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Introduction

Pharyngitis is defined as inflammation of the mucous membranes and submucosal structures of the pharynx. It accounts for over 40 million visits by adults to medical facilities each year in the U.S. More prescriptions are written for treatment of pharyngitis than any other respiratory infection including pneumonia and otitis.

A sore throat is one of the most common chief complaints encountered by an otolaryngologist. Most have a viral infection and are self-treated with over-the-counter preparations. The majorities who seek medical attention are diagnosed by clinical evaluation and respond to treatment with antibiotics or symptomatic medication, or they resolve with time. However, the pharyngeal mucosa exhibits a brisk inflammatory response to many other agents including opportunistic bacteria, fungal overgrowth, environmental pollutants, neoplasm, granulomatous diseases, and chemical or physical irritants. A sore throat of greater than 2 weeks duration, raises the possibility of additional, more sinister diagnoses.

The discussion of pharyngitis encompasses a broad range of illnesses. This review will address primarily the infections causes of pharyngitis and touch on the more common granulomatous diseases that may involve the pharynx. Clinical manifestations of tonsillitis, adenoiditis, laryngitis and deep space neck infection overlap those of pharyngitis, however, these topics are discussed in detail in other grand rounds.

Pharyngeal Anatomy

The pharynx is the continuation of the digestive and respiratory system from the

oral cavity and nose. It is a funnel-shaped fibromuscular tube, approximately 15 cm long, that is the common route for air and food. In its superior part, the pharynx receives the posterior opening of the nasal cavities called choanae. The pharynx is located posterior to the nasal and oral cavities and the larynx. The pharynx is divided into three parts: (1) the nasopharynx bounded superiorly by the skull base and choanae and inferiorly by the soft palate; (2) the oropharynx bounded superiorly by the soft palate and inferiorly by the base of tongue; and (3) the laryngopharynx or hypopharynx bounded superiorly by the base of tongue and inferiorly by the inferior border of the cricoid cartilage at approximately the level of the 6th cervical vertebrae. The widest portion of the pharynx (about 5 cm) is opposite the hyoid bone and its narrowest point is the most inferior aspect where it is continuous with the esophagus.

The pharyngeal wall is composed of five layers. From superficial to deep, they are: (1) a mucous membrane covered with pseudostratified ciliated epithelium superiorly and stratified squamous epithelium inferiorly; (2) a submucosa; (3) a fibrous layer forming the pharyngobasilar fascia, which is attached to the skull; (4) a muscular layer composed of inner longitudinal and outer circular parts; and (5) a loose connective tissue layer forming the buccopharyngeal fascia which is continuous with the fascia covering the buccinator and pharyngeal muscles and contains the pharyngeal plexus of nerves and veins.

There are six muscles in the pharynx, three overlapping constrictor muscles and three muscles that descend from the styloid process, the cartilaginous part of the auditory tube, and the soft palate. The external circular part of the muscular layer of the wall of the pharynx is formed by the paired superior, middle, and inferior constrictor muscles. The superior constrictor is innermost progressing to the inferior constrictor, which is outermost. All three contract involuntarily in a way that results in contraction taking place sequentially from the superior to the inferior end of the pharynx. The internal longitudinal muscles of the pharynx include the stylopharyngeus, palatopharyngeus, and the salpingopharyngeus muscle, which all function in elevating the larynx during swallowing and speaking. The salpingopharyngeus muscle originates from the cartilaginous part of the auditory tube and descends the lateral wall of the pharynx where it is covered by the salpingopharyngeal fold of mucous membrane. It has the added function of opening the pharyngeal orifice of the auditory tube during swallowing. All the muscles of the pharynx except the stylopharyngeus are innervated by the pharyngeal plexus of nerves, which run along the lateral aspect of the pharynx. The plexus is formed by the vagus (CN X) and glossopharyngeal (CN IX) nerves and by sympathetic branches from the superior cervical ganglion. The motor fibers in the pharyngeal plexus are derived from the cranial root of CN XI (the accessory nerve), and are carried by the vagus nerve to all muscles of the pharynx and soft palate, except the stylopharyngeus (supplied by CN IX) and the tensor veli palatini (supplied by CN V3).

The blood supply to the pharynx is derived primarily from branches of the external carotid artery. These include the ascending pharyngeal artery, dorsal branches from the lingual artery, tonsillar branches of the facial artery, and palatine branches from

the maxillary artery.

The retropharyngeal lymph nodes are the primary drainage site for the pharyngeal lymphatics. The nasopharynx empties to retropharyngeal lymph nodes and proceeds to the lateral pharyngeal and deep jugular nodal chains. The oropharynx drains to the superior deep cervical and jugular nodes and the hypopharynx drains to the lateral pharyngeal, deep cervical, and jugular nodes.

Evaluation

History

The chief complaint of pharyngitis is sore throat. Other local symptoms- throat scratchiness, coryza, cough, and irritation-are also common in pharyngitis, particularly in pharyngitis of viral origin. As with any symptom, the onset, duration, severity, and relieving and exacerbating factors are important to elicit. The medical history should also note the concurrence of similar symptoms within the patient's family as well as the community at large (1). In addition, the routine complete discussion of other significant medical problems (particularly history of acquired immunodeficiency syndrome (AIDS) diabetes, and other immunodeficiency disorders), past surgeries (particularly of the head and neck), history of previous irradiation to the head and neck area, current medications, and social history including tobacco, alcohol, and intravenous drug use, sexual practices, and home environment should be elicited.

Physical Exam

A full head and neck exam should be performed on any patient with complaint of sore throat with particular attention towards the neck, oral cavity, pharynx, and larynx. The neck exam often reveals cervical adenopathy. In addition, the thyroid should be palpated as inflammatory diseases of the thyroid gland may give patients the sensation of sore throat. The oral cavity and oropharynx should be examined for hypertrophy of lymphoid tissue, mucosal congestion, erythema, and exudate. Deviation of the uvula and anterior tonsillar pillar with erythema may indicate peritonsillar abscess. Bulges in the posterior pharyngeal mucosa may be suggestive of other suppurative processes. Indirect laryngoscopy (IDL) should be performed on all patients. If the patient is uncooperative, flexible laryngoscopy should be done. Nasal endoscopy may reveal signs of sinusitis such as purulence at the middle meatus, frontal recess or sphenoid ostium. Postnasal drip is a well-known cause of secondary pharyngitis because of irritation. The nasopharynx may be examined for visualization of the adenoids, torus tubaris, and the fossa of Rosenmuller.

Etiology

- I. Inflammatory**
 - Infectious
 - Viral

Common cold (coronavirus, rhinovirus)
Influenza
Herpes Simplex Virus
Varicella Zoster Virus
Epstein-Barr
Bacterial
Streptococcal (*S. pyogenes*, *S. pneumoniae*)
Haemophilus influenzae
Moraxella catarrhalis
Staphylococcus aureus
Anaerobes
Mycoplasma pneumoniae
Chlamydia pneumoniae
Bordetella pertussis
Rhinoscleroma (*Kebsiella rhinoscleromatis*)
Syphilis (*Treponema pallidum*)
Corynebacterium diphtheriae
Fungal
Candida albicans and other fungi
Allergy
Autoimmune (Wegener's, Hashimoto's, relapsing polychondritis)
AIDS
Sarcoidosis
Xerostomia
Postradiation
Sjogren's
Pharmacologic
Mouth breathing

II. Traumatic

Intraluminal tears
Foreign body
Caustic or irritant ingestion
Inhalation of irritant
Gastroesophageal reflux
External neck trauma

III. Neoplastic

Pediatric (Leukemia, Lymphoma, Rhabdomyosarcoma)
Adult (Squamous cell carcinoma, Lymphoma)
Congenital (Branchial cleft cyst; Thyroglossal duct cyst or lingual thyroid)

IV. Nutritional

Vitamin deficiency (A, B-complex, C)
Dehydration

V. Degenerative

Cervical spondylosis
Zenker's diverticulum
Cricopharyngeal Achalasia

VI. Miscellaneous

Temporomandibular joint pain
Elongated styloid (Eagle's syndrome)
Carotidynia
Coronary artery disease (angina pectoris)
Globus pharyngitis
Esophageal spasm
Glossopharyngeal neuralgia
Psychiatric
Self-mutilation
Factitious
Psychosomatic

Infectious causes of Pharyngitis

Viruses

The viruses that are major causes of acute respiratory disease include influenza virus, parainfluenza viruses, rhinoviruses, adenoviruses, respiratory syncytial virus, and respiratory coronaviruses. Viruses have been isolated in 12%-42% of patients with pharyngitis or tonsillitis (Huoven). The most common agents in pharyngitis are the rhinovirus and coronavirus, but adenovirus, parainfluenza viruses, and influenza viruses also have predilection for the pharynx.

Rhinovirus and coronavirus are both single stranded, positive-sense RNA picornaviruses. There are multiple serotypes of each of these viruses. They are distinguished from enteroviruses by having an optimum temperature of 33o C for in vitro replication. This temperature approximates that of the nasopharynx in the human host and may be a factor in the localization of pathologic findings at that site. The natural course of pharyngitis due to these viruses is usually self-limited and treatment is symptomatic. Because the clinical signs and symptoms may be identical to bacterial etiologies and cultures for viruses are not usually done, it is necessary to perform the usual work-up to rule-out treatable causes.

Epstein-Barr Virus

Epstein-Barr virus (EBV) is the etiologic agent of infectious mononucleosis (IM). It is a member of the group Herpesvirus (Herpes virus 4) and is a large-enveloped, double-stranded DNA virus (Sherris). EBV selectively infects B-lymphocyte populations (Thompson). Most early infection with EBV are asymptomatic; clinically apparent EBV infection occurs most frequently in populations in which primary EBV exposure has been

delayed until the second decade of life. The disease is thus seen most often in young adults. It is defined by the clinical triad of fever, lymphadenopathy, and pharyngitis combined with the transient appearance of heterophil antibodies and atypical lymphocytosis. Other clinical findings are splenomegaly (in 50%), infrequently hepatomegaly, and dermatologic finds (in 5%) including; macular, petechial, scarlatiniform, urticarial, or erythema multiforme-like rash. Symptoms may last for weeks to months. IM should be suspected if a sore throat and malaise persist despite antibiotic treatment. A white membrane covering one or both tonsils is characteristic. Hypersensitivity to ampicillin is increased in infectious mononucleosis and the antibiotic should be avoided: a severe urticaria follows its use in 90-100% of infected individuals.

Complications of IM include autoimmune hemolytic anemia, cranial nerve palsies, encephalitis, hepatitis, pericarditis and airway obstruction. Although this infection is rarely fatal, the most frequent causes of death in previously healthy individuals with primary EBV are neurologic complications, airway obstruction, and splenic rupture.

Diagnosis of IM is usually not difficult. The constellation of fever pharyngitis, and lymphadenopathy coupled with and atypical lymphocytosis and heterophil antibodies (detected by commercial tests – Monospot test) is virtually always due to primary EBV infection and require no further studies. The circulating lymphocytes are mostly T-cells reacting to the infected B lymphocytes (Thompson). Heterophil antibodies are demonstrated in 50% of children and 90-95% of adolescents and adults with mononucleosis. If IM is suspected in a young patient with negative heterophil antibodies, the presence of IgM antibodies to EBV viral capsid antigen (VCA) is diagnostic. A drop in heterophil titers indicates resolution of the acute illness. If a patient is not improving after several weeks, heterophil titers should be drawn.

Treatment of IM usually requires only supportive management. Patients should be advised to obtain adequate rest and avoid contact sports should be avoided for 6-8 weeks to avoid splenic rupture. Glucocorticoids may hasten defervescence and the resolution of pharyngitis, however, they are only indicated for certain specific complications including airway obstruction, hemolytic anemia and thrombocytopenia. They do not alter the course of neurologic complications.

Cytomegalovirus

Cytomegalovirus (Herpes virus 5) is ubiquitous, and in the developed countries approximately 50% of adults have antibodies to it. 10-15% of children are infected by CMV by the age of 5 years. Primary cytomegalovirus (CMV) infection is the illness most frequently confused with EBV-induced IM virus. About two-thirds of adults with heterophil-negative mononucleosis have CMV-induced mononucleosis. Patients with this illness are usually older than those with EBV IM. Fever and malaise seem to be the predominant presenting symptoms with pharyngitis and lymphadenopathy being less common. The diagnosis is made by isolating CMV from the blood or showing a 4 fold rise or greater in antibody titer to CMV. CMV is a common infection in patients with HIV. The pharynx may be involved, but esophagitis is more common.

Herpes Simplex Virus

The term herpes (from the Greek herpein, “to creep”) and the clinical description of cold sores date back to Hippocrates. Two distinct epidemiologic and antigenic types of herpes simplex virus (HSV) exist (HSV-1 and HSV-2). Although both types can be involved in infections of the upper aerodigestive tract, infection with HSV-1 is usually “above the waist” while HSV-2 usually involves areas “below the waist”. HSV infection occurs in both primary and recurrent forms. It is transferred through directed contact with mucus or saliva.

The clinical manifestations and course of HSV depend on the anatomic site of the infection, the age and immune status of the host. First episodes of HSV disease, especially primary infections (i.e. first infections in which the host lacks HSV antibodies in acute-phase serum), are frequently accompanied by systemic signs and symptoms, involve both mucosal and extramucosal sites, and have a longer duration of symptoms, a longer time during which virus is isolated from lesions, and higher rate of complications than recurrent episodes of disease. Gingivostomatitis and pharyngitis are the most frequent clinical manifestations of first-episode HSV-1 infection. These infections are usually seen in children and young adults. Clinical symptoms and signs include fever, malaise, myalgias, anorexia, irritability, and cervical adenopathy, which may last from 3-14 days. Physical exam usually reveals grouped or single vesicular lesions on an erythematous base involving the buccal mucosa and hard and soft palate that become pustular and coalesce to form single or multiple ulcers. HSV of the pharynx usually results in exudative or ulcerative lesions of the posterior pharynx and/or tonsillar pillars. The acute illness evolves over 7-10 days, followed by rapid regression of symptoms and resolution of the lesions. On mucosal surfaces the lesions reepithelialize directly. No substantial evidence suggests that reactivation of oral-labial HSV infection is associated with symptomatic recurrent pharyngitis.

In immunosuppressed patients infection may extend deep into mucosal and submucosal layers. Friability, necrosis, bleeding, severe pain, and inability to eat or drink may result. Persistent ulcerative HSV infections are among the most common infections in patients with AIDS. These patients should be treated aggressively with intravenous acyclovir to prevent disseminated disease.

HSV can be isolated from almost all lesions. Laboratory confirmation of HSV infection is best performed by isolation of the virus in tissue culture or demonstration of HSV antigens in scrapings from lesions. Identification can be made in a variety of cell culture systems within 48 hours after inoculation. Spin-amplified culture with subsequent staining for HSV antigen has shortened the time to identification to less than 24 hours. HSV PCR techniques may be more rapid and sensitive than viral isolation.

Recommendations for treatment of HSV infections are based studies looking at herpes labialis. Those include treatment with acyclovir, 400 mg PO 5 times daily for 10 days and equally effective is valacyclovir, 1000 mg PO bid for 10 days. In one

randomized controlled trial in patients with recurrent orofacial HSV, acyclovir, 400 mg PO 5 times per day for 5 days taken early in the attack led to a reduction in duration of symptoms from 12.5 to 8.1 days. More recent studies reveal reduction in recurrent disease from 36% to 19% of patients over a year who took acyclovir, 400 mg po bid every day.

Measles

The measles virus is classified in the paramyxovirus family, genus Morbillivirus. It contains linear, negative-sense, single-stranded RNA. The highest attack rates have been in childhood, usually sparing infants less than 6 months of age because of the presence of circulating maternal antibodies. Decline in reported cases over the past several decades has been attributed to increased immunization coverage. In the first half of 1990 there were 13,787 reported cases in the U.S. compared to 167 cases in 1993 during the same months. Many cases today are due to one-dose vaccine failures or groups who do not accept immunization.

The typical illness usually begins 9-11 days after exposure, with cough coryza, conjunctivitis, and fever. One to three days after onset, pinpoint gray-white spots surrounded by erythema appear on mucous membranes. This sign, called Koplik's spots, is usually most noticeable over the buccal mucosa. Within a day of these findings, patients develop the typical measles rash, which is maculopapular and begins on the head and progresses to the trunk and extremities. The rash persists for 3-5 days and then fades. Cervical lymphadenopathy is not uncommon.

Diagnosis is made clinically in most cases. The virus can be isolated from the oropharynx and urine and grown in cell cultures, producing multinucleated giant cells as can be seen in affected tissue from the patient. Serologic studies of acute and convalescent serum samples may also be performed.

Measles is usually self-limited. Patients should be followed closely, however, to watch for signs of bacterial superinfection such as acute otitis media, sinusitis, pneumonia, mastoiditis, and sepsis. Other complications include encephalitis, acute thrombocytopenic purpura, and acute appendicitis.

Prevention of measles involves vaccination of infants with live, attenuated measles vaccine. This vaccine should be administered after the first year of life (13-15 mo) usually as a trivalent vaccine with mumps and rubella.

Human Immunodeficiency Virus

Pharyngitis in patients with human immunodeficiency virus (HIV) or AIDS is usually due to opportunistic infections such as HSV, CMV, and Candida. However, direct effects of the virus on lymphoepithelial tissues of the pharynx occur. Viral particles have been documented in the pharyngeal epithelium and tonsils.

Bacteria

Streptococci

The genus *Streptococcus* comprises species of Gram-positive spherical or oval cocci that tend to be arranged in chains. These bacteria form a significant portion of the indigenous microflora of humans and animals; most are found in the oral cavity and nasopharynx. *Streptococcus* species are classified based on their type of hemolysis (either alpha or beta). Beta-hemolytic streptococci are and further subdivided into Lancefield groups based on cell membrane carbohydrates. Lancefield group A beta hemolytic streptococcus is the most important of the pathogens causing pharyngitis. The role of other beta-hemolytic streptococci (Groups B, C, F, and G) in causing pharyngitis is yet unresolved.

Group A streptococcus is the most common bacterial cause of acute pharyngitis followed by *Streptococcus pneumoniae*, and group C streptococci. Pharyngitis caused by group A streptococcus should always be treated; however, there has been no scientific evidence that treatment of non-group-A streptococci is beneficial. The rationale for treating group A infections are as follows: (1) relief from symptoms related to the infection – the main reason patients seek medical care; (2) treatment has led to a decrease in cases of rheumatic fever, (3) treatment can prevent suppurative sequelae, and (4) also prevents the further spread of the group A streptococcus in the community.

The typical presentation of Streptococcal pharyngitis is usually indistinguishable from non-streptococcal pharyngitis (usually viral) including sore throat, erythema of involved tissues with or without purulent exudate. Thus unless the physician is able to confidently exclude the diagnosis of streptococcal pharyngitis on epidemiological and clinical ground, a laboratory test should be performed to determine whether group A streptococci are present in the pharynx.

Methods to detect group A streptococcus include rapid antigen detection tests (RADTs) for the direct identification of group A streptococci from the pharynx, the overnight slide-culture test using a bacitracin disk, and the regular blood agar culture. Several rapid antigen detection kits for group A streptococci are available. The time required to obtain final results with these assays is usually about 10 minutes. These tests are highly specific but their sensitivity may be sub-optimal. Swabs of both tonsils and the posterior pharynx should be taken

The slide-culture test and the regular blood agar culture, require overnight incubation. In culture techniques, bacitracin-susceptible beta-hemolytic colonies found after incubation suggest the presence of group A streptococcus. This result, however, should be further confirmed by agglutination, using antisera for group A, B, C, D, F, and G streptococci, to avoid false-positive answers. Thus, the final result usually takes at least 2-3 days.

In the case of group A streptococcus, penicillin V for 10 days is the drug of choice. A second-choice drug (and the drug of choice for patients allergic to penicillin) is erythromycin. Ampicillin and amoxicillin have often been used to treat group A streptococcal infections. They are absorbed better than penicillin, however they have never been shown to have any advantages in the treatment of group A streptococcus. In addition, if the pharyngitis is caused by Epstein-Barr virus, ampicillin treatment may induce a whole-body rash.

Recurrent pharyngitis is often a challenging clinical problem. Several explanations have been proposed as to why penicillin treatment of group A streptococcal pharyngitis can fail: (1) Although group A streptococci are always penicillin-susceptible, tolerance (the bacteria are inhibited but not killed) has been suggested as one reason for recurrent infection. (2) Production of Beta-lactamase by staphylococci or by anaerobes such as *Bacteroides* species can inhibit the effect of penicillin in the pharynx. (3) The infection may in reality be a reinfection, e.g., from family members. (4) The peak serum levels of penicillin V vary significantly from person to person, indicating differences in the absorption of the drug. After the use of penicillin V in the first drug regimen proves ineffective, erythromycin or a second generation cephalosporin are valid choices for the second treatment. Also, dicloxacillin has been successfully used for children with recurrent streptococcal pharyngitis. Tonsillectomy is the best treatment to eliminate the series of persistent infections.

With the exception of very rare infection by certain of the other pharyngeal bacterial pathogens mentioned next (i.e.) *Corynebacterium diphtheriae* and *Neisseria gonorrhoeae*), antimicrobial therapy is of no proven benefit in the treatment of acute pharyngitis due to bacteria other than the group A streptococcus. It is therefore extremely important for physicians to be able to exclude the diagnosis of group A streptococcal pharyngitis to prevent inappropriate administration of antimicrobials to large number of patient with pharyngitis. The administration of such therapy unnecessarily exposes patients to the associated expense and hazards, and it may also contribute to the emergence of antibiotic-resistant bacteria, which is being reported with increasing frequency in the United States and elsewhere.

Neisseria gonorrhoea

Neisseria are Gram-negative diplococci. Of the two pathogenic types, *Neisseria gonorrhoea* can cause pharyngitis with exudate. Diagnosis requires a certain index of suspicion and the appropriate laboratory tests. Gonococcal pharyngitis should be suspected in those individuals with a suggestive sexual history. Gram stain revealing the presence of multiple pairs of bean-shaped, Gram-negative diplococci within a neutrophil is highly characteristic of gonorrhoea.. Sensitivity of the gram smear is 95%, however, the specificity is only 50 to 70% because of the presence of other bacteria with similar morphology. Culture should always be done. *N. gonorrhoea* grows well on chocolate agar with added carbon dioxide. Currently, rapid direct detection from pharyngeal exudate via nucleic acid probes are available and may provide results before the patient leaves the clinic. Due to the development of penicillinase-producing *N. gonorrhoea*, penicillin is no

longer used to treat gonococcal infections. Treatment of choice is 125 mg single intramuscular dose of Ceftriaxone plus Doxycycline, 100mg PO twice daily for 7 days.

Corynebacterium diphtheriae

Corynebacterium diphtheriae, the causative organism of diphtheria, produces a powerful exotoxin that is absorbed from the site of infection on the surface of the body and carried to the heart and nervous system where it causes severe damage. Human cases or carriers are the sole source of infection, which is spread by close contact. The organism is transferred by droplets or by contaminated articles. Diphtheria is especially common in children younger than 10 years of age. Although in the past, this was a common cause of pharyngitis, today it is rarely seen thanks to routine vaccination of infants and children.

C. diphtheria is a slender, non-motile, non-spore forming Gram-positive bacillus. Laryngopharyngitis due to *C. diphtheria* in the inadequately immunized patient is characterized by systemic symptoms from the diphtherial toxin production that are out of proportion to the pharyngeal examination. The patient is often fatigued, lethargic, and tachycardic beyond what might be expected from the patient's fever. Classically, there is a grayish membrane extending to the pharynx and often to the larynx rather than the tonsils. Extensive diphtheria of the throat is always accompanied by marked swelling of the neck resulting from enlargement of lymph nodes and edema of surrounding tissues. The painless swelling feels solid, and it is difficult to palpate the underlying lymph nodes. Failure to examine the throat of a patient with 'bull-neck' diphtheria may lead to a mistaken and tragic diagnosis of mumps. The child with serious diphtheria looks pale, limp, and toxic, whereas the child with mumps looks comparatively well. Moreover, the swelling of mumps lies superior to that of diphtheria and usually fills the hollow behind the angle of the mandible. Careful inspection of the throat settles the diagnosis.

Definitive diagnosis depends on the isolation of *C. diphtheriae* from local lesions. *C. diphtheriae* forms gray to black colonies on selective media containing potassium tellurite. The microbiology laboratory should be notified that diphtheria is suspected so that the appropriate culture media can be used. Polymerase chain reaction should also be performed on all primary isolates to screen for toxinogenicity.

Treatment for diphtheria is based on clinical diagnosis without definitive laboratory confirmation, since each day of delay is associated with increased mortality. First, the airway is secured and the patient is volume resuscitated. After allergy to horse serum has been ruled out by history and skin testing, the patient should be given diphtheria antitoxin. Epinephrine should be readily available. Antibiotics have little effect in treating acute wounds, however erythromycin, penicillin G, rifampin, or clindamycin is recommended by most authorities for the purpose of eradicating the carrier state in patients to prevent its spread.

Prevention by vaccination has led to diphtheria becoming an extremely rare occurrence. The vaccine is trivalent including diphtheria toxoid, tetanus toxoid and

pertussis (DTP) and is ideally administered at 6 weeks of age, then 2 subsequent doses after intervals of 4 to 8 weeks, and a fourth dose at 6-12 months after the third.

Treponema Pallidum

Treponema pallidum is the causative agent of syphilis, a venereal disease first recognized in the 16th century as an acute and often fatal disease. The discovery of *T. pallidum* in syphilitic material was made by Schaudinn and Hoffman in 1905. It is a member of the Spirochete family, which also includes other pathogenic bacteria such as *Borrelia*, *Leptospira* and *Fusobacteria* (present in the normal oropharyngeal flora). The morphology of spirochetes differ from that of other bacteria in that they have a flexible, peptidoglycan cell wall around which several axial fibrils are wound. These fibrils form a structure referred to as endoflagella.

T. pallidum infections are acquired from direct sexual contact with an individual who has an active primary or secondary syphilitic lesion. The spirochete reaches the subepithelial tissues through inapparent breaks in the skin or by passage between the epithelial cells of a mucous membrane. They then begin to multiply locally. A primary lesion then forms 2 to 10 days after infection as an indurated swelling at the site of infection. The surface necrosis to yield a hard-based ulcerated, nontender lesion termed, chancre. The basic pathologic lesion is an endarteritis. There are several stages of syphilis: Primary, which progresses to secondary which may either spontaneously resolve or progress to tertiary or latent syphilis. Syphilis may also be congenital.

Primary syphilis, as described above, is characterized by a single ulcer at the site of infection, which persists for approximately 3 to 8 weeks in the untreated patient, and then resolves spontaneously. Clinically it is also associated with regional painless enlargement of lymph nodes.

Diagnosis is made by dark-field or direct fluorescence antibody microscopy. Often microscopy is not available, however, and therefore serology is often used to make the diagnosis. Rapid plasma reagin (RPR) is the most frequently used initial screening tool for syphilis. It is based on detection of a nonspecific antibody called reagin produced along with specific antitreponemal antibody in response to the organism. This test is highly sensitive for primary and secondary syphilis but not for delayed disease. The reagin titer reflects the activity of the disease. If the RPR is positive, tests specific for *T. pallidum* should be done which include the fluorescent treponemal antibody-absorption (FTA-ABS) test and the microhemagglutination assay for antibodies to *T. pallidum* (MHA-TP). Treatment is benzathine penicillin G, 2.4 million units single dose IM (1.2 million units in each buttock). For those with penicillin allergy, tetracycline, 500 mg PO 4 times daily or doxycycline, 100 mg PO twice daily should be given for two weeks.

The disease is then silent for 2 to 10 weeks, during which a disseminated secondary stage develops. It is characterized by a symmetric mucocutaneous maculopapular rash and generalized nontender lymph node enlargement. About one third

of cases develop painless mucosal warty erosions called condylomata lata. In one third of untreated cases, host immune responses appear to resolve the infection. In the remainder, the illness enters a dormant or latent state. Diagnosis and treatment is the same as in primary syphilis.

Positive serologic testing for syphilis in the absence of clinical disease is consistent with latent syphilis. There are two types of latent syphilis: Early latent and late latent. Early latent syphilis, which occurs within 2 years of infection, is potentially transmissible because relapses associated with spirochetemia are possible. Late latent syphilis, which occurs more than 2 years after infection, is associated with immunity to relapse and resistance to reinfection: About one third of cases do not progress beyond this stage.

Tertiary syphilis occurs in approximately one third of untreated patients. Clinical manifestations of tertiary syphilis present on average of 15-20 years after initial infection but may happen as early as 5 years. Sequela include the following: CNS – Tabes dorsalis – demyelination of the posterior columns resulting in ataxia, loss of sensation of position, pain and temperature, meningovascular syphilis resulting in paresis, mental status changes (decreased memory to frank psychosis), and cardiovascular syphilis resulting in the development of aneurysms of the aorta.

Fusobacterium necrophorum

Fusobacterium necrophorum is an anaerobic Gram-negative bacillus. It is important in the discussion of pharyngitis as it is the etiologic agent of the uncommon but life threatening condition of Lemierre Syndrome. This condition, previously known as post-anginal septicemia, was first described in 1936. It consists of thrombophlebitis of the internal jugular vein following an episode of acute pharyngitis or tonsillitis. Typical presentation is a patient with high fever, lateral neck pain, and swelling. Usually, these symptoms occur after the symptoms of pharyngitis subside. Depending on the degree of inflammation there may be a marked decrease in range of motion of the neck due to parapharyngeal space involvement. Untreated, it progresses to septic thromboemboli to seeding of the lungs, renal impairment, hepatitis, peritonitis and joint involvement.

Diagnosis is made by clinical factors and CT scan with contrast confirming thrombosis of the internal jugular vein. Treatment in the past consisted of ligation and resection of the internal jugular vein, however this is no longer advocated. Initial treatment should consist of drainage of any suppurative processes (peritonsillar, parapharyngeal, or retropharyngeal abscess) followed by supportive therapy in an ICU setting with intravenous antibiotics.

Other Bacterial infections

Mycoplasma pneumoniae has been isolated from patients with pharyngitis. A similar intracellular organism, *Chlamydia pneumoniae*, has also been linked to pharyngitis. Both of these pathogens also cause other respiratory tract infections, such as

pneumonia. There is no current evidence that antimicrobial treatment will eradicate these pathogens or shorten disease. However, many physicians treat despite these facts.

Fungi

Candida albicans

Candida albicans is normally present in small numbers in the oral cavity. This colonization is aided by the ability of *C. albicans* to adhere to mucosal cells, a feature that distinguishes it from most other *Candida* species. Factors that allow *C. albicans* to increase its relative proportion of the flora (antibiotic therapy), that compromise the general immune capacity of the host (leukopenia or corticosteroid therapy), or that interfere with T lymphocyte function (AIDS, transplant patients taking anti T-cell medications such as cyclosporin, leukemia) are often associated with local and invasive infection. Diabetes mellitus also predisposes to *C. albicans* infection.

Superficial invasion of the mucous membranes by *C. albicans* produces a white, cheesy plaque that is loosely adherent to the mucosal surface. The lesion is usually painless, unless the plaque is torn away and the raw, weeping, invaded surface is exposed. Oral lesions called thrush, occur on the tongue, palate, and pharynx and in more severe cases may extend into the larynx and esophagus. Laryngeal candidiasis is not uncommon in patients who overuse inhaled steroids for the treatment of asthma or chronic obstructive pulmonary disease.

Diagnosis is usually made clinically in a patient who is immunosuppressed from one of the above mentioned conditions. Exudate or epithelial scrapings examined by KOH preparation or Gram smear can be done and demonstrate abundant budding yeast cells; if associated hyphae are present, the infection is almost certainly caused by *C. albicans*.

Treatment for oropharyngeal candidiasis is nystatin suspension taken as 10–15 milliliters mouth rinses five times per day. More severe or refractory infections may require oral fluconazole 400 mg PO bid. Disseminated candidiasis is treated with amphotericin B.

Other Mycoses

Many other fungi can affect the head and neck, however, specific infection of the pharynx is extremely rare. These include *Cryptococcus neoformans*, *Rhinosporidiosis seeberi*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Paracoccidioidomycosis brasiliensis*.

Granulomatous Disease of the Pharynx

A microscopic aggregation of epithelioid cells, usually surrounded by a collar of lymphocytes, is referred to as a granuloma. This pattern of inflammation that is characteristic of type IV (cell-mediated) hypersensitivity reaction is called granulomatous inflammation. There are a large number of disease processes that result in granuloma formation ranging from infectious processes such as tuberculosis and other mycobacteria, leprosy, and parasites, to systemic diseases such as Wegener's granulomatosis, sarcoid, and Crohn's disease.

Wegener's Granulomatosis

Wegener's granulomatosis (WG) is a distinct clinicopathologic entity characterized by granulomatous vasculitis of the upper and lower respiratory tracts together with glomerulonephritis. In addition, variable degrees of disseminated vasculitis involving both small arteries and veins may occur.

The histopathologic hallmarks of WG are necrotizing vasculitis of small arteries and veins together with granuloma formation. Immunopathogenesis of this disease is unclear, although the involvement of upper airway and lungs suggest an aberrant hypersensitivity response to an exogenous or even endogenous antigen that enters through or resides in the upper airway.

A typical patient presents with severe upper respiratory tract finds such as paranasal sinus pain and drainage and purulent or bloody nasal discharge with or without nasal mucosal ulceration. Nasal septal perforation may follow, leading to saddle nose deformity. WG usually does not affect the pharynx directly but inflammation in this area is usually secondary to irritation from post-nasal drip. More commonly, WG may involve the larynx. The subglottis is the most common single site of involvement, however granulomas can usually be found throughout the larynx.

The diagnosis of WG is a clinicopathologic one made by the demonstration of necrotizing granulomatous vasculitis on biopsy of appropriate tissue in a patient with clinical findings of upper and lower respiratory tract disease together with evidence of glomerulonephritis. Pulmonary tissue preferably obtained by open thoracotomy, offers the highest diagnostic yield. Nasal biopsy may also be performed if involvement is evident.

Although specific variations in treatment exist, the treatment of choice in this disease is cyclophosphamide given in doses of 2 mg/kg per day orally. This should be continued for 1 year following the induction of complete remission and gradually tapered and discontinued thereafter. At initiation of therapy, glucocorticoids should be administered together with cyclophosphamide. Specifically prednisone 1 mg/kg per day should be given with gradual conversion to alternate-day schedule followed by tapering and discontinuation after approximately 6 months. Using the above regimen, the prognosis of this disease is excellent; marked improvement is seen in more than 90% of patients and complete remission is seen in 75% of patients.

Tuberculosis

Mycobacterium tuberculosis is a Gram-negative bacillus that demonstrates the staining characteristic of acid-fastness. Tuberculosis is a disease of great antiquity that reached epidemic proportions during the major periods of urbanization in the 18th and 19th centuries. A resurgence of the disease has been seen in the past several decades in conjunction with the emergence and rising prevalence of HIV and AIDS.

Involvement of *M. tuberculosis* in the head and neck is uncommon. Specific localization to the pharynx is even less common. However, mycobacterial pharyngotonsillitis does occur and results from expectoration of infected sputum from pulmonary involvement. Clinical exam reveals an erythematous, infiltrative, granular or ulcerated surface mucosa. Tuberculous laryngitis is the most common granulomatous disease of the larynx and most often involves the posterior third of the larynx.

Diagnosis is made by demonstrating the tubercle bacilli in the sputum, urine, body fluids, or tissues of the patient. The staining characteristics of *M. tuberculosis* allow its ready identification. Sputum culture adds to the diagnostic yield and also permits the specific identification of acid-fast bacilli and the determination of drug susceptibility. Isolation from clinical specimens usually requires 4 to 8 weeks.

Daily treatment with regimes including isoniazid and rifampin for 9 to 12 months represents the most effective treatment available and is capable of achieving a favorable outcome in 99% of patients. Many clinicians add a third drug initially until the results of sensitivity tests become available; pyrazinamide is the optimal third drug, and ethambutol is also effective.

Sarcoidosis

Sarcoidosis is a chronic, multisystem disorder of unknown cause characterized in affected organs by an accumulation of T lymphocytes and mononuclear phagocytes, noncaseating epithelioid granulomas, and derangements of the normal tissue architecture.

Sarcoidosis is a relatively common disease affecting individuals of both sexes and almost all ages, races, and geographic locations. Females appear to be slightly more susceptible than males. Most patients are between the ages of 20 and 40 years.

Clinical manifestations may be generalized or focused to one or more organs. The lung is almost always involved and therefore the majority of patients present with respiratory complaints. 90% of patients have an abnormal chest X-ray which usually shows hilar adenopathy. The nasal mucosa is involved in up to 20% of patients, usually presenting with nasal congestion. Any of the structures of the mouth, pharynx and larynx can be involved, particularly the tonsils. The usual finding is erythema of the tonsil or hypertrophy. Sarcoidosis involves the larynx in about 5% of cases. The epiglottis is the most common site of involvement

Diagnosis can usually be made on clinical and radiographic findings alone, however if upper airway findings are present, biopsy of affected sites should be done to rule out other pathology and to confirm the presence of noncaseating granulomas. Biopsy of the lung is the most common method for confirming the diagnosis, however tissue samples taken from the skin, conjunctive, or lip may also be done.

Treatment of choice for sarcoidosis is glucocorticoids. Deciding when to treat is the major clinical dilemma. Because the disease clears spontaneously in about 50% of patients, and because the permanent organ derangements often do not improve with glucocorticoids, there is controversy among clinicians as to the criteria for treatment. Some use criteria based on gallium scan and level of angiotensin converting enzyme to indicate disease activity. Others base their decision for treatment solely on severity of specific clinical manifestations. The usual therapy is prednisone, 1 mg/kg, for 4 to 6 weeks, followed by a slow taper over 2 to 3 months. This is repeated if the disease again becomes active.

Crohn's Disease

Crohn's is an inflammatory disease of the bowel for which the exact etiology is unknown. It is more common in whites, occurs with an increased frequency in Jews, and exhibits some familial clustering suggesting that there may be a genetic predisposition to the development of disease.

Pathologically, Crohn's is characterized by chronic inflammation extending through all layers of the digestive tract wall. Unlike its counterpart, ulcerative colitis, it may affect any area of the digestive tract from the mouth to the anus. Crohn's is often discontinuous characterized by "skin lesions". Microscopically, granulomas are most helpful in distinguishing it from other forms of inflammatory bowel disease.

The major clinical features of Crohn's disease are fever, abdominal pain, diarrhea often without blood, and generalized fatigability. Pharyngeal involvement may be seen in 9% of patients during the course of their disease and usually follows intestinal manifestations.

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