Diagnosis and Management of Pharyngotonsillitis

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Abstract

The main cause of pharyngotonsillitis is group A beta-hemolytic streptococci (GABHS) infection, though other bacteria, viruses, and other infectious and noninfectious factors should be considered as well. Their identification is of utmost importance to assure early and appropriate treatment and prevent complications. Penicillin is currently the first-choice treatment for GABHS pharyngotonsillitis. However, it may fail to eradicate the disease in the presence of beta-lactamase-producing bacteria that "protect" GABHS or in the absence of bacteria that interfere with the growth of GABHS. Other reasons for penicillin failure are co-aggregation of GABHS and *Moraxella catarrhalis* and poor penetration of penicillin into tonsillar tissues and tonsillopharyngeal cells. The use of antimicrobials that can overcome and modulate these phenomena and achieve better cure of the infection is described. The use of antimicrobials that can overcome and modulate these phenomena and achieve better cure of the infection is described.

MeSH Words: Pharyngotonsillitis, Group A streptococci, Beta lactamase, Anaerobic bacteria, Penicillin, Interference

Introduction

Pharyngotonsillitis is a common illness in adults and children, often encountered by family and emergency medicine physicians. An infection in the pharynx, which is served by the lymphoid tissues of Waldeyer's ring, can spread to other parts of the ring, such as the tonsils, nasopharynx, uvula, soft palate, adenoids, and cervical lymph glands [1], causing pharyngitis, tonsillitis, pharyngotonsillitis, or nasopharyngitis. These illnesses can be acute, subacute, chronic, or recurrent.

Etiology (Table 1)

The most common pathogens causing pharyngotonsillitis are group A beta-hemolytic streptococci (GABHS), adenovirus, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, Epstein-Barr virus, and enterovirus. Although the risk of infection also depends on environmental conditions (exposure,

season, geographic location) and individual variables (age, host resistance, immunity), identifying the specific underlying agent is of utmost importance for the selection of proper therapy, which assures rapid recovery and prevents complications. However, in many cases, either the culprit cannot be determined or the involvement of a potential pathogen remains uncertain.

Recent studies suggest that pharyngotonisillits may be associated with one or more interactions between GABHS, other aerobic and anaerobic bacteria, and viruses [2]. The interactions may be synergistic (i.e., between Epstein-Barr virus and anaerobic bacteria), enhancing the virulence of the pathogens, or antagonistic (i.e., between GABHS and "interfering" alpha-hemolytic streptococci) [3]. Beta-lactamase-producing bacteria (BLPB) can protect both themselves as well as other bacteria from the effect of beta-lactam antibiotics [4].

Aerobic bacteria

GABHS are the best known cause of pharyngotonsillits because infection with these bacteria could have potentially serious suppurative and non-suppurative sequelae. Occasionally, groups B, C and G beta-hemolytic streptococci are responsible [1], though the clinical presentation is the same. The recovery rate of GABHS varies with patient age, with the highest prevalence in the school-age years. The isolation rate of non-GABHS pathogens is higher in adults [1].

Over the last 4 decades, nonrheumatogenic GABHS types have largely replaced rheumatogenic GABHS types in the United States, leading to a marked decline in the incidence of acute rheumatic fever [5]. Nevertheless, GABHS pharyngotonsillitis is still considered a potentially serious illness because rheumatic fever has not been eliminated altogether and because GABHS are manifesting increased virulence. Indeed, rates of GABHS sepsis, pneumonia, and toxic shock syndrome are rising. GABHS infection may also be involved in suppurative complications of tonsillitis, such as peritonsillar and retropharyngeal abscesses.

Streptococcus pneumoniae pharyngotonsillitis may be self-limited or it may spread to other sites. *Corynebacterium diphtheriae* produces a lethal exotoxin that is absorbed from the site of infection and carried to other organs, such as the throat, palate, and larynx.

Arcanobacterium hemolyticum infection affects the 15-18-year age group and accounts for 2.5-10% of all cases of pharyngotonsillitis. *Neisseria gonorrhoeae* infection is more common in homosexual males and may be associated with pharyngitis in adolescents. It can result in bacteremia and may persist after treatment. *Neisseria meningitidis* can cause symptomatic or asymptomatic pharyngotonsillitis which can be a prodrome for septicemia or meningitis. *Staphylococcus aureus* is often isolated from chronically inflamed tonsils and peritonsillar abscesses. The bacterium produces beta-lactamase which can interfere with the eradication of GABHS. Nontypable *H. influenzae* and *H. parainfluenzae* may be recovered from inflamed tonsils. These agents can cause invasive disease in infants and the elderly, as well as acute epiglottitis, otitis media, and sinusitis. High tissue concentrations of *H. influenzae, Staphlococcus aureus* and GABHS correlate with clinical parameters of recurrent infection and hyperplasia of the tonsils.

In rare cases, pharyngotonsillits is caused by *Francisella tularensis, Treponema pallidum*, *Mycobacterium* spp, or *Toxoplasma gondii.*

Anaerobic bacteria

The anaerobic species that have been implicated in pharyngotonsillitis are *Actinomyces*, *Fusobacterium,* and gram negative bacilli (e.g. pigmented *Prevotella* and *Porphyromonas* spp. and Bacteroides spp.) [2]. The role of anaerobes is supported by their predominance in tonsillar or retropharyngeal abscesses and Vincent's angina (*Fusobacterium* spp. and spirochetes). Furthermore, individuals with non-GABHS tonsillitis or infectious mononucleosis respond only to antibiotics that are effective against anaerobes (metronidazole) [6]. Elevated serum levels of antibodies to *Prevotella intermedia* and *Fusobacterium nucleatum* have been found in patients with recurrent non-GABHS tonsillitis and peritonsillar cellulitus and abscess [7].

Myocplasma

Mycoplasma pneumoniae and *Mycoplasma hominis* can also cause pharyngotonsillitis,

usually as a manifestation of a generalized infection. The prevalence of *Mycoplasma* infection increases with age.

Viruses and Chlamydia

The viruses that can cause pharyngotonsillits include, among others, adenovirus (concomitant conjunctivitis), coxsackie A virus, parainfluenza virus, enterovirus, herpes simplex, Epstein-Barr virus, respiratory syncytial virus, rubella virus, and cytomegalovirus.

Chlamydia pneumoniae pharyngotonsillitis often accompanies pneumonia or bronchitis.

Clinical Findings

In general, the onset of pharyngotonsilitis is sudden and characterized by symptoms of fever and sore throat, nausea, vomiting, headache, and rarely, abdominal pain. Physical examination at presentation reveals erythema of the throat and tonsils and enlarged cervical glands. The physician may also note an exudate or a membrane covering the tonsils, in addition to palatal petechiae, follicles, cervical adenitis, and scarlet fever rash, depending on the causative agent (Table 1); none of these findings is specific. The classical symptoms of viral infections, namely, cough, rhinitis, conjunctivitis, and diarrhea, are usually absent in bacterial pharyngotonsilitis. A history of exposure to the organism and presentation in winter are contributory.

Specifically, the clinical diagnosis of GABHS pharyngotonsillitis is based on findings of abrupt onset of fever, with or without "sore throat", in a child older than 2 years, accompanied by ill appearance, neck muscle pain, tenderness, abdominal pain, nausea, vomiting, flushed cheeks, circumoral pallor, palatal petechiae, and circular and semicircular red marks, early strawberry tongue, scarlatinaform rash, or a peculiar, sour-sweet yeasty breath odor. GABHS pharyngotonsillitis tends to present with exudative pharyngitis and enterovirus pharyngotonsilits, with ulcerative lesions. *Corynebacterium diphtheriae* infection causes a bull neck and an early exudative pharyngotonsillitis characterized by the development of a grayish-green thick membrane that is difficult to dislodge, and when torn off, often leaves a bleeding surface. About half the patients with *Arcanobacterium hemolyticum* infection present with a scarlatiniform rash. Patients with *N. gonorrhoae* pharyngotonsillitus are often asymptomatic, though some exhibit pharyngeal ulcers or exudates. Infection with anaerobic bacteria may be differentiated clinically by the presence of enlarged and ulcerated tonsils, fetid or foul odor from the mouth.

Besides GABHS infection, petechiae are often seen in infections due to Epstein-Barr virus, measles, and rubella viruses. Epstein-Barr virus infection is also characterized by exudative pharyngitis, liver and spleen enlargement, and cervical adenopathy; enterovirus infection by pharyngeal vesicles or ulcers and vesicles on the palms and soles in summer; herpes simplex infection by anterior oral and lip lesions and fever, and repiratory syncytial and rubella virus infections by oral erythema and Koplic spots prior to exanthema.

Viral pharyngotonsillitis is usually associated with nasal secretions and is generally self-limited (4-10 days), whereas bacterial illness, if left untreated, lasts longer.

Laboratory Tests

The diagnosis of pharyngotonsillitis is confirmed by culture. Samples obtained by swabbing both tonsillar surfaces and the posterior pharyngeal wall are transferred to sheep blood agar medium. The recovery rate may be increased by incubating the cultures under anaerobic conditions and using selective media. A single throat culture has a sensitivity of 90%-95% for the detection of GABHS in the pharynx. False-negative results are possible if the patient received antibiotics. The identification of GABHS by direct growth requires 24 to 48 hours; re-examination of the plates at 48 hours is advisable. The use of bacitracin disc provides presumptive identification. Attempts to identify beta-hemolytic streptococci other than group A may be worthwhile in older individuals. Commercial kits containing group-specific antisera are available [8]. There are also rapid methods for GABHS detection (10 to 60 minutes), but they are more expensive. Traditional antigen tests depend on the detection of the surface Lancefield group A carbohydrate. Newer tests that identify more pathogenic serotypes of GABHS include nucleic acid

(DNA) probes and polymerase chain reaction. Kits in use today have a sensitivity of 85 to 90%, although they are still associated with a 5-15% false-negative rate. Bacterial culture should be performed in cases of a negative rapid streptococcal test.

True infection, rather than colonization, is defined as the presence of more than 10 colonies of GABHS per plate. However, this method is difficult to implement because of the overlap between carriers and infected patients. An increase in antistreptolysin O (ASO) streptococcal antibody titer after 3-6 weeks can provide retrospective evidence of GABHS infection and assist the clinician in differentiating between carrier and infective states. ASO titers are considered definitive proof of GABHS infection.

In the absence of GAHBS growth, the clinician should seek other potential pathogens. However, many of them are part of the normal flora residing in the pharynx, making interpretation of the results difficult.

A finding of a membrane in the throat should prompt a search for corynebacteria. Culture samples should be obtained from beneath the membrane, and use of a special moisture-reducing transport medium is necessary. The material may be inoculated on a Loeffler slant, tellurite plate, or blood agar plate. Identification by fluorescent antibody technique is possible as well.

Viral cultures are available, as well as rapid tests for some viruses (e.g., respiratory syncytial viruses). A heterophile slide test or other rapid test for infectious mononucleosis can provide a specific diagnosis. The diagnosis of viral pharyngotonsillitis may also be confirmed by findings of fusiform bacilli, spirochetes, and other organisms on Gram staining.

Treatment (Tables 2-5)

Penicillin

Various antimicrobials are available for the treatment of GABHS pharyngotonsillitis. The currently recommended optimal treatment in acute cases is penicillin, administered 3 times a day for 10 days. Oral penicillin-VK is used more often than intramuscular benzathine penicillin-G. However, intramuscular penicillin can be given as initial therapy in patients who cannot tolerate oral medication or to ensure compliance. Amoxicillin has been found to be equally active against GABHS, and it has several advantages over penicillin: more reliable absorption, higher blood levels, longer plasma half-life, and lower protein binding. It also has a better taste than oral penicillin, so that compliance is improved. However, amoxicillin is contraindicated in patients with suspected infectious mononucleosis, in whom it can cause a skin rash.

Concerns have been raised by findings of a frequent inability of penicillin (35% failure rate for the oral route, 37% for the intramuscular route) to eradicate GABHS in patients with acute-onset pharyngotonsilitis despite its excellent in vitro efficacy [9]. The reported failure rates are 35% for the oral route and 37% for the intramuscualar route. Although about half the patients who harbor GABHS following therapy for acute disease may be carriers, the remainder could still show signs of infection and represent true clinical failures. Possible reasons (Table 4) include noncompliance with the 10-day course of therapy, reinfection, and penicillin tolerance, in addition to potential interactions between GABHS and pharyngotonsillar bacterial flora [10]. Some authors suggested that GABHS may be "shielded" from penicillins by several mechanisms. Repeated penicillin administration can result in a shift in the aerobic and anaerobic oral microflora that normally interferes with the growth of GABHS to predominantly beta-lactamase-producing strains of *S. aureus, Haemophilus* spp*., M. catarrhalis, Fusobacterium* spp*.,* pigmented *Prevotella* and *Porphyromonas* spp., and *Bacteroides* spp [4]. This assumption is supported by findings that less than one-third of patients with pharyngotonsillitis harbor organisms that interfere with the in vitro growth of potential pathogens, compared to 85% of healthy controls [3]. In addition, BLPB present in a localized soft-tissue infection can degrade penicillin in the infected area [4], thereby protecting not only themselves but also other penicillin-susceptible pathogens, such as GABHS [3,4]. Studies have shown that an increase in the in vitro resistance of GABHS to penicillin when it was inoculated together with *S. aureus, Haemophilus* spp., and pigmented *Prevotella* and *Porphyromonas* spp, *Bacteroides* spp. protected GABHS from

penicillin therapy in mice [4]. Other mechanisms that may shield GABHS from penicillin are the co-aggregation of *M. catarrhalis* and GABHS [11], and poor penetration of penicillin into the tonsillar tissues and the tonsillopharyngeal cells [12].

Alternative Medications (Tables 2,3)

Acute Disease

At present, cephalosporins and macrolides are considered good alternatives to penicillin in the acute setting [13,14]. Besides cost and social factors, the selection of the appropriate drug depends mainly on medical considerations, such as the risk of the presence of BLPB or absence of interfering organism and recent history of failed penicillin therapy (Table 5). Indeed, the reason for the consistently higher success rate of cephalosporins than penicillin in the treatment of acute GABHS pharyngotonsillits [15] may be their activity against aerobic BLPB, such as *S. aureus, Haemophilus* spp. and *M. cattarrhalis*. It is also possible that the nonpathogenic aerobic and anaerobic bacteria that compete with GABHS have a lower susceptibility to cephalosporins than to penicillin, so they are more likely to survive cephalosporin therapy [15].

The newer macrolides (clarithromycin and azithromycin) as an alternative therapy in pharyngotonsillitis have the advantage of higher compliance over erythromycin because of their longer half-life and fewer adverse gastrointestinal side effects. For *Corynebacterium diphtheriae* pharyngotonsillitis, however, erythromycin is the drug of choice and penicillin or rifampin are alternatives. At the same time, it should be emphasized that the increased use of macrolides has been associated with an increase in GABHS resistance, with rates of up to 70% in Finland, Italy, Japan, and Turkey [13,16]. In recent years, the United States, too, has witnessed a significant increase in bacterial resistance to macrolides, reaching to about half of specific populations. Current rates range from 5% to 16% [16]. It is therefore advisable to restrict macrolide use for GABHS pharyngotonsillitis to patients with type 1 penicillin allergy.

The duration of treatment of pharyngotonsillitis for medications other than penicillin has not been investigated in large comparative controlled studies. However, some of the newer agents have been administered for shorter courses of 5 days or more (Table 2). Early initiation of therapy results in faster resolution of the signs and symptoms. Nevertheless, even without antimicrobials, the fever and other symptoms usually disappear spontaneously within 3 to 4 days. Rheumatic fever can be prevented even when therapy is postponed up to 9 days.

Patients with a history of rheumatic fever should be given prophylactic treatment for GABHS infection with daily oral or monthly benzathine penicillin. The American Heart Committee guidelines for the prevention of rheumatic fever should be followed, and if any family members are carrying GABHS, the disease should be eradicated and the carrier state monitored [17].

Supportive therapy for pharyngotonsillitis includes antipyretics and analgesics such as aspirin or acetaminophen, and attention to proper hydration.

Recurrent and Chronic Disease

Failure rates of penicillin for recurrent and chronic disease may be even higher than for acute disease. For recurrent or chronic pharyngotonsillitis, lincomycin, clindamycin and amoxicillin-clavulanate are considered good alternatives to penicillin [4, 18-20] (Table 3). Both clindamycin and the combination of penicillin and clavulanic acid, a beta-lactamase inhibitor, which are active against GABHS and *Bacteroides*, were found to successfully eradicate the infection [18,20]. Lincomycin, clindamycin, and amoxicillin-clavulanate are not superior to penicillin for acute disease. Other options in the chronic setting are a combination of rifampin plus penicillin or a macrolide (erythromycin) plus metronidazole.

Referral of a patient for tonsillectomy should be considered only after medical therapeutic modalities have failed.

Table 1. Infectious agents of pharyngotonsillitis and their clinical features

	Agent	Clinical Lesions	Clinical Frequency
I.	**Bacteria**		
	Aerobic		
	Groups A,B,C and G streptococci	F, Er, Ex, P	A
	Streptococcus pneumoniae	E	C
	Staphylococcus aureus	F, ER, Ex	C
	Neisseria gonorrhoeae	Er, Ex	C
	Neisseria meningitides	Er, Ex	C
	Corynebacerium diphtheriae	Er, Ex	C
	Cornebacterium hemolyticum	Er, Ex	C
	Arcanobacterium hemolyticum	Er, Ex	C
	Bordetella pertussis	Er,Er	C
	Haemophilus influenzae	Er, Ex	C
	Haemophilus parainfluenzae	Er, Ex	C
	Salmonella typhi	Er	C
	Francisella tularensis	Er, Ex	C
	Yersinia pseudotuberculosis	Er	C
	Treponema pallidum	F, Er	C
	Mycobacterium sp.	Er	C
	Anaerobic		
	Peptostreptococcus sp.	Er, E	C
	Actinomyces sp.	Er, U	C
	Pigmented *Prevotella* and *Porphyromonas*	Er, Ex, U	B
	Bacteroides sp.	Er, Ex, U	C
II.	**Mycoplasma**		
	Mycoplasma pneumoniae	F, Er, Ex	B
	Mycoplasma hominis	Er, ex	C
III.	**Viruses and Chlamydia**		
	Adenovirus	F, Er, Ex	A
	Enteroviruses (Polio, Echo, Coxsackie)	Er, Ex, U	A
	Parainfluenzae 1-4	Er	A
	Epstein-Barr	F, Er, Ex	B
	Herpes hominis	Er, Ex, U	C
	Respiratory syncytial	Er	C
	Influenzae A and *B*	Er	A
	Cytomegalovirus	Er	C
	Reovirus	Er	C
	Measles	Er, P	C
	Rubella	P	C
	Rhinovirus	Er	C
	Chalmydia trachomitis		
IV.	**Fungi**		
	Candida sp.	Er, Ex	B
V.	**Parasites**		
	Toxoplasma gondi	Er	C
VI.	**Rickettsia**		
	Coxiella burnetii	Er	C

Clinical lesions:

F = Follicular
Er = Erythematous
Ex = Exudative
U = Ulcerative
P = Petechial

Frequency:

A = most frequent (more than 66% of cases)
B = frequent (between 66% to 33% of cases)
C = uncommon (less than 33% of cases)

Table 2: Oral antibiotics for 10-day course of treatment of acute GABHS pharyngotonsillitis

Generic Name	Dosage		
	Pediatric (mg/kg/d)	Adult (mg)	Frequency
Penicillin-V	25-50	250	q6-18 hrs
Amoxicillin	40	250	q8 hrs
Cephalexin[a]	25-50	250	q6-8 hrs
Cefadroxyla	30	1000	q12 hrs
Cefaclor[a]	40	250	q8 hrs
Cefuroxime-axetil[a]	30	250	q12 hrs
Cefpodoxime-proxetil[a]	30	500	q12 hrs
Cefidini[a,d]	7 mg 14 mg	300 600	q12 hrs q24 hrs
Cefprozil[a]	30	250	q12 hrs
Ceditoren	NA	200	q12 hrs
Azithromycin[d]	12	250[c]	q24 hrs
Clarithromycin	7.5	250	q12 hrs
Cefixime	8	400	q24 hrs
Ceftibuten	9	400	q24 hrs
Erythromycin estolate	40	250	q 8-12 hrs
Amoxicillin-calvulanate[b]	45	875	q12 hrs
Clindamycin[b]	2-=30	150	q6-8 hrs

[a] Effective also against aerobic BLPB
[b] Effective also against aerobic and anaerobic BLPB
[c] First day dose is 500mg
[d] Duration of therapy 5 days
NA=not approved for children younger than 12 years

Table 3. Oral antimicrobials for acute and recurrent GABHS tonsillitis

Acute	Recurrent/ Chronic	Carrier State
Penicillin (amoxicillin)	Clindamycin Amoxicillin-clavulanate	Clindamycin
Cephalosporins[b]	Metronidazole & macrolide	Penicillin & rifampin
Clindamycin	Penicillin & rifampin	
Amoxicillin-clavulanate		
Macrolides[a]		

[a] GAS may be resistant
[b] All generations
Remark: For dosages and length of therapy, see Table 2.

Table 4.

Possible reasons for antibiotic failure or relapse in GABHS tonsilitis
Bacterial interactions • Presence of beta-lactamase–producing organisms that "protect" GABHS from penicillins • Co-aggregation of GABHS and *Moraxella catarrhalis* • Absence of members of the oral bacterial flora capable of interfering with the growth of GABHS (through production of bacteriocins and/or competition for nutrients)
Internalization of GABHS (survives within epithelial cells, thereby escaping eradication by penicillins)
Resistance (i.e., erythromycin) or tolerance (i.e., penicillin) to the antibiotic used
Inappropriate dose, duration of therapy, or choice of antibiotic
Poor compliance with taking medication
Reacquisition of GABHS from a contact or an object (i.e. toothbrush, dental retainer or dental braces)
Carrier state, not disease

Table 5.

Indications for the use of antimicrobial other than a penicillin for GABHS tonsillitis
Presence of beta-lactamase-producing bacteria (recent antibiotic exposure, winter, region)
Absence of "interfering flora" (recent antibiotic therapy)
Recurrent GABHS tonsillitis
Past failures to eradicate GABHS
High failure of penicillins in the community
Co-morbidities
When failure is a medical, economic, or social hardship
Penicillin allergy (non-type I)

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