Editorial

Current Management of Streptococcal Pharyngitis

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The paper by Schrock in this issue of the Journal draws our attention once again to the problems surrounding the management of the patient with tonsillopharyngitis caused by group A β-hemolytic streptococci.[1] The virtual disappearance of acute rheumatic fever in the United States by the 1970s lulled physicians into complacency in managing streptococcal infections to prevent this dreaded complication.[2] The return of rheumatic fever, and the occurrence of severe and at times fatal streptococcal infections, in the late 1980s has emphasized again the importance of the proper management of patients with streptococcal respiratory infections.[3] Penicillin has long been the drug of choice in treating these infections, primarily because it has been shown to be effective in preventing the subsequent occurrence of rheumatic fever. Because penicillin treatment failures are relatively frequent, numerous studies have been done with other antistreptococcal drugs in an effort to find one that is superior to penicillin. The paper by Schrock is yet another example of such a study, this time evaluating clarithromycin, an erythromycin-like antibiotic. Schrock's paper exemplifies many of the problems that arise in these studies, and is used as the background to address the issues that should be considered in attempts to find a penicillin substitute.

Two erythromycin-like drugs have been developed that have promise in the treatment of streptococcal infections: clarithromycin, as studied by Schrock and his coworkers, and azithromycin.[4] Both appear to have some characteristics that make them superior to erythromycin. This is particularly important because erythromycin has been the first choice for use in patients with streptococcal pharyngitis who are allergic to penicillin. It is important also to determine whether one or both drugs are equal to or better than penicillin for treating streptococcal infections. Both drugs appear to cause fewer gastrointestinal problems than erythromycin, and because of long half-lives, can be administered at less frequent intervals. They both penetrate well into cells, including macrophages and polymorphonuclear leucocytes; azithromycin does this especially well, to the extent that it is still present in tissues for long periods after the drug is stopped. This could mean that streptococcal infections might be treated with azithromycin for periods shorter than 10 days, with antibacterial levels of the drug remaining in tissues for longer periods.

There are two potentially important issues to be considered with clarithromycin and azithromycin: resistance of the group A streptococcus, and the degree to which these drugs eradicate the organism from the pharynx. It has been known for many years that group A streptococcus developed resistance to erythromycin; this was a problem in Japan over 20 years ago but has not been a big problem in the United States.[5] The recent report from Finland, where resistance occurred in 20% to 24% of isolated strains, has signaled that this could be a potential problem in the United States.[6] In this regard, Schrock reports that 382 of 400 strains of streptococci were "susceptible in vitro to both clarithromycin and penicillin VK." As penicillin resistance has never been recorded, it must be assumed, though this is not clear in the article, that 18 of 400 strains (4.5%) were clarithromycin (and erythromycin) resistant. This figure is considerably higher than what is being observed in current studies at the University of North Carolina, Chapel Hill (Whittier PS, Gilligan PH. Unpublished data, 1992), but does serve as a warning to clinicians that they should watch current literature carefully to learn of the status of resistance patterns.

Penicillin is the only drug that has been demonstrated to prevent rheumatic fever. It is thought that prevention is predicated on eradication of streptococcus from the pharynx. Because it is now considered unethical to do studies with untreated controls, the present standard for treatment effectiveness is eradication of the organism. It is essential, therefore, that current studies be

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designed to demonstrate conclusively that new drugs eradicate streptococcus. That clarithromycin and azithromycin penetrate well into tissue suggests that long-term follow-up and the use of sensitive methods for isolation during the follow-up period are essential. The failure to demonstrate the development of anti-M protein antibodies over periods up to 6 months might also indicate eradication of the organism, as the presence of organisms in the pharynx over long periods is essential to the development of this type-specific antibody. The results reported by Schrock suggest that clarithromycin is as effective as erythromycin in eradicating streptococcus, and possibly more effective than penicillin. Further studies are necessary, however, to assure us that streptococcus has been truly eradicated by these new drugs.

The report in this issue of the Journal exemplifies several of the problems that are encountered frequently in studies of the treatment of streptococcal pharyngitis. The problem of adequate blinding is an important factor. Schrock states that his observations were "a single-blind [investigator-blind] randomized clinical trial" but gives no information regarding who made what observations. The administration of the drugs, one drug taken twice a day and the other three times daily, suggests that it would be very easy to break the treatment code. Another problem is the spacing of the periods of observation. In the present study, observations were made 5 to 7 days, 14 to 16 days, and 29 to 35 days following onset of treatment. Because most patients with untreated streptococcal pharyngitis are well by 5 to 7 days, observations made at that time are generally not satisfactory in determining treatment effectiveness. Symptoms or signs that present 14 to 16 days after the onset of treatment, or persist even if no treatment is given, would be unusual in patients with streptococcal pharyngitis and would probably indicate that the infection was not caused by group A streptococcus. Finally, the biggest problem in these studies is the accurate separation of those patients who continue to carry the infecting type of streptococcus from those who are infected with a new type.[7] Although Schrock states that the strains of group A streptococcus used in his study were "stored at −70° for group A serotyping," no further data about the specimens are given. Thus, it is not possible to assess precisely the effectiveness of either drug in eradicating the infecting streptococcus.

Schrock has outlined quite well the current theories about treatment failures in patients with streptococcal pharyngitis: the development of erythromycin-resistant (but *not* penicillin-resistant) strains of group A streptococci, the development of tolerance to penicillin, the presence of β-lactamase organisms in the pharynx which inactivate penicillin, and the failure of patients to comply with treatment recommendations.[3] The problem of erythromycin resistance is real. The roles of penicillin tolerance and β-lactamase organisms are controversial; conflicting results have been reported. Failure to comply with treatment recommendations is a large problem and probably is the cause of most treatment failures. It has been demonstrated that treatment compliance is related inversely to the number of daily doses of medicine, thus favoring drugs that can be given fewer times a day, and if possible, for shorter periods. This favors the new erythromycin-like drugs, but Schrock fails to mention that studies have been done that show that penicillin given twice a day is also an effective antistreptococcal therapy.[5]

In summary, the new erythromycin-like drugs are interesting developments that give some promise for improved management of patients with group A streptococcal tonsillitis. Their main advantages over erythromycin are that they can be given in fewer daily doses, are better tolerated by the patient, and at least with azithromycin, can possibly be administered for less than 10 days. The possible advantages over penicillin are that they can be used in penicillin-sensitive patients, may be effective in penicillin treatment failures, and have better dosage schedules.

The potential and real disadvantages of the new drugs are substantial. The greatest disadvantages are the possibility of drug resistance and the increased cost of the drugs. Furthermore, they have not been proved to be as effective as penicillin, at least in this author's opinion.

At present penicillin remains the drug of choice in treating patients with group A streptococcal pharyngitis, except in penicillin-allergic individuals. The new erythromycin-like drugs have some qualities that could make them especially effective drugs for the management of patients with streptococcal sore throats, but we must await further and more definitive studies before we can recommend them as first-line treatment. For treating patients who are allergic to penicillin, they do have some advantages over erythromycin.

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