

Management of acute streptococcal pharyngitis: still the subject of controversy

Review Article

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Abstract: Although most cases of acute pharyngitis are viral in origin, antibiotics are overused in its treatment. *Streptococcus pyogenes* (group A streptococcus, GAS), the principal bacterial pathogen of acute sore throat, is responsible for merely 5-30% of cases. Moreover, GAS pharyngitis is currently the only commonly occurring form of acute pharyngitis for which antibiotic therapy is definitely indicated. Therefore the differentiation between GAS pharyngitis and that of viral etiology is crucial. Accordingly, scientific societies as well as respected advisory bodies in Europe and North America, issued guidelines for the management of acute pharyngitis with the aim of minimizing unnecessary antibiotic prescriptions in its treatment. The aim of this review work is to confront the state of the art in acute GAS pharyngitis diagnosis and treatment with different approaches to its management represented by current European and North American guidelines. Although based on scientific evidence, international guidelines differ substantially in opinions whether GAS pharyngitis diagnosis should be based on microbiological testing, clinical algorithm or a combination of both. On the other hand, some European guidelines consider GAS pharyngitis to be a mild, self-limiting disease that does not require a specific diagnosis or antimicrobial treatment except in high-risk patients. There is an agreement among guidelines that if antibiotic therapy is indicated, phenoxymethyl penicillin should be the drug of choice to treat GAS pharyngitis.

Keywords: Group A streptococcus (GAS) • Pharyngitis • Guidelines • Rapid antigen detection test (RADT) • Throat culture • Penicillin

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1. Introduction

Most cases of acute pharyngitis are viral in origin. Rhinoviruses, coronaviruses, adenoviruses, Coxsackie A, influenza, parainfluenza, RSV and herpes family viruses account for 70%-85% of pharyngitis in children over 3 years of age and for 90-95% of cases in adults. *Streptococcus pyogenes* (group A streptococcus, GAS), the principal bacterial pathogen in this disease, is responsible for merely 5-30% of cases [1-3]. Beta-hemolytic streptococci belonging to other groups, predominantly C and G, are involved considerably less frequently [4-6]. Other bacteria cause acute pharyngitis only occasionally [1,2,7]. In patients with GAS pharyngitis antibiotic treatment prevents rheumatic fever and local complications such as peritonsillar abscess and mastoiditis [2,3,8,9]. However, viral pharyngitis should be treated merely symptomatically [2,10].

Since most cases are caused by viruses it seems that antibiotics in acute pharyngitis should be used only

exceptionally. On the contrary, however, they are overprescribed in its treatment, as well as in the treatment of other respiratory tract infections [11-15]. Inappropriate use of antibiotics is a major contributor to the rising incidence of antimicrobial resistance, currently recognized as a global health problem [14]. Scientific societies as well as respected advisory bodies in Europe and North America issued guidelines for the diagnosis and treatment of respiratory tract infections with the aim of minimizing unnecessary antibiotic prescriptions in primary health care [7,16-28]. Strategies for diagnosis of acute pharyngitis offered by international guidelines published in countries with low prevalence of rheumatic fever are primarily directed at identifying the patients who require antimicrobial treatment, providing that GAS pharyngitis is the only commonly occurring form of acute pharyngitis for which antibiotic therapy is definitely indicated [16]. However, recommendations differ substantially with regard to the decision rule proposed for diagnosis and treatment of GAS pharyngitis. The aim of this review

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work is to confront the state of the art in acute GAS pharyngitis diagnosis and treatment with different approaches to its management represented by current European and North American guidelines.

2. Diagnosis and treatment of acute GAS pharyngitis: state of the art

Clinical features of GAS pharyngitis are not specific and cannot be easily differentiated from other forms of pharyngitis. However, various clinical and epidemiological factors may indicate higher probability of streptococcal etiology. GAS pharyngitis is often seen in children between 3 and 14 years of age and tends to occur in colder months of the year. Patients with GAS pharyngitis often complain of pain while swallowing, fever, enlarged cervical lymph nodes and fatigue. Headache, nausea, vomiting and abdominal pain may be seen, particularly in children. Tonsils are reddened and swollen. The roof of the mouth may have fine petechial lesions. Although none of these are specific for GAS pharyngitis, absence of fever or presence of clinical features such as cough, hoarseness, conjunctivitis, runny nose, viral exanthem and diarrhea are common symptoms of viral upper respiratory tract infections [1-3,16]. Hence, the basic aim of clinical examination is to evaluate the likelihood of streptococcal etiology and identify these patients in whom microbiological tests are necessary to confirm the diagnosis [1]. Clinical scoring systems have been developed to predict the likelihood of streptococcal infection among children and adults presenting with sore throat. The most popular ones are Centor and modified Centor scores [29,30]. They are based on assessment of suggestive clinical findings: fever over 38°C, tonsillar swelling or exudates, tender and enlarged anterior cervical lymph nodes, and the absence of cough. Centor score awards one point for each of the above clinical signs. Modified Centor score, proposed by McIsaac, includes the criterion of age as well and adds one point for the age between 3 and 14 years. In patients who obtained 0-2 or 0-1 points in Centor and modified Centor scores, respectively, the likelihood of GAS pharyngitis is very low. Probability of GAS pharyngitis occurs in patients who obtained >2 and ≥2 points in Centor and modified Centor scores, respectively [29,30]. Other scoring systems include Breese, Attia and Welsh scales. Breese scale is based on nine epidemiologic, clinical and laboratory features, including the number of leukocytes in blood, which makes it less practical [31]. Four-point score developed by Attia et al. takes into account tonsillar swelling, tenderness and enlargement

of cervical lymph nodes, coryza, and scarlatiniform rash [32]. Welsh scale indicates high, moderate and low risk of streptococcal pharyngitis, considering recent exposure to streptococcal infection, pharyngeal exudate, enlarged or tender cervical lymph nodes, cough and fever greater than or equal to 38,3°C [33]. However, symptoms and signs, either individually or combined into prediction rules, are not powerful enough to discriminate GAS pharyngitis from other types of sore throat [34-36]. Thus, in children and adults in whom the clinical scoring systems indicate the risk of streptococcal pharyngitis, a definitive diagnosis of GAS pharyngitis requires identification of the bacterium in throat swab culture or rapid antigen detection test (RADT) [16,37]. RADT is based on acid extraction of cell-wall carbohydrate antigen and its detection with the use of specific antibody [38]. The success in isolating GAS in culture or obtaining a positive RADT result lies in a proper collection of throat swab. A sample must be obtained from both tonsils (or tonsillar fossae) and posterior pharyngeal wall [7,39]. Inoculation of a throat swab onto blood agar remains the gold standard for diagnosis, however its disadvantage is the delay (overnight or longer) in obtaining a result. RADT results are obtained faster, usually within minutes. The first RADTs used latex agglutination methodology, their sensitivity was as high as approximately 70 percent. The sensitivity of newer enzyme-linked immunosorbent assays, optical immunoassays and chemiluminescent DNA probes is much higher [38]. New generation immunoassays sensitivity proved to range between 65.6% and 98.9% and their specificity between 62.0% and 99.3%, depending on commercial RADT kit used [40-42]. However, the measured sensitivity of RADTs has been shown to depend on the clinical likelihood of GAS infection in the test population [43,44]. Since RADTs specificity is generally higher than their sensitivity, antibiotic therapy can be safely initiated if RADT result is positive [38,42]. However, due to lower sensitivity, a negative result does not exclude GAS pharyngitis, so in children a confirmatory throat culture is recommended if RADT is negative, particularly if the sensitivity of RADT in use is less than 90 percent [7,16,45]. In adults such confirmation is not required due to low prevalence of GAS pharyngitis and its sequelae, including rheumatic fever, in this population [10]. However, neither conventional throat culture nor RADTs accurately differentiate acutely infected persons from asymptomatic GAS carriers with intercurrent viral pharyngitis [16]. Carriers are individuals in whom upper respiratory tract is colonized with GAS without illness or immunologic response. During cold seasons in temperate climates, approximately 20% of asymptomatic school-age children are GAS carriers [46]. These

individuals should not be identified or treated as they are unlikely to be infectious or to develop suppurative or nonsuppurative GAS complications [47]. Therefore microbiological examination is not recommended in patients in whom clinical presentation suggests viral pharyngitis, since in such cases detection of GAS causes unnecessary “treatment” of carrier state [12,16-18].

When selecting an antimicrobial for the treatment of GAS pharyngitis, it is important to consider its efficacy, safety, antimicrobial spectrum (narrow versus broad), dosing schedule, compliance, and cost [16,45]. Penicillin has stood the test of time satisfactorily since no penicillin-resistant GAS strains have so far been detected. Moreover, it has narrow antimicrobial spectrum, low cost and impressive safety profile [45,48]. It is effective not only for treating acute pharyngitis but for preventing acute rheumatic fever as well [49]. This is why oral or intramuscular penicillin is currently antibiotic therapy of choice for GAS pharyngitis [1-3]. However, treatment failures with penicillin therapy, as high as 35% with orally administered penicillin, have been reported [50,51]. Some studies advocated higher efficacy of cephalosporins in comparison with penicillin in the treatment of GAS pharyngitis. In two meta-analyses Casey and Pichichero suggested an increased likelihood of bacteriological and clinical failure in children and adults with GAS pharyngitis treated with oral penicillin compared with oral cephalosporin [52,53]. However, both works have been severely criticized due to poor quality of included studies and methodological flaws, particularly “contamination” of the study group by chronic GAS carriers [48,49]. Since penicillin is ineffective in eradicating pharyngeal GAS carriage and cephalosporins are more efficient in this purpose, this issue is of particular importance [54]. However, in children with bona fide acute GAS pharyngitis, eradication rates achieved in those treated with cefadroxil (first generation cephalosporin) and penicillin proved to be comparable (95.0% versus 94.0%) [54].

It is not necessary to start antibiotic therapy immediately. Currently, there is sufficient clinical and epidemiological evidence that antimicrobial therapy can be initiated while awaiting laboratory confirmation only in some specific situations, such as the presence of scarlet fever rash, concurrent diagnosis of rheumatic fever or a past history of rheumatic fever [45]. Moreover, treatment begun up to 9 days following the onset of symptoms is effective in preventing acute rheumatic fever [16,37,45]. Thus, antimicrobial therapy should be prescribed only for proven episodes of GAS pharyngitis [16,17]. Delayed prescribing, based on the results of microbiological examination, is now considered to be a valid option [55].

3. Clinical prediction models or diagnostic testing?

Appropriate diagnosis and management of acute GAS pharyngitis are still the subject of much controversy [10,48,49,52,53,56]. International guidelines differ in opinions whether the decision about antibiotic therapy should be based on microbiological testing, clinical algorithm or a combination of both. Most guidelines state that the basic aim of clinical examination is to evaluate the likelihood of GAS pharyngitis and identify the patients who require RADT or culture to confirm the diagnosis. To achieve this aim American College of Physicians/American Society of Internal Medicine/Centers for Disease Control and Prevention (ACP-ASIM) and European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guidelines endorsed the use of Centor score, whereas Polish, Spanish and Italian guidelines suggest the usage of modified Centor score [7,17,18,26,28]. Instead, American Heart Association/American Academy of Pediatrics (AHA-AAP), Infectious Diseases Society of America (IDSA), Canadian Medical Association, Agence Française de Sécurité Sanitaire des Produits de Santé and Finnish Medical Association recommend careful analysis of clinical and epidemiological data to assess the risk of streptococcal pharyngitis [16,19-21,27].

However, ACP-ASIM guidelines allow to initiate antibiotic therapy without microbiological confirmation, solely on the grounds of clinical presentation suggesting high risk of GAS pharyngitis. The recommendations for adult patients with acute pharyngitis propose one of two following strategies:

1. empiric antibiotic treatment should be administered to adults who meet 3 or 4 Centor criteria
2. empiric antibiotic treatment should be administered to adults who meet all 4 criteria, RADT should be performed for patients who meet 3 criteria and administration of antibiotic treatment should be limited to those with positive RADT results [26].

This approach has been heavily criticized by IDSA due to the fact that positive predictive value (PPV) associated with 3 and 4 Centor criteria in adults proved to be approximately 40 percent. Consequently, about 60% of adult patients with acute pharyngitis will be treated with antibiotics unnecessarily, which is a particularly undesirable result in an age group with low prevalence of GAS pharyngitis and its nonsuppurative sequelae. Besides, according to IDSA, it is extremely unlikely that clinicians will elect second strategy indicated by ACP-ASIM guidelines, considering that they allow a decision to be made on clinical grounds alone. Moreover, the message perceived by physicians may be simply that microbiologi-

cal tests are no longer necessary for adults with acute pharyngitis [10].

Polish and Spanish guidelines recommend that ideally the decision about antibiotic treatment in patients who obtained ≥ 2 points in modified Centor score should be based on the results of RADT or throat culture. However, in patients who obtained 4 or 5 points, both guidelines allow to introduce empiric antibiotic therapy when waiting for the results of microbiological examination [7,28].

AHA-AAP, IDSA, ESCMID, as well as French, Finnish and Italian guidelines recommend performing RADT or culture to confirm the diagnosis in patients with clinical symptoms suggesting GAS pharyngitis [16-18,20,21,27]. In children, AHA-AAP, IDSA, as well as French, Finnish, Spanish and Polish guidelines recommend performing a throat culture if RADT is negative [7,16,20,21,27,28]. Nevertheless, recently published ESCMID and Italian guidelines do not recommend this strategy, considering the high both sensitivity and specificity (between 95% and 99%) of RADTs currently in use [17,18]. Canadian guidelines do not recommend performing RADTs, they advice the use of throat culture to confirm GAS pharyngitis [19].

4. Treatment options

Phenoxymethyl penicillin twice or three times daily for 10 days is currently antibiotic therapy of choice for GAS pharyngitis according to American, Canadian and most European guidelines. In case of suspected noncompliance one dose of intramuscular benzathine penicillin G is recommended [7,16,17,19-21,26-28]. Italian guidelines endorse amoxicillin instead of penicillin as a first-choice drug, since the latter is not available in Italy [18]. Currently, the AHA-AAP, IDSA and Spanish guidelines recommend amoxicillin once or twice daily for 10 days as alternative first-line therapy [16,27,28]. In comparative clinical trials, once-daily amoxicillin (50 mg/kg, to a maximum of 1000 mg) for 10 days has been shown to be effective for GAS pharyngitis [57,58]. It has the advantage of once-daily dosing, which may enhance compliance. Moreover, it is relatively inexpensive and the taste of the suspension is acceptable for young children [16,27]. However, administration of amoxicillin in the above-mentioned doses, enough to treat GAS pharyngitis, selects for *Streptococcus pneumoniae* strains resistant to penicillin. Therefore, amoxicillin is not recommended by Polish guidelines due to the fact that the percentage of penicillin-resistant *S. pneumoniae* strains in Poland proved to be one of the highest in Europe [7]. Second and third-line drugs recommended by guide-

lines include: first generation cephalosporin in patients with penicillin allergy who do not have immediate hypersensitivity to beta-lactam antibiotics and macrolides (e.g. erythromycin, azithromycin, clarithromycin) or clindamycin in those with hypersensitivity to beta-lactam antibiotics [7,16-21,26-28]. Azithromycin is the only drug that is given in a 5-day course as opposed to a 10-day course for all the other antibiotics. Although there are no strains of GAS resistant to penicillin, amoxicillin and cephalosporins, GAS susceptibility to macrolides varies depending on the region and the level of consumption, with the percentage of resistant strains reaching over 25% in some countries [59,60]. Since the susceptibility of the given GAS strain to macrolides is unpredictable, treatment with these drugs must be always preceded by performing antibiotic susceptibility test [7,28].

5. Should we really differentiate GAS pharyngitis from other forms of sore throat and treat it with antibiotics?

“In the 1950s and 1960s, the most compelling reason for antibiotic treatment of GAS pharyngitis was to prevent rheumatic fever. Although high rates persist in several areas of the world, the incidence of this disease in developed countries has declined dramatically, raising questions regarding whether the traditional approach to the diagnosis and treatment of streptococcal pharyngitis is still appropriate in such settings” [1]. Consequently, some European guidelines, among them British, Scottish, Dutch and Belgian consider GAS pharyngitis to be a mild, self-limiting disease that does not require a specific diagnosis or antimicrobial treatment except in high-risk patients, such as those with a history of valvular heart disease or acute rheumatic fever, immunosuppressed or severely ill. Therefore microbiological examination and antibiotic treatment should be reserved solely for well-selected cases [22-25]. Recently issued ESCMID guidelines represent similar approach stating that in children and adults:

1. Sore throat should not be treated with antibiotics to prevent the development of rheumatic fever and acute glomerulonephritis in low-risk patients (e.g. patients with no previous history of rheumatic fever).
2. The prevention of suppurative complications is not a specific indication for antibiotic therapy in sore throat. Clinicians do not need to treat most cases of acute sore throat to prevent quinsy, acute otitis media, cervical lymphadenitis, mastoiditis and acute sinusitis.
3. In patients with more severe presentations, e.g. 3-4

Centor criteria, physicians should consider discussion of the likely benefits of antibiotics with patients. Modest benefits of antibiotics, which have been observed in GAS-positive patients and patients with 3-4 Centor criteria, have to be weighed against side effects, the effect of antibiotics on the microbiota, increased antibacterial resistance, medicalization and costs [17].

6. Summary and conclusions

Although based on scientific evidence, international guidelines issued in countries with low prevalence of acute rheumatic fever differ substantially with regard to their approach to the management of acute GAS pharyngitis. This particularly concerns European guidelines, which represent two entirely different attitudes to the diagnosis and treatment of this disease. Both should be scrupulously assessed to standardize the recommendations.

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Unarguably, in the era of increasing antimicrobial resistance traditional *modus operandi* regarding the management of acute GAS pharyngitis should be re-evaluated in settings with low prevalence of acute rheumatic fever. For the moment, however, identification of the patients who may require antibiotic treatment should be based on reliable criteria, i.e. microbiological examination. Empiric treatment based upon symptoms and signs will undoubtedly lead to overuse of antibiotics. Benefits of antibiotic therapy should be carefully assessed in every patient. Delayed prescribing is a valid option as well, since it reduces unnecessary use of antibiotics.

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