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Management of Group A Pharyngeal Streptococcal Infection

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Introduction

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Group A streptococcal infections of the throat, sinuses, ears, and soft and bony structures of the head and neck (H & N) have been described since the time of Hippocrates. *Streptococcus pyogenes*, or group A streptococcus (GAS) also known as group A beta-hemolytic streptococcus (GABHS) is a facultative, gram-positive coccus that grows in chains and causes numerous infections in humans, including pharyngitis, tonsillitis, scarlet fever, cellulitis, erysipelas, rheumatic fever (RF), poststreptrococcal glomerulonephritis, necrotizing fasciitis, myonecrosis, and lymphangitis. Its only known niche is the skin and mucous membranes of the human host. Over the last 40 years in the Western world, GAS pharyngitis has become a mild disease, and during this time the prevalence of RF has reached an all-time low. Thus, some have argued that antibiotics should no longer be prescribed for GAS pharyngitis. Several epidemics of RF and severe invasive GAS infections have been described from many areas around the world. Thus, at present, it seems prudent to aggressively diagnose and treat GAS infections of the the throat to prevent RF, extension of infection into the vital structures of the H & N, and life threatening invasive infections such as bacteremia, necrotizing fasciitis, and streptococcal toxic shock syndrome (strep TSS).

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Infection by group A beta-hemolytic streptococcus (GABHS) also known as group A *Streptococcus pyogenes* (GAS) is the most common cause of bacterial pharyngitis in children. Although most affected patients improve symptomatically without any medical intervention whatsoever, a small number of children continue to develop complications such as peritonsillar abscess, renal and cardiac complications, and severe disease such as streptococcal necrotizing fasciitis. In addition, there is evidence that children with severe and frequent infections may benefit from tonsillectomy. As a result, the otolaryngologist must be familiar with the appropriate diagnosis and treatment of these infections and the history required to determine those children who are candidates for surgical intervention.

Pathogenesis

The streptococci are gram positive, catalase-negative cocci, characterized by their growth in long chains or pairs in culture. These organisms are traditionally classified into 18 groups with letter designations (Lancefield groups) on the basis of the antigenic carbohydrate component of their cell walls. While the group A Streptococcus is isolated from most patients with streptococcal pharyngitis,

group C, G, and B streptococci may also occasionally cause this disorder. Unlike GABHS, however, these organisms are not associated with nonsuppurative sequelae. Further subclassification of streptococci is made based on their ability to lyse sheep or horse erythrocytes in culture; the beta-hemolytic strains cause hemolysis associated with a clear zone surrounding their colonies, while alpha-hemolytic strains cause partial (green) hemolysis and gamma-hemolytic strains cause no hemolysis.

Pharyngotonsillitis caused by GABHS requires adherence of the organism to pharyngeal and tonsil epithelium. Attachment is accomplished by fimbriae, which are finger-like projections from the cell wall of the organism. However, resident alpha-hemolytic or viridans streptococci may compete with GABHS, inhibiting the establishment of infection to some degree.[1] The predilection of GABHS to affect the pharynx and other particular body sites has yet to be explained.

The primary determinant of streptococcal pathogenicity is an antigenically distinct protein known as the M protein, which is found within the fimbriae. More than 120 M serotypes have been identified by gene sequencing techniques, and it is likely that many more exist that are not yet characterized.[2] Numerous serotypes circulate simultaneously within a selected population; in most cases, those associated with pharyngitis are different from those associated with impetigo or pyoderma. However, strains causing pharyngitis in one individual may cause invasive disease when transmitted to other individuals.[3] The M protein of the *Streptococcus* allows the organism to resist phagocytosis in the absence of type-specific antibody. In the immunocompetent host, the synthesis of type specific anti-M and other antibodies, which belong primarily to the IgG class of immunoglobulins, confers long-term serotype-specific immunity to the particular strain in question. In laboratory-produced penicillin-resistant strains of GABHS, the M protein is absent, thereby rendering these strains more vulnerable to phagocytosis.[4] This finding may help to explain why there have been no naturally occurring penicillin-resistant GABHS isolated in more than 50 years of penicillin use.

The sequelae of GABHS infection result from suppurative, toxin-mediated, and/or immune-mediated mechanisms. The organism is capable of elaborating at least 20 extracellular substances that affect host tissue; the interested reader may find a complete discussion of these substances elsewhere. Among the most important are streptolysin O (an oxygen-labile hemolysin), and streptolysin S (an oxygen-stable hemolysin), which lyse erythrocytes and damage other cells such as myocardial cells. Streptolysin O is antigenic, while streptolysin S is not. GABHS also produce three erythrogenic or pyrogenic toxins (A, B, and C) whose activity is similar to that of bacterial endotoxin and are responsible for the clinical presentation of scarlet fever. Other agents of significance include exotoxin A, which may be associated with toxic shock syndrome, and bacteriocins, which destroy other gram-positive organisms. Spread of infection may be facilitated by a variety of enzymes elaborated by GABHS that attack fibrin and hyaluronic acid.

Epidemiology

"Strep throat" is well recognized as a common disease among children and adolescents. However, the incidence of GABHS pharyngitis has not been estimated

on the basis of population-based data.[5] St. Sauver et al. have estimated the incidence of recurrent GABHS pharyngitis (3 events in 12 months) in children 4 to 15 years of age at approximately 1%.[6] Streptococcal infection is more common in cooler, temperate climates with a peak incidence during the winter and spring seasons. Children between ages 5 and 15 are most commonly affected, but the disease has been seen more commonly in younger children in the last few decades. Transmission of GABHS is believed to occur through droplet spread; thus, close interpersonal contact in schools, military quarters, dormitories, and families with several children appears to be a risk factor for the disease. The risk of contagion most likely depends upon the inoculum size and the virulence of the infecting strain. As a result, individuals are most infectious early in the course of the disease. The incubation period is usually between 1 and 4 days; however, antibiotics rapidly suppress the infection and most physicians will allow affected children to return to school 36 to 48 hours after antimicrobial therapy is started. The role of individuals colonized with GABHS in the spread of the disease is uncertain, although data suggest that carriers rarely spread the disease to close contacts.[7] Available data do not support the notion that the disease may be transmitted by pets.[8]

Clinical features

Signs and symptoms of GABHS pharyngotonsillitis vary from mild sore throat and malaise (30 to 50% of cases) to high fever, nausea and vomiting, and dehydration (10%).[9] The disorder is acute in onset, usually characterized by high fever, odynophagia, headache, and abdominal pain. The pharyngeal and tonsillar mucosa are typically erythematous and occasionally edematous, with exudates present in 50 to 90% of cases. Cervical adenopathy is also common, seen in 30 to 60% of cases. Most patients improve spontaneously in 3 to 5 days, unless otitis media, sinusitis, or peritonsillar abscess occur secondarily. However, no constellation of signs or symptoms is specific for GABHS, and milder cases may represent viral illness in a GABHS-colonized individual.

Sequelae

Scarlet fever and streptococcal toxic shock syndrome (STSS) are Group A streptococcal toxin-mediated diseases. Both STSS and other invasive diseases such as necrotizing fasciitis are less common but have a high rate of mortality and long-term morbidity.

The post-infectious autoimmune sequelae of GAS infection are acute rheumatic fever (ARF) and acute post-streptococcal glomerulonephritis (APSGN). The risk of rheumatic fever following GABHS infection of the pharynx is approximately 0.3% in endemic situations, and 3% under epidemic circumstances.[9] A single episode of rheumatic fever places an individual at high risk for recurrence following additional episodes of GABHS pharyngitis. Acute glomerulonephritis occurs as a sequela in 10 to 15% of those infected with nephritogenic strains.[9] In patients who develop these sequelae, there is usually a latent period of 1 to 3 weeks. PANDAS (pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection) has been recognized as an immune mediated illness associated with GABHS infection, similar to Sydenham's chorea. In a prospective study identifying children with PANDAS, the most common presentation was

the abrupt onset of severe obsessive-compulsive disorder behaviors including hand washing, preoccupation with germs, and daytime urinary urgency or frequency in the absence of infection.[10] These behaviors resolved with treatment of the accompanying sentinel GABHS pharyngitis. Recurrence of obsessive-compulsive behaviors were seen in 50% of patients reinfected with GABHS and resolved with antibiotic treatment. The disorder has recently been reviewed in the otolaryngology literature.[11,12]

Diagnosis

Early diagnosis of streptococcal pharyngitis has been a priority in management of the disease, primarily due to the risk of renal and cardiac sequelae. A number of authors have studied the predictive value of various combinations of signs and symptoms in an effort to distinguish streptococcal from nonstreptococcal pharyngitis; however, none of these has been particularly reliable. Taken together, these studies demonstrate a false negative rate of about 50% and a false positive rate of 75%.[13] Adenopathy, fever, and pharyngeal exudate have the highest predictive value for a positive culture and rise in anti-streptolysin O (ASO) titer, and absence of these findings in the presence of cough, rhinorrhea, hoarseness, or conjunctivitis most reliably predicts a negative culture, or positive culture without rise in ASO.[13]

Although the cost effectiveness of throat culture has been questioned,[14] most clinicians still advocate this procedure as the gold standard to determine appropriate treatment for GABHS. The tonsils, tonsillar crypts, or posterior pharyngeal wall must be swabbed for greatest accuracy. Material obtained by throat swab is placed on a plate containing 5% sheep's blood agar and a bacitracin disk. Inhibition of bacterial growth is approximately 95% accurate for identification of GABHS. Cultures from infected children generally demonstrate heavier growth than those from patients who are colonized, but this criterion is too unreliable to distinguish the two groups.[15] The decision about whether to treat pending culture results or to delay treatment until the results are available remains controversial, although some studies suggest that early treatment hastens the clinical response to antibiotics.[16] In the mid-1980s, tests for rapid detection of the group-specific carbohydrate became available (QuickVue+® Strep A Test)*. Such assays, which include enzyme immunoassays, latex agglutination tests, and optical immunoassays have simplified the decision to treat at the time of the office visit, and have eliminated the need for additional post-visit communication. However, while most investigators report a specificity of greater than 90% for these tests, recent data suggest the false-positive rate can be as high as 15%.[17] In addition, their sensitivity is generally in the 60 to 90% range, depending on the clinical environment (i.e. highly organized clinical trials vs. hospital clinical laboratories) and varying with the spectrum of disease (higher clinical suspicion correlates with greater sensitivity).[18] As a result, many clinicians advocate

* A commercial kit can be found - Quick Vue+® Strep A Test (Quidel Corporation, San Diego, California, USA)

throat culture for children with suspected streptococcal disease and negative rapid strep tests. Rapid antigen detection (QuickVue+® Strep A Test)* is less expensivethan throat culture. It should be noted that rapid streptococcal antigen tests (QuickVue+® Strep A Test)* were developed for use in the diagnosis of GABHS pharyngotonsillitis.

Follow-up testing is an important consideration for the otolaryngologist treating "recurrent strep" in that it will help to distinguish the asymptomatic carrier from an infected individuals. Follow-up testing should also be performed in all patients with a history of rheumatic fever, and considered during outbreaks of group A beta-hemolytic streptococcal pharyngitis in closed communities.

Serologic tests are helpful in determining that true acute streptococcal infection has occurred, but are not as useful in diagnosing the disorder at its onset. A rise in ASO titer is usually demonstrable within 1 week of infection and peaks at 3 to 6 weeks. The subsequent decline usually occurs within 6 to 8 weeks but is less reliable and may not occur for months; therefore, a persistent elevation in ASO titer is not necessarily indicative of ongoing clinical disease. A positive test is defined as a twofold dilution increase in titer between acute and convalescent serum or any single value above 333 Todd units in children. Response to treatment does not predict a rise in antibody titer.[13] Results should be interpreted with caution, since streptolysin O is also elaborated by group C and G streptococci, ASO titers vary with age, and some antibiotics interfere with the ASO response.[19] Tests for anti-DNAse B and other extracellular antibodies may be useful in patients with suspected sequelae of GABHS infection who do not demonstrate a rise in ASO.[19]

The carrier state

It is critical for the otolaryngologist confronted with a patient with a history of "recurrent strep" to understand the implications of streptococcal carriage. Patients who have been exposed to GABHS may continue to carry the organism asymptomatically even after adequate antimicrobial therapy. Carriers are recognized as those individuals who demonstrate a positive culture for the organism but no rise in ASO convalescent titer. This condition is not associated with particular subtypes of the organism or any specific pharyngeal conditions. Carriage rates cited in the literature vary from 3 to 40%, depending on the population studied[20] and with the time of year; however, this figure may be overestimated because of the use of antibiotics, which interfere with the rise in ASO titer. Carriers appear to be at little risk to transmit GABHS, or to develop sequelae of the disease. James et al. demonstrated infection of family members by carriers only 9% of the time, and only 40% of those infected developed clinical disease.[21] Thus, only 3.5% of carriers produce clinical disease within their family. It is unknown whether carriers are at increased risk of recurrent pharyngitis. The high rate of streptococcal carriage complicates the distinction between bacterial and viral pharyngitis in the patient with sore throat and a positive culture. The

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American Academy of Pediatrics and the Infectious Disease Society of America currently recommend that testing for GABHS should not be performed in children with conjunctivitis, cough, hoarseness, coryza, diarrhea, oral ulcerations, or other clinical manifestations highly suggestive of viral infection.[22,23] A similar approach has recently been suggested for adults with suspected GABHS infection, requiring the presence of two Centor criteria (history of fever, absence of cough, swollen/tender anterior cervical nodes, tonsillar exudate) prior to consideration of GABHS testing.[24] When GABHS infection must be distinguished from non-streptococcal disease in a carrier, a convalescent ASO titer should be considered.

Treatment of the asymptomatic carrier is desirable in the following situations.

- Carriers in families with a history of rheumatic fever
- Carriers with a history of acute glomerulonephritis
- Carriers in families experiencing ping-pong spread of disease
- Carriers in schools experiencing GABHS epidemics
- Carriers who are food handlers
- Carriers who are hospital workers

In such cases, additional antibiotics, especially clindamycin and rifampin, have demonstrated some efficacy. In refractory cases, tonsillectomy should be considered.

Treatment

Medical therapy

The need to investigate and treat GABHS pharyngitis has been challenged in the literature, since most upper respiratory infections by GABHS resolve in 3 to 5 days without treatment and the risk of rheumatic fever is quite low except among impoverished populations.[25,26] However, studies suggest that antimicrobial therapy prevents suppurative and nonsuppurative sequelae including rheumatic fever, and may also hasten clinical improvement.[16,27,28] Some clinicians believe the degree of improvement may be underestimated since few studies have been conducted in children with culture-positive GABHS pharyngitis or those with severe symptoms, the group in whom the benefits of antibiotic treatment may be greatest.[27,29,30] A recent clinical trial also found a high rate of peritonsillar abscess in children treated with placebo, suggesting that failure to treat GABHS infection may result in an increase in suppurative complications.[29]

Treatment is therefore indicated in most patients with positive rapid tests for the group A antigen. When testing is negative, it is acceptable practice to treat for a few days while formal throat cultures are incubating, providing such treatment is discontinued in the event that final cultures are also negative. When testing is not available, it has been suggested that the presence of all four Centor criteria may be considered an indication for initiation of therapy.[24] Given the low sensitivity of rapid strep testing, a decision not to treat based on a negative test may not be the best choice.

Penicillin is the first-line antibiotic most commonly recommended for GABHS pharyngitis in clinical guidelines.[22,23] Penicillin has a long history of safety

and efficacy in the treatment of GABHS pharyngitis and protection against rheumatic fever, and no penicillin-resistant isolates have been identified in vitro. In addition, a 1993 meta-analysis found no increase in the bacteriologic failure rate with penicillin during the last 40 years.[31] Depot benzathine penicillin G is still advocated by the American Heart Association for primary treatment of GABHS pharyngitis; however, a 10-day course of penicillin orally is the most widely prescribed regimen. Twice-daily dosing by the oral route yields results similar to those obtained with four times a day dosing.[32] A once-daily oral dose of amoxicillin for 10 days also has demonstrated bacteriological efficacy similar to that of oral penicillin dosed three times a day for 10 days.[33] Courses of shorter duration are associated with bacteriologic relapse and are less efficacious in the prevention of rheumatic fever.

During the 1980s, several authors reported a decrease in bacteriologic control rates, attributed primarily to inoculum effects and to increased tolerance to penicillin. Relapses and persistent positive cultures were not associated with significant symptoms or with suppurative or nonsuppurative sequelae, but the goal of eradication to prevent rheumatic fever was not achieved. In one study, 35% of 284 patients treated with oral penicillin V and 37% of 271 patients treated with benzathine penicillin G were bacteriologic treatment failures.[34] Other studies suggest a 20% to 25% higher eradication rate with the use of more broad spectrum agents, such as cephalosporins[35] and azithromycin,[36] compared with penicillin. A recent meta-analysis suggested an increased likelihood of bacteriological and clinical failure in adult patients with GABHS treated with oral penicillin compared with oral cephalosporins,[37] although it has been argued that poor quality studies were included, and that results may be skewed since GABHS carriage is more effectively eradicated by cephalosporins than by penicillin.[38,39] Such data, however, support consideration of revised dosing regimens or alternative antimicrobials in the management of GABHS. However, while cephalosporins and macrolides are active against GABHS and their use as treatment for GABHS pharyngitis is considered an acceptable alternative to penicillin, their ability to prevent rheumatic fever remains unproven.

Macrolide has traditionally been the drug of choice for patients with penicillin allergy; however, increasing prevalence of macrolide-resistant GABHS throughout the world is changing this paradigm. Among pharyngeal cultures from Pittsburgh school children, clonal macrolide-resistant (erythromycin) GABHS was found in 48%.[40] As has been described in other studies, the unexpectedly high resistance rate was associated with increased local prescribing of macrolide antibiotics during the same period. Azithromycin, used as a 5-day therapy by many clinicians for patients expected to be poorly compliant, may similarly be associated with increasing resistance.

Most patients with positive cultures following treatment are GABHS carriers; these individuals need not be retreated if their symptoms have resolved. Other explanations for microbiologic failures, including the presence of beta-lactamase producing organisms in the respiratory tract, the presence of GABHS tolerant to penicillin, and the production of inhibitory substances by organisms in the upper

respiratory tract that promote persistence of GABHS, have not been convincingly demonstrated.[41,42] For patients in whom complete bacteriologic clearance is desirable, such as those with a family member with a history of rheumatic fever, a course of clindamycin or a second course of penicillin combined with rifampin may yield increased success. In patients with recurrent symptoms, serotyping may aid in distinguishing bacterial persistence from recurrence. There are no data available regarding the use of antibiotic prophylaxis in these patients, and in such cases tonsillectomy may be most advantageous.

During antimicrobial therapy, patients must be monitored carefully for fluid intake, pain control, and impending suppurative complications such as peritonsillar abscess. Small children may become dehydrated rapidly, and may require hospitalization for administration of fluids intravenously. Steroids are effective in the management of sore throat symptoms.[43]

Surgical therapy

Removal of the tonsils as prevention against infection has been a popular concept for decades. Although a number of clinical trials from the early 1900s suggested efficacy of tonsillectomy in reduction of recurrent throat infection, most were of questionable validity due to nonrandom selection of operated subjects, reliance on parents for postoperative data collection, and inappropriate statistical analysis. A series of trials by Paradise et al. at the University of Pittsburgh in the 1970s and 1980s sought to avoid these methodological flaws.

The first two trials were parallel studies with identical design, except that assignment to surgical or nonsurgical treatment was random in one and according to parental preference in the other.[44] Throat infection was defined to include one of the following features: temperature greater than 38.3°C, tender cervical adenopathy or nodes greater than 2 cm in size, tonsillar exudate, or positive culture for GABHS. No other attempt was made to determine the cause of the infection. Patients were entered into the study only if they had physician documentation of seven episodes in 1 year, five episodes a year for 2 years, or three episodes a year for 3 years.

Ninety-one patients completed the randomized trial and 96 completed the nonrandom trial. Tonsillectomized patients in the trial with random assignment had 1.85, 1.05, and 0.43 fewer episodes of throat infection than control patients for each of the first three postoperative years, respectively, while those in the parallel nonrandom trial had 1.32, 1.32, and 1.58 fewer episodes; these differences were statistically significant in the first 2 years. However, in both trials, most patients in the non-tonsillectomized group were enrolled on the basis of three episodes per year, while most tonsillectomized patients were in the five or seven episodes per year groups. As a result, it is difficult to conclude that the lower postoperative frequency of infection in the tonsillectomy group is due to the surgical intervention rather than to spontaneous improvement of patients affected for a shorter period. Furthermore, moderate and severe episodes were rare even in the control groups, and there was no statistical difference in total days spent with sore throat between the surgical and non-surgical groups. On the other hand, the effect of tonsillectomy may have been understated due to transfer of severely affected patients from the non-surgical to the surgical groups.

Based on these studies, tonsillectomy may offer a small advantage in the treatment of children in whom a pattern of severe recurrent pharyngotonsillitis has been well documented. The authors themselves state, however, that a decision whether or not to perform tonsillectomy should consider risks, preferences, and anxieties of parent and child, school absences due to illness, accessibility to health care services, cost, and availability of surgical facilities.

In a later study, Paradise et al. report the results of two trials in which the entrance criteria from the first two studies were made less stringent.[45] Patients entering the study had a lower frequency of infection or less severe episodes, or lacked the documentation of episodes required in the first study. These patients were grouped together and then assessed for indications for adenoidectomy. Those without such indications (N = 177) were assigned to the first trial and randomized to undergo tonsillectomy, adenotonsillectomy, or no surgery. Patients with indications for adenoidectomy (N =151) were assigned to the second trial and underwent adenotonsillectomy or no surgery. In both trials, the frequency of infection in both the surgical and non-surgical groups again dropped, although the decrease was marginally greater (approximately one episode per year) in the surgical groups. However, control subjects in both trials again developed far less than one episode of moderate or severe pharyngitis per year. Although the data were not dramatically different from those in the initial publication, in this study, the authors concluded that the small potential benefits of surgery did not justify the associated risk and expense. Furthermore, performing adenoidectomy in addition to tonsillectomy conferred no additional advantage in controlling throat infections when compared with tonsillectomy alone.

In a more recent study, Orvidas et al. conducted a retrospective cohort study of 290 children aged 4 to <16 years who were diagnosed with three or more episodes of GABHS pharyngitis in a 12 month period.[46] Their results suggested that children who did not have a tonsillectomy were 3.1 times more likely to develop a subsequent GABHS infection during follow up than children who underwent tonsillectomy. Non-tonsillectomized children also developed a GABHS pharyngeal infection sooner (median 0.6 vs.1.1 years) than their tonsillectomized counterparts. However, given the retrospective nature of the study, the authors were unable to establish that children entered into the study were infected individuals rather than carriers or that their subsequent events represented true infection. This is particularly important since the outcome measure was only a single episode of GABHS pharyngitis.

Another smaller study comparing GABHS infections among 36 tonsillectomized adults with 34 on a tonsillectomy wait list over a 90 day period found that streptococcal pharyngitis had recurred in 24% in the control group and 3% in the tonsillectomy group.[47] The number needed to undergo tonsillectomy to prevent one recurrence was 5, and days with throat pain and fever were significantly lower in the tonsillectomy group than in the control group. Again, diagnostic criteria were not specified. There are currently no clinical trials to support or refute the efficacy of tonsillectomy for streptococcal carriers with or without chronic sore throat.

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