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PHARYNGITIS

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Pharyngitis encompasses infection or irritation of the pharynx and tonsils. Rarely found in infants younger than 1 year and uncommon in infants younger than 2 years, the illness peaks between ages 4 to 7 years but recurs throughout life, especially whenever people congregate and in the winter months.[9] Viral agents are the usual culprits.[7,21] Although group A β-hemolytic streptococcus (GABHS) causes only 15% of all pharyngitis, it is the usual bacterial cause and may cause significant nonsuppurative sequelae in the form of acute rheumatic fever (ARF) or acute glomerulonephritis (AGN). All types of pharyngitis can lead to suppurative complications including cervical lymphadenitis, peritonsillar abscess, retropharyngeal abscess, sinusitis, and otitis media.

CAUSE

The usual and unusual causes of pharyngitis are listed:

- **Infectious Agents**
  - A. Viruses
    1. Common: each agent responsible for 6% to 20% of all cases
       a. Rhinovirus
       b. Adenovirus
    2. Less common: each agent responsible for 1% to 5% of all cases
       a. Epstein-Barr virus (EBV)
       b. Herpes simplex
       c. Influenza
       d. Parainfluenza
       e. Coronavirus
    3. Uncommon: each agent responsible for less than 1% of all cases
       a. Enterovirus (poliovirus, coxsackievirus, echovirus)

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b. Respiratory syncytial virus
c. Cytomegalovirus (CMV)
d. Rotavirus
e. Reovirus
f. Rubella
g. Herpes zoster
h. Rubeola (measles)
i. HIV-1

B. Bacteria
1. Common: each agent responsible for 6% to 20% of all cases
a. *Streptococcus pyogenes* (group A β-hemolytic, group C β-hemolytic)
2. Less common: each agent responsible for 1% to 5% of all cases
a. Mycoplasma (*M. pneumoniae, M. hominis* [possibly])
b. *Arcanobacterium haemolyticus*
3. Uncommon: each agent responsible for less than 1% of all cases
a. *Streptococcus pyogenes* (group G β-hemolytic, group B β-hemolytic [possibly])
b. *Chlamydia pneumoniae*
c. Neisseria (*N. gonorrhoeae, N. meningitidis*)
d. Corynebacterium (*C. diphtheriae, C. ulcerans, C. pyogenes* [possibly])
e. Anaerobic bacteria (*Peptostreptococcus* sp., *Fusobacterium* sp., *Bacteroids* sp.)
4. Rare
a. *Leptospira* sp.
b. *Actinomyces* sp.
c. *Francisella tularensis*
d. *Borrelia (B. burgdorferi, B. recurrentis)*
e. *Streptobacillus moniliformis*
f. *Salmonella typhi*
g. *Legionella pneumoniae*
h. *Yersinia enterocolitica*
i. *Treponema pallidum*
j. *Coxiella burnetii*
k. *Klebsiella pneumoniae*

C. Fungi: all rare
1. *Candida* sp.
2. *Rhinosporidium seeberi*
3. *Cryptococcus neoformans*
4. *Histoplasma capsulatum*
5. *Blastomyces dermatitidis*
6. *Paracoccidoides brasiliensis*

D. Parasites: rare
1. *Toxoplasma gondii*

- **Diseases of Unknown Cause**
A. Kawasaki disease
B. Stevens-Johnson disease
C. Behçet's syndrome
D. Aphthous stomatitis
E. Systematic lupus erythematosus

- **Other**
A. Allergy
B. Trauma

1. Foreign body
2. Burns

C. Chemotherapy
D. Neoplasia
1. Polyps
2. Cancer
3. Leukemia

E. Radiation
F. Irritation
1. Toxin
a. Inhaled
b. Swallowed
2. Dust
3. Smoke
4. Dryness

G. Psychosomatic
H. Referred pain
1. Subacute thyroiditis

- **Overuse syndromes**

Infection with a virus or a bacteria accounts for the vast majority of cases. A parasite or fungus rarely is at fault. Other causes include trauma, irritants, cancer, and various syndromes of unknown cause. Age, time of year, environment, and exposure all dictate likely cause. In young children viral agents predominate; in older children and adolescents GABHS and other bacteria more often are encountered; in adults less invasive bacteria and viruses are found with equal frequency. In a study of 106 adults with acute pharyngitis,[24] GABHS was found in 5, group C β-hemolytic streptococci in 13, group G in 5, group F in 1 (of questionable significance), *Mycoplasma pneumoniae* in 10, *Chlamydia pneumoniae* in 9, and viruses in 27. Thirty-three patients had no isolable organism, and 3 had simultaneous infection with two organisms.

VIRUSES

Most cases of acute pharyngitis are the result of viral infection.[7,21] Hundreds of viruses, most of which fail to induce prolonged immunity, can infect the throat. One hundred types and one subtype of rhinovirus cause about 20% of all pharyngitis.[21] Coronavirus (at least three types), adenovirus (types 1–7, 9, 14–16, and 21), and parainfluenza virus (types 1–4) each incite about 5% of cases of pharyngitis.[21] Other common viral causes include influenza virus (A and B), herpes simplex virus (1 and 2), coxsackievirus A (types 1–6, 8, 10, 16, and 22) and B. Many of these agents, EBV, or CMV can produce pharyngitis that is difficult to distinguish clinically from group A streptococcal infection.[7,21] HIV-1 recently has been noted to produce acute sore throat similar to infectious mononucleosis (IM).[47]

With a few exceptions, such as infectious mononucleosis, viral pharyngitis tends to develop after rhinitis, and in children it often accompanies cough. Rhinitis and cough are rare in GABHS pharyngitis. In viral disease the pharyngitis may not be the pressing complaint and is worsened by nasal blockade and breathing via the mouth especially during sleep. About 50% of people with rhinovirus or coronavirus colds have a scratchy, sore throat. Similarly, 50% to 80% of those with influenza A, parainfluenza, or adenovirus have pharyngeal discomfort. In adults with viral pharyngitis, fever and cough tend to be absent. Edema and redness of the pharynx are usual, but the degree of exudate is less effusive than in bacterial

disease and painful lymphadenopathy is unusual. The course of events is gradual and centers on the nasal discharge, which is initially clear then in 2 to 3 days is greenish, then in another 2 to 3 days clear, then in another 1 to 2 days gone. Although viral disease clinically cannot be differentiated definitely from bacterial disease, a few specific viral presentations allow some diagnostic accuracy.

Infectious Mononucleosis[14]

The primary agent of IM, EBV, usually spreads through saliva and rarely through blood transfusion. This self-limited illness incubates for 2 to 8 weeks before producing a severe pharyngitis, the most common complaint. Malaise, anorexia, chills, and headache usually occur before the development of sore throat, fever, and regional lymphadenopathy. Fatigue, generalized lymphadenopathy, hepatosplenomegaly, and complications follow in 5 to 14 days. Fever as high as 40°C (104°F), periorbital edema, palatal petechiae, and tonsillar exudate (anginose variety) are common (Fig. 1). About 5% of patients have a fine variable-form rash, but more than 90% given ampicillin develop a diffuse, itchy, maculopapular eruption of 5-days to 14-days duration (an unwanted but partially diagnostic clue). Nausea and vomiting afflict 20% of infected individuals. Diarrhea, renal failure, and uveitis also occur but in less than 1%.

Physical examination often shows extreme tonsillar hypertrophy with a coating, membranous exudate. The pharyngitis is severe for 5 to 7 days and may interfere with swallowing. During the next 10 days it resolves. Fever lasts 1 to 2 weeks or longer. In 3 to 6 weeks the lymphadenopathy and splenomegaly generally resolve, whereas malaise may persist for 6 months. Because EBV resides in nasopharyngeal cells, constant nasopharyngeal viral shedding commonly lasts up to 18 months, with intermittent shedding lifelong thereafter.[14] Patients without high fever and severe sore throat are more likely to suffer from prolonged fatigue, but most persons return to school or work in 1 to 3 weeks. Because of the rare

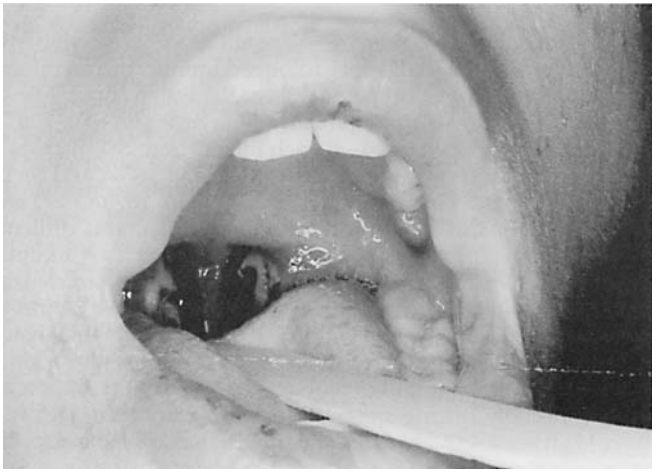


Figure 1. Infectious mononucleosis. Note the thick, continuous tonsillar exudate and swollen uvula.

complication of splenic rupture, contact sports should be avoided for 6 weeks. Other complications of EBV are listed:

- Hematologic (autoimmune-mediated): 1% to 2% of patients
  Thrombocytopenia
  Granulocytopenia
  Hemolytic anemia: anti-i antibody
- Neurologic: 1% to 2%
  Guillain-Barré syndrome
  Encephalitis (especially cerebellar)
  Neuropathy
    Cranial nerve (Bell's palsy)
    Peripheral mononeuritis or polyneuritis
  Transverse myelitis
  Aseptic meningitis
  Cognitive loss
  Depression
  Psychosis
  Seizures
- Cardiac: less than 1%
  Myopericarditis (EKG abnormality)
  Coronary artery spasm (infarction may occur)
- Pulmonary: less than 1%
  Obstruction of airway
  Pneumonitis
- Splenic rupture: extremely rare
- Hepatitis: 20% to 50%; 5% jaundiced

Diagnosis of IM rests on clinical suspicion coupled with positive antibody tests for EBV. Complete blood counts show atypical lymphocytosis or the hematologic complications listed previously. The monospot test reveals heterophil antibodies in up to 95% of patients with IM. These antibodies are not directed against EBV but are induced by EBV. EBV-specific viral capsid antigen IgM antibody, the best indicator of primary infection, develops in 100% of cases. Viral capsid antigen IgG is a marker for prior infection. Epstein-Barr nuclear antigen antibody develops within 3 to 6 weeks and is a useful marker of acute infection if initially negative tests become positive. Early antigen-diffuse antibodies suggest severe disease. A positive early antigen-diffuse IgA correlates with a higher risk of nasopharyngeal carcinoma, whereas a positive early antigen-restricted IgA suggests a risk of Burkitt's lymphoma.

Early in childhood, EBV infection is often asymptomatic, but adolescents and young adults are particularly likely to develop severe pharyngitis. The older the individual, therefore, the more likely EBV is at fault. The carriage of concomitant GABHS has been reported in 2% to 33% of cases of IM.[14] Whether these individuals truly are infected is unclear. When in doubt, the wisest choice is to culture the throat or do a rapid streptococcal antigen test and treat when either is positive.

Treatment for EBV is largely symptomatic. Little if any evidence supports the old advice that bed rest is helpful. Acetaminophen or ibuprofen eases pain and fever. Steroids dramatically relieve airway obstruction, sore throat, and fever; seem to improve thrombocytopenia and hemolytic anemia; and may help in other life-threatening complications, but they are not useful for neurologic disease. Prednisone, 1 mg/kg/24 h for 7 to 10 days (often with a 5-day to 7-day tapering added), is one useful regimen. Despite worries to the contrary, rebound pharyngitis following steroid therapy is rare and, when present, usually responds to a second

course.[5] However, the long-term consequences of prescribing steroids to patients infected with a virus that can survive in the tissues for years is unknown. EBV is especially worrisome because of its link to cancer; therefore, the clinician probably should avoid routinely prescribing steroids. Specific antiviral therapy with acyclovir, ganciclovir, and interferon-α has no clinical benefit, although these drugs do reduce viral shedding.

Cytomegalovirus[23]

Patients with typical IM who are monospot or EBV titer negative may have CMV pharyngitis. Patients infected with CMV are often older and sexually active and have higher fever and greater malaise but less prominent pharyngitis and lymphadenopathy.[23] In fact, the pharynx may look relatively normal. Patients are ill for 2 to 6 weeks. Diagnosis rests on isolation of CMV from blood or other deep tissue, or from urine or saliva when coupled with a fourfold or greater antibody titer rise. The best diagnostic tests are CMV-specific IgM and IgG antibody titers, with a positive IgM suggesting recent infection. Treatment is symptomatic unless patients are immunocompromised, in which case ganciclovir or foscarnet may provide effective control.[50]

Adenovirus

Adenovirus may produce typical pharyngitis *or* pharyngoconjunctival fever, which occurs in about one half of cases.[7,21] The clue to the latter diagnosis is conjunctivitis. It is most commonly follicular and in about one fourth of patients bilateral. The sore throat is more intense than that of a common upper respiratory tract infection, and extreme pharyngeal erythema and exudate are often evident. Military personnel tend to be sicker with hoarseness, chest pain, and respiratory distress.[1] The illness resolves spontaneously in 6 to 7 days. In children uncomplicated pharyngitis is most commonly caused by adenovirus, types 1 to 3 and 5.[10]

Coxsackievirus

Coxsackievirus has a peak occurrence in the late summer and early fall. Multiple small vesicles of 1-mm to 2-mm size on the tonsils, tonsillar pillars, uvula, or soft palate suggest herpangina caused by coxsackievirus A. Vesicles may enlarge to 4 mm or have a red ring up to 10 mm in size, and they may number from 1 to 20. The remainder of the pharynx is usually normal. When the lesions are whitish and nodular, the illness is referred to as lymphonodular pharyngitis. After a 3-day to 10-day incubation period the presenting complaint is usually the sudden onset of fever to 41°C (106°F), often with coryza. Young children have severe odynophagia, and because of the fever height, they easily may develop dehydration. One quarter also vomit. Older children develop neck pain, headache, and back pain. Most cases fortunately remain relatively mild, and in 3 to 6 days the illness subsides.

Coxsackie A16 is the major cause of hand, foot, and mouth disease. After a 4-day to 6-day incubation period, patients develop intraoral 4-mm to 8-mm ulcers on the tongue, buccal mucosa, or occasionally tonsillar pillars. Vesicles develop on the hands and feet or occasionally buttocks, but afflicted persons are rarely severely ill. In about 1 week the illness abates.

Herpes Simplex

Mild herpes simplex virus pharyngitis is indistinguishable from other viral presentations, but severe disease usually resembles acute GABHS. Painful, shallow ulcers with red borders or vesicles on the soft palate, gums, lips, or buccal surface help distinguish herpes simplex from other causes. Fever and lymphadenopathy are frequent. In children younger than the age of 5 years, herpes gingivostomatitis produces severe ulcerative lesions on the buccal mucosa, tongue, and soft palate; high fever (up to 41°C [106°F]); and intense pain. Recurrent HSV-1 in the form of cold sores is common. In individuals with immunodeficiency, large painful, persistent oral ulcers suggest herpes simplex. Acyclovir (5 mg/kg every 8 hours intravenously, or 200 mg five times a day orally for 5 days), famciclovir, and valacyclovir (250 mg three times a day orally for 5 days) all may prove helpful in severely afflicted individuals.

Human Immunodeficiency Virus

HIV-1 characteristically causes febrile pharyngitis.[47] Approximately 4 weeks of incubation is followed by sore throat, fever, myalgia, arthralgia, and lethargy. Lymphadenopathy and rash follow. Exudate on the tonsils rarely, if ever, occurs, which is a sign that HIV is not present. Ulcerations such as aphthous ulcers and pharyngeal hyperemia are common. A detailed history should reveal those at risk.

Influenza

In influenza A or B pharyngitis is a major complaint, but myalgia, headache, and cough are also prominent. Severe pharyngitis is particularly common with influenza A. The time of the year for epidemics, that is, winter and early spring, coincides with the peak occurrence of GABHS. Extreme elevations in temperature to 40°C (104°F) are common, but pharyngeal or tonsillar exudate is not. Tender cervical nodes are uniformly absent. The pharyngitis usually resolves in 3 or 4 days. Treatment with anti-influenzal drugs (amantadine, 4.4 to 8.8 mg/kg/d divided into two doses with a maximum of 150 mg for those aged 1 to 9 years, or 100 mg twice daily for those aged 19 years or older for 5 to 7 days, or rimantadine) may hasten resolution.

The surveillance system of the public health department provides the real tip-off to the presence of influenza in the neighborhood. All patients at special risk, those older than age 65 years and those wishing protection, should receive timely (late October to early November) influenza vaccination.

BACTERIA

The bacteria causing pharyngitis are listed previously. The most common and most important is GABHS. Because pharyngeal infection with this organism is associated with ARF and to a lesser extent with AGN, the diagnosis and treatment of pharyngitis must be part of the common base of knowledge for all primary care physicians. Unlike otitis media, which can damage end-organ function (i.e., hearing), or sinusitis, which can persist for a prolonged, irritating time, most bacterial pharyngitis is self-limiting and uncommonly produces sequelae. When complications such as retropharyngeal abscess, peritonsillar abscess, or suppurative cervical lymphadenitis occur, however, they can be readily treated surgically. Non-

suppurative end-organ damage to the heart in ARF or to the kidneys in AGN is not managed so easily.

Important bacteria previously listed are reviewed in the following section. Noticeably absent are *Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus* and *epidermidis*, and *Streptococcus pneumoniae*. These bacteria cause many other localized upper airway infections but not pharyngitis.

GABHS Pyogenes

The GABHS is the most important agent in acute pharyngitis because of its ability to produce local suppurative disease such as peritonsillar abscess, overwhelming systemic illness such as toxic shock, and the nonsuppurative sequelae of ARF and AGN. This organism produces many extracellular toxins: three types of pyrogenic exotoxin (A, B, C) that cause the scarlet fever rash; streptolysin O, toxic to erythrocytes and leukocytes and inhibited by oxygen, and streptolysin S, toxic to numerous cells and thermolabile; four types of DNase; hyaluronidase; streptokinase (a boon to cardiac thrombosis therapy); NADase; proteinase; amylase; and esterase. These toxins allow great tissue penetration. GABHS replicates about every 20 minutes, and it spreads rapidly. Almost every body tissue is subject to infection, but the skin and the throat are favorite targets because of host-dependent surface receptor sites.

The streptococcal M protein is the key to the commonality of this organism and its link to ARF.[15] This protein is highly variable with more than 80 different known structures, making single antibody protection virtually impossible. It projects out of the streptococcus so that each organism appears as a fuzzy ball under higher-power microscopy. At its N-terminus is a negative charge that repels neutrophils. It also binds factor H, a human serum regulatory protein, thereby masking the whole bacteria from macrophage detection. Most importantly, the coiled-coil structure of all M proteins is strikingly similar to myocardial muscle protein. Antibodies made to M proteins therefore inadvertently cross-react with myocardial cells, resulting in carditis. The peak in ARF in late childhood may reflect the time needed to go through several bouts of GABHS pharyngitis and thus produce higher antibody levels in response to infection. The higher antibody levels eventually cause severe cardiac damage. This reaction luckily wanes in adults so that ARF is distinctly unusual in older individuals. Any M protein serotype can be rheumatogenic, but only specific serotypes (e.g., 12, 49, 55, 57, Red Lake strain) cause AGN, a complication due to antigen-antibody deposition in the kidney.

In the first 2 years of life pharyngitis is rare.[9] In one series only 29 of 715 cases of pharyngitis occurred in children younger than 2 years of age, and these were not related to GABHS.[10] Because of the infrequency of GABHS and the almost total absence of ARF in infants younger than 2 years old, the usefulness of diagnostic tests for GABHS in this age group is limited. Seromucoid rhinitis (streptococcosis) does affect this age group. Nonsuppurative sequelae do not occur, however.

Clinical Presentation of GABHS

Endemic year-round, GABHS pharyngitis has its peak occurrence in the late winter and early spring.[10,26] After an incubation period of 2 to 5 days, patients develop the sudden onset of a sore throat, painful swallowing, chills, and fever up to 40.5°C (105°F). Headache, nausea, vomiting and abdominal pain are common.

On physical examination, marked erythema of the throat and tonsils is accompanied by patchy, discrete tonsillar exudate; enlarged, tender anterior cervical lymph nodes; uvular edema; and sometimes a typical scarlet fever rash or palatal

petechiae (Fig. 2). Scarlet fever affects the trunk, cheeks, palms, and soles; is most evident in the antecubital space (Pastia's sign) or axilla; and often is accompanied by circumoral pallor or minute vesicles on the abdomen (miliary sudamina). When it resolves, skin desquamation is usual. It is not, of course, a sign of ARF. Urticaria may occur in response to GABHS infection. An initial white strawberry tongue denudes to become the classic red strawberry tongue. Severe rhinitis, cough, conjunctivitis, laryngitis, croup, and diarrhea suggest a cause other than GABHS. The white blood cell count is often high and may show eosinophilia.

Untreated GABHS pharyngitis is short-lived. Sore throat resolves in 3 to 4 days, fever in 3 to 5 days, and scarlet fever in 5 to 6 days. Antibiotic speeds recovery to 1 to 3 days. The percentage of persons with acute GABHS pharyngitis who are severely ill versus those who are mildly affected is unknown. As many as 30% of school children carry streptococci in their throats each winter; yet a bout of significant GABHS pharyngitis occurs on average only about every 4 years for each child.[10] Many infections therefore must be relatively asymptomatic. Nearly asymptomatic patients unfortunately still contract ARF. In one study[52] of 43 patients with ARF, only 32 had any symptoms of upper respiratory tract infection, only 20 had sore throat, only 11 were taken to a physician, and only 8 had throat cultures. Only six throat cultures were positive, and compliance rate with prescribed antibiotics was unknown.

Diagnosis

Throat culture remains the most effective method for diagnosis of GABHS. To culture the throat for GABHS, a sterile cotton swab should be rubbed over both tonsils or the tonsillar fossae and the posterior pharynx, preferably for more than 10 seconds but practically only for a few. If necessary, the swab can be placed in a dry, sterile paper wrapper and left at room temperature for up to 24 hours, but preferably less than 6 hours. A 5% sheep blood agar plate is inoculated with the swab (Fig. 3). Stabs are made into the agar, and a bacitracin disc (0.04 U of bacitracin, the A disc) is applied. Plates can be read in 24 hours. A positive culture shows beta hemolysis, a ring of inhibition about the A disc, and pinhead-sized

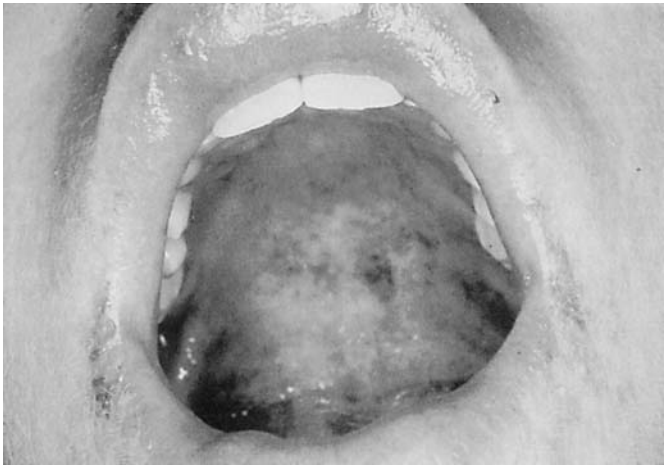


Figure 2. Palatal petechiae. Commonly seen in GABHS or EBV pharyngitis.

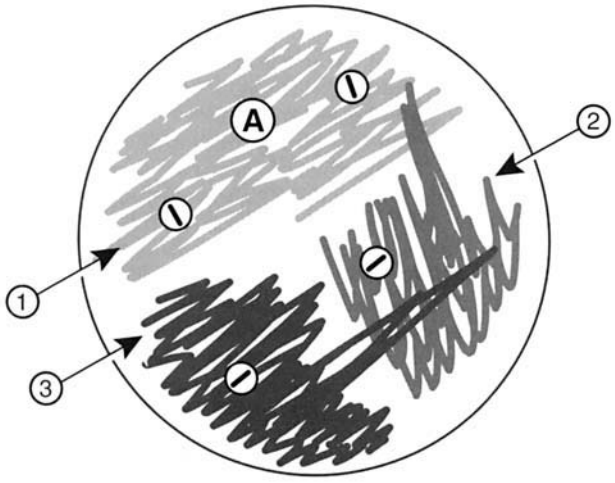


Figure 3. Plating for GABHS requires rolling the throat swab across area 1 of sheep blood agar plate. A wire loop is heated to red then briefly cooled. Two passes are made into area 1 and spread in area 2. This process is repeated from area 2 to 3 in an attempt to isolate single colonies of GABHS. The loop is heated again and then stabs (⊖) are made through the agar, first in area 3, then 2, then two in area 1. The loop is flamed red again after use. Finally, an A disc (A) is applied and lightly tapped down in area 1. The plate is labeled and incubated upside down at 37°C.

white colonies with a ring of hemolysis at least twice as large that can be slid across the agar without disruption. A recent study[39] has confirmed that this traditional method is as accurate as carbon dioxide–enhanced incubation, selective blood agar medium, special transport medium, Todd-Hewitt broth, or an anaerobic incubation atmosphere. A single sheep blood agar plate has a 96% sensitivity compared with these other systems. Throat culture plates cost about 60 cents each, but the time to set up and read them and Clinical Laboratory Improvement Act monitoring increase costs.

Rapid streptococcal antigen detection kits are also of great utility in making this diagnosis. Some 19 manufacturers produce these kits.[36] Although most claim a 95% to 99% specificity (true negatives), clinical trials suggest that 90% is more accurate. The manufacturers' claims of 90% to 95% sensitivity (true positives) have not been substantiated by the 60% to 80% found in clinical trials, however. In a case of suspected GABHS, therefore, a negative rapid streptococcal antigen test should be confirmed with a throat culture.[10] Rapid streptococcal kits cost between $2 and $4 each.[36] Optical immunoassay technology may offer results superior to standard rapid streptococcal tests.[42]

Figure 4 presents a scheme to use these tests appropriately. A decision about the severity of the pharyngitis, especially whether it is the major complaint, is required initially. This plan avoids excessive testing because the majority of rapid streptococcal tests are negative in mild disease and throat cultures then are necessary in addition. Rapid streptococcal tests might be beneficial in severe disease, but many physicians treat on the basis of clinical findings in this setting, whereas most withhold treatment in the moderately ill.

If both these tests are negative, but GABHS still is suspected or if a carrier state is suspected and proof of GABHS invasion is desired, blood tests for antibodies to streptococcal exotoxins are employed. The antistreptolysin O titer is pos-

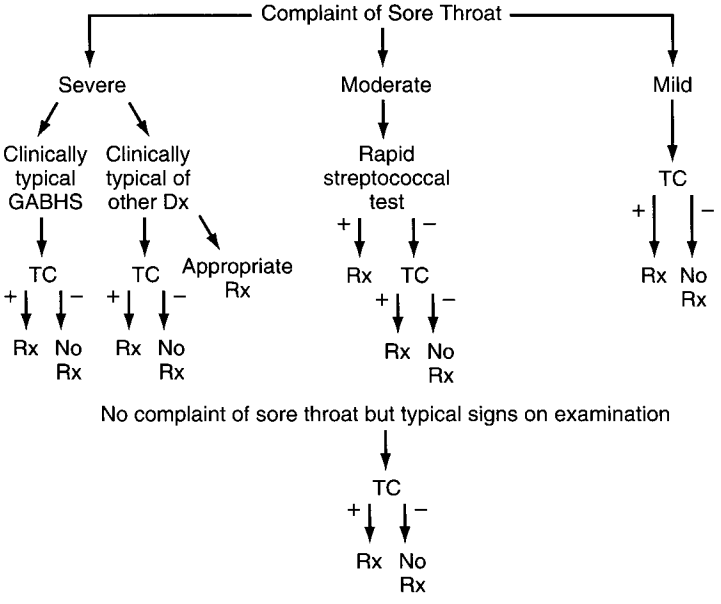


Figure 4. Diagnostic scheme for GABHS pharyngitis. Rx = treatment; + = positive; − = negative; TC = throat culture; Dx = diagnosis.

itive if it is more than 240 Todd U. A Streptozyme test for antistreptolysin-O, anti-DNase B, antihyaluronidase, anti-NADase, and antistreptokinase may be positive.

Treatment

All patients with GABHS (or any other form of pharyngitis) should receive symptomatic treatment. Gargling warm saltwater, drinking warm liquids, and resting are important. In one study[2] ibuprofen proved superior to acetaminophen for symptomatic relief in 6-year-old to 12-year-old children, but simultaneous use of both may be better. It is arguable whether definitive therapy in the form of antibiotics needs to be provided immediately to relieve symptoms in GABHS pharyngitis. The relief obtained with immediate antibiotic treatment is generally small (usually 1°F of fever and a 13% improvement in sore throat) and delayed (at least 9 hours).[33] Symptomatic support seems to provide excellent relief with or without immediate penicillin treatment.[28] Although some experts fear that early treatment may predispose to a higher rate of recurrent GABHS pharyngitis, one major review[16] suggests that this problem is unlikely. However, immediate treatment might allow earlier return to work or school, but this supposition remains unproven.

Definitive treatment is the prescription of penicillin V, 250 mg orally three or four times a day for 10 days or, if total compliance can be assured, twice a day for 10 days.[38] Penicillin is cheap, effective in preventing ARF, and relatively nontoxic.[44] GABHS is uniformly sensitive to penicillin. Recovery after 7 days of treatment is much lower than after 10 days so patients must use a 10-day regimen.[41]

If IM is not a possibility, amoxicillin may be substituted because it tastes better than penicillin, but one risks diarrhea, rash, and increasing resistance of other

bacteria to amoxicillin. Intramuscular benzathine penicillin G, 600,000 U for those weighing less than 60 lbs (27 kg) or 1.2 million U for heavier individuals, is also definitive treatment for those who cannot take oral penicillin. For individuals allergic to penicillin, erythromycin, 40 mg/kg in two to four divided doses per day, up to 1 g maximum, for 10 days, is suitable.[38] Erythromycin-resistant streptococci are reported but not a major problem in the United States.[3]

Clarithromycin and azithromycin[32] are also effective but too costly to use as first-line therapy. These two agents, however, eliminate almost all the other bacteria that cause pharyngitis as well. Clarithromycin comes as 125 mg or 250 mg per 5 mL or 250-mg or 500-mg tablets, and it is given 7.5 mg/kg twice a day, up to 500 mg/dose maximum, for 10 days. Azithromycin is available as 100 mg or 200 mg per 5 mL or 250-mg capsules, and it is given 12 mg/kg once a day for 5 days. A first-generation cephalosporin (cephalexin, 12.5 mg/kg or 250 mg three or four times a day for 10 days) is effective initially or in recurrent disease. Clindamycin is useful for individuals with recurrent pharyngitis who have failed penicillin treatment or are allergic to cephalosporin. Higher generation cephalosporins (cefadroxil[29]) are effective but expensive alternatives for this common problem. Tetracyclines and sulfonamides do *not* work.[9,10]

After penicillin treatment about 15% of throat cultures remain positive for GABHS. Alternative antibiotics that eliminate GABHS from the throat in about 97% of cases include ceftibuten,[35] cefpodoxime proxetil,[34] cefprozil [30]cefuroxime axetil,[18] cefixime[4] loracarbef,[12] cephalexin,[13] cefaclor,[37] azithromycin,[32] clarithromycin,[32] amoxicillin/clavulanate,[32] and likely others. However, these agents offer no advantage over penicillin in prevention of ARF or AGH,[35] in speed of recovery, or initial elimination of GABHS from the throat.[22] Treatment with penicillin or other appropriate antibiotic blunts the production of antistreptolysin-O and anti-DNase B antibody.[35] Tonsillectomy may help those with recurrent GABHS pharyngitis but should be reserved for children with at least seven documented infections in 1 year, five in each of 2 years, or three in each of 3 years.[11] With these prerequisites pharyngitis rates decrease about 50% after tonsillectomy.

Carriers of GABHS

At the end of any antibiotic therapy, some individuals remain positive for GABHS. When a patient carries GABHS for several weeks, it is no longer dangerous for that individual. Serum antibody reaction does not occur. The number of colonies of streptococci found on a throat culture is usually lower in a carrier than in the acutely infected.[10] One postulate is that many initially falsely negative throat cultures represent carriers rather than truly infected individuals. Contagiousness to others luckily is related inversely to length of time of carrying GABHS.[10] Reculture to avoid this problem is not recommended. Five percent to 30% of repeat throat cultures are positive for GABHS, probably because of noncompliance with the 10-day antibiotic regimen. ARF and symptomatic pharyngitis are rare in this situation, however. Other suggestions to account for the failure of penicillin such as bacterial tolerance or synergistic bacterial protection of GABHS have not been proven.

Most authorities presently advise culture of contacts only if the contacts are symptomatic. Clinicians should caution responsible persons to question children about the presence of symptoms because of the possibility of ARF occurrence in the relatively asymptomatic.[44] The reservoir of GABHS is most likely other humans outside the family. Although pets have been implicated as a potential source for recurrent disease, a recent study found no GABHS carriage in a random screen of 230 animals.[51] In a survey of 42 households with a child with acute pharyngitis, 26 children and no pets were found to harbor GABHS.[51] Siblings of those with

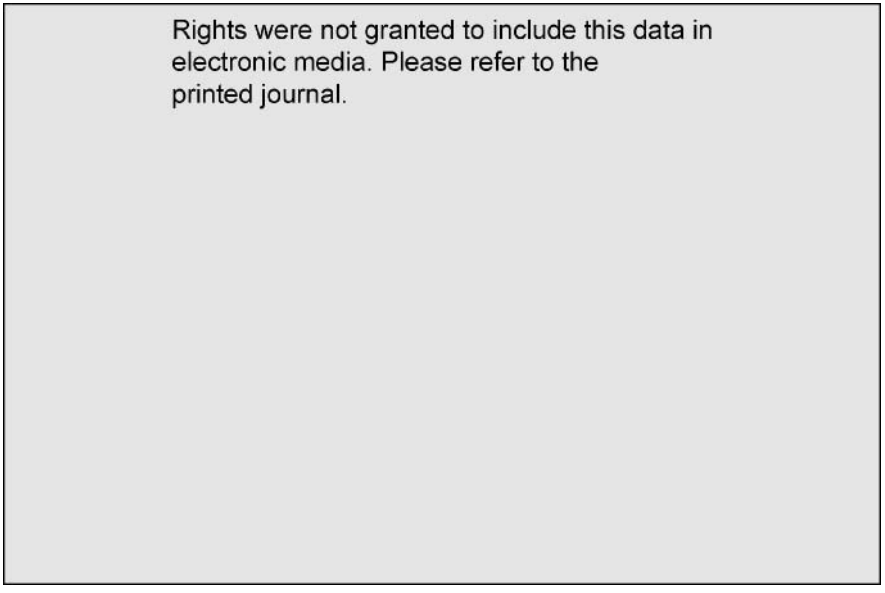
acute GABHS pharyngitis may have GABHS themselves, but these are often different serotypes. Recurrence rates may be no higher in families with GABHS-infested siblings (carriers).[40] These data challenge the traditional idea that children within a single household constantly pass GABHS from one to another.

Acute Rheumatic Fever

An increasing incidence of ARF since 1986 requires continued attention to GABHS pharyngitis.[3] The revised Jones criteria for the diagnosis of ARF are listed in Table 1.[20] Recent experience unfortunately has shown that many persons developing ARF have never been ill with pharyngitis and therefore have never seen a physician.[52] The experience at the Children's Hospital of Pittsburgh in 171 patients with ARF found between 1982 and 1993 is that outpatient treatment is frequently satisfactory.[27] Of these patients, 39 (23%) had only carditis, 34 (20%) had only arthritis, 28 (16%) had only chorea, 45 (26%) had carditis and arthritis, 21 (12%) had carditis and chorea, 3 (2%) had chorea and arthritis, and 1 (1%) had chorea, carditis, and arthritis. Overall, 106 (62%) children had carditis. These children usually recover without permanent valvular damage. In contradistinction, 90% of adults with ARF have arthritis, whereas carditis is uncommon.

Appropriate treatment of GABHS pharyngitis will abort the initial attack of ARF, which usually occurs 2 to 5 weeks after the pharyngitis. Delayed onset carditis and chorea are common. In individuals who suffer one attack of ARF, prophylactic treatment can prevent further bouts of ARF and significant cardiac damage. Four regimens are approved for prophylaxis[38]:

Table 1. JONES CRITERIA FOR RHEUMATIC FEVER



From Guidelines for the diagnosis of rheumatic fever—Jones criteria, 1992 update. JAMA 268:2070, copyright 1992, American Medical Association; with permission.

1. Penicillin V, 250 mg orally twice a day
2. Benzathine penicillin G, 1.2 million U intramuscularly every 4 weeks
3. Sulfisoxazole, 1 g orally once a day for persons who weigh more the 27 kg (60 lbs) or 500 mg for those weighing less
4. Erythromycin, 250 mg orally twice a day

Other daily antibiotics, including those used for acne, are also likely to be effective. Patients given sulfisoxazole should get a blood count 2 to 3 weeks after therapy is begun to look for leukopenia.

Debate about the duration of ARF prophylaxis can be mitigated through introspection. Because the risk of ARF is highest before age 18, all ARF victims should take prophylaxis at least until that age (although some favor age 30 years as the cutoff). Additionally, a minimum of 5 years of prophylaxis seems wise (although some favor lifelong treatment). Patients with severe carditis in the initial bout of ARF, those with existing severe ARF carditis, those living in GABHS-epidemic conditions, or those wishing to receive prophylaxis should be offered the longer courses.

Guidelines for prevention of subacute bacterial endocarditis are available in multiple sources, including the *1994 Red Book.*[38] These guidelines indicate how to prevent cardiac infection, not pharyngitis.

Poststreptococcal Glomerulonephritis

AGN following GABHS pharyngitis afflicts mostly early school-aged children in the winter or spring. Familial occurrence is common. Attack rates are about 15% after infection with a nephritogenic strain. Because these strains are unusual or spread in epidemic waves, the overall occurrence of AGN is 0% to 3%. A 10-day latency following onset of pharyngitis is followed by edema, hypertension, and rusty urination. Urinalysis reveals proteinuria and hematuria. One mechanism proposed to account for renal damage is antigen-antibody deposition in the glomeruli.

Penicillin treatment of pharyngitis unfortunately does not seem to prevent AGN, but it can abort dissemination of a nephritogenic strain. Treatment is otherwise supportive, aimed at the control of blood pressure and edema. Renal scarring with lifelong proteinuria or hematuria, or infrequently renal failure, can occur.

Non–Group A Streptococcal Pharyngitis

Non–group A streptococci produce pharyngitis indistinguishable from that of GABHS. College students and adolescents suffer from group C disease,[46] whereas community-wide and food-borne (cold, hard-boiled eggs) pharyngitis have been connected to group G organisms.[17,45] These organisms are not linked to nonsuppurative sequelae such as ARF and do not produce a major antibody response such as that which follows GABHS infection. The treatment therefore is aimed solely at symptomatic relief. Group C pharyngitis is often less severe than that of GABHS. Penicillin or erythromycin provides effective therapy, but the ideal length of treatment is unclear. Because groups C and G do not cause ARF, once the patient is asymptomatic, the reasons for continuing therapy for 10 days could be to prevent carriage, and hence the potential for hazard to others, or to prevent recurrence. Whether these goals are achieved by fewer than 10 days of treatment has not been investigated fully.

Anaerobic Pharyngitis

With anaerobic infection, a foul breath odor accompanies a membranous purulent exudate on the pharynx and tonsils. Malnutrition, leukopenia, immunodeficiency, and therapeutic neck irradiation predispose to this disease. Most anaerobes, including peptostreptococcus, fusobacterium, and bacteroides, are sensitive to penicillin. Complicating peritonsillar abscess (quinsy) or postanginal septicemia (Lemierre's disease) with jugular vein thrombophlebitis[31] poses fearful consequences in the immunocompromised patient. Anaerobes are the most frequent isolates from peritonsillar abscesses following any throat infection. Clindamycin, penicillin, cephalosporins, and β-lactamase–resistant penicillins fortunately are generally effective once the abscess has been drained.

Arcanobacterium haemolyticus

Arcanobacterium haemolyticus is a gram-positive (early culture) to gram-variable (later culture) rod that probably causes an acute pharyngitis indistinguishable from GABHS pharyngitis.[49] Afflicted adolescents and young adults, especially soldiers, uniformly develop sore throat with pharyngeal erythema; 70% develop exudate; 50% lymphadenopathy, primarily anterior cervical or submandibular; 40% fever to 39.2°C (102.2°F); 33% pruritus; and a variable percentage (up to 67%) nonproductive cough (a tip-off that GABHS is not involved). Palatal petechiae and strawberry tongue are not found. In 30% to 70% a scarlatiniform rash follows pharyngitis in 1 to 4 days, beginning on the extensor surfaces then spreading to the chest, back, and buttocks.[25] Half of those patients with rash have pruritus, and some develop urticaria. Desquamation is rare. Other manifestations include sepsis, skin infection, or deep localized infection.

Diagnosis depends on finding typical pharyngitis, often with a rash in an adolescent or young adult with a negative test for GABHS. In this setting *A. haemolyticus* may be equal in incidence to GABHS (i.e., up to 30% of pharyngitis cases). Culture on blood agar shows beta hemolysis after 48-hours to 72-hours incubation. Ideal treatment has not been defined, but erythromycin, 250 mg orally four times a day for 10 days, is probably adequate. Penicillin is probably ineffective, whereas the role of cephalosporins or quinolones is unclear. Clarithromycin and azithromycin are likely efficacious.

Borrelia

Borrelia burgdorferi, the agent of Lyme disease, can produce isolated pharyngitis, but most persons have other Lyme-related symptoms as well.[43] *B. recurrentis* causes relapsing fever that infrequently produces mild sore throat.

Chlamydia

Chlamydia pneumoniae can produce fever, cough (again mitigating against GABHS), and sore throat.[19] Pharyngitis can occur without pneumonia, concomitantly with it, or precede it by 2 to 4 weeks. Prolonged pharyngitis has been reported. Oral erythromycin may not clear all cases but is best for children, whereas it or tetracycline is useful in adults.

Corynebacterium

The most terrible form of pharyngitis is diphtheria, which still strikes in underdeveloped countries or in underimmunized populations. A recent outbreak in Russia has led to diphtheria in citizens of the United States.[48] After an incubation period of 2 to 4 days, it presents with a slowly worsening, mild sore throat and low-grade fever. The tonsillar or pharyngeal exudate is thick, membranous, and gray in appearance. Removal of the membrane reveals a bleeding surface. Victims develop weakness, prostration, cervical adenopathy, and swelling of the neck typical of a bull. The anterior nares often have a white membrane, and serosanguinous discharge is common. As the illness travels down into the larynx, respiratory stridor develops so that nonintubated patients become exhausted and die. Cardiac and neurologic toxicity are common. Fortunately, diphtheria is fully preventable through immunization. When coupled with supportive care, penicillin or erythromycin is an effective treatment. Diphtheria antitoxin is useful and available from the Centers for Disease Control and Prevention.

Corynebacterium ulcerans causes pharyngitis in persons who drink raw milk. It is debatable whether *C. pyogenes* causes human disease.

Mycoplasma

Pharyngitis can be the predominant symptom of infection by *Mycoplasma pneumoniae*.[7,21] An insidious onset of headache and fever is followed by sore throat often with cough (contrary to GABHS) and coryza. The throat is red with a slight exudate; anterior cervical lymph nodes are tender and prominent; and pneumonia or tracheobronchitis also may be present. Tetracycline or erythromycin provides effective treatment. The incidence of *M. pneumoniae* pharyngitis is debatable. Estimates range from 1% to 10% of all cases, but it may afflict young adults more commonly.

Neisseria

After orogenital sexual activity, *Neisseria gonorrhoeae* infects the pharynx in 10% to 20% of women with a gonorrhea-infected partner and 3% to 7% of men.[7,21] Homosexual men have higher rates of infection. Most infections are asymptomatic, but mild pharyngitis with cervical lymphadenopathy is well described. Adolescents or adults with oral or oropharyngeal ulcers with ragged borders may have gonorrheal disease. Of course, syphilis also must be suspected. Pharyngeal infection is best treated with ceftriaxone, 125 mg intramedullarly once, plus doxycycline, 100 mg orally twice a day for 7 days. *N. meningitides* pharyngitis has been reported to precede sepsis, but such illness must be rare.

Tularemia

Francisella tularensis can present as an oropharyngeal infection with an acute membranous or exudative pharyngitis with cervical lymphadenitis.[7,21] Rabbit-associated and tick-borne transmission infect the cervical lymph nodes in about 6% of cases.

Yersinia enterocolitica

In adults, *Yersinia enterocolitica* can produce pharyngitis without the gastroenteritis commonly found in children or the mesenteric adenitis that mimics appendicitis.[8] Fever and prominent cervical adenopathy are usual; exudate has been described. In some cases a fulminant course leads to death, making early recognition critical.[6] Treatment with aminoglycosides, third-generation cephalosporin, or trimethoprim-sulfamethoxazole is effective, but penicillin is not.

Kawasaki Disease

Kawasaki disease has the specific diagnostic clues listed in Table 2.[38] Infants and toddlers younger than age 5 often are affected most, but older children reportedly have been affected. Within 3 days of the onset of fever, the findings presented in Table 2 develop. Conjunctivitis, erythematous lips or mouth, single-rode anterior cervical adenopathy, and prolonged high fever despite antibiotic treatment present a distinctive clinical picture. Associated vasculitis in the coronary arteries can lead to vascular aneurysm, rupture or thrombosis, and death. Other complications in untreated patients include anterior uveitis in 80%, sterile pyuria in 70%, arthritis in 35%, aseptic meningitis in 5%, carditis with congestive failure and pericardial effusion in about 5%, arrhythmias in 20%, and gallbladder hydrops, sometimes with jaundice, in about 10%. Desquamation of the skin is usual after 10 to 14 days (Fig. 5).

Overall, the disease lasts 2 months untreated. Treatment is immediately effective and consists of high-dose, intravenous immunoglobulin within 10 days of onset, given at 2 g per kg once, plus aspirin, 80 to 100 mg/kg/d in four divided doses. After the fever is controlled, the dose is reduced to 3 to 5 mg per kg in one daily dose for 2 months. An echocardiogram at 3 weeks and 8 weeks detects the formation of coronary artery aneurysm.

OTHER CAUSES OF PHARYNGITIS

Allergic diatheses, especially chronic rhinitis, frequently produce pharyngitis manifested by redness, dryness, and mucus in the pharynx. Trauma is, of course, usually sudden in onset, but delayed irritation, especially in alcohol users, is com-

Table 2. CRITERIA FOR KAWASAKI DISEASE

Number 1 plus at least four other criteria must be present:

1. Fever (generally up to 40°C [104°F]) of at least 5-days duration (despite antibiotic use)
2. Bilateral, nonpurulent, bulbar conjunctivitis
3. Erythematous mouth and pharynx, strawberry tongue, and cracked, red lips
4. A generalized polymorphous, erythematous rash
5. Usually a solitary anterior cervical lymph node enlargement of more than 1.5 cm in diameter
6. Edema and erythema of the hands and feet; periungual desquamation and peeling of the palms later

Other disease processes must be excluded. The erythrocyte sedimentation rate often is elevated markedly.

Data from Report of The Committee on Infectious Diseases. *In* 1994 Red Book, ed 23. Elk Grove Village, IL, AAP, 1994, p 437.

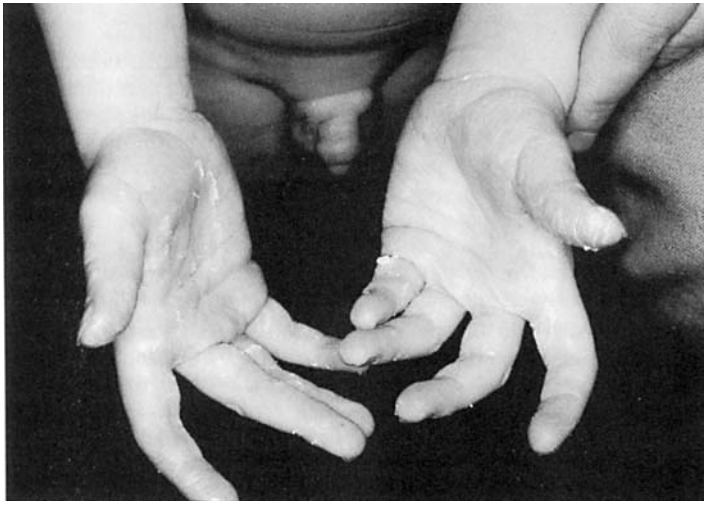


Figure 5. Kawasaki disease. Peeling skin is a defining criterion.

mon. Swallowed foreign bodies, including dentures, may cause drooling and odynophagia. Burns from hot foods, acid, or alkali are often severe and may scar. Ingestion of less toxic, orally irritating substances should be questioned. Occupational history may be helpful. For example, ammonia preservatives in food such as cheese crackers can irritate the throat if these foods are ingested hot off the production line or to excess.

Cigarette smoke can be especially bothersome, producing recurrent sore throats in the children of household smokers. Smoke inhalation from fires and irritants from chewing tobacco can cause pharyngitis.

Dryness of the throat often causes a complaint of early-morning sore throat. Persons with obstructive sleep apnea, nasal blockade, palatal dysfunction, or breathing through the mouth are particularly prone to this problem. Afflicted children frequently snore at night while dryness and colds exacerbate the issue. Stress at home or work can induce psychosomatic sore throat, often a prolonged and difficult problem. Excessive shouting, cheering, or singing can produce sore throat and hoarseness.

When chronic nasal blockage is present, adenoidal hypertrophy, nasal polyps, and even nasopharyngeal cancers should be considered. The latter is related to EBV and is found mainly in adults but has been found in adolescents who also may suffer from lymphoma or Hodgkin's disease. The triad of painful swallowing, otalgia (particularly with serous otitis media in an adult), and hoarseness suggests nasopharyngeal carcinoma.

Patients with epiglottitis caused by *H. influenzae* type b (preventable with appropriate use of conjugate Hib vaccine), supraglottitis caused by GABHS, croup or laryngotracheobronchitis caused by a virus (usually parainfluenza), and laryngitis usually viral or stress-induced also may present with a complaint of sore throat, although the throat appears normal. Trench mouth or ulcerating gingivitis may involve the tonsils with ulcerations and bleeding or a yellow-gray membrane and is particularly common in human immunodeficiency syndrome or with neutropenia. Subacute thyroiditis can produce referred pain to the throat.

Uvulitis

Infrequently, fever, painful swallowing, and drooling without a complaint of sore throat signal the presence of uvulitis. Because GABHS (after age 5 years) or *H. influenzae* type b (before age 5 years) are the usual culprits, concomitant tonsillitis or epiglottitis respectively may occur. If the uvula is red and swollen, cultures of the blood and uvula usually reveal the offending organism(s). Treatment is with a broad spectrum, β-lactamase–resistant antibiotic intravenously until cultures allow a narrower choice.

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