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Nonstreptococcal Pharyngitis

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Pharyngitis is the third most common illness diagnosed by pediatricians in the United States. Group A β-hemolytic streptococci account for only approximately 30% of episodes of symptomatic pharyngitis. A broad list of other pathogens, including both bacteria and viruses, as well as Toxoplasma gondii and Candida species, are suggested frequently as the pathogens responsible for the remaining 70% of cases. This article reviews the evidence for a causative role of β-hemolytic streptococci other than Streptococcus pyogenes and other bacteria and viruses in outbreaks and sporadic cases of pharyngitis. Recommendations for the diagnosis and management of pharyngitis caused by pathogens other than S pyogenes are offered.

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Pharyngitis is the third most common illness diagnosed by pediatricians in the United States.1 Numerous pathogens have been associated with symptomatic pharyngitis. Attention has focused primarily on group A β-hemolytic streptococci (GABHS), which are estimated to be responsible for about 30% of all episodes of pharyngitis.2 This attention has been reinforced by the fact that treatment of pharyngitis caused by GABHS abbreviates the course of the clinical illness and prevents the development of rheumatic fever. The remaining cases of pharyngitis are caused by a broad list of other pathogens, including a variety of viruses and bacteria, as well as Toxoplasma gondii and Candida species (Table 1).1

Bacteria

β-Hemolytic Streptococci Other Than Streptococcus Pyogenes

Streptococci from Lancefield groups other than A (especially Groups C and G) have been associated definitively with outbreaks (often food-borne) of pharyngitis.3,4 However, their roles in causing sporadic cases of pharyngitis remain controversial. Little evidence exists to suggest that either group B or F streptococci are frequent or important causes of pharyngitis.6,7

The genetic heterogeneity of Lancefield groups C and G streptococci probably has contributed to the lack of consensus on the role(s) of these bacteria as causes of endemic pharyngitis. Lancefield group C streptococci are distinguished morphologically as being large or small colony formers.8,9 Large-colony β-hemolytic group C streptococci are identified as Streptococcus equi. There are three subspecies (ssp) within S equi: equi, equisimilis, and zooepidemicus.8,9 Neither S equi ssp equi nor S equi ssp zooepidemicus is recovered frequently from human sources. However, the latter subspecies has caused human infections after ingestion of unpasteurized milk or dairy products, and many patients identified in these outbreaks developed glomerulonephritis.5,9 In contrast, S equi ssp equisimilis regularly is recovered from humans. There are also small- and large-colony β-hemolytic group G streptococci. Of interest, S equi ssp equisimilis and human biotypes of large-colony β-hemolytic group G streptococci are closely related.5 Among the small-colony group C β-hemolytic bacteria, S anginosus is also recovered frequently from humans.6,10

Most of the initial evaluations of the roles of groups C and G beta-hemolytic streptococci as causes of pharyngitis did not differentiate among the various species and subspecies found in these groups. In a study that did not specify strains of group C streptococci, Hayden et al reported similar rates of groups C and G streptococci recovered from the throats of children with pharyngitis (mean age 11 years) compared with cultures obtained from healthy age-matched controls.11 Recovery of these strains occurred more frequently in older children and adolescents, however. In addition, these investigators reported an increased rate of recovery and group C (but not group G) streptococci from college students with pharyngitis compared with similarly aged controls observed for noninfectious problems.12 Patients with pharyngitis caused by group C streptococci experienced an illness similar to that caused by GABHS. They were more likely to have fever, headache, tonsillar exudate, and anterior cervical adenopathy than were symptomatic students whose cultures were negative for β-hemolytic streptococci.

Recent investigations have tended to take into account the genetic relationships of groups C and G streptococci. Cinolai et al performed a case-control study of children older than 2 years of age with clinical evidence of pharyngitis.6 Although differences in the rates of recovery of groups C and G streptococci were not appreciated between patients and controls, a trend towards significance was noted when results from the genetically-related S equi ssp equisimilis and large-colony strains of
Although M proteins similar to those found in rheumatogenic equisimilis S anginosus equisimilis prospective controlled trials. disease caused by heavy growth of either of the closely related species of streptococci. Accordingly, these investigators suggested that a Group differences between cases and controls in the rates of recovery of when the comparison was limited to moderate or heavy growth. fever might be caused by these bacteria. Evidence that treat- ing that both could be found as normal flora in as,~anptomatic individuals. However, in a companion article, this same group 

| Bacteria                              | Viruses                  | Fungi               |
|---------------------------------------|--------------------------|---------------------|
| Streptococcus pyogenes                | Adenoviruses             | Actinomyces        |
| Streptococcus equi ssp equisimilis    | Epstein-Barr virus       | Candida sp          |
| Streptococcus equi ssp zooepidemic*   | Herpes simplex 1 and 2   |                     |
| Group G B-hemolytic strepto-          | Enteroviruses            |                     |
| cocci (large colony)                  | Rhinovirus               |                     |
| Arcanobacterium haemolyticum          | Influenza A and B        |                     |
| Mycoplasma pneumoniae                 | Parainfluenza virus      |                     |
| Neisseria gonorrhoeae                 | Coronavirus              |                     |
| Corynebacterium diphtheriae           | HIV                      |                     |
| Corynebacterium ulcerans              |                          |                     |
| Yersinia enterocolitica               |                          |                     |
| Yersinia pestis                       |                          |                     |
| Treponema pallidum                    |                          |                     |
| Francisella tularensis                |                          |                     |

*Associated with pharyngitis in food-borne outbreaks.

Group G were combined. This difference became significant when the comparison was limited to moderate or heavy growth (2+, 3+) of these streptococci. In contrast, they did not find differences between cases and controls in the rates of recovery of Group C S anginosus or other non-Group A beta-hemolytic streptococci. Accordingly, these investigators suggested that a heavy growth of either of the closely related species of S equi ssp equisimilis or beta-hemolytic group G streptococci may be associated with clinical pharyngitis in children, whereas other B-hemolytic streptococci were unlikely to cause clinical disease.

Fox et al compared the rates of recovery of S equi ssp equisimilis and S anginosus in college-aged patients with pharyngitis and healthy controls. Similar rates of recovery of both bacterial subspecies were found from cases and controls, suggesting that both could be found as normal flora in asymptomatic individuals. However, in a companion article, this same group of investigators reported that patients who had S equi ssp equisimilis recovered from their throats had clinical features more similar to those observed with pharyngitis caused by GABHS than to the symptoms observed in patients from whom S anginosus was isolated. The investigators concluded that disease caused by S equi ssp equisimilis probably developed in some older adolescents, whereas S anginosus was unlikely to be a true pathogen.

Data regarding the usefulness of treating pharyngitis caused by these organisms are not available. The major indications for treatment of patients would be either to prevent nonsuppura- tive sequelae or to provide symptomatic relief of pharyngitis. Although M proteins similar to those found in rheumatogenic strains of GABHS have been detected in some group C (including S equi ssp equisimilis) and group G streptococci, no cases of rheumatic fever after pharyngitis with either group have been reported. However, investigators have not looked in a systematic fashion for groups C or G streptococci in patients with rheumatic fever. Thus, it is possible that some episodes of rheumatic fever might be caused by these bacteria. Evidence that treatment will provide symptomatic relief needs to be established in prospective controlled trials.

In summary, S equi ssp equisimilis and large-colony B-hemolytic group G streptococci may be causes of pharyngitis. However, current data do not support active efforts to confirm this diagnosis or to offer treatment to patients with this syndrome.

**Arcanobacterium Haemolyticum**

Arcanobacterium haemolyticum (formerly known as Corynebacterium haemolyticum) is an uncommon cause of pharyngitis in adolescents and young adults. The clinical syndrome associated with infection caused by A haemolyticum is indistinguishable from that caused by GABHS. Typical symptoms include sore throat, fever, and lymphadenopathy. A skin rash, often described as scarletinaform, occurs in more than 50% of cases and usually follows onset of pharyngeal symptoms by 1 to 4 days.

The diagnosis of pharyngitis caused by A haemolyticum is based on recovery of the organism from a throat culture of a symptomatic patient. A haemolyticum is a gram-positive pleomorphic rod whose colonies exhibit a 1 mm zone of hemolysis on human and rabbit blood agar. Production of hemolysis is inferior when the organism is grown on sheep's blood agar. The presence of colonies of A haemolyticum should be suspected by recognition of a black opaque dot that can be observed if the colony is scraped away after 48 hours of growth. To date, routine culturing for the presence of A haemolyticum for patients with pharyngitis is not recommended, and infected patients are likely to be missed by standard throat culture techniques.

The necessity of treating pharyngitis caused by A haemolyticum is unproven. However, antimicrobial therapy is said to be associated with a shortened duration of clinical illness. In vitro susceptibility tests have shown A haemolyticum to be susceptible to penicillin and erythromycin, as well as a number of other agents. Nonetheless, treatment of suspected cases of pharyngitis caused by A haemolyticum should be undertaken with erythromycin, as there have been reports of clinical failure and in vitro tolerance when penicillin has been used.

**Chlamydia and Mycoplasma**

Komaroff et al have suggested an etiological role for Chlamydia trachomatis and Mycoplasma pneumoniae in cases of pharyngitis in adults. Using serological evidence as the basis of diagnosis, these investigators reported that approximately 20% and 10% of 763 adults with pharyngitis had a four-fold rise in antibodies against C trachomatis and M pneumoniae, respectively. However, subsequent studies have failed to confirm this observation. McMillan and colleagues performed a case-control study of the causes of pharyngitis in school-age children (4 to 18 years). The etiological diagnosis was based on cultures performed for M pneumoniae, C trachomatis, and respiratory viruses. The investigators did not recover a single positive culture for C trachomatis from any of 302 children with sore throat or from any of 308 healthy controls. Similarly, Gerber et al did not recover a single positive culture for C trachomatis from 95 college students with acute pharyngitis. Huovinen and colleagues also evaluated the role of Chlamydia and Mycoplasma in pharyngitis in adults by culture and serology. Similar to the studies of McMillan and Reed, none of 106 patients was found to have evidence of C pneumoniae.
**Pneumoniae**

Adenoviruses are the most common viral agents associated with pharyngitis. Viral infections account for the vast majority of episodes of pharyngitis, particularly in children under 5 years of age. Edwards et al recovered adenoviruses from approximately 15% of young children prospectively followed from birth up to 7 years of age who presented with acute pharyngitis. Additionally, evidence that adenoviruses may account for approximately 10% of episodes of pharyngitis in older children and adolescents, recommendations for routine diagnosis and treatment of this pathogen in patients with sore throats have not been made.

**Other Bacteria**

A number of other bacteria have been identified as uncommon causes of pharyngitis. These organisms include *Neisseria gonorrhoeae, Corynebacterium diphteriae, Corynebacterium ulcerans, Yersinia enterocolitica, Yersinia pestis, Treponema pallidum, and Francisella tularensis*, as well as anaerobes (*Vincent's angina,*). Consideration of these organisms as causes of pharyngitis should be limited to appropriate epidemiological circumstances.

**Viruses**

Viral infections account for the vast majority of episodes of pharyngitis. Viral causes of pharyngitis are distinguished most easily from disease caused by GABHS by their frequent presentation with manifestations of upper (eg, the common cold) or lower respiratory tract disease (eg, laryngotracheitis, bronchiolitis, or pneumonia). The most frequent and important viral causes of pharyngitis include adenoviruses, Epstein-Barr virus (EBV), herpes simplex viruses types 1 and 2, enteroviruses, and the common respiratory viruses (rhinoviruses, respiratory syncytial virus, influenza, parainfluenza virus, and coronavirus). The topic of viral pharyngitis recently was comprehensively reviewed in this journal. Accordingly, the current review will highlight several of the most frequent viral pathogens associated with pharyngitis, as well as the role of HIV as a cause of acute pharyngitis.

**Adenoviruses**

Adenoviruses are the most common viral agents associated with pharyngitis, particularly in children under 5 years of age. In contrast, pharyngitis caused by adenoviruses occurs infrequently in older children and adolescents. Edwards et al recovered adenoviruses from approximately 15% of young children prospectively followed from birth up to 7 years of age who presented with fever and pharyngitis. Similarly, Moffet et al reported adenoviruses in 23% of young children hospitalized with exudative pharyngitis. Unfortunately, the clinical presentation of pharyngitis caused by adenovirus is not specific and often is accompanied by the presence of coryza or otitis media. Bronchiolitis, croup, and pneumonia are observed less frequently. One relatively characteristic result suggestive of adenoviral infection is the association of pharyngitis with conjunctivitis, known as pharyngoconjunctival fever. Although most adenoviral diseases occur during the winter and spring, this latter syndrome classically presents during the summer and is likely to spread through swimming.

**Epstein-Barr Virus**

EBV is the major cause of classic infectious mononucleosis. This infection typically occurs in the older child or adolescent who presents with fever, malaise, anorexia, exudative pharyngitis, diffuse lymphadenopathy, or splenomegaly. Although many episodes of EBV infection may be asymptomatic or atypical in younger children, a classic presentation also may occur. Sumaya et al found that 64 of 113 children diagnosed with EBV-associated mononucleosis were less than 6 years of age. Approximately 50% of both older and younger patients presented with exudative pharyngitis. The constellation of symptoms associated with EBV disease was similar in children less than 4 years of age compared with older children, except that younger patients were more likely to have hepatosplenomegaly, mucopurulent nasal discharge, and a rash. The diagnosis may be missed in the younger child because the heterophile response is decreased in children under 4 years of age. The diagnosis can be confirmed by a panel of specific EBV serologic tests. Recent studies have failed to show any benefit of treatment of EBV-associated mononucleosis with oral acyclovir alone or in combination with steroids.

**HIV**

HIV recently has been recognized to cause pharyngitis as part of the acute retroviral syndrome. Fever and pharyngitis have been identified as the primary sign of HIV infection in a cluster of cases of HIV that were linked by sexual contact. In addition to the symptom of pharyngitis, patients experiencing the acute retroviral syndrome often develop an illness that mimics infectious mononucleosis. The significance of recognizing this syndrome may be the opportunity to provide antiretroviral therapy before the dissemination of HIV within the body.

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