Group A Streptococcus and Pharyngotonsillitis

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Acute pharyngitis is defined as an infection of the pharynx and/or tonsils. It is a very common pathology among children and adolescents [1-4], and it accounts for 5-20 % of all annual visits to emergency departments and outpatient care services around the world. [1-3,5,6] Viruses are the most common cause of acute pharyngitis. Respiratory viruses, such as adenovirus, influenza, parainfluenza, rhinovirus, and respiratory syncytial virus, frequently cause acute pharyngitis. Other acute pharyngitis causing viral agents are: coxsackievirus, echoviruses, and herpes simplex virus. The Epstein-Barr virus frequently causes acute pharyngitis, which appears together with features of a clinical syndrome called infectious mononucleosis (e.g. generalized lymphadenopathy and splenomegaly). Systemic infections with cytomegalovirus, rubella, measles, and a number of other viral agents may also be associated with acute pharyngitis. Human metapneumovirus and human bocavirus may cause lower respiratory tract infection in children, but their respective roles in causing pharyngitis, if any, are unknown [3,7-10] .

Group A beta-hemolytic Streptococcus pyogenes (GAS) is the most common cause of bacterial pharyngitis, and accounts for 15 to 30% of all acute pharyngitis cases in children and adolescents.[1-3,6-8, 10-16], although it may also be caused by other bacteria. *Arcanobacterium haemolyticum* is a rare cause of acute pharyngitis that may be associated with a rash similar to that seen in patient with scarlet fever, particularly teenagers and young adults. *Neisseria gonorrhoeae* can occasionally cause acute pharyngitis in sexually active persons, and *Francisella tularensis and Yersinia enterocolitica* are infections that may also be caused by other bacteria. Pathogens, such as, *Chlamydia pneumoniae* (1%) and *Mycoplasma pneumoniae* (1%) can cause pharyngitis in adolescents. Other bacterial causes of pharyngitis are *Group C* (GCS) and *G beta-hemolytic streptococcus*(GGS), accounting for 5% of total cases, especially in older children and adults. Although the infection is similar, it does not lead to significant complication typical of a GAS infection. In addition to endemic pharyngitis, GCS can cause epidemic food-borne pharyngitis acquired after eating contaminated products, such as unpasteurized cow milk. There are several descriptions of GCS pharyngitis outbreaks among family groups or in schools. Despite the fact that there are a number of well-documented food-borne outbreaks of group G streptococcal (GGS) pharyngitis, as well as a community-wide respiratory outbreak of GGS pharyngitis in children, the etiologic role of GGS in acute, endemic pharyngitis remains unclear. Acute rheumatic fever has not been described as a complication of either GCS or GGS pharyngitis. Reports have attempted to link acute glomerulonephritis with GGS pharyngitis, but a causal relationship has not yet been established. As it is extremely unusual

to find acute glomerulonephritis as a complication of GCS pharyngitis, the primary way to identify either GCS or GGS as the etiologic agent of acute pharyngitis is to initiate an antibiotic therapy that may reduce the clinical impact of the illness. Currently, controlled studies show no convincing evidence of a clinical response to antibiotic therapy in patients with acute pharyngitis and either GCS or GGS isolated from the throat. Several recent reports have documented the isolation of *Fusobacterium necrophorum* from throat swabs of adolescents and young adults with nonstreptococcal pharyngitis. Some studies also suggest *F. necrophorum* plays a role in cases of recurrent or persistent pharyngitis (with or without bacteremia or Lemierre's syndrome). *Fusobacterium* is the main causal agent of Lenmierre's Syndrome (internal jugular vein thrombophlebitis, that may cause bacteremia and septic emboli in the lungs), a lethal but rare complication that must be treated immediately with an antibiotic therapy. At present, the evidence of *F. necrophorum* as a primary pathogen in acute pharyngitis in adolescents and young adults is only suggestive. Further study is required in order to determine the role it plays in acute pharyngitis, as well as the need to have and use an effective antibiotic therapy [3,10,7,17].

***Group A beta-hemolytic Streptococcus* – GAS**

Group A streptococcus (GAS) is an important gram-positive extracellular bacterial pathogen. The Lancefield classification scheme of serological grouping distinguished the beta-hemolytic streptococci based on their group A carbohydrate, composed of N-acetylglucosamine linked to a rhamnose polymer backbone. As pathogens, they have developed complex virulence mechanisms to avoid host defenses [18].

The most important GAS virulence factor is M protein, an adhesin found on the bacterial surface [19]. Streptococci are serologically separated into M protein serotypes, and more than 80 M protein serotypes have currently been identified [(18)]. Serotyping of GAS based on protein M has been used for a long time as the gold standard for the epidemiological surveillance of infections caused by this pathogen [(20)], as it exploits the antigenic specificity of GAS [19]. In recent years, it has been widely replaced by an equivalent approach based on sequencing the hypervariable region of the *emm* gene encoding the M protein (*emm* type gene) [20].

This is why GAS is responsible for a wide range of pathologies ranging from mild pharyngitis, impetigo and serious infections such as necrotizing fasciitis and streptococcal toxic shock syndrome (**Table 1**). Furthermore, repeated GAS infections may trigger autoimmune diseases, including acute poststreptococcal glomerulonephritis, acute rheumatic fever, and rheumatic heart disease. Combined, these diseases account for over half a million deaths per year globally [21].

Table 1. Clinical symptoms and epidemiology of the major group A Streptococcus infections [21]

DISEASE	ESTIMATED GLOBAL INCIDENCE	PROTEIN M ASSOCIATED
SUPERFICIAL		
Pharyngitis	>600 million/year	1, 3, 5, 6, 12, 14, 17, 19, 24
Impetigo	111million/year	33, 41, 42, 52, 53, 70
SEQUELAE		
Acute rheumatic fever	471.000/year	1, 3, 5, 6, 11, 12, 14, 17, 18, 19, 24, 27, 29, 30, 32, 41
Rheumatic heart disease	15.6 million–19.6 million	
Acute poststreptococcal glomerulonephritis	470.000/year	1, 4, 12, 49, 55, 57, 60
INVASIVE DISEASE		
Bacteremia	660.000 cases and 160.000 deaths/year (all invasive diseases)	28
Necrotizing fasciitis		1,3,8,28
Streptococcal toxic shock syndrome		1,3

Pharyngitis

Although caused by GAS, pharyngitis is usually a benign and a self- limited infection. However, the introduction of antibiotics is recommended because early treatment of group A streptococcal pharyngitis is believed to shorten the duration of symptoms, decrease the incidence of suppurative complications, diminish the probability of spreading, and eradicate the pathogen. Additionally, the appropriate treatment of group A beta-hemolytic streptococcal pharyngitis significantly reduces the risk of developing acute rheumatic fever, a complication that can be prevented, by and large, if an adequate course of antibiotic treatment is received within 9 days after the onset of symptoms [11].

A sore throat due to GAS occurs mainly in 5 to 15 years old school-aged children, is uncommon in children under 3 years old [3,10] and very rare in children under 2 years old [23]. Most authors describe streptococcal sore throat occurring more frequently in winter or early spring [3,8,10,24,25]. Classically, clinical findings suggestive of bacterial disease are: 1) fever, sudden onset of sore throat, headache, vomiting and abdominal pain; 2) hyperemia, hypertrophy and purulent exudate on tonsils; 3) painful anterior cervical lymphadenopathy; 4) petechiae on the palate; 5) absence of signs and symptoms of upper respiratory tract infections (URTI), such as cough, rhinorrhea, conjunctivitis, dysphonia or diarrhea [10,22,26].

However, clinical and epidemiological data are not specific or sensitive enough to diagnose sore throat caused by GAS. Thus, since the 1970`s, several authors in various countries have attempted, unsuccessfully, to establish a high-sensitivity and sensitivity clinical score to detect streptococcal sore throat.

In 1981, Centor *et al*. [27] proposed a clinical model to determine the probability of streptococcal infection occurring in adult patients presenting sore throat and fever history in emergency rooms. The model consisted in the evaluation of four clinical variables: tonsillar exudate, painful cervical lymphadenopathy, fever and no coughing. Over the years, several authors have adopted this scoring system as a selection criterion to diagnose and treat sore throat. The Centor criteria was modified and used as a basis to define new clinical scores for the diagnosis of pharyngitis, especially in the pediatric age group. However, the described feature results in sensitivity variation scores of 12 to 93% and a specificity of 30-93% [13,14,24,28-31,33]. These results led the Committee of Rheumatic Fever, Endocarditis, the Kawasaki Disease American Heart Association, the American Academy of Pediatrics, the American Pediatric Society, and more recently, the Brazilian Society of Pediatrics to recommend that the diagnosis of sore throat in patients with clinical and epidemiological suspicion of GAS pharyngitis should be confirmed through the use of microbiological techniques [2,3,23,26,34-36]. Thus, except when obvious viral clinical and epidemiological features are present, a laboratory test should be performed to determine whether GAS is present in the pharynx. Efforts have been made to incorporate the clinical and epidemiological features of acute pharyngitis into scoring systems that attempt to predict the probability that a particular illness is caused by GAS pharyngitis.

These clinical scoring systems are helpful in identifying patients who are at such low risk of streptococcal infection that a performance of a throat culture or a Rapid Antigen Detection Test (RADT) is usually unnecessary. However, the signs and symptoms of streptococcal and nonstreptococcal pharyngitis overlap too broadly to allow a diagnosis with the required precision, merely on the basis of clinical grounds alone.

Even subjects with all clinical features in a particular scoring system can be confirmed to have streptococcal pharyngitis only about 35%-50% of the time, and this is particularly the case in children. Even the most experienced physicians cannot make the clinical diagnosis of GAS pharyngitis with certainty, and bacteriologic confirmation is required [7].

In contrast, medical societies in the United Kingdom, Scotland, Netherlands and Belgium consider sore throat, although GAS, a benign self-limiting infection that does not, therefore, need to be treated empirically with antibiotics. The main argument of the authors is that, due to the low incidence of rheumatic fever in these as well as in other developed countries, empirical antibiotic therapy and etiological investigation are not necessary. The position taken by the research carried out in these countries indicates the use of antibiotics in selected cases, in order to assure they are used prudently, preventing the emergence and spreading of bacterial strains resistant to antibiotics, and thus avoiding the occurrence of adverse events caused by their use [3,10,35].

Laboratory Diagnosis

Throat Culture - *A culture of a throat swab* on a sheep-blood agar plate has been the standard used to document the presence of GAS pharyngitis in the upper respiratory tract, confirming the clinical diagnosis of acute streptococcal pharyngitis [37]. If performed correctly, culture of a single throat swab on a blood agar

plate is 90%– 95% sensitive for detecting GAS pharyngitis. Several variables affect the accuracy of throat culture results, for example, the manner in which the swab is obtained plays an important role on the yield of streptococci. Throat swab specimens should be obtained from the surface of either tonsils (or tonsillar fossae) and the posterior pharyngeal wall, as other areas of the oral pharynx and mouth are not acceptable sites. Furthermore, false-negative results may be obtained if the patient has received an antibiotic shortly before the throat swab is obtained. Another variable that can affect the throat culture result is the duration of incubation as, once plated, a culture should be incubated at 35°C–37°C for 18–24 hours before reading. It is rather difficult to ascertain the clinical significance of the number of GAS colonies on the throat culture plate. Although patients with true acute GAS pharyngitis are likely to have more strongly positive cultures than patients who are streptococcal carriers (e.g. individuals with chronic GAS colonization of the pharynx), there is too much overlapping to establish an accurate differentiation based only on this data [7,38].

Rapid Antigen Detection Test (RADT) - A major disadvantage of throat cultures is the delay (overnight or longer) in obtaining results. RADTs have been developed to identify GAS pharyngitis directly from throat swabs, with shorter turnaround time. The rapid identification and treatment of patients with GAS pharyngitis can reduce the risk of it spreading, thus allowing the patient to return to school or work sooner, and reducing the acute associated morbidity. The use of RADTs for patients in emergency rooms was reported to result in a significant increase in the number of patients appropriately treated for streptococcal pharyngitis, when compared with traditional throat cultures. RADTs currently available are highly specific (approximately 95%) when compared with blood agar plate cultures. False-positive test results are highly unusual, and therefore reliable therapeutic decisions can be made on the basis of a positive test result. Unfortunately, the sensitivity of most of these tests is 70%–90% compared with blood agar plate culture. Newer tests based on enzyme immunoassay techniques offer increased sensitivity and a more sharply defined endpoint. More recently, RADTs using chemiluminescent DNA probes or optical immunoassays have been developed; but optical immunoassays are no longer commercially available. A variety of RADTs are available, not all with equal performance characteristics. Their sensitivity varies depending on the intensity of the disease, sampling technique, the amount of antigens and type of kit used [32,38-41]. In view of the fact that the sensitivities of the various RADTs are <90% in most populations of children and adolescents studied, and the proportion of acute pharyngitis due to GAS in children and adolescents is sufficiently high (20%–30%), a negative RADT should always be followed-up or backed-up by a throat culture in this age group, although under usual circumstances it is an unnecessary step in adults. Furthermore, a negative RADT result in a child or adolescent must be confirmed with a throat culture, unless the physicians involved have ascertained that the RAD test carried out in their office is comparable to a culture [7,25,38].

Neither conventional throat culture nor RADTs accurately differentiate acutely infected persons from asymptomatic streptococcal carriers with intercurrent viral pharyngitis. Nevertheless, they allow physicians to withhold antibiot-

ics from the great majority of patients with sore throats whose culture or RADT results are negative. This is extremely important, as at the domestic level up to 70% of patients with sore throats seen in primary care settings receive prescriptions for antimicrobials, while only 20%–30% are likely to have GAS pharyngitis. Both RADTs and throat cultures may be affected by spectrum bias. This refers to the phenomenon that, with a greater pretest probability of GAS pharyngitis, the sensitivities of RADTs and throat culture are greater [7]. Measurement of antistreptococcal antibody titers is often useful to diagnose non-suppurative sequelae of GAS pharyngitis, such as acute rheumatic fever and acute glomerulonephritis. However, such testing is not useful to diagnose acute pharyngitis because antibody titers of the two most commonly used tests, antistreptolysin O (ASO) and anti-DNase B, may not reach maximum levels until 3–8 weeks after the onset of an acute GAS pharyngeal infection, and may remain high for months even without an active GAS infection present [7].

The impact of using Laboratory Diagnosis

Several studies have shown that microbiological methods, throat culture or RADT, are important tools to define the etiological diagnosis of throats accurately and at an early stage. This avoids the transmission of GAS; decreases the risk of suppurative and non-suppurative complications such as rheumatic fever; improves symptoms, decreases morbidity caused by the infection; and finally, avoids the unnecessary use of antibiotics.

A careful use of antibiotics plays an important role in the prevention of bacterial resistance to antimicrobials, reducing health care costs, and improving individual patient care [42]. However, the use of antibiotics to treat acute respiratory infections of the upper airways with a viral etiology is common, both in developed and in developing [43].

The inappropriate use of antibiotics in the United States was estimated at around 25-50% of total prescriptions issued [42]. In a study conducted in São Paulo, Brazil, it was found that 68% of antibiotics prescriptions issued to children with acute respiratory infections under seven years of age were inadequate [43].

This is due to multiple factors, among which the difficulty in clinically differentiating viral from bacterial etiology of the infections, lack of knowledge regarding the probable adverse events associated with the inappropriate use of antibiotics as well as the significant impact caused by the inappropriate use of antibiotics, resulting in increased bacterial resistance [12,42-44].

The emergence and spreading of bacterial strains resistant to antimicrobials are public health problems that affect both developed and developing countries [33,42,44-47]. Resistant infections cause increased morbidity and mortality, higher costs and increase the progression time of the disease, with longer persistence of signs and symptoms [1,33,42.44,45]. Interventions to reduce inadvertent prescription of antibiotics should be provided urgently, especially due to the declining production and creation of new multi-resistant bacteria antimicrobials [42,45]. These interventions should take into account the country and resources available, which may range from a change in the behavior of health care professionals to the medical use of supplementary diagnostic techniques [34,42,44-51] such as RADT.

Moreover, the risk of serious adverse events resulting from the use of antibiotics must also be taken into account. An anaphylactic reaction to the use of penicillin occurs in 0.015% cases with a shock mortality rate of 0.002%. In general, a 10-days treatment with antibiotics may result in some morbidity, amounting to about 10% of cases [10].

Furthermore, although rare, if no microbiological methods are used in the lab to confirm pharyngitis, this may delay or prevent the identification of GAS as the cause of the infection. Under these circumstances, there is an increased risk of suppurative and non-suppurative complications occurring, such as rheumatic fever (RF).

Rheumatic fever (RF) is an acute inflammatory disease, immune-mediated, non-suppurative infection that can occur after GAS [19,21,52], which may emerge as arthritis, carditis, Korea Sydehan, *erythema marginatum* and subcutaneous nodules [(53,54)]. Some patients do not exhibit any clinical symptoms before the onset of RF, hindering and sometimes even delaying its diagnosis and treatment. These pathological events usually begin after one to three weeks from the onset of an acute streptococcal disease have elapsed [(19,52)]. When pharyngitis is untreated or inadequately treated, 0.3 to 3% of 5 to 15 years old infected patients may develop RF [40,50,52,54-56], and one to two thirds of them may develop rheumatic heart disease[54]. Repeated exposure to GAS infections often precedes the development of RF [19].

The pathogenesis of acute rheumatic fever involves an interaction between the virulence factors of GAS and host susceptibility [19].

Approximately 616 million cases of pharyngitis and 111 million cases of impetigo caused by GAS are diagnosed in the world every year [21,53]. It is estimated that the worldwide secondary mortality rate related to GAS caused diseases and its sequelae (rheumatic fever, rheumatic heart disease, post-streptococcal glomerulonephritis and invasive disease) amounts to some 500,000 cases a year. The global prevalence of rheumatic heart disease (RHD) is 15.6 million cases, with an incidence of 282,000 and a mortality rate of 233,000 each year [21,52-55,57].

Despite the decline in the prevalence of RF reported in developed countries over the last three decades, rheumatic heart disease (RHD) secondary to rheumatic fever remains the most common acquired heart disease in children and young adults, in developing countries and among disadvantaged populations in developed countries [52]. In Brazil, rheumatic heart disease is still the leading cause of acquired heart disease among children and young adults [54]. However, the hypothetical prevention of rheumatic fever should take into account the risk of developing bacterial resistance to antimicrobials and its consequences [1,33,42,44,46].

Treatment of Pharyngitis

Patients with acute GAS pharyngitis should be treated with an appropriate antibiotic at an appropriate dose for the duration likely to eradicate the organism from the pharynx (usually 10 days). Based on their narrow spectrum of activity, infrequency of adverse reactions, and modest cost, penicillin or amoxicillin are the recommended drugs of choice for those non-allergic to these agents.

Treatment of GAS pharyngitis in penicillin-allergic individuals should include a first generation cephalosporin (for those not anaphylactically sensitive) for 10 days, clindamycin or clarithromycin for 10 days, or azithromycin for 5 days.

A number of antibiotics have been shown to be effective in treating GAS pharyngitis, such as: penicillin and others of its kind (e.g. ampicillin and amoxicillin), as well as numerous cephalosporins, macrolides, and clindamycin. However, penicillin remains the treatment of choice due to its proven efficacy and safety, its narrow spectrum, and its low cost. Penicillin-resistant GAS has never been documented. In comparative clinical trials, once-daily amoxicillin (50 mg/kg, to a maximum of 1000 mg) over 10 days has proven to be effective for GAS pharyngitis. Most oral antibiotics must be administered over the conventional 10 days to achieve maximum rates of pharyngeal GAS eradication.

Antimicrobials for GAS pharyngitis may be given either orally or parenterally. Intramuscular benzathine penicillin G therapy is preferred for patients deemed unlikely to complete a full 10-day course of oral therapy. Certain antimicrobials are not recommended for treatment of GAS pharyngitis: tetracyclines should not be used due to the high prevalence of resistant strains. Sulfonamides and trimethoprim-sulfamethoxazole should not be used because they do not eradicate GAS from patients with acute pharyngitis. Older fluoroquinolones (e.g. ciprofloxacin) have limited activity against GAS pharyngitis and should not be used to treat this disease. Newer fluoroquinolones (e.g. levofloxacin) are active *in vitro* against GAS, but are not recommended for a routine treatment of GAS pharyngitis as they are too expensive, and have an unnecessarily broad spectrum of activity.

Clindamycin resistance among GAS isolates in the United States is approximately 1%, and this is a reasonable agent for treating penicillin-allergic patients.

An oral macrolide (erythromycin or clarithromycin) or azalide (azithromycin at a dose of 12 mg/kg/day, up to a maximum of 500 mg) is also reasonable for patients allergic to penicillin. Ten days of therapy is indicated for all but azithromycin, which is given for 5 days. Erythromycin is associated with substantially higher rates of gastrointestinal side effects than those caused by other agents. Strains of GAS resistant to these agents have been highly prevalent in some areas of the world and have resulted in treatment failures. In recent years, macrolide resistance rates among pharyngeal isolates have amounted to around 5% - 8% in most areas of the United States. Adjunctive therapy is often useful in the management of GAS pharyngitis. If warranted, use of an analgesic/antipyretic agent such as acetaminophen or an non steroidal anti-inflammatory drug (NSAID), for treatment of moderate to severe symptoms or control of high fever associated with GAS pharyngitis should be considered as an adjunct to an appropriate antibiotic. However, aspirin should be avoided in children, and the use of an adjunctive therapy with a corticosteroid is not recommended [7].

GAS Carriers

Chronic pharyngeal carriers have GAS present in the pharynx, but have no evidence of an active immunologic response to the organism, such as rising antistreptococcal antibody titers. During the winter and spring in temperate climates, as many as 20% of asymptomatic school-age children may be GAS carriers. They may be colonized by GAS pharyngitis for ≥6 months, and during that time may experience episodes of intercurrent viral pharyngitis. Testing of such patients often shows evidence of GAS in the pharynx, and they may thus mimic patients with

acute streptococcal pharyngitis. Individuals who are identified as chronic pharyngeal GAS carriers do not usually require further antimicrobial therapy. Carriers appear to be unlikely to spread the organism to their close contacts and are thought to be at very low risk, if any, for developing suppurative or invasive complications or non-suppurative complications (e.g. acute rheumatic fever). Additionally, it is more difficult to eradicate GAS pharyngitis from the throats of carriers than from patients with acute streptococcal infections. This is particularly true for penicillin or amoxicillin therapy, and may also apply to some other antimicrobials. Clinical and epidemiological evidence suggests that, in published studies showing penicillin or amoxicillin to have relatively high failure rates for eradicating GAS pharyngitis, the patient population was likely "contaminated" by chronic carriers.

Although antimicrobial therapy is not indicated for most chronic streptococcal carriers, there are special situations in which eradication of carriage may be desirable, including the following: (1) during a community outbreak of acute rheumatic fever, acute poststreptococcal glomerulonephritis, or invasive GAS infection; (2) during an outbreak of GAS pharyngitis in a closed or partially closed community; (3) in the presence of a family or personal history of acute rheumatic fever; (4) in a family with excessive anxiety about GAS infections; or (5) when tonsillectomy is being considered only because of carriage. A number of antimicrobial schedules have been demonstrated to be substantially more effective than penicillin or amoxicillin in eliminating chronic streptococcal carriage.

In routine practice, it is often difficult to differentiate a GAS carrier with an intercurrent viral infection from a patient with acute streptococcal pharyngitis. Helpful clues include: patient's age, season, local epidemiological characteristics (e.g. local prevalence of influenza and/or enteroviral illnesses), and the precise nature of the presenting signs and symptoms. In many instances, however, the clinician may not be able to distinguish persistent carriage from acute infection and will elect to administer another course of antimicrobials. For a single episode of pharyngitis associated with laboratory confirmation of GAS that occurs shortly after completion of a course of appropriate antimicrobial therapy, treatment with other agents is appropriate. Since patient adherence to oral antimicrobial therapy is often an issue, intramuscular benzathine penicillin G should be considered. For these individual second episodes, it is not necessary to obtain additional throat swab specimens for culture after the second course of therapy unless the patient remains or becomes symptomatic, or unless one of the special circumstances noted above is present [7,58].

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