CASE ONE

Boy with Acute Pharyngitis

1.1. PATIENT HISTORY

The patient was a 6 year-old male who had been in good health with no significant medical problems. In late September he presented to his pediatrician’s office with a complaint of sore throat, fever, headache, and swollen glands in his neck for the past 36 h. On physical examination (PE), he had a fever of 38°C (100.4°F), a red posterior pharynx, yellowish exudate on his tonsils, and multiple, enlarged, tender cervical lymph nodes (Fig. 1.1). There were no other pertinent symptoms.

1.2. DIFFERENTIAL DIAGNOSIS

This patient had acute pharyngitis, the painful inflammation of the pharynx and surrounding lymphoid tissues.

Infectious Causes

The major causes of pharyngitis in an immunocompetent host are bacterial and viral. Mycobacteria, fungi, and parasites do not cause acute pharyngitis in a normal host.
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**FIGURE 1.1** Acute pharyngitis.

*Bacteria*

*Arcanobacterium haemolyticum*—a much less common cause of pharyngitis seen predominantly in teenagers and young adults

*Corynebacterium diphtheriae*—rarely seen in the United States but should be considered with an appropriate travel history to Africa, Asia/South Pacific, South America, Haiti, Albania, and the former Soviet Republic countries

*Mycoplasma pneumoniae*—a cause of pharyngitis in teenagers and young adults

*Neisseria gonorrhoeae*—considered if suspecting child abuse

Streptococci, groups C and G—a cause of self-limited pharyngitis in young adults

*Streptococcus pyogenes* [group A strep (GAS)]—this is the most common bacterial cause of pharyngitis

*Viruses*

Adenovirus—causes pharyngitis, conjunctivitis, and acute respiratory disease

Epstein-Barr virus—causes infectious mononucleosis, which is seen predominantly in the 15–25 year-old age group and frequently starts with pharyngitis

Other respiratory viruses—rhinovirus, coronavirus, parainfluenza virus, influenza A and B viruses, coxsackievirus, cytomegalovirus

*Fungi and Parasites*

There are no agents in these categories that routinely cause acute pharyngitis.
1.3. LABORATORY TESTS

A patient with GAS pharyngitis typically has a sore throat, fever, and pain on swallowing, as well as erythema with or without exudate on the tonsils and tender cervical lymph nodes. There are no clinical indicators that would make it possible to accurately predict the cause of this child’s pharyngitis. Laboratory tests are required to make a diagnosis.

When deciding whether to perform a laboratory test, clinical and epidemiological features as well as the availability and usefulness of treatment must be considered. While viruses are the most common cause of acute pharyngitis in both adults and children, lab testing for viruses is not warranted because antiviral agents are not used to treat acute pharyngitis. Given the age of this patient, the absence of travel, and the lack of suspicion of child abuse, GAS is the most likely etiologic agent.

Since GAS pharyngitis is the most commonly occurring form of pharyngitis for which antibiotic therapy is indicated, lab testing should be directed at ruling out GAS. Appropriate laboratory tests for this would include:

- **Rapid strep test.** This is not a culture; the test detects a unique carbohydrate on the cell wall of GAS.
- **Throat culture.** This test will grow the GAS organism from a throat specimen taken from the patient and will require overnight incubation at the minimum. Most labs offer a specific “rule out GAS” throat culture.

The specimen required for each of these tests is a throat swab. Use of a double-swab format allows one to obtain sufficient specimen to perform both tests if necessary. As with any microbiology test, the quality of the results is contingent on whether the laboratory receives a well-taken specimen. The double swab should be firmly rubbed over much of the surface of both tonsils and the posterior pharyngeal area and rolled to ensure that there is ample specimen on each swab tip. If exudate is present, it should also be sampled on the same swabs. Care should be taken to avoid touching other areas of the oropharynx, mouth, and tongue.

Direct Gram stains from throat swabs are not at all useful because many bacteria normally reside in the throat, including nonpathogenic streptococci that have Gram stain appearance identical to that of GAS.
1.4. RESULTS

Rapid tests for detection of GAS directly from throat swabs are based on the detection of the group A–specific carbohydrate N-acetylglucosamine. While the sensitivity of these tests varies considerably, the specificity when compared to culture is excellent, ranging within 95–100% in most studies. For this reason, a positive antigen test is considered diagnostic of GAS and does not require throat culture confirmation. A negative antigen test result, however, must be confirmed with a throat culture. In comparison to most rapid tests, which take 5–10 min to perform, a throat culture requires 48 h to complete. The disadvantage of time delay when performing a throat culture has led to widespread use of the rapid antigen tests.

The rapid antigen test performed on one of the swabs obtained from this patient was negative (Fig. 1.2); the second swab was used to perform the throat culture. Culture of a throat swab on a single sheep blood agar plate is still the gold standard for confirming GAS pharyngitis. Assuming that an adequately collected specimen was submitted, a throat swab culture has a sensitivity of 90–95% for the detection of GAS. Once the swab is cultured, the plate should be incubated at 35–37°C for 18–24 h before reading. While many cultures will be positive after the initial overnight incubation, it is recommended that the plates be reincubated and examined again after another 24 h incubation. A considerable number of GAS do not appear until the second day and would be missed without the additional incubation time.

Streptococci demonstrate three types of hemolysis when grown on sheep blood agar: alpha (α), beta (β), and gamma (γ) (Fig. 1.3). α-Hemolysis is a result of incomplete destruction of red blood cells resulting in a green coloration of the media immediately surrounding the colony. β-Hemolysis
FIGURE 1.3 Blood agar plate with three types of hemolysis.

is complete lysis and destruction of the red blood cells resulting in a distinct clear zone around the colony. $\gamma$-Hemolysis is actually no hemolysis, and the result is the absence of a visible effect around the colony.

Group A streptococci are $\beta$-hemolytic and should show a distinct clear zone around each individual colony; however, not all $\beta$-hemolytic colonies are GAS, and further testing of $\beta$-hemolytic colonies is required. Even if a patient has GAS pharyngitis, many other bacteria representing normal colonizing flora will be present on the culture plate along with the GAS (Fig. 1.4).

FIGURE 1.4 $\beta$-Hemolytic streptococci on selective (left) and nonselective media (right).
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The plate is visually inspected for colonies that display $\beta$-hemolysis, and, if present, such colonies are further tested using the catalase test and a Gram stain for microscopic examination. The catalase test checks for the production of the enzyme catalase, using hydrogen peroxide as a substrate. A single $\beta$-hemolytic colony is mixed with a drop of 3% hydrogen peroxide on a glass slide, and immediate bubbling is seen if the test is positive (Fig. 1.5). Streptococci are gram-positive cocci in chains and are catalase-negative (no bubbles). In contrast, staphylococci (which can also display $\beta$-hemolysis) are gram-positive cocci in clumps or clusters and are catalase-positive. Gram-positive, catalase-negative cocci would then be further tested.

The bacitracin disk test provides a presumptive identification of GAS because $>95\%$ of GAS demonstrate a zone of growth inhibition around a disk containing the antibiotic bacitracin (Fig. 1.6). While this is a commonly used test in physician’s offices, it requires another 18–24 h of incubation to perform. An alternative used by many clinical laboratories because it gives an immediate result is the PYR test, which detects the enzyme L-pyroglutamylaminopeptidase and can be performed within minutes using a single $\beta$-hemolytic colony. GAS are positive for PYR (Fig. 1.7).

The definitive method of identifying the $\beta$-hemolytic streptococci is by detecting the group-specific cell wall carbohydrate antigen directly from an isolated bacterial colony. These unique antigens classify the $\beta$-hemolytic streptococci into serogroups, designated by Dr. Rebecca Lancefield, as groups A, B, C, D, F, G, and so on. Kits containing group-specific antiserum attached to latex beads are commercially available for this purpose and are used by many clinical microbiology laboratories. A single isolated colony is mixed with a drop of group-specific antibody, and if clumping of the coated latex particles occurs, it specifically identifies the serogroup.

The culture performed using the second swab taken from this patient was positive for $\beta$-hemolytic group A streptococcus ($S.\ pyogenes$). This is sufficient to confirm the diagnosis of GAS pharyngitis.
1.5. PATHOGENESIS

Streptococcal pharyngitis is spread via aerosols from person to person, or less commonly by eating contaminated food. *S. pyogenes* is a successful pathogen since it possesses several virulence factors that allow it to invade tissue and escape host defenses. Some strains produce pyrogenic exotoxins, which cause serious systemic illness, such as toxic shock–like syndrome, which is associated with a high morbidity and mortality. The principal virulence factors produced by *S. pyogenes* are listed in Table 1.1.
Infection with *S. pyogenes* may present in children as scarlet fever, which is fever and sore throat with a diffuse rash. The rash is caused by an erythrogenic exotoxin that has now been designated as one of the streptococcal pyrogenic exotoxins or Spe. The incidence of scarlet fever fell significantly in the 1950s largely because of the widespread use of penicillin.

The two major sequelae of untreated *S. pyogenes* infection, rheumatic fever (RF) and acute glomerulonephritis (GN), occur weeks after the streptococcal infection. The organism can no longer be cultured from the throat or skin when the patient presents with symptoms of RF or GN. RF occurs in <3% of people with strep pharyngitis. The patient presents with swelling and pain in more than one joint (migrating arthritis) and with a new heart murmur due to damage to the heart muscle and heart valves. The patient may also have a group of neurologic symptoms, including jerky or twitching movements (chorea). GN may occur 10 days or later after a skin infection with *S. pyogenes*. The patient has signs and symptoms of kidney dysfunction, such as swollen ankles and eyelids (edema), elevated blood pressure (hypertension), blood and protein in the urine, and decreased urine output. Deposition of antigen–antibody–complement complexes can be seen in a kidney biopsy using immunofluorescent stains.

The damage to the heart and kidney is not caused by systemic infection with the bacteria, but is theorized to be a result of direct damage
by toxic streptococcal products (streptolysin O, streptokinase, and Spe) or an autoimmune response by the host. When the streptococcal bacteria are lysed by the host cells, antigens are released that evoke an immune response. Antibodies produced to the antigenic components of the bacteria cross-react with the patient’s cardiac proteins, allowing the antibodies to attack the heart tissue and cause valvular damage. Later in life these damaged heart valves are a prime site where bacteria lodge and cause an infection of the heart known as endocarditis.

There is no antibiotic treatment for RF or GN; however, prophylactic penicillin is given to people with a history of RF to prevent recurrent streptococcal infections. Tests needed in the diagnosis of RF or GN may include antibody tests, such as antistreptolysin O or anti-DNase B to detect a recent infection after the viable organisms have disappeared. An acute (immediate) and a convalescent serum (drawn 14 days later) may be submitted for antibody titers to prove that the patient had a recent GAS infection. A fourfold rise in titer between the acute and convalescent sera indicates a recent infection, for example, an acute titer of 1:8 increases to 1:64 in the convalescent serum.

1.6. TREATMENT AND PREVENTION

Treatment of group A streptococcal pharyngitis is important in order to relieve the patient’s symptoms and to prevent the transmission to others. Prompt treatment will also prevent complications such as peritonsillar abscess and acute rheumatic fever. Symptoms will often disappear within 3–4 days even without antibiotics, but early antibiotics can shorten the duration of symptoms. Pharyngitis caused by *S. pyogenes* can be effectively treated with a penicillin. In children, like this patient, amoxicillin is routinely prescribed. Patients must complete the course of antibiotic to eradicate the organisms from the pharynx. For patients who are allergic to penicillin, erythromycin would be an acceptable alternative. If left untreated, patients with GAS infection may develop the sequellae of heart valve damage (RF) or kidney damage (GN).

Susceptibility tests on GAS would not be performed since resistance to penicillin has not been documented in these organisms to date. Carriers maintain *S. pyogenes* in their throats despite appropriate antibiotic therapy; it is not because the organisms are resistant to penicillin. Carriers are not symptomatic but can spread the organism to others who may develop an infection.

1.7. ADDITIONAL POINTS

- Who gets strep pharyngitis? A school-age child, 5–14 years old, would most likely become infected through contact with someone who carries the organism in their respiratory tract. While antibody does protect a
person from repeat infection, the antibody is directed toward the M protein, and there are >80 serotypes of M protein, so that one can become infected with a different serotype again and again. Adults who have close contact with school-age children may acquire the infection more often. In adults, pharyngitis is most often the initial symptom of a viral illness that is accompanied by fever, runny nose, sneezing, and coughing.

■ While not widely in use, there are now molecular tests for the detection of GAS. Results from molecular testing can be available in less than 6 h, but since most labs perform the test once or twice a day, a more realistic turnaround time is 24 h. Negative molecular tests do not require culture confirmation, which saves time. Positive rapid tests (EIA) allow immediate results for the patients and physicians in busy emergency departments and clinics.

■ Infectious mononucleosis from Epstein–Barr virus (EBV) becomes more likely when clinical symptoms of rash, fatigue, hepatomegaly, and/or splenomegaly accompany the pharyngitis. If such were the case, then appropriate additional laboratory tests would include a complete blood count (CBC) and differential, and EBV-specific or non-EBV-specific serology tests. A relative lymphocytosis with an atypical lymphocytosis (>10%) is highly suggestive when combined with appropriate clinical findings. Nonspecific serologic confirmation would include a positive heterophil antibody titer or a positive Monospot slide test. A fourfold rise in antibody titer specific for EBV, or the presence of IgM antibody to EBV, serves as specific serologic evidence of recent infection.

■ Teenagers and young adults may develop pharyngitis with rash caused by a gram-positive rod, *Arcanobacterium haemolyticum*. This organism may resemble a β-hemolytic streptococcus on the culture media, but it is not a gram-positive coccus; it is a gram-positive rod. The organism will respond to most antibiotics used to treat strep pharyngitis.

■ Young adults, especially those of college age, may become infected with group C or G streptococci, which can cause an infection similar to that due to *S. pyogenes*. The rapid strep test will be negative since the group-specific carbohydrate is different in each Lancefield group. A throat culture will grow these organisms, but the physician may have to request further workup of these bacteria so that the group C or G strep is reported. Groups C and G streptococci are rarely associated with the sequella of GN and can raise ASO titers. The same antibiotic therapy for GAS may be given to relieve clinical symptoms and decrease transmission of infection.

■ Diphtheria is rarely seen in developed countries where healthcare practices provide for adequate immunization. A travel history to countries where diphtheria is endemic may require a throat culture for this organism. A gray membrane covering the posterior pharynx of a patient who lacks the common childhood immunizations should raise suspicions of diphtheria. The physician must notify the lab so that the appropriate media can be used to culture *Corynebacterium diphtheriae*. 
SUGGESTED READING


