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# Optimal Diagnosis and Treatment of Group A Streptococcal Pharyngitis

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Group A streptococcus (GAS), or *Streptococcus pyogenes*, is the most common pathogen responsible for bacterial pharyngitis, which has the following characteristic clinical manifestations: fever, tender cervical lymphadenopathy, exudative pharyngeal discharge, and absence of common cold symptoms (cough, coryza, rhinorrhea, diarrhea, oral ulcer) [1, 2]. In addition to these Centor criteria, GAS pharyngitis has an acute onset, and is prevalent during winter and early spring in children between 5 and 15 years of age. Among the types of pharyngitis, GAS constitutes about 20-30% of cases in children and 5-10% of cases in adults [1, 2]. Although immunologic complications such as rheumatic fever and post-streptococcal glomerulonephritis are currently very rare in developed countries, GAS pharyngitis is still important due to its prevalence and emergence of antibiotic resistance.

## Diagnosis

As clinical manifestations of viral and bacterial pharyngitis sometimes overlap, it is very difficult to make a diagnosis based solely on patient history and physical examination [1, 2]. There are two screening options for diagnosis of GAS pharyngitis: rapid antigen detection test (RADT) and culture. Currently available RADTs using immunochromatographic methods have relatively good sensitivity and provide quick results. Since RADTs are very specific, it is diagnostic for the positive result [2]. If bacterial pharyngitis is highly suspected and RADT results are negative, bacterial culture, a more sensitive test, is necessary to make a diagnosis [1, 3]. As it takes between one and two days to obtain culture results, the patient is required to return to the clinic. These laboratory tests should be utilized more often, especially when bacterial pharyngitis is suspected [2].

## Treatment

Although bacterial pharyngitis often resolves spontaneously, antibiotic treatment is recommended to reduce immunological complications, as well as to ameliorate the signs and symptoms of pharyngitis [1, 2]. To minimize overuse of antibiotics for the treatment of pharyngitis, physicians should be encouraged to use the laboratory tests mentioned above. Oral

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penicillin, the drug of choice for treatment of bacterial pharyngitis, is not available in Korea. Instead, oral once-daily amoxicillin is recommended as first-line therapy [1-3], and first generation cephalosporins could be considered for patients with penicillin allergy. In addition to β-lactams, newer macrolides such as azithromycin or clarithromycin are commonly used [1-3]. All of the aforementioned antibiotics should be taken for 10 days with the exception of azithromycin [2]. Children diagnosed with bacterial pharyngitis are recommended to stay home for one day after the initial administration of antibiotic to reduce the transmission of bacteria to classmates [1]. Eradication of bacteria may fail in approximately 10% of patients, and these children might be chronic carriers [1, 2].

## Antibiotic resistance

GAS is highly sensitive to penicillin, amoxicillin, and cephalosporin *in vitro* [2]. Resistance to macrolides varies according to time period and countries studied. Although erythromycin resistance rates were over 20% in many countries until early 2000s, there are many recent reports of decreasing erythromycin resistance rates. Decline of erythromycin resistance rates might be due either to efforts to reduce usage of macrolides in society [4, 5] or to clonal changes in resistance genotypes [6-9]. There are three well-known genotypes representing macrolide resistance: *erm (A)* for the $MLS_B$ (macrolide, lincosamide, and streptogramin B) inducible phenotype, *erm (B)* for the $MLS_B$ constitutive phenotype, and *mef (A)* for the M phenotype. As clindamycin resistance is induced after several days of treatment, another antibiotic should be considered for inducible $MLS_B$. Strains with the constitutive $MLS_B$ phenotype have very high minimal inhibitory concentrations for both erythromycin and clindamycin. In the case of M phenotype strains, GAS is resistant to erythromycin, but susceptible to clindamycin. It is not necessary to report the erythromycin phenotype routinely, except in cases where inducible resistance is observed.

In a German study, antibiotic treatment was restricted to patients with positive RADT or culture results. In comparison with the early 2000s, the erythromycin resistance rate decreased from 13.6% to 2.6% during the late 2000s after introduction of this policy in the region [4]. A regional intervention to promote appropriate antibiotic use in children reversed trends in erythromycin resistance in Bologna, Italy [5]. The use of macrolides decreased 24% during the study period from 2007 through 2013. Accordingly, erythromycin resistance significantly declined from 23% to 9% during the same period.

In Korea, a significant decrease in erythromycin resistance rate was noted between the early and late 2000s. However, macrolide consumption increased during the same period. Clonal changes in erythromycin resistant *emm* genotypes were suggested to be responsible for the decline in the erythromycin resistance rate rather than restriction of antibiotics [6]. In Portugal, a declining rate of erythromycin resistance was noted: 10% in 2007 and 1% in 2013. Despite a high consumption of macrolides, high clonal instability might attribute this phenomenon [7]. In Italy a very high erythromycin resistance rate was noted in 2002 (38.6%), followed by a significant decrease to 5.2% in 2012 [8]. In this study, changes in bacterial population clonality (e.g. *emm* genotypes) were suggested to be responsible for the decline of erythromycin resistance rather than horizontal transfer of resistance determinants. In a large scale of survey in a southern European region, the erythromycin resistance rate decreased from 11.7% in 2006 to 2.8% in 2012, although macrolide consumption was similar throughout the study period [9]. There was a fluctuation in several clones representing erythromycin resistance, which was suggested to explain the decrease in the erythromycin resistance rate during the period.

In conclusion, although GAS is the most common etiologic agent of bacterial pharyngitis, neither the government, nor the academy of infection specialists in Korea has provided guidelines for optimal diagnosis and treatment. More accurate diagnosis protocols and treatment guidelines should be developed for primary care physicians. The epidemiology of GAS is very dynamic, as is the antibiotic resistance rate. Therefore, continuous epidemiological studies should be performed to monitor clonal changes in GAS.

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