

## Pharyngitis, Diagnosis and Empiric antibiotic treatment Considerations

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**Abstract:** Pharyngitis is the common disorder more in children than adults. Pharyngitis is common in the developing countries. In the United States pharyngitis is diagnosed in 11 million patients in emergency department and ambulatory setting annually. Viruses are frequently cause of viral pharyngitis, with adenovirus, rhinovirus, enterovirus, influenza A and B parainfluenza viruses. Streptococcus pyogenes group A (GAS) or group A beta hemolytic streptococcus (GABS) is the bacterial agent of acute pharyngitis. Fusobacterium necrophorum and Mycoplasma pneumonia also been reported. Virulence factors leads to pharyngitis, invasive disease, acute rheumatic fever, and acute glomerulonephritis. Bacterial signs include pharyngeal erythema, tonsillar enlargement, and grayish-whitish exudate covering the posterior pharynx and tonsillar pillars. Symptoms such as conjunctivitis, coryza, oral ulcers, cough and diarrhea suggest a viral cause. Modified Centor score may be used for diagnosis. A 10 days course of penicillin remains treatment of choice, macrolide for penicillin allergic patients, amoxicillin has the advantage of less frequent dosing. Use of broad spectrum antibiotics thought to contribute to antibiotic resistance. Role of tonsillectomy or adenoidectomy in GBHS pharyngitis incidence is poorly understood.

**Keywords:** Pharyngitis, Pharyngotonsillitis, Rheumatic fever, Diagnosis, and Treatment.

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### I. Introduction

Pharyngitis is the inflammation of the pharynx- the word comes from Greek word pharynx meaning "throat" and the suffix -itis meaning "inflammation". In most cases it is quite painful and it is the most common cause of sore throat [1,2]. If the inflammation includes tonsillitis, it may be called pharyngotonsillitis [3]. Another sub classification is nasopharyngitis (the common cold) [4]. Pharyngitis is the common disorder in adults and children. In a recent prospective family study of 16% adults and 41% children reported an illness with sore throat over a 1-year time frame [5]. In the United States, the National Ambulatory Medical Care survey and the National Hospital Ambulatory Medical Care Survey have documented between 6.2 to 9.7 million visits to primary care physicians, clinics and emergency departments each year for children with pharyngitis, and more than five million visits per year for adults [6]. Hing and colleagues reported that pharyngitis is diagnosed in 11 million patients in U.S. emergency departments and ambulatory settings annually [7]. School-aged children of 5 to 18 years of age usually account for the greatest overall number of cases of pharyngitis, similar to disease from Group A streptococci, or Group A beta-hemolytic streptococci (GAS/GABHS) [5,7]. The reported prevalence of GAS pharyngitis is influenced both by the age of the patient and the examining setting, with higher rates found in younger people evaluated in urgent care and emergency centers [8]. Population-based data demonstrate serologically proven GAS pharyngitis occurs at a rate of 0.14 cases per child year in the developed world and is estimated to be 5 to 10 times greater in developing countries [9]. In temperate climates, most cases of pharyngitis occur in winter and early spring, corresponding to peak times of respiratory virus activity. This also true for GAS pharyngitis, in which as many as half of the cases in children may be due to this etiologic agent during these peak months [10]. Most acute cases are caused by viral infections (40-80%), with remainder caused by bacterial infections, fungal infections, or irritants such as irritants such as pollutants, or chemical substances [2]. In patients with acute febrile respiratory illness, physicians accurately differentiate bacterial from viral infections using only the history and physical examination findings about half of the time [11]. Empiric treatment for bacterial pharyngitis include penicillin VK, erythromycin for penicillin allergic patients, and clindamycin, amoxicillin-clavulanate for late relapse or recurrent patients for 10 days [12]. The paper reviews the diagnosis, and empiric antibiotic treatment of pharyngitis.

### II. Infective Agent

Viruses are the single most common cause of pharyngitis and account for 25 % to 45 % of all cases, often occurring with other signs or symptoms of upper respiratory tract infections [13]. Essentially all viruses known to cause upper respiratory tract infections have been described in both adults and children with pharyngitis. Although the methodology between different studies is highly variable, adenovirus is frequently identified as the most prevalent viral cause of pharyngitis reported in 12% to 23 % of cases [13]. Other viruses

that cause pharyngitis include rhinoviruses, enteroviruses, influenza A and B parainfluenza viruses, respiratory syncytial virus, coronaviruses, human metapneumovirus, and human bocavirus [14]. Several human herpesviruses such as Epstein-Barr virus, herpes simplex virus (HSV), and human cytomegalovirus have also been reported to cause pharyngitis, as well as human immunodeficiency virus type 1 (HIV-1) [15].

*Streptococcus pyogenes*, group A streptococcus (GAS) or group A beta hemolytic streptococci (GABS), is the bacterial etiology of greatest concern in cases of acute pharyngitis because of the association between GAS and acute rheumatic fever. GAS is responsible for approximately 10% to 30% of cases in adults and 15% to 30% of cases in children [16,17]. *Fusobacterium necrophorum*, a gram-negative, non-spore forming anaerobe, is a bacterial cause of sore throat in as many as 10% of cases of pharyngitis [18]. This organism has also been implicated in recurrent or chronic sore throat syndromes and may be identified in as many as 21% of such cases [19]. *Corynebacterium diphtheria* is also a cause of pharyngitis and is of concern for travelers to areas where vaccination programs are not well established or have failed [20]. Pharyngitis due to gonorrhea should be considered in sexually active adolescent and young adults. Throat cultures yield *N. gonorrhoeae* in as many as 1% to 6% of individuals in sexually transmitted disease clinics [21]. *Mycoplasma pneumoniae* (identified in 3% to 14% of cases of pharyngitis), and *Chlamydia pneumoniae* (less frequently detected in 3% to 8% of cases, should also be considered as potential etiologic agents of pharyngitis [10]. Some cases of pharyngitis are caused by fungal infection such as *Candida albicans* causing oral thrush [2].

### III. Pathophysiology

The mechanisms responsible for the development of the signs and symptoms of pharyngitis have not been fully delineated. Previous studies demonstrated that bradykinin is induced in symptomatic rhinovirus infections and that bradykinin challenge in healthy volunteers produces significant sore throat when delivered to either the oropharynx or the nasal mucous [22]. Other inflammatory mediators, including prostaglandins, have been postulated to play a role with bradykinin via their actions on the sensory nerve endings in the pharynx [23]. Several randomized, controlled trials demonstrated a beneficial effect of either nonsteroidal anti-inflammatory drugs or corticosteroids on throat pain, also suggesting that inflammatory mediators play a key role in the pathophysiology of sore throat [24].

Among bacterial causes of pharyngitis, the pathogenesis of GAS has been studied most extensively. Multiple virulence factors have been identified that ultimately lead to the manifestation of acute pharyngitis. Despite the growing fund of knowledge, major gaps exist regarding the events leading to tonsillopharyngeal disease. Furthermore, the mechanism underlying asymptomatic carriage has been the subject of much speculation. The role that the immune system and possible molecular genetic changes in GAS play in asymptomatic carriage remains elusive. Proteins involved in immune avoidance (M protein, hyaluronic acid capsule, C5a peptidase), adherence to epithelial cells (plus, fibronectin binding proteins, lipoteichoic acid), spreads through host tissues (hyaluronidase, streptokinase, DNAases), and numerous exotoxins (streptolysin, superantigenic toxins) have been described [25]. Expression of these virulence factors leads to symptomatic pharyngitis and complications such as invasive disease, acute rheumatic fever, and acute glomerulonephritis. The mechanism by which GAS pharyngitis results in acute rheumatic fever is unknown. However, autoimmunity through molecular mimicry is suspected. A growing body of evidence supports the existence of rheumatogenic GAS serotypes. Comparing M-type distribution between two periods separated by 40 years, Shulman and colleagues were able to demonstrate that decreases in our complete disappearance of certain M-types were associated with the decline in the evidence of acute rheumatic fever. Whether other strain specific GAS virulence factors are involved is unknown [26].

### IV. Clinical Presentation

It is well documented that the etiology of pharyngitis in individual patients cannot be accurately discerned based on clinical characteristics alone, certain pathogens may cause more readily recognizable syndromes [15]. Frequently isolated pathogens of pharyngitis include:

**Group A Streptococcus [15].** Pharyngitis is attributable to GAS is sudden in onset in older children and adults. Sore throat association with GAS may result in difficulty in swallowing. Fever, headache, and gastrointestinal symptoms (nausea, vomiting, abdominal pain) are also associated with strep throat but are not always present. Physical examination generally reveals pharyngeal erythema, tonsillar enlargement, and a gray-whitish exudate covering the posterior pharynx and tonsillar pillars [15]. Petechiae are sometimes observed on the soft palate with erythema and edema of the uvula. Anterior cervical lymphadenopathy, often at the angle of the jaw, is typical of GAS pharyngitis and nodes may be quite large and tender. Patients may also present with a characteristic scarlatiniform rash that typically begins at the trunk, spreads to the extremities, and spares the palms and soles. The rash is usually described as confluent with a sandpaper-like quality. Scarlet fever is caused by one or more of the pyogenic exotoxins produced by the pharyngeal strains of GAS. Signs and symptoms most indicative of

GAS pharyngitis are tonsillitis or pharyngeal exudate, tender anterior cervical nodes, fever or history of fever and absence of cough [8].

**Non-group A Streptococci[15] and A haemolyticum.** Group C and G streptococci are commonly found as normal flora in human pharynx; however, they are also become increasingly recognized as potential causes of pharyngitis. *Streptococcus dysgalactiae* subspe *quisimilis* (group C) is the most commonly isolated non-GAS associated with sore throat[27], although recently *S equi* subsp, *zoopidemicus* has emerged as a potentially important human pathogen[28]. The distinguishing clinical features of pharyngitis due to **A haemolyticum** is the rash that may occur in as many as one half of infected individuals. The is scarlatiniform. macular, or macupapular and is most frequently in adolescents and young adults[29]. The rash begins on the distal extremities, typically involving the extensor surfaces but sparing the palms and soles, followed by centripetal spread[30,]. Rarely, *A. haemolyticum* may cause more severe infection (e.g., pneumonia and pyomyositis), but in these cases is most often a coinfecting agent[31].

**Corynebacterium diphtheriae.** Diphtheria is rare in the developed countries due to widespread vaccination. The majority of respiratory infections caused by *C. diphtheriae* are tonsillopharyngeal. Sore throat is one of the most common symptoms of diphtheria and is usually accompanied by low grade- fever and malaise [32]. Formation of a membrane on the tonsil or pharyngeal surface is the hallmark of diphtheria but occurs in only one third of the patient. A relative lack of fever and the formation of a membrane distinguish diphtheria from pharyngitis caused by group A  $\beta$  hemolytic streptococcus and viral etiologies. The membrane that forms in diphtheria is described as white early in the course of illness; it becomes dark gray and leather like, with attempts to dislodge the membrane potentially causing bleeding[33]. Membrane formation is the result of local toxin production and spreading of membrane indicates more systematic toxicity. Extensive spreading of the membrane may lead to tonsillar, anterior cervical, and submandibular lymphadenopathy as well as swelling of the neck (so called bull neck). Continued progress may lead to respiratory distress and death [15].

**Neisseria gonorrhoeae.** Pharyngeal infection of *N. gonorrhoeae* is often asymptomatic; sore throat is reported by patients with tonsillar involvement. A review of the published cases of oropharyngeal gonorrhea found that more than 10% were classified as tonsillitis [33]. Fever is in common as a cervical lymphadenopathy. Among patients with tonsillitis, a whitish yellow exudate was observed in 20%. Because the clinical presence of pharyngitis caused by *N. gonorrhoeae* is nonspecific and symptoms may be mild, a thorough history including risk factors for sexually transmitted infections should be obtained in adolescents and young adults with pharyngitis to make diagnosis[33]. A careful and complete sexual history of patient and patient's sexual orientation is important. History must be taken in terms understandable to patient, rather than technical jargon (e.g., "Do you practice fellatio?") [34].

**Mycoplasma pneumoniae.** *M. pneumoniae* and *C. pneumoniae* have been identified as a cause of pharyngitis in all age groups with a higher prevalence generally noted for *M. pneumoniae* [35]. Eposito and colleagues [35], described several case series of children with pharyngitis caused by *M. pneumoniae* or *C. pneumoniae* and identified dysphagia in 25% to 36%, tonsillar hypertrophy in 76% to 83%, cervical adenopathy in approximately 50%, and exudate in 25% to 39%. Although these findings were not specific to pharyngitis due to atypical bacterial infection compared with common viral cases of pharyngitis, children with infection due to *M. pneumoniae* or *C. pneumoniae* were significantly more likely to have a history of recurrent pharyngitis [36]. In addition, children with pharyngitis due to atypical bacterial infections treated with azithromycin had lower rates of subsequent respiratory infections, including lower tract disease, compared with children given symptomatic treatment [37].

**HIV –AIDS** and pharyngitis. The common presenting symptoms of fever, pharyngitis, rash and a lymphadenopathy, it is easy to understand how primary HIV-1 infection may be confused with infectious mononucleosis, secondary syphilis, acute hepatitis A or B, toxoplasmosis or other viral syndromes. Infact, Schaker and colleagues [38], noted that only one fourth of patients with symptoms of primary HIV-1 infection had the diagnosis suspected at the initial medical evaluation. A recent report estimating the prevalence of primary HIV-1 infection in symptomatic adolescent and adult ambulatory patients found that pharyngitis was due to primary HIV-1 infection in 1.3 patients per 1000 cases [39]. Because as many as one half of all new HIV-1 infections occur in adolescents, physicians who care for adults and children should be familiar with the clinical characteristics of primary HIV-1 infection to maintain high index of suspicion for this disorder [40].

**Epstein- Barr virus (EBV)** Infectious mononucleosis is a multisystem disorder caused by primary infection with EBV and defined by the triad of fever, pharyngitis, and adenopathy [41]. Among 150 young adults with serologically confirmed acute EBV infection, three fourth reported sore throat and fatigue, with approximately

half noting fever, painful cervical adenopathy, and headache at their initial visit[42].The pharyngitis that accompanies infectious mononucleosis is subacute in onset and may be accompanied by mild to moderate enlargement of the tonsils as well as exudates and palatal petechiae.Symptoms substantially improve over first month of illness and after 6 months are almost completely resolved [41,42].Periorbital or eyelid edema as symptom of primary EBV infection seems to be unique to children[43].

**Miscellaneous viral agents.** Other viral agents involved in viral pharyngitis include non- polioenteroviruses have identified in 8% to 29% of cases of pharyngitis in children using reverse transcriptase polymerase chain reaction[44].Examining sore throat or pharyngitis specifically adenovirus is identified as the etiologic agent in 25% of cases in children and 3% of ambulatory adults[35].Primary infection with herpes simplex virus(HSV) commonly causes gingivostomatitis in young children, whereas pharyngitis is noted among adolescents and young adults. In a series of 35 young college students with HSV pharyngitis infections occurred year round, with majority of patients presenting with fever, pharyngeal erythema, exudates, and enlarged, tender cervical adenopathy[45].

## V. Diagnosis

Pharyngitis is one of the most common symptoms a physician may encounter; diagnosis of treatable etiologies is paramount. The prevention of rheumatic fever requires antimicrobial treatment and eradication of GAS from the pharynx [46].Certain clinical findings help to distinguish GAS from viral causes of pharyngitis. As noted, tonsillar or pharyngeal exudates, tender interior cervical lymphadenopathy, and fever are commonly associated with GAS. Alternatively, symptoms such as conjunctivitis,coryza,oral ulcers, cough, and diarrhea suggest a viral cause [47].

Multiple clinical prediction rules have been developed to aid in the diagnosis of GAS pharyngitis. Scoring system attempt to use clinical and epidemiologic data to assign a probability that acute pharyngitis is attributable to GAS [48].Prediction rules for the diagnosis of GAS pharyngitis are limited because the signs and symptoms of many viral causes of acute pharyngitis overlap with infection caused by GAS, and rules are best for identifying patients with a low probability of GAS infection. **Modified Centor score may be used for diagnosis e.g.,score 1,(risk 5% to 10%),score 2,(risk 11% to 17%),score 3( risk,28%to 35%),score ≥4,(risk 51% to 53%)**[49].Based on 5 clinical criteria, it indicates that probability of a streptococcal infection[50].One point is given for each of the criteria e.g. Absence of cough, swollen and tender cervical lymph nodes, temperature >38.0 °C(100.4 °F),age less than 15(a point is subtracted if age >44)[50].The McIsaac criteria adds to the Centor: age less than 15:add one point, age greater than 45: subtract one point[51].

For these reasons, the guidelines from the Infectious Disease Society of America(IDSA),the committee on Infectious Diseases of American Academy of Pediatrics, and the American Heart Association recommended confirmation of GAS infection by rapid antigen test(RADT),throat cultures, or both[47].In contrast, the guidelines issued by the Centers for Disease Control and Prevention(CDC) and the American College of Physicians-American Society of Internal Medicine suggest empirical treatment based on a pharyngitis score alone with or without microbiologic confirmation[52].Specific media and techniques are necessary to identify other causes of pharyngitis.If diphtheria is suspected, the laboratory must be notified,Recently multiplex PCR has been used for identification of *C.diphtheriae* and to differentiate toxin production from nontoxigenic strains[53].Molecular detection of *Fusobacterium* has been used in some studies[54].The diagnosis of primary EBV infection is also confirmed by serology, by either a heterophile antibody test(monospot or monoslides) or detection of immunoglobulin M antibodies to EBV viral capsid antigen in an acute serum specimen. Although 85% of adolescents and adults develop heterophile antibodies usually at approximately 1 week into the illness, specific serology for EBV is necessary to make the diagnosis in children, especially those younger than 4 years [43,45].

## VI. Treatment

Prescribing antibiotics for patients with sore throat is a common practice and is often done to in an effort to prevent potential complications of pharyngitis[55].A more recent evaluation used a national database of more than one million cases of sore throat and found that although there was a decrease in the incidence of quinsy after the use of antibiotics, the number needed to treat to prevent one case was 4300,suggesting that the small decrease in risk of an uncommon complication did not warrant the widespread use of antibiotics for a self-limited disease[56].The goal of therapy for GAS pharyngitis is to decrease the time to resolution of symptoms, reduce the risk of transmission, and reduce the incidence of suppurative and nonsuppurative sequelae.Penicillin has been the mainstay of therapy for GAS pharyngitis for more than 60 years .Despite this long- term use, there has yet to be a confirmed resistance of penicillin in GAS.A 10 days course of penicillin remains the treatment of choice and is recommended by the Infectious Disease Society of America and the American Academy of Pediatrics for the treatment of pharyngitis caused by GAS[47].Penicillin allergic patients be given a

macrolide(erythromycin) or first generation cephalosporin for non-immunoglobulin F-mediated allergy. Currently, the use of broad- spectrum cephalosprins such as cefixime and cefibuten,although supported by the U.S. Food and Drug Administration for the treatment of GAD pharyngitis, is not endorsed[47].

Evidence is building for the use of amoxicillin in the treatment of GAS pharyngitis.The use of penicillin derivatives such as amoxicillin has the advantage of less frequent dosing and improved taste for children, leading to better compliance. Two relatively small studies showed that treatment of GAS pharyngitis with once-daily amoxicillin for ten days achieved similar clinical and bacteriologic outcomes compared with traditional penicillin dosing[57].Antimicrobial therapy should not be used for the prevention of GAS pharyngitis except in special circumstances. Continuous antimicrobial prophylaxis for the prevention of GAS pharyngitis is indicated in those with a previous episode of rheumatic fever[58]Short course anti-microbial prophylaxis has also been used during outbreaks of acute rheumatic fever, post streptococcal glomerulonephritis, or close contacts of persons with invasive infections such as necrotizing fasciitis or streptococcal toxic shock syndrome[54].Treatment of choice for *Fusobacterium* infections include a penicillin in combination with a  $\beta$ -lactamase inhibitor(e.g.,amoxicillin/sulbactam) together with metronidazole[59,].Resistance to penicillin has been reported, but this is not widespread. Penicillin and erythromycin are the only two agents recommended for treatment of *C. diphtheriae*, although newer macrolides such as azithromycin are commonly used in clinical practice[60].Treatment of pharyngitis caused by *N. gonorrhoeae* a problematic because pharyngeal eradication of the organism is more difficult, repeat cultures, at the end of therapy to confirm eradication are recommended[61].In a recent surveys demonstrated a significant increase in the use of broad-spectrum antibiotics for the treatment of pharyngitis, a practice that thought to contribute to the growing problem of antibiotic hesitance and the “medicalization”of a generally benign illness[62].

## VII. Pahryngitis And Complications

The potential supportive complications of pharyngitis, include peritonsillitis abscess, (quinsy),pharyngeal space abscess,lymphadenitis,sinusitis,otitis media mastoiditis and invasive infections e.g.,necrotizing fasciitis and toxic shock syndrome with GAS[63].In older adults the signs and symptoms of a peritonsillar or parapharyngeal space abscess may be subtle,and the disease seems to be more common in those with underlying immunocompromising conditions[64].Acute rheumatic fever and acute glomerulonephritis are potential nonsuppurative complications of pharyngitis caused by GAS.Rheumatic heart disease and its complications affect almost 2 million individuals each year, primarily in the developing countries [9].Acute rheumatic fever has become rare in the United States except for sporadic outbreaks of rheumatogenic strains of GAS[65].Lemeierre’s syndrome is an uncommon complications of pharyngitis in adolescents and young adults characterized by septic thromphlebitis of the internal jugular vein and metastatic lesions(septic emboli) of distant sites after acute sore throat most commonly caused by *Fusobacteriumnecrophorum*[59].

## VIII. Conclusion

Pharyngitis is the common illness in adults and children. Complications of pharyngitis include rheumatic fever and acute glomerulonephritis. Modified Centor score is helpful forthe diagnosis and treatment of pharyngitis. Penicillin and erythromycin is the antibiotic of choice, broad spectrum antibiotics for relapse or recurrent cases

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