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Article / Review

QUICK DETECTION OF CHILDREN'S ACUTE STREPTOCOCCAL TONSILLOPHARYNGITIS

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Abstract.

Acute tonsillopharyngitis (ATP) and the most frequent cause of bacterial ATP, group A β-hemolytic streptococcus (GABHS), an airborne disease that only affects humans, are the topics of this article. Up to 40 % of pediatric patients are affected, and school-age children are most frequently affected, with a peak frequency between the ages of 6 and 11. Because the symptoms of the streptococcal and viral variants of GABHS are identical, determining ATP of GABHS origin is difficult. Irrational use of antibacterial medication has been shown to raise the risk of antibiotic resistance, patient problems, and the strain on medical staff and the healthcare system. Simultaneously, GABHS in the pharynx is almost eliminated by antibiotic therapy of acute streptococcal tonsillopharyngitis performed in compliance with clinical guidelines, which greatly lowers the risk of sequelae. There is evidence to support the significance of actively implementing diagnostic assays that enable the quick (5–10 min) distinction between streptococcal and viral causes of ATP. Express testing for the detection of group A streptococcus antigens in a smear from the back wall of the pharynx using test systems based, in particular, on the immunochromatography method («Express Test»), the «gold standard» for diagnosing streptococcal ATP, is a straightforward and trustworthy way to confirm the streptococcal etiology of ATP. Using this method does not require additional training for medical personnel. The «Express test» findings enable prompt and appropriate prescription of the required treatment for the patient.

Key words: immunochromatography, diagnostics, β-hemolytic streptococcus group A, acute tonsillopharyngitis, and express test.

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Overview

Pharyngitis (infectious inflammation of the mucous membrane of the posterior pharyngeal wall) and tonsillitis (infectious inflammation of the lymphoid structures of the pharyngeal ring) are combined under the name acute tonsillopharyngitis (ATP). Antibacterial treatment is not necessary for the majority of ATPs, which are caused by a variety of viral agents, including influenza, coronavirus, rhinovirus, adenovirus, enterovirus, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, and herpes simplex virus. Group A β-hemolytic streptococcus (GABHS, Streptococcus pyogenes) is responsible for 15–30% of ATPs in children. This pathogen can cause scarlet fever, impetigo, erysipelas, and ATP [1]. The Greek words «streptos» (meaning «chain») and «coccus» (meaning «grain») are the origin of the microorganism's name «Streptococcus,» which describes how these bacteria look as a chain of spherical or ovoid parts.

Although streptococci were initially identified (and given their names) by T. Bilroth as the cause of erysipelas, there was still no one categorization for them even a century ago. The German scientists Schott-Müller and Braun then separated different strains into three categories based on their hemolytic activity: α, β, and γ. They were investigating the growth of bacteria on blood agar. In erythrocytes, alpha-hemolytic streptococci (also known as «greening streptococci») cause hemoglobin to oxidize, giving the colonies a greenish halo. Because beta-hemolytic streptococci destroy erythrocytes, they create a translucent environment around themselves.

Streptococci that are gamma-hemolytic do not alter blood agar. Rebecca Lancefield, a distinguished American microbiologist, published a paper titled «Serologic differentiation of human and other groups of hemolytic streptococci» [2]. Based on the findings of her analysis of 106 distinct strains, she suggested a new classification based on variations in the structure of the cell wall's polysaccharide antigens. Five groups—A, B, C, D, and E—were identified throughout her observations. Later, the letter M was added to the categorization based on the suggested criteria [3].

The microbiological features of GABHS

β-hemolytic streptococci of groups A and B are the most significant in human

disease. S. pyogenes is a typical extracellular pathogen that causes a variety of infections, including impetigo, pharyngitis, and more serious infections. It is the sole agent that causes infections in humans and is a member of serological group A. According to statistical statistics, GABHS is accountable for over 616 million ATP cases globally annually [4]. With 1.6–1.9 million base pairs, the GABHS genome encodes around 1717 genes and contains 0–10 prophage elements, 0–1 plasmids, 57–67 tRNA, and 5–6 16s rRNA operons [5]. The virulence components of GABHS are all attracted to human cells.

Surface proteins and secreted factors expressed by the bacterial chain cause immunoglobulins and complement factors (EndoS, Mac, and C5a peptidase) to degrade; complement is inhibited (by M-protein and capsule expression);

• cytotoxic and cytolytic activity against different host cells;

• dysregulation of coagulation; • binding of extracellular matrix and serum proteins through many microbial surface components that identify sticky matrix molecules (M-protein, Cpa, Eno, Epf) [6].

Superantigens can be expressed and secreted in varying levels by various GABHS serotypes [6, 7]. As a somewhat effective pathogen, GABHS regulates the expression of genes that produce virulence factors, reducing the quantity of proteins that the immune system can recognize [8]. Ninety percent of GABHS serotypes are known to develop microcolonies and biofilms, which decrease the efficiency of antibiotic treatment and are now the subject of ongoing research [9]. For instance, when fixed in the upper respiratory tract, the development of microcolonies there may be linked to the failure of traditional antibacterial treatment, resulting in patients' persistent infection[10]. In these situations, the presence of the F1 protein, a virulence component that promotes host cell internalization, makes isolates more likely to be resistant to macrolide antibiotics [10]. More than 20 years ago, when treating infections brought on by GABHS, doctors came across antibiotic resistance. Research has indicated that this phenomenon is linked to the properties of the biofilm that GABHS colonies develop [11]. During tonsillectomy, GABHS biofilms were examined in the lacunae of excised tonsils [12]. Through adhesion, information sharing, and unification in the extracellular matrix—which is made up of polymeric materials including proteins, polysaccharides, and extracellular DNA—planktonic bacteria create microcolonies.

Within the matrix, the bacterial cell is subjected to significant oxidative stress, leading to spontaneous mutations and the emergence of microbial subpopulations.

Place and role of GBS in the etiology of ATP

As an exclusively human pathogen, S. pyogenes is transmitted from person to person by airborne droplets with a short incubation period (2–5 days) and is most common in the child population aged 5–15 years with a peak at 7–8 years, causing up to 30% of ATP cases. It is rare in children under 3 years of age (although some researchers note that the incidence of GBS in the child population under 5 years of age has been increasing in recent years [13]) and even rarer in adulthood (from 5 to 15% of ATP cases)[14]. More common in adults and teenagers, pharyngitis caused by β-hemolytic streptococcus of groups C and G usually does not result in serious repercussions, unlike GAS infection [15]. owing to the unique crowding of children during these months and their decreased outside presence owing to cold weather, the peak of GAS-associated ATP occurs between December and March. ATP outbreaks in schools are common [16].

While GABHS is the most common bacterial cause of ATP, other bacteria can also cause these symptoms, including Neisseria gonorrhoeae (which causes gonorrhea), Corynebacterium diphtheriae (which causes diphtheria), Fusobacterium necrophorum (which causes necrobacillosis), and even Chlamydophila psittaci (which causes ornithosis). ATP produced by Mycoplasma pneumoniae and Chlamydophila pneumoniae has been seen in recent decades as a result of the rising incidence of these illnesses. Furthermore, the causal agent may not always be identified (as in the case of mixed anaerobic infection, for instance) [17].

Some researchers have identified fungal pathogens in addition to viral (70–85%) and bacterial (15–30%) causes of ATP development. However, Candida albicans, which causes 80% of fungal infections of the oropharynx, is a normal microflora that triggers the development of pathological processes against the backdrop of systemic or local immunodeficiency[18].

ATP-related effects brought on by GABHS

Acute rheumatic fever (with minor chorea occurring in isolation), acute post-streptococcal glomerulonephritis (APSGN), post-streptococcal arthritis, rheumatic heart

disease, PANDAS (PANS) syndrome (childhood autoimmune neuropsychiatric disorders associated with streptococcal infection), and streptococcal toxic shock syndrome (which has a significantly higher mortality rate than staphylococcal toxic shock) are all possible outcomes of GABHS-associated ATP, even though ATP is typically tolerated fairly easily and viral infections are self-curable. It is reported that over 500,000 people die each year from illnesses that follow a GABHS infection[19].

The most frequent cause of acute nephritis in children globally is acute poststreptococcal glomerulonephritis. Data from 2021 indicates that there are 472 thousand instances of APSGN annually. In children, the prevalence of APSGN ranges from 5 to 10% for pharyngitis and 25% for skin infections. Group A streptococcus nephritogenic type M is the cause of APSGN. The most prevalent nephritogenic kinds after ATP are 1, 3, 4, 12, 25, and 49. kinds 2, 49, 55, 57, and 60 are typically found with APSGN following a skin infection (such as impetigo). Glomerulonephritis develops 1-3 weeks after ATP and 3-6 weeks following a cutaneous infection. [20].

With an annual prevalence of 1-2 occurrences per 100,000 people, post-streptococcal reactive arthritis (PSRA) is a noncarditis polyarthritis linked to high serum streptolysin O antibody titers. In the US, it is almost twice as common as acute rheumatic fever [21]. Persistent, nonmigratory acute arthritis that persists for an average of two months (range: one week to eight months) in spite of nonsteroidal anti-inflammatory medication (NSAID) therapy is one of the joint symptoms of PSRA. Acute rheumatic fever-related arthritis is often self-limiting, migratory, and resolves within two days after beginning NSAID therapy.[22].

Since its initial definition in 1998, PANDAS (PANS) syndrome—also known as «pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections» or, more widely, «childhood acute-onset neuropsychiatric syndrome»—has been the subject of debate regarding its relationship to streptococcal infection. A increased risk of obsessive-compulsive disorder, tics, and «mental disorders» following streptococcal ATP or other respiratory tract infections was shown by two large cohort studies carried out in Taiwan [23] and Denmark [24] between 2016 and 2017[25].

The significance of prompt and precise diagnosis of viral and bacterial ATP with the appointment of the required treatment, including antibacterial medication, becomes evident when considering the aforementioned difficulties that may emerge with bacterial ATP.

ATP's differential diagnosis and clinical symptoms

Streptococcal and viral ATP symptoms are extremely similar: the patient may have acute-onset sore throat, swallowing discomfort, and feverish body temperature increases. Additionally, symptoms of headache, nausea, vomiting, and abdominal discomfort may be made. Enlarged palatine tonsils, tonsillopharyngeal erythema with or without exudate (white, yellow, or grayish), and painful lymphadenitis of the cervical and submandibular lymph nodes may be seen on a direct physical examination (pharyngoscopy).

There may be scarlet fever-like rash, uvulitis, and palate petechiae. Runny nose, cough, hoarseness, and conjunctivitis are more common symptoms of viral infections when viral ATP is present, but they do not rule out GABHS infection (albeit they are seen in around 10% of patients with GABHS-associated ATP). Since there are no clinical indicators that are specific to GABHS infection, a third of patients have tonsillopharyngeal erythema with exudate and petechiae on the palate, which were once thought to be indicators of GABHS infection. Other symptoms include infectious mononucleosis, sore throat, lymphadenopathy, and febrile fever. Epstein-Barr virus-induced infectious mononucleosis can resemble primary HIV infection and present as diffuse lymphadenopathy, weight loss, acute myelopathy, and subfebrile fever[17].

When you first meet a patient who has a sore throat, it's critical to look for «red flags,» particularly nonverbal ones such unilateral neck enlargement, salivation, and dysphagia. Telemedicine consultation is not advised for patients with sore throats because a direct examination is not possible in these cases. This is because conditions that need emergency care must be ruled out, such as epiglottitis and submandibular/peritonsillar abscess (in contrast to peritonsillar abscess, enlargement of the tonsils with ATF occurs symmetrically).

Differentiating the causes of ATP appears to be crucial in order to avoid prescribing antibacterial therapy to patients who do not require it. This will help to decrease antibiotic resistance, complications from inappropriate antibiotic prescriptions, and the strain on the healthcare system (unnecessary hospitalizations, late complications, and therapy

costs). Differentiating between ATP of viral or GBS genesis only based on identifying the clinical picture «at the patient's bedside» appears to be challenging. The Centor and McIssac scales are the most often used in clinical practice, however other tables have been developed for the differential diagnosis of streptococcal and viral causes of ATP.

A score of 0–1 on the Centor scale denotes a low risk of GABHS infection and does not necessitate further testing or antibiotic treatment. To start antibiotic treatment, a GABHS infection score of two to three must be confirmed in a lab. The American College of Physicians advises starting therapy at a score of 4, although the Infectious Diseases Society of America advises waiting for further test confirmation[14]. The Centor scale for antibacterial treatment prescription is improved by the McIssac scale. The McIssac scale has high sensitivity and specificity (roughly 90%), according to some studies [26]. However, other studies have shown that these algorithms are not available for diagnosing GABHS infection; the inclusion of children with severe symptoms or a rise in the frequency of viral infections exhibiting the same symptoms could be the cause of these data discrepancies. [27].

The aforementioned characteristics of clinical data-based differential diagnosis make it clear that quick, affordable, and precise laboratory tests are required. There are now two primary techniques for diagnosing GABHS in a laboratory setting: an express test for identifying group A streptococcal antigens in a smear from the pharynx's posterior wall and a culture analysis of the smear. Both the measurement of inflammatory markers (CRP, procalcitonin) and antibodies to streptolysin O are not advised in ordinary practice (except from suspected post-streptococcal sequelae). Upon hospitalization and/or suspicion of infectious mononucleosis, a clinical blood test is conducted.

The «gold standard» for identifying a GABHS infection is rapid testing.

The preparation and growth of the culture on blood agar takes a certain amount of time (24–48 hours, up to 7 days for antibiotic sensitivity testing), which slows down diagnosis and therapy even though culture testing is very sensitive and specific. Rapid tests are becoming more and more advantageous since they may be done «at the patient's bedside» and at the initial session, don't require specialized staff, and provide findings in less than ten minutes.

Enzyme immunoassay, optical immunoassay, and latex agglutination are the three categories of quick diagnostics. According to systematic reviews and meta-analyses, fast tests have a sensitivity of around 85% and a specificity of 90–96% [28]. The first commercially accessible quick tests appeared in the 1990s, although attempts to develop rapid tests date back to the 1950s. Currently, there are around 20 trade names for different rapid tests. Their specificity and sensitivity differ. Even high school kids have shown that they can correctly complete the quick test after a brief lesson, however sensitivity is affected differently by the proper swab method (from the back of the throat, tonsils, and not the tongue, lips, or inside surface of the cheeks)[29].

Therefore, a throat culture or quick testing should be done if the symptoms point to a potential GABHS infection. Since even a single dosage of the medication might skew test findings, any test should be carried out prior to the initiation of antibiotic therapy. Rapid testing makes it possible to reliably identify GABHS antigens in a smear. A positive result unequivocally shows that GABHS was present in the smear sample and, in light of antibiotic medication, shows that the pathogen was not eradicated at the time of the test. Except in circumstances of contamination—which is challenging to achieve in practice when there is no contact with the pathogen—not following the instructions will not result in a favorable outcome.

Given the excellent specificity of quick diagnostics for GABHS infection, a culture investigation is not recommended in the event of positive rapid test findings. Due to the low occurrence of GABHS tonsillopharyngitis and the minimal risk of rheumatic fever development in this patient group, a culture investigation is not necessary in the event that the fast test yields negative findings in adult patients. A culture study should be performed to validate a negative quick test result in children and adolescents with suspected ATP caused by GABHS. Testing should only be done on children under three if they have complex anamnesis (e.g., older siblings with proven GABHS).

The «Express Test,» which is intended for the quick identification or differential diagnosis of GABHS in ATP, is the most widely available express test in Uzbekistan. The test's specificity is 95% (96% CI 92-97%) and its sensitivity is 97% (96% CI 91-99%). Comparing this to a cultural research, the positive predicted value is 86% (96% CI 79–91%), while the negative is 99% (96% CI 97–100%) [30]. Monoclonal antibodies that

identify group A streptococcal antigens are applied to the Streptatest membrane.

Because «Streptatest» is widely available and reasonably priced, it can be used at home, in kindergarten or school, and by medical professionals in both inpatient and outpatient settings. It also gives you the results in as little as five minutes. Being able to independently perform express testing at home helps parents feel less anxious when taking care of their children and, in certain situations, avoid self-prescription of antibiotics.

Antibacterial treatment is necessary if fast testing or culture confirms the presence of GABHS-associated ATP. Penicillin is the preferred medication; first- and second-generation cephalosporins are used in cases of penicillin allergy. Although findings from certain research show that antibacterial treatment might produce disappointing outcomes in certain cases of streptococcal ATP, oral or intramuscular penicillin is still an effective way to eradicate GABHS[31]. The ineffectiveness of antibacterial therapy can be attributed to a number of factors, such as improper dosage selection, insufficient penetration of penicillin metabolites into the tonsil epithelial tissues, dysbiosis of the oral cavity, potential re-infection from the environment and surrounding objects (toothbrush, braces), and failure to adhere to the required therapy duration of at least 10 days (with GABHS-associated ATP, improvement occurs by the second to fourth day, which prompts patients or patients' parents to believe they no longer need therapy) [31, 32]. Additionally, the interaction between GABHS and the tonsil bacterial flora can decrease the efficacy of antibacterial therapy: Moraxella catarrhalis and GABHS increase GABHS colonization, and bacteria that colonize the tonsils and pharynx produce the enzyme β-lactamase, which deactivates the antimicrobial action of penicillin [33]. Frequent penicillin courses cause oral dysbiosis, which encourages the growth of β-lactam-producing strains of S. aureus, Haemophilus species, M. catarrhalis, Fusobacterium species, Porphyromonas species, and Bacteroides species[34].

Concomitant therapy, such as NSAIDs to lower body temperature and ease discomfort, is sometimes necessary in addition to the obligatory prescription of antibacterial medications. Lozenges, sprays, and pills for rinsing are examples of local therapy that can be used starting at age 4. It's crucial to keep in mind that supportive care is all that is needed for viral pharyngitis; antibiotics are not. Patients who demand for antibacterial therapy, as well as their parents, link their expectations with quick alleviation from the uncomfortable condition rather than the medicine's direct antimicrobial impact. This demonstrates even more how crucial the «doctor-patient» relationship is, which is based on adequate knowledge and confidence and without which complete compliance is impossible.

In conclusion

Because acute streptococcal tonsillopharyngitis is so prevalent and can cause serious consequences, antimicrobial treatment should only be recommended if the etiology of GBS has been established. Express testing, which provides results in 5–10 minutes, is one of the most practical, affordable, and Russian clinical guidelines-approved techniques for verifying the GBS etiology of ATP. Medical professionals do not need additional training to apply the «Express Test» express diagnostic test system, which is a simple, dependable, and successful approach. The «Express Test» findings enable you to provide the patient the required therapy in a timely and sufficient manner.

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