

Group A Streptococcal Infections

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Objectives After completing this article, readers should be able to:

1. Discuss the differential diagnosis of pediatric acute pharyngitis and the epidemiology and transmission of group A *Streptococcus* (GAS) pharyngitis.
2. Delineate the rationale for and the treatment regimens of GAS pharyngitis as well as the complications of GAS pharyngitis.
3. Know the carrier state of GAS.
4. Describe the clinical criteria for rheumatic fever and streptococcal toxic shock syndrome.

Introduction

Group A *Streptococcus* (GAS) causes the widest range of syndromes of any bacterium, including simple skin infections and pharyngitis, severe suppurative infections, the toxin-mediated streptococcal toxic shock syndrome (STSS), and immune-mediated illnesses such as acute rheumatic fever and acute glomerulonephritis. Specific manifestations of GAS infections represent the complex interplay of bacterial virulence factors and host immunogenetic factors.

Pharyngitis

GAS accounts for about 15% to 30% of acute pharyngitis cases in children. Children ages 5 to 11 years have the highest incidence of GAS pharyngitis, although it occurs among all age groups. The major rationale for accurate diagnosis and treatment of GAS pharyngitis is the prevention of acute rheumatic fever (ARF) and rheumatic heart disease (RHD). In temperate climates, GAS pharyngitis is more common during the winter and early spring months. The incubation period for streptococcal pharyngitis is short (2 to 5 days). Transmission occurs with close contact via inhalation of organisms in large droplets or by direct contact with respiratory secretions.

GAS is only one of the causes of acute pharyngitis; others are listed in Table 1. One of the most crucial decisions in evaluating a patient who has pharyngitis is whether to perform a rapid antigen test or bacterial culture of the throat for GAS. The clinician must keep in mind three important principles. First, accurate detection and treatment of GAS pharyngitis are needed to prevent ARF and other complications. Second, unnecessarily performing these tests in patients who present with typical viral upper respiratory tract symptoms (eg, rhinorrhea, cough, hoarseness) can result in the misdiagnosis of GAS pharyngitis in asymptomatic chronic GAS carriers who have an intercurrent viral illness. GAS pharyngeal carriers generally do not progress to invasive or immunologic sequelae and, therefore, do not require treatment with antimicrobials. Third, the phenomenon of the GAS carrier state negates the conclusion that a positive rapid GAS antigen test (or throat culture) result in a patient who has acute pharyngitis always means that the patient has GAS pharyngitis. Indeed, this is not always the case, but because it is difficult to prove a timely alternative diagnosis, antibiotic treatment usually is administered when test results are positive and the clinical findings are consistent with GAS infection. These three principles should remind

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Table 1. Non-Group A Streptococcal Causes of Pharyngitis

Bacteria	Viruses
Beta-hemolytic streptococci: groups C, G	Epstein-Barr
<i>Corynebacterium diphtheriae</i>	Adenovirus
<i>Arcanobacterium haemolyticum</i>	Enterovirus
<i>Neisseria gonorrhoeae</i>	Herpes simplex
<i>Chlamydophila pneumoniae</i>	Influenza
<i>Chlamydia trachomatis</i>	Parainfluenza
<i>Mycoplasma pneumoniae</i>	Rhinovirus
<i>Francisella tularensis</i>	Coronavirus
<i>Coxiella burnetii</i>	Respiratory syncytial
<i>Yersinia enterocolitica</i>	
<i>Yersinia pestis</i>	

the physician to obtain throat swabs only from patients whose symptoms are consistent with GAS pharyngitis.

Because pharyngitis accompanied by rhinitis, stridor, hoarseness, conjunctivitis, cough, or diarrhea is highly likely to have a viral etiology, a bacterial throat culture generally is unnecessary when these symptoms are present. Symptoms such as an abrupt onset of fever, throat pain, headache, abdominal pain, and dysphagia and signs such as exudative pharyngitis, palatal petechiae, uvulitis, and tender anterior cervical nodes suggest GAS pharyngitis. In addition, the absence of rhinitis, hoarseness, conjunctivitis, and cough is more suggestive of GAS pharyngitis. Patients who have symptoms for longer than 4 to 5 days are unlikely to have GAS pharyngitis, a self-limited illness that usually lasts 3 to 5 days even without therapy. An erythematous, diffuse, sandpapery exanthema combination known as scarlet fever sometimes accompanies GAS pharyngitis, as well as other streptococcal illnesses, and is caused by streptococcal pyrogenic exotoxins (A, B, C). The rash usually is concentrated in flexor skin creases (Pastia lines), blanches with pressure, and generally spares the circumoral region. Signs and symptoms suggestive of GAS pharyngitis are listed in Table 2.

Patients who have a constellation of signs and symptoms suggestive of GAS pharyngitis should be tested for infection by obtaining a throat

swab of the posterior pharynx. Relying solely on a clinical impression to decide if treatment is warranted results in the gross overdiagnosis of GAS pharyngitis and is discouraged. Because children younger than 3 years of age develop classic GAS pharyngitis infrequently and almost never develop acute rheumatic fever, documentation and treatment of GAS in this age group is optional.

Pharyngeal Complications of GAS Pharyngitis

GAS pharyngitis is a self-limited illness, generally not lasting more than 3 to 5 days, even in the absence of treatment. If a patient has not responded to treatment, complications or a nonstreptococcal illness must be considered. GAS pharyngitis can be complicated by peritonsillar cellulitis and subsequent abscess formation, usually occurring at the superior pole of the tonsil. Patients who have parapharyngeal abscesses usually are adolescents and present with severe sore throat, muffled voice, dysphagia, difficulty opening the jaw fully, and drooling, although some may appear well. In these instances, the posterior pharynx should be inspected for deviation of the uvula and unilateral bulging of the peritonsillar area. Gentle palpation of the peritonsillar area may reveal fluctuance.

Retropharyngeal abscess (abscess formation between the posterior pharyngeal wall and prevertebral fascia) also may complicate GAS pharyngitis. Affected children present with symptoms similar to those of GAS pharyngitis plus reluctance to move the neck. It usually occurs in younger children, and affected patients also may present with hyperextension of the neck. A lateral radiograph may help identify a retropharyngeal mass by demonstrating increased dimension of the retropharyngeal space at the level of C2 (normally 3 to 6 mm). Contrast-enhanced computed tomography is more precise than plain radiog-

Table 2. Clinical Signs and Symptoms Suggestive of GAS Pharyngitis

Symptoms	Signs*
Abrupt onset of fever, throat pain, dysphagia	Exudative pharyngitis
Headache	Palatal petechiae
Abdominal pain without diarrhea	Uvulitis
Absence of cough, hoarseness, rhinitis	Tender anterior cervical lymph nodes
Symptoms occurring for fewer than 5 days	Scarlet fever exanthem

*Viruses also cause exudative pharyngitis, lymphadenopathy

Table 3. Criteria for Streptococcal Toxic Shock Syndrome

Hypotension or shock plus at least two of the following:

- Renal impairment
- Disseminated intravascular coagulation
- Hepatic abnormalities
- Acute respiratory distress syndrome
- Scarletiform rash
- Soft-tissue necrosis

A definite case has hypotension, at least two of the above criteria, and isolation of GAS from a sterile body site

A probable case has hypotension and at least two of the above criteria and isolation of GAS from a nonsterile body site

raphy in showing posterior pharyngeal structures and abscess formation.

STSS

GAS and *Staphylococcus aureus* strains that produce superantigens or toxins that trigger massive cytokine release have been demonstrated to cause TSS. STSS often is accompanied by focal infection such as cellulitis or necrotizing fasciitis. Patients who have STSS and necrotizing fasciitis have a high rate of mortality. Defining characteristics of classic STSS include hypotension or shock plus at least two of the following six criteria: scarlatiniform rash, hepatic abnormalities, renal abnormalities, disseminated intravascular coagulation, respiratory distress syndrome, or extensive soft-tissue necrosis (necrotizing fasciitis). These disorders must occur in the absence of other explanations or other positive bacterial cultures (Table 3).

Nonsuppurative Poststreptococcal Diseases

ARF and poststreptococcal glomerulonephritis (PSGN) both follow acute GAS infection after an asymptomatic latent period; they virtually never occur in the same patient. ARF follows pharyngeal infection only; PSGN can follow either skin or pharyngeal infection. A full discussion of these illnesses is beyond the scope of this article, but they are discussed briefly.

Rheumatic heart disease remains the leading cause of acquired heart disease worldwide in children. The pathogenesis of ARF is not understood clearly, and no animal model exists, but it appears to be an immune response to GAS antigen(s) that cross-react with human tissue through molecular mimicry. The latent period following GAS pharyngitis is usually 2 to 4 weeks. Clinical criteria

Table 4. Jones Criteria for Diagnosis of Rheumatic Fever

Diagnosis requires one major and two minor or two major criteria along with supporting evidence of recent GAS infection

Major Criteria

- Carditis
- Polyarthritides
- Chorea
- Erythema marginatum
- Subcutaneous nodules

Minor Criteria

- Arthralgia
- Fever
- Elevated acute-phase reactants
- Prolonged PR interval

Supporting Evidence of Recent GAS Infection

- Rising or elevated antistreptococcal antibody titers or positive throat culture or rapid antigen test

for ARF were developed by T. Duckett Jones in 1944, and the revised Jones criteria are still used to aid in diagnosis today (Table 4). Diagnosis requires supporting evidence of an antecedent GAS infection. In addition, two major criteria or one major criterion and two minor criteria are required. GAS infection can be documented by a positive throat culture or rapid antigen test or by an elevated or rising streptococcal antibody titer. Major criteria include carditis, polyarthritides, chorea, erythema marginatum, and subcutaneous nodules. Arthritis occurs in approximately 75% of affected patients, is usually migratory, and involves the larger joints. Carditis may involve any or all of the myocardium, pericardium, and endocardium. If carditis is present, valvulitis resulting in a cardiac murmur almost always is found. Echocardiographic evidence of valvular insufficiency without the presence of a cardiac murmur does not fulfill this criterion.

Erythema marginatum is a rare, serpiginous, macular, transitory rash seen in 4% of ARF patients. Subcutaneous nodules rarely occur and develop on the extensor surface of tendons. Sydenham chorea, sometimes called St. Vitus dance, is manifested by incoordination, an uncontrolled movement disorder, and facial grimacing that disappears in sleep and is exacerbated by stress. Because the latent period for the development of chorea extends for months (mean of approximately 5 mo) after the initial infection, titers of antistreptococcal antibodies are not always elevated at the time of its occurrence. Minor manifestations

of ARF include arthralgia, fever, elevated acute-phase reactants (erythrocyte sedimentation rate, C-reactive protein), and prolonged PR interval on electrocardiography.

PSGN was described first in the early 19th century as hematuria following scarlet fever. The renal disease results from deposition of immune complexes in the glomerulus. PSGN usually follows about 10 days after GAS pharyngitis or about 3 to 4 weeks after GAS skin infection. Common findings include hematuria, edema, hypertension, and oliguria. Total hemolytic complement levels and C3 almost always are decreased in the initial illness, although C4 values usually are normal. Most children have a favorable prognosis.

Diagnosis

Because throat culture requires 24 to 48 hours for GAS diagnosis, rapid antigen detection systems for identification of GAS have been developed. Standard rapid antigen tests generally have very high specificity (95% to 98%), but their sensitivity varies from 70% to 90%. Sensitivity varies with inoculum quantity and technical expertise in processing and interpreting the sample. GAS pharyngitis, therefore, can be diagnosed presumptively with a positive standard rapid antigen test for GAS (confirmatory testing by culture is not needed), but a negative test result generally should be confirmed by a throat culture. Highly sensitive rapid antigen detection systems have been developed by using optical immunoassay technology. Rapid antigen tests using this technology have been shown in some studies to be as sensitive as the throat culture when performed in the office setting; some experts suggest that a confirmatory throat culture is not needed if a high-sensitivity rapid antigen test result is negative. This recommendation, however, remains controversial. Therefore, if physicians wish to rely on a high-sensitivity rapid antigen test alone, they should consider confirming the reliability of the assay in comparative studies with throat culture among their own patients before using this test without backup cultures in daily practice.

Throat culture has long served as the gold standard for diagnosis of GAS pharyngitis and has a 90% to 95% sensitivity for identifying GAS in the nasopharynx. Proper specimen collection is important to increase culture sensitivity. It is optimal to rub both tonsils and the posterior pharyngeal wall with a cotton- or synthetic

fiber-tipped swab. Specimens should be inoculated promptly or placed in transport media, then inoculated onto 5% sheep blood agar and incubated in an aerobic chamber with 5% to 10% carbon dioxide at 37°C for at least 24 hours. If no beta-hemolytic organisms grow after 24 hours, the plate should be reincubated for another 24 hours at room temperature. On microscopy, GAS appear as gram-positive cocci in pairs and chains. On blood agar, they form small gray-white colonies with a zone of beta-hemolysis (a clear rim that surrounds the colonies). Other beta-hemolytic streptococci include groups B (*S agalactiae*), C, G, and F. Beta-hemolytic organisms should be confirmed as group A *Streptococcus* by latex agglutination, inhibition of growth around a bacitracin disc, or other techniques. Bacterial throat culture also may be useful in detecting *Neisseria gonorrhoeae* in the sexually active patient who has acute pharyngitis. GAS may remain part of resident oropharyngeal flora,

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resulting in chronic colonization, with the patient becoming a chronic carrier. Therefore, growth on routine culture in such a patient does not prove acute streptococcal pharyngitis or identify the cause of pneumonia, otitis media, sinusitis, or meningitis.

Serologic testing for acute GAS pharyngitis generally is not useful in acute infection because antistreptococcal antibodies increase only weeks after infection. Antibodies against streptolysin O, deoxyribonuclease B, hyaluronidase, and streptokinase are used to confirm a recent (but not current) GAS infection for those in whom the likelihood of culturing GAS is poor but confirmation of a recent GAS illness is needed, such as in suspected ARF or PSGN.

Treatment

Pharyngitis

Accurate diagnosis and treatment of acute GAS pharyngitis reduces suppurative complications (such as retro-

Table 5. Recommended Antimicrobial Drugs for GAS Pharyngitis

	Medication	Pediatric Dosage	Adult Dosage	Duration
First-line Therapy	Penicillin VK	≤27 kg (60 lb): 400,000 U (250 mg) bid or tid >27 kg (60 lb): 800,000 U (500 mg) bid or tid	500 mg tid	10 d
	Intramuscular penicillin G benzathine	≤27 kg (60 lb): 600,000 U >27 kg: 1.2 million U single dose OR 900,000 U benzathine penicillin G + 300,000 U procaine penicillin Once daily regimen [†] :	1.2 million U	Single dose
Drugs for Penicillin-allergic Patients	Amoxicillin	50 mg/kg qd (maximum 750 mg) 20 to 40 mg/kg divided bid–qid 40 mg/kg per day divided bid–qid (maximum 1 g/d)	Once daily regimen: 750 qd 500 mg bid 500 mg bid	10 d
	Erythromycin estolate [†]			10 d
	Erythromycin ethylsuccinate [†]			10 d
	Clarithromycin	7.5 mg/kg per dose bid	250 mg bid	10 d
	Cephalexin	25 to 50 mg/kg per day divided bid	500 mg bid	10 d
	Clindamycin	10 to 20 mg/kg per day divided tid	150 mg tid	10 d
	Azithromycin	12 mg/kg per day qd × 5 d (not to exceed adult dose)	500 mg qd × 1 d, then 250 mg qd × 4 d	5 d

*This regimen appears to be effective but is not yet approved by the United States Food and Drug Administration or recommended by the American Academy of Pediatrics.

[†]First-line therapy.

pharyngeal or peritonsillar abscesses), decreases transmission of GAS, and to a limited degree, shortens the duration of pharyngeal symptoms. In addition, therapy markedly reduces the risk of ARF. However, therapy has not been shown to reduce the risk of acute PSGN. Prevention of ARF is most effective if therapy is initiated within 9 days of the onset of symptoms. Although GAS pharyngitis is self-limited, appropriate treatment resolves symptoms about 1 day earlier than observation.

GAS remains universally sensitive to penicillin, which is the first-line therapy for GAS pharyngitis (as recommended by the American Academy of Pediatrics, the American Heart Association, and the Infectious Diseases Society of America) because of its narrow spectrum, low cost, and proven efficacy (Table 5). A clinical isolate of GAS that is resistant to penicillin or a cephalosporin in vitro has never been documented. Parenteral therapy can be administered if needed to ensure compliance; a single intramuscular dose of benzathine penicillin G is bactericidal for up to 28 days. However, parenteral penicillin is a painful injection and is associated with more potentially serious allergic reactions than oral therapy. Therefore, many clinicians prefer to use oral penicillin V, which must be continued for 10 days to ensure eradication of GAS. Twice-daily regimens of 500 mg in adults and children weighing 60 lb (27 kg) or 250-mg doses in smaller children achieve similar cure rates for GAS pharyngitis as thrice-daily dosing.

An alternative medication used primarily because of its increased palatability and greater associated compliance is amoxicillin. Previously published and ongoing studies show that once-daily amoxicillin at 50 mg/kg (up to 750 mg once daily) in children and adults who have GAS pharyngitis results in bacteriologic cure rates equal to those achieved with thrice-daily penicillin dosing. Although once-daily amoxicillin treatment for GAS pharyngitis is not approved by the United States Food and Drug Administration, it appears to be an excellent alternative to penicillin.

For individuals who are allergic to penicillin, the drug of choice is erythromycin; other macrolide antibiotics, such as clarithromycin and azithromycin, are acceptable (although more costly) alternatives. Azithromycin, administered at a higher dose of 12 mg/kg, often is chosen because of once-daily dosing and a treatment course of only 5 days that provides 10 days of antimicrobial activity. In areas of the world that have heavy macrolide use, a direct relationship has been shown between overall macrolide usage and GAS macrolide resistance rates. In 2000 to 2001, a high rate of macrolide-resistant GAS (up to 48%) was described in Pittsburgh, Pennsylvania, rais-

ing concerns about possibly increasing United States macrolide resistance rates. However, ongoing nationwide surveillance has not confirmed this high rate of resistance in other parts of the country. Studies indicate a nationwide macrolide resistance rate of approximately 4% to 6% from 2000 to 2004. First-generation cephalosporins may be used for patients who are penicillin-allergic if there is no history of immediate severe hypersensitivity to the penicillins, but these agents have broader antimicrobial activity than is necessary and are more expensive. Clindamycin may be used if other antibiotics are not an option. Tetracyclines and sulfonamides should *not* be used to treat GAS pharyngitis because they are ineffective in eradicating the organism.

Patients who have streptococcal pharyngitis are considered to be noncontagious 24 hours after initiation of treatment. In the United States, it is unnecessary to reculture the posterior pharynx routinely following GAS pharyngitis because the incidence of ARF remains low in almost all areas. Clinical treatment failure of GAS pharyngitis is rare. If a patient returns for evaluation of recurrent symptoms compatible with GAS pharyngitis and has a positive throat culture within a few weeks of treatment, the possibilities of the chronic pharyngeal carrier state with intercurrent viral pharyngitis, noncompliance with medication, or a new infection with a different strain of GAS should be considered. Recurrent pharyngitis caused by the same GAS strain is uncommon.

Peritonsillar/Retropharyngeal Abscess

Deep oropharyngeal abscesses require incision and drainage and immediate consultation with an otolaryngologist. Adequate suction is needed to drain the pus that is released. Because of occasional mixed flora with oropharyngeal anaerobes or *S aureus*, ampicillin-sulbactam with or without added clindamycin is used empirically until culture results are obtained. Emergency tonsillectomy occasionally is needed for peritonsillar abscess. Needle aspiration often can be performed for peritonsillar abscess; retropharyngeal abscesses usually require surgical drainage.

STSS

Treatment of STSS requires appropriate antibiotic treatment, including penicillin and clindamycin, which is used

for its antitoxin effects. Some experts also recommend intravenous immune globulin, which neutralizes toxins, to ameliorate disease severity. In addition, supportive care is needed, including aggressive fluid management and urgent debridement of any foci of necrotic tissue.

ARF and PSGN

Treatment of ARF involves: 1) antimicrobials to eradicate GAS from the nasopharynx followed by long-term prophylactic antimicrobials to prevent further intercurrent GAS illness, 2) anti-inflammatory treatment, and 3) supportive care. Initial treatment can be intramuscular benzathine penicillin or 10 days of oral penicillin or erythromycin. Anti-inflammatory medications usually include salicylate, but this agent may need to be replaced with corticosteroids initially in those who have significant carditis with cardiomegaly or congestive heart failure. PSGN treatment primarily involves supportive care to control hypertension, oliguria, and renal failure.

Conclusion

GAS causes a wide variety of clinical syndromes. Knowledge of the epidemiology and clinical presentations of these illnesses will aid the clinician in recognizing and treating GAS infections and their complications.

Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

10. The *primary* rationale for diagnosing and treating group A beta-hemolytic streptococcal (GAS) pharyngitis is prevention of:
 - A. Acute glomerulonephritis.
 - B. Acute rheumatic fever.
 - C. Otitis media.
 - D. Prolonged colonization.
 - E. Toxin-mediated shock syndrome.
11. A previously healthy 5-year-old girl developed a sore throat 2 days ago, copious clear rhinorrhea yesterday, and slight hoarseness this morning. The sore throat makes her uncomfortable, but she is breathing normally and is taking fluids well. Her mother calls in the evening for advice. Of the following, the *most* appropriate recommendation is to:
 - A. Call in a prescription for penicillin.
 - B. Direct her immediately to an after-hours clinic.
 - C. Order a throat swab at a local laboratory.
 - D. Provide reassurance and analgesia.
 - E. Schedule an office visit in the morning.
12. A previously healthy 5-year-old girl presents to your office with a 12-hour history of sore throat accompanied by fever, headache, and abdominal pain. Physical examination reveals only erythema of the soft palate without petechiae and slightly enlarged and tender cervical lymph nodes. Results of the standard GAS rapid antigen test are negative. Of the following, the *most* appropriate next step is:
 - A. A 5-day course of azithromycin.
 - B. A mononucleosis spot test.
 - C. A throat culture for GAS.
 - D. Reassurance and analgesia.
 - E. Treatment with 10 days of penicillin.
13. A previously healthy 5-year-old girl has a 12-hour history of sore throat and fever without other symptoms. In your office, a standard GAS rapid antigen test turns quickly positive. She is not allergic to beta-lactam antibiotics but is a picky medicine-taker. She weighs 25 kg. Of the following, the *preferred* therapy is:
 - A. Amoxicillin 750 mg once daily for 10 days.
 - B. Azithromycin 300 mg once daily for 10 days.
 - C. Clindamycin 125 mg three times daily for 10 days.
 - D. Erythromycin estolate 250 mg twice daily for 10 days.
 - E. Penicillin VK 250 mg twice daily for 5 days.
14. Following the recommendations of the American Academy of Pediatrics, you have begun treatment of documented GAS pharyngitis in a 5-year-old girl. A resident asks you about the need for follow-up after completion of therapy. The *most* appropriate response is that:
 - A. Eradication of GAS must be documented by culture.
 - B. Examination for new heart murmurs is essential.
 - C. Inspection of skin and joints is mandatory.
 - D. Recurrence of sore throat warrants re-evaluation.
 - E. Urinalysis to rule out hematuria is recommended.