Otolaryngology – Head and Neck Surgery Elective Syllabus

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Structure of content:

- Learning objectives
- Disease
    - Background
    - Epidemiology
    - Pathophysiology/Anatomy
    - History
    - Physical
    - Diagnosis and Differential Diagnosis
        - Establishing the diagnosis
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    - Management (Medical and Surgical Treatment)
    - Complications
    - References
- Practice questions
- Ready to get pimped
    - This section is dedicated to information in a question and answer format to prepare students for when they are on service

Use of images/videos:

- Images when helpful
    - Public domain when possible
        - Wikimedia Gray's Anatomy plates
        - Radiopaedia (must link back)
    - Hyperlink when necessary

Otitis Media (OM):

Background

- What is otitis media (OM)?
  - Infection of the middle ear space (from tympanic membrane to otic capsule)
- Variants of OM include:
  - Acute otitis media (AOM)
    - Characterized by rapid onset of signs and symptoms
  - Otitis media with effusion (OME)
    - OME is a chronic inflammatory condition characterized by fluid in the middle ear without acute signs of acute inflammation
    - May result in conductive hearing loss
  - Chronic suppurative otitis media (CSOM)
    - CSOM is persistent otorrhea from tympanic membrane perforation (discharge persisting a minimum of 2-6 weeks)
    - CSOM may occur from an acute OM or otitis media with effusion

Epidemiology

- AOM, OME and CSOM predominantly affect children (especially < 5 years old)
- Risk factors for AOM include:
  - Day care attendance, tobacco exposure and allergies

Pathophysiology/Pathoanatomy

- How does the eustachian tube (ET) play a role in OM?
  - The ET runs from the anterior middle ear to the nasopharynx and functions to equalize pressure in the middle ear space to prevent fluid build-up **(Figure 1)**
    - The middle ear normally has negative pressure (and therefore a propensity for fluid to build up)
  - The ET opens in response to yawning, talking and the Valsalva maneuver with the actions of 4 muscles:
    - Salpingopharyngeous, tensor veli palatine, tensor tympani and levator veli palatine
  - ET dysfunction > failure to equalize pressure > middle ear effusion
    - ET dysfunction may be caused by viral infections or anatomic variants
  - In children, the ET is flatter and less rigid > susceptible to dysfunction
    - Fluid build-up from ET dysfunction may become infected by pathogens found in nasopharynx
- Which pathogens most commonly cause AOM?
  - Most commonly viral
  - Bacterial causes:
    - *Streptococcus pneumoniae* (35-40%)
    - *Haemophilus influenza* (30-35%)
    - *Moraxella catarrhalis* (15-25%)

History

- AOM

    - Acute onset of otalgia, fever and irritability
    - Patient may tug at the ear and have difficulty sleeping
- OME
    - Usually asymptomatic
    - May present with conductive hearing loss
- CSOM
    - Aural discharge present for a minimum of 2-6 weeks
    - Other common symptoms include: hearing impairment, sense of fullness in ears and tinnitus

Physical

- Remove obstructing cerumen to visualize the tympanic membrane using gentle suction or irrigation
- Examine the tympanic membrane with an otoscope
    - Normal tympanic membrane
        - Ground-glass appearance, translucent and pearly gray
    - Abnormal tympanic membrane
        - Bulging, erythematous, and opaque or cloudy
        - Perforation may be present
- Pneumatic otoscopy may be used to test for the presence of effusion
    - With insufflator bulb attached to a closed head otoscope, apply gentle pressure
        - Effusion present = ear drum will not move
        - No effusion present = ear drum will move

Diagnosis

- **Establishing the diagnosis**
    - AOM
        - Moderate to severe bulging of the tympanic membrane that is not associated with otitis externa
        - Mild bulging of the tympanic membrane and < 48 hours of otalgia or erythema of the tympanic membrane
        - Middle ear effusion may be present and diagnosed with pneumatic otoscopy
    - OME
        - Hearing difficulties, chronic congestion and/or otalgia but without the other symptoms of AOM
        - Confirm diagnosis with pneumatic otoscopy
    - CSOM
        - Confirmed with otoscopy revealing tympanic membrane perforation and middle ear inflammation
        - Persistent otorrhea for a minimum of 2-6 weeks

- **Differential diagnosis**
    - AOM
    - OME
    - CSOM

- Cholesteatoma
- Otitis externa
- Upper respiratory infection

Management of AOM

- **Medical**
  - First-line
    - Amoxicillin (80-90 mg/kg/day orally in two divided doses)
      - For < 2 years old or all children with severe symptoms (e.g. severe otalgia, temperature ≥ 102.2 degrees F), treat for 10 days
      - For 2-6 years old with mild-moderate symptoms, treat for 7 days
      - For >6 years old with mild-moderate symptoms, treat for 5 days
    - Amoxicillin-clavulanate (Amoxicillin 90 mg/kg/day + clavulanate 6.4 mg/kg/day orally in two divided doses)
      - Additional beta-lactamase coverage if patient received amoxicillin in last 30 days
      - If patient has concurrent conjunctivitis
      - If the patient failed initial treatment with amoxicillin after 48-72 hours
    - If penicillin allergic, use cephalosporins for AOM:
      - Cefdinir 14 mg/kg/day orally once daily or in 2 divided doses
      - Cefuroxime axetil 30 mg/kg/day orally in 2 divided doses
      - Cefpodoxime 10 mg/kg/day orally in 2 divided doses
      - Ceftriaxone 50 mg/kg intramuscularly once daily for 1 to 3 days
- **Surgical**
  - Surgery is reserved for:
    - Persistent CSOM that has not responded to a 6 to 12-week course of medical treatment
    - Recurrent cases of AOM (at least three episodes in 6 months or four episodes in 12 months)
    - Complications of AOM (e.g. meningitis)
    - Complications of ET dysfunction (e.g. ossicular erosion)
  - Tympanostomy tube placement
    - Most common ambulatory procedure in the United States
    - Small cylinder sits in the tympanic membrane that lasts 6 months to 1 year
    - Drains fluid and equalizes middle ear pressure
    - May be used in acute OM to prevent build-up of fluid and subsequent infection
    - May be used in OME to remove fluid and improve hearing
    - Tube falls out on its own (natural desquamation of tympanic membrane)
  - Tympanocentesis
    - Direct trans-tympanic membrane needle aspiration of middle ear fluid
      - Cultures of retrieved effusion may direct antibiotic selection

Management of OME

- **Medical**

- OME does not benefit from antibiotics, corticosteroids, decongestants or antihistamines - important to differentiate from AOM
- Watchful waiting recommended for 3 months from date of effusion onset (if known) or date of diagnosis (if unknown) for children that are not at increased risk for speech, language or learning problems
- Re-examine at 3- to 6-month intervals until effusion no longer present or need for further care identified

- **Surgical**
  - Tympanostomy tube placement
    - May be used in OME to remove fluid and improve hearing

Management of CSOM

- **Medical**
  - First-line
    - Ototopical antibiotic drops (e.g. ofloxacin often with dexamethasone) + aural toilet ≥ 2-3 times/week to keep ear clean and dry
  - Dry ear precautions
- **Surgical**
  - Tympanoplasty
    - Surgical reconstruction of the tympanic membrane to:
      - Improve hearing
      - Seal the middle ear and reduce risk of recurrent infection
    - Reserved for patients with persistent perforations following resolution of infection
      - Generally performed 6-12 months following resolution of infection

Complications of OM:

- Complications may be classified as extracranial/intratemporal or intracranial (Table 1)
- These complications may result from 3 main pathways:
  - Hematogenous spread
  - Direct extension through bony erosion or preformed pathways
    - Examples of preformed pathways include: congenital ear anomalies, trauma from previous surgery and prior temporal bone fractures
  - Thrombophlebitis of local perforating veins
- How do you treat complications of OM?
  - Medical therapy
    - Broad-spectrum IV antibiotics with activity against aerobes and anaerobes are initially used in most cases (Table 2)
    - Tailored antibiotic therapy can be achieved following culture results
    - Consider cerebrospinal fluid penetration when suspicious of intracranial complications
  - Surgical intervention
    - Generally recommended when/if medical therapy fails, there is further development of complications or if complications are intracranial (Table 2)

- Neurosurgical consult may be obtained if complications are intracranial

Table 1: Complications of otitis media classified as extracranial/intratemporal or intracranial.

Extracranial/Intratemporal	**Intracranial**
Tympanic membrane perforation	Meningitis
Mastoiditis (coalescent, masked or chronic)	Otitic hydrocephalus
Abscess (postauricular, Bezold or temporal)	Abscess (epidural, subdural, brain)
Petrous apicitis	Lateral sinus thrombosis
Labyrinthe fistula	Sigmoid sinus thrombosis
Facial nerve paresis	
Acute suppurative labyrinthitis	
CSF leak	
Encephalocele	
Hearing loss (conductive and sensorineural)	

Table 2: General treatment strategies for complications of OM

Complication	**Medical therapy**	**Surgical intervention**
Acute mastoiditis	IV antibiotics	± Tympanocentesis, ± mastoidectomy
Coalescent mastoiditis	IV antibiotics	Mastoidectomy
Postauricular abscess	IV antibiotics	Incision and drainage, mastoidectomy
Bezold abscess	IV antibiotics	Incision and drainage, mastoidectomy
Temporal abscess	IV antibiotics	Incision and drainage, mastoidectomy
Petrous apicitis	IV antibiotics, ± steroids	± Mastoidectomy, ± petrous apex drainage
Labyrinthe fistula	± IV antibiotics	Cholesteatoma removal, ± fistula repair
Facial nerve palsy	± IV antibiotics, ± steroids	± Tympanocentesis, ± facial nerve decompression, ± removal of cholesteatoma
Acute suppurative labyrinthitis	IV antibiotics, ± steroids	± Mastoidectomy
Encephalocele, CSF leak	No antibiotics	Mastoid or middle fossa approach repair
Meningitis	IV antibiotics, steroids	Tympanocentesis, ± mastoidectomy
Intraparenchymal brain abscess	IV antibiotics	± Incision and drainage, mastoidectomy
Subdural abscess	IV antibiotics	Incision and drainage, mastoidectomy

Epidural abscess	IV antibiotics	Incision and drainage, mastoidectomy
Sigmoid sinus thrombosis	IV antibiotics, ± steroids, ± anticoagulation	Mastoidectomy, ± clot removal, ± ligation of internal jugular vein
Otitic hydrocephalus	IV antibiotics, ± steroids, ± anticoagulation, ± diuretics	Mastoidectomy, ± clot removal, ± serial lumbar punctures

- Tympanic membrane perforation
  - Majority of cases heal spontaneously within 2-3 weeks
  - Those that do not heal require surgical intervention (i.e. tympanoplasty) to prevent/treat long term sequelae such as conductive hearing loss, chronic otorrhea and migratory cholesteatoma
- Acute mastoiditis
  - Inflammation of the mastoid air cells of temporal bone inside the mastoid process **(Figure 2)**
  - Presentation:
    - Fever, post-auricular erythema, tenderness and ear proptosis
  - Diagnosis
    - Currently, there is no consensus on the diagnostic criteria for acute mastoiditis in children
    - Diagnosis is typically made based on history and clinical findings
    - Imaging with CT may reveal loss of mastoid air cell trabeculations or temporal bone destruction but is not required for diagnosis
  - Treatment
    - Medical: IV antibiotics
    - Surgical: ± Tympanocentesis, ± mastoidectomy
  - Complications
    - Bezold abscess
      - Infection erodes through the mastoid cortex and tracks inferiorly along the sternocleidomastoid muscle (SCM) sheath resulting in abscess formation deep to the SCM
      - Diagnose with CT imaging of the temporal bone **(Figure 3)**
    - Citelli abscess
      - Cervical infection extending along the posterior belly of the digastric muscle that develops into an abscess
- Petrous apicitis
  - OM infection may spread within the temporal bone into the petrous apex
  - Presentation:
    - Gradenigo syndrome – triad of symptoms including retro-orbital pain, ipsilateral abducens nerve palsy and otorrhea
  - Diagnosis
    - Non-contrast CT may demonstrate bony erosion within the petrous apex **(Figure 4)**
- Labyrinthitis

    - Inflammation of the vestibular nerve
    - Presentation:
        - Vertigo, oscillopsia, nausea, vomiting and sensorineural hearing loss
- Intracranial
    - Intracranial complications of OM include:
        - Meningitis, otitic hydrocephalus, abscess (epidural, subdural, brain), lateral sinus thrombosis and sigmoid sinus thrombosis
    - Intracranial complications may present with altered level of consciousness
    - Other signs/symptoms of intracranial complications include:
        - Nuchal rigidity, papilledema, cranial nerve palsies or other focal neurologic findings
    - MRI is more sensitive for diagnosis of intracranial complications
        - Detects cerebral edema, abscess, vascular patency (better than CT) and dural enhancement
    - Neurosurgical consult may be obtained

Practice Question:

A 3-year old boy is brought to the pediatrician's office by his mother due to 2 days of fever and moderate ear pain. The patient also complains of rhinorrhea and nasal congestion for the past 7 days. He recently completed a course of oral antibiotics for an ear infection 4 weeks ago. The patient has no history of chronic conditions and does not take any medications. The patient attends day care and his mother states that some of the other children there have recently been sick as well. His current temperature is 39.2 C (102.6 F). In the exam room, the patient appears to be irritable and tugging at his right ear. Otoscopy reveals a bulging and erythematous right tympanic membrane. Pneumatic otoscopy is performed revealing poor mobility of the right tympanic membrane. The oropharynx appears normal without lesions or sores. Cardiac and pulmonary exams are unremarkable. The remainder of the exam is unremarkable. What is the next best step in the management of this patient?

A. Ototopical ofloxacin with dexamethasone
B. Watchful waiting
C. Tympanocentesis and culture
D. Myringotomy with tympanostomy tube placement
E. Oral amoxicillin

This patient has acute otitis media (AOM). Risk factors include day care attendance and recent upper respiratory infection. Diagnosis is confirmed on otoscopy by the presence of signs of middle ear inflammation (e.g. erythematous and bulging tympanic membrane) and a middle ear effusion (confirmed by lack of tympanic membrane mobility with pneumatic otoscope). Antibiotic therapy should be prescribed for AOM (bilateral or unilateral) in children 6 months and older with severe signs or symptoms (i.e. moderate or severe otalgia or otalgia for at least 48 hours or temperature 39°C [102.2°F] or higher).
Chronic suppurative otitis media (CSOM) is treated with ototopical ofloxacin which is often paired with dexamethasone. However, this patient does not have tympanic membrane perforation or otorrhea.

Watchful waiting may be an appropriate course of action in children ≥6 months of age with mild or moderate signs or symptoms (i.e. mild or moderate otalgia or otalgia for < 48 hours or temperature < 39 C or 102 F).

Tympanocentesis and culture during myringotomy with tympanostomy tube placement is generally reserved for recurrent cases of AOM (at least 3 episodes in 6 months or 4 episodes in 12 months). The patient recently had an ear infection (presumably AOM) 4 weeks ago. They would be a candidate for surgery if another case AOM developed within the next 5 months.

Ready to Get Pimped:

1. ***What is the most common complication of OM?***
   Otitis media with effusion (OME). OME is a chronic inflammatory condition characterized by fluid in the middle ear without acute signs of acute inflammation. It may lead to conductive hearing loss.

2. ***What is Queckenstedt's sign?***
   Queckenstedt's sign is a test performed to determine whether CSF flow is obstructed in the subarachnoid space of the spinal canal. The clinician applies bilateral pressure on the internal jugular veins during lumbar puncture. If pressure does not rise during this maneuver, obstruction of CSF flow is suggested. Queckenstedt's sign can be seen in meningitis or lateral sinus thrombophlebitis.

3. ***What is otitic hydrocephalus?***
   Otitic hydrocephalus is a rare intracranial complication of chronic suppurative otitis media (CSOM) that was more common in the pre-antibiotic era. Patients present with vomiting, headaches, blurred vision, papilledema, and a picket fence fever curve. It is thought to be due to reduced absorption of CSF following obstruction of lateral sinus which affects cerebral venous outflow. Diagnosis is established by elevated opening pressure during lumbar puncture with normal CSF composition and radiographic evidence of sinus thrombosis.

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Otosclerosis:

Background

- Otosclerosis or "hardening of the ear" is altered bony metabolism in the otic capsule resulting in cyclic resorption and deposition of bone ultimately resulting in fixation of ossicular chain (e.g. stapes) and consequent conductive hearing loss
- The otic capsule is a segment of the temporal bone that envelops the membranous labyrinthine of the inner ear
- Otosclerosis may be divided into clinical or histological disease
    - Clinical otosclerosis – symptomatic and presenting with combination of hearing loss, tinnitus and rarely vertigo
    - Histological otosclerosis – asymptomatic, more common than clinical otosclerosis and typically diagnosed postmortem
- Otosclerosis may also be classified according to which structure is predominantly affected; however, this classification system is losing utility as many clinicians consider these subtypes to be on a continuum rather than two distinct entities
    - Stapes predominantly affected – fenestral otosclerosis
    - Cochlea predominantly affected – retrofenestral otosclerosis

Epidemiology

- Predominantly Caucasians in the second to fifth decades of life
- Female to male preponderance of 2:1

Pathophysiology/Pathoanatomy

- Endochondral ossification of the otic capsule is completed by one year of age with little to no remodeling occurring after initial development
- In otosclerosis, there is abnormal osteoblast and osteoclast activity resulting in replacement of normal bone with poorly organized bone that is well-vascularized (i.e. spongiotic) and/or densely mineralized (i.e. sclerotic)
- The footplate of the stapes may eventually be affected ultimately resulting in complete fixation of the stapes
- The stapes can no longer transmit sound waves from the incus to the oval window resulting in conductive hearing loss
- Less commonly, the cochlea may be impacted resulting in sensorineural hearing loss (i.e. retrofenestral)

History

- Adult-onset unilateral or bilateral progressive conductive hearing loss
    - Less commonly, patient may present with sensorineural hearing loss (retrofenestral otosclerosis)
    - Paracusis of Willis: patient may report improved hearing in loud environments
- Other symptoms include tinnitus and vertigo (uncommon)
- Family history – studies have supported an autosomal dominant pattern of inheritance with incomplete penetrance

Physical

- Physical exam is limited with most patients presenting with a normal external auditory canal and tympanic membrane
- Schwartze sign
    - Tympanic membrane may display a reddish discoloration during otoscopic exam due to increased vascularity
    - Present in approximately 10% of cases
- Rinne and Weber tests
    - Help differentiate conductive and sensorineural hearing loss
    - Otosclerosis will typically result in conductive hearing loss (discussed above)

Diagnosis

- **Establishing the diagnosis**
    - Audiometric studies
        - Typically reveals conductive hearing loss that is worse at low frequencies
        - Cahart notch on pure-tone audiometry – sensorineural hearing loss ("dip") at 2000 Hz due to fixation of stapes
    - Tympanometry
        - Objective test of middle ear function
        - Stapedial reflex
            - May be present early in the disease course but become absent late in the disease course due to fixation of stapes
        - Impedance tympanometry
            - Type A_s curve - normal middle ear pressure with decreased middle ear compliance
    - Imaging
        - Typically unnecessary to establish diagnosis; however, high resolution CT may be helpful for surgical planning
- **Differential diagnosis**
    - Cerumen impaction
    - Foreign body in external ear
    - Tympanosclerosis
    - Otitis externa
    - Otitis media

Management

- **Medical**
    - Medical therapy is not consistently recommended due to unknown efficacy
    - Sodium fluoride – promotes remineralization and reduces bone remodeling
    - Bisphosphonates – inhibits osteoclastic activity
    - Hearing aids are a conservative alternative to surgery
- **Surgical**
    - Goal of surgery – allow sound waves to transmit from the tympanic membrane through the ossicular chain to the oval window while bypassing the fixed stapes footplate

        - Success of surgery is objectively evaluated using audiometry which will demonstrate a decrease in the air-bone gap when comparing preoperative pure-tone audiometry and postoperative pure-tone audiometry
    - Stapedotomy
        - Small hole is created in the stapes footplate
        - A prosthesis may be added in patients with otosclerosis with fixation of the stapes footplate
        - The prosthesis may be omitted if the otosclerosis is limited to the anterior part of the stapes footplate
        - If added, the prosthesis connects the incus to the oval window by sitting in the groove formed in the stapes footplate
    - Stapedectomy
        - Stapes footplate is completely or partially removed and replaced with a prosthesis
        - The prosthesis connects the incus to the oval window
    - Risks of surgery include:
        - Sensorineural hearing loss (including deafness), vertigo, facial nerve injury, dysgeusia, prosthesis extrusion or displacement and tympanic membrane perforation
    - Considerations for bilateral otosclerosis
        - Bilateral otosclerosis occurs in ~70% of patients
        - Poorer hearing ear is typically operated on first
        - Assuming the first operation is successful, the contralateral affected ear is operated on 6 months later
    - Revision stapes surgery
        - Surgical correction of otosclerosis is overwhelmingly successful; however, revisions are sometimes performed to correct conductive hearing loss, vertigo, sensorineural hearing loss or distortion of sound
        - Explore other explanations for symptoms prior to performing revision surgery (e.g. superior semicircular canal dehiscence)
        - Revision surgery is discouraged as it is associated with decreased success rates and increased risk of sensorineural hearing loss

Complications of otosclerosis

- Progressive hearing loss

Practice Question

A 34-year-old female complains of difficulty hearing in both ears. She reports the difficulty hearing is worse on the left side compared to the right side. She denies ear pain or discharge. Her past medical history is significant for previous pregnancy 6 months ago that was complicated by pyelonephritis and necessitated antibiotic therapy. She takes no medications aside from a daily multivitamin and occasional ibuprofen for lower back pain. Her blood pressure is 124/78 mm Hg and pulse is 72/min. Cardiac and pulmonary exam are unremarkable. Rinne test is performed reveals bone conduction is greater than air conduction on the left side. Rinne test on the right side reveals air conduction is greater than bone conduction. Weber test is performed and reveals

lateralization to the left side. Neurological exam is otherwise normal. Audiometry is also performed and reveals left low-frequency hearing loss. What is the most likely diagnosis?

A. Chronic otitis media with effusion
B. Meniere's disease
C. Otosclerosis
D. Presbycusis
E. Antibiotic treatment

Causes of conductive hearing loss (CHL) include obstruction (e.g. cerumen impaction), chronic otitis media and otosclerosis. A normal Rinne test reveals air conduction that is greater than bone conduction bilaterally (AC > BC). This patient has bone conduction that is greater than air conduction (BC > AC) in the affected (left) ear suggesting conductive hearing loss. A normal Weber test (midline Weber) is vibration being heard equally on both sides without lateralization. Patients with CHL lateralize to the affected ear (left in this case).

This patient likely has bilateral otosclerosis with the left ear being more affected than the right. In otosclerosis, altered bony metabolism in the otic capsule results in cyclic resorption and deposition of bone ultimately leading to fixation of the ossicular chain (e.g. stapes) and consequent conductive hearing loss. Otosclerosis often presents in the second to fifth decades of life and has a female to male preponderance of 2:1. Treatment involves hearing amplification with hearing aids or surgical stapedectomy/stapedotomy.

Chronic otitis media with effusion may present with CHL. However, CHL is typically accompanied by chronic congestion, otalgia and/or tinnitus.

Meniere's disease presents with a triad of recurrent vertigo, unilateral SHL and tinnitus. It may also present with ear fullness/pain. It is thought to be due to an accumulation of endolymph in the inner ear.

Presbycusis is a form of SHL, often at higher frequencies. It is typically progressive and bilateral and presents at advanced age.

Ototoxic antibiotics such as aminoglycosides usually result in SHL as opposed to CHL.

Ready to Get Pimped

1. ***Why do radiologists often refer to 'otospongiosis' when speaking about otosclerosis?***
   High resolution CT may demonstrate lucency (as opposed to sclerotic) focus in the temporal bone near the oval window **(Figure 1)**. CT imaging is not routinely needed to establish the diagnosis of otosclerosis. However, it may prove useful for surgical planning.

2. ***What should be done if a persistent stapedial artery or overriding facial nerve is encountered intraoperatively during a stapedotomy?***

The stapedial artery develops from the 2nd aortic arch and normally degenerates during the 10th week in utero. If the stapedial artery fails to regress, it is called a persistent stapedial artery (PSA), which may complicate stapes surgery. Disrupted ossicular development may result in a facial nerve that dives sooner and more anterior within the middle ear to emerge from the stylohyoid foramen. Here, it can override the stapes complicating stapes surgery similarly to a PSA.

The surgery may proceed with added precautions if these anatomic anomalies are encountered intraoperatively. An overriding facial nerve may be retracted gently to allow access to the stapes footplate for the creation of the fenestra. Historically, there was concern for damage to the facial nerve or neural structures if the PSA was damaged. However, no neurological sequelae have been described following transection of a PSA and/or stapes surgery in presence of a PSA. Recent research suggests middle ear surgery is safe in patients with a PSA. Therefore, coagulation or ligation of the stapedial artery may be performed if needed.

If the surgeon believes the procedure cannot continue due to safety concerns, then they can terminate the procedure. The patient may instead be managed conservatively with hearing aids.

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Cholesteatoma:

Background

- A cholesteatoma is a benign inclusion cyst of the temporal bone composed of keratinizing squamous epithelium
- If left untreated, a cholesteatoma can enlarge and destroy adjacent structures
- The word *cholesteatoma* is somewhat of a misnomer as there is no cholesterol or fat within cholesteatomas

Epidemiology

- Acquired cholesteatomas may affect both children and adults
- Congenital cholesteatomas present in childhood

Pathophysiology/Pathoanatomy

- The origin of a cholesteatoma depends on the type (Table 1)

Table 1: Different types of cholesteatomas and their associated origin

Type	Origin
Congenital	Keratinizing squamous epithelium in the middle ear cleft with an intact tympanic membrane
Primary acquired	Occurs in the setting of tympanic membrane retraction
Secondary acquired	Occurs in the setting of tympanic membrane perforation

- Congenital cholesteatomas
    - Hypothesized to originate from keratinizing squamous epithelium of the middle ear cleft
- Primary acquired cholesteatomas
    - Typically originates in the setting of tympanic membrane retraction, usually resulting from otitis media and chronic eustachian tube dysfunction
- Secondary acquired cholesteatomas
    - Typically arises in the setting of tympanic membrane perforations with epithelial migrations
- The origin of cholesteatomas, whether congenital or acquired, remains controversial and there are several proposed theories (e.g. epidermoid cell rests, invagination, etc.)
- Cholesteatomas may become infected and erode bone and other surrounding structures

History

- Congenital cholesteatoma
    - Generally asymptomatic and discovered through routine exam
    - Typically, does not result in otorrhea as the tympanic membrane remains intact
    - May present after having grown over several years with more serious symptoms
        - Slow progressive conductive hearing loss, facial nerve paresis, vertigo or intracranial infection
- Acquired cholesteatoma
    - May present with persistent foul-smelling otorrhea

    - Like congenital cholesteatomas, acquired cholesteatomas may present with more serious symptoms after having grown over time
        - Slow progressive conductive hearing loss, facial nerve paresis, vertigo or intracranial infection
- Fever is an atypical presentation for a cholesteatoma and may indicate a more serious complication (e.g. intracranial)

Physical

- Congenital cholesteatoma
    - Otoscopic exam may reveal a white or yellow mass in the anterior superior quadrant of the middle ear
    - Tympanic membrane generally intact
- Acquired cholesteatomas
    - Otoscopic exam may reveal posterior superior retraction pockets seen at the margin of the tympanic membrane with surrounding keratin debris
    - Tympanic membrane may be perforated

Diagnosis

- **Establishing the diagnosis**
    - Clinical diagnosis based on patient's history and otoscopic exam
- **Differential diagnosis**
    - Acute otitis media
    - Chronic suppurative otitis media
    - Otitis externa
    - Cholesterol granuloma
    - Malignancy of ear canal
    - Tympanosclerosis

Management

- **Medical**
    - Cholesteatomas are typically managed surgically
    - Conservative medical management involves removal of infected debris, water restrictions, ototopical agents (cover aerobes and anaerobes with attention to antibiotic resistance) and topical steroids for chronic inflammation
- **Preoperative assessment**
    - Imaging
        - CT imaging may help in preoperative planning as the extent of disease, involved structures and relevant anatomy may be elucidated
        - MRI is typically not used but may be helpful in appraising intracranial complications
    - Location of cholesteatoma
        - A cholesteatoma around the oval window carries an increased risk of sensorineural hearing loss and suppurative labyrinthitis
        - If the cholesteatoma erodes into the lateral semicircular canal, there is a risk of a perilymphatic fistula
    - Risks of surgery

        - Incomplete removal of cholesteatoma, hearing loss (including deafness), facial nerve injury, dysgeusia, infection, bleeding, vertigo, encephalocele and need for second-stage surgery
    - Audiograms
        - Pre-op audiograms evaluate baseline hearing
        - Medical-legal implications in the event of an operative complication
- **Surgical**
    - Goals of surgery – complete removal of disease, preservation of hearing, prevention of residual or recurrent disease and improvement of ear hygiene
    - There are various surgical approaches the selection of a specific approach is largely dependent on the extent of disease and surgeon experience/comfort level
    - Surgical approaches include:
        - Atticotomy
            - Mainly used when disease is limited lateral to the malleus and incus as well as in the "attic"
        - Cortical mastoidectomy with or without facial recess
            - Performed when the cholesteatoma extends medially to the ossicles and into the mastoid through the antrum
        - Mastoidectomy
            - Treatment of choice in most patients
            - Categorized based on whether the posterior wall of the external auditory canal is removed (canal wall down) or preserved (canal wall up)
            - Canal wall down
                - Provides superior visualization during and after cholesteatoma removal
                - However, generally not performed due to difficulty reconstructing the middle ear and significant risk of otorrhea, poor hearing and need for life-long canal cleaning and long-term water restrictions
                - Relatively contraindicated in children as the temporal bone is still developing
            - Canal wall up
                - Preserve anatomy of the middle ear
                - Better hearing outcomes
                - Does not require regular canal cleaning
                - No water restrictions
    - Second-stage procedure
        - Required in the occasion of recurrence or residual disease, a common occurrence in children
        - Timing and decision of a second-stage procedure is not well established
        - Typically performed 9-12 months after the original surgery in adults and 6-9 months after the original surgery in children
- **Postoperative follow-up**
    - Regular follow-up required due to high rates of recurrence and residual disease

- Follow-up includes visualization of the ear under the operating microscope, annual audiograms, and imaging
- MRI is preferred over CT as it is better at differentiating soft tissues and fluid in the middle ear and mastoid

Complications

- Cholesteatomas tend to become infected and erode surrounding structures
- A variety of intracranial and extracranial complications associated with chronic otitis media (e.g. acute mastoiditis, meningitis)

Practice Question

1. An 11-year-old girl comes to the office complaining of right-sided ear discharge that has persisted for the last 4 weeks. She has completed a course of antibiotics that were prescribed during a previous visit with her primary care provider. She also complains of hearing loss on the right side. On exam, she is afebrile. Otoscopy reveals an intact right tympanic membrane with a retraction pocket and peripheral skin debris. What is the most likely diagnosis?
   A. Otosclerosis
   B. Acute otitis media
   C. Cholesteatoma
   D. Middle ear osteoma
   E. Meniere's disease

   A diagnosis of cholesteatoma should be considered in any patient with continued ear drainage despite appropriate antibiotic therapy and new-onset hearing loss. Otoscopic exam may reveal a retraction pocket in the tympanic membrane that may fill with keratinized squamous debris.

   Otosclerosis is characterized by bony overgrowth of the stapes ultimately resulting in fixation and conductive hearing loss. Otorrhea would not be present.

   Acute otitis media (AOM) may result in otorrhea; however, this would likely occur in the setting of a perforated tympanic membrane. Moreover, AOM typically presents with acute onset of otalgia, fever and irritability. Otoscopy may also reveal a tympanic membrane that is erythematous and/or bulging. Furthermore, acute otitis media should resolve after appropriate antibiotic therapy.

   An osteoma is a solitary bony overgrowth that is typically found within the external auditory canal close to the meatus. The findings on this patient's tympanic membrane is more typical of a cholesteatoma.

   Meniere's disease results from an accumulation of endolymph in the inner ear. It classically presents with a triad of sensorineural hearing loss, vertigo and tinnitus.

Ready to get pimped

1. ***What CT finding is commonly seen in acquired cholesteatomas?***
   Blunting or erosion of the scutum. The scutum is a sharp bony spur in the lateral portion of the middle ear and superior portion of the external auditory canal.

2. ***What role does endoscopy play in the surgical treatment of cholesteatoma?***
   Endoscopy allows better visualization of areas known to have high incidence of residual disease as you are no longer limited to the linear view of a microscope. It is also a less invasive.

3. ***Specifically, what is the best imaging modality for the detection of post-operative middle ear cholesteatoma?***
   Non-echo-planar diffusion-weighted MRI

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Acute rhinosinusitis (ARS):

Background:

- Acute rhinosinusitis (ARS) is defined as symptomatic inflammation of the nasal and paranasal sinus mucosa for ≤ 4 weeks **(Figure 1)**
- Recurrent acute rhinosinusitis (RARS) is defined as 4+ episodes of ARS per year, with each episode lasting 7-10+ days with symptom resolution between episodes

Epidemiology

- Major burden on health care system with rhinosinusitis being the 5th most common diagnosis made during family physician visits

Pathophysiology/Pathoanatomy

- Sinonasal mucosa lined by pseudostratified columnar ciliated epithelium
- Inflammation of the nasal and paranasal sinus mucosa with subsequent edema is the initiating factor in the disease
- Edema may cause obstruction of sinus drainage, compromised mucociliary clearance and a change in local immune system function
- Initial inflammation is most often caused by viral infection (67%) and less commonly by bacterial infection
- Most common bacterial culprits are the same as those that cause acute otitis media:
    - *Streptococcus pneumoniae*
    - *Haemophilus influenza*
    - *Moraxella catarrhalis*

History

- "Major" symptoms include nasal discharge with nasal obstruction and facial pressure or pain
    - Other "major" symptoms include fever and hyposmia
- "Minor" symptoms may include cough, fatigue, ear fullness or pain and maxillary toothache
- Important to distinguish viral rhinosinusitis (VRS) from acute bacterial rhinosinusitis (ABRS)
    - VRS typically has a rapid onset with duration of 4-7 days
    - Persistence of infection beyond 10 days (but less than 12 weeks) or worsening symptoms after they were initially improving ("double sickening/worsening") suggests ABRS
    - ABRS may also present with more severe symptoms at the onset including fever ≥ 39 degrees C (102 degrees F) and purulent nasal discharge lasting ≥ 3-4 consecutive days

Physical

- Presence of a fever (in conjunction with other symptoms) may suggest extension of infection into the orbit or intracranial structures
- Tenderness with palpation of sinuses
- Tenderness with percussion of maxillary teeth

- Anterior rhinoscopy may show purulent secretion or nasal obstruction in association with a narrowing middle meatus which can be observed using a nasal speculum or wide speculum mounted on an otoscope
- Otoscopic exam is warranted if the patient exhibits ear symptoms (e.g. ear pain) to evaluate for middle ear effusions and eustachian tube dysfunction

Diagnosis

- **Establishing the diagnosis**
    - Diagnosis is mainly based on history with specific signs and symptoms and their timing serving as the most important components in establishing the diagnosis of ARS (viral or bacterial)
    - Imaging
        - Not recommended for uncomplicated ARS
        - Computed tomography (CT) - reserved for patients with RARS (≥ 4 episodes within 1 year) or when suppurative complications are suspected
        - MRI with gadolinium – for patients with suspected CNS complications of ABRS
    - Consider obtaining cultures in patients where first- and second-line antibiotics have failed or have high risk of antibiotic resistance (e.g. > 65 years old, immunocompromised status, or recent hospitalization)
- **Differential diagnosis**
    - Viral upper respiratory infection
    - Rhinitis medicamentosa
    - Allergic rhinitis
    - Migraine

Management

- **Medical**
    - VRS treatment involves symptomatic management as antibiotics have no efficacy
        - e.g. analgesics, antipyretics, decongestants, nasal irrigation
    - ABRS treatment varies depending on guidelines
        - In general, empiric antibiotics are reserved for patients that meet criteria for ABRS
        - However, many clinicians may opt for "watchful waiting" and symptomatic treatment as studies have shown 60% to 70% of those with ABRS improve spontaneously within 7-12 days
    - First-line antibiotics
        - Amoxicillin-clavulanate is recommended as the first-line empiric therapy
            - Amoxicillin-clavulanate is often selected due to increasing prevalence of beta-lactamase producing *H. influenzae* and *M. catarrhalis*
            - High-dose amoxicillin-clavulanate (90 mg/kg/day PO BID or 2 grams PO BID) is recommended for those at risk of antibiotic resistance (e.g. > 65 years old, immunocompromised status, or recent hospitalization)

        - Treat for 5-10 days if adult or 10-14 days if child for uncomplicated ABRS
        - If symptoms worsen after 48-72 hours of treatment or fail to improve after 3-7 days, clinicians should be suspicious of a resistant pathogen or a noninfectious source
    - If penicillin allergy,
        - Doxycycline (only in adults due to risk of teeth discoloration)
        - Respiratory fluoroquinolones – levofloxacin or moxifloxacin
  - Second-line antibiotics
    - Macrolides – clarithromycin or azithromycin
    - Trimethoprim-Sulfamethoxazole (TMP-SMX)
    - Second or third generation cephalosporins – cefpodoxime, cefixime, cefdinir
    - Clindamycin
- **Surgical**
  - Treatment of uncomplicated ARS does not involve surgical intervention
  - However, serious complications of ABRS may require surgical intervention (e.g. subperiosteal or orbital abscess, intracranial abscess)

Complications

- Complications of ABRS can be classified as orbital or intracranial
- Orbital complications
  - Due to ethmoid sinusitis, this is the most common complication of ABRS
  - Chandler classification – classifies orbital complications of ABRS
    - Stage 1: preseptal cellulitis
        - Impaired venous outflow from sinusitis and edema > inflammation and edema anterior to the orbital septum
    - Stage 2: orbital cellulitis
        - Extension of inflammation to include orbital contents posterior to the septum
        - Causes impaired extraocular movements, proptosis and chemosis
    - Stage 3: subperiosteal abscess
        - Accumulation of pus between the lamina papyracea and the medial periorbita **(Figure 2)**
        - May be managed medically in children if the medially located abscess does not affect vision and there is no systemic involvement
        - If surgery is required > ethmoidectomy and drainage of the abscess
    - Stage 4: orbital abscess
        - May cause severe visual impairment and complete ophthalmoplegia
    - Stage 5: cavernous sinus thrombosis
        - Development of retrograde phlebitis and coagulation of vascular contents extending up the cavernous sinus
        - Characterized by bilateral ocular symptoms and other CNS signs and symptoms including bilateral cranial neuropathies

- Intracranial complications
    - Serious complications requiring neurosurgery and infectious disease consults
        - Examples: venous sinus thrombosis, meningitis, brain abscess, Pott puffy tumor of the frontal sinus
    - Broad-spectrum antibiotics with enough blood-brain barrier penetration is typically required
    - Systemic steroids may reduce inflammation
    - Anticoagulation is required for patients with thrombosis although this is controversial
    - Involved sinuses tend to require endoscopic surgical drainage

Practice Question

A 6-year-old boy is brought to the pediatrician's office due to a worsening cough and nasal discharge. Two weeks ago, the patient developed nasal congestion and a runny nose, which initially improved over a few days. However, for the past 10 days he has had increasing amounts of thick, "yellow-green" nasal discharge. He has stayed home from school the past 2 days due to his worsening symptoms. He has no chronic medical conditions and takes no medications. Immunizations are up to date. Temperature is 37.0 C (98.6 F), pulse is 94/min, and respirations are 16/min. Pulse oximetry is 99% on room air. Physical exam shows an alert and active child with intermittent coughing. Anterior rhinoscopy with a nasal speculum reveals erythematous and edematous middle meatuses and thick, purulent drainage. Bilateral tympanic membranes are translucent and mobile. Lungs are clear to auscultation. What is the most appropriate next step in the management of this patient?

A. Intranasal corticosteroids
B. Nasal irrigation
C. Observation and close follow-up
D. CT scan of paranasal sinuses
E. Oral antihistamines
F. Sinus fluid culture
G. Oral antibiotics

This patient with worsening cough and purulent nasal discharge likely has acute bacterial rhinosinusitis (ABRS). The most common bacterial pathogens that cause ABRS are *S. pneumoniae, H. influenzae and M. catarrhalis.* These bacteria typically cause ABRS following an initial viral upper respiratory infection. Acute viral rhinosinusitis (VRS) typically self-resolves in 7-10 days. In contrast, ABRS may be diagnosed by one of the following criteria:

1. Symptoms are severe in onset (including fever ≥ 39 degrees C (102 degrees F) and purulent nasal discharge lasting ≥ 3-4 consecutive days
2. Persistence of infection beyond 10 days (but less than 12 weeks) without improvement
3. Worsening symptoms after they were initially improving ("double sickening")

Severe or worsening symptoms ("double sickening"), as seen in this patient, are treated with empiric antibiotics (e.g. amoxicillin ± clavulanate) at the time of diagnosis. Observation and

close follow-up ("watchful waiting") is an acceptable course of action in patients with *persistent* symptoms but a milder course.

Intranasal corticosteroids, oral antihistamines and nasal irrigation are used in the symptomatic treatment of allergic rhinitis. This child has no history of seasonal allergies. Furthermore, this child has thick, yellow-green mucus. Allergic rhinitis presents with rhinorrhea that is clear.

ABRS is generally a clinical diagnosis. Furthermore, a CT scan of the paranasal sinuses will not help in differentiating VRS from ABRS. A CT scan may be useful if the patient were to develop suppurative complications.

A sinus fluid culture is not required for the diagnosis of uncomplicated ABRS. Cultures may be obtained in patients where first- and second-line antibiotics have failed or have high risk of antibiotic resistance (e.g. > 65 years old, immunocompromised status, or recent hospitalization) to better tailor antibiotic therapy.

Ready to get pimped

1. ***What type of abscess may form as a complication of ABRS involving the frontal sinus?***
   Subdural or epidural abscess **(Figure 3)**

2. ***What is a Potts Puffy Tumor?***
   Complication of ABRS in which there is extension of frontal sinusitis resulting in frontal bone osteomyelitis and subperiosteal abscess **(Figure 4)**. Treatment involves prompt surgical drainage and broad-spectrum antibiotics.

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Chronic rhinosinusitis (CRS):

Background:

- Chronic rhinosinusitis (CRS) is chronic inflammation of the mucosal lining of the nasal passages and paranasal sinuses lasting ≥ 12 weeks
- Clinically, rhinosinusitis is defined by clinical symptoms (subjective) + suggestive endoscopic and/or CT changes (objective)
- CRS may be classified as:
    - CRS with nasal polyps (CRSwNP)
    - CRS without nasal polyps (CRSsNP)
    - Allergic fungal rhinosinusitis (AFRS)
- Chronic rhinosinusitis (CRS) causes significant symptoms, has a negative impact on quality of life, and can substantially impair daily functioning

Epidemiology

- 60-67% of cases reported to occur in women
- Incidence of physician-diagnosed CRS is 1% of the population (or approximately 3,282,000 people)

Pathophysiology/Pathoanatomy

- The pathophysiology of CRS is complex and a topic of ongoing research
- Overall, CRS is thought to be a multifactorial inflammatory process characterized by a dysfunctional local host-environment interaction **(Figure 1)**

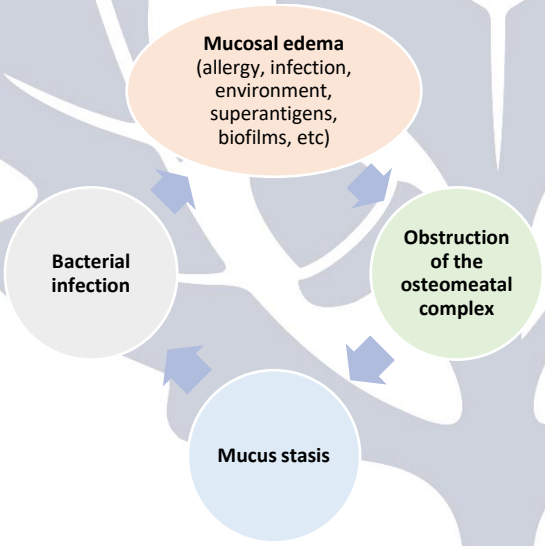

Figure 1: CRS is caused by a multifactorial inflammatory process involving an interplay between mucosal edema, obstruction of the osteomeatal complex, mucus stasis and bacterial infection.

- Classification by presence or absence of nasal polyps is largely based on the type of inflammatory pathway that leads to the specific form of CRS
    - CRSwNP – Th2-mediated pathway (IL-4, IL-5 and IL-13)
    - CRSsNP – Th1-mediated pathway (IFN-γ)

- Aspirin Exacerbated Respiratory Disease
    - Characterized by nasal polyps, aspirin sensitivity, asthma and eosinophilic CRS
    - Patient has a dysfunction in the arachidonic acid metabolism pathway resulting in an increase in proinflammatory leukotrienes and a decrease in anti-inflammatory prostaglandins
    - Aspirin and NSAIDs exacerbate respiratory disease (e.g. bronchospasm, mucosal edema)

History

- Subjective history is integral in establishing the diagnosis of CRS
- Key symptoms include:
    - Nasal congestion, facial pressure or fullness
    - Nasal blockage or obstruction
    - Anterior rhinorrhea or postnasal drip
    - Reduced sense of smell
    - Cough
- Other minor symptoms include:
    - Ear pain
    - Sleep disturbance
    - Headache
- Severe headache, neck stiffness and ocular findings suggest more serious complications of CRS (e.g. cavernous sinus thrombosis, meningitis)
- Asthma is present in up to 50% of patients with CRSsNP and in up to 80% of patients with CRSwNP
- Aspirin sensitivity characterized by wheezing or worsening asthma with aspirin administration may point to AERD
- Smoking may contribute to the pathogenesis of CRS

Physical

- Anterior rhinoscopy may reveal:
    - Nasal mucosal erythema
    - Nasal discharge
    - Nasal polyposis
    - Evidence of anatomic abnormality (e.g. septal deviation)
- Nasal endoscopy may confirm sinonasal inflammation and reveal:
    - Nasal polyps
    - Mucopurulent discharge
    - Mucosal edema
- Lund-Kennedy score
    - Calculated based on assessment with nasal endoscopy
    - Evaluates the presence of polyps, nasal discharge, and edema/scarring/adhesions/crusting
    - Scores range 0-20 with a higher score indicating worse outcomes

Diagnosis

- **Establishing the diagnosis**

- As previously mentioned, the diagnosis of CRS is established by a combination of subjective and objective findings
    - Table 1 and Table 2 – derived from data from the American Academy of Otolaryngology – Head and Neck Surgery
- Diagnostic criteria of CRS in children is comparable to adults except cough is accepted as a symptom of CRS in pediatric patients
- Imaging
    - CT is the modality of choice
    - Generally reserved for when a patient fails medical management, there is concern of a complication, or for pre-operative planning
    - CT allows visualization of mucosal thickening, air fluid levels, bony structures and the osteomeatal complex
- AFRS is diagnosed based on the presence of 5 criteria:
    - Nasal polyposis
    - Atopic history
    - CT scan with evidence of hyperdense sinus infiltrates or calcifications
    - Eosinophilic mucin
    - Positive fungal culture or histopathology
        - Typically more common in the Southern or Southwestern part of the country

Table 1: Subjective findings in the diagnosis of CRS.

≥ 12 weeks of 2 or more symptoms:

Either	Facial pain or pressure/fullness **OR** Decreased sense of smell
±	Mucopurulent drainage (anterior, posterior or both)
±	Nasal blockage/obstruction/congestion

Table 2: Objective findings in the diagnosis of CRS.

Either endoscopic signs and/or CT changes

Endoscopic signs	Nasal polyps
	Mucopurulent discharge
	Mucosal edema
CT changes	Inflammation of the paranasal sinuses (e.g. mucosal thickening or opacification of the paranasal sinuses)

- **Differential diagnosis**
    - Recurrent acute rhinosinusitis
    - Acute rhinosinusitis (viral and bacterial)

- Allergic fungal sinusitis
- Allergic rhinitis
- Migraine

Management

- **Medical**
  - Length and type of therapy dependent on clinical symptoms and objective findings, stage of disease and underlying triggers
  - First-line
    - Intranasal corticosteroids to control inflammatory component of disease
  - Nasal saline irrigation for symptom relief
  - Oral corticosteroids for severe CRS
  - Smoking cessation highly recommended
  - Antibiotic therapy plays a limited role
    - Short-term antibiotics may be given for acute exacerbations
    - Long-term antibiotics best given after obtaining culture results to tailor treatment, especially considering the incidence of antibiotic-resistant bacteria
  - AERD
    - Avoid COX-1 inhibitors
    - Treat asthma according to guidelines
    - Leukotriene-modifying drugs
    - ASA desensitization
- **Surgical**
  - Goal of surgery – facilitate natural drainage of sinuses, eradicate pathogenic bacteria and remove nasal polyps or other mucosal disease
  - Functional endoscopic sinus surgery (FESS)
    - Indicated for disease that is refractory to medical management
    - Not considered curative – rather adjunctive therapy
    - Outcome data has shown that patients who elect FESS experienced significantly higher levels of improvement compared to patients managed by medication alone

Complications

- Poor quality of life
- Severe complications are rare and typically due to effects on surrounding bone
- Other serious complications may result from spread of bacterial infection
  - Meningitis
  - Orbital cellulitis
  - Cavernous sinus thrombosis

Practice Question

A 34-year-old Caucasian male presents to his PCP with complaints of recurrent nasal discharge and increasing nasal congestion. He has a persistent sensation of dripping in the back of his throat and states that he can't taste his food anymore. His past medical history is significant for a

visit to the ED one year ago after having taken naproxen for right knee pain and developed severe wheezing. He has no history of head trauma. He also does not smoke cigarettes but reports sparse recreational use of cocaine. What is the most likely diagnosis?

A. Inverted papilloma
B. Perforated nasal septum
C. Angiofibroma
D. AERD

This patient likely has aspirin exacerbated respiratory disease (AERD) given the history of wheezing and a visit to the ED following naproxen consumption in conjunction with his complaints of recurrent nasal discharge and postnasal drip. AERD diagnosis may be made when a patient has nasal polyps, aspirin sensitivity, asthma and eosinophilic chronic rhinosinusitis. The patient's symptoms of anosmia and recurrent nasal discharge/congestion are typical in patients with nasal polyps. Anterior rhinoscopy or endoscopy will likely reveal nasal polyps. Nasal polyps may be removed by functional endoscopic sinus surgery but they have a high rate of recurrence. Therefore, management often is medical in nature (e.g. inhaled corticosteroids).

An inverted papilloma is a tumor of unknown origin that presents clinically with signs of unilateral nasal obstruction and/or epistaxis. It is not associated with AERD.

Patients with a perforated nasal septum often complain of nasal discomfort and a feeling of obstruction within the nose. They may also complain of crusting and bleeding.

Juvenile nasal angiofibroma (JNA) is a rare, benign tumor of the nasopharynx that can cause nasal obstruction and drainage. However, it usually results in epistaxis. It also typically presents in male teenagers.

Ready to get pimped

1. ***Which sinus is most often affected in CRS?***
   Anterior ethmoid sinuses.

2. ***Which microorganisms are associated with CRS?***
   The microorganisms found in CRS are the same ones found in acute rhinosinusitis. However, coagulase-negative *Staphylococcus* species, *S. aureus, P. aeruginosa,* gram-negative rods and anaerobes are more frequently associated with CRS. The incidence of antibiotic-resistant bacteria in the pathogenesis of CRS is high necessitating the need for broad-spectrum coverage when antibiotics are utilized.

3. ***What is Samter's triad?***
   Samter's triad is another name for aspirin-exacerbated respiratory disease (AERD). Traditionally, Samter's triad was used to describe a triad of nasal polyps, asthma and aspirin-induced respiratory reactions. Recently, AERD has replaced Samter's triad to be inclusive of chronic rhinosinusitis in addition to the classic triad. Research has also

shown that sensitivity in those with AERD is not limited to aspirin but includes other COX-1 inhibitors as well (e.g. ibuprofen).

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Epistaxis

Background

- Epistaxis is acute bleeding from the nose or nasopharynx
- Epistaxis can originate from the anterior or posterior nasal blood supply
    - Anterior epistaxis is most common and most often originates from Little's area in Kiesselbach's plexus,
    - Posterior bleeds commonly originate from the sphenopalatine artery distribution
- In addition to anterior vs posterior bleeds, epistaxis may be classified as primary vs secondary
    - Primary epistaxis – spontaneous bleed without any identified precipitant
    - Secondary epistaxis – underlying cause results in nosebleed (e.g. coagulopathy)

Epidemiology

- Commonly occurs in all age groups with a bimodal distribution in the young (< 10 years) and the elderly (> 50 years)
- Clear majority are benign and self-limited

Pathophysiology/Pathoanatomy

- Blood supply of the nasal cavities
    - Anterior and posterior ethmoid arteries
        - Internal carotid artery > ophthalmic artery > anterior and posterior ethmoid arteries
        - Supply the superior nasal cavity and septum
    - Sphenopalatine artery
        - External carotid artery > maxillary artery > sphenopalatine artery
        - Supplies the posterior lateral nasal wall and nasal cavity
    - Facial artery
        - External carotid artery > facial artery
        - Provides additional supply to the anterior nasal cavity
    - Kiesselbach's plexus
        - Confluence of vessels arising from both the internal and external carotid artery systems
        - Supplies Little's area, which is an area on the anterior-inferior nasal septum
        - Most common site for epistaxis
    - Woodruff's plexus
        - Plexus of thin-walled veins located posteriorly in the inferior meatus
        - Previously thought to be arterial and contribute to posterior bleeds
- Anterior epistaxis
    - Majority of nosebleeds originate anteriorly (90% to 95%), most often in Little's area within Kiesselbach's plexus
    - Easily exposed to excoriation (nose picking/local trauma)
    - Easily accessible and managed with conservative measures (e.g. pressure)
- Posterior epistaxis
    - Generally, result from distribution of the sphenopalatine artery
    - More difficult to control often requiring nasal packing

- Nasal mucosa may become damaged resulting in either anterior or posterior bleeds
    - Dry air – irritates mucosa
    - Rhinitis – mucosa becomes friable
    - Swelling of nasal turbinates (e.g. allergy)
    - Trauma
    - Septal deviation or perforation
    - Drug use, especially nasal steroid sprays

History

- Thorough HPI should be performed (timing, frequency, sidedness, and severity)
- Associated symptoms indicative of blood loss includes lightheadedness or dyspnea
- Explore predisposing conditions such as trauma, recent surgery, coagulopathy, cancer, medications and illicit drug use, and contributory chronic medical issues
- Medications, drugs and herbal supplements worth asking about include:
    - Nasal steroids, aspirin, warfarin, clopidogrel, nasal decongestant, intranasal cocaine, garlic, ginger, St. John's wort
- Ask about family history of bleeding disorder or epistaxis

Physical

- First assess patient's airway and cardiovascular stability
- Anesthesia can be provided prior to localizing the source of bleeding
    - Can use topical sprays or cotton strips with 2% lidocaine or 4% cocaine
- Oxymetazoline (or phenylephrine) can be given for vasoconstriction to minimize bleeding
- Anterior rhinoscopy
    - Nasal speculum used to find source of bleeding
    - Inspect relevant anatomy (Kiesselbach's plexus, septum, and turbinates)
    - Identify ulcerations, excoriations or erosions of nasal mucosa
    - Often enough for anterior bleeds but insufficient for posterior bleeds
    - May be used with suction to help remove clots
- Nasal endoscopy
    - Performed if source of bleeding is not elucidated by anterior rhinoscopy or if posterior epistaxis is suspected on history
    - May also be performed if conservative measures have not been successful or a tumor/lesion is suspected on history

Diagnosis

- **Establishing the diagnosis**
    - Diagnosis is made by clinical exam
    - Determination of the type of epistaxis (anterior vs posterior) made by clinical exam or response to therapy
- **Differential diagnosis**
    - Trauma - most often digital
    - Inflammatory - upper respiratory or infection
    - Medications - antiplatelet, anticoagulants, nasal sprays
    - Vascular - aneurysm

- Congenital/Developmental – septal abnormality
- Genetic – Osler-Weber-Rendu syndrome/hereditary hemorrhagic telangiectasia (HHT)
- Systemic disorders – hypertension, blood dyscrasias
- Neoplastic – benign or malignant masses

Management

- **Medical**
  - Initial management in exam room for mild epistaxis
    - Instruct patient to gently blow the nose to remove blood/clots
    - Have patient lean head forward
      - Prevents posterior drainage of blood which would otherwise increase the risk of bloody aspiration and/or gastric irritation
    - Intranasal administration of nasal decongestant spray such as oxymetazoline (a selective alpha-1 agonist/partial alpha-2 agonist)
    - Instruct the patient to pinch the nasal alae against the septum to apply hemostatic pressure, and hold for 10-15 minutes
    - Place a cold compress over the bridge of the nose
  - If bleeding does not stop with initial management, consider conservative management
    - Apply pledget or cotton ball soaked with decongestant on side of nose that is bleeding
    - Once pledget has been removed and source of bleeding is identified, consider cautery around and over bleeding point
    - Silver nitrate chemical cautery
      - Works by cauterizing superficial blood vessels
      - Bleeding must be minimal (and ideally unilateral) to be successful
      - Mucosa needs to by dry for silver nitrate to work so first apply topical decongestant and pressure
      - Place silver nitrate stick at the origin of the bleed and hold applicator until mucosa becomes gray (< 10 seconds)
      - Apply topical saline or decongestant to halt the chemical reaction
  - If bleeding does not stop following conservative management, consider nasal packing
    - Anterior nasal pack
      - Can use either gauze or nasal tampons that expand with addition of saline
      - First apply topical anesthetic/analgesic intranasally
      - Coat the pack with antibiotic ointment
        - Serves as lubrication and possible prevention of toxic shock syndrome
      - Slide anterior pack into place and expand with saline
    - Posterior nasal pack
      - First remove anterior pack if previously applied due to suspected anterior bleed and reapply topical 2% lidocaine

- Posterior packing previously involved cotton packs or Foley catheters but more recently has involved inflatable balloon devices
- Obtain adequate anesthesia
- For the double-balloon approach, apply mupirocin (Bactroban) nasal ointment 2% to the double-balloon catheter, and advance the device completely into the nostril
- Inflate the posterior balloon with up to 7-10 mL of sterile water
- Withdraw the catheter until posterior balloon seats
- The balloon stops at the posterior nasal cavity
- Inflate the anterior balloon with up to 15-30 mL of sterile water
- Apply padding (e.g. Xeroform wrap) to prevent alar necrosis
- Admit patient for close monitoring (i.e. telemetry, pulse oximetry) and consider prophylactic antibiotics (with *S. aureus* coverage)
    - Nasal-cardiac reflex: long-term mechanical pressure on the nasal mucosa in combination with mental factors can precipitate a drop in blood pressure and heart rate
- Remove the balloons within 3-5 days to prevent tissue necrosis and infection
- Complications include:
    - Pain and discomfort, respiratory difficulty, infection, alar/septal necrosis, pharyngeal fibrosis/stenosis

- **Surgical**
    - May be necessary if conservative management and nasal packing fails to control bleeding (more common with posterior epistaxis)
    - Surgical options include:
        - Endoscopic diathermy
        - Laser photocoagulation
        - Septal surgery
        - Arterial ligation
            - Endoscopic ligation of sphenopalatine artery or internal maxillary artery frequently used in management of posterior epistaxis
        - Embolization

Complications

- Blood loss may complicate existing cardiopulmonary conditions

Ready to get pimped

A. ***How does sphenopalatine artery ligation compare to embolization when managing posterior epistaxis?***

Embolization is more expensive than surgical ligation and is not as effective in bleeding control. Generally reserved for patients that cannot tolerate general anesthesia or are poor surgical candidates.

B. What is Osler-Weber-Rendu syndrome/hereditary hemorrhagic telangiectasia (HHT)?

Rare autosomal dominant genetic disorder characterized by multiple arteriovenous malformations (AVMs) that manifest later in life. The diagnosis is based on Curacao criteria or by identification of causative genetic mutation. Curacao criteria includes spontaneous/recurrent epistaxis, mucocutaneous telangiectasias, visceral lesions (e.g. hepatic, pulmonary, cerebral, gastrointestinal AVMs) and an affected first-degree relative. Generally, epistaxis is the first manifestation of the disease

C. ***How do you manage epistaxis in a patient on anticoagulation for cardiac disease?***
    - First obtain a complete blood count including platelets for all patients
        - Also obtain PT/INR if the patient is on warfarin
    - If the patient has a mechanical heart valve, INR dictates warfarin administration
        - INR is supratherapeutic: hold warfarin
        - INR is therapeutic: continue warfarin
    - Consult cardiology if life-threatening bleeding occurs in a patient with a mechanical heart valve
    - For patients without a mechanical heart valve:
        - No life-threatening bleeding: continue aspirin or clopidogrel
        - Life-threatening bleeding: consult cardiology about the utility of platelet transfusion
        - On warfarin with therapeutic INR: continue warfarin
        - On warfarin with supratherapeutic INR: hold warfarin

D. ***Does hypertension play a role in epistaxis?***
Population-based studies have yet to confirm a causative link between hypertension and epistaxis.

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Thyroid Nodules and Disorders of the Thyroid Gland:

Background:

- A thyroid nodule is a lesion of the thyroid gland that is radiologically distinct from surrounding tissue
- Most thyroid nodules are asymptomatic
- Nonpalpable thyroid nodules are frequently detected incidentally on ultrasound (20% to 67% of patients)
- More than half of thyroid glands found to contain nodules have more than one nodule
- Thyroid nodules are most often benign (90%), yet there is a risk of malignancy (10%)
- Thyroid nodules can be classified clinically and pathologically **(Table 1)**

Table 1: Clinical and pathological classification of thyroid nodules

Non-neoplastic nodules	Hyperplastic – spontaneous or compensatory (after partial thyroidectomy)
	Inflammatory – acute bacterial thyroiditis, subacute thyroiditis, Hashimoto's thyroiditis
Benign neoplasms	Non-functioning (cold nodules) – adenoma or cystic
	Functioning (hot nodules) - adenoma
Malignant neoplasms	Papillary carcinoma
	Follicular carcinoma
	Anaplastic carcinoma
	Medullary carcinoma
	Thyroid lymphoma
	Thyroid metastasis from other primary cancers

- Due to the many causes of thyroid nodules, including malignancy, comprehensive workup should be performed
- We will focus primarily on the general workup for a thyroid nodule and the management of primary thyroid cancers

Epidemiology

- Those most affected include:
  - Women (4x more than men)
  - Elderly
  - Persons with history of radiation exposure
  - Persons with iodine deficiency
- Those with higher risk of malignancy include:
  - Male
  - Age <20 years and >60 years
  - Family history of thyroid malignancy
  - Radiation exposure as a child
  - Rapidly growing nodule
  - Painful nodule
  - Compressive symptoms (e.g. dysphagia)

- Cervical lymphadenopathy
- Hoarseness

Pathophysiology/Pathoanatomy

- Normal thyroid anatomy **(Figure 1)**
  - The thyroid gland is in the anterior neck
  - It lies behind the sternohyoid and sternothyroid muscles and envelops the superior tracheal rings with the cricoid and thyroid cartilages located superiorly
  - It is located within the visceral compartment of the neck (bounded by pretracheal fascia), along with the trachea, esophagus and pharynx
  - Arterial blood supply **(Figure 2)**
    - Common carotid artery > external carotid artery > superior thyroid artery > thyroid gland
    - Subclavian artery > thyrocervical trunk > inferior thyroid artery > thyroid gland
    - In about 10% of people, the thyroid gland may also be supplied by the thyroid ima artery, which branches most often from the brachiocephalic trunk
  - Venous drainage
    - Drained by superior, middle and inferior thyroid veins which forms a venous plexus
- Normal thyroid histology and physiology
  - Follicles within the thyroid gland are lined by thyroid follicular epithelial cells
  - Iodide is taken up by thyroid follicular cells and thyroid hormones (T4 and T3) are synthesized within the follicular lumen by thyroid peroxidase (TPO) through a process of iodide oxidation, organification and coupling before release into the blood
    - Peripheral conversion of T4 to T3 by 5'-deiodinase produces most T4 in the body
  - Regulation of thyroid hormone production and release **(Figure 3)**
    - Hypothalamus releases thyrotropin-releasing hormone (TRH) to stimulate the anterior pituitary to release thyroid-stimulating hormone (TSH)
    - TSH stimulates thyroid follicular cells to produce and release T3 and T4 act on effector organs
    - T3 and T4 feedback inhibit TSH and TRH release when in excess
  - Parafollicular C cells are located adjacent to thyroid follicles and synthesize and secrete calcitonin
- Papillary carcinoma
  - Malignant neoplasm originating from follicular cell with histology demonstrating papillae
- Follicular adenoma
  - Benign neoplasm without capsular invasion originating from follicular cell
- Follicular carcinoma
  - Malignant neoplasm with capsular invasion originating from follicular cell
- Medullary thyroid cancer
  - Malignant neoplasm with capsular invasion originating from parafollicular C cell

    - Can secrete calcitonin and carcinoembryonic antigen (CEA) as well as prostaglandins, histaminases and serotonin
    - High propensity for invasion into muscle and trachea as well as hematogenous spread to the lungs and viscera (50% at presentation)
    - More aggressive than well-differentiated thyroid cancers (papillary and follicular thyroid cancers)
    - Multiple endocrine neoplasia (MEN)
        - Several distinct syndromes featuring tumors of endocrine glands, each with its own characteristic pattern
            - MEN type I: pancreas, pituitary, parathyroid adenomas
            - MEN type IIa: medullary carcinoma of thyroid, pheochromocytoma, parathyroid
            - MEN type IIb: medullary carcinoma of thyroid, pheochromocytoma, mucosal neuromas
- Anaplastic carcinoma
    - Poorly-differentiated and extremely aggressive malignant neoplasm
    - 80% occur in pre-existing thyroid mass suggesting malignant de-differentiation within existing tumor
- Non-malignant thyroid disease
    - Pathophysiology varies depending on the non-malignant cause of the thyroid nodule

History

- Nodules may be discovered by palpation or incidentally during imaging for another reason
- Most patients with benign and malignant thyroid nodules are asymptomatic
- Patients may present with symptoms of hyperthyroidism/hypothyroidism, compression or with cosmetic concerns
- Rapidity of growth
    - Slow growth – possible benign hyperplastic nodules
    - Progressive growth – potential malignancy
    - Rapid growth – potentially hemorrhage into a benign thyroid nodule or cyst
- Multinodular goiter
    - Often asymptomatic
    - May present with cosmetic complaints, compressive symptoms or sudden transient pain if hemorrhage occurs
- Acute thyroiditis
    - Patient often has a history of preexisting thyroid disorder
    - Typically presents with anterior neck pain and tenderness that is exacerbated by swallowing
    - Other findings include: fever, pharyngitis and dermal erythema
- Subacute granulomatous thyroiditis
    - Prodrome: low-grade fever, fatigue and pharyngitis symptoms
    - Thyroid gland is exquisitely painful and tender

Physical

- Check for signs of hyperthyroidism
    - General - systolic hypertension, weight loss
    - Cardiac – tachycardia, atrial fibrillation, heart failure (from thyroid storm or decompensation with underlying heart disease)
    - Neuro – resting tremor, proximal muscle weakness, hyperactive reflexes
    - Skin – warm and moist skin, hair loss, hair thinning, palmar erythema
- Check for signs of hypothyroidism
    - General - weight gain, facial puffiness or edema
    - Cardiac – bradycardia, pericardial effusion
    - Lungs – pleural effusion, respiratory depression (severe)
    - Neuro – cerebellar ataxia, lethargy, somnolence, memory defects
    - Skin – dry and cool skin, coarse and brittle hair
- Thoroughly inspect and palpate the thyroid gland and the anterior and lateral compartments of the neck
- Cervical lymphadenopathy
- Physical exam may be normal if nodule is small

Diagnosis

- **Establishing the diagnosis**
    - Thyroid nodules are diagnosed by ultrasound or other imaging studies
    - Fine needle aspiration (FNA) biopsy, when indicated, may aid in diagnosis
- **Differential diagnosis**
    - For other causes of neck masses
        - Brachial anomalies
        - Cystic hygroma
        - Thyroglossal duct cyst
        - Lymphadenopathy
        - Sialadenitis
        - Neck abscess
        - Parathyroid hemorrhage
    - For thyroid cancers
        - Papillary carcinoma (70% to 85%)
        - Follicular carcinoma (15% to 30%)
        - Hurthle cell carcinoma (3% to 5%)
        - Medullary carcinoma (3% to 10%)
        - Anaplastic carcinoma (< 2%)
        - Insular or poorly differentiated carcinoma (rare)
        - Other: lymphoma, squamous cell carcinoma, metastases

Management

- **Thyroid nodule**
    - Primary goal of a thyroid nodule workup is exclusion of malignant lesions
    - Discovered thyroid nodules should prompt a comprehensive history and physical exam
    - Labs including thyroid function assay and serum calcium should be obtained
    - Ultrasonography should also be obtained

- FNA
    - Ultrasound features that are indications for a fine needle aspiration (FNA) include:
        - All nodules >1 cm, or smaller if other high-risk features are present (as below)
        - Microcalcification
        - Irregular margins
        - Nodule that is solid rather than cystic
        - Internal vascularity
        - Multiple nodules
        - Enlarged cervical lymph nodes on the same side of the neck
    - Diagnostic accuracy of FNA cytology
        - Accuracy 95%; false negative rate 2.3%; false positive rate 1.1%
    - FNA cytopathologic categories of thyroid nodules
        - Benign: 70%
        - Malignant: 5%
        - Suspicious: 10%
            - 10-20% of suspicious lesions will likely be follicular carcinomas on surgical pathology
        - Indeterminate: 15%
- Molecular testing
    - Allows for nodules in the "indeterminate" cytopathologic category to be "ruled-in" as cancer or "ruled out" as benign nodules
    - Potentially prevents unnecessary surgeries
    - Mutation panel testing
        - Tests for mutations commonly seen in thyroid cancer (*BRAF, RAS, RET/PTC, PAX8/PPAR-gamma*)
        - Positive test use to "rule in" cancer with a positive predictive value of 100%
        - Limitation: 30% of thyroid cancers do not currently have a known mutation
    - Gene expression testing
        - Tests for >140 genes expressed differently between benign and malignant thyroid nodule
        - Negative test used to "rule out" cancer with a negative predictive value of 95%
        - Limitation: expensive

- **Non-neoplastic nodules**
    - The medical management of non-neoplastic nodules depends on the underlying medical condition
    - Often, these medical conditions can be managed conservatively by the patient's primary care provider in conjunction with an endocrinologist
    - Surgery (e.g. thyroidectomy) is generally reserved for
        - Nodules causing compressive symptoms
        - Cosmetic purposes, if requested by patient

        - Nodules in which malignancy is suspected
        - Toxic multinodular goiter for definitive treatment of hyperthyoridism

Benign thyroid nodule

- Follow-up for a benign thyroid nodule is based on recommendations that vary according to organization
- Generally, serial ultrasounds are recommended (every 6-12 months) to assess changes in size or characteristics
    - If nodule changes characteristics, repeat FNA may be warranted
- Cysts that recur after multiple FNAs should be considered for surgical excision to establish a diagnosis
- Suppression by exogenous T4 is NOT recommended

- **Well-differentiated thyroid cancers (papillary and follicular thyroid carcinomas)**
    - TNM staging **(Table 2)**
        - Considers tumor size (T), spread to nearby lymph nodes (N) and metastasis to distant sites (M)

Table 2: TNM staging for well-differentiated thyroid cancer.

T1	Tumor ≤ 2 cm in greatest dimension and limited to the thyroid
T1a	Tumor ≤ 1 cm in greatest dimension and limited to the thyroid
T1b	Tumor > 1 cm but ≤ 2 cm in greatest dimension and limited to the thyroid
T2	Tumor > 2 cm but ≤ 4 cm in greatest dimension and limited to the thyroid
T3	Tumor > 4 cm and limited to the thyroid
T4	Tumor is any size and has extended beyond the thyroid
T4a	Tumor has spread beyond the thyroid to nearby soft tissues, the larynx, trachea, esophagus or recurrent laryngeal nerve
T4b	The tumor has spread beyond the regions stated in T4a
N0	No evidence of regional lymph node metastasis
N1	Metastasis to regional nodes
N1a	Metastases to the central compartment: pretracheal, paratracheal and prelaryngeal nodes
N1b	Metastases beyond the central compartment, including unilateral, bilateral, contralateral or mediastinal nodes
M0	Cancer without distant metastases
M1	Cancer with distant metastases
Mx	Distant metastases not assessed.

    - AJCC Prognostic Staging Groups **(Table 3)**
        - Utilizes TNM staging to help determine prognosis
        - Age cutoff for staging of thyroid cancers increased to 55 years old (previously 45 years old) to more accurately stage low-risk patients that were in the advanced disease category

Table 3: Staging for Well Differentiated Thyroid Cancer

Papillary or Follicular Thyroid Tumors < 55 years old	
Stage 1	Any T, any N, M0

Stage II	Any T, any N, M1
Papillary or Follicular Thyroid Tumors > 55 years old	
Stage I	T1N0M0
Stage II	T2 or T3N0M0
Stage III	T4N0M0 or any T any N M1
Stage IVA	T4a, any N M0 or T1-3 N1b M0
Stage IVB	T4b, any N M0
Stage IVC	Any T, any N M1

- Clinical prognostic indicators
  - AMES: Age; Metastasis; Extent; Size of primary tumor
    - Low risk: age < 40 (M) or < 50 (F); tumor < 4 cm and within thyroid gland
    - High risk: age > 41 (M) or > 51 (F); extrathyroid invasion; size > 5 cm
  - MACIS: Metastasis; Age; Completeness of Resection; Invasion; Size of tumor
    - High risk: age > 40; invasion of thyroid gland; incomplete tumor resection; size > 4 cm
- Treatment
  - Treatment for well-differentiated thyroid cancer is total thyroidectomy (complete removal of all visible thyroid tissue)
    - Near-total thyroidectomy - surgeon may elect to leave a very small amount of thyroid tissue around the parathyroid glands or recurrent laryngeal nerve to reduce morbidity
    - Sub-total thyroidectomy - ill-defined and results in large amounts of thyroid tissue left behind
      - Not acceptable for of treatment for thyroid cancer
    - Lobectomy is not generally performed as it has a higher risk of local recurrence in most cases
      - Exception – lobectomy may be performed in papillary thyroid cancer cases where tumor size is < 1 cm
  - Radioactive iodine (RAI) I-131 ablation
    - Performed several weeks following thyroidectomy to destroy or ablate residual thyroid tissue remaining after thyroidectomy
    - RAI is performed following thyroid hormone withdrawal (THW) or recombinant human TSH (rhTSH) administration
      - THW is used to produce high levels of TSH in patients by stopping thyroid hormone pills and causing short-term hypothyroidism
      - rhTSH has been shown to maintain quality of life and reduce radiation dose delivered to the body compared with thyroid hormone withdrawal
    - RAI allows for the detection of persistent disease by total body scanning
    - RAI also improves specificity of thyroglobulin assays

        - External beam radiation therapy
            - High-energy radiation is delivered to destroy cancer cells
            - Generally performed if I-131 uptake is minimal or for medullary and anaplastic thyroid cancers
        - Neck dissection
            - Prior to thyroidectomy, the central compartment (zone VI) and lateral neck (zones II-IV) should be assessed for metastases to regional lymph nodes
            - If patient does not have biopsy-proven nodal metastases, a "prophylactic" neck dissection may be elected at the time of thyroidectomy to eliminate the need for a second additional surgery in the occasion cancer recurred and spread to regional nodes
            - Not performed for follicular thyroid cancer as metastasis to regional nodes is rare
            - May be elected in papillary thyroid cancer if there is a large primary tumor (T3/T4)
        - Treatment for stage I and II papillary or follicular thyroid cancer
            - Total thyroidectomy
            - I-131 thyroid ablation following total thyroidectomy
            - External-beam radiation therapy if I-131 uptake is minimal
        - Treatment for stage III papillary or follicular thyroid cancer
            - Total thyroidectomy + removal of involved lymph nodes or other sites of extrathyroid disease
            - I-131 thyroid ablation following total thyroidectomy if the tumor demonstrates uptake
            - External-beam radiation therapy if I-131 uptake is minimal
        - Treatment for stage IV papillary or follicular thyroid cancer
            - Surgery – total thyroidectomy and neck dissection as indicated
            - Treatment of distant metastases is usually not curative
            - Metastasis with uptake may be ablated by I-131
            - External-beam radiation therapy for local lesions that are unresponsive to RAI
            - Consider resection of limited metastases, especially if symptomatic
            - Patients unresponsive to I-131 should be considered for chemotherapy such as inhibitors of VEGF receptors
- **Medullary thyroid cancer**
    - Screen for MEN type II tumors if patient has positive *RET* mutation
        - Pheochromocytoma:
            - 24-hour urine catecholamine study + abdominal scan
        - Parathyroid adenoma:
            - Serum calcium and PTH
    - Genetic screening for family
        - *RET* proto-oncogene and MEN type II tumors
    - Staging for medullary thyroid cancer is seen in **Table 4**

Table 4: Staging of medullary thyroid cancer

Stage I	T1N0M0
Stage II	T2, T3 N0M0
Stage III	T1-3 N1a M0
Stage IVA	T4a, any N M0 or T1-T3, N1b M0
Stage IVB	T4b, any N, M0
Stage IVC	Any T, any N, M1

    - Imaging
        - Evaluate locoregional and distant metastases with MRI, PET, sestamibi and indium-labeled somatostatin scans
    - Treatment
        - Total thyroidectomy and neck dissection (as needed) with resection of any additional involved structures is recommended
        - Children with medullary thyroid cancer should undergo total thyroidectomy before the age of 2
    - Long-term follow-up with serial calcitonin and CEA is recommended
- **Anaplastic thyroid cancer**
    - Staging
        - All anaplastic thyroid tumors are classified as stage IV, regardless of tumor size, location or metastasis
        - Stage IVA: anaplastic tumor that has spread to nearby structures, T4a
        - Stage IVB: tumor has spread beyond nearby structures, T4b
        - Stage IVC: there is evidence of metastasis (any N or M)
    - Almost all cases are advanced at time of presentation with patient's having a median survival of < 6 months
    - Palliative care
        - Doxorubicin, radiation and palliative surgery (debulking and tracheostomy) can be considered to improve quality of life
- **Recurrent thyroid cancer**
    - Approximately 10% to 30% of patients develop recurrence and/or metastases
    - Approximately 80% develop recurrence with disease in the neck alone while 20% develop recurrence with distant metastases (e.g. lungs)
    - About 50% of patients operated on for recurrent tumors can be rendered free of disease with a second operation
    - Recurrences that are detected by I-131 scan and not clinically apparent can be treated with I-131 ablation with great prognosis
    - Patients with iodine-refractory advanced thyroid cancer may respond to multi-tyrosine kinase inhibitor therapy

Complications

- Thyroid cancers in general may lead to invasion of other neck structures
- Complications of thyroidectomy and/or neck dissection include:
    - Hypocalcemia (transient or permanent)

    - Recurrent or superior laryngeal nerve injury (transient or permanent)
    - Postoperative bleeding
    - Complication related to general anesthesia
- Follicular carcinoma:
    - Hyperthyroidism
- Medullary thyroid cancer:
    - Bronchial obstruction
    - Fracture
    - Spinal cord compression
    - Cushing syndrome (ACTH release from medullary carcinoma)
- Anaplastic carcinoma:
    - Airway compromise > suffocation

Practice Question

A 46-year-old female visits her primary care provider due to a thyroid nodule that she first noticed a three weeks ago and which seems to have enlarged. The patient denies heat or cold intolerance or recent change in appetite or weight. Her past medical history is significant for hypertension treated with lisinopril; the patient has no history of significant exposure to radiation. Family history is negative for thyroid disease. Blood pressure is 124/72 mm Hg and pulse is 74/min. On physical exam, her neck shows a hard, fixed, nontender nodule in the left thyroid lobe. Serum TSH level is normal. Ultrasound of the thyroid gland shows a 4-cm right lobe nodule. Fine-needle aspiration biopsy shows a large number of follicular cells dispersed in clusters and microfollicles. Which of the following additional findings would be most consistent with a diagnosis of follicular thyroid cancer in this patient?

A. Lymph node involvement
B. Presence of round microscopic calcific collections
C. Presence of Hurthle cells
D. Invasion of tumor capsule and/or blood vessels
E. Elevated serum calcitonin levels

Diagnosis of follicular thyroid cancer (FTC) is not possible by fine needle aspiration (FNA). The FNA cytologic findings are similar to the findings of a benign follicular adenoma (large number of follicular cells dispersed in clusters and microfollicles). What differentiates FTC from benign follicular adenoma is invasion of the tumor capsule and/or blood vessels. This finding is usually made on examination of a surgically excised nodule. FTC is different from most carcinomas in that it often metastasizes to distant sites hematogenously rather than through the lymphatic system.

Papillary thyroid cancer is the most common thyroid epithelial malignancy. It spreads slowly into local tissues and regional lymph nodes. Histopathology may demonstrate round calcific collections commonly referred to as psammoma bodies.

Hurthle cells are large, polygonal cells with distinct cell borders. They contain eosinophilic cytoplasm and a high content of mitochondria. These cells may be seen in FTC; however, they

are a nonspecific finding as they may also be seen in benign adenomas and Hashimoto thyroiditis.

Calcitonin is secreted by parafollicular C cells of the thyroid gland. Serum levels of calcitonin are used in the diagnosis and follow-up of medullary thyroid cancer.

Ready to get pimped

1. ***How does the presence of lymph node metastasis in well-differentiated thyroid cancer affect the prognosis?***
   Research isn't completely clear on this. Some studies demonstrate increased risk of local recurrence and low survival with nodal metastasis. Other studies demonstrate a survival difference only in patients older than 45 years old.

2. ***Is RAI used in the management of low-risk thyroid cancer patients (i.e. complete tumor resection; no nodal involvement; T1 or T2 stage I patients > 45 years)?***
   This is controversial topic without a definite answer. Most recent systematic reviews and meta-analysis suggest that RAI has no role in improving survival or recurrent rates of low-risk papillary thyroid cancer. Furthermore, long-term complications of RAI include second malignancies, sialadenitis, and lacrimal and salivary gland dysfunction. Ultimately, the decision to treat with RAI in this population of thyroid cancer patients is an individualized one.

3. ***Is lobectomy or total thyroidectomy better for patients with micropapillary thyroid cancer (< 1 cm)?***
   This is yet another controversial subject. On one hand, lobectomies are associated with less post-operative complications. On the other hand, there is a small risk of recurrence (5% to 10%) in the contralateral thyroid. In general, total thyroidectomies are often curative in patients with micropapillary thyroid cancer.

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Disorders of the Parathyroid Glands:

Background

- The superior parathyroid glands develop from the 4th pharyngeal pouch, while the inferior parathyroid glands develop from the third pharyngeal pouch along with the thymus
- Most people have 4 parathyroid glands; however, and increased or decreased number of parathyroid glands is not uncommon
- The average parathyroid gland weighs 35-50 milligrams and is 1-5 mm in diameter
- Parathyroid glands are often found in association with the poles of the thyroid gland **(Figure 1)**
    - Ectopic locations include the superior mediastinum, thymic capsule, retroesophagus, within the carotid sheath and medial to the superior thyroid pole
- Hyperparathyroidism is characterized by increased parathyroid hormone (PTH) release and may be classified as primary, secondary or tertiary hyperparathyroidism
- Hypoparathyroidism is rare and characterized by decreased parathyroid hormone (PTH) release
- We will primarily focus on hyperparathyroidism

Epidemiology

- Primary hyperparathyroidism
    - Most common in adults > 50 years old
    - 3-4x more common in females compared to males
    - Third most common endocrine disorder
- Secondary hyperparathyroidism
    - Patients with low calcium levels, particularly those with chronic kidney disease (CKD) and vitamin D deficiency are most affected
- Tertiary hyperparathyroidism
    - Most common in patients with CKD, usually following renal transplantation

Pathophysiology/Pathoanatomy

- Normal anatomy
    - Parathyroid glands are often found in association with the poles of the thyroid gland **(Figure 1)**
    - Approximately 15 % of patients can have aberrantly located parathyroid glands (e.g. carotid bifurcation)
    - Primary blood supply is from the inferior thyroid artery, or more rarely from the posterior branch of the superior thyroid artery
- Normal physiology
    - The parathyroid glands release parathyroid hormone (PTH) in response to hypocalcemia to raise blood calcium levels
    - PTH acts on the bone and kidneys to raise blood calcium levels and decrease blood phosphate levels
        - Kidney
            - Increases calcium reabsorption at the distal convoluted tubule
            - Increases activity of 1-alpha-hydroxylase which synthesizes 1,25-dihydroxyvitamin D3

        - 1,25-dihydroxyvitamin D3, in turn, increases gastrointestinal calcium and phosphate reabsorption
    - Increases excretion of phosphate
- Bone
    - Stimulates the activity of osteoclasts resulting in resorption of bone and calcium release into the blood

- Primary hyperparathyroidism
    - Caused by the overproduction of PTH resulting in hypercalcemia (high PTH, high Ca^{2+})
    - Etiology is usually due to:
        - Solitary parathyroid adenoma (85%)
        - Multiple hyperplastic glands (10% to 15%)
        - Multiple adenomas (3% to 4%)
        - Parathyroid carcinoma (< 1%)
- Secondary hyperparathyroidism
    - Caused by an overproduction of PTH in response to chronic hypocalcemia
    - Most commonly caused by CKD or dietary vitamin D deficiency
    - CKD causes secondary hyperparathyroidism through 2 mechanisms:
        - Decreased synthesis of 1,25-dihydroxyvitamin D3 > decreased blood calcium > increased PTH release
        - Decreased phosphate filtration > increased blood phosphate > decreased blood calcium (binds phosphate) > increased PTH release
    - Although chronic hypocalcemia is the stimulant for secondary hyperparathyroidism, labs may show mild hypercalcemia due to the effective compensation by PTH
    - Renal osteodystrophy
- Tertiary hyperparathyroidism
    - Results from long-term secondary hyperparathyroidism that results in autonomous parathyroid function, even when underlying causes (e.g. vitamin D deficiency) are corrected
- Familial hypocalciuric hypercalcemia
    - Inactivating mutation results in a defect in calcium-sensing receptors in multiple tissues (e.g. parathyroids, kidneys)
    - A higher blood calcium threshold is required to suppress PTH release
    - Excessive calcium reabsorption at kidneys > mild hypercalcemia and hypercalciuria with normal to increased PTH levels
- Hypoparathyroidism
    - Decreased PTH release > chronic hypocalcemia
    - Iatrogenic causes include parathyroidectomy or thyroidectomy
    - DiGeorge syndrome
        - 22q11 microdeletion > failure to develop 3rd and 4th pharyngeal pouches > absent thymus and parathyroids
- Multiple endocrine neoplasia (MEN)
    - Several distinct syndromes featuring tumors of endocrine glands, each with its own characteristic pattern; two of which include the parathyroid
    - MEN type I: pancreas, pituitary, parathyroid adenomas

- MEN type IIa: medullary carcinoma of thyroid, pheochromocytoma, parathyroid

History

- Primary/Tertiary hyperparathyroidism
  - Often asymptomatic and only discovered to have parathyroid derangement incidentally (e.g. labs)
  - May present with symptoms of hypercalcemia
  - Classic symptoms of hypercalcemia
    - "Stone, bones, groans and psychiatric overtones"
      - GI disturbance (nausea, constipation, peptic ulcer and pancreatitis)
      - Muscle weakness
      - Renal stones
      - Neuropsychiatric symptoms (depression, fatigue and memory loss)
    - Cardiac symptoms include hypertension and arrhythmia
  - Tertiary hyperparathyroidism will always be preceded by longstanding secondary hyperparathyroidism (usually associated with chronic kidney disease)
- Secondary hyperparathyroidism
  - May be asymptomatic and discovered incidentally or present with symptoms of longstanding hypocalcemia:
    - Neuropsychiatric symptoms
    - Cataracts
    - Symptoms associated with raised intracranial pressure
  - A history of CKD or lack of sun exposure is often associated with secondary hyperparathyroidism

Physical

- Primary/Tertiary hyperparathyroidism
  - Most often normal
  - In severe cases:
    - Depressed mood or flat affect (suggesting depression)
    - Pallor, coarse skin, nail changes (signs of anemia)
    - Stomach pain (peptic ulcer disease)
    - Muscle atrophy or weakness
    - Abnormal heart sounds (valvular calcifications)
    - Red and swollen joints (pseudogout)
    - Loose teeth
    - Band keratopathy
- Secondary hyperparathyroidism
  - Skin – calciphylaxis, dry and scaly skin, coarse and brittle hair
  - HEENT – cataracts
  - Extremities – look for signs of renal osteodystrophy
  - Neuro - depression

Diagnosis

- **Establishing the diagnosis**
  - Primary hyperparathyroidism

        - Increased serum total calcium and increased or very high PTH
        - Serum phosphate is decreased or low-normal
    - Secondary hyperparathyroidism
        - Hypocalcemia or normocalcemia with elevated PTH in patients with:
            - CKD
            - Vitamin D deficiency
            - Inadequate calcium intake or absorption
    - Tertiary hyperparathyroidism
        - Increased serum total calcium and elevated PTH in patients with longstanding history of secondary hyperparathyroidism (most commonly after renal transplant)
- **Differential diagnosis**
    - The differential diagnosis for primary/tertiary hyperparathyroidism involves ruling out other causes of hypercalcemia:
        - Metastatic cancer from lung, breast or prostate
        - Multiple myeloma
        - PTH-secreting tumors
            - Small cell lung cancer, ovarian cancer, thymoma
        - Granulomatous diseases
            - Sarcoidosis, tuberculosis, histoplasmosis, leprosy, Wegener
        - Drugs
            - Thiazide diuretics, lithium, theophylline, hypervitaminosis A and D
        - Immobilization
        - Milk alkali syndrome
        - Benign familial hypocalciuric hypercalcemia
        - Adrenal insufficiency
        - Hyperphosphatemia
    - The differential diagnosis for secondary hyperparathyroidism often involves ruling out other causes of hypocalcemia or hyperphosphatemia
        - Hypocalcemia
            - Hypoparathyroidism
            - Hypomagnesemia
        - Hyperphosphatemia
            - Vitamin D overdose
            - Rhabdomyolysis
            - Tumor lysis syndrome
            - Hemolysis
            - Acute leukemia

Management

- **Primary hyperparathyroidism**
    - Imaging
        - Technetium 99m sestamibi scintigraphy
            - Sestamibi localizes into the mitochondria of parathyroid cells
            - Late phase images at 2 hours allows for sestamibi to clear from the thyroid gland but not the parathyroid

        - Single adenoma detection is high with sensitivity of 100% and specificity of 90%
        - Less useful for 4-gland hyperplasia
    - Ultrasound
        - Superior than other techniques for identifying intrathyroid parathyroid adenomas as its quicker and involves no radiation
        - False positive rate is 15% to 20%
    - MRI
        - Adenomas appear with high intensity on T2-weighted images
        - Useful in identifying ectopic adenomas and in patients requiring exploration following initial surgery
- Surgical
    - Parathyroidectomy is recommended for all symptomatic patients
    - Indications for surgery in asymptomatic patients:
        - Age is < 50 years old
        - Serum calcium is > 1.0 mg/dL above the upper limit of normal
        - GFR < 60 mL/min
        - Osteoporosis (T-score ≤ -2.5 at any site) and/or previous fragility fracture or evidence of vertebral compression fracture on spine imaging
    - Intraoperative PTH monitoring
        - PTH has a half-life of 3-5 minutes
        - Goal of PTH surgery is to observe a decrease in the PTH level by more than 50% at 10 min after removal of a parathyroid adenoma or hyperplasia
        - Intraoperative PTH monitoring allows focused parathyroid surgery (i.e. one-gland surgery) can prevent unnecessary bilateral four-gland exploration
    - Surgical options include:
        - Single gland disease + positive MIBI scan: directed unilateral exploration with intraoperative PTH monitoring to assess adequacy of resection
        - MEN syndrome: bilateral cervical exploration and four-gland identification
        - Negative MIBI scan: bilateral exploration with selective biopsy of suspicious glands and intraoperative PTH monitoring to assess adequacy of resection
    - Autotransplantation of parathyroid tissue
        - Parathyroid tissue can be either autotransplanted at the time of surgery or cryopreserved for up to 18 months and transplanted later
        - Transplanted tissue usually functions within 3 months and has a success rate of 50%
        - Occurs most commonly in the sternocleidomastoid (SCM) or into the brachioradialis of the arm
    - Complications of surgery

        - Transient or permanent hypocalcemia
        - Recurrent laryngeal nerve injury
        - Post-operative hematoma or infection
- **Secondary hyperparathyroidism**
    - Management is dependent on underlying cause of secondary hyperparathyroidism
    - In general:
        - Correct hypocalcemia
        - Replete vitamin D analogues
        - Address underlying cause (e.g. CKD)
    - Consider parathyroidectomy in patients with stage 3-5D CKD if severe hyperparathyroidism (PTH] level > 800 pg/mL) does not respond to medical therapy
- **Tertiary hyperparathyroidism**
    - Mainstay of treatment is surgery
    - Bilateral neck exploration is standard of care for all patients
    - Subtotal or total parathyroidectomy with autotransplantation are the most common surgical approaches
    - Consider also performing thymectomy if an inferior gland cannot be found or if radioguided probe signals increased activity within the thymus

Complications

- Complications of primary and tertiary hyperparathyroidism include complications associated with hypercalcemia:
    - Hypercalcemic crisis (total calcium > 14 mg/dL or ionized calcium > 10 mg/dL)
    - Renal complications
        - Nephrogenic diabetes insipidus and dehydration
        - Nephrolithiasis
        - Nephrocalcinosis
    - Skeletal complications
        - Osteitis fibrosa cystica
        - Fragility fractures
        - Osteoporosis
    - Cardiovascular complications
        - Hypertension
        - Left ventricular hypertrophy
        - Impaired diastolic filling
        - Myocardial calcification
    - Proximal muscle weakness and muscular
    - Neuropsychiatric complications
        - Depression
        - Anxiety
        - Dementia
        - Sleep disturbances
    - Acute pancreatitis
- Complications of secondary hyperparathyroidism include:
    - Osteomalacia

- Bone disease
  - Renal osteodystrophy
  - Osteoporosis
  - Pathologic bone fracture
  - Bone pain
  - Osteitis fibrosa cystica
- Calciphylaxis
- Soft tissue and vascular calcifications

Practice question

A 29-year-old male visits his primary care provider after 3 months of continuous burning upper abdominal pain that is only partially relieved by OTC ranitidine or antacids. He also has experienced recent-onset constipation and excess urination. The patient reports no weight loss or decreased appetite. The patient's father has a history of hypertension, dyslipidemia, recurrent stomach ulcers and multiple kidney stones. His mother has a history of hypertension and GERD. His temperature is 36.8 C (98.2 F), blood pressure is 128/88 mm Hg, pulse is 74/min, and respirations are 12/min. Abdominal exam shows normal bowels sounds, tenderness in the epigastric region and no palpable masses. His stools are positive for occult blood. Calcium is elevated at 11.4 mg/dL. What is the likely diagnosis?

A. Sarcoidosis
B. Medullary thyroid cancer
C. Metastatic gastric cancer
D. Primary hyperparathyroidism

Out of the options given, this patient likely has primary hyperparathyroidism due to type 1 multiple endocrine neoplasia syndrome (MEN1). MEN1 is an autosomal dominant condition characterized by 3 primary tumor type ("the 3 P's"): parathyroid adenomas/hyperplasia, gastrointestinal/pancreatic endocrine tumors (e.g. gastrinoma), pituitary adenomas. The patient's constipation, polyuria and tenderness in the epigastric region in the setting of an elevated calcium level suggest symptomatic hypercalcemia, likely from primary hyperparathyroidism. An elevated PTH level would further confirm this diagnosis. His continuous burning upper abdominal pain that is only partially responsive to ranitidine and antacids is concerning for Zollinger-Ellison syndrome, which is characterized by severe and refractory peptic ulcer disease due to a gastrinoma. The patient's father's history of recurrent stomach ulcers and multiple kidney stones suggests he too may have had MEN1.

Sarcoidosis, a granulomatous disease, may cause hypercalcemia due to extra-renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. However, pulmonary symptoms are much more common than GI symptoms. Sarcoidosis also fails to explain the family history of recurrent kidney stones and peptic ulcers.

Medullary thyroid cancer is a component of MEN2 and typically presents as a thyroid nodule.

Gastric cancer can cause abdominal pain with GI ulceration and bleeding. However, it is commonly associated with weight loss, dysphagia, and early satiety. It would be rare to see gastric cancer in a patient this young. Furthermore, gastric cancer is less likely to explain the patient's hypercalcemia.

Ready to get pimped

1. ***What is the advantage of parathyroid autotransplantation in the brachioradialis over the SCM?***
   You can remove parathyroid tissue under local anesthetic if the transplant becomes hyperplastic.

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Salivary Gland Tumors:

Background

- Various benign and malignant masses may be found in a salivary gland **(Table 1)**
- Proper workup is required to "rule out" malignancy and appropriately manage salivary gland masses

Table 1: Benign and malignant tumors of the salivary glands.

Benign	Malignant
Pleomorphic adenoma*	Mucoepidermoid carcinoma^
Basal cell carcinoma	Adenoid cystic carcinoma
Warthin's tumor	Acinic cell carcinoma
Clear cell adenoma	Basal cell carcinoma
Sebaceous lymphadenoma	Epithelial-myoepithelial tumor
Oncocytoma	Hyalinizing clear cell carcinoma
Myoepithelioma	Squamous cell carcinoma
Inverted ductal papilloma	Undifferentiated carcinoma
Oncocytic papillary cystadenoma	Malignant mixed tumor
Sialadenoma papilliferum	Salivary duct carcinoma
Hemangioma	Adenocarcinoma
Monomorphic adenoma	Carcinoma ex pleomorphic adenoma
	Polymorphous low-grade adenoma
	Metastases

*****Most common benign tumor of salivary glands.
^Most common malignancy of the parotid gland.

Epidemiology

- 2% to 3% of all head and neck neoplasms

Pathophysiology/Pathoanatomy

- Normal anatomy
    - Parotid gland
        - Borders of the parotid gland
            - Medial and anterior – masseter
            - Superior – zygomatic arch
            - Posterior – Tragal cartilage and sternocleidomastoid (SCM)
            - Inferior – Ramus of the mandible and SCM
        - Arterial supply
            - External carotid artery lies medial to the parotid gland and bifurcates into the maxillary artery and superficial temporal artery, which course through the gland
        - Stensen's (Parotid) duct
            - Courses superficial to the masseter muscle and enters the oral mucosa adjacent to the second upper molar
        - Facial nerve

            - Exits the stylomastoid foramen and branches to form the postauricular auricular nerve, branch to the posterior belly of the digastric muscle and stylohyoid muscle before entering the parotid gland posteriorly
        - Glossopharyngeal nerve
            - Provides parasympathetic secretomotor innervation
    - Submandibular gland
        - Submandibular triangle
            - Region found deep and inferior to the mandible
            - Anterior border – anterior belly of the digastric muscle
            - Posterior border – posterior belly of the digastric muscle
            - Superior border – mandible
        - Wharton's (Submandibular) duct
            - Courses deep to the lingual nerve and enters the oral cavity at the anterior floor of the mouth
        - Chorda tympani nerve
            - Provides parasympathetic secretomotor innervation
    - Sublingual gland
        - Located adjacent to the lingual frenulum and superficial to the mylohyoid muscle
        - Ducts of Rivinus (minor sublingual ducts)
            - Approximately 8-20 ducts that drain the sublingual gland into the oral cavity
        - Chorda tympani nerve
            - Provides parasympathetic secretomotor innervation
- Overexpressed receptors in salivary gland tumors
    - C-kit
        - Proto-oncogene that can stimulate growth and differentiation
        - Mainly increased in adenoid cystic carcinoma (78% to 92%) and some mucoepidermoids (0% to 40%)
    - EGFR
        - Increased in adenoid cystic carcinoma (36 to 85%), mucoepidermoid (53% to 100%), adenocarcinoma (60%), salivary duct cancers (9% to 40%), and others
    - HER-2/neu
        - Involved in cell growth and differentiation
        - Increased mostly in salivary duct cancers (44% to 83%)
        - Can also be found in adenocarcinomas (14% to 21%), mucoepidermoids (0% to 38%), and adenoid cystic carcinoma (2% to 36%)
    - Androgen receptor
        - Increased in salivary duct cancers (43% to 100%) and adenocarcinomas (21%)
- Recurring translocations may produce fusion proteins in salivary gland cancers
    - t(11;19) CRTC1-MAML2
        - Seen in mucoepidermoid carcinomas (found in about 30%)
    - t(6;9) MYB-NFIB

        - Seen in adenoid cystic carcinomas
        - Estimated that 80% to 90% of adenoid cystic carcinomas have MYB activation by gene fusion
    - t(12;15) ETV-NTRK3
        - Seen in mammary analogue secretory carcinomas (found in >90%)
- Histology of mucoepidermoid carcinoma
    - Histology reveals mucinous and epidermoid cells (
    - Number of mucinous cells and the level of epidermoid differentiation determine tumor grade
    - Low-grade tumors have greater number of mucinous cells compared to well-differentiated epidermoid cells
    - High-grade tumors have a dearth of mucinous cells with a preponderance of poorly differentiated epidermoid cells
- Histology of adenoid cystic carcinoma
    - Divided into 3 histologic subtypes:
        - Tubular subtype
            - Characterized by tumor cells arranged in nests surrounded by variable amounts of eosinophilic, hyalinized stroma
            - Best prognosis
        - Cribriform subtype
            - Composed of basaloid cells arranged around multiple rounded collections of central cyst-like basophilic material
                - "Swiss-cheese" appearance
            - Occurs most frequently
            - Intermediate prognosis
        - Solid pattern
            - Contains aggregates of basaloid cells without tubular or cystic formation
            - Worst prognosis

History

- The patient may be asymptomatic
- Benign tumors usually present as slow-growing, painless masses that are non-tender, mobile, and firm
- Malignant tumors enlarge over several weeks and are frequently painless

Physical

- Tumors may cause dysarthria
- Nodal metastases may be not be palpable
- Malignant lesions may be fixed and difficult to palpate
- Malignant lesions may also cause facial nerve paralysis
- Tumor may be ulcerated
- Patient may present with neck mass

Diagnosis

- **Establishing the diagnosis**
  - Fine needle aspiration (FNA) biopsy
    - Cytologic assessment confirms diagnosis and distinguishes between malignant disease
    - Detects malignant salivary gland tumor in patients with parotid gland mass, but sensitivity too low to rule out malignancy with negative result
  - Imaging
    - Role
      - Localizes lesion
      - Assesses nature of lesion (e.g. solid or cystic)
      - Helpful in tumor staging and mapping for preoperative planning
      - Image-guided tissue sampling
    - Ultrasound
      - Best at differentiating cystic from noncystic tumors
      - However, CT is routine and MRI may be helpful
    - CT or MRI **(Figure 1)**
      - Used to identify origin of mass, as surgical approach may differ depending on origin
    - MRI is performed on…
      - any tumor showing malignant cytology, regardless of location
      - all deep lobe parotid lesions, regardless of cytology
      - sublingual and minor salivary glands, due to high likelihood of malignancy
  - The combination of FNA biopsy and imaging helps differentiate benign from malignant processes and often yields a diagnosis
- **Differential diagnosis**
  - Inflammatory conditions of salivary glands (e.g. acute suppurative sialadenitis)
  - Lymphadenopathy

Management

- **Medical**
  - Staging of salivary gland tumors **(Table 2)**
  - Management of most salivary gland tumors
    - Surgical resection +/- adjuvant radiation therapy +/- chemotherapy
    - Exception: clinical T4b or unresectable T4a
  - Adjuvant radiation therapy
    - Used for high grade histology and advanced tumors
  - Chemotherapy
    - Paclitaxel reserved for advanced stage or metastatic disease not amenable to local therapies
  - Clinical T4b or unresectable T4a disease
    - Surgery is generally not an option due to extensive nature of tumor
    - Options include definitive radiation therapy or chemoradiation therapy

Table 2: Staging of salivary gland tumors.

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 2 cm in greatest dimension without extraparenchymal extension
T2	Tumor > 2 cm but ≤ 4 cm in greatest dimension without extraparenchymal extension
T3	Tumor > 4 cm and/or having extraparenchymal extension
T4a	Moderately advanced disease; tumor invades skin, mandible, ear canal, and/or facial nerve
T4b	Very advanced disease; tumor invades skull base and/or pterygoid plates and/or encases carotid artery
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension
N2	Metastasis in a single ipsilateral node > 3 cm but ≤ 6 cm in greatest dimension
N2a	Metastasis in single ipsilateral lymph node > 3 cm but ≤ 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, ≤ 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, ≤ 6 cm in greatest dimension
N3	Metastasis in a lymph node, > 6 cm in greatest dimension

- **Surgical**
  - Salivary gland tumors are generally resected (except clinical T4b or unresectable T4a)
  - Clinically benign or clinical T1 or T2 disease
    - Surgical resection
    - Consider adjuvant radiation therapy for malignant disease
  - Clinical T3 or T4a
    - If parotid disease, perform parotidectomy
    - If other salivary gland is affected, perform surgical resection with lymph node dissection if lymph node involvement
    - Consider adjuvant radiation therapy if adenoid cystic histology or adverse features present (e.g. lymph node metastases)
  - Recurrent or persistent disease
    - Surgical resection
    - Consider definitive radiation therapy or adjuvant radiation therapy depending on the presence or absence of adverse features
  - Hayes-Martin maneuver in submandibular gland removal
    - Maneuver used to preserve the marginal mandibular nerve
    - The facial vessels that run deep to the marginal mandibular nerve are ligated before superior retraction to lift the nerve out of the surgical field
  - Parotidectomy
    - Partial parotidectomy
      - Resection of parotid pathology with a margin of normal parotid tissue
      - Standard operation for benign pathology and favorable malignancies

        - Superficial parotidectomy
            - Resection of the entire superficial lobe of parotid
            - Used for metastases to the parotid lymph nodes from skin cancers and for high grade malignant parotid tumors
        - Total parotidectomy
            - Resection of the entire parotid gland, usually with preservation of the facial nerve
        - Extracapsular parotidectomy
            - Tumor is carefully dissected along its capsule without identifying the facial nerve
            - Facial nerve monitoring is relied upon to avoid injury to the branches
        - Identifying the facial nerve is crucial for a successful parotidectomy
            - 1 cm deep and inferior to the tragal pointer
            - 6 to 8 mm anterior and inferior to the tympanomastoid suture line
            - Superior to the cephalic portion of the posterior belly of the digastric muscle
            - Superficial/lateral to the styloid process
            - Retrograde dissection after finding the marginal mandibular branch as it passes over the facial artery and vein at the anterior border of the masseter muscle
            - Retrograde dissection after finding the zygomatic branch as it courses over the zygomatic arch 2/3 of the way from the tragus to the lateral canthus of the eye
            - Mastoidectomy with anterograde nerve dissection
    - Frey syndrome
        - Gustatory sweating of the skin overlying the surgical site of a parotidectomy
        - Caused by postoperative growth of the interrupted preganglionic parasympathetic nerve fibers of the parotid into the superficial sweat glands
        - Prevent by limiting parotid dissection, placing graft material between the residual skin and parotid bed, or altering subcutaneous tissue plan flap elevation
        - Treat with botox injection, topical antiperspirants, surgery to place graft between skin and parotid bed and Jacobson's neurectomy

Complications

- Risk of malignancy
- Parotid gland lesions may cause facial nerve palsy

Ready to get pimped

1. ***What is Jacobson's neurectomy?***

Surgical interruption of Jacobson's nerve, which carries preganglionic parasympathetic nerves to the parotid. It is performed to treat Frey's syndrome, a complication of parotidectomy.

2. ***What is the role of facial nerve monitoring during parotidectomy?***
   The monitor can be useful in confirming an identified nerve. It's often used according to surgeon's preference. However, facial nerve monitoring should never be relied on as the only means of facial nerve identification. Research has shown that although it does not improve the facial prognosis in first-line parotidectomy, it does improve the facial prognosis in reoperations.

3. ***What is the role of elective neck dissection in treating a salivary gland malignancy?***
   Neck dissection may be elected in cases of high-grade tumor, advanced tumor stage, presence of facial nerve paralysis preoperatively, histologic demonstration of extraglandular spread, histologic demonstration of perilymphatic invasion or nasopharyngeal minor salivary gland malignancies. Although radiation therapy may be used instead, surgical treatment of the neck allows for accurate staging.

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Acute suppurative parotitis:

Background

- The parotid gland is a major salivary gland located behind the ramus of the mandible
- Acute suppurative parotitis refers to an acute purulent infection of the parotid gland

Epidemiology

- Common in geriatric population, especially after inciting event (e.g. hospitalization, surgery)
- Infants are also most affected with most cases occurring within the first 2 weeks of life

Pathophysiology/Pathoanatomy

- Most common causes include:
  - *Staphylococcus aureus* (50%-90% of cases)
  - *Streptococcus pneumoniae*
  - *Streptococcus pyogenes* (beta-hemolytic streptococcus)
  - *Haemophilus influenzae*
- Salivary stasis
  - Microbes may travel from the oral cavity through Stensen (parotid) duct and infect the parotid gland
  - Associated with:
    - Duct obstruction (malignancy, strictures, adhesions or sialolithiasis)
    - Dehydration
    - Medications (e.g. anticholinergics)
    - Recent surgery
    - Chemotherapy and radiation therapy

History

- Patient often presents with acute localized pain over the parotid gland
- Persistent painful swelling of whole gland with overlying skin erythema and tenderness
- Most often unilateral
- Recent surgery
  - Postoperative parotitis usually appears within 2 weeks after the procedure

Physical

- Fever, chills and malaise
- Skin over parotid gland may appear red and inflamed
- Redness, induration, heat, or edema over parotid gland or mandibular angle
- Tender to palpation
- Cervical lymphadenopathy

Diagnosis

- **Establishing the diagnosis**
  - H/P consistent with acute suppurative parotitis
  - Diagnosis confirmed by culture of purulent exudate or needle aspirate samples

        - Elucidates bacterial cause which guides antibiotic therapy
    - Imaging
        - Generally, not needed to make diagnosis but may be helpful to rule out abscess formation in the patient fails to improve after 48 hrs of antibiotic therapy
    - Blood tests
        - May help confirm presence of infection
        - White blood cell count, blood cultures, and serum amylase
- **Differential diagnosis**
    - Infectious causes
        - Viral parotitis (mumps most common)
        - Dental abscess
        - Granulomatous infections
            - Tuberculosis
            - Atypical mycobacteria
            - Actinomyces
            - *Bartonella henselae* (cat-scratch disease)
            - Toxoplasmosis
    - Non-infectious causes
        - Salivary gland stone
        - Salivary gland tumor
        - Sarcoidosis
        - Sjogren syndrome
        - Lymphoma

Management

- **Medical**
    - Treat underlying medical condition
    - Conservative management
        - Warm compresses
        - Sialagogues (e.g. citrus lozenges)
        - Massage of parotid gland
        - Hydration
    - Empiric antibiotic therapy
        - Oral amoxicillin/clavulanate
        - IV ampicillin/sulbactam
        - Dosing differs between adults and pediatric patient
    - Definitive therapy should follow empiric therapy once culture and sensitivity results return
- **Surgical**
    - Indicated if patient does not respond to medical therapy within 48 hours or there is an obstruction or abscess
    - Incision and drainage

Complications

- Chronic recurrent parotitis
- Sepsis

- Abscess
- Osteomyelitis
- Thrombophlebitis
- Extension of infection into the face or ear
- Facial nerve dysfunction

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Sialolithiasis:

Background

- A salivary gland stone (sailolith) may form resulting in obstruction of salivary flow
- Stones tend to be unilateral and most commonly affect the submandibular (72%-95%) and parotid glands (4%-28%)
- Typically presents with recurrent periprandial salivary gland pain and swelling
- Commonly results in bacterial sialadenitis

Epidemiology

- Most common cause of salivary gland obstruction affecting men and women equally
- Peak incidence at age 30-60 years
- Uncommon in children

Pathophysiology/Pathoanatomy

- Saliva contains an abundance of hydroxyapatite (main component of stones)
- Aggregates of mineralized debris can serve as a nidus promoting calculi formation, obstruction and salivary stasis
- Submandibular gland is more susceptible than the parotid gland
    - Longer, upward course of submandibular duct (Wharton duct)
    - Produces thicker, more mucoid secretions than other salivary glands
- Salivary stasis due to mechanical obstruction by stone may result in painful swelling and infection

History

- Recurrent (rather than chronic or acute) salivary gland swelling that is exacerbated by eating
- Submandibular gland frequently exhibits pain
- Fever or discharge may suggest bacterial sialadenitis

Physical

- Fever may be present if complicated by bacterial infection
- Visible stone may be present
- Diffuse submandibular and parotid swelling
    - Discrete swelling is more consistent with neoplasm
- Local skin warmth and erythema
- Gland tender to palpation
- Purulent discharge at distal end of submandibular duct
- Perform intra-oral palpation around Stensen duct for parotid glands
- Also perform a duct massage
    - No saliva > obstruction
    - Purulence > infection
- Cervical adenopathy common

Diagnosis

- **Establishing the diagnosis**
  - Diagnosis may be made if the stone is readily visible on physical exam
  - If the stone is not readily visible, ultrasound may be performed **(Figure 1)**
  - If ultrasound is negative, consider CT scan **(Figure 2)**
- **Differential diagnosis**
  - Ductal stenosis without stone obstruction
  - Fibromucinous plug
  - Intraductal polyp
  - Sjogren syndrome
  - Mucocele of salivary gland
  - Salivary gland tumors
  - Acute suppurative parotitis
  - Chronic recurrent parotitis
  - Viral infections (mumps most common)

Management

- Medical
  - Conservative management involves sialagogues, warm compresses, antibiotics and hydration
- Surgical
  - If refractory to conservative management, consider gland-reserving therapies
  - In general, approach depends on size and mobility of stone
  - Gland-preserving therapies
    - Interventional sialendoscopy
      - 76% success rate when performed alone
      - 91% success rate when performed as part of combined surgical approach
    - Laser lithotripsy
      - Laser-generated shock waves used to fragment salivary stones into smaller fragments
    - Transoral duct slitting
      - Surgical incision is made to remove calculus
  - Sialadenectomy (excision of salivary gland)
    - Considered if gland-preserving therapies fail
    - Complications include nerve injury
      - Transient/permanent facial nerve palsy after parotidectomy
      - Lingual nerve injury after submandibular gland excision

Complications

- Acute or chronic bacterial sialadenitis
- Chronic sclerosing submandibular sialadenitis
- Fistulas (sialo-cutaneous and/or sialo-oral)
- Recurrence following stone removal

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Mucocele of Salivary Gland:

Background

- Mucoceles are cyst-like lesions appearing in the mouth or on lips
- Result from dilatations of the minor salivary gland ducts due to accumulated mucous secretions and mucous extravasations into the connective tissue

Epidemiology

- Fairly common
- Children and adolescents are most affected

Pathophysiology/Pathoanatomy

- Causes by mechanical trauma, usually from repeated biting
- Rupture of obstructed or traumatized ducts causes mucin leakage and collection
- Accumulation of fluid b/w epithelium and adjacent tissue creates lesion

History

- Patient will report lesion on the lower lip or within the mouth following trauma

Physical

- Painless, slowing growing, pale, smooth, bluish-hued submucosal cysts
- Ranula
    - Simple
        - True cyst with an epithelial lining that occurs intraorally with elevation of mouth floor
    - Plunging
        - Extends cyst herniates through mylohyoid muscle to involve neck
        - Pseudocyst without epithelial lining

Diagnosis

- **Establishing the diagnosis**
    - Diagnosis is made clinically based on H/P
- **Differential diagnosis**
    - Lymphangioma
    - Dermoid cyst

Management

- **Medical**
    - Cyst may resolve if patient bites it
- **Surgical**
    - May be indicated if patient has not yet developed teeth or if mucocele becomes keratinized
    - Simple Ranula
        - Simple excision of cyst with possible removal of associated gland (low chance of recurrence)

- Plunging Ranula
  - Excision - intraoral or combined with a cervical incision and extirpation of the associated gland
  - Recurrence can occur with inadequate incision

Complications

- Complications are rare
- Keratinization may necessitate surgery

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Cancer of the Oral Cavity and Oropharynx:

Background

- Oral cavity cancers are malignant carcinomas located in the lips, buccal mucosa, anterior tongue, floor of the mouth, hard palate, upper and lower gingiva, and retromolar trigone
    - Lip cancer is sometimes considered separately because the vermillion of the lip is exposed to external environment factors (e.g. ultraviolet radiation)
- Oropharyngeal cancers are malignant carcinomas located in the base of tongue, vallecula, tonsils, pharyngeal wall, or soft palate
- Majority of oral cavity and oropharyngeal cancers are squamous cell carcinomas (SCC)
- Despite their proximity, oral cavity and oropharynx cancers often behave differently and thus are treated differently
- Historically, staging of oral cavity and oropharyngeal cancers had been the same
- As human papillomavirus (HPV) changed the evaluation and management of oropharyngeal cancer, staging of oropharyngeal cancer has also changed to reflect HPV status
- Staging of oral cavity and oropharyngeal tumors is now divided as:
    - Oral cavity and HPV-negative oropharyngeal cancer
    - HPV-positive oropharyngeal cancer
- Prognosis of HPV-positive oropharyngeal cancer is better than prognosis of HPV-negative oropharyngeal cancer

Epidemiology

- Oral cavity cancer
    - Approximately 23,000 cases are diagnosed annually in the United States with 5,300 patients dying from the cancer
    - Men are 2-4x more likely to develop cancer of the oral cavity than women
    - Incidence increases with age (average age is 62 years)
    - Tobacco and alcohol use are the principal risk factors for developing oral cavity squamous cell carcinoma
- Oropharyngeal cancer
    - Approximately 7,500 cases are diagnosed annually in the United States with 1,340 patients dying from the cancer
    - HPV-positive
        - More common in men than in women and in high-risk populations (e.g. HIV-positive)
        - Comprise > 80% of oropharyngeal SCC cases
    - HPV-negative
        - Most often associated with patients who use tobacco and/or alcohol
        - Decreasing in incidence

Pathophysiology/Pathoanatomy

- Both the oral cavity and oropharynx are lined by squamous epithelium > most common cancer is SCC

    - Other malignant tumors found in the head and neck include minor salivary gland malignancies (most commonly adenoid cystic carcinoma), sarcomas, melanoma and rarely lymphomas
- Oral cavity cancer
    - Repeated exposure of irritants (tobacco and alcohol) causes gene mutations or deletions that result in hyperplasia, followed by dysplasia or carcinoma in situ and subsequently invasive carcinoma
    - Only a small percentage (< 3%) of oral cavity cancers are truly HPV driven (contrast with oropharyngeal cancer)
    - Oral cavity premalignant clinical lesions
        - Leukoplakia; white keratotic plaque or patch that cannot be wiped off
        - Erythroplakia: red mucosal plaque with much higher malignant potential than leukoplakia
        - Oral lichen planus: lacy white lines primarily noted on buccal mucosa
- HPV-negative oropharyngeal cancer
    - Pathogenesis is like cancer of the oral cavity
- HPV-positive oropharyngeal cancer
    - Oral HPV infection spreads through replication of basal cells an incorporates early proteins (E1-E7)
    - E6 and E7 oncoproteins inactivate tumor suppressor proteins p53 and retinoblastoma (Rb), respectively, causing cyclin-dependent kinase (CDK) inhibitor 2A/multiple tumor suppressor 1 (p16) levels to increase
    - No precursor lesions have been identified in HPV-positive oropharyngeal cancer
    - HPV-positive cancer is much more common in the oropharynx (>80% of oropharyngeal cancers) than any other head and neck site, including the oral cavity, possibly due to:
        - Susceptibility of mucosa in the oropharynx
        - Deep pockets in tonsillar crypts may serve as a reservoir for HPV infection
    - HPV-16 is the most common subtype of HPV associated with oropharynx SCC
        - Types 18, 31, and 33 are also considered high-risk subtypes, but are not commonly seen in oropharyngeal cancer

History

- Oropharyngeal cancer
    - Early stage oropharyngeal cancer rarely causes symptoms, therefore patients commonly present with advanced disease
    - Common symptoms include:
        - Neck mass, sore throat or tongue, chronic dysphagia, odynophagia, referred otalgia, globus, dysarthria, hemoptysis, weight loss, change in voice
- Oral cancer
    - Patient may present with a non-healing ulcer, bleeding, pain, ill-fitting dentures
    - Locally advanced disease may result in dysarthria, dysphagia, neck mass or referred otalgia
- Both oropharyngeal and oral cavity cancers

- Increased suspicion of cancer if symptom duration > 3 weeks
- Family history
  - Ask about family history of head and neck cancer
- Social history
  - Alcohol and tobacco use
  - Multiple sexual partners

Physical

- Perform a complete head and neck exam, including a clinical oral exam
  - Most common subsites for oral cavity SCC are the lips (lower > upper) and tongue (lateral > dorsal)
  - Primary sites of oropharyngeal cancer associated with HPV are the tonsil and the base of tongue
- Look for presence of mass or ulceration in oral cavity or oropharynx
- Other findings may include:
  - Early premalignant changes (e.g. leukoplakia)
  - Bleeding
  - Loose teeth
  - Tongue deviation
- Assess for neck mass and cervical lymphadenopathy
  - Oropharyngeal cancer more likely to present with isolated neck mass without other symptoms than oral cancer
- Fiberoptic nasopharyngolaryngoscopy
  - May be helpful in the identification of lesions in the oropharynx, base of the tongue, tonsils, vocal cords and lining of the throat
  - Typically performed in the office with local anesthesia

Diagnosis

- **Establishing the diagnosis**
  - Clinical suspicion based on history and physical exam
  - Definitive diagnosis is based on imaging studies and biopsy

- **Differential diagnosis**
  - Trauma
  - Leukoplakia or erythroplakia
  - Leukoedema
  - Eosinophilic granuloma
  - Sore throat
  - Chemical injury

Management

- **TNM staging**
  - Oral cancer **(Table 1)**
    - Size of the tumor is the major factor determining T-stage
    - Nodal staging the same for most head and neck squamous cell cancers
  - Oropharyngeal SCC
    - Staging dependent on HPV status **(Tables 2 and 3)**

Table 1: Staging of cancer within the oral cavity.

Tx	No information available on primary tumor
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor < 2 cm
T2	Tumor size 2-4 cm
T3	Tumor size > 4 cm
T4a:	Moderately advanced local disease
Lip	Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face
Oral cavity	Tumor invades adjacent structures only (e.g., through cortical bone [mandible or maxilla], into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, styloglossus], maxillary sinus, skin of face) Note: superficial erosion alone of bone/tooth socket by gingival primary is not enough to classify a tumor as T4
T4b	Very advanced local disease. Tumor invades masticator space, pterygoid plates, or skull base, and/or encases internal carotid artery
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2a	Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension
M0	No distant metastases
M1	Distant metastasis

Table 2: Clinical staging of HPV-negative oropharyngeal SCC.

Tx	No information available on primary tumor
Tis	Carcinoma in situ
T1	Tumor < 2 cm
T2	Tumor size 2-4 cm
T3	Tumor size > 4 cm
T4a:	Moderately advanced local disease: tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate or mandible
T4b	Very advanced local disease: tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base, and/or encases internal carotid artery
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension

N2a	Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension
M0	No distant metastases
M1	Distant metastasis

Table 3: Clinical staging of HPV-positive oropharyngeal SCC.

Tx	No information available on primary tumor
T0	No evidence of primary tumor
T1	Tumor < 2 cm
T2	Tumor size 2-4 cm
T3	Tumor size > 4 cm
T4a	Moderately advanced local disease: tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate or mandible
T4b	Very advanced local disease: tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base, and/or encases internal carotid artery
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2a	Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm
N2b	Metastasis in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension
N3a	Metastasis in a lymph node > 6 cm in greatest dimension
N3b	Metastasis in any nodes

- **Initial workup**
  - Labs
    - Complete blood count and comprehensive metabolic panel
    - p16 immunohistochemistry on pathologic specimens and is commonly utilized as a surrogate marker for HPV-positive tumors
  - Imaging
    - CT, MRI or both imaging modalities are often utilized for tumor detection and to determine extension of the lesion
    - MRI with gadolinium is especially useful if dental artifact on CT scan obscures view of tumor
    - Chest radiograph may be used to evaluate distant metastasis or second primary malignancy
      - CT chest and PET/CT may alternatively be utilized
    - Use of PET/CT as the primary staging imaging modality for all head and neck cancer patients is generally not favored
  - Tissue biopsy

        - Fine-needle aspiration (FNA) biopsy is highly sensitive, specific, and accurate for the initial histologic diagnosis
        - If cervical node biopsy is needed, complete nodal resection is preferable to prevent extracapsular metastatic spread and tumor spillage, which would require more radical treatment
    - Dental evaluation
        - Establishes baseline prior to radiotherapy
- **Treatment**
    - Oral cavity cancer
        - First-line therapy for early oral cavity cancer is surgical resection of primary tumor
            - A margin of normal tissue is often excised during lesion removal
            - Generally accepted pathologically negative margin is 5 mm
            - Due to tissue shrinkage, clinical margins measured and excised by the surgeon intraoperatively are 1 to 1.5 cm
        - Post-operative adjuvant therapy
            - Includes radiotherapy or chemotherapy
            - Recommended for all patients at intermediate to high risk of locoregional recurrence
            - Tumor factors that increase risk of locoregional recurrence
                - Locally advance T3 or T4 lesions
                - High-grade histology
                - Presence of perineural invasion or lymphovascular invasion on pathology
                - Infiltrating rather than pushing borders of tumor
                - Positive or close (< 5 mm on pathologic specimen) margins of surgical resection
                - Surgeon concern regarding adequacy of resection regardless of histologic surgical margins
            - Nodal factors that increase risk of locoregional recurrence
                - N stage higher than N1
                - Surgical contamination (excisional or incisional nodal biopsy prior to definitive surgery)
                - Presence of extracapsular extension
    - Oropharyngeal cancer
        - Currently, there is a lack of data to recommend changes in treatment or less-intensive treatment for HPV-associated disease based on HPV positivity
        - Oropharyngeal cancer is commonly treated primarily with radiation +/- chemotherapy
            - Nonsurgical treatment of oropharyngeal cancer provides similar oncologic outcomes to surgery with postoperative radiation and significantly less morbidity
            - Contrast with oral cavity cancer where surgical excision is the first-line treatment
        - Transoral Robotic Surgery (TORS)

- TORS has shown efficacy with both early and advanced-stage oropharyngeal cancer

Complications

- Disease-related complications
  - Dysphagia
  - Difficulty speaking
- Radiation therapy-related complications
  - Mucositis
  - Xerostomia
  - Dysphagia
  - Radiation-induced malignancy

Ready to get pimped

1. ***Where in the neck does regional metastases of oral cavity SCC most commonly spread appear?***
   Regional nodal disease from oral cavity SCC commonly presents in the upper cervical nodes: level I, level II and level III **(Figure 1).** Elective nodal dissection in patients with oral cavity SCC commonly involves these levels (i.e. supraomohyoid neck dissection).

2. ***What is the primary lymphatic drainage of the oropharynx?***
   Lymphatic drainage is primarily to the jugular lymphatics in level II, III, and IV **(Figure 1).** Nodal metastases are most commonly seen in level II.

3. ***How does the presence of cervical node metastases affect overall prognosis for oral cavity and oropharynx cancer?***
   Cervical node metastasis is associated with worse prognosis, with survival rates diminished by up to 50% compared with patients lacking cervical nodal disease.

4. ***How do oral and pharyngeal neoplasms refer pain to the ipsilateral ear?***
   Otalgia is referred from the pharynx by CNs IX and X, which also provides sensory innervation to the ear. The floor of the mouth and tongue are innervated by the lingual branch of CN V3. CN V3 also provides sensation to the external auditory canal, tympanic membrane and temporomandibular joint via the auriculotemporal nerve.

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Laryngeal Cancer

Background

- Laryngeal cancer is the 2nd most common cancer of the head and neck (1st is oral cavity/oropharynx) representing about one-third of all head and neck cancers
- Most often diagnosed in patients with significant smoking history
- Laryngeal cancers can involve different subsites of the larynx leading to differences in presentation, patterns of spread, staging and treatment

Epidemiology

- About 12,370 new cases of laryngeal cancer annually
- About 30% of laryngeal cancer cases will result in death due to laryngeal cancer
- Laryngeal cancer affects men almost 4x more often than women
- Mean age of a laryngeal cancer patient is 65 years
- Laryngeal cancer most commonly arises in the glottis (60%), followed by supraglottis (38%) and subglottis (2%)
- Tobacco and alcohol are the primary risk factors for laryngeal cancer.

Pathophysiology/Pathoanatomy

- Normal larynx anatomy
    - Divided into 3 regions **(Figure 1)**
        - Supraglottis
            - Can be thought of as a 3-D box containing a suprahyoid and infrahyoid epiglottis, the aryepiglottic folds, arytenoids, ventricles and false vocal cords
            - Extends from tip of the epiglottis and superior edge of the aryepiglottic folds to a horizontal plane passing through the lateral margin of the ventricle and ending at the superior surface of the true vocal folds
            - Bilateral lymphatic drainage to the upper and middle jugular lymph nodes
        - Glottis
            - Begins at the superior surface of the true vocal fold and extends inferiorly 1 cm
            - Laterally bordered by the thyroid cartilage with the lateral ventricle coming to the superior most extent
            - Contains superior and posterior commissures
        - Subglottis
            - Begins at the inferior border of the glottis (1 cm below the supraglottis) and ends at the inferior border of the cricoid cartilage
    - Paraglottic space
        - Fibrofatty-filled space
        - Medial boundary: conus elasticus and quadrangular membrane
        - Lateral boundary: thyrohyoid membrane and thyroid cartilage lamina
        - Posterior boundary: medial mucosa of the piriform sinus

- Pre-epiglottic space
  - Fibrofatty-filled space
  - Superior boundary: hypoepiglottic ligament
  - Anterior boundary: thyrohyoid membrane and thyroid cartilage
  - Posterior boundary: epiglottis and thyroepiglottic membrane
- Innervation
  - The larynx is innervated by the superior laryngeal nerve and the recurrent laryngeal nerve **(Table 1)**

Table 1: The larynx is innervated by the superior laryngeal nerve and recurrent laryngeal nerve, both of which branch from the vagus nerve at different locations.

	Superior laryngeal nerve	**Recurrent laryngeal nerve**
Branches from	Vagus nerve Origin—base of skull, level of jugular foramen	Vagus nerve Origin—R side: subclavian; L side: arch of aorta
Sensory innervation	Larynx above vocal cords; pyriform sinus	Larynx at/below vocal cords
Motor Innervation	Cricothyroid muscle (external branch)	All other intrinsic laryngeal muscles

- Blood supply
  - External carotid artery > superior thyroid artery > larynx
  - Subclavian artery > thyrocervical trunk > inferior thyroid artery > larynx
- Lymphatic drainage
  - Levels II, III and IV **(Figure 2)**
- Muscle groups that act on the larynx
  - Intrinsic – includes muscles of the vocal cords and cartilages contained within the larynx
  - Extrinsic – infrahyoid (strap) muscles and pharyngeal constrictors; responsible for laryngeal elevation and pharyngeal constriction

- Normal hypopharynx anatomy
  - Piriform sinus
    - Inferior extent of hypopharynx
    - Typically subdivided into anterior, lateral, posterior, and apical walls
    - Medial boundary: larynx, aryepiglottic folds, arytenoids and cricoid
  - Postcricoid space
    - From the posterior aspect of the arytenoids to the esophageal introitis
    - Anterior to the posterior pharyngeal wall
  - Posterior pharyngeal wall
    - Extends from the level of the hyoid bone to the cricopharyngeus muscle
- Laryngeal cancer
  - Most cases are well-differentiated squamous cell carcinoma (SCC)

- Minority of cases involve other carcinomas including verrucous carcinoma, spindle cell carcinoma, and neuroendocrine carcinoma
    - Verrucous carcinoma
        - Warty in appearance
        - Low metastatic potential
        - Histopathology demonstrates well-deafferented tissue with rete pegs
    - Spindle cell carcinoma
        - Many spindle cells
        - May be confused with sarcoma
- Supraglottic laryngeal cancer
    - May be further divided into suprahyoid and infrahyoid epiglottic tumors
        - Suprahyoid epiglottic tumors
            - May grow exophytically and superiorly
            - May alternatively invade inferiorly into the tip of the epiglottis and destroy associated cartilage
        - Infrahyoid epiglottic tumors
            - Tend to grow circumferentially and involve the aryepiglottic folds
            - Can infiltrate inferiorly into the false vocal cords
            - May also invade anteriorly into the preepiglottic fat space and subsequently the vallecula and base of the tongue
    - Cancer may spread to lymph node levels II, III, and IV
        - 55% of patients with supraglottic laryngeal cancer present with nodal involvement
- Glottic laryngeal cancer
    - Typically, present confined to the anterior portion of the upper free margin of one vocal cord
    - Can induce vocal cord fixation due to mass effect
    - May involve intrinsic muscles and ligaments
    - Rarely involves the recurrent laryngeal nerve
    - Does not present a risk of lymphatic involvement due to scarce lymphatic supply
- Subglottic laryngeal cancer
    - Lymphatic drainage may collect into levels IV and VI
- Direct extension of laryngeal cancer
    - In addition to regional lymphatic spread, laryngeal cancer may also spread through local extension via the paraglottic and pre-epiglottic spaces

- Hypopharyngeal cancer
    - Piriform sinus
        - Most common site for hypopharyngeal cancer (65% to 75%)
        - Cancer may extend into subglottis, thyroid cartilage, postcricoid region or the cricoarytenoid joint
        - 75% of patients with hypopharyngeal cancer in the piriform sinus have regional metastases
    - Postcricoid space

        - Cancer may directly extend into the cricoid and involve the recurrent laryngeal nerve
    - Posterior pharyngeal wall
        - Can extend posteriorly into prevertebral tissues

History

- Patient may present with hoarseness, dysphagia, odynophagia, referred otalgia, globus sensation, weight loss or a neck mass
- Glottic cancer
    - Often present with hoarseness
    - Airway obstruction and hemoptysis are later findings
- Supraglottic cancer
    - Often present with dysphagia and odynophagia
    - Otalgia may occur due to pharyngeal extension
    - Hoarseness may occur secondary to transglottic extension or arytenoid involvement
- Subglottic cancer
    - Present with signs and symptoms of early airway obstruction (e.g. stridor)

Physical

- Perform a thorough head and neck exam
- Assess for a neck mass and enlarged lymph nodes
- Flexible fiberoptic laryngoscopy
    - Typically performed in the office with local anesthesia
    - Can help characterize lesion by location, size, endophytic/exophytic nature, vocal cord mobility and patency of airway

Diagnosis

- **Establishing the diagnosis**
    - Clinical suspicion based on history and physical exam
    - Definitive diagnosis is based on imaging studies and biopsy

- **Differential diagnosis**
    - Laryngoceles or other laryngeal cysts
    - Epiglottitis
    - Croup
    - Granulomatous reaction to tuberculosis, leprosy or syphilis
    - Relapsing polychondritis

Management

- **TNM staging**
    - Staging is based on site of origin in the supraglottis, glottis or subglottis **(Table 2)**
    - Regional nodal involvement and distant metastases are staged similarly to other sites in the head and neck

Supraglottis	**T1**	Limited to one subsite, with normal vocal cord mobility

	T2	Invades mucosa of more than one adjacent subsite of the supraglottis or glottis or a region outside the supraglottis, without fixation of larynx
	T3	Limited to the larynx with vocal cord fixation and/or invasion of the postcricoid area, pre-epiglottic tissues, paraglottic space, and/or erosion of the inner laminae of the thyroid cartilage
	T4a	Invades through the thyroid cartilage and/or tissues beyond the larynx
	T4b	Invades the prevertebral space, encases the carotid artery, or invades the mediastinal structures
Glottis	**T1a**	Limited to one vocal cord
	T1b	Involves both vocal cords
	T2	Extends to the supraglottis and/or subglottis, and/or with impaired cord mobility
	T3	Limited to the larynx with vocal cord fixation or involvement of the inner layer of cartilage
	T4a	Invades through the thyroid cartilage and/or tissues beyond the larynx
	T4b	Invades the prevertebral space, encases the carotid artery, or invades the mediastinal structures
Subglottis	**T1**	Limited to the subglottis
	T2	Extends to the vocal cord(s) with normal/impaired mobility
	T3	Limited to the larynx with vocal cord fixation
	T4a	Invades the cricoid or thyroid cartilage and/or tissues beyond the larynx
	T4b	Invades the prevertebral space, encases the carotid artery, or invades the mediastinal structures

- **Workup**
  - Biopsy
    - Frequently used to make an initial tissue diagnosis when patient presents with neck mass
    - May be done in the office using fiberoptic laryngoscope and topical anesthesia
    - Alternatively, may be done via direct laryngoscopy under general anesthesia
  - Imaging
    - Imaging used to assess the degree of local infiltration, involvement of regional lymph nodes and presence of distant metastases or second primary tumors
    - If glottic cancer with no nodal metastases, then imaging is not required
    - In cases other than T1 glottic primary, imaging should be obtained
    - CT of the neck is most frequently utilized
    - MRI may be more sensitive in differentiating soft tissue and cartilage involvement
    - PET-CT may be used to evaluate for metastases (and recurrence following treatment)
    - Chest radiograph should be obtained to evaluate for metastases
      - If chest radiograph is abnormal, order a chest CT

- Lung lesions can either be from metastases or a second primary tumor (smoking is a common risk factor)

- **General treatment**
  - Early Stage (I and II)
    - Either surgery OR radiation
  - Advanced Stage (III and IV)
    - Surgery AND radiation
      - T3 and T4 tumors: total laryngectomy, chemotherapy and radiation
      - T1, T2, and sometimes T3: partial laryngectomy
    - Radiation should start within 6 weeks of surgery and last for 6-7 weeks
      - Side effects of radiation include:
        - Mucositis
        - Chronic xerostomia
        - Less common: radionecrosis, esophageal stricture, hypothyroidism
  - Treatment of the Neck
    - If risk of nodal metastasis > 15 %, should treat even if no apparent nodal metastases
    - N0 or N1: either surgery or irradiation
      - Neck dissection helpful in regards to prognostication
    - N2 or N3: combined modality treatment
- **Surgical treatment for early laryngeal cancer**
  - Options include conservation surgery, transoral robotic surgery, transoral laser surgery and open surgery
  - Contraindications to conservation surgery:
    - More than 5 mm of subglottic extension
    - Extension into the postcricoid space
    - Involvement of the base of tongue or piriform sinus
    - Cartilage invasion
      - Bilateral vocal cord fixation
    - Bilateral arytenoid involvement
  - Glottic T1a tumors may be treated with cordectomy
  - Larger T1 or T2 lesions may be treated with vertical partial laryngectomy through an open or transoral approach
  - Supraglottic T1 and T2 lesions may be treated with supraglottic laryngectomy
- **Hemilaryngectomy, vertical partial laryngectomy and supraglottic (horizontal) laryngectomy**
  - Goal of hemilaryngectomy and vertical partial laryngectomy:
    - Remove cancer yet still maintain the three primary functions of the larynx: breathing, swallowing, and phonating
  - Hemilaryngectomy
    - Removes the anterior soft parts of the larynx in continuity with the underlying thyroid cartilage

- Vertical partial laryngectomy
  - Like hemilaryngectomy but may include modifiers to more specifically define the extent of laryngeal removal
  - Laterovertical partial laryngectomy – a standard hemilaryngectomy wherein a vocal cord, up to the anterior commissure, is resected with underlying cartilage extending posteriorly to include part of the arytenoid if necessary
  - Anterovertical partial laryngectomy - includes resection of the anterior commissure, which generally requires that part of the contralateral vocal cord to be resected as well
    - Larger resection including both the anterior commissure, ipsilateral vocal cord, and underlying cartilage
- Supraglottic laryngectomy
  - Performed with cancer involving the glottic larynx that extends beyond that encompassed by strictly defined vertical partial laryngectomy
  - Designed to preserve voice in those whose cancers are located at the anterior glottis or those with extensive pre-epiglottic space involvement
  - Removes the bilateral supraglottis but spares the true vocal folds and arytenoids
  - Half of patients remain dependent on tracheotomy

Complications

- Complications of laryngeal cancer
  - Dysphagia
  - Dysarthria
  - Metastatic spread (locally and distantly)
- Complications of treatment
  - Vocal problems
    - Hoarseness, raspy and rough voices common
    - Failure with tracheoesophageal speech
  - Swallowing problems
    - Aspiration after partial laryngectomy
    - Xerostomia from radiation therapy
    - Due to surgical scarring
  - Loss of taste and smell
    - Radiation can permanently damage taste buds
    - Lack of airflow through nose and mouth due to anatomic changes from total laryngectomy
  - Fistula development
    - Connection between pharynx and skin of neck
    - Failure of pharyngeal surgical closure to seal after laryngectomy
    - Leakage of pharyngeal contents into the neck
    - Initial fluid collection ruptures → leakage of mucoid and fluid material onto the skin
  - Airway problems

        - Can have significant aspiration or inadequate airway→ become dependent on tracheostoma
        - Excessive laryngeal edema
        - Total laryngectomy: excessive secretions and crusting mucus can occlude the tracheostoma
    - Cranial Nerve Injury
        - Risk of injury to VII, IX, X, XI and XII during partial or total laryngectomy
    - Hypothyroidism
        - Can be caused by lower anterior neck radiation or de-vascularization during surgery

Ready to get pimped

1. ***How does smoking affect recurrence of laryngeal cancer?***
   Patients who continue to smoke throughout their treatment of laryngeal cancer are at a greater risk of recurrence and development of a second primary lesion.

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