Acute Pharyngo-tonsillitis

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When referring to tonsillitis, the correct designation is pharyngo-tonsillitis (PT) as the pharynx has lateral cords with the same type of tissue as in Waldeyer's lymphatic ring. It is very rare to have a patient with an isolated tonsillitis, as the lymphatic ring is generally involved, and therefore pharyngo-tonsillitis is the correct term. The same analogy can also be made with sinus pathology, as the nasal tissue is also involved in cases of allergy or infection, and the patient has a rhino-sinus pathology.

Definition

PT is a self-limited infection, generally restricted to the tonsils, posterior pharynx, uvula, posterior soft palate and the lymph nodes of the Waldeyer's lymphatic ring that drain the anterior cervical region.

PT is one of the most complaints that take a child to the offices of pediatricians, otorhinolaryngologist and general practitioners. In a survey involving 429 pediatricians in the United States, upper respiratory tract infections and ear infections were the most common causes for a visit, and PT was the third most common problem, responsible for 17% of the visits, according to the age of the child[3].

3 – Etiology

3.1 – Predisposing factors

PTs are infections transmitted from person to person. The nasopharynx and oropharynx are the main sites for organisms to colonize.. Aerosol secretions of the upper respiratory tract act as a primary transmitting source of the causative agents. The presence of a susceptible host is necessary and spreading is facilitated by a very close contact. A larger group of children, as in day care centers and schools where they are in close contact with potentially infected persons, is associated with a more frequent transmission of the disease.

In children, the bacteria most commonly associated with PT are the Group A *Streptococcus pyogenes* (GAS) or Group A beta-hemolytic *Streptococcus (*GABHS). In the last 50 years, since antibiotics became available, most pharyngo-tonsillar infections caused by GABHS are benign, self-limiting processes, with no complications. However, a small number of affected individuals will develop a severe disease as the necrotizing fasciitis and its sequelae, as renal and cardiac complications after infections by GABHS. There are reports that administration

of an antibiotic in an early stage is very useful in the treatment of GABHS. As a result, it is mandatory to have an adequate diagnosis and timely treatment of these infections.

It is believed that GABHS is transmitted by saliva microdroplets being spread. Risk of contagion depends on the amount that was inoculated and on the virulence of the strain. Thus, individuals are more prone to become infected in the early stages of the disease. The incubation period is from 1 to 4 days, and as antibiotics suppress the infection, most physicians allow children to go back to school 48 to 72 hours after the antimicrobial treatment is started.

3.2 – Triggering factors

A wide variety of organisms can cause tonsillar inflammation, including aerobic and anaerobic bacteria, viruses, *Mycoplasma*, *Toxoplasma* and *Candida* species.

I – Bacteria

Aerobic: *Streptococcus pyogenes* Groups A, B, C and G, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, *Neisseria gonorrhoeae*, *Corynebacterium diphtheriae*, *Corynebacterium hemolyticum*, *Bordetella pertussis*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Salmonella typhi*, *Francisella tularensis*, *Yersinia pseudotuberculosis*, *Treponema pallidum*, *Mycobacterium* species.

Anaerobic: *Peptococcus* species, *Peptostreptococcus* species, *Actinomyces* species, *Bacteroides melaninigenicus*, *Bacteroides oralis*, *Bacteroides fragilis.*

II- Mycoplasmas

Mycoplasma pneumoniae and *Mycoplasma hominis*.

III- Viruses and Chlamydia

Adenovirus, Enterovirus (polio, ECHO, coxsackie), Parainfluenza Virus, Epstein-Barr Virus, Herpes simples Virus, Respiratory Syncytial Virus, Influenzae A and B Virus, Citomegalovirus, Reovirus, Measles Virus, Rubella Virus, Rhinovirus and *Chlamydia trachomatis*.

IV- Fungi

Candida species.

V- Parasites

Toxoplasma gondii.

VI- Rickettsia

Coxiella burnetii.

4 – Pathogenesis

It is estimated that over 50% of all PTs are caused by viruses. PTs are essentially viral before two years of age or even before three years, according to some authors. Most viral PTs are mild, self-limited and do not demand treatment with antibiotics. The exception is the Coxsackie A virus, characterized by presence of vesicles (that evolve into ulcers) on the tonsils, anterior pillars, palate and posterior pharynx. In general, children infected by this virus seem to be more severely sick than when infected by other viruses. Another important virus is Epstein-Barr, agent of infectious mononucleosis. Infections caused by this virus generally occur in pre-adolescents and adolescents, and vary from a mild form, with only upper respiratory tract, to a multisystemic disease.

Acute tonsillitis is traditionally considered as a streptococcal disease. Streptococci are gram-positive organisms characterized by their typical growth in cultures as long chains or pairs. It is important to know that, based on the carbohydrate antigen component of the cell wall, Lancefield's classification includes 18 groups of *Streptococcus pyogenes*, and Groups C, G and B can cause PTs, which are however different from those caused by Group A or GABHS. The latter can be associated with suppurative sequelae but other *Streptococcus pyogenes* groups are not.

The incidence of infections caused by GABHS reach a peak in winter and spring, in children and children and adolescents, mainly in those exposed to a very close contact as in schools. It is infrequent in children younger than three years of age. In Brazil, studies carried out with children between 3 and 12 years of age demonstrated positive GABHS cultures in 24% of acute PTs[11]. Some "carriers" will transport GABHS but without symptoms, even after treatment, but do not transmit them to others[4].

5 – Pathophysiology

The infection by GABHS requires that the organism adheres to the epithelium in the pharynx and tonsils. The binding is achieved by fimbriae, finger-like projections from the cell wall of the organism.

The "*modus operandi* "of GABHS can include classical suppurative mechanisms, mediated by toxins and/or immunomediated. The primary pathogenicity determinant of GABHS is an antigenically distinct protein, known as protein M, found inside the fimbriae. More than 120 M serotypes were obtained by using genetic sequencing techniques. Many serotypes circulate in selected populations at the same time. Those associated with pharyngitis are different from those related to impetigo or pyodermitis. Strains that cause pharyngitis in an individual will generally cause an invasive disease when transmitted to other individuals. *Streptococcus pyogenes* protein M protects the organism against phagocytosis in the absence of type-specific antibody. The synthesis of type-specific antibody against the M protein in an immunocompetent host provides long-term serotype specific immunity against this particular strain. The antibody belongs primarily to the IgG immunoglobulin class.

There is a possibility that common saprophyte organisms, such as *Streptococcus viridans* (alpha-hemolytic) will compete with GABHS, preventing the infection from becoming established in some degree. The preference of GABHS for infecting the pharynx or some other particular site of the human body has not been explained so far. Eradication of the normal flora of the oropharynx, mainly alpha-hemolytic streptococci can increase the susceptibility of patients to a subsequent infection by GABHS, the presence of the alpha-hemolytic streptococci being associated with the resistance to infection by GABHS.

Antibiotics can eradicate or suppress the bacterial flora of the host, with alterations in the oropharynx ecosystem. A treatment with penicillin, for example, causes a significant quantitative decrease in the alpha-hemolytic streptococci of the throat. This effect generally persists for weeks after the treatment. The elimination of alpha-hemolytic streptococci from the throat nullifies its ability to produce

bacteriokines, part of the natural resistance of the host against colonization by GABHS. The use of gargle preparations or sprays with alpha-hemolytic streptococci prepared from bacteria of the patient's throat were suggested as a possible therapeutical strategy in the prevention of infection by GABHS, particularly in the recurrence of PT[7].

6- Diagnosis

6.1- Clinical picture

Viral pharyngo-tonsillitis

The predominance of viral infections is very high in children younger than 3 years of age, an age group where PTs caused by GABHS are rare[8]. An irritation of the pharynx / tonsils is frequently found in patients with Rhinovirus, Adenovirus, Influenza, Parainfluenza or Respiratory Syncytial Virus and with infections by the Epstein-Barr virus.

In viral infections, the PT signs and symptoms are very similar to those of PT caused by GABHS, although differences in the clinical picture can be found. Children with viral infections often have extra-pharyngeal signs and symptoms, as nasal secretion, conjunctivitis, cough, hoarseness, diarrhea, ulcerations, or other clinical manifestations highly suggestive of viral infections.

The infection by adenovirus, a common cause of prolonged exudative pharyngo-tonsillitis, for example, can include conjunctivitis (pharyngoconjunctival fever). However, a generalized lymphadenopathy and splenomegaly can be found in infections by the Epstein-Barr virus, as well as in mononucleosis. The Coxsackie and Herpes Simplex viruses often cause stomatitis and pharyngitis, and can include vesicles or ulcerative lesions.

Bacterial pharyngo-tonsillitis

Signs and symptoms of PT caused by GABHS can vary from mild pain in the throat and malaise (30 to 50% of cases), to high fever, nausea, vomiting and dehydration (10% of cases). The onset is sudden, acute, characterized by odinophagia, high fever, headache and abdominal pain. The mucosa in the pharynx and tonsils is typically hyperemic, with occasional edema, exudate being present in 50-90% of the cases. Cervical adenopathy is very common (30-60% of cases). When present in the classical form, the scarlatiniform exanthema is very indicative of a bacterial infection, but is not frequent. According to some studies, palatal petechiae, tonsillar exudate and painful lymph nodes can be predominant signs and symptoms of PT caused by GABHS. In some other studies, odinophagia and scarlatiniform exanthema have statistical significance in PT cases by GABHS. However, signs and symptoms can vary in studies involving similar samples.

An alternative clinical presentation was recently identified in association with infections caused by GABHS – PANDAS (pediatric autoimmune neuropsychiatric disorder), with relevant compulsive/obsessive components (frequent hand washing for fear of being contaminated by organisms, or the need for frequent micturition without any urinary tract infection).

Other less common bacteria that cause PT are *Streptococcus pyogenes* Groups C and G, leading to an infection similar to that caused by GABHS, but with self-limited evolution and no rheumatic fever sequelae. Pharyngo-tonsillitis caused by

Neisseria gonorrhoeae is rare and typically occurs in adolescents (the exam reveals a genital infection concomitant with PT). The role of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* as causes of PT is uncertain. These infections are generally followed by other signs of respiratory infection, namely cough. Because of immunization, diphtheria is a rare cause of PT and can be recognized by a gray-colored asymmetric membrane on the pharynx, reaching the tonsillary pillars, soft palate and uvula. *Arcanobacterium hemolyticum* is not frequent, and if it should happen it will be found in adolescents, with a scarlatiniform exanthema associated with pharyngo-tonsillitis.

6.2- Laboratory

The golden standard for the definite etiological diagnosis of a PT caused by GABHS is the culture from the tonsils, tonsil crypts or pharynx, with approximately 95% specificity in GABHS identification[2, 9]. There is also a rapid detection diagnostic test for a specific group of carbohydrates, including immunoassays and enzyme agglutination with latex [10]. Although the specificity of the rapid test for GABHS detection (Quick Vue+® Strep A Test*)[6] is higher than 90%, there is a false positive rate of 15% and sensitivity varies between 60 and 90% (depending on the site the material was obtained from, such as a hospital, clinic, physician office). As a result, many physicians ask for a throat culture for a child with a suspicion of streptococcal PT when the rapid test for GABHS is negative. Serological tests such as an elevated ASLO (anti-streptolysin O antibody) should be carefully interpreted, as anti-streptolysin O is also produced by *Streptococcus* C and G, and these titers vary also with age and the use of some antibiotics. The 2003 guidelines of the American Academy of Pediatrics suggest the use of microbiological methods to detect GABHS, namely the culture of oropharynx material[1].

All patients with a positive rapid test for the Group A antigen should be treated. When the rapid test is negative, however, some authors suggest the use of antibiotics for some days, while the culture results are not available. The treatment is then interrupted if the culture result is negative. Others consider that it is possible to wait for the culture result using only drugs to treat the symptoms (fever, pain or dehydration if present), without any antibiotic, which should only be given when the culture is positive.

6.3- Pathology

Recurrent infections of the pharynx-tonsillar tissue can lead to tonsillar hyperplasia and/or nodularity. Under the microscope, there is an expansion of the lymphoid follicles with formation of prominent germinative centers. Polymorphonuclear cells can be seen in the epithelium, and inflammatory cells and bacteria aggregates can be found in the tonsil crypts. If the infection has a viral component, multinuclear giant cells can also be found.

7- Differential diagnosis

PTs have a viral etiology in up to 50% of cases in children and 10% in adults. GABHS is responsible for some 25-30% of PTs in children and up to 10% of

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

adults. In adolescents and young adults, the differential diagnosis of a PT caused by GABHS should include infection by *Streptococcus* Groups C and G and *Neisseria gonorrhoeae*. Anaerobic bacteria are involved with deeper infections such as peritonsillar and retropharyngeal abscesses.

Some throat pains are often "idiopathic". It is not clear if their etiology is viral, unidentified or known, or if they are related to other factors such as posterior nasal drip, allergy, active or passive smoking, etc.

8- Complications

Therapy with antibiotics can prevent suppurative complications of GABHS, including peritonsillar abscess, cervical adenitis, supraglottitis, cellulitis, fasciitis, peritonitis, arthritis, osteomyelitis, thyroiditis, pneumonia, bacteremia and meningitis.

Rheumatic fever is well established among the non-suppurative complications caused by GABHS that are prevented by the antibiotic treatment. However, a final conclusion has not been reached yet about post-streptococcal acute glomerulonephritis being prevent by antibiotic therapy.

Many of the PT complications include the obstructive, infectious, toxin-mediated or immunomediated. Patients with tonsillar hyperplasia can have breathing difficulties, in general when the acute tonsillar inflammation leads to edema. In certain infections, as caused by the Epstein-Barr virus, the degree of edema can be so severe that tonsils that are generally non-obstructive can interfere with breathing.

In some patients, the streptococcal PT can result in glomerulonephritis. The acute nephritic syndrome can develop 1 to 2 weeks after and acute streptococcal infection. The early administration of antibiotics does not prevent this sequela. The most frequent form of glomerulonephritis is the IgA-mediated nephropathy, associated with chronic tonsillitis.

Acute rheumatic fever is the most serious infectious complication of the acute streptococcal infections. This clinical entity is a disease with three distinctive clinical features although related: arthritis, carditis and chorea. It can also lead to a heart valve disease.

Scarlet fever is a classical, toxin-mediated form of infection by GABHS.

Another toxin-mediated disease associated with GABHS is the necrotizing fasciitis or Toxic Shock Syndrome.

The most common infectious complication today is the peritonsillary abscess, resulting from an extensive acute exudative tonsillitis. Another sequela of acute PT is the parapharyngeal or retropharyngeal abscess.

It is important to remember that patients exposed to GABHS can continue to asymptomatically "carry" the organism, even after an appropriate antimicrobial therapy. Carriers are recognized as individuals that have a positive culture for this organism, although there is a very low risk that they will transmit GABHS or even develop sequelae. The rate of carriers reported in the literature varies from 3 to 40%, depending on the population being assessed[5].

9- Treatment

The treatment should be aimed at relieving the symptoms of the acute disease (antipyretics and analgesics), eliminate transmissibility and prevent both suppurative and non-suppurative sequelae.

The principles of a rational use of antibiotics in pharyngo-tonsillitis should:

- Be based on the diagnosis from microbiological and laboratory test (culture and/or rapid test) and the epidemiological and clinical findings;
- Deal only with the infections caused by GABHS or other specific bacterial agents;
- Select penicillin that is still the antibiotic of choice.

GABHS are highly susceptible to penicillins and cephalosporins. They are also sensitive to macrolids. GABHS resistance to macrolids occurs and can develop in a community or in a country, because of selective pressure caused by its extensive use.

The benzathine penicillin injections maintain a bactericide level against GABHS during 21 to 28 days.

Oral administration of amoxicillin is equivalent to penicillin, but not superior in the bacteriological eradication of GABHS. Amoxicillin is bactericidal against GABHS. Amoxicillin is much more effective against the pathogens that cause otitis media. The mid-ear infections are concomitant with PT caused by GABHS in 15% of the pediatric patients.

When being used, azithromycin should be given for five days because the antibiotic persists in the pharyngo-tonsillar tissue and its bacteriostatic level is maintained during 10 days after the treatment is withdrawn. Macrolids should be used when patients are allergic to penicillin.

Cephalosporins are very efficient in PT caused by GABHS. However, there are certain concerns about its use as the first line therapy in PT. Its antimicrobial spectrum is wider than necessary, and the potential side effects and cost are also higher. It is important to know that the assymptomatic GABHS carrier can persist even with an intensive antibiotic treatment. The eradication of GABHS carrier status is rarely achieved with penicillin.

10- Summary and conclusion (See Algorithm for PT)

As most PT episodes are not caused by GABHS, the empiric antibiotic therapy would be an over-treatment with antibiotics, resulting in negative alterations of the oropharynx ecosystem.

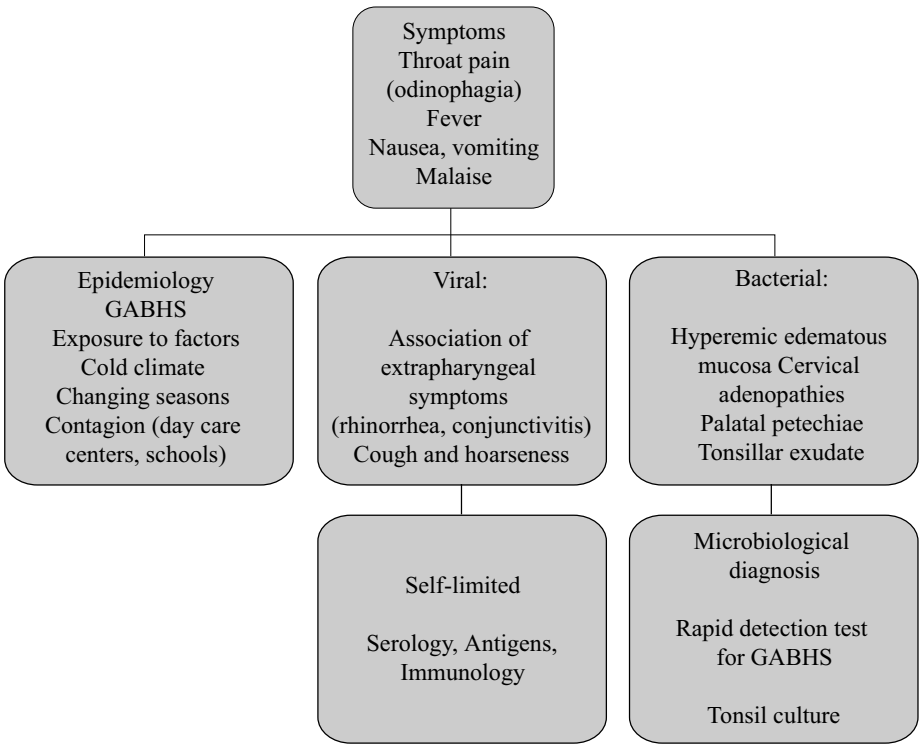
The availability of specific microbiological assays (rapid test for *Streptococcu*s Group A - GABHS - and/or throat culture) for the diagnosis of infections caused by GABHS provides an efficient diagnostic strategy, with a favorable cost/benefit ratio. This is the correct approach to avoid the excessive use of antibiotics.

Unfortunately, most physicians base their treatment rationale on reasons that do not justify the use of antibiotics, and perhaps they even give in because parents expect an antibiotic prescription, although the organism is not GABHS. This approach, with use of antibiotics in PTs, results in the following situation: in the US, some 70% of PTs are treated with antibiotics although only 15-25% of all PTs are caused by GABHS. A lower use of antibiotics reduces the selection of

resistant bacteria, the agents present in the airways (*Streptococcus pneumoniae* and *Hemophilus influenzae*) and the agents on the skin and the digestive system. Symptoms and/or signs that characterize the PTs cannot be used to differentiate the viral and bacterial infections, and the diagnosis of streptococcal PT in patients with clinical or epidemiological suspicion should always be based on microbiological tests.

The care of a child with PT should be more accurate. In the initial evaluation, the rapid test or culture must be used if possible. The advantage from the public health point of view is clear: lower use of antibiotics and reduction in the development of resistance by several bacteria. Considering all the evidences, it seems to be a matter of time until the investigation of *Streptococcus pyogenes* Group A (GABHS) in acute PT before the prescription of antibiotics becomes mandatory and/or regulated.

Algorithm for PT



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