Streptococcal throat. *Therapeutic options and macrolide resistance*

Arif M. Al-Hamad, *PhD, DipHIC.*

Group A Streptococcus (GAS) is the most common cause of acute bacterial pharyngitis, accounting for 20-30% of episodes of pharyngitis in children and 5-15% in adults.[1] Streptococcal pharyngitis is a benign illness; however, it can be associated with suppurative tonsillopharyngeal complications or non-suppurative immune mediated complications such as acute rheumatic fever (ARF), rheumatic heart disease (RHD), and poststreptococcal glomerulonephritis. Other nonsuppurative post-streptococcal sequelae include streptococcal toxic shock syndrome, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS), poststreptococcal autoimmune dystonia secondary to striatal necrosis, poststreptococcal reactive arthritis, and Sydenham's chorea and other autoimmune movement disorders. Although the exact relationship between streptococcal pharyngitis and rheumatic fever is not totally clear, failure to eradicate the organism from the pharynx has been identified as a significant risk factor. The incidence of RHD is considerably higher in countries where aggressive treatment with effective antibiotics is not always available or undertaken. The asymptomatic carrier rate for GAS is up to 20%;[1] therefore, treating all sore throat with antibiotics will remain questionable. In an open study of prescribing strategy in over 700 patients with sore throat randomized to antibiotic versus no prescription versus delayed prescription for 3 days, Little et al[2] found no difference in duration of illness, proportion of patients better by day 3, days missed from work or school, or proportion of patients satisfied with treatment.[2] The Centor clinical prediction score can be used to assist the decision on whether to prescribe an antibiotic, but cannot be relied upon for a precise diagnosis.[3] More recently, a 5-item FeverPAIN (fever, purulence, attend rapidly, inflamed tonsils, no cough, or coryza) clinical score has been proposed, which has been shown to reduce the use of antibiotics by 30% without worsening other outcomes, costs, and antibiotic resistance.[4] In the USA, the wide use of rapid antigen diagnostic tests for GAS inform the clinical decision on the management of pharyngitis without requiring culture results, improving opportunities for the primary prevention of ARF. However, culture back up and sensitivity results are required when non-beta-lactam antimicrobial agents are used to confirm sensitivity. Although these point-of-care antigen tests are promising, concerns on the sensitivity and specificity, and variation between test methodologies have limited their clinical use. The standard management of GAS pharyngitis is 10 days of oral penicillin V or a single dose of benzathine penicillin G given intramuscularly.[1] Amoxicillin is often used for increased palatability and compliance. However, ampicillin-based antibiotics, including co-amoxiclav, may cause a rash when used in the presence of glandular fever. In nonanaphylactic cases of penicillin allergy, a first-generation cephalosporin is recommended.[1] For individuals with severe penicillin allergy, alternative therapy includes macrolide or azalide antibiotics, which include erythromycin, clarithromycin, and azithromycin, or possibly clindamycin. All recommended oral treatment courses extend for 10 days except for azithromycin, for which a 3-5-day treatment course is recommended due to its long half-life. The short course and the once-daily dosing of azithromycin may lead clinicians to prescribe azithromycin for patients who have no clear contraindication to penicillin or cephalosporin. Unfortunately, the increased incidence of macrolide-resistant GAS has limited utility of azithromycin for the treatment of Streptococcal pharyngitis. The growth in rates of resistance correlates with increased macrolide utilization. Worldwide macrolide resistance (MR) has ranged from 1.1-98%, indicating that surveillance data are of paramount importance to inform the clinical decision for the treatment of Streptococcal pharyngitis in a given population. Recently, a scarlet fever outbreak in China and Hong Kong has been associated with MR.[5] Variation in MR rates has been attributed to several factors, including horizontal gene transfer and spread of dominant resistance clones, overconsumption of macrolide antibiotics, and temporal variation in the distribution of emm types. Although all GAS are universally sensitive to beta-lactam antibiotics, MR in GAS has been described since the 1950s. Resistance to macrolides in GAS arises by 2 distinct mechanisms: (i) active drug efflux via a transmembrane pump encoded by *mef* genes and (ii) ribosomal modification by Erm methylase. The later confers cross-resistance to macrolides, lincosamides, and streptogramins (MLSB phenotype). Clinical significant MR was well documented in several countries in the 1970s, which was correlated with a massive increase in macrolide consumption. In Saudi Arabia, it has been reported that 6.3% of the 335 GAS collected from hospital laboratories in 5 different geographical areas during 2003 were resistant to macrolide.[6] **Figure 1** shows the

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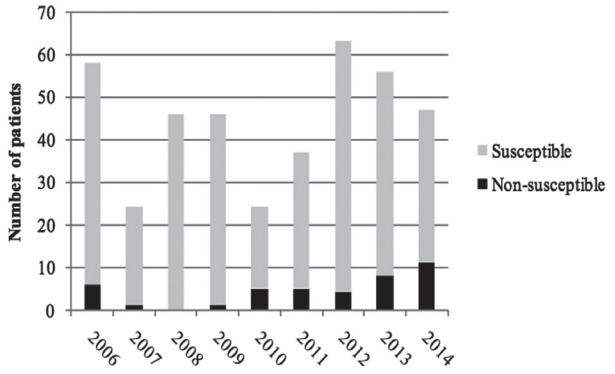

Figure 1 - Erythromycin susceptibility among Group A beta-hemolytic Streptococci at Qatif Central Hospital, Qatif, Saudi Arabia.

epidemiology of MR in GAS in the population served by our institution over a 9-year period. Overall, a total of 578 consecutive isolates of GAS recovered from throat swab specimens (non-duplicate) were tested in our microbiology laboratory during the study period. Susceptibility tests were performed by an automated system (BD Phoenix, Riyadh, Saudi Arabia) or disk diffusion method following the recommendation by the Clinical and Laboratory Standard Institute. Results have shown increasing MR rates from an average of 4.5% between 2006 and 2009 to an average of 12% between 2010 and 2014. During 2014, MR increased to 23.4%, which highlights the need for continued surveillance. These data also indicate the importance of taking swabs to confirm sensitivity when using azithromycin to treat sore throat and to allow monitoring of resistance.

In view of the antibiotic resistance crisis and in line with antibiotic stewardship programs, unnecessary prescribing of antibiotics for minor viral self-limiting illness should be avoided. The use of azithromycin in the management of GAS pharyngitis is considered to be a third-line therapy and should be limited to patients with severe penicillin allergy. If azithromycin must be used to treat streptococcal pharyngitis, culture and susceptibility testing should be performed to avoid clinical or microbiological treatment failure.

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From the Division of Clinical Microbiology, Department of Pathology and Laboratory Medicine, Qatif Central Hospital, Qatif, Kingdom of Saudi Arabia. Address correspondence and reprints request to: Dr. Arif M. Al-Hamad, Division of Clinical Microbiology, Department of Pathology and Laboratory Medicine, Qatif Central Hospital, PO Box 18476, Qatif 31911, Kingdom of Saudi Arabia. E-mail: arifhamad@gmail.com/aralhamad@moh.gov.sa

References

1. Shulman ST, Bisno AL, Clegg HW, Gerber MA, Kaplan EL, Lee G, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. ***Clin Infect Dis*** 2012; 55: e86-e102.
2. Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL. Open randomised trial of prescribing strategies in managing sore throat. ***BMJ*** 1997; 314: 722-777.
3. Ebell MH, Smith MA, Barry HC, Ives K, Carey M. The rational clinical examination. Does this patient have strep throat? ***JAMA*** 2000; 284: 2912-2918.
4. Little P, Hobbs FD, Moore M, Mant D, Williamson I, McNulty C, et al. Clinical score and rapid antigen detection test to guide antibiotic use for sore throats: randomised controlled trial of PRISM (primary care streptococcal management). ***BMJ*** 2013; 347: 5806.
5. Davies MR, Holden MT, Coupland P, Chen JH, Venturini C, Barnett TC, et al. Emergence of scarlet fever *Streptococcus pyogenes* emm12 clones in Hong Kong is associated with toxin acquisition and multidrug resistance. ***Nat Genet*** 2015; 47: 84-87.
6. Shibl AM. Patterns of macrolide resistance determinants among *S. pyogenes* and *S. pneumoniae* isolates in Saudi Arabia. ***J Int Med Res*** 2005; 33: 349-355.