ecchymosis ("raccoon eyes") (Fig. 25.3), step-offs and mobility of the nasal bridge and infraorbital rims with manipulation of the maxilla, cerebrospinal fluid (CSF) rhinorrhea, and epistaxis.

Le Fort III fractures are typically associated with orbital, intracranial, and/or cervical spine injuries due to the greater

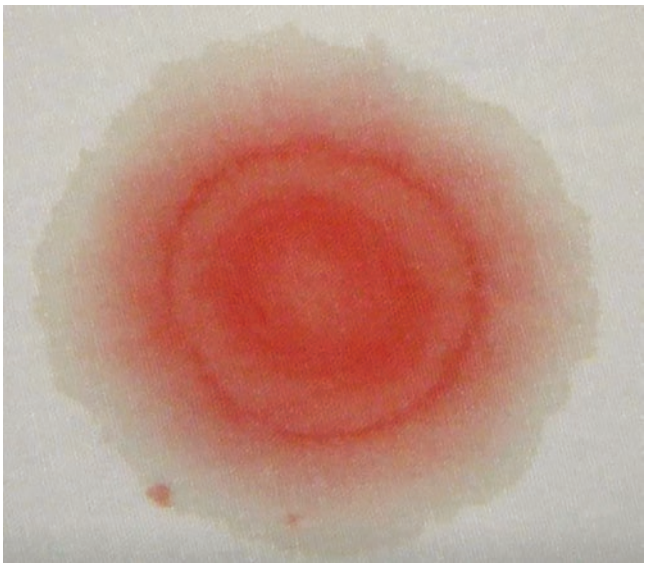


Fig. 25.4 A clinical photograph demonstrating a positive "halo" sign. CSF has migrated centrifugally while blood has remained in the center

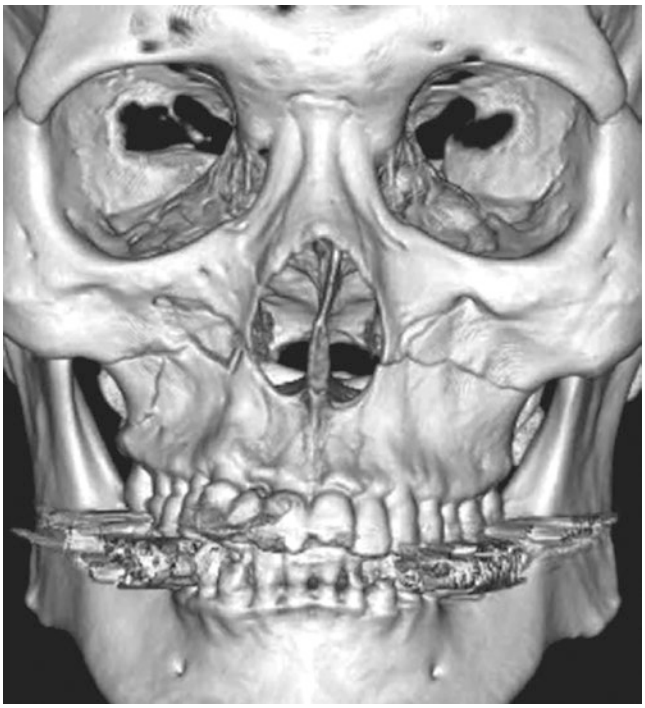


Fig. 25.5 A maxillofacial CT reformatted with 3D reconstruction demonstrating a bilateral Le Fort I fracture

amount of force sustained at the time of trauma and should be suspected at the time of evaluation. Manipulation of the maxilla will likely elicit mobility of the zygomaticofrontal and nasofrontal sutures. CSF rhinorrhea or otorrhea, "racoon eyes" and Battle sign (ecchymosis over the mastoid process) are indicative of a base of skull fracture. Suspected CSF leakage, secondary to a dural tear at the base of the skull, should be tested and appropriate consultation to neurosurgery placed. At the time of clinical evaluation, this fluid can be tested by placing a drop of the suspected fluid onto a white paper towel and assessing the migration pattern of the fluid via capillary action. If present, CSF will migrate centrifugally on the paper towel while the blood will remain in the center, suggestive of a positive "halo" sign (Fig. 25.4).

Radiographic evaluation is best accomplished by CT imaging with thin cuts of 1 mm through the maxillofacial skeleton. Close evaluation of the pterygoid plates and maxillary buttresses should be completed. Reformatting with 3D images can aid in treatment planning complex, comminuted Le Fort fractures (Fig. 25.5).

A systematic clinical and radiologic approach will allow the provider to correctly identify these patterns of injury.

Treatment

Although surgical techniques involved in the repair of Le Fort fractures are beyond the scope of this chapter, the pre- and postoperative management of these fractures will be discussed. Overall, ideal management of midface fractures should be completed within 10–14 days as it may become difficult to mobilize and reduce the fractures beyond this period due to osseous healing. The exact timing of repair will depend upon the patient's clinical status including the need for other urgent surgical intervention (e.g., neurosurgical) and/or medical optimization prior to surgery. Patients with multisystem injuries may undergo surgical intervention for injuries over the course of multiple operations and/or may be completed concurrently with other surgical specialties, depending on the nature of the injuries.

Isolated Le Fort I fractures are typically treated via an intraoral vestibular incision, similar in design to that of the horizontal fracture above the level of the maxillary teeth to access the fracture. Adequate mobilization of the fractured maxilla followed by maxillomandibular fixation, where the maxillary and mandibular teeth are wired intraoperatively to the patient's pre-injury dental occlusion, and four-point rigid internal fixation with titanium plates and screws across the fracture is completed to achieve adequate reduction of the fracture and restoration of the patient's facial height and dental occlusion (Fig. 25.6). The patient typically does not require postoperative maxillomandibular fixation; however, it can be utilized if additional stability is required for adequate reduction. A patient in maxillomandibular fixation with wires should be provided a pair of wire cutters should there be an acute airway emergency.

Similar concepts and principles are applied to the management of Le Fort II and III fractures. Le Fort II fractures typically require fixation not only at the level of the zygomaticomaxillary buttress with a vestibular incision but also at the level of the infraorbital rims. Rigid fixation at the

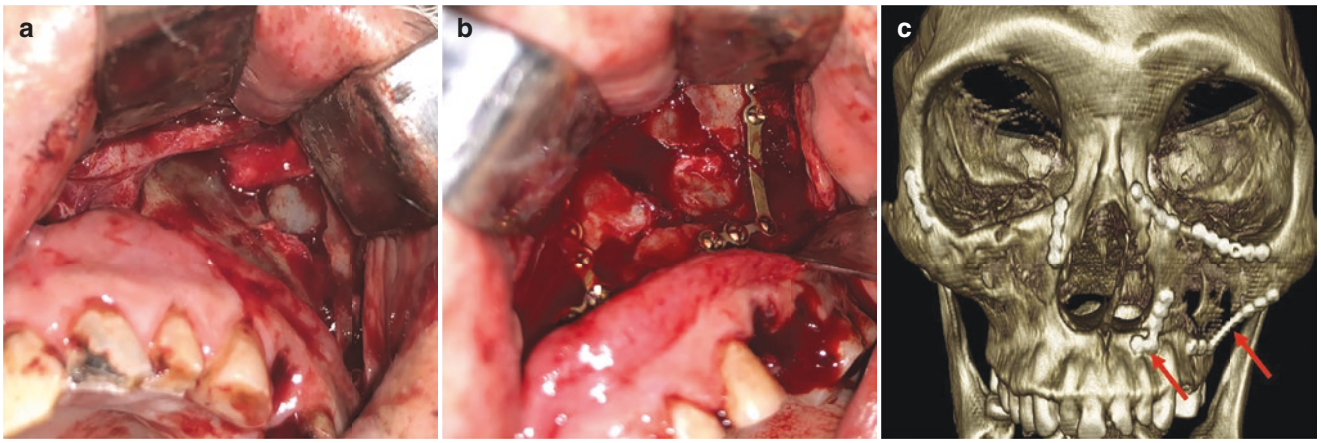


Fig. 25.6 An intraoperative clinical photograph of a left hemi Le Fort I fracture before (**a**) and after (**b**) fixation (red arrows) and a post-operative maxillofacial CT reformatted with 3D reconstruction (**c**)

infraorbital rims can be achieved via several approaches, including subciliary, transconjunctival, and infraorbital incisions, all of which possess their inherent advantages and disadvantages. Existing overlying lacerations may aid in the exposure of these fractures and allow the clinician to avoid additional incisions to access these areas. Le Fort III fractures often require more extensive exposure for adequate reduction and fixation. Access to these fractures typically requires a coronal incision to access the zygomaticofrontal, zygomaticotemporal, and nasofrontal sutures. It is imperative that the patient's pre-injury dental occlusion, if present and achievable, is established and verified prior to the application of rigid fixation.

Palatal fractures can be addressed most predictably with an occlusal splint, which can be fabricated pre-operatively. Dental impressions of the patient's maxilla and mandible are obtained pre-operatively and maxillary model surgery is completed to reestablish the patient's pre-injury occlusion onto which a maxillary occlusal splint is fabricated. Intraoperatively, the patient's maxilla is reduced, as outlined previously, with the aid of the prefabricated occlusal splint for adequate reduction.

Patients who have sustained midface maxillofacial trauma may possess additional facial fractures, including the mandible, which may require a systematic approach in addressing all the injuries at the time of surgery.

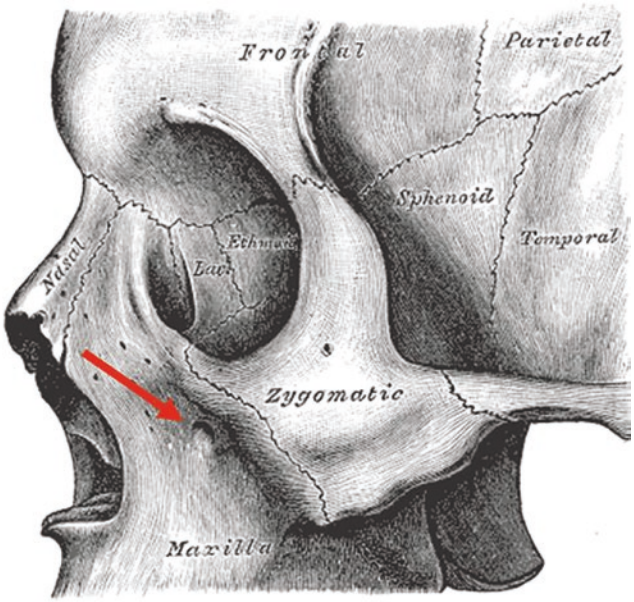


Fig. 25.7 Zygomaticomaxillary complex in lateral view. The second division of the trigeminal nerve exits the maxillofacial skeleton at the infraorbital foramen (arrow)

Zygoma and Zygomatic Arch Fractures

Anatomy

The zygomatic bone is the "cheek bone" of the facial skeleton and is an important structure providing the lateral and anterior projection of the midface. It is a quadrilateral bone that articulates onto the maxilla, sphenoid, temporal, and frontal bones. The zygomatic bone also forms part of the lateral and inferior walls of the orbit and, therefore, a fracture of the zygomatic bone should raise suspicion for a fracture in these structures as well. The second division of the trigeminal nerve (CN V_2) exits the facial skeleton just medial to the zygomaticomaxillary suture (Fig. 25.7) and a deficit in CN V_2 is often an accompanying clinical finding in zygomatic fractures.

The zygomatic arch consists of the union between the zygomatic and temporal bones and is positioned laterally in the maxillofacial skeleton. It is a relatively thin and weak structure, lending itself to frequent fracture, and can occur as an isolated fracture.

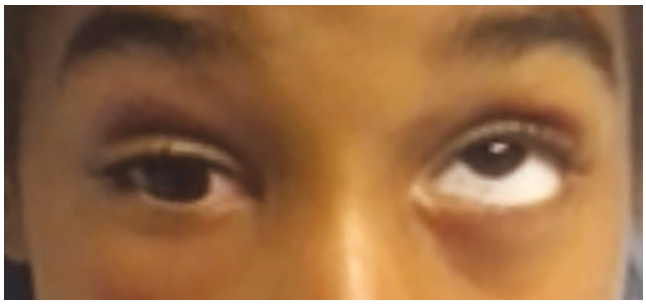


Fig. 25.8 A clinical photograph of a 9-year-old patient with entrapment of the right globe on upward gaze

Diagnosis

On clinical exam, the patient may present with periorbital edema and ecchymosis, conjunctival hemorrhage, flattening of the malar eminence ("flat cheek bone"), orbital dystopia, diplopia, or enophthalmos. Entrapment of the globe is considered an urgent indication for release and repair and should be completed within 24–48 h to avoid ischemia of the entrapped extraocular muscle(s) resulting in permanent gaze restriction (Fig. 25.8). Bony stepoffs at the zygomaticofrontal, zygomaticotemporal, and zygomaticomaxillary sutures may be palpable. Patients may report paresthesia or hypoesthesia in the CN V_2 distribution due to bony impingement of the infraorbital nerve. Trismus (the inability to open one's mouth to its fullest extent) with a maximum incisal opening of 30 mm or less accompanied with pain may also be present especially in patients with zygomatic arch fractures. This is due to the inability of the coronoid process of the mandible to translate anteriorly during mouth opening or impingement of the temporalis muscle by the zygomatic arch.

Zygomatic bone and arch fractures can be assessed radiographically with CT imaging with thin cuts through these structures in the axial, sagittal, and coronal planes (Fig. 25.9). Due to the intricate bony articulations of the zygomatic bone and arch, 3D reconstruction of these structures will aid in the diagnosis and treatment planning of these injuries (Fig. 25.10).

Treatment

Indications for surgical management of zygomatic bone and arch fractures include functional and cosmetic deficits. Functional indications include diplopia, enophthalmos, trismus, ocular entrapment, and paresthesia in the CN V_2 distribution, while cosmetic indications include a depressed malar eminence or arch [8]. As with Le Fort fractures, most zygomatic bone and arch fractures can be addressed within a 10–14 day period to allow for resolution of facial edema and more accurate treatment planning, unless a more urgent or emergent indication for repair (e.g., ocular entrapment, retrobulbar hematoma) exists.

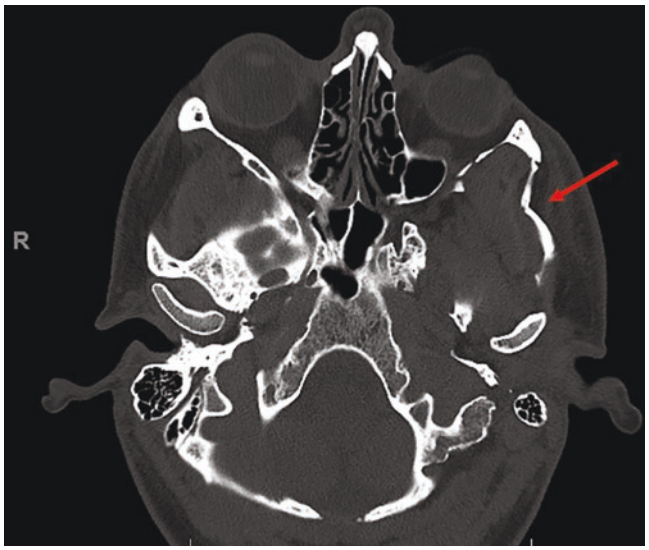


Fig. 25.9 A maxillofacial CT in the axial view demonstrating a left zygomatic arch fracture with medial displacement of the arch (arrow)

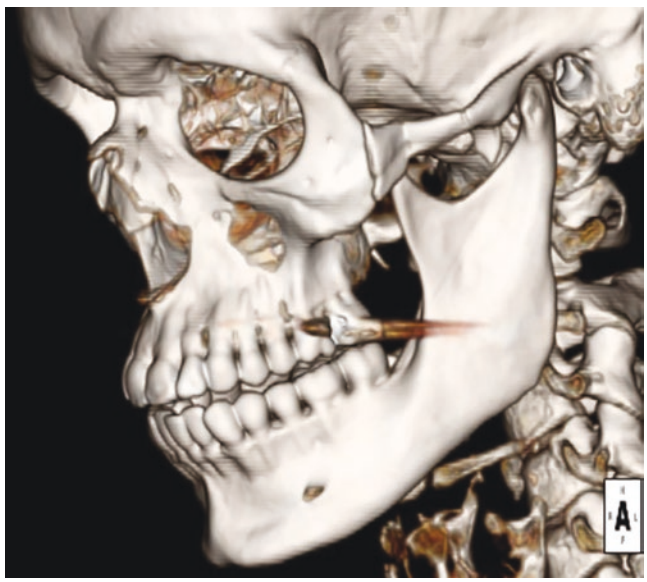


Fig. 25.10 A maxillofacial CT with 3D reformatting demonstrating a left zygomatic arch fracture

Surgical approaches to the maxillofacial skeleton will depend upon the specific fracture pattern and degree of displacement of the fracture and can include a combination of approaches including coronal, transconjunctival, subciliary, infraorbital, lateral canthotomy, upper eyelid, eyebrow, intraoral vestibular, Gillies and Keen (zygomatic arch), or through existing lacerations. The goal of surgical intervention is to restore the patient's functional and/or cosmetic defects with adequate rigid fixation to prevent relapse. Postoperative evaluation should include clinical and radiographic evaluation to

confirm the resolution of functional and cosmetic deficits. The resolution of orbital entrapment should be confirmed and the development of an iatrogenic retrobulbar hematoma should be ruled out.

Orbital Wall Fractures

Fractures of the orbital walls can result in ophthalmologic deficits including diplopia and enophthalmos. Orbital wall fractures may also result in more urgent and emergent conditions such as ocular entrapment or retrobulbar hematoma, requiring timely diagnosis and repair.

Anatomy

The orbit consists of seven facial bones: sphenoid, palatine, frontal, maxillary, zygomatic, lacrimal, and ethmoid bones (Fig. 25.11). The orbital contents include the globe, extraocular muscles (superior, inferior, medial and lateral recti, superior and inferior oblique, and the levator palpebrae superioris), cranial nerves (optic, oculomotor, trochlear, abducens, and branches of the ophthalmic and sympathetic nerves) and ciliary ganglion, vessels (ophthalmic artery and vein) and lymphatics, lacrimal gland and sac, and orbital fat.

The orbit is a bony vault that houses the globe and the orbital rim (superior, lateral, and inferior) is composed of dense cortical bone designed to protect the contents of the orbit. The medial orbital rim and the walls within the orbit are composed of thinner bone and the orbital floor and medial walls frequently fracture after trauma to the midface. This evolutionary mechanism serves as a protective feature for the globe and orbital contents: the increased intraorbital pressure resulting from medial and inward displacement of the midfacial bones reduces the orbital volume and places the globe at risk for rupture. The thin walls of the orbit, however, protect against this increased intraorbital pressure by expansion or fracture of the walls, allowing herniation of the orbital contents into adjacent spaces such as the maxillary sinus and ethmoid air cells. The orbital floor is a common location for a fracture with increased intraorbital pressure and this "blow out" fracture typically results in herniation of the orbital contents into the maxillary sinus inferiorly (Fig. 25.12).

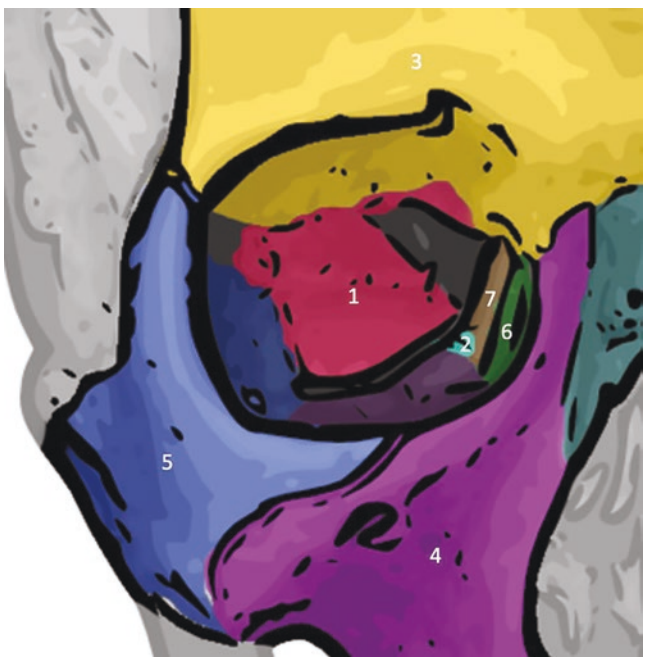


Fig. 25.11 The seven bones of the orbit. (1) Sphenoid, (2) Palatine, (3) Frontal, (4) Maxilla, (5) Zygoma, (6) Lacrimal, and (7) Ethmoid [9]

Diagnosis

An orbital wall fracture should raise suspicion of an injury or deficit in any of these structures and should be ruled out with a thorough exam. A patient presenting with an orbital wall fracture may report diplopia or decreased visual acuity, which may be secondary to edema but should not be assumed. Ecchymosis of the surrounding eyelids and soft tissue or conjunctiva may be present. Lacerations of the surrounding structures (e.g., eyelids) or perforations of the globe proper should be explored to rule out foreign body impaction. Extraocular muscle function should be assessed by having the patient move their globes in an upward, downward, medial and lateral gaze or with a forced duction test in an unconscious patient. A gaze palsy is indicative of an extraocular muscle paresis such as extraocular muscle entrapment, superior orbital fissure syndrome, or orbital apex syndrome. The bony orbital rim should be palpated to assess for step-offs or mobility. Neurosensory testing of the intraorbital (e.g., optic, oculomotor, trochlear), extraorbital (e.g., supraorbital and supratrochlear [branches of CN V_1]) and infraorbital (branch of V_2) cranial nerves should be completed.

An in-depth review of the pupillary exam is beyond the scope of this chapter and the reader should be directed to a more comprehensive resource for this information; therefore, a generalized overview of this exam will be covered in this text. Visual acuity should be tested independently in each eye with a Snellen chart with and without the patient's corrective lenses, if present. A pupillary exam examining the shape, size, symmetry (e.g., anisocoria) (Fig. 25.13), and reactivity should be completed. Previous eye procedures or surgeries or the recent use of medications or drugs may elicit an irregular pupillary exam or response and should be taken into consideration during the exam. A tonometer should be used to assess intraocular pressure if a retrobulbar hematoma is suspected. The provider should suspect the presence of a retrobulbar hematoma with a tonometer reading of over 20 mmHg. Conversely, a "soft eye" is indicative of a globe rupture. A slit lamp exam will evaluate the contour of the globe, integrity of the cornea, and assess for hemorrhage or

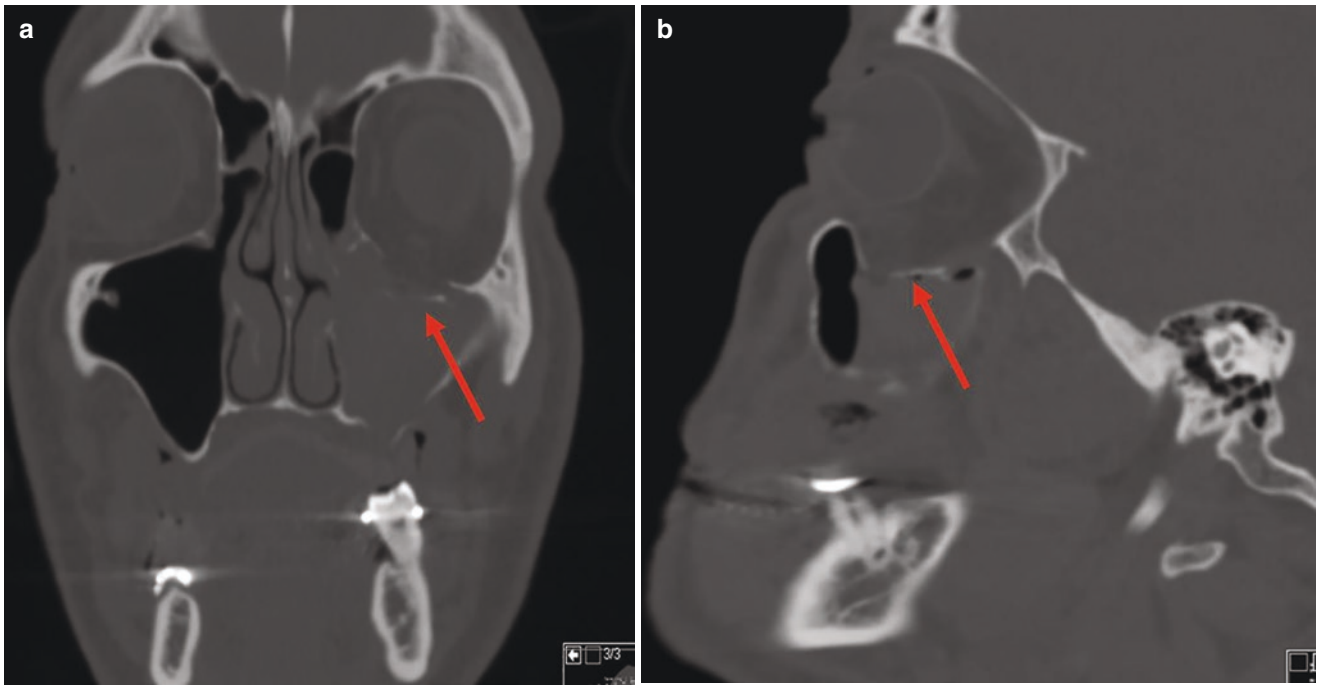


Fig. 25.12 Maxillofacial CT in the coronal (**a**) and sagittal (**b**) view demonstrating a left orbital floor fracture with displacement of the floor into the left maxillary sinus (arrow)

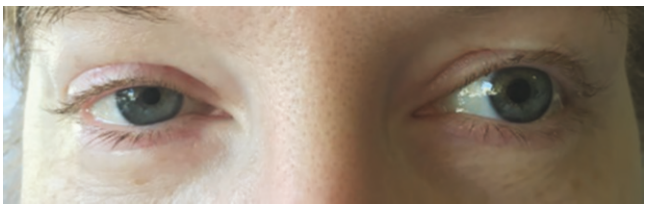


Fig. 25.13 A clinical photo of a patient with anisocoria secondary to right superior cervical ganglion compression (Horner syndrome)

foreign body impaction. Proper consultation with ophthalmology is imperative for the evaluation and diagnosis of ocular trauma.

As with the evaluation of other maxillofacial injuries, CT scans are the standard of care when assessing a patient with orbital trauma. The CT scan may be a part of the maxillofacial CT scan protocol, or a dedicated orbital CT with 1 mm cuts may be obtained to assess for orbital trauma. The coronal and sagittal views of the orbits are particularly helpful in diagnosing injuries to the orbital walls with or without muscle entrapment whereas an axial view can provide visualization of a retrobulbar hematoma. An MRI can be useful in assessing soft tissue injury or muscular entrapment and foreign body impaction.

Treatment

Indications for orbital wall trauma are functionally and cosmetically driven. Loss or impairment of visual acuity or entrapment should be absolute indications for surgical intervention and should be completed in a timely manner to avoid permanent deficits. Emergent management of a retrobulbar hematoma includes a lateral canthotomy and initiation of intravenous steroids. If there are no indications for emergent surgical management, it is reasonable to delay surgical repair until after the edema resolves at which time the patient can be re-evaluated to assess for the extent of the deficit (e.g., diplopia secondary to enophthalmos) and a more accurate surgical repair may be accomplished.

Naso-Orbito-Ethmoid Fractures

The naso-orbito-ethmoid (NOE) region houses the medial canthal tendon and lacrimal apparatus and, due to its proximity, is frequently associated with central nervous system injuries and CSF rhinorrhea [10]. Adequate diagnosis and early management of NOE fractures are critical in restoring functional and cosmetic deficits including telecanthus, orbital dystopia, blunted palpebral fissures, and cerebrospinal fistula formation [10–14].

Anatomy

The NOE region consists of an intersection of the cranium, orbit, nose, and maxilla [15]. The frontomaxillary buttress is the primary vertical support and the supraorbital rims, infraorbital rims, and zygoma serve as the horizontal support in this region. The medial portion of this region is made up of

weaker, thinner bones, including the lamina papyracea, lacrimal bones, and the perpendicular plate of the ethmoid bone, which act as a "crumple zone." The proximity of these structures to the cribriform plate posteriorly results in common associated injuries including CSF rhinorrhea, pneumocephalus, or olfactory dysfunction.

The medial canthal tendon, which is an extension of the tarsal plates of the upper and lower eyelids and orbicularis oculi muscles, anchors the medial portion of the orbit and pulls the medial commissure forward and inferiorly [16]. An NOE fracture typically results in the disruption in the attachment of the medial canthal tendon, leading to the widening of the intercanthal distance due to unopposed muscle pull of the orbicularis oculi muscle [15]. Although there are ethnic variations, a normal intercanthal distance is between 28 mm and 35 mm [17, 18]. An intercanthal distance of over 35 mm is indicative of an NOE fracture and greater than 40 mm is considered diagnostic [19].

The lacrimal apparatus is composed of the lacrimal gland in the superolateral aspect of the orbit and the drainage system medially [15]. Tears formed in the lacrimal gland drain into the upper and lower canaliculi, which converge into the common canaliculus then the lacrimal sac, the nasolacrimal duct, and finally into the inferior meatus of the nasal cavity. Trauma to the NOE region may disrupt this system and result in epiphora.

Diagnosis

Patients with NOE fractures often demonstrate edema and ecchymosis in this region. Nasal dorsal flattening, retrusion, and gross mobility are indicative of an NOE fracture [15]. The NOE region and orbital rims should be palpated for stepoffs. Rounding of the medial commissures and a widened intercanthal distance are also indicative (Fig. 25.14). The attachment of the medial canthal tendon can be evaluated with the traction or "bowstring" test where lateral traction is applied to the eyelids while palpating the medial canthal tendon attachment. The test is considered positive when the bowing of the fractured segment is palpable.

Intranasal exam should be completed to evaluate the nasal septum, turbinates, and mucosa. CSF rhinorrhea is indicative of a base of skull and cribriform plate fracture. Disruption of the lacrimal system may result in epiphora and can be confirmed with a Jones test [20].

NOE fractures are classified into three types and can present unilaterally or bilaterally. Most commonly, NOE fractures are diagnosed based on the Markowitz type I, II, or III classification, which was first described by Markowitz in 1991 [21] (Fig. 25.15). A Markowitz type I NOE fracture consists of an intact medial canthal tendon attachment to a single, central fragment fracture and is the simplest form of the NOE fracture. A Markowitz type II fracture is defined by a comminuted central fragment with the medial canthal tendon attached to a single segment large enough to be fixated. The most complex NOE fracture is the Markowitz type III, which is demonstrated by severe comminution with the avulsion of the medial canthal tendon or attachment to a fractured segment too small to be fixated.

A maxillofacial CT with thin cuts of 1 mm or less and 3D reconstruction will aid in the diagnosis and treatment planning of NOE fractures.

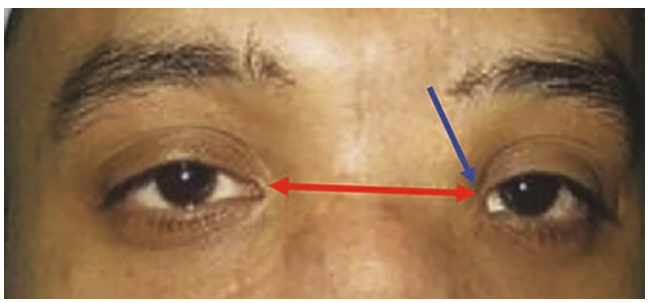


Fig. 25.14 A clinical photo of a patient with traumatic telecanthus (red arrow) and round of the left medial commissure (blue arrow) indicative of an NOE fracture

Treatment

The surgical management of NOE fractures encompasses a myriad number of techniques, and a comprehensive review of these techniques is beyond the scope of this chapter. The overall goal of treatment of NOE fractures includes reconstruction of the medial orbital wall and reducing the medial canthal tendon to the appropriate preinjury anatomical location. Reduction of the fractures may require rigid fixation of the fractured segments with plates and screws or transnasal canthopexy, or both. If the lacrimal system is noted to be injured, a dacryocystorhinostomy may be indicated.

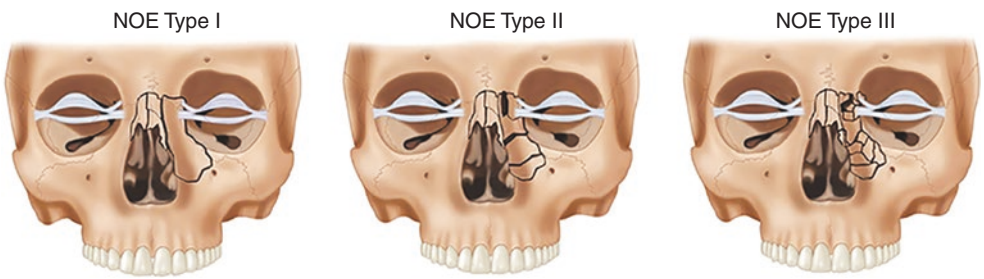


Fig. 25.15 Illustrations of NOE type I, II and III fractures [22]

The fractures can be accessed via existing lacerations or a combination of coronal, lower eyelid, and an intraoral vestibular incision. Once the NOE region has been adequately exposed, identification and assessment of the medial canthal tendon and fractured bony segments will dictate the surgical techniques and steps for repair.

Nasal Fractures

Nasal bones are the most frequently fractured bone of the face in adults and, due to the location on the face, less force is required to fracture this structure than any other facial bone [23–25]. Nasal bone fractures are most common due to motor vehicle accidents, interpersonal violence, and sports related trauma [26].

Anatomy

The nasal complex is composed of the following structures: paired nasal bones, midline bony and cartilaginous septum, upper and lower cartilages, underlying nasal mucosa, and turbinates [27, 28]. The vascular supply is from both the external and internal carotid systems. The second division of the trigeminal nerve (CN V_2) innervates this region.

Diagnosis

A thorough exam of the nasal complex is completed with an external and internal exam. The nasal complex is evaluated for edema, ecchymosis, abrasions, or lacerations. The nasal bridge is examined for deviation (Fig. 25.16), crepitus, or mobility, which are indicative of an underlying bony or cartilaginous fracture. Epistaxis will likely be a presenting sign of a nasal fracture; however, CSF rhinorrhea should be ruled out. A widened intercanthal distance should raise suspicion for an NOE fracture. Intranasally, the nasal septum should be assessed for deviation and the presence of a septal hematoma. The significant deviation may result in inadequate nasal airflow with obstruction. Anosmia may be present if the cribriform plate has been violated. On CT imaging, the fractures and nasal deviation can be best viewed in the axial plane (Fig. 25.17). Although there is not one universally accepted classification, nasal fractures can be described as open vs closed, deviated vs non-deviated, and comminuted or non-comminuted [29].

Treatment

Indications for the management of nasal fractures are based on functional and cosmetic factors. Goals of management include restoration of anatomy (e.g., correcting a cosmetic deformity) and adequate nasal airflow. Surgical management of nasal fractures can be closed and/or open, and under local anesthesia, conscious sedation, or general anesthesia. Closed reduction of fractures can be stabilized with an external thermoplastic splint with or without intranasal packing. Open reduction and internal fixation of nasal bone fractures with a strut graft may be indicated in more severe cases or if concomitant with an NOE fracture.

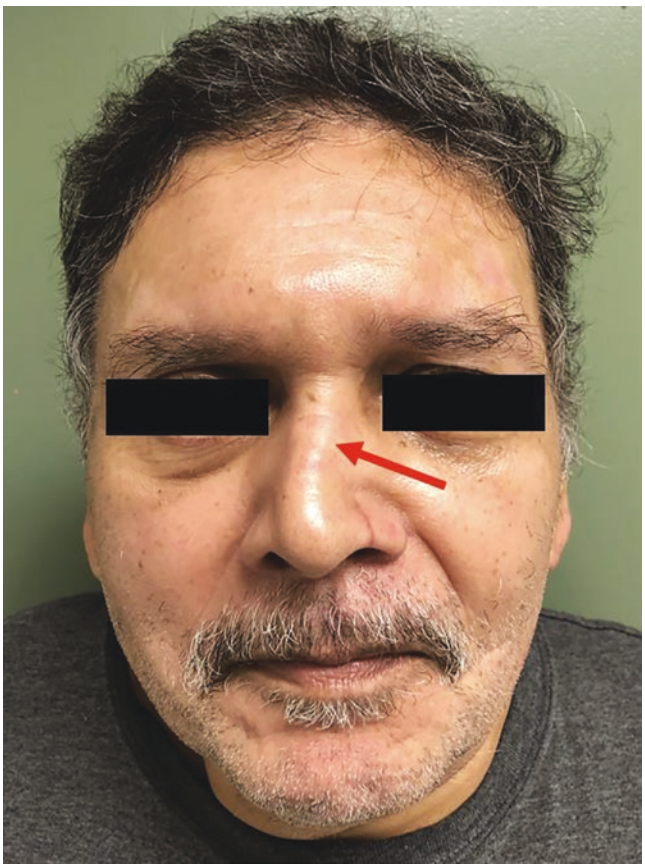


Fig. 25.16 A patient who sustained a nasal fracture presenting with a deviation of the nasal dorsum (arrow)

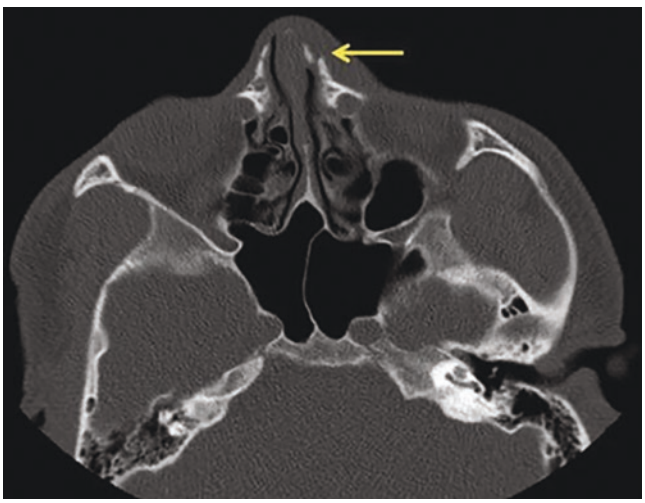


Fig. 25.17 A maxillofacial CT in the axial plane demonstrating a nasal bone fracture (arrow) with deviation to the right

Pediatric Midface Trauma

Much of the evaluation, diagnosis, and management of pediatric midface trauma are similar to that of adults; however, a few key differences exist between the pediatric and adult midface trauma patient. The full breadth and depth of the evaluation, diagnosis, and management of pediatric midface trauma can be found in other resources.

Motor vehicle accidents, falls, sports related injuries, and interpersonal violence are common causes of pediatric trauma. Obtaining an adequate history from a pediatric midface trauma patient may be challenging due to communication (e.g., a young, non-communicative child), absent or distraught caregiver or family member, and the need for urgent or emergent intervention at the time of evaluation. The mnemonic "AMPLE" or another, thorough and systematic approach to the patient's history should be utilized.

Clinical and radiographic exam of the patient must consider the age and physiologic differences to that of an adult patient. Because of the relative increase in body surface area due to a smaller body size, pediatric injuries in one area should raise suspicion for the involvement of adjacent structures [30]. Initial evaluation with ATLS should be completed, including securing the airway, and ruling out life or limb-threatening injuries.

Fractures of the pediatric facial skeleton are not as common as that in the adult, owing to the elastic nature of pediatric bone. The underdevelopment of maxillofacial sinuses (e.g., maxillary) and unerupted dentition act as additional buttresses to protect the pediatric midface from fractures. The pattern of maxillofacial development also contributes to the pediatric midface fracture pattern. The cranium is the most likely structure to be fractured in infants due to its relative size when compared to the maxillofacial skeleton, but as the child reaches age 6 or 7 the growth of the midface and mandible in conjunction with the pneumatization of sinuses and eruption of teeth results in an increased incidence of midface and mandibular fractures.

Evaluation of pediatric midface trauma is completed with a thorough clinical and radiographic exam. Diagnostic imaging with a CT scan with lower radiation or other imaging modalities such as MRI should be considered in the pediatric patient.

Surgical management for pediatric midface fractures should consider the growth potential of the patient given the patient's age. For example, if open reduction of a midface fracture is indicated in a growing child, the use of resorbable plates or removal of non-resorbable, titanium plates after healing has completed should be considered to reduce the likelihood of growth disturbances. Although the management of adolescent trauma patients mirrors that of adults, all pediatric trauma patients should be followed to assess long-term growth, development, and function.

Complications

Thorough documentation of the preoperative exam is imperative to record preoperative deficits especially relating to neurologic deficits and globe injuries. In addition to general post-operative complications such as excessive bleeding and infections, functional and/or cosmetic complications of midface trauma repair include enophthalmos, diplopia, telecanthus, epiphora, and dental malocclusion. More urgent and emergent complications include ocular muscle entrapment (can be caused iatrogenically at the time of repair when it did not exist on preoperative exam) and retrobulbar hematoma, which require immediate assessment and timely repair to avoid resultant functional deficits including blindness.

Conclusion

The management of midface maxillofacial trauma is an important aspect of caring for a trauma patient. These patients often require a multidisciplinary approach by medical clinicians. A basic understanding in the evaluation, diagnosis, and treatment of these injuries will allow for the expeditious and consistent management of these patients, increasing the likelihood of positive patient outcomes.

References

1. Yeung AY. Initial and postoperative management of the craniomaxillofacial trauma patient. In: Fonseca RJ, editor. Oral and maxillofacial surgery. Missouri: Elsevier; 2018. p. 1–8.
2. Manson PN, Hoopes JE, Su CT. Structural pillars of the facial skeleton: an approach to the management of Le fort fractures. Plast Reconstr Surg. 1980;66:54.
3. Manson PN, Shack RB, Leonard LG, et al. Sagittal fractures of the maxilla and palate. Plast Reconstr Surg. 1983;72:484.
4. Gruss JS, Mackinnon SE. Complex maxillary fractures: role of buttress reconstruction and immediate bone grafts. Plast Reconstr Surg. 1986;78:9–22.
5. Perry MT, Moutray T. Advanced trauma life support (ATLS) and facial trauma: can one size fit all? Part 4: "can the patient see?" timely diagnosis, dilemmas and pitfalls in the multiply injured, poorly responsive/unresponsive patient. Int J Oral Maxillofac Surg. 2008;37:505–14.
6. Fonseca RJ, Allen S, Awad MK, Fonseca M. Initial assessment and intensive care of the trauma patient. In: Fonseca RJ, Walker RV, Barber HD, Powers MP, Frost DE, editors. Oral & maxillofacial trauma. 4th ed. Missouri: Elsevier; 2013. p. 48–76.
7. Bellamy JL, Mundinger GS, Reddy SK, et al. Le fort II fractures are associated with death: a comparison of simple and complex midface fractures. J Oral Maxillofac Surg. 2013;71:1556–62.
8. Zachariades N, Mezitis M, Anagnostopoulos D. Changing trends in the treatment of zygomaticomaxillary complex fractures: a 12-year evaluation of methods used. J Oral Maxillofac Surg. 1998;56(10):1152–6. discussion 1156–1157.
9. Je at uwo at English Wikipedia., CC BY 2.5 <https://creativecommons.org/licenses/by/2.5>, via Wikimedia Commons.
10. Cruse CW, Blevins PK, Luce EA. Naso-ethmoid-orbital fractures. J Trauma. 1980;20:551.

11. Converse JM, Smith B. Naso-orbital fractures. Trans Am Acad Ophthalmol Otolaryngol. 1963;67:622.
12. Converse JM, Smith B. Naso-orbital fractures and traumatic deformities of the medial canthus. Plast Reconstr Surg. 1966;38:147.
13. Dingman RO, Grabb WC, Oneal RM. Management of injuries of the naso-orbital complex. Arch Surg. 1969;98:566.
14. Duvall AJ, Banovetz JD. Nasoethmoidal fractures. Otolaryngol Clin N Am. 1976;9:507.
15. Morris CD, Tiwana PS. Diagnosis and treatment of midface fractures. In: Fonseca RJ, Walker RV, Barber HD, Powers MP, Frost DE, editors. Oral & maxillofacial trauma. 4th ed. Missouri: Elsevier; 2013. p. 416–50.
16. Jank S, Schuchter B, Emshoff R, et al. Clinical signs of orbital wall fractures as a function of anatomic location. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;96:149.
17. Tharanon W, Ellis E 3rd. A method to accurately determine the preinjury intercanthal distance. J Oral Maxillofac Surg. 1991;49:1023.
18. Merkx MA, Freihofer HPM, Borstlap WA, et al. Effectiveness of primary correction of traumatic telecanthus. Int J Oral Maxillofac Surg. 1995;24:344–7.
19. Paskert JP, Manson PN, Iliff NT. Nasoethmoidal and orbital fractures. Clin Plast Surg. 1988;15:209.
20. Jones LT, Wobig JL. Surgery of the eyelids and lacrimal system, vol. 59. Birmingham, Ala: Aesculapius; 1976. p. 742.
21. Markowitz BL, Manson PN, Sargent L, et al. Management of the medial canthal tendon in nasoethmoid orbital fractures: the importance of the central fragment in classification and treatment. Plast Reconstr Surg. 1991;87:843.
22. Harold Lee HB, Grecco GG, Moorthy M, Burgett K. Midfacial fractures. In: Cohen A, Burkat C, editors. Oculofacial, orbital, and lacrimal surgery. Cham: Springer; 2019. https://doi.org/10.1007/978-3-030-14092-2_58.
23. Rhee SC, Kim YK, Cha JH, et al. Septal fracture in simple nasal bone fracture. Plast Reconstr Surg. 2004;113:45–52.
24. Murray JA, Maran AG, Mackenzie IJ, et al. Open v closed reduction of the fractured nose. Arch Otolaryngol. 1984;110:797–802.
25. Haug RH, Prather JL. The closed reduction of nasal fractures: an evaluation of two techniques. J Oral Maxillofac Surg. 1991;49:1288–92.
26. Ziccardi VB, Braidy H. Management of nasal fractures. Oral Maxillofac Surg Clin North Am. 2009;21:203–8.
27. Oneal RM, Beil RJ. Surgical anatomy of the nose. Clin Plast Surg. 2010;37:191–211.
28. Daniel RK, Letourneau A. Rhinoplasty: nasal anatomy. Ann Plast Surg. 1988;20:5–13.
29. Fattahi T. Nasal fractures. In: Miloro M, Ghali GE, Larsen P, Waite P, editors. Peterson's principles of oral and maxillofacial surgery. 3rd ed. Connecticut: People's Medical Publishing House; 2012. p. 539–44.
30. Browne GJ, Cocks AJ, McCaskill ME. Current trends in the management of major paediatric trauma. Emerg Med. 2001;13:418–25.

Part V

Other

Michael T. Goupil

Forensic Odontology

26

Jacqueline S. Reid

Introduction

The Merriam-Webster dictionary defines *forensic* as belonging to, used in, or suitable to courts of judicature or to public discussion and debate. A forensic scientist utilizes specific professional skills to gather and analyze evidence to assist the justice system for the public good.

Forensic analysis of evidence can come in many forms and often requires those with special skills and knowledge to interpret and explain the causal relationships of the facts and evidence collected in the investigation of a crime. Subject matter experts are routinely used to assist the trier of fact in their deliberations. These subject matter experts include but are not limited to pathologists, anthropologists, crime scene investigators, entomologists, accountants, toxicologists, digital multimedia IT specialists, document and handwriting experts, radiologists, and dentists (many belonging to sections of the American Academy of Forensic Science, (AAFS)). To that end, any special or technical skill applicable to the subject at hand can be applied.

Forensic Odontology

Forensic odontology (forensic dentistry) is the application of dentistry to civil and criminal law.

A forensic dentist is called upon when a civil or criminal event requires the analysis of some form of dental evidence.

Dental evidence may include the investigation of fraud, the standard of care, negligence, bitemark pattern injury analysis, child abuse, intimate partner violence (IPV), elder abuse, dental age assessment, immigration issues, and sex trafficking. This often requires the presentation of testimony as an expert witness. By far, the most prevalent use of dentistry in forensics is for the identification of human remains.

Historical Use of Dentistry for Identification

One famous example of dental identification involved Paul Revere who is best known for his famous horse ride from Boston to Lexington to warn residents of the invasion of British Troops. Paul Revere was a silversmith and when economic times became difficult, he would provide dental services cleaning teeth and wiring into place false teeth made from ivory. After the American Revolutionary War, he performed the first recorded dental autopsy and identification. General Warren, a well-known surgeon in Boston, was conscripted into the army. At the battle of Bunker Hill, he was shot and killed and buried in a mass grave without his uniform. After the war, the mass grave was exhumed, and General Warren was identified by Paul Revere based on the dental work Revere had made for Warren years earlier. Revere replaced a missing tooth with a walrus tooth and had wired it into his mouth [1].

Identification

In addition to determining the cause and manner of death, the medical examiner has the legal mandate to identify the deceased and issue a death certificate.

When it comes to establishing an identification of an individual, there are four scientific and legally recognized means of making a valid identification that will allow for the processing of a death certificate.

Visual
DNA
Fingerprint
Dental/medical

J. S. Reid (✉)
Dental Residency Program, Hospital Dentistry, Robert Wood Johnson University Hospital, New Brunswick, NJ, USA

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_26

Visual

Visual identification is a method that is used when remains are intact, not decomposed, are viewable and/or when the death was witnessed. When a visual identification is made on a viewable body that is not disfigured, it would always be accompanied by other identifying features. These features include any identifying marks, tattoos, scars, and piercings. Additionally, any personal effects found with the remains including but not limited to ID cards, jewelry, cell phones, etc. would be used to help strengthen the visual identification.

DNA

DNA is a biometric method of identification. A DNA comparison relies on the ability to obtain antemortem data. However, unlike other antemortem data that involve the gathering of evidence from the living presumptive decedent, DNA can utilize familial relatives. Of course, the best sources for DNA material are from a reference sample of the decedent obtained during life [2]. Examples of these DNA sources would include blood, a tissue biopsy slide, a pap smear, tooth remnants, and a hair sample (with roots). A secondary source of DNA from an individual would include a toothbrush, comb, bedding, or clothing. If there are no reference samples directly from the individual, a DNA sample from a biological relative(s) (mitochondrial DNA from a maternal relative) can be utilized. This kind of DNA testing requires more time, effort, and a higher cost than other identification methods. The degree to which human remains are fragmented or degraded is also an important consideration in the value of DNA analysis to the identification process. Understandably, large intact body parts lend themselves to identification by less costly and time-consuming methods. These include dental remains, radiographic imaging, and fingerprints [2].

Fingerprint

Identification by fingerprint is a biometric method of human identification, commonly used when the soft tissue of the fingers is intact and an adequate impression or image of the friction ridges can be obtained. Further, it assumes that antemortem fingerprint records are available for the individual [2].

Burned, severely decomposed, skeletal, and fragmented remains may not readily exhibit fingerprints [2]. Fingerprints, however, do have the advantage of having large known national and international databases to search and, therefore, do not require a presumptive identification in order to obtain or find antemortem records and/or evidence.

Medical

Using radiological and anthropological biometric methods of identification relies on the unique characteristics of the human skeleton and comparing postmortem radiographic imaging with antemortem imaging and any written medical records [2]. The examiner is looking for bony anomalies, heal fractures, pathology, and medical and surgical hardware, which may or may not have serial numbers associated with them.

Often, an individual's radiologic images are not available, but more advanced images such as MRIs and CT scans may exist. These imaging studies can be used to make comparisons to postmortem records, as long as the examiner understands how to compare the views and account for the differences in interpreting a postmortem radiographic view with the antemortem imaging view [2].

Dental

Dental identification is the most common biometric method for identifying burned, decomposed, skeletonized, and fragmented remains for multiple reasons [2].

- Tooth enamel is the hardest biological substance in the human body. The teeth, especially the molars, are well protected by soft tissue structures such as the tongue, facial musculature, and adipose tissue.
- Teeth can survive prolonged immersion in fluid, soft tissue decomposition, desiccation, extensive trauma, and heat in excess of 1000 °F.
- Tooth morphology, the presence or absence of teeth, tooth position, dental restorations, dental and oral pathology, bony anatomy, periodontal anatomy, maxillary and frontal sinus morphology, and many other features of the oral cavity and maxillofacial complex are available for comparison. No two individuals have the exact same dental features.
- Many people have been to a dentist and have a dental chart and radiographs.
- A postmortem dental examination (clinical and radiographic) can be done quickly and inexpensively.
- Dental records of missing persons are kept in several national databases to compare with newly discovered remains.
- In mass fatality incidents, it is often the most expedient method for identifying burned, fragmented, and decomposed human remains [2].

Since the complete adult human dentition consists of 32 teeth that may be virgin, missing, or restored on one or more of each tooth's five surfaces, a great many combinations of

dental patterns exist that are helpful in making a dental identification. In addition, the postmortem radiographic appearance of the victim's teeth, restorations, bone, anomalies, and maxillary and frontal sinuses are essential when determining a dental identification [2].

Dental Records

The dental record is the primary form of dental evidence in forensic dentistry and can include: examination forms, dental radiographs, laboratory prescriptions, treatment/progress notes, photographs, and study models. All can provide valuable information regarding the patient. Accurate records with thorough documentation should contain an odontogram (dental charting) of the patient's existing restorations, anomalies, missing teeth, etc. (Fig. 26.1).

All dental treatment rendered should be detailed in the treatment /progress notes.

Typical radiographs found in a patient chart would include a full mouth series of radiographs (Fig. 26.2) usually taken in a 3–5-year interval for adult patients, and annual bitewing radiographs of the maxillary and mandibular molars in occlusion (screening for caries) Many adolescents and adults will have panoramic radiographs as part of their dental charts associated with screening for orthodontics, evaluation of third molars for removal, or examination of pathologic structure trauma, and infections of the peri-oral structures.

For a patient in active treatment, there may be study models, working models, removable appliances, digital scans, cone beam computed tomography imaging, and dental and facial photographs associated with their dental record. Any of this information can be useful to assist in the dental identification of an individual. But by far, the "*gold standard*" of dental identifications is dental radiographs [3].

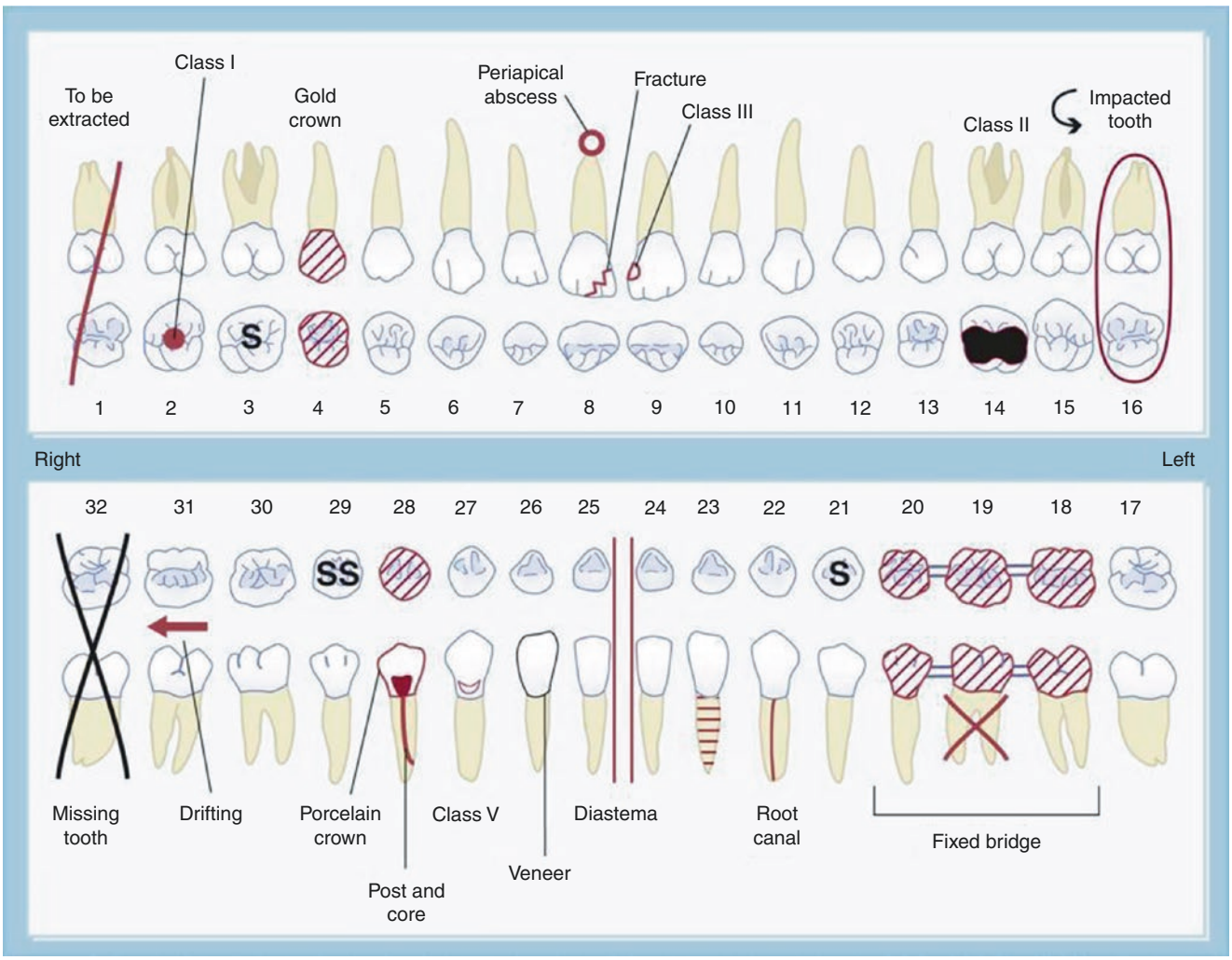


Fig. 26.1 Odontogram charting symbols. Note. Anatomic diagram, in Chap. 12, The Dental Examination, Pocket dentistry, in 2015. (https://www.pocketdentistry.com/12-the-dental-examination/)

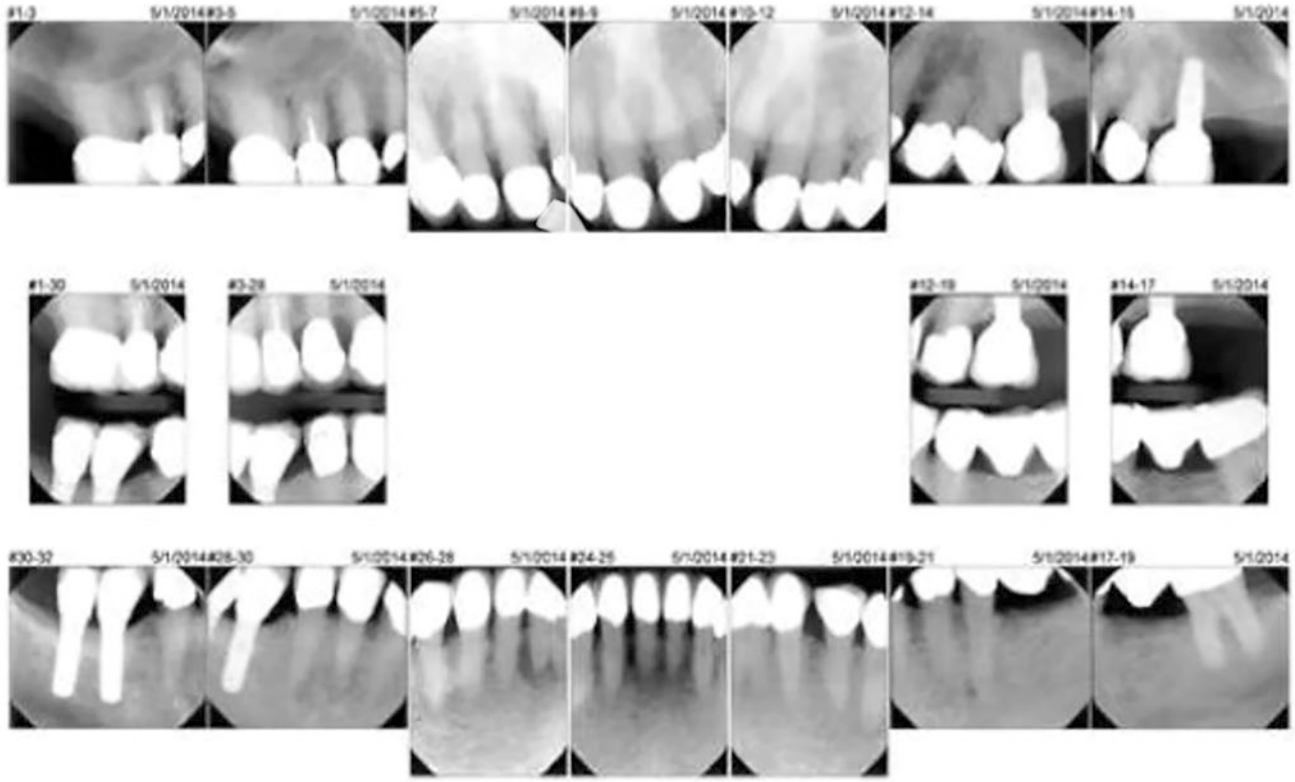


Fig. 26.2 Typical full mouth series of radiographs. Note. Dental Identification Report, Reid, J. (2014)" own work"

The radiological profile of teeth, their morphology, restorations, bone anomalies, trabecular bony patterns, and anatomy of the maxillary and frontal sinus are all essential to make a determination of identity.

The dental record is a legal document that is owned by the dental office as a custodian. Records must be maintained by the dental office for a minimum of 7 years after the last date of a patient visit.

The dental record of an individual while they are alive is called the *antemortem* record. The dental record of a deceased individual performed by a dentist in the morgue is called the p*ostmortem* dental record.

When a dental record is requested by the medical examiner it is not subject to HIPPA via 45 code of federal regulations 164.512 (g) (1).

Nomenclature in Dental Charts

Antemortem dental records from different countries may use different tooth numbering systems (Fig. 26.3), which can add difficulty when deciphering the chart. In the United States, the most common system is *universal.*

Postmortem Dental Evidence Collection

Like an antemortem dental record, a postmortem record typically contains dental charting and examination, a full mouth series of dental radiographs, and photographs of the decedent, collected by the forensic dentist performing the dental autopsy.

The dental autopsy, depending on the condition of the remains, can be very easy or extremely difficult [4]. It is necessary to have a completely unrestricted view of the oral cavity in order to collect the dental evidence. Gaining access to dental structures in cases with burned remains is challenging, and usually requires the forensic dentist to perform resection and reflection of the boney and soft tissues to gather the postmortem dental evidence [4]. The procedures used to gain access to the teeth can vary and the dentist must always consider the condition of the remains when selecting the methods in which to collect the dental evidence.

The request to perform a dental identification on a decedent comes from the medical examiner or coroner. The dental autopsy is completed after the medical examiner and /or forensic pathologist performs their autopsy. Whenever the collection of dental evidence requires dissection of the facial structures, permission must be given by the medical examiner first.

	Lower Right								Lower Left							
	3M	2M	1M	2P	1P	C	I2	I1	I1	I2	C	1P	2P	1M	2M	3M
Other	LR8	LR7	LR6	LR5	LR4	LR3	LR2	LR1	LR1	LR2	LR3	LR4	LR5	LR6	LR7	LR8
Hareup	8-	7-	6-	5-	4-	3-	2-	1-	-1	-2	-3	-4	-5	-6	-7	-8
Palmer	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8
Universal	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17
FDI	48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38
Bosworth	H	G	F	E	D	C	B	A	A	B	C	D	E	F	G	H
Lowlands	M3	M2	M1	P2	P1	C	I2	I1	I1	I2	C	P1	P2	M1	M2	M3
Europe	d8	d7	d6	d5	d4	d3	d2	d1	g1	g2	g3	g4	g5	g6	g7	g8
Holland	diM3	diM2	diM1	diP2	diP1	diC	dil2	dil1	gil1	gil2	giC	giP1	giP2	giM1	giM2	giM3
FDI Modified	38	37	36	35	34	33	32	31	41	42	43	44	45	46	47	48
Other	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17

	Upper Right								Upper Left							
	3M	2M	1M	2P	1P	C	I2	I1	I1	I2	C	1P	2P	1M	2M	3M
Other	UR8	UR7	UR6	UR5	UR4	UR3	UR2	UR1	UL1	UL2	UL3	UL4	UL5	UL6	UL7	UL8
Hareup	8+	7+	6+	5+	4+	3+	2+	1+	+1	+2	+3	+4	+5	+6	+7	+8
Palmer	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8
Universal	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
FDI	18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
Bosworth	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8
Lowlands	M3	M2	M1	P2	P1	C	I2	I1	I1	I2	C	P1	P2	M1	M2	M3
Europe	D8	D7	D6	D5	D4	D3	D2	D1	G1	G2	G3	G4	G5	G6	G7	G8
Holland	sdM3	sdM2	sdM1	sdP2	sdP1	sdC	sdI2	sdI1	ssg1	sgI2	sgC	sgP1	sgP2	sgM1	sgM2	sgM3
FDI Modified	18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
Other	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16

Fig. 26.3 Common tooth numbering systems. Note. Common Tooth Numbering Systems Chart. From, ABFO image series, "Medical Examiners and Coroners" power point presentation, 2015

Comparison

All methods of human identification, including fingerprint, visual, anthropologic, radiographic, and DNA involve comparison of known antemortem data to collected postmortem data to establish a positive identification. These comparisons are based on the idea that each person has a unique data profile that can be compared to the profile of the unidentified person [2].

Comparison of dental structures is based on the discernible difference in anatomy and morphology of teeth. Along with the human alteration of teeth through restorations and iatrogenic effects that can be visualized, an established profile of these features is unique, stable, and explainable even over the passage of time.

Once all the postmortem evidence has been collected and the antemortem records have been received and analyzed, a comparison can be performed. The forensic odontologist will do a side-by-side review of the antemortem data to the postmortem data. Each tooth should be compared and annotated by the dentist following these classifications:

- If there is information that is missing, usually from the antemortem data,
- then *no comparison* can be made for that tooth.
- When the antemortem and postmortem data are the same for a tooth, the finding is noted as *consistent*.
- When there is a difference between the antemortem charting and the postmortem charting it is noted as *inconsistent.*
- When a finding is found to be inconsistent, there are two variables to consider:
- Is it *explainable* or is it *unexplainable?*

An *"explainable inconsistency"* between the antemortem records of a tooth and the postmortem condition of a tooth would be one that can be explained by the passage of time. Further, the alteration found in the dental condition is chronologically based in one direction.

For example, a tooth in the antemortem condition has no restored surfaces (virgin), but in the postmortem findings, the tooth has a filling (restoration). The path/direction of change in this case is logical; at some point between the antemortem and postmortem data collection, the decedent had received the restoration. In this case, the dentist will carefully review all the records and radiographs, and note other distinguishing features between the antemortem and postmortem condition of the tooth, so the inconsistency can be reconciled.

An *"unexplainable inconsistency"* between antemortem and postmortem records of a tooth, would be unexplainable

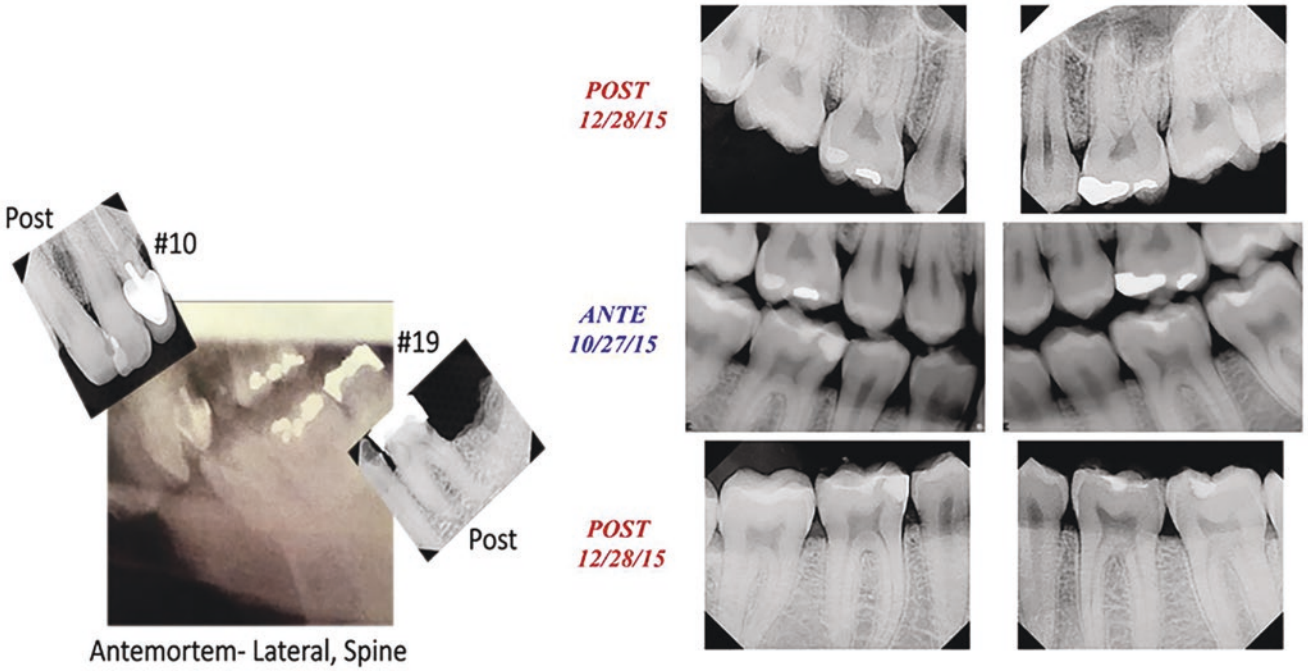


Fig. 26.4 Comparisons. Note. Dental Identification Reports, Reid, J. (2019)"own work"

with the passage of time. For example, a tooth is missing in the antemortem condition but present in the postmortem findings.

It is important to note just one unexplainable inconsistency in the comparison of the antemortem to postmortem records represents an irreconcilable difference and thereby nullifies the identification [2].

Additional Comparison Techniques

The evaluation of antemortem data and comparison to the postmortem data are not just limited to side-by-side comparison of dental radiographs. Removable appliances such as bleaching trays, night guards, sports guards, orthodontic appliances, removable partial dentures, and full dentures can be used when available by placing the appliance in the decedents mouth to confirm the fit [2]. When a decedent is found with a denture in place, it should be examined for identifying information. Most states have laws mandating dentures and other removable dental prosthetics have identifying information embedded into the acrylic [2]. Another source of information is from the study models made from an impression of the dental arches and compared to the teeth of the decedent.

When dental records are not available, it is important to consider other medical records that may have dental information that can be used for comparison. Often there is valuable dental information found in head CT scans, and skull and spinal radiographs associated with emergency room visits [2] (Fig. 26.4).

While not as desirable as other records for comparison, a close-up full smile photograph in high resolution of the individual taken while alive can be used for superimposition. With the advent of social media, selfies, Facebook, etc., and the use of high-resolution cameras on smartphones, this information is often readily available [2].

To do this, the forensic dentist would create an overlay to compare the anterior six upper teeth contained in the smile view.

Terminology

The American Board of Forensic Odontology (ABFO) has defined the categories for the levels of certainty for a dental identification. They are listed below.

Positive Identification.

The antemortem and postmortem data are concordant in sufficient detail to establish that they are from the same individual and there are no irreconcilable discrepancies [5].

Possible Identification.

The antemortem and postmortem data have consistent features, but, due to the quality of either the postmortem remains or the antemortem evidence, it is not possible to confirm a dental identification [5].

Insufficient Evidence.
The available information is insufficient to form a conclusion [5].
Exclusion.
The antemortem and postmortem data are clearly irreconcilable.
This is a valid form of identification in certain instances [5].

Uses and Limitations

As stated before, dental identification is the most requested and widely known application of forensic odontology worldwide [4].

Forensic dentists assist local jurisdictions for all manner of nonviewable and questionable remains from fires, fishing and boating accidents, car accidents, suicides, homicides, etc. The key feature in these types of cases is there is a presumption as to the decedent(s) identity. Investigators will obtain the antemortem dental records and, once the dentist completes the dental autopsy, can complete the comparison of data to confirm or validate the presumptive ID to a scientifically accepted positive ID for issuance of a death certificate [2].

When there is no presumptive identification as in the case of the discovery of remains in a clandestine grave, the forensic dentist will perform a postmortem examination, including photographs, radiographs, and dental charting [2]. All the postmortem data collected, including anthropologic, DNA (when able) and dental data, are put in multiple computer databases for potential linkage to a missing person's dental profile to potentiate a positive identification. (NCIC, NamUs).

In mass fatality incidents (MFI) resulting from such things as plane crashes, train accidents, building collapses, terrorist attacks, suicide bombers, floods, fires, mudslides, hurricanes, and tsunamis, forensic dentists trained to respond are called to assist along with pathologists, anthropologists, and DNA and fingerprint experts [6].

These disasters can be open or closed population events. Closed population events include plane crashes where a manifest exists of the victims, and an open population event includes mudslides or avalanches [6].

While dental identification is a fast, economically effective, and reliable means of making an identification, it hinges on the availability of antemortem dental records or other medical records containing dental information. Dental records that do not contain radiographs and only contain charting and progress notes should be used with caution when making the determination of a positive identification [4].

Dental Age Assessment

Forensic age assessment has been defined as the scientific process that estimates an individual's chronologic age by assessing skeletal and dental development and maturation [7].

The scientific rationale for dental age assessment is divided into three categories: tooth formation and development, post-formational changes within the tooth, and biochemical changes.

Historical and Current Uses of Dental Age Assessment

Over 2000 years ago, the Romans utilized molar eruption patterns to determine if a male individual had reached the age for military conscription [8]. Today, dental age assessment is commonly used to narrow the search of possible unidentified victims, estimate the age at death of an individual, aid immigration authorities with undocumented individuals, and aid the legal system in determination of the legal age of the majority [7].

Tooth Formation and Development

Tooth formation and developmental growth changes are changes that occur through the progressive morphological development of the crown, root, and apex of any given tooth and/or its timed emergence and eruption sequence. These observations are used to assess the age of infants, children, and adolescents. Dental age assessment techniques have long been established as the most accurate indicators of chronologic age in these age groups [1].

In infants and children, two types of methods are available to perform these age assessments—atlases and charts. Both require staging of developing teeth, and both necessitate the use of good-quality radiographs.

Atlases utilize schematic diagrams representing the morphologic and developing tooth structures, displaying an associated eruption pattern. *Eruption* is defined as the process of a tooth's migration from its initial position within its bony crypt until it establishes occlusion with the opposing dentition [7]. This term however is now more commonly referred to as emergence (Fig. 26.5).

The adolescent interval of human development follows the onset of puberty through the time an individual reaches adulthood. For purposes of forensic age assessment, this age interval is 12–20 years [1].

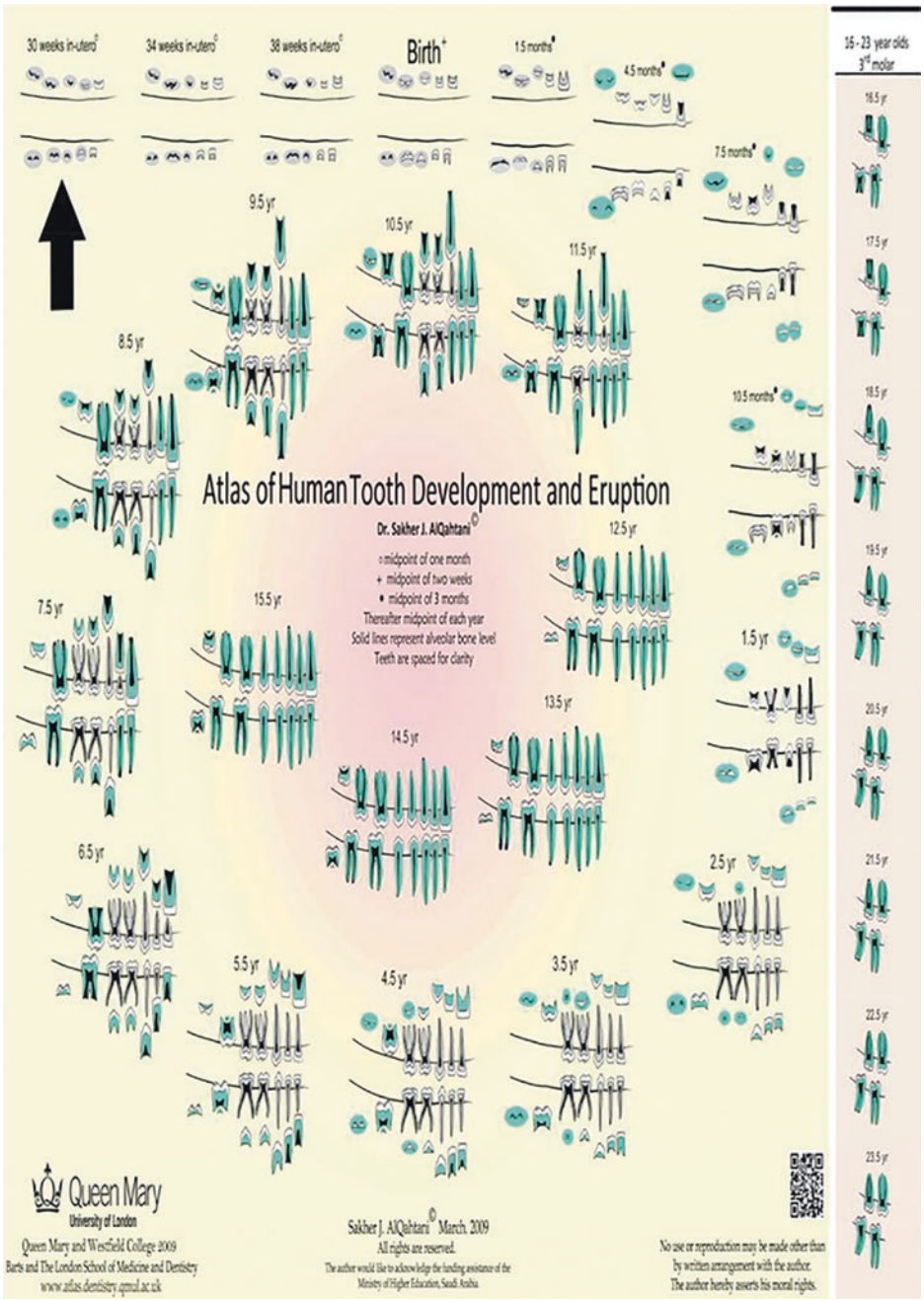


Fig. 26.5 London atlas of human tooth development and eruption. Note. Atlas of Human Tooth development, tables from AlQahtani, Hector and Liversidge 2010. (https://www.qmul.ac.uk)

Postformation Changes

Postformational changes are used in the assessment of age in adults and can be separated into two categories—gross anatomical changes and histological changes. Gross anatomical changes include attrition (wear), periodontal status, apical root resorption, and pulp/tooth size ratio (as one ages, the pulp recedes and becomes smaller inside the tooth). Histologic changes include secondary dentin formation, cementum apposition, dentin transparency, and cementum annuli [7].

Biochemical

Biochemical and histologic changes in teeth can be utilized in any age group and can provide a high degree of accuracy, but there are also many disadvantages to these techniques. Typically, these procedures are very time-consuming, expensive, and require the use of specialized equipment. This requires a tooth extraction, so can only be performed on the deceased or in the living only when a tooth extraction is necessary for medical reasons. These techniques include amino acid racemization within the tooth dentin and Carbon 14 dating of enamel [7].

Other Factors Affecting Age Estimation

In addition to selecting the correct age-related study in which to perform an assessment of dental age, the investigator must also select the correct gender and anthropologic ancestry study. Among other factors that must be considered are nutrition, occupation, disease processes (those with endocrine disorders should not be assessed), and habits [7].

Limitations

It is imperative that the odontologist in the cases of age estimate takes great care when performing age assessments. Accuracy can only be accomplished through the application of the proper technique, using the best population-specific study, and understanding the limitations of the data.

Age estimation opinions must come from scientific methodology using peer-reviewed studies and should provide an estimated age and range of two standard deviations along with an error rate. Additionally, when proffering an opinion of a living individual reaching the age of majority, an empirical probability of attaining that given age should be reported [7].

There are many organizations throughout the world that establish standards and guidelines for performing dental age assessments. Two of the more prominent organizations are the American Board of Forensic Odontologists (ABFO) and the International Organization for Forensic Odonto-Stomatology (IOFOS). Published guidelines and standards can be found on their respective websites and can provide additional and more comprehensive information.

Bitemarks

While no written records exist, William I (the Conqueror) in stories and folktales claimed that he used his distinctive teeth to bite into the Seal of England as a means of authenticating his correspondence [9]. This acknowledgment from the past suggests that even long ago, an array of teeth when impressed in a substance left behind a recognizable pattern.

Bitemarks belong to the class of evidence considered pattern injuries. A pattern injury is an injury in the tissue with distinctive configuration and features indicating the characteristics of the contacting surfaces of the object or objects that made the injury [10]. A pattern injury can be caused by the impact of a weapon or other object on the body or by contact of the body with a patterned surface. Pattern injuries can be grouped into three types: Blunt force, sharp force, and thermal. Any number of objects can create a pattern injury including but not limited to rings, watches, necklaces, belt buckles, electrical cords, tools, tires, shoes, hands, fingers, fingernails, teeth, knives, medical devices such as EKG leads and catheters, burn marks from cigarettes, clothes iron, and curling iron [11].

The initial assessment of bitemark evidence, as with all other types of pattern injury evidence must be examined and documented by the medical examiner (in the deceased) and/or emergency room doctor (in the living) in the investigation of a crime. When a pattern injury is considered to be a bitemark, the forensic odontologist is consulted [12].

These injury patterns found on a body are often important pieces of evidence in criminal investigations. They may be instrumental in determining what object caused the injury, possibly leading to finding the object itself, and perhaps who was in control of the object at the time the injury was inflicted. Because of the nature of these injuries, they are inherently associated with extreme violence and are thus routine parts of investigations [11].

When an injury is suspected to be a bitemark and a forensic odontologist is consulted, the first determination that must be made is whether the injury in question is a bitemark. Bitemarks are a specific subset of patterned injuries that are made by teeth. These injuries can be inflicted by the attacker or by the victim for self-defense. While it is not possible to make a positive identification as to a specific biter, the information that is preserved in these injuries can provide vital information to assist an investigation [13].

The most important aspect of identifying a bitemark on a victim of a violent crime is that it can yield a direct source of DNA directly linked to the violent act. The importance of this cannot be understated [12]. DNA found at a crime scene may be passive in nature and may or may not be part of the crime. However, when DNA collected is part of the violent wound in an attack, it is considered an important key piece of evidence [12].

It is imperative that the medical examiner and/or emergency room physician upon recognition of a suspected bitemark, swab and collect the salivary DNA prior to cleaning the wound!

Beyond being a site for DNA collection, bitemarks are important pieces of evidence that should not be devalued. Bitemarks can demonstrate pain and suffering, they are offensive and defensive, and they are acts of violence that can produce permanent injuries (Fig. 26.6). The presence of a bitemark elevates a battery to an aggravated battery [11]. A bitemark sometimes will have distinctive features that will allow the examiner (forensic odontologist) to give a profile of the dentition that created the bite (such as missing, chipped, rotated teeth and diastemata). It may be possible to determine whether the bite was from an adult or a child. The bitemark can be aged…is it fresh, healing, or an old scar? In abuse cases, many bites over time can show a pattern of abuse, not just a single episode. A bitemark can give perspective as to the position of the subjects in relation to the attack [11].

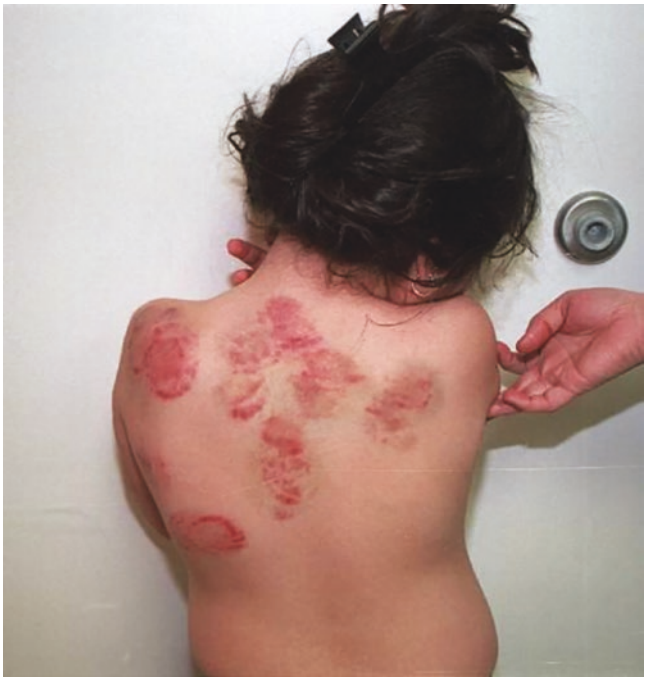


Fig. 26.6 Bitemarks. Note. Bitemarks in child abuse case. From, ABFO image series, "General Public," power point presentation, 2015

Evidence Value

Paramount to all bitemark analysis is the quality of the evidence collected. High-quality photographic images of the bitemark(s) must be used that are free from distortion with scale in place. (ABFO #2 Ruler) and the bitemark itself must exhibit all the hallmarks associated with a high-quality pattern injury for analysis [14]. These details include but are not limited to a semi-circular or ovoid mark exhibiting an interrupted linear pattern and exhibits class and individual characteristics of teeth.

Uses and Limitations

It is important to note that in bitemark analysis, there are two separate and independent conclusions to reach.

1. Analysis of the injury pattern, and its measurements meet the criteria of having been made by teeth [10].
2. If and only if the pattern injury is definitively determined to be a bitemark, can a process of investigating the bitemark move forward to performing comparisons to suspect dentitions? [10].

Another extremely important point to note is regarding the conclusions and opinions statements that are sanctioned by the American Board of Forensic Odontology (ABFO) in their standards and guidelines for pattern, pattern injury, and bitemark evidence linking to a dentition [10].

Only the following statements are permitted:

1. **Inconclusive—"**the evidence is found to be i*nconclusive"* [10].
2. **Excluded—"**the dentition is e*xcluded* as to having made the bitemark" [10].
3. **Not excluded—"**the dentition is *not excluded* as to having made the bitemark" [10].
4. **Insufficient—"**the evidence is i*nsufficient* to draw a conclusion" [10].

While using bitemark analysis to ascertain the guilt of an individual should not be undertaken, especially when DNA has not been collected from the bitemark, it can aid in ruling out the wrongfully accused especially if the suspect arch shape and tooth arrangement are radically different than the pattern injury. This type of analysis is particularly useful in child abuse cases, where a closed population of individuals has access to a child [14].

As this is an introductory review of the use of bitemark analysis, more detailed information can be found on the ABFO website.

Conclusion

Dentistry has been long established to be useful for the public good beyond the clinical practice of dentistry. From providing closure to victims' families, aiding the trier of fact in the judicial system, assisting citizens in dental civil cases, or responding to a mass fatality event, (MFI) forensic odontology is a skill set that will always be needed. For further information and interest visit the ASFO.org, and ABFO.org.

References

1. Senn DR, Stimpson PG. Forensic dentistry. 2nd ed. Boca Raton, FL: Talyor and Francis Group; 2010. p. 1–437.
2. Loomis PW, Reid JS, Tabor MP, Weems RA. Dental identification and radiographic pitfalls. In: David TJ, Lewis JM, editors. Forensic odontology principles and practice. London: Elsevier; 2018. p. 25–44.
3. ABFO Image Series. Copyright American Board of Forensic Odontology. ABFO.org. 2015.
4. Senn DR, Weems RA. Manual of forensic odontology. 5th ed. Boca Raton, FL: Taylor and Francis Group; 2013. p. 1–377.
5. ABFO Diplomates reference manual, standards and guidelines, 2018. ABFO standards and guildelines for dental Identification.
6. Loomis PW. Disaster victim identification. In: David TJ, Lewis JM, editors. Forensic odontology principles and practice. London: Elsevier; 2018. p. 25–44.

7. Lewis JM, Kasper KA. Assessment of dental age. In: David TJ, Lewis JM, editors. Forensic odontology principles and practice. London: Elsevier; 2018. p. 145–66.
8. Muller N. Zur altersbestimmung beim menschen unter besonderer beruckschtigung der weisheitszahne (MD thesis). Erlangen: University of Erlangen-Nurnberg; 1990.
9. Lerner KLB. Odontology, historical cases. World of Forensic Science; 2006.
10. ABFO diplomates reference manual, Standards and guidelines, 2018. ABFO standards and Guidelines for Pattern Injuries, and Bitemark Evidence.
11. Silver WE, Souviron RR. Odontoglyphics-bitemarks. In: Dental autopsy. Boca, Raton, FL: Taylor Francis Group; 2009. p. 151–84.
12. David TJ, Lewis JM. Pattern injury analysis and bitemark comparison. In: David TJ, Lewis JM, editors. Forensic odontology principles and practice. London: Elsevier; 2018. p. 174–8.
13. Hahn S. Forensic Science and forensic Identification, a law enforcement perspective. In: David TJ, Lewis JM, editors. Forensic odontology principles and practice. London: Elsevier; 2018. p. 1–2.
14. Senn DR, Souviron RR. Bitemarks. In: Senn DR, Stinton PG, editors. Forensic dentistry. 2nd ed. Boca Raton, FL: Taylor and Francis Group; 2010. p. 305–68.

Osteonecrosis of the Mandible

27

Ronald Akiki, Peter F. James, and Mohammad Banki

Medication-Related Osteonecrosis of the Jaws

Medication-related osteonecrosis of the jaw (MRONJ) was first described in the early 2000s [1]. It was initially termed BRONJ (bisphosphonate-related osteonecrosis of the jaws), which is defined as an area of bone that is exposed via intraoral or extraoral fistulas. By definition, the fistulas need to be present for at least 8 weeks [1]. In the 1990s, intravenous bisphosphonate formulations were introduced to treat cancer metastases to bone [2]. While they were beneficial for these diagnoses, they were found to cause osteonecrosis in a subset of patients. Higher-potency bisphosphonates, such as those used in the treatment of solid organ tumors, were particularly associated with development of BRONJ. Later, a similar phenomenon was observed in patients who were being treated by bone antiresorptive agents such as denosumab, and the more inclusive designation of MRONJ was implemented [2].

There appears to be an association between antiosteoclastic activity and antiangiogenic properties of bisphosphonates, features that contribute to their association with MRONJ. Due to lack of normal bone turnover caused by osteoclastic inhibition, the resultant senescent bone is highly corticated and hypovascular, thus more at risk for osteonecrosis after a dental extraction. This bone may also further become super-infected due to diminished immune surveillance, thereby leading to osteomyelitis. In all instances, reduced vascularity results in the tissue's inability to meet the metabolic requirements for healing and repair and to fight off oral pathogens [3]. Cancer patients exposed to zoledronate have been shown to be at 50–100 times greater risk of developing MRONJ than cancer patients treated with placebo [1].

MRONJ is uncommon in the general public with an overall risk of 0–6.7% [4]. There are, however, a host of risk factors that have been associated with increased risk of MRONJ, including duration of medical therapy, female sex, and exposure to dental procedures [1]. Interestingly, patients receiving antiresorptive or antiangiogenic medications for the treatment of osteoporosis are at significantly lower risk of developing MRONJ when compared to cancer patients, with risks close to placebo levels [5, 6]. Development of MRONJ is significantly associated with tooth extraction and endosteal implants, with and without periimplantitis [4]. For this reason, when possible, oral surgeons should avoid dental implants and extractions after patients are started on bisphosphonate treatment. If required, bisphosphonate therapy should be delayed until the bone is healed with good mucosal coverage [4, 7].

Diagnosis and Classification of MRONJ

A diagnosis of MRONJ may be made if all of the following is true: (1) the patient has a history of treatment with antiresorptive or antiangiogenic medications (e.g., bisphosphonates); (2) there is evidence of exposed bone; and (3) the patient has no history of radiation therapy or metastatic disease to the mandible [1]. In terms of disease staging, the most commonly employed paradigm includes four main stages (0–3), increasing in disease severity. Notably, radiographic signs are not included in the staging system for concern that inclusion of these findings may lead to overdiagnosis of the condition. The paradigm endorsed by the American Association of Oral and Maxillofacial Surgeons is presented in Table 27.1.

R. Akiki
Department of Plastic Surgery, Warren Alpert Medical School of Brown University, Providence, RI, USA

P. F. James
Department of Otolaryngology, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

M. Banki (✉)
Department of Surgery, Warren Alpert Medical School of Brown University, Providence, RI, USA

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_27

Table 27.1 Staging system for medication-related osteonecrosis of the jaws

Lesion staging	Description
At risk	No apparent exposed/necrotic bone in patients who have been treated with either antiresorptive or antiangiogenic agents
Stage 0	Nonspecific clinical findings and symptoms such as jaw pain or osteosclerosis but no clinical evidence of exposed bone
Stage I	Exposed, necrotic bone or fistula that probes to bone; no symptoms or evidence of infection
Stage II	Exposed, necrotic bone or fistula that probes to bone, associated with infection, pain, and erythema in the regions of the exposed bone; purulent drainage may also be present
Stage III	Exposed, necrotic bone or fistula that probes to bone in patients with pain, infection, and one or more of the following: Pathologic fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border or sinus floor

Treatment of MRONJ

The primary treatment goals for patients who suffer from MRONJ are the control of pain, the preservation of quality of life, the control of secondary infection, prevention of lesion extension, and patient education [1]. A foundational component of MRONJ management is prevention and risk reduction. In patients receiving intravenous resorptive or antiangiogenic medications for malignancy, the likelihood of developing MRONJ can be reduced via maintenance of good oral hygiene and dental health. Avoidance of dental or alveolar procedures, including dental implant placement, plays an important role in prevention [1]. There are no established guidelines for patients taking oral bisphosphonates.

In patients who meet the diagnostic criteria for MRONJ, the above preventative measures still remain useful. These patients, however, may benefit from more directed therapy. An antibiotic mouth rinse may be employed, especially in lower-stage disease, and may be augmented by oral antibiotics. In severe cases, or when nonoperative techniques fail, operative management may be indicated, including debridement, tooth extraction, bony contouring, or resection [1]. The potential usefulness of hyperbaric oxygen therapy has been explored, though the results have been equivocal in randomized controlled trials [8]. An outline of available treatment options by disease stage is illustrated in Table 27.2 [1].

Table 27.2 MRONJ treatment options by disease stage

Lesion staging	Treatment
At risk	Patient education, prevention strategies
Stage 0	Pain management, oral antibiotics, prevention strategies
Stage I	Antimicrobial mouth rinse, pain control, close follow-up, medication cessation
Stage II	Antimicrobial mouth rinse, oral antibiotics, pain control, close follow-up, medication cessation, possible surgical debridement
Stage III	Antimicrobial mouth rinse, oral antibiotics, pain control, close follow-up, medication cessation, possible surgical debridement or resection

Illustrative Case

A 75-year-old female presented with acute onset of pain involving a right mandibular second molar (Fig. 27.1). Patient's past medical history was significant for treatment of osteoporosis with alendronate for 5 years. However, the medicine had been discontinued about 6 months prior to this presentation. Patient underwent extraction of the inciting tooth without any complications. Her follow-up appointment, a week later, revealed the socket to be healing as expected. A small quantity of granulation tissue was noted, but no exudate was present. Patient did report slight paresthesia involving the area of distribution of the right inferior alveolar nerve. Patient returned 3 weeks later and was noted to have developed an orocutaneous fistula in the right submandibular region. Exposed alveolar bone measuring 7 mm was also noted at the extraction site. Radiographic evaluation revealed onset of new areas of radiolucency with irregular borders involving the right posterior mandible. A culture was obtained that revealed a polymicrobial etiology along with presence of *Actinomyces* species. A diagnosis of medication-related osteonecrosis of the jaw was made and, in consultation with an infectious disease specialist, she was placed on intravenous penicillin G for 8 weeks followed by a 4-month course of amoxicillin orally. The orocutaneous fistula eventually healed after 12 weeks and the extraction site mucosalized.

Osteoradionecrosis

The first case of osteoradionecrosis (ORN) was reported in 1922. At that time, it was believed that osteoradionecrosis was a bacterial bone infection that occurred in the context of irradiation [9, 10]. In 1970, the treatment of osteoradionecrosis

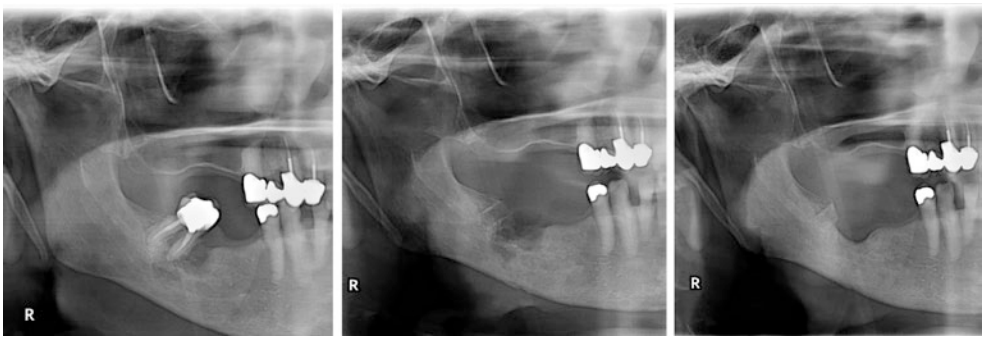


Fig. 27.1 The radiograph from left to right demonstrates the infected molar tooth, early MRONJ, and the healed surgical site. (Radiographic images courtesy of author MB)

was penicillin. Marx controversially introduced the "three H" theory; he postulated that osteoradionecrosis was caused by hypoxia, hypocellularity, and hypovascularity. In his findings, he demonstrated that bacteria did not play a role in the course of osteoradionecrosis. In fact, he found those bacteria to be located only on the most superficial areas of the exposed bone. He found that one-third of ORN cases did not involve a traumatic injury and thus argued that trauma could not be a factor in the development of osteoradionecrosis [11]. The radiation-induced fibro-atrophic theory complemented Marx's findings. This theory suggests that radiation creates free radicals and injures endothelial cells causing fibroblast deregulation that in turn leads to vulnerability to inflammation [11].

Today, the definition of osteoradionecrosis is the presence of irradiated bone exposed through a soft tissue wound for a duration of 3 to 6 months. Recurrent malignancies and tumors during treatment are excluded from the diagnosis [12]. The most common bone attributed to this diagnosis is the mandible. However, ORN can occur in the maxilla, temporal bones, and hyoid. The vascular supply to the mandible includes the facial arteries and inferior alveolar arteries. Its blood supply is relatively less vascular than the other bones in the face and neck [9, 13]. Furthermore, the mandible is much more likely to be exposed to radiation when treating oral and pharyngeal cancers. Osteoradionecrosis is a very painful disease and has a significant impact on patients' daily lives [14].

ORN is typically diagnosed after radiation therapy for oropharyngeal tumors. This is especially true for significantly advanced primary tumors (radiation doses greater than 60 Gy) [9, 12]. Recent studies have found that periapical radiolucencies increased patients' odds of developing ORN after radiotherapy [15]. Other contributing factors include smoking and alcohol abuse [12].

Classification of Osteoradionecrosis

Multiple osteoradionecrosis classifications exist. One of the most commonly used is the Schwartz and Kagan classification [14]. Table 27.3 summarizes each stage.

Table 27.3 Osteoradionecrosis: Schwartz and Kagan classification

Lesion staging	Description
Stage I	Superficially exposed bone with small soft tissue defects and necrosis confined to the exposed cortical bone
Stage II-A	Small soft tissue defects
Stage II-B	Extensive soft tissue involvement and cutaneous fistula formation
Stage III-A	Small tissue defects
Stage III-B	Soft tissue necrosis and possible cutaneous fistula formation

The diagnosis of osteoradionecrosis is clinical and radiographic. Panoramic imaging is classically used for assessment of possible ORN. Typical lesions will be heterogeneously radiolucent with spots of radiodensity. On imaging, osteonecrosis may appear similar to osteomyelitis due to the possible presence of sequestra [13, 16]. Unlike osteomyelitis, however, initial lesions in osteonecrosis can be identified on imaging before the symptoms appear clinically through osteolytic lesions. Pathologic fractures are typically observed with stage III lesions and can be found on orthopantomograms [9]. Sequestration formations can be visualized on computed tomography (CT) imaging. Magnetic resonance imaging (MRI), when necessary, will show low-intensity lesions on T1. Clinicians should have a low threshold for ORN when these lesions are observed distantly from the primary tumor or when they appear 2 years or later after radiotherapy [9, 13].

Treatment

Given its difficult management, osteonecrosis prevention is of particular importance [17]. As in the case of MRONJ, clinicians should avoid performing dental implants and extractions before patients are started on bisphosphonate treatment, and bisphosphonate treatment should be adequately delayed to allow for complete healing [4, 7]. Patients with higher rates of caries and poor oral hygiene were three times more likely to develop osteoradionecrosis [18]. To optimize the therapeutic effect of radio-

therapy, teeth with periodontitis or periapical radiolucency and impacted teeth/root tips should be extracted at least 2 weeks before the start of radiotherapy. Osteoradionecrosis, in most cases, is diagnosed within 1 year of radiation [10].

ORN is treated conservatively by minimizing irritation to the exposed site. Patients are advised to avoid using their dental prostheses if they have one and to stop smoking. Patients are typically prescribed antimicrobial agents such as chlorhexidine. Intravenous antibiotics can be used when there is a concern of an acute infection of the exposed necrotic bone [9]. Beyond conservative management, hyperbaric oxygen may be used. The goal of hyperbaric oxygen is angiogenesis. This is achieved through pressurized oxygen delivered to tissues [19]. It has been used prophylactically and as a treatment for wound healing in osteoradionecrosis. Patients with a history of head and neck radiation pending extraction often undergo prophylactic hyperbaric oxygen therapy [9, 13]. Hyperbaric oxygen by itself has shown little to no success in treating osteoradionecrosis [12]. The current guidelines recommend 20–30 dives for 90–120 min, as well as 20–30 preoperative and 10 postoperative dives relative to a planned extraction. In addition, 40–50 10-min sessions of ultrasound therapy have been shown to promote angiogenesis. This can be done until mucosal coverage is achieved [9].

For medical management, tocopherol, pentoxifylline, and clodronate are recommended for osteogenesis stimulation. Pentoxifylline dilates patent blood vessels in the bone and reduces inflammation. Vitamin E can be given in conjunction to pentoxifylline as it helps collect reactive oxygen species during oxidative stress. Clodronate inhibits bone resorption and is reserved for severe cases of ORN [9, 12]. The recommended medical management protocol includes 800 mg pentoxifylline and 1000 IU Vitamin E for 6 months, continued while healing progresses. In severe osteonecrosis, an additional 16,000 mg of clodronate is recommended, five times per week [17]. In one study that used this protocol, researchers achieved complete healing in 89% of their patients [17].

Surgical management is indicated when conservative management fails or when the patient has a pathologic fracture. Surgical debridement should be continued until bleeding is encountered.

In general, stage II lesions heal with conservative management or surgery and stage III require surgery [9]. Free flap reconstruction is considered for extensive resections (91% success rate) [9, 13].

References

1. Ruggiero S, Dodson T, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. J Oral Maxillofac Surg. 2014;72(10):1938–56. https://doi.org/10.1016/J.JOMS.2014.04.031.
2. Assael L. Bisphosphonates and oral health: primer and an update for the practicing surgeon. Oral Maxillofac Surg Clin North Am. 2011;23(3):443–53. https://doi.org/10.1016/J.COMS.2011.04.002.
3. Kyzas P. Evidence-based oral and maxillofacial surgery. J Oral Maxillofac Surg. 2008;66(5):973–86. https://doi.org/10.1016/J.JOMS.2008.01.024.
4. Dodson T. The frequency of medication-related osteonecrosis of the jaw and its associated risk factors. Oral Maxillofac Surg Clin North Am. 2015;27(4):509–16. https://doi.org/10.1016/J.COMS.2015.06.003.
5. Papapoulos S, Chapurlat R, Libanati C, et al. Five years of denosumab exposure in women with postmenopausal osteoporosis: results from the first two years of the FREEDOM extension. J Bone Miner Res. 2012;27(3):694–701. https://doi.org/10.1002/JBMR.1479.
6. Grbic J, Black D, Lyles K, et al. The incidence of osteonecrosis of the jaw in patients receiving 5 milligrams of zoledronic acid: data from the health outcomes and reduced incidence with zoledronic acid once yearly clinical trials program. J Am Dent Assoc. 2010;141(11):1365–70. https://doi.org/10.14219/JADA.ARCHIVE.2010.0082.
7. Ruggiero S, Mehrotra B, Rosenberg T, Engroff S. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg. 2004;62(5):527–34. https://doi.org/10.1016/J.JOMS.2004.02.004.
8. Freiberger J, Padilla-Burgos R, McGraw T, et al. What is the role of hyperbaric oxygen in the management of bisphosphonate-related osteonecrosis of the jaw: a randomized controlled trial of hyperbaric oxygen as an adjunct to surgery and antibiotics. J Oral Maxillofac Surg. 2012;70(7):1573–83. https://doi.org/10.1016/J.JOMS.2012.04.001.
9. O'Dell K, Sinha U. Osteoradionecrosis. Oral Maxillofac Surg Clin North Am. 2011;23(3):455–64. https://doi.org/10.1016/J.COMS.2011.04.011.
10. He Y, Liu Z, Tian Z, Dai T, Qiu W, Zhang Z. Retrospective analysis of osteoradionecrosis of the mandible: proposing a novel clinical classification and staging system. Int J Oral Maxillofac Surg. 2015;44(12):1547–57. https://doi.org/10.1016/J.IJOM.2015.04.006.
11. Marx RE. Chronic osteomyelitis of the jaws. Oral Maxillofac Surg Clin North Am. 1991;3(2):367–81. https://doi.org/10.1016/S1042-3699(20)30505-7.
12. Lyons A, Ghazali N. Osteoradionecrosis of the jaws: current understanding of its pathophysiology and treatment. Br J Oral Maxillofac Surg. 2008;46(8):653–60. https://doi.org/10.1016/J.BJOMS.2008.04.006.
13. Balaji S. Evidence-based maxillofacial surgery. Ann Maxillofac Surg. 2019;9(1):3. https://doi.org/10.4103/AMS.AMS_115_19.
14. Schwartz H, Kagan A. Osteoradionecrosis of the mandible: scientific basis for clinical staging. Am J Clin Oncol. 2002;25(2):168–71. https://doi.org/10.1097/00000421-200204000-00013.
15. Kojima Y, Yanamoto S, Umeda M, et al. Relationship between dental status and development of osteoradionecrosis of the jaw: a multicenter retrospective study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2017;124(2):139–45. https://doi.org/10.1016/J.OOOO.2017.04.012.
16. Owosho A, Kadempour A, Yom S, et al. Radiographic osteoradionecrosis of the jaw with intact mucosa: proposal of clinical guidelines for early identification of this condition. Oral Oncol. 2015;51(12):e93–6. https://doi.org/10.1016/J.ORALONCOLOGY.2015.09.009.
17. Delanian S, Depondt J, Lefaix J. Major healing of refractory mandible osteoradionecrosis after treatment combining pentoxifylline and tocopherol: a phase II trial. Head Neck. 2005;27(2):114–23. https://doi.org/10.1002/HED.20121.

18. Bruins H, Koole R, Jolly D. Pretherapy dental decisions in patients with head and neck cancer. A proposed model for dental decision support. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;86(3):256–67. https://doi.org/10.1016/S1079-2104(98)90169-X.

19. Ceponis P, Keilman C, Guerry C, Freiberger J. Hyperbaric oxygen therapy and osteonecrosis. Oral Dis. 2017;23(2):141–51. https://doi.org/10.1111/ODI.12489.

Local Anesthesia

28

Daniel Beauvais

Introduction

Local anesthetics have been used routinely in dental practice for well over 100 years. The first local anesthesia used by surgeons and dentists was cocaine, which was used primarily as a topical agent. Over the years, the development of synthetic anesthetics circumvented the reliance on cocaine for local anesthesia, and the addition of epinephrine to anesthetic solutions allowed for prolonged anesthetic effects. Today, there are multiple formulations of local anesthetics, each with unique properties for a variety of clinical uses in both dentistry and medicine. This chapter will explore the fundamentals in pharmacology of local anesthetics, clinical use, as well as side effects and complications.

Physiology

The fundamental concept behind the action of local anesthetics is the prevention of both the generation and the conduction of a nerve impulse. When a local anesthetic is present in a given area, there is effectively a signal blockade between the area being manipulated and the brain. At the level of the nerve, a stimulus, such as a needle or scalpel blade, causes excitation, also known as depolarization, of a nerve segment. This leads to a transient increase in permeability of the cell membrane to sodium ions, which leads to the formation of an action potential. Simply put, the action potential is propagated along the nerve toward the brain where the stimulus can then be interpreted appropriately. Local anesthetics work by decreasing the rate of depolarization, which effectively limits the formation of an action potential in the nerve. There are several theories as to where local anesthetics work at the nerve level; the leading theory is known as the specific receptor theory. The specific receptor theory proposes that local anesthetics act by binding to a specific receptor on the sodium channel [1, 2]. Once the local anesthetic has bound its receptor, the permeability of sodium ions has temporarily decreased, thereby preventing action potential formation and interrupting nerve conduction.

Pharmacology

Once a local anesthetic is injected into soft tissue, the solution diffuses through the tissue by means of concentration gradients. Some of the anesthetic will travel toward the intended nerve, while a significant portion either travels through surrounding tissues, is diluted in interstitial fluid, is removed by capillaries and lymphatics, or is hydrolyzed in the case of ester-type anesthetics. In order to exert its effects on nerve tissue, local anesthetics must first become ionized from its acid salt form into a base and cation. The rate at which this occurs is known as the dissociation constant, or pKa. Factors that control induction time of a local anesthetic are the concentration of the drug, pKa of the local anesthetic, and the pH of the surrounding tissue. Local anesthetics with lower pKa values possess a more rapid onset than those with higher pKa values. Tissues with lower pH values slow the onset of anesthesia; thus, in tissues where infection or inflammation is present, the resultant acidic environment prolongs the onset of anesthesia. The potency of a given anesthetic is dependent on its lipid solubility. Greater lipid solubility allows for easier penetration of the nerve membrane. The duration of a local anesthetic relies on protein-binding capacity. Local anesthetics possessing greater degrees of protein binding attach more securely to the protein receptor sites and possess a longer duration of activity [3].

There are two primary routes for metabolism of local anesthetics. Ester local anesthetics are hydrolyzed in the plasma by the enzyme pseudocholinesterase. Clinically, patients with pseudocholinesterase deficiency will be at an increased risk for toxicity from ester-type anesthetics. Amide

D. Beauvais (✉)
Oral and Maxillofacial Surgery, UConn Health, Farmington, CT, USA
e-mail: beauvais@uchc.edu

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_28

anesthetics primarily undergo biotransformation in the liver. Nearly the entire metabolism process occurs in the liver for the amide class of local anesthetics: lidocaine, mepivacaine, etidocaine, and bupivacaine. Thus, patients with hepatic dysfunction are more susceptible to amide toxicity. Articaine is a hybrid molecule containing both ester and amide components and undergoes metabolism both in the liver and in plasma. Local anesthetics and their metabolites are excreted from the body via the kidneys [4].

The use of vasoconstrictors in local anesthetic formulations offers numerous benefits for the administration of local anesthesia. Local anesthetics, with the exception of cocaine, have vasodilatory properties, which hastens the redistribution of local anesthetic into the bloodstream. By utilizing a vasoconstrictor, blood flow at the site of injection is decreased, which allows for less absorption of local anesthetic into the cardiovascular system, lower blood levels of local anesthetic, higher concentrations of local anesthetic at the intended site of action, and a decrease in bleeding at the site of administration [5–10]. The most commonly used vasoconstrictor in local anesthetic cartridges today is epinephrine, which acts on alpha- and beta-adrenergic receptors. The intended effect for local anesthetic purposes is activation of alpha-1 receptors on the smooth muscle of blood vessels, which causes vasoconstriction. In general, epinephrine-containing local anesthetics are well tolerated, though some controversy exists in regard to patients with cardiovascular disease. There is incomplete data to suggest a safe level of vasoconstrictor in patients with severe cardiovascular disease. However, the inclusion of a vasoconstrictor should be considered routinely for the majority of patients [11].

Clinical Properties of Anesthetics

There are several different types of local anesthetics currently available in North America. These include lidocaine, mepivacaine, prilocaine, and articaine. All of these anesthetics are amides, though as mentioned previously articaine has both amide and ester properties. It is important to understand the approximate onset and duration of these agents, as well as maximum doses and routes of metabolism.

Lidocaine

Lidocaine hydrochloride (HCl) was synthesized in 1943 and was the first amide local anesthetic marketed. It replaced procaine (Novocain) as the drug of choice for local anesthesia with its more rapid onset of action, more profound anesthetic effects, longer duration of action, and greater potency. Lidocaine remains the gold standard for local anesthetics in medicine and dentistry. Currently, lidocaine HCl is available in two different formulations, both with epinephrine (2% with 1:100,000 epinephrine and 2% with 1:50,000 epinephrine). Onset of action for both formulations is less than 2 min. Duration of pulpal anesthesia is approximately 60 min, and soft tissue anesthesia is 3–5 h. Per U.S. Food and Drug Administration (FDA) guidelines, the maximum dosage is 7.0 mg/kg for both adult and pediatric patients, with a maximum total dose of 500 mg [12].

Mepivacaine

Mepivacaine hydrochloride was first approved for use in 1960 and was introduced the following year as a 3% formulation without a vasoconstrictor, which is the form used today. Mepivacaine has less vasodilating properties than other local anesthetics, affording it a longer duration of action when compared to other anesthetics when used without a vasoconstrictor. The duration of pulpal anesthesia is 20–40 min and approximately 2–3 h for soft tissue anesthesia. Therefore, 3% mepivacaine is best used for shorter procedures or for patients for whom a vasoconstrictor is contraindicated. The maximum dosage is 6.6 mg/kg, with a maximum total dose of 400 mg [13].

Prilocaine

Prilocaine hydrochloride was FDA approved in 1965. Prilocaine is unique compared to the other amines in that some of its metabolism also takes place in the kidney and plasma. Of note, one of the metabolites, orthotoluidine, can induce the formation of methemoglobin, which can cause methemoglobinemia when administered in large doses. Limiting the total dose to 600 mg avoids symptomatic cyanosis, which include grayish or slate blue cyanosis of the lips, mucous membranes, and nail beds, and infrequently respiratory distress. Methemoglobinemia may be reversed with intravenous administration of 1% methylene blue at a dose of 1–2 mg/kg over a 5-min period. Prilocaine is a component in EMLA cream (eutectic mixture of local anesthetics lidocaine and prilocaine), which is commonly applied to the skin prior to venipuncture and cosmetic procedures [14].

Articaine

Articaine hydrochloride has been available in Europe and Canada for the past several decades, though was only recently approved for use in the United States in 2000. As previously mentioned, articaine has an ester group, which causes it to be metabolized in both the liver and plasma. Many claims have been made regarding articaine, including that it has a faster

onset and increased success rates, yet also that it leads to an increased incidence of paresthesias. There is evidence that articaine has a superior anesthetic effect for local infiltration in the mandibular soft tissues [15, 16] as well as the ability to achieve palatal anesthesia when injected into the buccal soft tissues of the maxilla [17]. There have also been studies demonstrating an increased incidence in paresthesia, particularly when used for inferior alveolar nerve blocks [18, 19]. An epidemiological study by Hillerup et al. in 2011 [20] calculated a 3.1–8.6-fold increased risk in neurosensory disturbance with injection of articaine relative to other anesthetics on the market. Clinicians should therefore consider using an alternative agent for nerve blocks when possible. The formulation with 1:100,000 epinephrine provides 60–75 min of pulpal anesthesia and 3–6 h of soft tissue anesthesia, and the 1:200,000 formulation provides approximately 45–60 min and 2–3 h, respectively [21].

Bupivacaine

Bupivacaine hydrochloride has been available since the early 1980s. It is available in a 0.5% solution with 1:200,000 epinephrine. Bupivacaine has a slower onset time (6–10 min) and a prolonged duration of action (90–180 min of pulpal anesthesia and 4–9 h of soft tissue anesthesia). Given these properties, bupivacaine is particularly useful for lengthy dental procedures and for management of postoperative pain. When supplemented with non-steroidal anti-inflammatory drugs (NSAIDs), bupivacaine can reduce the need for prescription pain medication. It should be used with caution in pediatric patients and those who are at an increased risk of soft tissue injury in the postoperative period, such as persons who are physically or cognitively disabled. The maximum recommended dosage is 90 mg [22].

Complications

Complications associated with the administration of local anesthesia can be divided into those that occur locally and those that are systemic. Local complications include paresthesia, facial nerve paralysis, ocular complications, and trismus. Systemic complications include toxic reactions as a result of overdosage and allergic reactions.

Local Complications

Paresthesia

Trauma to the nerve sheath during injection of a local anesthetic can result in the development of paresthesia in the distribution of a given nerve. Other causes as a result of local anesthetic include hemorrhage into or around the nerve sheath, edema, and chemical toxicity from the local anesthetic agent itself. Though exceedingly rare, paresthesias most commonly occur following local injections for mandibular nerve blocks. Estimates for the incidence of paresthesias vary; however, one 20-year retrospective study by Haas and Lennon in 1995 found an incidence of approximately 1 in 785,000. Patients may occasionally report feeling numb many hours or days following a local anesthetic injection. This is a rare yet often unpreventable condition that can have a profound impact on a patient's quality of life. Complaints may range from numbness, tingling, drooling, loss of taste, tongue biting, and speech dysfunction. Persistent anesthesia is rarely total; in most cases it is partial and transient. Management of paresthesias as a result of anesthetic injection includes a thorough examination including mapping of the region of neurosensory disturbance. Patients should be counseled that often times paresthesias are transient, though resolution may take weeks or months and may be incomplete. Tricyclic antidepressants and gabapentin may also provide symptom relief, though patients should understand that these are not curative measures [23].

Facial Nerve Paralysis

Injection of local anesthetic into the capsule of the parotid gland is the most common cause of transient facial nerve paralysis. This is commonly a result of injecting posteriorly during an inferior alveolar nerve block, or over insertion during a Vazirani-Akinosi nerve block. Patients may experience loss of motor function to the muscles of facial expression, including inability to voluntarily close the eye, which is usually transient, and there is no known treatment. Prevention is aimed at adhering to protocol with mandibular nerve blocks. Management includes patient reassurance in the temporary nature of the problem, and removal of contact lenses and application of an eye patch until eyelid function returns to normal in order to prevent corneal abrasion [24].

Ocular Complications

Ocular complications may arise following inadvertent intra-arterial injection of local anesthetic or as a result of diffusion of the anesthetic through myofascial spaces or bony openings. A systematic review of 89 cases of ocular complications following intraoral local anesthetic injections documented a variety of symptoms, including double vision, mydriasis, ptosis, strabismus, and blindness. Ninety-two percent of these cases were transient, lasting no more than several hours, while six patients developed vision impairment and two developed an isolated fixed pupil [25]. Ocular complications are best prevented by aspiration prior to injection to avoid intra-arterial injection. If a patient develops ocular complications following injection, patients should be monitored and re-assessed for resolution of symptoms. For symp-

toms that do not resolve in the first several hours following injection, patient counseling and referral to an ophthalmologist is warranted [26].

Trismus

The most common cause of trismus following injection of local anesthesia is trauma to muscles or blood vessels within the infratemporal fossa. Other causes of trismus include hemorrhage around the muscles of mastication and low-grade infection after injection [27]. Development of trismus may be seen more frequently with multiple injections for inferior alveolar nerve blocks and posterior superior alveolar nerve blocks. Patients may experience muscle spasm, pain, and limitation of jaw movement. Chronic hypomobility may occur due to hematoma organization and scarring, though this is rare. In most instances of trismus, patients report pain and difficulty opening in the days following injection. In the acute phase, heat therapy, NSAIDs, and, if necessary, muscle relaxants aid in relieving symptoms. Patients should be instructed to begin physiotherapy consisting of jaw opening and closing exercises in order to re-establish normal functioning of the muscles of mastication. Complete resolution is expected prior to 6 weeks post injection, though most patients report significant improvement after the first 48–72 h [28].

Systemic Complications

Overdose

Local anesthetic overdose is related to the blood level of the anesthetic in certain tissues. Predisposing factors include patient factors, such as age, weight, other drugs, and comorbid medical conditions, as well as drug factors, such as concentration, dose, vascularity of injection site, and route of administration. Young patients, who have relatively low body mass, and elderly patients, who have delayed metabolism and excretion, are more susceptible to overdose. Similarly, conditions that affect hepatic and renal dysfunction increase the incidence of anesthetic toxicity. Adhering to FDA and manufacturer-recommended maximum doses is essential, though overdose may still occur at these doses in susceptible individuals. Providers must take into account these specific patient factors when considering appropriate doses of anesthetic to administer.

Manifestations of local anesthetic overdose include an initial excitatory phase in the central nervous system (CNS) and cardiovascular system, followed by a depression phase at higher doses of anesthetic toxicity. Initial excitatory symptoms may include shivers and tremors, as well as hypertension and tachycardia. The depression phase is characterized by myocardial depression, resulting in bradycardia, hypotension, and ectopic rhythms. CNS depression may manifest as the development of tonic-clonic seizures and loss of consciousness.

The management of local anesthetic overdose varies depending on the severity of the manifestation(s), though begins with assessing the patient's airway, breathing, and circulation.

Treatment is supportive, yet basic life support principles must be followed to ensure patient safety and to prevent adverse outcomes. Vital signs should be closely monitored, and supplemental oxygen should be administered to support oxygenation. If tonic-clonic seizures are present, all instruments should be removed from the mouth, and the patient should be placed in a supine position. An anticonvulsant, such as a beta blocker, may be administered for prolonged seizures though it is often not necessary for seizure resolution. The emergency response team should be called early for the unstable patient [29].

Allergy

Allergic reactions to local anesthetics range from mild and delayed responses occurring as long as 48 h following exposure to immediate and life-threatening reactions. Allergy to local anesthetic is exceedingly rare; it accounts for approximately 1% of all adverse reactions during administration of dental anesthesia. Of these, the majority of cases are contact dermatitis. The majority of patients reporting allergies to anesthetics are in fact not experiencing symptoms caused by allergies, but rather are psychogenic or related to the administration of epinephrine (palpitations, headache, sweating, shaking). Hyperventilation, dizziness, and peripheral paresthesias may also be a result of patient anxiety, rather than the local anesthetic. Report of a patient experiencing itching, hives, rash, or edema is more likely to be the result of an allergy. Careful patient medical and dental history taking can help differentiate between a true allergy and other causes of their symptoms. Patients with true allergies to local anesthetics commonly have an allergy to ester-type anesthetics and not amides. In this case, amides may be used safely. An alternative to both ester and amide anesthetics is 1% diphenhydramine with 1:100,000 epinephrine, which has been shown to provide pulpal anesthesia for up to 30 min. In many instances, however, patients who are unable to tolerate local anesthesia may require an operating room setting with general anesthesia for dental care [30].

Summary

Local anesthetics are a crucial component of modern dentistry in that they facilitate a comfortable and safe patient experience. There are several types of local anesthetics available on the market today, each with a unique profile that can be catered to the individual patient. While complications associated with local anesthetics are rare, providers must be aware of potential adverse reactions and appropriate management.

References

1. Beri S, Biswas NR, Shende DR, Das GK, Pandey RM, Ghose S. Injectable centbucridine and lidocaine hydrochloride for intraocular surgery. Ophthalmic Surg Lasers. 1997;28(12):1027–9.
2. Vacharajani GN, Parikh N, Paul T, Satoskar RS. A comparative study of centbucridine and lidocaine in dental extraction. Int J Clin Pharmacol Res. 1983;3:251–5.
3. Bieter RN. Applied pharmacology of local anesthetics. Am J Surg. 1936;34:500–10.
4. Malamed SF. Handbook of local anesthesia. 7th ed. St Louis, MI: Elsevier; 2020a. p. 29–31.
5. Brown G. The influence of adrenaline, noradrenaline vasoconstrictors on the efficacy of lidocaine. J Oral Ther Pharmacol. 1968;4:398–405.
6. Carpenter RL, Kopacz DJ, Mackey DC. Accuracy of Doppler capillary flow measurements for predicting blood loss from skin incisions in pigs. Anesth Analg. 1989;68:308–11.
7. Cowan A. Further clinical evaluation of prilocaine (Citanest), with and without epinephrine. Oral Surg Oral Med Oral Pathol. 1968;26:304–11.
8. Finder RL, Moore PA. Adverse drug reactions to local anesthesia. Dent Clin N Am. 2002;46:447–57.
9. Moore PA, Hersh EV. Local anesthetics: pharmacology and toxicity. Dent Clin N Am. 2010;54:587–99.
10. Myers RR, Heckman HM. Effects of local anesthesia on nerve blood flow: studies using lidocaine with and without epinephrine. Anesthesiology. 1989;71:757–62.
11. Malamed SF. Handbook of local anesthesia. 7th ed. St Louis, MI: Elsevier; 2020b. p. 41–54.
12. Malamed SF. Handbook of local anesthesia. 7th ed. St Louis, MI: Elsevier; 2020c. p. 63–6.
13. Malamed SF. Handbook of local anesthesia. 7th ed. St Louis, MI: Elsevier; 2020d. p. 66–7.
14. Malamed SF. Handbook of local anesthesia. 7th ed. St Louis, MI: Elsevier; 2020e. p. 67–71.
15. Katyal V. The efficacy and safety of articaine versus lignocaine in dental treatments: a meta-analysis. J Dent. 2010;38(4):307–17.
16. Shurtz R, Nusstein J, Al R, et al. Buffered 4% articaine as a primary buccal infiltration of the mandibular first molar: a prospective, randomized, double-blind study. J Endod. 2015;41(9):1403–7.
17. Al-Mahalawy H, Abouhashish H, Chathoth S, et al. Articaine versus lidocaine concentration in the palatal tissues after supraperiosteal buccal infiltration anesthesia. J Oral Maxillofac Surg. 2018;76(2):315.e1–7.e7.
18. Haas DA, Lennon D. A 21 year retrospective study of reports of paresthesia following local aensthetic administration. J Can Dent Assoc. 1995;61(4):319–20. 323–6, 329–30.
19. Malamed SF, Gagnon S, Leblanc D. Articaine hydrochloride: a study of the safety of a new amide local anesthetic. J Am Dent Assoc. 2001;132(2):177–85.
20. Hillerup S, Jensen RH, Ersboll BE. Trigeminal nerve injury associated with injection of local anesthetics. J Am Dent Assoc. 2011;142(5):531–9.
21. Malamed SF. Handbook of local anesthesia. 7th ed. St Louis, MI: Elsevier; 2020f. p. 71–4.
22. Malamed SF. Handbook of local anesthesia. 7th ed. St Louis, MI: Elsevier; 2020g. p. 74–5.
23. Malamed SF. Handbook of local anesthesia. 7th ed. St Louis, MI: Elsevier; 2020h. p. 310–6.
24. Malamed SF. Handbook of local anesthesia. 7th ed. St Louis, MI: Elsevier; 2020i. p. 316–7.
25. Alamanos C, Raab P, Gamulescu A, et al. Ophthalmologic complications after administration of local anesthesia in dentistry: a systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;121(3):e39–50.
26. Malamed SF. Handbook of local anesthesia. 7th ed. St Louis, MI: Elsevier; 2020j. p. 317–8.
27. Kitay D, Ferraro N, Sonis ST. Lateral pharyngeal space abscess as a consequence of regional anesthesia. J Am Dent Assoc. 1991;122:56–9.
28. Hinton RJ, Dechow PC, Carlson DS. Recovery of jaw muscle function following injection of a myotonic agent (lidocaine- epinephrine). Oral Surg Oral Med Oral Pathol. 1986;59:247–51.
29. Malamed SF. Handbook of local anesthesia. 7th ed. St Louis, MI: Elsevier; 2020k. p. 331–47.
30. Malamed SF. Handbook of local anesthesia. 7th ed. St Louis, MI: Elsevier; 2020l. p. 347–59.

Anxiety Management

29

Christopher Haxhi

Introduction

Dental fear and anxiety are all too common issues for the dental health care provider. It will not take long for even a new provider to encounter a patient with some level of dental anxiety. The etiologies of patient dental phobia are complex and multifactorial including anticipation of pain, sensory overstimulation, and, even, the propagation of dental providers as villainous in popular culture [1]. In fact, images of ill-intentioned dental practitioners portrayed in film and television offer an early foundation for the misconception of the dental experience [1]. As will be discussed further in this chapter, dental anxiety is a destructive cycle of impediment to receiving preventative care. This delay often necessitates more invasive and more painful procedures that could have otherwise been avoided. It is for these reasons that abating dental anxiety is of the utmost important for any dental practitioner, regardless of specialty. The prevalence of dental anxiety cannot be underestimated as it will go both diagnosed and undiagnosed throughout a dental health care provider's entire career. Dental fear and phobia will hinder not only the therapeutic alliance but also the delivery of care, sometimes to the most vulnerable populations. As such, recognition and management of dental anxiety is equally as important as a provider's treatment skills. This chapter will discuss both pharmacologic and non-pharmacologic options for managing dental anxiety in the patient creating a positive experience for patients.

Prevalence and Etiology of Dental Anxiety

The etiologies of dental fear and anxiety are complex and multifaceted. This fear has roots in personal factors, dental factors, and social factors [2]. These personal factors include but are not limited to patient temperament, history of assault or abuse, and comorbid psychiatric diagnoses (attention deficit/hyperactivity disorder [ADHD], generalized anxiety, etc.) [2]. Social factors play an important role in the development of dental fear. As mentioned earlier, patients are introduced to various inappropriate stereotypes of dentists through much of the media that they consume from an early and impressionable age [1]. Furthermore, social and other external factors include social learning from family and peers [2]. If a young patient's parents display anxiety surrounding a child's dental appointment, or even around the parent's own dental treatment, dental anxiety can become a learned behavior [2]. This is a form of modeling and is an excellent reason as to why it is so vital for the dental practitioner to do their best to manage anxiety in the dental environment [2]. The dental factors surrounding fear and anxiety may be the most evident, but are still worth discussing as these are the most under the provider's control. The most referenced dental factor by patients is usually the fear of dental pain, whether personally experienced or anticipated [2]. The dental experience, including the anticipation of pain, discomfort, and invasion of personal space, can cause the patients to perceive a loss of control in the situation [2]. This loss of control can be linked to stress and panic igniting the physiologic fight or flight response. Moreover, the dental experience can be sensory overload for some individuals, especially those with preexisting neurodevelopment issues. There are unique and poignant smells and sounds that are only experienced in the office with uncomfortable or painful experiences.

The prevalence of dental anxiety is underestimated in the general population. Studies have been carried out to examine the prevalence of dental fear in the general population. The prevalence of dental fear in a study group of almost two thousand Dutch patients was found to be as high as 24.3% [3]. This study was from the *European Journal of Oral Sciences* and found that the presence of dental fear was essentially equivalent to that of the fear of general physical harm (27.2%) and not far removed from the prevalence of the fear of heights (30.8%) [3]. In addition, frank dental

C. Haxhi (✉)
Department of Anesthesia, Duke University Hospital, Durham, NC, USA

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_29

phobia was found to be the most common phobia with a prevalence of 3.7% in the study group with a phobia of heights being at 3.1% [3]. These phobias were evaluated using the DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*) criteria to establish a true diagnosis of phobia, or severe fear with physiologic sequelae [3]. Other studies have estimated the prevalence of dental fear in the general population to be 19.8% [4] with similar estimates in multiple other epidemiologic studies. Studies of various populations across Europe estimate that up to 7% of patients in the general population have experienced fear strong enough to prohibit them from seeking care [4]. There is so much that a dental health care provider can do given the multifactorial etiology of dental anxiety. The domain we have most control over is in the dental environment and helping to manage the anxiety we perceive in our patients.

A Self-Perpetuating Cycle

The importance of dental anxiety cannot be overemphasized and special attention needs to be paid to the public health impacts of dental anxiety. There is a cyclic nature that was described as early as 1984 and the downstream effects of dental fear can have lasting impacts not only on oral health, but also on overall health and quality of life [5]. The cycle begins with the etiologic inputs that were discussed in the previous section of this chapter: personal, dental, and societal factors that create dental anxiety [2]. The cycle can then be simplified and begins at the onset of dental fear and anxiety, which causes patients to avoid prophylactic, routine, and less invasive treatments. The avoidance of this prophylactic care results in the continued decline of a patient's oral health. This decline necessitates the need for more invasive procedures, discomfort, and patient stress [5]. Patients who finally reach a point at which they can no longer put off receiving treatment will be receiving care in an even more vulnerable condition and will have the anticipation of more pain and discomfort [2]. The need for more treatment, and consequently more expensive treatment as well, will contribute to more dental anxiety and the cycle has a high likelihood of perpetuating itself [2, 5]. The cycle has been modified and can be illustrated in Fig. 29.1. The link between oral health, overall health, and quality of life is well studied and the avoidance of prophylactic dental care contributes to a clear decrease in quality of life [6].

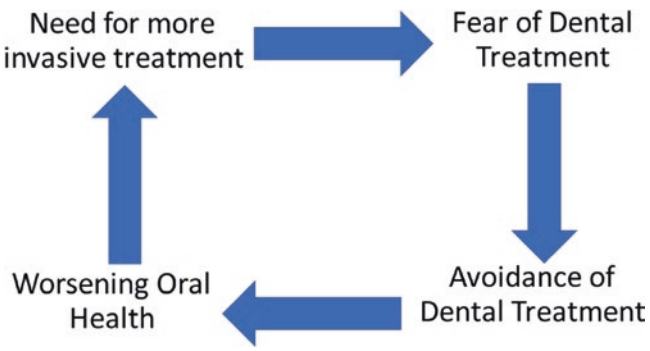


Fig. 29.1 An illustration of the modified cycle of dental anxiety

Pharmacologic Anxiety Management Strategies

Pharmacologic anxiety management is referred to as anxiolysis. Anxiolysis is defined as the reduction or elimination of anxiety in a conscious patient [7]. It is the mildest form of sedation that one can practice and should not create a depression of consciousness [7]. When employed appropriately, the patient should remain awake and responsive and there should be minimal risk of respiratory, cardiovascular, or protective physiologic reflex compromise [7]. Anxiolysis in the dental office comes down to three main routes of administration, each with their own set of advantages and disadvantages. The three main routes are inhalation, oral, and intravenous (IV). These three routes for pharmacologic anxiolysis are routinely practiced and their prevalence varies based on the discipline of dentistry. Inhalational route is used widely in both general practice and pediatric dentistry and is used somewhat less frequently in the practice of endodontology and oral surgery. Intravenous sedation is most commonly used in the oral and maxillofacial surgery specialty because of their extensive training, but it is not just limited to the practice of oral and maxillofacial surgery. With the recent recognition of dental anesthesiologists as a certified dental specialty, the prevalence of intravenous sedation will likely continue to grow in non-specialist offices. The three routes of administration will be reviewed in this section of the chapter.

Inhalational Anxiolysis

The inhalational agent used by dentists for anxiolysis, or the elimination of anxiety, is nitrous oxide. It is a colorless gas with a faint sweet smell that is not apparent to every patient [8]. Nitrous oxide was discovered in the late-1800s and has been the agent of choice for anxiolysis in the dental practice since the mid-1900s [8]. While thought of as a tool for anxiolysis in the dental office, it has application in operating room anesthetics as well. The sedative effects of nitrous oxide are exerted through many target receptors both in the brain and spinal cord [8]. The anxiolytic effects of nitrous oxide are mediated through activation of the gamma-aminobutyric acid-A (GABA-A) receptors, which are the

same target for oral anxiolytic drugs that will be discussed later in the chapter [9]. Of note, its ability to cause anesthesia, or decreased consciousness, is mediated through non-competitive *N*-methyl-*D*-aspartate (NMDA) inhibition and its analgesic, or pain-relieving, properties are mediated through a similar mechanism to opiate pain medications [9].

There are many advantages to using nitrous oxide for anxiolysis, first of which is that the administration of nitrous oxide is easy and the effect is rapidly titratable [8]. Nitrous oxide has a rapid uptake and elimination, meaning that the effects will be seen rapidly and will dissipate rapidly as well [8]. The effects are titratable and there is a wide margin of safety [8] as a provider would need to provide over 100% nitrous oxide in order to produce general anesthesia. From a systems-based practice standpoint, nitrous oxide requires minimal patient or practice preparation and quick recovery with no lasting effects means that patients can be rapidly turned over and a patient does not need an escort home [8]. Nitrous oxide administration does have drawbacks including the initial cost of investment in the administration systems, a patient must be cooperative enough to breathe through their nose, and the nasal hood makes anterior dental work technically difficult [8]. Not every patient is a candidate for nitrous oxide administration including critically ill patients, and patients with severe cardiovascular disease or lung disease, history of middle ear surgery, substance abuse, psychiatric disorders, pulmonary hypertension, first trimester pregnancy, and certain metabolic disorders [8, 10]. A medical consult may be necessary prior to the administration of nitrous oxide in a medically complex patient.

The administration of nitrous oxide is relatively simple from a technical standpoint and can be employed relatively quickly. An example of a nitrous oxide administration unit is represented in Fig. 29.2. Once it has been confirmed that the patient has not had a heavy meal prior to treatment, the nasal hood can be attached to the patient [8]. The patient should be pre-oxygenated with 100% oxygen for anywhere from 60 s to 5 min. The provider can slowly titrate the nitrous oxide starting at 10% and move in slow increments until desired anxiolysis is achieved [8]. Adequate anxiolysis can be achieved at various levels; however, 20–30% is usually adequate for the average patient. This is dependent on patient-specific factors and the level of anxiety pre-procedurally. While side effects from nitrous oxide are rare, they are possible and patients should not be administered nitrous oxide above 50% [8]. These side effects can include dizziness, nausea, vomiting, and dissociation [10, 11]. After the completion of the procedure, it is of the utmost importance that the patient receives 100% oxygen for 5–10 min to help fully breathe off built-up nitrous oxide levels. This is in order to avoid a phenomenon referred to as diffusion hypoxia, which, based on concentration gradients of oxygen to nitrous oxide, causes a patient to have blood oxygen level desaturations [10].

Fig. 29.2 An example of a nitrous oxide administration unit, including oxygen and separate nitrous oxide hosing

Overall, nitrous oxide has a long history of safe and efficacious use of anxiolysis and is a relatively safe agent to use in the average patient. It is easy to administer once the systems are in place and does not require too much disruption to the workflow of established practices.

Oral Anxiolysis

The use of oral medications for anxiolysis is also quite common and may be the route of administration that comes to a patient's and/or medical provider's mind first when thinking about managing their anxiety. Like with inhalational agents, there are advantages and disadvantages to the oral route of administration. Most patients are very familiar with oral medications and it is reasonable to assume that it is the preferred method of administration of a drug [12], giving the per oral route a clear advantage. Moreover, as discussed earlier in the chapter, patient anxiety stems from a sense of loss of control. The physical act of taking their own medication can be psychologically empowering and help a patient feel as though they have some level of control in their situation. Some patients will find the nasal hood of nitrous oxide claustrophobia inducing and others have fear of needles and intravenous line placement. Additionally, the oral medications have a lower cost than their IV alternatives making them a superior choice for the cost-conscious patient [12]. The agents used orally have more severe side effects than nitrous oxide; however, there is still a relatively low incidence of adverse reactions and the severity of these reactions is decreased when compared to intravenous sedation [12].

Table 29.1 Pharmacokinetics of anxiolytic oral medications

Drug	Bioavailability	Peak plasma concentration	Active metabolites	Available dosing
Diazepam	90–100%	1–1.5 h	Yes	2, 5, and 10 mg tablets
Alprazolam	80–100%	1–2 h	No	0.25, 0.5, 1.0, and 2.0 mg tablets

The biggest disadvantage to oral agent is that the onset of action is much slower than inhalational agents. This makes oral agents a suboptimal anxiolytic in urgent situations, as they require some level of preparation. The patient may need an escort to their appointment if the medication is prescribed to be taken prior to their appointment and they will need an escort home as well. Additionally, patient compliance with taking their medications is an important aspect as well. A specific prescription must be given so that a patient does not have extra pills and takes too much prior to their appointment. As mentioned earlier in the section, the oral agents typically used can have a depressive effect on the cardiovascular system and on the respiratory drive [13]. The dosing for anxiolysis is significantly lower than that prescribed to produce a sedative effect. There is also the risk for anaphylaxis when administering an oral agent, which is especially dangerous if the patient is to take their anxiolytic prior to presenting to their appointment [13].

There are many agents to choose from, but the mainstay of anxiety management is the benzodiazepine group of anxiolytics [14]. While there are many other drugs that can be used orally for both anxiolysis and oral conscious sedation, this section will focus on the benzodiazepine class as it more widely used than any other class for anxiolysis.

The benzodiazepine class is a broad category of medications that includes a wide array of agents. These agents are divided into subcategories of anti-anxiety medications and sedative-hypnotics. The benzodiazepines are CNS (central nervous system) depressants, their mechanism of action occurs at the GABA inhibitory channels, and they increase the frequency of opening these chloride channels. The GABA receptors provide inhibitory input in the central nervous system. These medications have a high therapeutic index [14], meaning that there is a wide dosing range to produce a desired effect without experiencing toxicity from the drug. The dosing to reduce anxiety is considerably lower than the dose needed to produce conscious sedation. Generally, at low doses required for anxiolysis, these drugs do not have a significant effect on respiratory or cardiovascular system at the doses required for anxiolysis. This again is dose dependent and also dependent on patient factors. These factors include patient age, health history, drug abuse history, and whether they are benzodiazepine naïve. The contraindications to benzodiazepine use are patients with anaphylaxis or hypersensitivity reactions to benzodiazepines, narrow-angle glaucoma, and age greater than 65 [15]. The specific benzodiazepines used for anxiolysis will be discussed below, and please refer to Table 29.1 for quick reference regarding the pharmacokinetics of the anxiolytic benzodiazepines.

Diazepam, or Valium, is one of the original benzodiazepines and has been used for anxiolysis and sedation for many years. The drug has a bioavailability of 90–100% when taken fasted and reaches peak plasma concentration between one and one-and-a-half hours after taking the medication [16]. Diazepam has active metabolites that contribute to its long half-life of 48 h. While still used by some providers, there has been a practice shift toward shorter-acting agents. Valium is available as a tablet in 2 mg, 5 mg, or 10 mg formulations [16]. Recommended dosing for anxiolysis is 2–10 mg, per package insert, and would be taken at least an hour prior to a procedure [16].

Alprazolam, or Xanax, is an anxiolytic and amnestic benzodiazepine and is indicated for anxiety and panic disorders [17]. This drug does not have active metabolites. It is readily absorbed by the digestive tract and will reach peak plasma concentrations between 1 and 2 h after administration [17]. It is available in 0.25 mg, 0.5 mg, 1.0 mg, and 2.0 mg tablets and the recommended dosing is 0.25–0.5 mg per dose [17].

While benzodiazepines at low dose all have anxiolytic properties, there are some with a much stronger effect as a sedative-hypnotic medication. These medications include midazolam, lorazepam, and triazolam (Versed, Ativan, and Halcion, respectively). These medications are better suited for oral conscious sedation and will not be discussed here.

Intravenous Agents

The intravenous agents used for anxiolysis include parenteral formulations of the above- described benzodiazepines, among other agents. However, the use of intravenous agents is primarily indicated for deeper sedation and general anesthetics. A general anesthetic is not indicated to be anxiolytic in nature and requires formalized training for administration, whether it is a dental anesthesiologist or a trained dental provider and their team, operating under the "sole-operator" model. As such, medications like intravenous midazolam, fentanyl, propofol, and ketamine will not be discussed.

Non-Pharmacologic Anxiety Management

Pharmacologic anxiety management techniques should be considered an adjunct to the treatment of dental anxiety. As was discussed in the etiology of dental fear section, there are

multitudes of contributing factors to the development of dental fear. Optimizing the dental practice to better accommodate those with dental anxiety will have a two-pronged effect, the first of which is the management of those with preexisting dental anxiety and, second, it will reduce the "dental factors" aspect of dental fear. To reduce this would, hopefully, abate some of the development of dental anxiety in patients. There are various ways in which a dentist can optimize their practice for those with dental fear.

Practice Environment

The practice environment is a space in which a series of simple changes can have an impact in helping to alleviate dental anxiety and fear, the first of which is that dentists and staff should make an utmost effort to be pleasant, positive, and comforting to all patients. An effort should be made to keep the waiting room as isolated from the treatment rooms as possible, so that ambient treatment noises cannot be heard from the waiting room. Additionally, it has been noted that reduced wait times for patients allow less time for them to absorb any negative stimuli [18]. Additionally, shorter wait times reduce the amount of time the patient have to reflect on any past negative dental experiences or on anxiety-provoking thoughts [18]. Studies have also found that covering up the chemical smells associated with dental offices with pleasant odors can help to calm patients as well. The scent of lavender and its essential oil is frequently invoked for its ability to reduce stress [19]. Furthermore, a modern, comfortable waiting room and treatment room are helpful in both making a patient physically more comfortable and mentally distancing themselves from pop culture imagery of dreadful dentists. Warm colors, soft music, distractions (television, books, magazines), or even Wi-Fi for smart phones can make a meaningful impact in creating an environment conducive to relaxation.

Restoring Control to the Patient

As discussed earlier in the chapter, one patient factor that a provider can help alleviate to the development of dental anxiety is the perceived loss of control that some patients experience. It is here where a good rapport and therapeutic alliance can overcome this perceived loss of control. Genuine introductions, compassionate history taking, and thoughtful responses are the first step to building a good therapeutic alliance. Normalizing anxiety in the dental chair will show a compassion, which the patient will likely appreciate [18]. Furthermore, patients should be actively involved in the informed consent process and they should be encouraged to ask as many questions as necessary [18]. After this, affirming for the patient that they are ultimately in control of their health and the treatment they receive is an important building block. Frequent "check-ins" during procedures should occur to ensure that the patient is doing well and for psychologically reinforcing that while they may be in a vulnerable position, they are still in control. In addition to this, a patient can be given a certain signal to use so that the procedure can be paused if there is an overwhelming feeling of pain, discomfort, or anxiety [18]. This technique is called behavioral control and can help restore a sense of control that the patient may otherwise feel they are missing.

There are many psychotherapeutic interventions that do not require specialized training that can enhance a sense of control for a patient [18]. The first is "tell-show-do" and it is employed primarily in pediatrics but can have success in enhancing a sense of control in adults as well [20]. The technique begins with laying out exactly what will be done on a patient; in layman terms, this is the "tell" aspect. For the "show" aspect of the technique, the patient will be shown the instruments that will be used, allowed to hold whatever he or she desires, and allowed to have as immersive an experience as possible. And, finally, to "do" is to complete the procedure in succession with the tell and the show phases. This rapid succession of introducing the plan, the instruments that will be used, and the execution of the plan is designed to reduce the uncertainty that facilitates the sense of losing control [20].

Another technique that has been found to be helpful in reducing anxiety and fear, especially with dental treatments that the patient is unfamiliar with, is "modeling." This most simply allows the patient to witness the proposed procedure [18], whether this is on another consenting patient similar in demographics to the patient or, more feasibly, via video or slideshow [18]. This technique again allows the patient to reduce the amount of uncertainty that can fuel this loss of control.

Relaxation Techniques

There are many guided relaxation techniques to help patients physically relax. Studies show that if the body is physically relaxed, one cannot be psychologically anxious concurrently [18]. These relaxation techniques can be taught to patients and there are even online resources for patients to practice them at home. They can then be employed chairside prior to treatment commencing.

One of the techniques that can be employed by a provider and a patient is called the Jacobsen's progressive muscular relaxation technique. The technique, simplistically, involves the activation of specific muscle groups for 5–7 s with a period of relaxation lasting 20 s [21]. Activation of muscle groups in the legs, arms, abdomen, and face is usually employed [18, 21].

Patients will have increased benefit from exercises like Jacobsen's progressive muscular relaxation when practiced in conjunction with breathing exercises. Such breathing exercises, like diaphragmatic breathing, help a patient focus solely on their breathing and distract them from any potential dental anxiety. Breathing exercises are also able to be deployed chairside and the patient may have some familiarity with them already from recreational activities like yoga and other exercise activities. To practice diaphragmatic breathing, a patient will need to enter a neutral body position, feel their chest and their abdomen with their hands, and practice even and slow inhalations, until a feeling of fullness, and exhalations, until a feeling emptiness in the chest [18].

Advanced Anxiety Management Techniques

While there are many aspects of the dental experience that can be optimized for patient comfort and techniques employed chairside to alleviate anxiety, there are some cases that may require more advanced therapeutic measures. These techniques to treat severe dental anxiety and dental phobia require dentists to either refer their patients to additional providers or to seek additional education and certifications in order to safely employ them. These techniques include but are not limited to cognitive behavioral therapy (CBT) and hypnotherapy.

Cognitive behavioral therapy (CBT) is a longitudinal therapy process that involves a restructuring of negative thoughts and behaviors relating to specific stimuli [22]. CBT is a widely used therapy in outpatient psychology settings and has been shown to be efficacious for many psychological disorders including fears and phobias [18, 22]. It is a gradual process and is usually performed by a trained therapist but dentists can obtain special training and certification to employ this practice [18]. It is a potential management option in those patients evaluated to have a severe anxiety or phobia. The dental provider should anticipate slow and gradual improvement and it is best employed in patients where there is a good therapeutic alliance and strong longitudinal relationship.

Studies are showing that there is a role for hypnotherapy in the treatment of dental anxiety [18, 23]. Hypnotherapy is a practice of assisting a patient to enter an altered state of consciousness, without pharmacologic intervention [23]. The patient is then more receptive to suggestion and relaxation [23]. There is a developing body of literature to show hypnotherapy's positive impacts on those with dental anxiety both alone and in conjunction with other anxiety management therapies [23]. Research is still ongoing to the benefits of employing hypnotherapy for relaxation [18]. The dental practitioner either needs additional formal training or referral to a trained hypnotherapist.

Summary

Dental anxiety is a common problem for both patients and dental health care providers. This problem has a downstream effect on patient quality of life and has far-reaching public health impacts. It is important to understand the complex causes of dental anxiety and phobia including patient factors, social factors, and dental factors. With an understanding of what can cause dental anxiety, it is possible to employ appropriate strategies to manage the anxious patient. These strategies include inhalational and oral pharmacologic agents and non-pharmacologic strategies. The non-pharmacologic strategies include practice engineering, rapport building, relaxation techniques, and advanced therapies that patients can be referred to.

References

1. Thibodeau E, Mentasti L. Who stole Nemo? J Am Dent Assoc. 2007;138(5):656–60. https://doi.org/10.14219/jada.archive.2007.0238.
2. Willumsen T, Haukebø K, Raadal M. Aetiology of dental phobia. In: Öst L-G, Skaret E, editors. Cognitive behaviour therapy for dental phobia and anxiety; 2013. https://doi.org/10.1002/9781118499825.ch4.
3. Oosterink FMD, De Jongh A, Hoogstraten J. Prevalence of dental fear and phobia relative to other fear and phobia subtypes. Eur J Oral Sci. 2009;117:135–43. https://doi.org/10.1111/j.1600-0722.2008.00602.x.
4. Agras S, Sylvester D, Oliveau D. The epidemiology of common fears and phobia. Community Dent Health. 1969;10:151–6.
5. Berggren U, Meynert G. Dental fear and avoidance: causes, symptoms, and consequences. J Am Dent Assoc. 1984;109(2):247–51. https://doi.org/10.14219/jada.archive.1984.0328.
6. Vigu A, Stanciu D. When the fear of dentist is relevant for more than one's oral health. A structural equation model of dental fear, self-esteem, oral-health-related well-being, and general well-being. Patient Prefer Adherence. 2019;13:1229; https://link.gale.com/apps/doc/A602106437/AONE?u=duke_perkins&sid=summon&xid=8accadc2.
7. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology. 2002;96(4):1004–17.
8. Mohan R, Asir V, Shanmugapriyan, Ebenezr V, Dakir A, Balakrishnan, Jacob J. Nitrousoxide as a conscious sedative in minor oral surgical procedure. J Pharm Bioallied Sci. 2015;7(5):250. https://doi.org/10.4103/0975-7406.155939.
9. Emmanouil DE, Quock RM. Advances in understanding the actions of nitrous oxide. Anesth Prog. 2007;54(1):9–18.
10. Knuf K, Maani CV. Nitrous Oxide. [Updated 2021 Jul 23]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. https://www.ncbi.nlm.nih.gov/books/NBK532922/.
11. van Amsterdam J, Nabben T, van den Brink W. Recreational nitrous oxide use: prevalence and risks. Regul Toxicol Pharmacol. 2015;73(3):790–6. https://doi.org/10.1016/j.yrtph.2015.10.017.
12. Matear D, Clarke D. Considerations for the use of oral sedation in the institutionalized geriatric patient during dental interventions: a review of the literature. Spec Care Dentist. 1999;19(2):56–63. https://doi.org/10.1111/j.1754-4505.1999.tb01369.x.

13. Gill CJ, Michaelides PL. Dental drugs and anaphylactic reactions: report of a case. Oral Surg Oral Med Oral Pathol. 1980;50:30.
14. Becker D. Pharmacodynamic considerations for moderate and deep sedation. Anesth Prog. 2012;59(1):28–42. https://doi.org/10.2344/0003-3006-59.1.28.
15. Bounds CG, Nelson VL. Benzodiazepines. [Updated 2018 Nov 13]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2018. https://www.ncbi.nlm.nih.gov/books/NBK470159/.
16. Valium [package insert] south. San Francisco, CA: Roche Pharmaceuticals Inc; 2016.
17. Xanax [package insert]. New York, NY: Pfizer Pharmaceuticals Inc; 2011.
18. Appukuttan D. Strategies to manage patients with dental anxiety and dental phobia: literature review. Clin Cosmet Investig Dent. 2016;35:35. https://doi.org/10.2147/ccide.s63626.
19. Lehrner J, Marwinski G, Lehr S, Johren P, Deecke L. Ambient odors of orange and lavender reduce anxiety and improve mood in a dental office. Physiol Behav. 2005;86(1):92–5.
20. American Academy of Pediatric Dentistry Special issue. Proceedings of the conference on behavior management for the pediatric dental patient. Pediatr Dent. 2004;26(2):110–83.
21. Jacobson E. Progressive relaxation. Chicago: University of Chicago Press; 1938.
22. Getka EJ, Glass CR. Behavioral and cognitive-behavioral approaches to the reduction of dental anxiety. Behav Ther. 1992;23(3):433–48.
23. Venkiteswaran A, Tandon S. Role of hypnosis in dental treatment: a narrative review. J Int Soc Prev Community Dent. 2021;11(2):115–24. https://doi.org/10.4103/jispcd.JISPCD_320_20.

Pharmacologic Pain Management

30

Michael T. Goupil

Introduction

Over the counter (OTC) and/or prescription medications are a major part of any pain management program. The current opioid crisis has altered some of these strategies, encouraging a more thoughtful approach tailored to the individual patient.

The basis of any treatment requires an assessment of the patient's current complaint and a review of their medical history. Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. A distinction needs to be made on whether the pain condition is acute or chronic. Acute pain can usually be attributed to a defined precipitating event whereas the exact etiology of chronic pain may be more difficult to ascertain. Chronic pain is defined as a pain that lasts beyond the normal healing time for a given injury. Any pain lasting more than 3 months is classified as chronic in nature [1].

It is important to elicit from the patient what treatments they are or have used for the current painful condition and which of these have or have not been successful. In addition, it is important to determine whether the patient has followed the instructions for the prescribed pain treatments.

Pain is a very personal thing. There is a significant difference on how individuals will react to the same stimulus. It is important to assess the patient's expectations. Total pain relief, especially when dealing with chronic pain, in all likelihood is impossible to achieve. A more realistic goal is pain management and return to a more reasonable and normal lifestyle.

Acute pain is commonly managed with short-term analgesics, most frequently acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and opioids, whereas chronic pain management may include muscle relaxants, antidepressants, and complementary modalities. A variety of non-pharmacologic pain management strategies should also be considered. These include various alternative and complementary techniques, such as acupuncture—relaxation techniques that are beyond the scope of this chapter.

Opioid Crisis

The U.S. Department of Health and Human Services declared the misuse of opioids had become a public health emergency in 2017. This included both prescription and non-prescription use of opioids. A major factor in the overuse of opioid prescriptions was the marketing of oxycontin as a safe, non-addicting opioid for chronic pain. Unfortunately, oxycontin was proven to be highly addictive, and it was frequently being prescribed for acute pain management. Over 60% of drug overdose events in 2016 were related to opioids [2].

Prescribing opioids even for the short term to young adults has the potential to lead to narcotic addiction. Even though opioid prescribing has decreased, there continues to be an increasing use of non-medical opioids with deadly effects.

The opioid crisis has led to changes in pain management recommendations. Guidelines have been developed and instituted at both the federal and state levels, which has resulted in a decrease in opioid prescriptions [3]. Recommendations for pain management are now more reliant on non-opioids such as acetaminophen and/or non-steroidal anti-inflammatory drugs (NSAIDs).

Odontogenic Pain

Odontogenic pain is of tooth origin resulting in irritation to nerves within the dental pulp of a tooth. This pain may be the result of an insult that is readily visible such as a tooth fracture or a large carious legion, which are easily diagnosed. Unfortunately, the pain may result from an insult that is not easily detected such as a cracked tooth or repeated microtrauma leading to non-vitalization of the dental pulp.

M. T. Goupil (✉)
Carmel, IN, USA

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_30

A patient may present with a complaint of odontogenic pain that cannot be attributed to tooth injury. One of the more common diagnoses would be a maxillary sinusitis presenting as pain in the teeth of the posterior upper jaw. Another example, although rare, would be pain in the left lower jaw region that rather than of odontogenic origin could be an early manifestation of a cardiac event.

Periodontal

Pain may originate from the supporting tooth structures or the periodontium. Patients are likely to present with a loose tooth, swelling or bleeding of the gums, or purulent drainage from the gingiva–tooth margin. This type of pain would be more likely in an older population and be of a more intermittent or chronic nature.

Endodontic

This type of pain is secondary to inflammation of the dental pulp as noted above but may also be secondary to a periodontal infection. When patients present with a pain complaint after having had the dental pulp removed by root canal therapy, the cause is most likely irritation and inflammation of the bone at the apex of the offending tooth. Swelling of the mucosal tissue in the region surrounding the tooth is indicative of a localized odontogenic infection.

Oral/Maxillofacial Surgical Issues

Dentoalveolar

The cause of oral and maxillary surgical-related pain may be either preoperative or postsurgical issues. Preoperative pain within the dentoalveolar complex (tooth-bearing bone) is usually due to an infectious process secondary to the above-discussed causes. The most appropriate treatment for infection continues to be the removal of the cause. This does not always mean removal of the tooth. An incision and drainage procedure can be accomplished if discrete swelling is noted and/or the use of antibiotics. Penicillin in the non-allergic patient continues to be the antibiotic of choice.

Most postoperative dentoalveolar procedures producing pain will either be the removal of one or more teeth or the placement of dental implants. The pain is secondary to localized bone trauma and thus inflammatory in nature and not an infection. Tooth extraction pain usually reaches its peak within 24 h and typically has a duration of 3 days or less. Any pain lasting more than 3 days that requires prescription pain medication needs to be investigated for a postoperative complication. The most common complication would be a postoperative infection, which should be treated with drainage and/or antibiotics. Another common complication following a tooth extraction would be alveolar osteitis, commonly called a “dry socket.” This is not uncommon following the removal of third molars (wisdom teeth). The complaint is a new, radiating pain occurring 3 to 4 days following the surgical procedure. Treatment should be local palliative measures and not more opioids.

Trauma

Maxillofacial trauma maybe of soft tissue or bone and is usually a combination of both. Local palliative measures should be considered for soft tissue injuries. Bony fractures need to be stabilized to prevent motion, which causes localized soft tissue injury and inflammation resulting in pain. It would not be unusual for a patient to experience pain for 10–14 days. This would include elective trauma such as orthognathic (jaw) surgery.

Neurogenic Pain

Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system. In the head and neck region this can include any of the cranial nerves with one of the most commonly described being tic douloureux (trigeminal neuralgia). Similar complaints may also involve the other cranial nerves such as the facial or glossopharyngeal nerve. Patients presenting with neurogenic pain will complain of a sharp, shooting, sporadic pain.

Neurogenic pain can be very difficult to manage and requires a multimodal approach. Opioids should be used with caution as the risk of dependence or addiction is high. The use of anti-epileptic drugs (AEDs) should be considered along with complementary measures. Nerve ablation may be required.

Temporomandibular Joint Dysfunction Pain

Patients may present with the complaint of “I have TMJ.” This pain complaint is known by a variety of names, most common being myofascial pain dysfunction (MPD) or temporomandibular joint dysfunction (TMD). This is a very complex problem beyond the scope of this chapter. A wide variation of etiologies and treatment strategies have been proposed in the literature for more than 100 years.

A simplistic approach for pain control divides the concern in two major categories: intracapsular (within the actual joint itself) or extracapsular issues. Intracapsular pain is most

likely caused by inflammatory mediators and therefore anti-inflammatory medications are part of the multimodal approach. For extracapsular issues, muscle spasm frequently may be the source of pain and muscle relaxants might be considered along with a variety of non-pharmacologic measures like heat, cold, and physical therapy.

Acute Pain Pharmacologic Strategies

Acute pain management should be a multimodal approach modified to the individual's pain complaint. Non-pharmacologic measures such as cold or heat to the affected area, especially in a postsurgical situation, can be quite effective in reducing pain. Since most of the pain complaints are caused by inflammatory pain mediators, non-opioid medications should be the primary focus of pain control. For non-opioids to be effective, they need to be prescribed on a fixed time interval usually at a minimum of every 6 h for 3 days. It is important for the patient to understand that these drugs are disrupting the action of pain mediators thus preventing the pain impulse from occurring and, thus, to be effective must be taken as directed on a fixed interval rather than as needed for pain.

Local anesthesia is an underutilized modality in dental pain management. Long-lasting anesthetics such as bupivacaine should be considered at the end of a surgical procedure. This technique can prevent the transmission of a pain impulse for 8–12 h. This same method could be considered in the night/emergency room setting, which hopefully would allow the patient to see a dental provider for more definitive care.

Commonly Used Medications for Acute Pain

Acetaminophen: Although its analgesic mechanism is complex and not completely understood, it continues to be one of the most commonly used OTC pain medications. Current thought is that acetaminophen acts on the transient receptor potential vanilloid 1 (TRPV1) and cannabinoid I in the brain as well as TRPV1 receptors in the spinal column [4]. Acetaminophen is available OTC as an immediate-release 325 mg tablet and is usually prescribed as 325 mg to 1 g orally with a minimum dosing interval every 4 h. The maximum single dose is 1000 mg with a maximum dose of 4 g per 24 h. Onset of activity is 30–45 min with its peak effect reached at ½–1 h with an action duration of 4–6 h. Liver toxicity has been reported and dosage should be adjusted downward in those patients with liver disease. Acetaminophen does not have a significant effect on platelet activity.

Ibuprofen: This is the most popular and commonly used non-steroidal anti-inflammatory drug (NSAID) used for both its analgesic and antipyretic properties. It is a non-selective inhibitor of cyclo-oxygenase 1 and 2 (COX-1, COX-2), which are involved in the production of prostaglandins [5]. Ibuprofen is available in 200 mg (OTC) tablets and 400, 600, 800 mg prescription tablets as well as liquid preparations. Doses of ibuprofen over 600 mg do not appear to have an increased analgesic benefit [6]. For adults it is usually prescribed as 200–400 mg orally every 4–6 h as needed with a maximum prescription strength dose of 3200 mg/day (prescription strength) or 1200 mg/day for over the counter (OTC) use. The analgesic effect has an onset of 30–60 min with a duration of 4–6 h.

Hydrocodone: This is a semi-synthetic analgesic that acts as an agonist on the mu-receptor. It is available in combinations with acetaminophen or ibuprofen for the control of moderate to severe pain. Due to the opioid crisis, it was reclassified in 2014 by the U.S. Food and Drug Administration (FDA) as a Schedule II narcotic. Although it is available in a sustained form, for acute pain it should only be prescribed in the quick-release preparation. The recommended dosage of hydrocodone 5 mg with acetaminophen 325 mg is 1–2 tablets every 4–6 h with a maximum dosage of 8 tablets every 24 h, whereas hydrocodone 7.5 mg with ibuprofen 200 mg is dosed at 1 tablet every 4–6 h, not to exceed 5 tablets per 24 h. Onset of action is 10–30 min with a peak effect at ½–1 h and a duration of 4–6 h.

There are two things the provider needs to remember when prescribing hydrocodone preparations.

1. Hydrocodone is only available in combination with acetaminophen or ibuprofen. When used as part of an analgesic plan, the total dosages of acetaminophen or ibuprofen within a 24-h period need to be calculated and adjusted to stay within maximum recommended doses. This is particularly important when prescribing hydrocodone for breakthrough pain.
2. Hydrocodone is available in a variety of preparations ranging from 5 to 10 mg per tablet. It is equivalent to morphine on a milligram-to-milligram basis. Current recommendations are that opioids should not exceed 50 morphine milligram equivalents (MME).

Prescribing Strategies (See Table 30.1)

1. For mild pain, the primary drug should be an NSAID such as ibuprofen 400 mg at a fixed interval of 6 h whether there is pain or not for 3 days. The NSAID is being used to interfere with pain mediators. There is a placebo effect in providing a prescription as opposed to using the OTC 200 mg preparation.
2. For mild to moderate pain, consider alternating the ibuprofen dose with an acetaminophen dose 325 mg every

Table 30.1 Acute pain management strategies

Pain level	Pain score	Analgesic strategy
Mild	1–2	Ibuprofen 200–400 mg q 4–6 h for 3 days
Mild to moderate	3–4	Ibuprofen 400–600 mg q 6 h for 3 days
Moderate	5–6	Ibuprofen 600 mg q 6 h for 3 days and acetaminophen 325 mg q 6 h take as needed pain
Moderate to severe	7–8	Ibuprofen 600 mg q 6 h for 3 days with acetaminophen 650 mg q 6 h
Severe	9–10	Ibuprofen 600 mg q 6 h for 3 days and hydrocodone 5 mg/acetaminophen 325 mg, 1–2 tablets q 4–6 h take as needed pain not to exceed 8 tablets in 2 h

Note: The dose recommendations given above are for healthy adults; they need to be adjusted for the medically compromised and/or geriatric patients; dosages for children should be weight calculated

4 h, which would allow the patient to take a pain medication every 2–3 h if needed.

3. For moderate pain, use ibuprofen 600 mg every 6 h. Consider alternating with acetaminophen 325–650 mg every 4 h.
4. For more severe pain, use 600 mg ibuprofen and 500 mg acetaminophen every 6 h. The acetaminophen can be increased to 1000 mg.
5. Consider using a combination of ibuprofen and acetaminophen together. This combination has a greater effect without the adverse effects of narcotics [6].
6. Hydrocodone/acetaminophen may be used for breakthrough or uncontrolled pain. Keep in mind that if acetaminophen was part of the pain management strategy, then an adjustment will need to be made so as not to exceed the maximum acetaminophen dose of 4 g per 24-h period.
7. Adjunct therapy such as ice and moist heat are also essential to the multimodal approach to pain management.
8. NSAIDs should be on a fixed time interval for 3 days.
9. For pain lasting more than 3 days, the patient should be evaluated for potential complications rather than providing new prescriptions.

Chronic/Neuropathic Pain Pharmacologic Strategies

A multimodal approach to chronic pain is essential and should not rely on prescription medications. The patient and their family support system need to have a clear understanding of the pain problem and have realistic and achievable goals. A variety of complementary practices should be included in the pain management. This may include but not be limited to acupuncture, massage therapy, a variety of relaxation techniques, physiotherapy, and laser therapy [7]. Prescription medications are usually required but should avoid opioids if at all possible. For the most part the use of opioid therapy for chronic, non-cancer pain does not provide the anticipated treatment outcomes of pain relief, improved quality of life, and improved functional capacity [8].

NSAIDs: Similar to acute pain management, NSAIDs are the foundation of the management of chronic orofacial pain (COP), which frequently has an inflammatory component. Long-term use of these drugs requires monitoring for long-term adverse effects including gastrointestinal bleeding and renal and liver dysfunction. Naproxen has a longer acting profile than ibuprofen and can be dosed less frequently: 220 mg 2–3 times a day, not to exceed 660 mg per day.

Antidepressants: In the tricyclic antidepressant (TCA) drug class, the secondary amines (nortriptyline and desipramine) have few side effects. For patients with nocturnal bruxism and poor sleep (which has a negative effect on coping mechanisms), amitriptyline can be considered.

The newer serotonin and norepinephrine reuptake inhibitors (SNRIs) like venlafaxine and duloxetine are gaining increased usage in the treatment of chronic and neuropathic pain [9].

Anti-Epileptic Drugs (AEDs): AEDs are commonly used in the treatment of neuropathic pain. There action is to limit neuronal excitation. Carbamazepine (200–1200 mg/day) is the classic first-line drug for the treatment of tic douloureux (trigeminal neuralgia). It is a prognostic marker for tic douloureux—if the drug eliminates the pain, the diagnosis for trigeminal neuralgia has been made.

Newer anticonvulsive drugs like oxcarbazepine (600–1800 mg/day), gabapentin (600 mg tid), and pregabalin (50–100 mg tid) have fewer side effects in the treatment of neuropathic pain [10].

Muscle Relaxants: For the most part, muscle relaxants appear to have a limited use in the treatment of COP. Most of them are very sedative and will interfere with normal daily activities.

Botulinum Toxin: Temporomandibular joint disorders (TMD) are a common cause of COP and affect 10% of the population. Although TMD is a multifactorial problem and it is difficult to elicit a specific cause, approximately 50% of patients exhibit painful masticatory muscles. Botulinum toxin is a neurotoxin and has been shown to be effective in the treatment of these disorders. Its mode of action is a temporary denervation of skeletal muscle as well as inhibiting the release of pain neurotransmitters. Its effect is temporary, lasting 10–12 weeks [11].

Cannabis: There is some evidence that cannabis-based medications may have some benefit as part of a multimodal approach to chronic pain management. In those states and countries where cannabis is legal, this can be considered a third-line option by a provider well versed in prescribing and monitoring these products [12].

Centers for Disease Control and Prevention (CDC)

Because of the opioid crisis in the USA, the CDC issued guideline for the management of patients with chronic pain [13]:

1. Non-pharmacological and non-opioid therapy are the preferred modalities.
2. Clinicians should establish treatment goals with patients (Pain Management Contract).
3. Discuss with the patients the known risks and benefits of opioid therapy (Informed Consent).
4. Use immediate-release opioids.
5. Prescribe the lowest effective dose.
6. In the treatment of precipitating acute pain, prescribe for expected pain duration, usually 3 days.
7. Evaluate benefits of pain management plan within 1 to 4 weeks.
8. Evaluate for opioid risk factors prior to treatment.
9. Review the patient's controlled substance prescriptions prior to treatment.
10. Use urine drug testing prior to treatment and periodically thereafter.
11. Avoid prescribing opioids and benzodiazepines concurrently.
12. Offer medication-assisted and behavior therapies for opioid use disorders.

Similar guidelines are recommended for acute pain management.

Summary

Acute pain of dental origin in most cases is inflammatory in nature and can be effectively managed with the use of non-opioid medications prescribed on a fixed interval basis. Early diagnosis and treatment of the cause of the pain is necessary. Posttreatment dental pain can be anticipated after dental extractions, periodontal treatment, and endodontic procedures. Postoperative pain is usually of short duration, 2 to 4 days, and can be managed very effectively with fixed interval non-opioids. On occasion, opioids may be required but only small amounts should be prescribed, and prescriptions should not be renewed. Patients requesting an opioid prescription renewal beyond the expected pain duration of 3 days should be evaluated for a potential postoperative complication.

Chronic pain of dental origin can be very difficult to manage, and a multimodal approach is required. In addition to a course of fixed interval non-opioids, the prescription of muscle relaxants, anti-epileptics, and antidepressants may be indicated. Complementary and alternative medicine methods such as massage therapy, relaxation techniques, and acupuncture may prove helpful. Extreme caution is required when prescribing opioids in this vulnerable population, and for the most part opioid treatment is not recommended. Medication prescriptions for chronic pain patients are best managed using only a single prescribing health care provider.

References

1. Tompkins DA, Hobelmann JG, Compton. Providing chronic pain management in the "fifth vital sign" era: historical and treatment perspectives on a modern-day medical dilemma. Drug Alcohol Depend. 2017;173:S11–21.
2. Stoicea N, et al. Current perspectives on the opioid crisis in the US healthcare system: a comprehensive literature review. Medicine. 2019;98:20.
3. Soelberg CD, Brown RE Jr, Du Viver D, Meyer JE, Ramachandran BK. The US opioid crisis: current federal and state legal issues. Anesth Analg. 2017;125(5):1675–81.
4. Ohashi N, Kohno T. Analgesic effect of acetaminophen: a review of known and novel mechanisms of action. Front Pharmacol. 2020;11:580289. https://doi.org/10.3389/fphar.2020.580289.
5. Bushra R, Aslam N. An overview of clinical pharmacology of ibuprofen. Oman Med J. 2010;25(3):155–1661. https://doi.org/10.5001/omj.2010.49.
6. Moore PA, Hersh EV. Combining ibuprofen and acetaminophen for acute pain management after third-molar extractions. JADA. 2013;144(8):898–908.
7. Jackson HJ, Reneau M. Complementary therapies for acute pain management: what does the evidence say? Nurse Pract. 2019;44(12):8–11.
8. White PF. What are the advantage of non-opioid analgesic treatment in the management of acute and chronic pain? Expert Opin Pharmacother. 2017;18(4):329–33.
9. Ganzberg S. Pain management part II: pharmacological management of chronic orofacial pain. Anesth Prog. 2010;57:114–9.
10. Halpern L, Willis P. Orofacial pain: pharmacologic paradigms for therapeutic interventions. Dent Clin N Am. 2016;60:381–405.
11. Dutt CS, Ramnani P, Thaker D, Panadit M. Botulinum toxin in the treatment of muscle specific oro-facial pain: a literature review. J Maxillofac Oral Surg. 2015;14(2):171–5.
12. Häuser W, et al. European pain federation (EFIC) position paper on appropriate use of cannabis-based medications and medical cannabis for chronic pain management. Eur J Pain. 2018;22:1547–64.
13. Dowell D, Haegerich TM, Chou R. CDC guidelines for prescribing opioids for chronic pain—United States, 2016. JAMA. 2017;315(1):1624–45.

Oral Management of the Chemotherapy Patient

31

Alessandro Villa, Khawaja Shehryar Nasir, and Ahmed S. Sultan

Introduction

Cancer patients have unique oral health needs and, depending on the cancer diagnosis and treatment, may be at significant risk for various oral toxicities and potential systemic complications. In 2021, 1.9 million new cases of cancer were expected in the United States, leading to an estimated 608,570 cancer deaths [1]. Most patients receiving chemotherapy for cancers develop some form of oral complication including, but not limited to, infections, stomatitis, dry mouth, mucositis, and dental caries [2]. Treatment-related oral complications negatively affect patients' quality of life, and their ability to tolerate treatment increases cancer treatment-associated costs and may lead to worse cancer prognosis [3].

The severity of oral complications depends on the cancer stage and the type of agent used, the oral health status, and comorbid risk factors [3]. The population of cancer patients and survivors is growing constantly and recent advances in oncology have led to the development of new agents, many of which are associated with both acute and chronic oral complications and have resulted in increasing numbers of cancer survivors. Dentists, oral medicine specialists, and health care practitioners play a significant role for cancer patients by promoting oral health and disease prevention. Involving dental specialists in the care of cancer patients results in lower costs and shorter treatment duration for acute oral complications [4]. In addition, dental providers provide comprehensive oral health care for the cancer patient before cancer chemotherapy begins, during cancer therapy, and after completion of treatment [5].

In summation, not only do oral medicine and dental oncology specialists assist patients' oral needs during their cancer therapy, but also they may be the first ones to diagnose complications from cancer therapy and are essential in the management of the acute and chronic oral toxicities of survivors [6]. This book chapter will describe the most common oral complications from chemotherapy and elucidate the role of dental providers in the oral management of the chemotherapy patient.

The Role of the Dentist Prior to Chemotherapy

Oral and dental evaluation of patients scheduled to receive chemotherapy should begin as early as possible before initiation of therapy [7, 8]. The goal of a dental screening program prior to initiation of chemotherapy is to minimize complications during and after treatment. During certain chemotherapeutic regimens (e.g., in preparation for a hematopoietic stem cell transplant [HSCT]), patients may become immunosuppressed placing them at risk for a life-threatening infection/septicemia. Therefore, elimination of all potential sources of oral infection is an important aspect in the preparation of patients for chemotherapy. Sufficient time between the completion of dental treatment and the patient's anticipated state of immunosuppression (absolute neutrophil count [ANC]: <500–1000 cells/mL) is needed. In general, non-emergent dental treatment should not be performed in a dental office if the patient presents with severe thrombocytopenia (<50,000 platelets/mL) [7].

A. Villa (✉)
Miami Cancer Institute, Miami, FL, USA

Department of Translational Medicine, Herbert Wertheim College of Medicine, Miami, FL, USA

Faculty, Department of Orofacial Sciences, University of California San Francisco, San Francisco, CA, USA
e-mail: Alessandro.villa@baptisthealth.net

K. S. Nasir
Department of Internal Medicine, Shaukat Khanum Memorial Cancer Hospitals and Research Centres, Pakistan, Lahore, Pakistan
e-mail: shehryarnasir@skm.org.pk

A. S. Sultan
Department of Oncology and Diagnostic Sciences, School of Dentistry, University of Maryland, Baltimore, MD, USA

University of Maryland Greenebaum Cancer Center, Baltimore, MD, USA
e-mail: asultan1@umaryland.edu

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_31

Communication between the dental and oncology team around the patient's past medical history and oncology treatment plan is fundamental to minimize future oral side effects from cancer therapy. In particular, the oncologist should provide the dentist with information on the type of cancer, stage, present medications, hematologic status and immunologic status, and other medical conditions and details on the treatment plan.

Cancer patients typically undergo a complete dental evaluation to eliminate or stabilize oral diseases that could otherwise lead to local and systemic complications during or following chemotherapy. During the preparation, a thorough oral and dental exam is performed, including full-mouth periodontal charting, and radiographs to diagnose caries, periodontal disease, and visualize partial soft tissue impacted third molars. Dental interventions are directed to restore all carious teeth. If caries extends to the pulp, endodontic therapy or extraction should be considered.

According to the guidelines set forth by the National Cancer Institute, teeth with apical periodontitis should be managed only if they are symptomatic and if the size of the periapical lesion is ≥5 mm [9]. Dental extractions are recommended for teeth with severe periodontitis (probing depth of ≥8 mm) and/or mobility III. All possible sources of oral trauma and irritation, such as sharp edges of teeth, ill-fitting dentures, orthodontic brackets, and other appliances, should be removed.

Antibiotic prophylaxis prior to invasive surgical oral procedures may be needed in some cases, and dentists should follow the current American Heart Association (AHA) protocol for infective endocarditis. Management guidelines relative to invasive dental procedures are presented in Table 31.1.

Patients with a diagnosis of multiple myeloma may be on antiresorptive therapy (e.g., bisphosphonate therapy or denusamab), which places them at risk for developing jaw osteonecrosis. In these cases, oral surgical procedures should be performed as atraumatically as possible, and patients should be prescribed broad-spectrum antibiotic therapy for at least 14 days following the surgical procedure or until the soft tissue wound has closed along with chlorhexidine rinses.

Finally, patients should receive educational material and be instructed to maintain good oral hygiene during and after chemotherapy. Routine professional dental hygiene is important to reduce the incidence and severity of oral complications from cancer treatment. Patients should be informed of the rationale for the routine oral hygiene programs as well as the potential side effects of cancer chemotherapy.

Table 31.1 Guidelines relative to invasive dental procedures in the cancer patient

Medical condition	Recommendations
Neutrophils count	Order complete blood count with differential
> 2000/mm^3	No prophylactic antibiotics needed
1000–2000/mm^3	American Heart Association (AHA) prophylactic antibiotic recommendations (low risk)
< 1000/mm^3	Amikacin 150 mg/m^2 1 h pre-surgery; ticarcillin 75 mg/kg intravenous ½ h pre-surgery; repeat both 6 h post-operatively
Platelets count[a]	
> 60,000/mm^3	No additional support needed
30,000–60,000/mm^3	Platelet transfusions are optional for non-invasive dental treatment; consider platelet transfusion before the procedure and 24 h later for invasive surgical procedures (such as dental extractions); additional transfusions are based on clinical course
< 30,000/mm^3	Platelets should be transfused 1 h before the surgical dental procedure; obtain an immediate post-infusion platelet count; transfuse regularly to maintain counts >30,000–50,000/mm^3 until initial healing has occurred
Patients with chronic indwelling venous access lines (e.g., Hickman)	Follow the American Heart Association prophylactic antibiotic recommendations (low risk)

[a]If all other coagulation indices are within normal limits

Infections

Superficial Oral Infections

The oral cavity is one of the most heavily colonized sites in the body and contains innumerable numbers of bacteria, viral, and fungal species [10]. Furthermore, the oral cavity promotes a favorable niche for harmless commensalism of microbial species. However, in states of immunocompromise, a shift to a pathogenic state can occur [10, 11]. As patients undergoing chemotherapy are immunosuppressed, they are susceptible to developing oral candidiasis and deep fungal, bacterial, and viral infections. Specifically, oncologic patients undergoing chemotherapy who develop salivary hypofunction are predisposed to oral candidiasis owing to a lack of salivary antimicrobial effectors (sIgA, antimicrobial peptides, etc.) [12]. Even with appropriate antiviral prophylaxis, recrudescent oral herpes simplex virus (HSV) infection is frequent in this immunocompromised cohort of patients [13]. Of note, both keratinized and non-keratinized sites can be involved in oral HSV infection in oncology

patients, whereas usually keratinized sites are involved in immunocompetent individuals. Oral herpes zoster recrudescence occurs much less commonly than oral HSV and there is wide variability in the experience of prodromal symptoms or a dermatome-specific localization among affected patients. Moreover, in cases of severe immunocompromise, oral infections may present with unusual patterns and may resolve slowly despite prolonged and intensive therapy [13]. Importantly, in the context of prolonged chemotherapy-induced neutropenia and ulcerative oral mucositis in which there is a breach in the protective oral epithelial barrier, dissemination of superficial oral infections may occur [13, 14].

Healthcare-Associated Infections

The findings of a large-scale analytical study of over 50,000 hospitalized patients with cancer of the oral cavity, lip, and pharynx determined a rate of healthcare-associated infections of 1.2% [15]. Importantly, it has been demonstrated that healthcare-associated infections in this cohort of patients is associated with an increased burden of illness that infers negative consequences such as longer hospital stays, increased financial costs, and increased morbidity [15]. The majority of healthcare-associated infections in inpatients with oral cancer is central-line-associated bloodstream infections [15].

Bacteremia and Odontogenic Infections

The management of certain malignancies often requires intensive or long periods of chemotherapy. Multiple rounds of chemotherapy (e.g., induction, consolidation) are utilized for the management of hematologic malignancies with intent to achieve clinical remission and prevent relapse. The resultant chemotherapy-associated neutropenia from prolonged cycles of chemotherapy poses a definite risk of potentially life-threatening bacteremia. Ulcerative oral mucositis is a common and significant complication of chemotherapy and establishes a potential portal of entry into the bloodstream for microorganisms arising from odontogenic infections or from periodontal disease. Poor dental health status has been associated with an increased risk of viridans streptococcal bacteremia of oral cavity origin, especially in recipients of allogeneic hematopoietic stem cell transplants (allo-HSCTs) [16]. However, this finding is not consistent throughout all studies conducted on this topic and some studies have concluded that compromised dentition status is not associated with an increased risk of bacteremia of potential oral source or does not impact with induction chemotherapy patient outcomes [17, 18]. It is important to note that many centers employ stringent antimicrobial protocols and pre-HSCT dental screening/clearance protocols for oncology patients [19]. Therefore, the possible combined effects of these prophylactic measures such as an antibiotic prophylaxis regimen, a gut decontamination protocol, and mouth care disinfection protocols are likely to effectively reduce the burden of microorganisms of potential oral source and significantly limit bacteremia risk and other complications (local, loco-regional, or systemic complications) [19, 20]. In fact, the joint task force of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) and the European Society for Blood and Marrow Transplantation (EBMT) issued a position paper that includes a clinical protocol that necessitates that all patients undergo a comprehensive oral evaluation as early as possible prior to initiation of high-dose chemotherapy or allo-HSCT in order to identify and eliminate any potential odontogenic sources of infection [21]. This careful pre-emptive screening process will reduce the likelihood of necessitating emergency dental care for acute odontogenic infections that may arise during critical periods of in-patient care that may compromise the patient's systemic health [22]. It is recommended that any oral foci of infection with acute signs or symptoms be eliminated prior to chemotherapy initiation or in the early remission phase unless there is insufficient time for post-extraction wound healing before the start of chemotherapy [20]. Moreover, it was recently demonstrated that conservative pre-HSCT dental treatment based on an infection risk classification system resulted in a low odontogenic complication rate post-HSCT [23].

Fortunately, as opposed to radiation therapy, chemotherapy-induced oral complications are often transient and reversible in nature, and resolve once patients have recovered from chemotherapy and have had their blood levels normalize [20]. For instance, high-dose chemotherapy for hematologic malignancies induces severe neutropenia (ANC <500/μL) that predisposes patients to serious infections. Importantly however, on cessation of chemotherapy, the ANC normalizes, and the risk of infectious complications is greatly reduced.

Xerostomia

Xerostomia is defined as the subjective patient-reported feeling of dry mouth, whereas the objective measurement of reduced salivary flow is referred to as salivary hypofunction [24]. The majority of xerostomia and hyposalivation cases are secondary to polypharmacy [25, 26]. Salivary hypofunction may result in an increased occurrence of dental caries, opportunistic infections (such as oral candidiasis), halitosis, and bacterial sialadenitis, and may cause discomfort for denture wearers and a general burning sensation in the mouth [24, 27] (See Chap. 23).

The clinical oral dryness score (CODS) is an easy to use and reliable tool for the routine assessment of the severity of dry mouth of patients and achieves good correlation with objective measurements of salivary flow [28, 29]. Clinically observed features of salivary hypofunction may include changes in the consistency of saliva (e.g., frothy or thick ropey saliva), lip dryness, depapillation and erythema of tongue dorsum, fissured tongue, desiccated shiny tongue, no salivary floor of mouth pooling, atrophic mucosa, residual food debris, and cervical or root caries [24, 26].

Notably, xerostomia is a frequent complication of chemotherapy but, fortunately, chemotherapy-induced xerostomia is often transiently experienced and on cessation of chemotherapy, symptoms reside. Patients receiving radiation in addition to chemotherapy often display more severe symptoms and suffer from a more protracted course. Additionally, a commonly observed oral feature of chemotherapy-induced salivary hypofunction is coated or hairy tongue. The lack of the cleansing effect of saliva, coupled with an overgrowth of the filiform papillae on the tongue dorsum leads to retention keratosis. Chemotherapy patients who are required to fast prior to chemotherapy may experience coated tongue more often. Of note, this condition should not be confused with oral candidiasis.

The mainstay of treatment for chemotherapy-induced xerostomia is over-the-counter saliva substitutes (e.g., rinses, sprays, lozenges, gels), avoidance of caffeinated drinks, and encouraging regular sips of water especially during mealtimes. Other topical therapies for xerostomia have been explored such as gel-releasing devices but more evidence is needed to determine their efficacy [30]. In severe cases, parasympathomimetics sialogogues such as pilocarpine or cevimeline are effective. In cases of oral candidiasis secondary to salivary hypofunction, topical antifungal agents in liquid formulations are recommended.

Mucositis

Etiopathogenesis, Grading Systems, and Clinical Course

Gastrointestinal ulcerative mucositis is a frequent complication associated with chemotherapy regimens and may result in significant morbidity and mortality. Ulcerative oral mucositis is a continuation of gastrointestinal ulcerative mucositis and is frequently observed secondary to conventional chemotherapy agents such as 5-fluorouracil, cisplatin, methotrexate, cyclophosphamide, and hydroxyurea [26, 31]. Ulcerations seen in oral mucositis are usually multifocal and diffuse and do not resemble aphthous ulcerations. Additionally, oral ulcerations have been seen secondary to multitargeted kinase inhibitors, and in the setting of transplant patients who are on mycophenolate mofetil or tacrolimus [26]. A significant impact on quality of life is observed in patients with ulcerative oral mucositis and many patients require opioid medications, limitations in diet, gastrostomy or parenteral feeding, and are likely to experience weight loss [31]. In fact, not only do patients who suffer from oral mucositis incur a greater financial cost but also because de-escalation of chemotherapy may be needed in severe cases, there is a significant impact on the patient's cancer treatment outcome [31].

With respect to the etiopathogenesis, a cascade of biological events intermingled with various host immune factors and the influence of microbial dysbiosis are significant in the development of this toxicity [32]. The sequence of mucositis involves five main stages: (1) initiation, (2) primary damage response, (3) signal amplification, (4) ulceration, and (5) healing/migration [33].

Several grading systems are available to appropriately quantify the severity of oral mucositis and include but are not limited to the World Health Organization (WHO) scale, the Cancer Institute Common Terminology Criteria for Adverse Events scale (v5), the Oral Mucositis Assessment Scale, Radiation Therapy Oncology Group scale, and the Eastern Cooperative Oncology Group common toxicity criteria [14, 31]. Some scales are mainly used in research settings; others record many different sites of involvement in the oral cavity, but, importantly, certain scales record both functional (diet limitations) and objective clinical findings.

The trajectory of the clinical course differs based on the chemotherapy regimen. For instance, patients receiving cycled chemotherapy or conditioning regimens prior to HSCT develop early signs of oral erythema approximately 3 to 4 days following infusion and subsequently, 2 to 4 days after this, ulcer formation begins to develop. Finally, healing occurs 10 days following this [14, 31]. On the contrary, in patients receiving chemoradiation, the course is more severe and protracted.

Management

Management is generally palliative and depends on the type of chemotherapy used. Overall, the treatments listed below have variable success rates and oral mucositis management protocols differ between institutions. More research is needed to determine which protocol is most effective and incurs the least side effects. New clinical practice guidelines exist and the MASCC/ISOO provides evidence-based recommendations for prevention and management of oral mucositis secondary to chemotherapy [34]. Of these, recommendations based on the highest level of evidence (LoE; 1) included: (1) intraoral photobiomodulation therapy with low-level laser therapy for oral mucositis prevention, (2)

keratinocyte growth factor-1 intravenously in certain HSCT patients for oral mucositis prevention, and (3) in HSCT patients, glutamine (parenteral) was not recommended for oral mucositis prevention [34]. Of note, although not of the highest LoE, other recommendations that were determined to be potentially beneficial included (1) multiagent combination basic oral care protocols and (2) oral cryotherapy [34].

Dysgeusia

Chemotherapeutic agents can alter taste perception (dysgeusia) and may cause food to taste unpleasant, bitter, or metallic. Similarly, there may be a decrease in taste intensity (hypogeusia) or complete loss of taste perception (ageusia) [35, 36].

The exact mechanism of alteration in taste perception is not fully known. However, it is perceived that chemotherapeutic and targeted agents may alter the taste perception by damaging the sensory receptor epithelial cells, interfere in the cellular turnover process, and cause abnormalities in neuronal activities. Similarly, these agents may indirectly affect the taste perception by modifying the salivary flow or by inducing nausea or mucositis [35–37].

The prevalence of chemotherapy-associated alteration in taste perception ranges between 45 and 84% [35, 36, 38, 39]. The reason for this wide range is due to the heterogeneity of the samples studied, chemotherapeutic agents investigated, and the use of non-validated questionnaires or methodologies for assessing self-reported chemosensory alterations [36]. Nonetheless, a systematic review on dysgeusia induced by cancer therapies calculated a mean prevalence of approximately 56% [35]. Chemotherapeutic agents commonly found to result in taste changes include capecitabine, cisplatin, cyclophosphamide, docetaxel, dacarbazine, doxorubicin, epirubicin, 5-fluorouracil, methotrexate, mechlorethamine, paclitaxel, and vincristine. The changes usually reverse after the completion of chemotherapy [35, 36, 39]. Nevertheless, they may linger for up to 3 months in some cases, and rarely may become chronic. The prevalence of taste alteration increases in patients with concurrent salivary flow issues, nausea, gastrointestinal reflux disease, oral infections, or poor oral hygiene [35–37].

Mild alterations in taste perception are generally well tolerated. However, dysgeusia reduces appetite and caloric intake, which subsequently causes weight loss and affects the nutritional status of the patient. Altogether, it has a significant impact on the quality of life of the patient [35, 36, 39].

There are various strategies suggested for the management of dysgeusia. However, the clinical efficacy of these modalities is variable. Zinc (45 mg taken three times a day) and vitamin D supplementations have been suggested to improve dysgeusia [40, 41]. Similarly, ondansetron and clonazepam may have a therapeutic effect on taste perception [42, 43]. Dronabinol (tetrahydrocannabinol) may significantly intensify and enhance taste perception, increase appetite and appreciation of food, and increase caloric intake [44]. Conservative or lifestyle modifications consist of maintaining good oral hygiene, drinking ample quantities of fluids during meals to assist in translocation of taste buds, and switching food groups during meals to prevent acclimatization of taste buds. Furthermore, sugar-free chewing gum or sour candy may help mask the taste perception and stimulate saliva [37, 45].

Chemotherapy-Induced Neuropathy

Chemotherapy-induced neuropathy is an adverse event associated with chemotherapy, resulting from damage or dysfunction of one or more sensory nerves. Clinically this may result in a spectrum of sensory alteration, including numbness, altered sensation (tingling, pins-and-needles, or burning), and pain. Sometimes, sensory changes may be accompanied by motor and autonomic changes. Furthermore, chemotherapy-induced neuropathy may diminish the quality of life of the patient, and may require chemotherapy dose reduction and rarely cessation, which can increase cancer-related morbidity and mortality [46, 47].

The pathophysiology of chemotherapy-induced neuropathy is poorly understood. Bortezomib-induced neuropathy is associated with morphological alterations in the spinal cord, dorsal root ganglia, and peripheral nerves. Similarly, oxaliplatin-induced neuropathy has been proposed to be caused by the downregulation of voltage-gated potassium channels (KCNQ2) in the trigeminal ganglion neurons [48]. The mechanism of action of taxane-induced neuropathy has been suggested to be associated with interference with microtubule-based axonal transport, macrophage activation in both the dorsal root ganglia and peripheral nerve, and microglial activation within the spinal cord [47]. Likewise, epothilones cause neuropathy by inducing tubulin polymerization into microtubules by interfering with anterograde and retrograde axonal transport. In addition, they cause damage to the ganglion soma cells and neuroaxons by disrupting microtubules of the mitotic spindle and by interfering with axonal transport and cytoplasmic flow in the affected neurons [47]. Thalidomide-induced neuropathy is associated with antiangiogenic properties of the chemotherapeutic agent or secondary to functional and metabolic changes in the dorsal root ganglia [47].

Chemotherapy-induced neuropathy may onset within days (taxanes) to weeks (alkaloids, platinum-based compounds) after administration of chemotherapy [49]. The prevalence of chemotherapy-induced peripheral neuropathy has been assessed to be 68.1% after the first month. However, the prevalence decreases with time. At 6 months or more, it has been estimated to be 30% [46]. The exact prevalence of

chemotherapy-induced neuropathy in the orofacial region is unknown. However, it is relatively low compared to the incidence of peripheral (fingertips and toes) events [47, 50].

Chemotherapy-induced neuropathy has been reported to be associated with the presence of neuropathy at baseline, history of smoking, abnormal creatinine clearance, cold allodynia, cold hyperalgesia, single or cumulative dose level, prior or concomitant administration of platinum compounds, and duration of infusion [46, 47]. The most common chemotherapeutic agents associated with chemotherapy-induced neuropathy include bortezomib, cisplatin, docetaxel, ixabepilone, oxaliplatin, paclitaxel, and thalidomide [46, 47].

There are no universally available preventative or therapeutic protocols for chemotherapy-induced neuropathy. However, multiple studies have suggested improvement in symptoms with the use of serotonin-norepinephrine reuptake inhibitors (duloxetine and venlafaxine), tricyclic antidepressants (amitriptyline and nortriptyline), gabapentinoids (gabapentin and pregabalin), opioids, and photobiomodulation (low-level cold laser) therapy [49, 51].

Tyrosine Kinase Inhibitor (TKI)-Induced Oral Dysesthesia

Tyrosine kinase inhibitors are target-specific antineoplastic agents that affect tumor cell angiogenesis and proliferation [52–54]. They are commonly used to treat renal cell carcinoma, hepatocellular cell carcinoma, soft tissue sarcomas, and cancers affecting lung, colon, and breast. They are categorized into subgroups based on their ability to block epidermal growth factor receptor (EGFR), human epidermal growth factor receptor-2 (HER2), platelet-derived growth factor receptor (PDGFR), or vascular endothelial growth factor receptor (VEGFR) [53, 54]. The use of TKI is associated with various adverse events. These include but are not limited to hand–foot skin reactions, oral mucocutaneous events, fatigue, anorexia, diarrhea, abdominal pain, hypothyroidism, hypertension, and myelosuppression [52, 55, 56].

The prevalence of oral mucocutaneous adverse events is around 23%. These consist of oral ulcers, cheilitis, dysgeusia, pigmented lesions, dysphagia, and mouth pain without evidence of any intraoral lesion (oral dysesthesia) [52, 55, 56]. Overall, a more significant percentage of adverse events are associated with the use of VEGFR-directed TKI than with the other subgroups of TKI (31.1% vs. 11.2%) [55]. These events may appear as soon as a week after initiation of treatment. However, usually, they present within 8 weeks, and these are significant enough to result in dose alteration of TKI in nearly a quarter of the cases [52, 55].

The prevalence of oral dysesthesia associated with the use of TKI is around 12%. It is more commonly observed with VEGFR-directed TKI agents, such as cabozantinib (34.8%), regorafenib (26.7%), sorafenib (26%), and sunitinib (23–36%), than other-TKI agents, such as imatinib (0.7%) [55]. The duration of oral dysesthesia varies considerably among the agents, from 0.4 to 2.8 months [52, 55].

There are no specific guidelines for the management of TKI-induced oral dysesthesia. The goal of management is to alleviate sensitivity and pain. It consists of dietary modifications such as avoiding acidic and spicy foods, reducing fizzy and alcoholic drinks, using a soft diet, and maintaining adequate oral care. For symptomatic relief, over-the-counter rinses (Biotine, saltwater, and/or baking soda), single-agent rinses as a swish and spit (viscous or aqueous lidocaine 2–4% solution, clonazepam solution 0.1 mg/mL, doxycycline 0.5%, morphine 0.2%), or compound rinses (magic mouthwash: diphenhydramine, lidocaine, and bismuth subsalicylate or aluminum/magnesium hydroxide) can be used. If topical therapy provides minimal relief, then systemic therapy consisting of clonazepam 0.5–2 mg/day, gabapentinoids, or serotonin-norepinephrine re-update inhibitors, either alone or in combinations, can be used [55–57].

mTOR-Inhibitor-Associated Stomatitis

Inhibitors of the mammalian target of rapamycin (mTOR) are immunosuppressant drugs inhibiting the cell cycle and preventing T-cell proliferation. mTOR inhibitors (e.g., sirolimus) have been used extensively to prevent graft rejection in solid organ transplantation and as an intervention for advanced malignancies [58, 59]. The presence of aphthous-like oral ulcers is a reported side effect in patients on mTOR inhibitors. Oral ulcers usually affect the non-keratinized mucosa, present as solitary or multiple lesions, and are characterized by a round shape with a central yellowish-gray area surrounded by erythema [60, 61]. Aphthous-like oral ulcers develop after drug administration and may resolve spontaneously [62]. Treatment is usually with topical corticosteroids.

Calcineurin-Induced Inflammatory Fibrovascular Hyperplasia

Calcineurin inhibitors (e.g., cyclosporine, tacrolimus, and pimecrolimus) are immunosuppressant medications that block T-cell proliferation by inhibiting its key signaling phosphatase calcineurin. Studies have shown that these drugs can induce inflammatory fibrovascular hyperplasias in the mouth. Tacrolimus typically causes localized pyogenic granulomas that affect the tongue and buccal mucosa. Cyclosporine is associated with a generalized overgrowth of fibrous tissue of the gingivae [63]. More severe cases may be excised together with maintenance of optimal oral hygiene and use of chlorhexidine rinses two to three times a day.

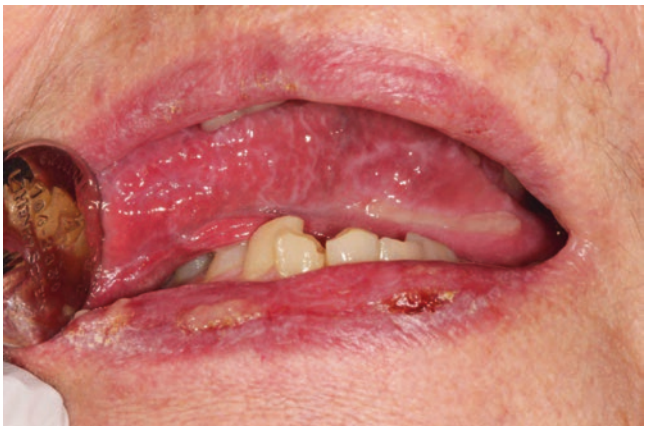


Fig. 31.1 Oral erythema-multiforme-like lesions in a patient receiving pembrolizumab. (Photo courtesy of author AV). White reticular changes and ulceration of the right tongue and ulcerations of the lower lip secondary to pembrolizumab use

Oral Adverse Events Associated with Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are now FDA (Food and Drug Administration) approved for several advanced solid tumors and hematologic malignancies. Oral complications from immune checkpoint inhibition include lichenoid changes of the oral mucosa, ulcers, or oral erythema-multiforme-like lesions (Fig. 31.1). Severe dry mouth and dysgeusia have also been reported. Patients with oral lesions often present with concomitant intestinal, cutaneous, and rheumatological immune-related adverse events [64]. Most cases of oral lesions require systemic steroids or other steroid-sparing immunosuppressive drugs.

Pigmentation

Oral mucosal pigmentation may be caused by exogenous material (e.g., graphite, amalgam) or endogenous pigmentation (melanin or hemosiderin). Oral pigmentation associated with medications may be caused by one of the following mechanisms: (a) pigmented breakdown of drug products, (b) drug metabolites chelated with iron, and (c) induction of melanin by specific medications [65]. Certain chemotherapy agents have been reported to cause oral mucosal pigmentation, the most notable of which are doxorubicin, docetaxel, and cyclophosphamide [25]. Imatinib, a TKI, which is indicated for the treatment of several malignancies such as chronic myeloid leukemia, myelodysplastic/myeloproliferative diseases, dermatofibrosarcoma protuberans, and malignant gastrointestinal stromal tumors, may result in hypo- and hyperpigmentation of the skin, nails, and oral mucosa [26]. Specifically, the oral mucosal pigmentation has a characteristic pattern of diffuse blue-gray macular pigmentation on the hard palatal mucosa [65]. It has been postulated that the mechanism of oral mucosal pigmentation secondary to imatinib is due to a drug metabolite that is chelated to iron and melanin [65].

Medication-Related Osteonecrosis of the Jaw (MRONJ)

Definition and Risk Factors

Medication-related osteonecrosis of the jaw (MRONJ) refers to areas of exposed necrotic bone, or non-exposed devitalized bone, or non-healing extraction sockets secondary to antiresorptive medications and others. Importantly, the definition of MRONJ requires an area of exposed bone or bone that can be probed through a fistula that has persisted for more than 8 weeks in the absence of any previous history of head and neck radiation therapy or metastatic disease to the jaws [66] (See Chap. 29).

The exact etiopathogenesis of MRONJ has not yet been fully elucidated. However, it is postulated that medications that significantly delay bone turnover (over-suppression of bone resorption), alter bone remodeling, or cause angiogenesis inhibition are likely to result in increased bone density and consequent devitalization.

Antiresorptive medications indicated to treat postmenopausal osteoporosis or used to reduce skeletal-related events in cancer patients (skeletal metastases) are implicated in the etiology of MRONJ [27, 66]. Additionally, antiangiogenic agents (e.g., bevacizumab, sunitinib, aflibercept) that act as anti-VEGF therapies have also been reported to cause MRONJ [27]. Moreover, multitargeted kinase inhibitors have been reported to cause non-antiresorptive MRONJ [27]. Of note, intravenous or subcutaneous administration of antiresorptive medications carries a greater risk of MRONJ than oral formulations [66, 67]. Furthermore, duration of antiresorptive therapy and dentoalveolar surgery are considered important risk factors for the development of MRONJ. In patients with advanced cancer, the risk of MRONJ is estimated to be between 1 and 15% [67, 68]. MRONJ may result in significant morbidity (pain and diet limitations) and in severe cases may pose a serious risk of jaw fracture or infection.

MRONJ Management

The management of MRONJ is stage dependent (at risk, stages 0–4) [66]. Current management recommendations for at risk patients include patient education, discussion of modifiable risk factors, comprehensive dental assessments, avoidance of elective dentoalveolar surgery, and preventing

dental disease in order to eliminate the need for future dental extractions [67]. Stage 0 MRONJ refers to non-exposed bone with non-specific clinical and radiographic changes. This stage may require pain medication and antibiotics [66]. Stage 1 MRONJ refers to areas of exposed necrotic bone or fistulas that probe to bone in asymptomatic non-infected patients and should be managed with antimicrobial mouth rinses and regular follow-up [66]. Stage 2 MRONJ refers to exposed necrotic bone or fistulas that probe to bone in symptomatic infected patients and should be managed with pain medication, antibiotics, antimicrobial mouth rinses, debridement, and regular follow-up [66]. Stage 3 MRONJ refers to exposed necrotic bone or fistulas that probe to bone in symptomatic infected patients with the necrotic bone extending beyond the region of alveolar bone resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to inferior border of the mandible or sinus floor [66]. This stage necessities surgical debridement or resection in addition to the aforementioned management strategies for stage 2 [66, 68].

Irrespective of the MRONJ stage, it is recommended that moveable bony sequestrum should be removed without exposing uninvolved bone and extraction of symptomatic teeth within exposed necrotic bone should be considered [66]. Removed bony sequestrum should be submitted for histopathological examination. Characteristic histology reveals necrotic non-viable bone lacking osteocytes, prominent Howship's lacunae, no evidence of osteoclasts, and bacterial colonies that fill medullary spaces (Fig. 31.2).

It is emphasized that optimal care can be achieved only through a multidisciplinary approach with the oncology team, the dentist, and a dental specialist (e.g., oral medicine or oral and maxillofacial surgery specialist) with experience in managing MRONJ cases [67]. The long half-life of many antiresorptive agents and the importance of these antiresorptive agents for the oncologic benefit to patients suggest that antiresorptive drug holidays before invasive dentoalveolar surgery should be approached with caution. Further, to date, insufficient high-level evidence is available to support or refute the recommendation of antiresorptive drug holidays prior to invasive dentoalveolar surgeries [67].

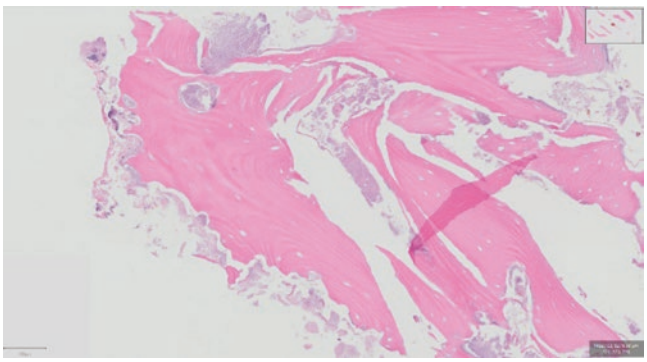


Fig. 31.2 Photomicrograph of MRONJ. (Courtesy of author AS). Necrotic non-viable bone lacking osteocytes, prominent Howship's lacunae, no evidence of osteoclasts, and bacterial colonies that fill medullary spaces

Dental Care After Chemotherapy

Chemotherapy-related oral adverse events can be severe and affect the quality of life and treatment outcomes of cancer patients. These complications can often persist long after the completion of treatment. Due to this, patients who have received chemotherapy should be monitored closely to optimize dental care to manage residual oral issues. Similarly, close monitoring is required for reinforcing prevention, early diagnosis, and management of late complications. These complications can be chronic oral mucositis, dry mouth, mucosal sensitivity and pain, taste alteration, infection, dental demineralization, dental caries, periodontal disease, soft tissue injuries, and MRONJ [69, 70].

Patients should be educated about the importance of maintaining adequate oral hygiene to reduce the risk of developing dental or periodontal infections. Patients should be instructed on the use of atraumatic tooth brushing. They should use soft or ultrasoft manual toothbrushes, or, if there are dexterity-related concerns, they can use ultrasonic or electric toothbrushes. Likewise, other dental cleaning aids can be used to reach harder to clean areas of the oral cavity, such as interdental brushes or home-based ultrasonic teeth cleaning devices. Patients should be advised to use prescription toothpaste with 5000 ppm fluoride for brushing their teeth. However, it may not be tolerated by patients with mucosal sensitivity or pain. Such patients may find relief with the use of fluoride oral rinses. Similarly, patients should be encouraged to have a non-cariogenic diet and advised to avoid or reduce alcohol, tobacco, betel, and areca nut consumption [69, 70].

The frequency of dental visits should be tailored and individualized based on the level of hyposalivation, demineralization, dental caries, periodontal health, and the compliance of the patient to follow recommendations. Upon completion of chemotherapy, cancer patients should be followed every month for the first 3 months, then every 3 months for the first year, and every 6 months for the next 3 years [69, 71].

Patients should undergo routine dental cleaning and avoid any possible trauma to the mucosa and gingivae. Fluoride varnish or gel can be applied to the teeth to prevent tooth demineralization and decay. Any invasive periodontal procedures should be avoided because of the risk of developing osteonecrosis of the jaw. Patients with removable dentures and restorations should be assessed for fit, cracks, and their potential to retain food debris. Furthermore, removable dentures should be examined for the likelihood of inducing a

soft tissue injury. Necessary modifications to dentures and restorations should be made, where possible [70].

Endodontic or root canal therapy should be preferred to extractions when possible. However, if not practicable, precautions should be taken to minimize the likelihood of developing MRONJ, such as following atraumatic extraction technique, removal of any bone edges, appropriate wound closure, and prophylactic use of antibiotics. Similarly, elective surgical procedures, including dental implants, should be avoided, especially if the patient is undergoing antiresorptive therapy or has had a history of taking antiresorptive medications [72].

Conclusions

The oral cavity is a common site for acute and chronic toxicities of chemotherapy. Oral complications from cancer therapy range significantly in their nature, frequency, and severity, with dramatic effects on overall patients' quality of life and cancer prognosis. The consequences associated with oral adverse events lead to longer hospital stays, use of analgesics and antibiotics, hospitalizations for pain control, diagnostic testing, nursing resource use, and need for a feeding tube. The impact on financial costs is significant. Dental providers and health care practitioners play an important role in the prevention of oral and systemic complications by eliminating sources of mucosal irritation and reducing the risk of developing a possible odontogenic infection during and after the completion of chemotherapy. In addition, dental specialists work closely with the oncology team to manage oral complications associated with antiresorptive therapies, mTOR-inhibitors, and immune checkpoint inhibitors.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin. 2021;71(1):7–33.
2. Sroussi HY, Epstein JB, Bensadoun R-J, Saunders DP, Lalla RV, Migliorati CA, et al. Common oral complications of head and neck cancer radiation therapy: mucositis, infections, saliva change, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis. Cancer Med. 2017;6(12):2918–31.
3. Villa A, Sonis S. Toxicities associated with head and neck cancer treatment and oncology-related clinical trials. Curr Probl Cancer. 2016;40(5-6):244–57.
4. Choi SE, Choudhary A, Sonis S, Villa A. Benefits of the involvement of dentists in managing oral complications among patients with oral cavity and oropharyngeal cancer: an analysis of claims data. JCO Oncol Pract. 2021;17:e1668.
5. Epstein JB, Güneri P, Barasch A. Appropriate and necessary oral care for people with cancer: guidance to obtain the right oral and dental care at the right time. Support Care Cancer. 2014;22(7):1981–8.
6. Woo S-B. Oral epithelial dysplasia and premalignancy. Head Neck Pathol. 2019;13(3):423–39.
7. Brennan MT, Woo S-B, Lockhart PB. Dental treatment planning and management in the patient who has cancer. Dent Clin North Am. 2008;52(1):19–37, vii. eng.
8. Levi LE, Lalla RV. Dental treatment planning for the patient with oral cancer. Dent Clin North Am. 2018;62(1):121–30.
9. Oral complications of chemotherapy and head/neck radiation (PDQ(R)): health professional version. PDQ cancer information summaries. Bethesda, MD. 2002.
10. Sultan AS, Kong EF, Rizk AM, Jabra-Rizk MA. The oral microbiome: a lesson in coexistence. PLoS Pathog. 2018;14(1):e1006719; PubMed PMID: 29370304. PMCID: PMC5784999. Epub 2018/01/25. eng.
11. Vila T, Sultan AS, Montelongo-Jauregui D, Jabra-Rizk MA. Oral candidiasis: a disease of opportunity. J Fungi (Basel). 2020;6(1):15; PubMed PMID: 31963180. Epub 2020/01/16. eng.
12. Vila T, Rizk AM, Sultan AS, Jabra-Rizk MA. The power of saliva: antimicrobial and beyond. PLoS Pathog. 2019;15(11):e1008058; PubMed PMID: 31725797. PMCID: PMC6855406. Epub 20191114. eng.
13. Palmason S, Marty FM, Treister NS. How do we manage oral infections in allogeneic stem cell transplantation and other severely immunocompromised patients? Oral Maxillofac Surg Clin North Am. 2011;23(4):579–99, vii. PubMed PMID: 21982611. eng.
14. Villa A, Sonis ST. An update on pharmacotherapies in active development for the management of cancer regimen-associated oral mucositis. Expert Opin Pharmacother. 2020;21(5):541–8. PubMed PMID: 31990597. Epub 20200128. eng.
15. Sankaran SP, Villa A, Sonis S. Healthcare-associated infections among patients hospitalized for cancers of the lip, oral cavity and pharynx. Infect Prev Pract. 2021;3(1):100115; PubMed PMID: 34368735. PMCID: PMC8336044. Epub 20210113. eng.
16. Graber CJ, de Almeida KN, Atkinson JC, Javaheri D, Fukuda CD, Gill VJ, et al. Dental health and viridans streptococcal bacteremia in allogeneic hematopoietic stem cell transplant recipients. Bone Marrow Transplant. 2001;27(5):537–42; PubMed PMID: 11313689. eng.
17. Sultan AS, Zimering Y, Petruzziello G, Alyea EP, Antin JH, Soiffer RJ, et al. Oral health status and risk of bacteremia following allogeneic hematopoietic cell transplantation. Oral Surg Oral Med Oral Pathol Oral Radiol. 2017;124(3):253–60. PubMed PMID: 28823316. Epub 20170616. eng.
18. Schmalz G, Tulani L, Busjan R, Haak R, Kottmann T, Trümper L, et al. Dental and periodontal treatment need after dental clearance is not associated with the outcome of induction therapy in patients with acute leukemia: results of a retrospective pilot study. Adv Hematol. 2020;2020:6710906. PubMed PMID: 32373173. PMCID: PMC7191429. Epub 20200421. eng.
19. Mawardi H, Treister N, Felemban O, Alamoudi W, Algohary G, Alsultan A, et al. Current practice of oral care for hematopoietic stem cell transplant patients: a survey of the eastern mediterranean blood and marrow transplantation group. Hematol Oncol Stem Cell Ther. 2021;16:42. PubMed PMID: 33631114. Epub 20210211. eng.
20. Spijkervet FKL, Schuurhuis JM, Stokman MA, Witjes MJH, Vissink A. Should oral foci of infection be removed before the onset of radiotherapy or chemotherapy? Oral Dis. 2021;27(1):7–13. PubMed PMID: 32166855. PMCID: PMC7818265. Epub 20200601. eng.
21. Elad S, Raber-Durlacher JE, Brennan MT, Saunders DP, Mank AP, Zadik Y, et al. Basic oral care for hematology-oncology patients and hematopoietic stem cell transplantation recipients: a position paper from the joint task force of the multinational Association of Supportive Care in cancer/International Society of Oral Oncology (MASCC/ISOO) and the European Society for Blood and Marrow Transplantation (EBMT). Support Care Cancer. 2015;23(1):223–36. PubMed PMID: 25189149. PMCID: PMC4328129. eng.

22. Walsh LJ. Clinical assessment and management of the oral environment in the oncology patient. Aust Dent J. 2010;55(Suppl 1):66–77. PubMed PMID: 20553247. eng.
23. Hansen HJ, Estilo C, Owosho A, Solano AK, Randazzo J, Huryn J, et al. Dental status and risk of odontogenic complication in patients undergoing hematopoietic stem cell transplant. Support Care Cancer. 2021;29(4):2231–8. PubMed PMID: 32901321. Epub 20200908. eng.
24. Das P, Challacombe SJ. Dry mouth and clinical oral dryness scoring systems. Prim Dent J. 2016;5(1):77–9. PubMed PMID: 29029657. eng.
25. Scully C, Bagan JV. Adverse drug reactions in the orofacial region. Crit Rev Oral Biol Med. 2004;15(4):221–39. PubMed PMID: 15284187. Epub 20040701. eng.
26. Yuan A, Woo SB. Adverse drug events in the oral cavity. Dermatol Clin. 2020;38(4):523–33. PubMed PMID: 32892860. Epub 20200811. eng.
27. Yuan A, Woo SB. Adverse drug events in the oral cavity. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;119(1):35–47. PubMed PMID: 25442252. Epub 20140917. eng.
28. Osailan SM, Pramanik R, Shirlaw P, Proctor GB, Challacombe SJ. Clinical assessment of oral dryness: development of a scoring system related to salivary flow and mucosal wetness. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;114(5):597–603. PubMed PMID: 22959491. Epub 20120907. eng.
29. Osailan S, Pramanik R, Shirodaria S, Challacombe SJ, Proctor GB. Investigating the relationship between hyposalivation and mucosal wetness. Oral Dis. 2011;17(1):109–14. PubMed PMID: 21029258. Epub 20101028. eng.
30. Furness S, Worthington HV, Bryan G, Birchenough S, McMillan R. Interventions for the management of dry mouth: topical therapies. Cochrane Database Syst Rev. 2011;12:CD008934. PubMed PMID: 22161442. Epub 20111207. eng.
31. Villa A, Sonis ST. Mucositis: pathobiology and management. Curr Opin Oncol. 2015;27(3):159–64. PubMed PMID: 25774860. eng.
32. Vasconcelos RM, Sanfilippo N, Paster BJ, Kerr AR, Li Y, Ramalho L, et al. Host-microbiome cross-talk in oral mucositis. J Dent Res. 2016;95(7):725–33. PubMed PMID: 27053118. PMCID: PMC4914867. Epub 20160406. eng, 725.
33. Sonis ST. The pathobiology of mucositis. Nat Rev Cancer. 2004;4(4):277–84. PubMed PMID: 15057287. eng.
34. Elad S, Cheng KKF, Lalla RV, Yarom N, Hong C, Logan RM, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2020;126(19):4423–31. PubMed PMID: 32786044. PMCID: PMC7540329. Epub 20200728. eng.
35. Dysgeusia Section OCSGMAoSCiCISoOO, Hovan AJ, Williams PM, Stevenson-Moore P, Wahlin YB, KEO O, et al. A systematic review of dysgeusia induced by cancer therapies. Support Care Cancer. 2010;18(8):1081–7. en, 1081.
36. Amézaga J, Alfaro B, Ríos Y, Larraioz A, Ugartemendia G, Urruticoechea A, et al. Assessing taste and smell alterations in cancer patients undergoing chemotherapy according to treatment. Support Care Cancer. 2018;26(12):4077–86. en, 4077.
37. Wong HM. Oral complications and management strategies for patients undergoing cancer therapy. Sci World J. 2014;2014:1–14. en.
38. Jensen SB, Mouridsen HT, Bergmann OJ, Reibel J, Brünner N, Nauntofte B. Oral mucosal lesions, microbial changes, and taste disturbances induced by adjuvant chemotherapy in breast cancer patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;106(2):217–26. eng, 217.
39. Gamper E-M, Giesinger JM, Oberguggenberger A, Kemmler G, Wintner LM, Gattringer K, et al. Taste alterations in breast and gynaecological cancer patients receiving chemotherapy: prevalence, course of severity, and quality of life correlates. Acta Oncol. 2012;51(4):490–6. eng, 490.
40. Fink M. Vitamin D deficiency is a cofactor of chemotherapy-induced mucocutaneous toxicity and dysgeusia. J Clin Oncol. 2011;29(4):e81–2. eng, e81.
41. Yamagata T, Nakamura Y, Yamagata Y, Nakanishi M, Matsunaga K, Nakanishi H, et al. The pilot trial of the prevention of the increase in electrical taste thresholds by zinc containing fluid infusion during chemotherapy to treat primary lung cancer. J Exp Clin Cancer Res. 2003;22(4):557–63. eng.
42. Edelman MJ, Gandara DR, Meyers FJ, Ishii R, O'Mahony M, Uhrich M, et al. Serotonergic blockade in the treatment of the cancer anorexia-cachexia syndrome. Cancer. 1999;86(4):684–8. eng, 684.
43. Heckmann SM, Kirchner E, Grushka M, Wichmann MG, Hummel T. A double-blind study on clonazepam in patients with burning mouth syndrome. Laryngoscope. 2012;122(4):813–6. eng, 813.
44. Brisbois TD, de Kock IH, Watanabe SM, Mirhosseini M, Lamoureux DC, Chasen M, et al. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. Ann Oncol. 2011;22(9):2086–93. eng, 2086.
45. Murtaza B, Hichami A, Khan AS, Ghiringhelli F, Khan NA. Alteration in taste perception in cancer: causes and strategies of treatment. Front Physiol. 2017;8:134.
46. Seretny M, Currie GL, Sena ES, Ramnarine S, Grant R, MacLeod MR, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. Pain. 2014;155(12):2461–70. en, 2461.
47. Argyriou AA, Kyritsis AP, Makatsoris T, Kalofonos HP. Chemotherapy-induced peripheral neuropathy in adults: a comprehensive update of the literature. Cancer Manag Res. 2014;2014(6):135–47. eng.
48. Ling J, Erol F, Viatchenko-Karpinski V, Kanda H, Gu JG. Orofacial neuropathic pain induced by oxaliplatin: downregulation of KCNQ2 channels in V2 trigeminal ganglion neurons and treatment by the KCNQ2 channel potentiator retigabine. Mol Pain. 2017;13:174480691772471. en.
49. Vadalouca A, Raptis E, Moka E, Zis P, Sykioti P, Siafaka I. Pharmacological treatment of neuropathic cancer pain: a comprehensive review of the current literature: neuropathic cancer pain pharmacotherapy. Pain Pract. 2012;12(3):219–51. en, 219.
50. Benoliel R, Epstein J, Eliav E, Jurevic R, Elad S. Orofacial pain in cancer: part I—mechanisms. J Dent Res. 2007;86(6):491–505. eng, 491.
51. Hou S, Huh B, Kim HK, Kim K-H, Abdi S. Treatment of chemotherapy-induced peripheral neuropathy: systematic review and recommendations. Pain Physician. 2018;21(6):571–92. eng, 571.
52. Lee WJ, Lee JL, Chang SE, Lee MW, Kang YK, Choi JH, et al. Cutaneous adverse effects in patients treated with the multitargeted kinase inhibitors sorafenib and sunitinib. Br J Dermatol. 2009;161(5):1045–51. PubMed PMID: 19558553. Epub 20090505. eng.
53. Shawver LK, Slamon D, Ullrich A. Smart drugs: tyrosine kinase inhibitors in cancer therapy. Cancer Cell. 2002;1(2):117–23. PubMed PMID: 12086869. eng.
54. Arora A, Scholar EM. Role of tyrosine kinase inhibitors in cancer therapy. J Pharmacol Exp Ther. 2005;315(3):971–9. PubMed PMID: 16002463. Epub 20050707. eng.
55. Yuan A, Kurtz SL, Barysauskas CM, Pilotte AP, Wagner AJ, Treister NS. Oral adverse events in cancer patients treated with VEGFR-directed multitargeted tyrosine kinase inhibitors. Oral Oncol. 2015;51(11):1026–33. PubMed PMID: 26403941. Epub 20151005. eng.

56. Boers-Doets CB, Epstein JB, Raber-Durlacher JE, Ouwerkerk J, Logan RM, Brakenhoff JA, et al. Oral adverse events associated with tyrosine kinase and mammalian target of rapamycin inhibitors in renal cell carcinoma: a structured literature review. Oncologist. 2012;17(1):135–44. PubMed PMID: 22207567. PMCID: PMC3267813. Epub 20111229. eng.
57. Khawaja SN, Bavia PF, Keith DA. Clinical characteristics, treatment effectiveness, and predictors of response to Pharmacotherapeutic interventions in burning mouth syndrome: a retrospective analysis. J Oral Facial Pain Headache. 2020;34(2):157–66. PubMed PMID: 32255581. eng, 157.
58. Johnson RWG. Sirolimus (Rapamune) in renal transplantation. Curr Opin Nephrol Hypertens. 2002;11(6):603–7. en, 603.
59. Trotter JF. Sirolimus in liver transplantation. Transplant Proc. 2003;35(3 Suppl):193S–200S. eng, S193.
60. de Oliveira MA, Martins E, Martins F, Wang Q, Sonis S, Demetri G, George S, et al. Clinical presentation and management of mTOR inhibitor-associated stomatitis. Oral Oncol. 2011;47(10):998–1003. eng, 998.
61. Martins F, de Oliveira MA, Wang Q, Sonis S, Gallottini M, George S, et al. A review of oral toxicity associated with mTOR inhibitor therapy in cancer patients. Oral Oncol. 2013;49(4):293–8. eng, 293.
62. Lo Muzio L, Arena C, Troiano G, Villa A. Oral stomatitis and mTOR inhibitors: a review of current evidence in 20,915 patients. Oral Dis. 2018;24(1-2):144–71. eng, 144.
63. Al-Mohaya M, Treister N, Al-Khadra O, Lehmann L, Padwa B, Woo S-B. Calcineurin inhibitor-associated oral inflammatory polyps after transplantation. J Oral Pathol Med. 2007;36(9):570–4. eng.
64. Xu Y, Wen N, Sonis ST, Villa A. Oral side effects of immune checkpoint inhibitor therapy (ICIT): an analysis of 4683 patients receiving ICIT for malignancies at Massachusetts General Hospital, Brigham & Women's Hospital, and the Dana-Farber Cancer Institute, 2011 to 2019. Cancer. 2021;127(11):1796–804. eng.
65. Li CC, Malik SM, Blaeser BF, Dehni WJ, Kabani SP, Boyle N, et al. Mucosal pigmentation caused by imatinib: report of three cases. Head Neck Pathol. 2012;6(2):290–5. PubMed PMID: 22209988. PMCID: PMC3370028. Epub 20111231. eng.
66. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. J Oral Maxillofac Surg. 2014;72(10):1938–56. PubMed PMID: 25234529. Epub 20140505. eng.
67. Yarom N, Shapiro CL, Peterson DE, Van Poznak CH, Bohlke K, Ruggiero SL, et al. Medication-related osteonecrosis of the jaw: MASCC/ISOO/ASCO clinical practice guideline. J Clin Oncol. 2019;37(25):2270–90. PubMed PMID: 31329513. Epub 20190722. eng, 2270.
68. Khan AA, Morrison A, Kendler DL, Rizzoli R, Hanley DA, Felsenberg D, et al. Case-based review of osteonecrosis of the jaw (ONJ) and application of the international recommendations for management from the International Task Force on ONJ. J Clin Densitom. 2017;20(1):8–24. PubMed PMID: 27956123. Epub 20161209. eng.
69. Samim F, Epstein JB, Zumsteg ZS, Ho AS, Barasch A. Oral and dental health in head and neck cancer survivors. Cancers Head Neck. 2016;1(1):14. en.
70. Ruggiero S, Gralow J, Marx RE, Hoff AO, Schubert MM, Huryn JM, et al. Practical guidelines for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in patients with cancer. J Oncol Pract. 2006;2(1):7–14. eng, 7.
71. Caribé-Gomes F, Chimenos-Küstner E, López-López J, Finestres-Zubeldia F, Guix-Melcior B. Dental management of the complications of radio and chemotherapy in oral cancer. Med Oral. 2003;8(3):178–87. eng, spa.
72. Japanese Study Group of Cooperative Dentistry with M, Hasegawa T, Kawakita A, Ueda N, Funahara R, Tachibana A, et al. A multicenter retrospective study of the risk factors associated with medication-related osteonecrosis of the jaw after tooth extraction in patients receiving oral bisphosphonate therapy: can primary wound closure and a drug holiday really prevent MRONJ? Osteoporos Int. 2017;28(8):2465–73. en, 2465.

Minimally Invasive Facial Cosmetic Surgery

32

Flaviah Muchemi, Faith T. Ajiboye, and Elie M. Ferneini

Introduction

Aging is an intrinsic and extrinsic phenomenon that is influenced both by genetics and environmental factors. Intrinsic features of aging refer to skin atrophy and laxity, which is the result of gravity over time, while extrinsic features refer to effects such as photoaging and smoking that cause skin dryness and wrinkles due to damage of the dermis and epidermis. Surgical procedures, which correct for muscle laxity, recontouring, repositioning, and removal of excess skin, may be used to correct the effect of intrinsic aging. Extrinsic aging on the other hand is treated with chemical peels, lasers, whitening agents, fillers, and botulinum toxin [1].

The most common cosmetic minimally invasive procedures in 2020 include Botulinum Toxin Type A injection, soft tissue fillers, laser skin resurfacing, chemical peels, and intense pulsed light [2]. Injectables such as neurotoxin, dermal fillers, and deoxycholic acid have been found to be efficient with positive results. Likewise, skin resurfacing procedures such as chemical peels, lasers, and microneedling are considered minimally invasive procedures with minimal recovery time. These procedures aim to optimize facial esthetics by creating a youthful appearance, enhancing symmetry, augmenting facial contours, and improving proportions of the face and neck [3].

F. Muchemi · F. T. Ajiboye
Division of Oral and Maxillofacial Surgery, Department of Craniofacial Sciences, University of Connecticut, Farmington, CT, USA
e-mail: fmuchemi@uchc.edu; ajiboye@uchc.edu

E. M. Ferneini (✉)
Greater Waterbury OMS/Beau Visage Med Spa, Cheshire, CT, USA

Division of Oral and Maxillofacial Surgery, Department of Craniofacial Sciences, University of Connecticut, Farmington, CT, USA

Neurotoxins and dermal fillers are used to improve the facial contours in areas such as the frontalis, glabella, lateral orbital canthus, and the nasolabial fold. Deoxycholic acid is used to dissolve unwanted fat specifically in the submental region. The changes caused by aging, acne, and skin pigmentation can be treated using skin rejuvenation and resurfacing procedures such as laser treatment, microneedling, and chemical peels. These skin resurfacing procedures can treat fine lines, sun damage, and irregular pigmentation and are preferred due to minimal downtime and recovery. Minimally invasive facial cosmetic procedures are overall safe and effective in improving patient appearance and increasing patient satisfaction.

Patient Evaluation

Prior to the procedure, it is important to obtain histories including relevant medical history, medications, allergies, prior cosmetic procedures, and any previous complications. Patient's expectations must also be discussed and must be realistic to ensure overall satisfaction with achieved results. Evaluation of the patient's soft tissue profile is important prior to facial cosmetic surgery. The overall skin laxity, quality, and presence of existing lesions must be evaluated as these may contribute to the success or failure of the procedure. Facial analysis including facial proportions and symmetry must also be evaluated. For instance, patients with prominent platysmal bands or significant skin laxity are not ideal candidates for injection lipolysis as a reduction in submental fat would result in unaesthetic outcomes [4]. The Fitzpatrick scale may sometimes be used to evaluate the effect of ultraviolet radiation on the skin for laser resurfacing treatment. The Glogau classification may also be used to assess the effect of photoaging on the skin and to determine the amount of facial wrinkling present prior to a chemical peel. Extensive preoperative workup and planning is often required prior to

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4_32

Table 32.1 The Fitzpatrick classification

Skin type	Description
I	Always burns; no tanning
II	Burns easily; minimal tanning
III	Moderate burning; easy tanning to light brown
IV	Minimal burning; always tans
V	Rarely burns; pigmented skin
VI	Never burns; black skin

Table 32.2 The Glogau classification

Skin type classification	Typical age	Description
1. Mild	28–35	Early photoaging; minimal wrinkles
2. Moderate	35–50	Early moderate photoaging; wrinkles with motion
3. Advanced	50–65	Advanced photoaging; wrinkles at rest
4. Severe	60–75	Severe photoaging; heavy wrinkles

invasive surgeries such as rhinoplasty or rhytidectomy but not for minimally invasive surgeries discussed in this chapter (Tables 32.1 and 32.2).

Minimally Invasive Procedures

Neurotoxins

Botulinum toxin A widely known as *Botox* is one of the toxins produced by the bacteria *Clostridium botulinum* and was originally used for treatment of strabismus and benign essential blepharospasm commonly known as crossed eyes and eye twitching, respectively. It was approved by the Food and Drug Administration (FDA) in 2002 for the correction of glabellar frown lines. Botox can also be used for the correction of spasms in the upper limb, for cervical dystonia to decrease severity of abnormal head position, and for axillary hyperhidrosis in adult patients. Since its approval, Botox has been proven to be effective when used in the upper, mid, and lower face and commonly used in the frontalis, glabella, and lateral canthal areas. Injection of botulin neurotoxin is used to treat and prevent the formation of wrinkles on the face and neck. Botulinum toxin injection is the leading male and female minimally invasive cosmetic procedure in the United States, with 4.4 million procedures performed in 2020 alone [2]. Botulinum toxin type A works by inhibiting the release of acetylcholine at the neuromuscular junction. This leads to denervation of the treated muscle and temporarily diminished muscle activity. Denervation of the treated muscle takes 2 to 4 days to weaken muscle and 7 to 10 days to reach maximal effect. The effect is temporary because nerve endings form "peripheral sprouts" with time [3]. With this, it is important to inject the accurate amount of Botox into the area to prevent unwanted outcomes.

The most common area for botulinum toxin treatment is the upper face, which includes the glabella, forehead, brows, and crow's feet [5]. For the lower face, treatment includes targeted therapy for the depressor angularis oris, orbicularis oris, masseter muscles, and mentalis muscle. The upper face is treated with Botox 2–4 U, while the lower face is treated with Botox 4–5 U. It is a common practice to individualize dosage, injection points, and dilution based on the patient's variation in anatomy, muscle mass, asymmetry, and, most importantly, desired outcomes [5]. The glabella is very commonly injected with a recommended dose of 20 units although some practitioners may adjust the dose based on factors such as patient's preference for specific outcome, gender, skin pattern, etc. Although clinical trials emphasized the efficacy of full doses, having frozen and nonmoving facial features are not the desired outcome. The goal however is to soften undesirable lines without eliminating expressiveness.

Fillers

Neurotoxins address many concerns associated with aging, such as muscle-controlled fine lines and wrinkles. Fine etched lines and those caused by photodamage do not improve solely with neurotoxin treatment [3]. The use of soft tissue fillers has increased with more than 3.4 million soft tissue fillers administered in the United States in 2020 [2]. Soft tissue fillers are used for facial rejuvenation and volume restoration that is lost because of aging or disease process. Fillers are used for cheek and chin augmentation, tear trough correction, nose reshaping, mid-facial volumization, lip enhancement, hand rejuvenation, and the correction of facial asymmetry [6]. The most common locations for injection of fillers remain the nasolabial folds, lips, and perioral region. One of the most commonly injected fillers is hyaluronic acid (HA). Hyaluronic acid (HA) is used due to its efficacy, safety, biocompatibility, and reversibility. Other fillers include biostimulatory products like calcium hydroxyapatite (Radiesse) and poly-*L*-lactic acid (Sculptra) [3] as well as silicone oil, which stimulates a foreign body reaction that induces collagen and allows for more augmentation.

Cosmetic effects of hyaluronic acid fillers are short lived as the body reabsorbs them within a short period. Effects of HA fillers generally last for 6–18 months depending on the source and extent of cross-linking and concentration particle of each product. HAs are linear polymeric dimers of *N*-acetyl glucosamine and glucuronic acid, which differ in the proprietary methods used to cross-link their dimers, their degree and method of chain cross-linking, the uniformity and size of their particles, and their concentration. Increased cross-linking and concentration increases viscosity, elasticity, and

has a longer duration of effect and increases the risk of inflammation and granuloma formation [6]. Hyaluronic acid duration is dependent upon the type of filler used, the area injected, the expressiveness of the face, and metabolic rate. Therefore, hyaluronic acid dermal fillers can stimulate the body's collagen supply and last longer. Sculptra may last up to 2 years while silicone effect may be permanent [7].

Injection Lipolysis

Noninvasive procedures for submental fat reduction are becoming more popular. The loss of chin profile definition owing to unwanted submental fat distributed both superficially and deep to the platysma muscle is one of the signs of aging of the lower face and neck that may lead to a negative self-image [8]. Liposuction and lower face and neck lift were traditionally used and are effective methods used for submental fat removal and to improve the neck profile and chin. Although effective, liposuction comes with risks including infection, deformity, ecchymosis, and bruising. The noninvasive removal of submental fat using deoxycholic acid such as Kybella can be done effectively with little down time and is optimal for localized areas.

Deoxycholic acid, which is a bile acid produced in the intestines, functions to emulsify and dissolve dietary fat. Deoxycholic acid works by disrupting the membranes of adipocytes through solubilization of the membrane lipids, leading to cell breakdown, inducing a local inflammatory response that clears the adipocyte debris [8]. The use of deoxycholic acid for submental lipolysis began in 2007 and was approved by the FDA in 2015. The safety of deoxycholic acid use lies in the understanding of the anatomy of the submental region as there are arteries, nerves, and glands that may become damaged if injected inappropriately. The synthetic deoxycholic acid is available in a 2 mL bottle formulation and when injected results in lipolysis of fat in the area [8, 9]. After the initial injection, a series of mechanisms such as induction of pores, membrane rupture and lysis, as well as inflammatory processes involving neutrophils, macrophages, and fibroblast occur [9]. This process may take up to 28 days. Therefore, patients should be counseled that up to six sessions spaced 1 month apart may be needed to achieve desired reduction in submental fat [4]. Effects can last years and may be permanent without significant weight gain, although this is yet to be confirmed. The overall effect is improvement in the visual appearance of the submental area, reduction of submental fat, and increased patient satisfaction.

Laser Therapy

Laser therapy is considered among the skin resurfacing techniques that are used for treatment of aging effects and skin irregularities, including pigmentation. Aging causes epidermal hyperplasia, atrophy, and dysplasia, leading to an atrophic and flat epidermis [3]. Laser therapy can stimulate collagen synthesis to improve fine lines, wrinkles, and the appearance of skin.

Carbon dioxide (CO_2) laser treatment was the gold standard and was used in a pulsed or scanned mode that resulted in removal of the entire epidermis and controlled section of the dermis. Erbium: yttrium aluminum garnet (Er:YAG) laser was also introduced in the mid-to-late 1990s and was capable of more superficial ablation than CO_2 laser but resulted in reduced heat-induced collagen contraction and dermal remodeling. Ablative lasers vaporize the superficial layers of the skin by heating the dermis to stimulate new collagen production by fibroblasts, while nonablative lasers stimulate collagen growth by creating focal thermal injury within the dermis [3]. Both CO_2 laser and Er:YAG are ablative skin resurfacing techniques and cause more complications including prolonged recovery, skin infections, and pigment changes as compared to fractionated laser technology [10]. Fractionated laser technology is minimally invasive and works by producing microscopic zones of thermal injury in the skin that enable rapid healing without sacrificing clinical effect [10]. It can be ablative or nonablative. The microscopic zones of thermal injury are surrounded by islands of spared skin that improve the safety profile and provide for shortened recovery times.

Chemical Peels

Chemical peels are a type of facial rejuvenation procedure used to conquer the effect of photoaging, acne, and superficial facial pigments. Exfoliative agents are used to remove cells in the layer of the epidermis and dermis, depending on the depth of peeling agent used. Regeneration of the epidermis and dermis subsequently occurs, creating a new layer of skin cells. Agents such as alpha-hydroxy acid are considered superficial and penetrate to the epidermis. Trichloroacetic acid (TCA) is an example of superficial to medium depth peel that penetrates to the level of the papillary dermis while phenol is an example of deep peel that can penetrate and extend into the reticular dermis.

Chemical peels are widely used because they are cost effective, safe, and less invasive. Chemical peels are used to create an injury of a specified skin depth with the aim of stimulating new skin growth and improving surface appearance and texture [3]. They are classified into the following fields: superficial, medium, and deep. Superficial peels are used in the treatment of acne, dyschromia, post-inflammatory pigmentation, and in achieving skin radiance [11]. Medium-depth peels are used in the treatment of dyschromia, including solar lentigines, multiple keratosis, superficial scars, pigmentary disorder, and textural changes [11]. Deep peels are used

for severe photoaging, deep or coarse wrinkles, scars, and occasionally precancerous skin lesions [11]. Individualized care regimens should be established based on each patient's skin characteristics, area to be treated, and healing time.

Microneedling

Microneedling is a popular procedure that is used for wrinkles, scars, and stretch marks. It is a procedure in which micropunctures are introduced into the skin using thin needles. The needles penetrate the stratum corneum and create small holes known as microconduits with minimal damage to the epidermis [12]. These micropunctures initiate the inflammatory cascade stimulating collagen and elastin production in the papillary layer. Platelets and neutrophils are recruited and release Transforming growth factor (TGF)-alpha, TGF-beta, and platelet-derived growth factor (PDGF). Increased collagen production paired with elastin fiber production results in skin remodeling [11]. Microneedling is preferred to chemical peels and laser because it can be used on all parts of the body, including abdominal stretch marks, and on all skin tones. Microneedling is also safe to use during pregnancy and breastfeeding. Because the epidermis is retained, microneedling comes with a lower risk of infection, post-inflammatory hyperpigmentation, and scarring compared with other resurfacing modalities [3]. Complications of microneedling include scarring that is due to poor-quality needles being used on the roller device [3].

Diagnostic Imaging (Ultrasound)

Ultrasound imaging in the field of cosmetic surgery is relatively new. It requires an understanding of facial anatomy, a level of manual dexterity, as well as knowledge of ultrasound technology. Although the knowledge of vascular facial anatomy is essential, each individual's facial anatomy might be variable. There is a need for minimally invasive imaging modalities to account for these observed variations in anatomy. Even in the hands of experienced practitioners respecting safety procedures, intra-arterial injection of soft tissue fillers may cause embolization and may lead to localized skin necrosis, blindness, and cerebral artery embolism [13]. Ultrasound, with the use of high-frequency transducers, can be used to accurately guide injection of filler products. This could lead to better patient outcomes [14].

Ultrasound can not only be used to guide injection of filler products, but also it can be used to inject Hyaluronidase to selectively dissolve hyaluronic acid gels where overcorrection has occurred [14]. Conventional facial arterial network evaluation techniques such as computed tomography (CT) angiography and magnetic resonance angiography (MRA) may use intravenous (IV) contrast and expose patients to radiation that would be more invasive as compared to ultrasound [13]. Although ultrasound imaging does not identify the complete 3D arterial network of the face, it could help practitioners improve technique, manage adverse outcomes, and allow for more esthetic outcomes of cosmetic filler procedures.

Complications

Although minimally invasive procedures are preferred by patients compared to invasive surgical procedures, there are risks associated as with every type of procedure. Every surgical procedure has the risk of pain, bleeding, swelling, and infection. More specific to injectables are erythema, esthetic complications such as uneven distribution, clumping, and Tyndall effect that occur when fillers are injected too superficially. The key to avoiding some of these complications is through understanding of the dosages and injection patterns into the appropriate facial anatomy. Knowledge of these complications will therefore allow for practitioners to prevent and immediately identify and manage these complications.

Botulinum Toxin

Botulinum toxin effect may occur if the toxin spreads beyond the intended area of injection. These effects include generalized muscle weakness, diplopia, ptosis, urinary incontinence, dysphagia, and dysphonia [15, 16]. There have been no serious effects reported if recommended dose for facial cosmesis and the recommended diluent are used. Botulinum toxin complications may include bleeding, swelling, erythema, ecchymosis, pain at the injection sites, and headache. Some of these complications may be avoided with dilution of Botox with saline. Hypersensitivity reactions such as anaphylaxis, serum sickness, edema, and dyspnea may also occur, and further injection must be avoided with medical intervention initiated as this can be life threatening. Other complications include malaise, nausea, flu-like symptoms, and ptosis, which is one of the most feared complications of Botulinum toxin. Ptosis can occur if the toxin is injected into levator palpebrae superioris, which can be avoided if the Botox is injected about 1 cm above the orbital rim. Treatment of ptosis includes administration of alpha-adrenergic agonist ophthalmic drops. Ecchymosis and purpura are complications that rarely occur and can be avoided through use of proper injection techniques. Botox should be injected in minimal concentrations with the appropriate dose injected at least 1 cm from the superior, inferior, or lateral margin of the orbital bone. Furthermore, patients should be instructed to avoid manipulating injected sites for 2 to 3 h and to remain upright for 3 to 4 h following the procedure [15].

Fillers

Soft tissue fillers have a high safety profile compared to invasive cosmetic procedures. Understanding the facial anatomy and landmarks for injection of fillers contributes to its safety. Although safe, serious adverse events including intra-arterial injections, necrosis, and visual symptoms such as blindness have been documented [17]. Infections have also been documented and are caused by pathogens on the surface of the skin. Cellulitis may occur days after treatment and typically presents as pain, swelling, erythema, blistering, and desquamation of the site. Injections at the dorsum of the nose and glabella are associated with embolization, leading to vision loss, corneal and iris ischemia, panophthalmoplegia, and brain infarction. Soft tissue fillers may also cause hypersensitivity reactions that present with induration, edema, and erythema. These effects are seen immediately or within hours of injection, while nodules present within 1 to 2 weeks or months and may last for years [18]. These adverse effects are mostly due to improper administration and deposition techniques. Necrosis may also occur if the filler is injected intra-arterially resulting in occlusion of the artery. More specifically, if the filler is injected into the supratrochlear or supraorbital artery, it can potentially lead to blindness. Complications such as arterial occlusion and necrosis can be life threatening but are often rare. Overall, complications from fillers may be temporary or long-lasting and can be detrimental to the patient's physical and mental health. Knowledge of several chemical and physical properties of the different fillers will help to prevent many of these complications.

Injection Lipolysis

Prior to injection lipolysis, review of medical problems and history of prior problems with deoxycholic acid must be discussed. Prior conditions such as dysphagia, facial nerve dysfunction, and presence of scars in the submental area must be discussed as these can cause distortion in the facial anatomy. Complications of deoxycholic acid are due to the local inflammatory response that is induced by adipocyte lysis and is responsible for the clearance of cellular debris and removal of breakdown products [8]. Adverse events associated with injection lipolysis using deoxycholic acid are related to the area of treatment. These include injection-site pain, swelling, numbness, erythema, bruising, and induration [8]. Swelling may also cause dysphagia [4]. Pain is the most significant of these adverse events and is managed with topical anesthetic preparations and cooling with ice. Numbness can be caused by incorrect injection technique with injury to the marginal mandibular nerve or the cervical branch of the facial nerve, also known as the pseudomarginal mandibular nerve. It is therefore important to assess for presence of facial nerve paresis after injection.

Laser

Fractionated lasers are safer skin resurfacing techniques that have faster healing times and generally provide less discomfort to patients. Complications that can occur with these lasers include immediate post-procedure erythema and edema that usually lasts up to 3 days. Some patients with a history of acne can also report presence of short-term acne after laser resurfacing or scar revision. The most common infectious complication, however, is reactivation of latent herpes simplex virus (HSV) with reported incidences of up to 2% [10]. This can be prevented with antiviral prophylaxis in patients with a history of HSV. Other complications including infections, post-inflammatory hyperpigmentation in patients with darker skin tones, delayed onset hypopigmentation, and hypertrophic scarring are rarely reported with fractionated laser resurfacing.

Chemical Peels

Chemical peels are a safe procedure, but adverse effects can occur following peeling and vary according to peel depth. It is important that the chemical peeling process begins from an area of thicker skin such as the forehead, prior to completing areas of periorbital and perioral skin. Sharp demarcation lines may also occur if the peeling agent is not applied evenly. A feathering technique as well as an upward direction may be used. Minor complications include irritation, burning, erythema, pruritus, edema, and blistering [3]. Major complications, alternatively, include allergic reactions, laryngeal edema, toxic shock syndrome, cardiotoxicity, salicylism, acute kidney injury, lower lid ectropion, corneal damage, significant scarring, and dyspigmentation. Crusting may be treated with an antibacterial agent [9].

Patient Considerations

Knowledge of anatomic landmarks and facial anatomy can maximize the safety and predictability of facial filler injections [19]. Patients may experience mild pain. This pain can be minimized by using smaller-gauge needles, depositing smaller quantities of injectables, and withdrawing the syringe as the injection is being performed. Aspiration before injections should always be performed before deposition of any injectable to avoid deposition into an artery. If any complications are noted, the procedure should be stopped immediately. In the case of filler leading to necrosis, for example, the necrosis protocol should be initiated. This includes the use of warm compresses, aspirin 325 mg, nitroglycerin paste, hyperbaric oxygen, prednisone, and cephalexin [20]. Patients should be transferred to a hospital setting for more formal evaluations if they are experiencing

symptoms such as pain, headache, vision loss, ptosis, and ophthalmoplegia, as these are clues of possible arteriole occlusion [18]. Finally, patients should always be informed about potential risks, benefits, and alternatives of all minimally invasive procedures.

Conclusion

Esthetic concerns usually have a strong influence on patients' psychosocial well-being. As more patients continue to explore ways to achieve a more youthful appearance and discover minimally invasive procedures, it is imperative to be aware of options available, their indications, complications, and management. Many patients are hesitant to undergo surgery for esthetic concerns and are therefore likely to seek less invasive nonsurgical methods. Although minimally invasive procedures discussed in this chapter are widely accepted by patients due to decreased office time and overall recovery, patients should be evaluated with expectations discussed and should also be informed about potential complications. Practitioners, on the other hand, should be aware of proper use of products, appropriate dosages, contraindications, as well as prevention and management of complications to ensure patient safety.

References

1. Lima L, Olivetti I, Arroyo H, de Oliveira I, Jurado J. Innovations in minimally invasive facial treatments. Facial Plast Surg. 2013;29(03):154–60. https://doi.org/10.1055/s-0033-1347004.
2. 2020 plastic surgery statistics report. American Society of Plastic Surgeons.
3. Devgan L, Singh P, Durairaj K. Minimally invasive facial cosmetic procedures. Otolaryngol Clin N Am. 2019;52(3):443–59. https://doi.org/10.1016/j.otc.2019.02.013.
4. Liu M, Chesnut C, Lask G. Overview of kybella (deoxycholic acid injection) as a fat resorption product for submental fat. Facial Plast Surg. 2019;35(03):274–7. https://doi.org/10.1055/s-0039-1688943.
5. Monheit G. Neurotoxins: current concepts in cosmetic use on the face and neck—upper face (glabella, forehead, and crow's feet). Plast Reconstr Surg. 2015;136:72S. https://doi.org/10.1097/prs.0000000000001771.
6. Funt D, Pavicic T. Dermal fillers in aesthetics. Plast Surg Nurs. 2015;35(1):13–32. https://doi.org/10.1097/psn.0000000000000087.
7. Ghali GE, Larsen P, Miloro M, Waite P. Adjunctive facial esthetic procedures. In: Peterson's principles of Oral and maxillofacial surgery. Hamilton, ON: B C Decker; 2004. p. 1609–20.
8. Ascher B, Hoffmann K, Walker P, Lippert S, Wollina U, Havlickova B. Efficacy, patient-reported outcomes and safety profile of ATX−101 (deoxycholic acid), an injectable drug for the reduction of unwanted submental fat: results from a phase III, randomized, placebo-controlled study. J Eur Acad Dermatol Venereol. 2014;28(12):1707–15. https://doi.org/10.1111/jdv.12377.
9. Farina GA, Cherubini K, de Figueiredo MA, Salum FG. Deoxycholic acid in the submental fat reduction: a review of properties, adverse effects, and complications. J Cosmet Dermatol. 2020;19(10):2497–504. https://doi.org/10.1111/jocd.13619.
10. Aslam A, Alster TS. Evolution of laser skin resurfacing. Dermatol Surg. 2014;40(11):1163–72. https://doi.org/10.1097/01.dss.0000452648.22012.a0.
11. Nair PA, Arora TH. Microneedling using Dermaroller a means of collagen induction therapy. Gujarat Med J. 2014;69(1):1.
12. Iriarte C, Awosika O, Rengifo-Pardo M, Ehrlich A. Review of applications of microneedling in dermatology. Clin Cosmet Investig Dermatol. 2017;10:289–98. https://doi.org/10.2147/ccid.s142450.
13. Mespreuve M, Waked K, Hendrickx B. Visualization techniques of the facial arteries. J Cosmet Dermatol. 2020;20(2):386–90. https://doi.org/10.1111/jocd.13477.
14. Arlette J, Velthuis PJ, Schelke LW. Ultrasound for soft tissue filler facial rejuvenation. J Cutan Med Surg. 2021;25(4):456–7. https://doi.org/10.1177/12034754211008167.
15. Satriyasa BK. Botulinum toxin (Botox) a for reducing the appearance of facial wrinkles: a literature review of clinical use and pharmacological aspect. Clin Cosmet Investig Dermatol. 2019;12:223–8. https://doi.org/10.2147/ccid.s202919.
16. Botox Cosmetic: Botulinum Toxin A: full prescribing information. 2010.
17. Beauvais D, Ferneini EM. Complications and litigation associated with injectable facial fillers: a cross-sectional study. J Oral Maxillofac Surg. 2020;78(1):133–40. https://doi.org/10.1016/j.joms.2019.08.003.
18. Ferneini E, Gady J, Nuveen E. Complications associated with facial soft-tissue fillers. Am J Cosmet Surg. 2014;31(4):238–42. https://doi.org/10.5992/ajcs-d-14-00014.1.
19. Ferneini EM, Hapelas S, Watras J, Ferneini AM, Weyman D, Fewins J. Surgeon's guide to facial soft tissue filler injections: relevant anatomy and safety considerations. J Oral Maxillofac Surg. 2017;75(12):2667.e1. https://doi.org/10.1016/j.joms.2017.08.026.
20. Halepas S, Peters SM, Goldsmith JL, Ferneini EM. Vascular compromise after soft tissue facial fillers: case report and review of current treatment protocols. J Oral Maxillofac Surg. 2020;78(3):440–5. https://doi.org/10.1016/j.joms.2019.10.008.

Index

C. E. Niekrash et al. (eds.), *Dental Science for the Medical Professional*, https://doi.org/10.1007/978-3-031-38567-4