COMMENTARY

This commentary will appear in the June 2004 issue of PEDIATRICS (Vol. 113 no. 6)

So What's Wrong With Penicillin for Strep Throat?

"Change is one thing, progress is another."
Bertrand Russell (1872–1970)

Group A β-hemolytic streptococcal (GABHS) pharyngitis is one of the most common infections of children. For 5 decades, penicillin has been the treatment of choice for this infection, and it is currently recommended by the American Academy of Pediatrics, the American Heart Association, the World Health Organization, and the Infectious Diseases Society of America.[1–4] Amoxicillin is often utilized in young children in place of penicillin V because of taste considerations. Although the problem of increasing antimicrobial resistance among bacteria is one of the most important infectious diseases issues of our time,[5] GABHS remarkably have never developed resistance to any of the penicillins or cephalosporins or to show any increase in penicillin MIC's (minimal inhibitory concentrations) over at least 5 decades.[6] However, it is appropriate to reconsider periodically whether penicillin should remain the treatment of choice or whether a compelling argument can be made to change the recommendation to a different agent such as a cephalosporin. In the April issue of *Pediatrics*, Casey and Pichichero present a meta-analysis of 35 clinical trials performed between 1970 and 1999 in which a cephalosporin was compared to penicillin for the treatment of GABHS pharyngitis.[7] Based on this analysis, they conclude that cephalosporins should be added "as a treatment of choice for GABHS tonsillopharyngitis…." However, this report has several major flaws that make it impossible to accept the validity of this conclusion.

Meta-analysis is "a statistical analysis which combines or integrates the results of several clinical trials considered by the analyst to be 'combinable.'"[8] Over time, meta-analysis research is thought to have led to improved conduct and reporting of clinical trials, including the removal of major sources of bias that, for example, occur in studies that are not double-blinded. [9] Meta-analysis can be a powerful analytical tool but, as with all such tools, can be misused and misinterpreted. For the results of a meta-analysis to be credible and reproducible, it is essential that the individual studies included be of high quality.[9] Statisticians who assess the benefits and limitations of meta-analysis have repeatedly referred to the classic criticism of "garbage-in, garbage-out", indicating that when the quality of data is poor, the meta-analysis is unlikely to be reliable.[10] Some of the major limitations of meta-analysis include its inability to improve the quality or reporting of the original studies, the unavoidable heterogeneity of the included studies, and the frequent presence of a publication bias (against "negative studies") as well as a "Tower of Babel" bias (e.g., only "positive" results from non–English-speaking countries tend to be published in English language journals) that can result in significantly flawed analyses.[10]

Unfortunately, the value of the meta-analysis by Casey and Pichichero is limited severely by the poor quality and major design flaws of many of the studies included in the analysis. For example of the 35 studies included in the analysis, only 6 were double-blinded, only 9 were investigator-blinded, only 3 reported dropout rates for each treatment group, only 9 provided details about patients' signs and symptoms at enrollment, and only 9 based bacteriologic cure upon follow-up throat cultures obtained in the optimal 3 to 14 day period after completion of antimicrobial therapy. In addition, typing of organisms to rule-out a new infection with a different strain of GABHS was not performed in 11 studies, in 10 studies patients with 1+ positive cultures were arbitrarily excluded from the analysis, in 9 studies no test of compliance was performed, and in 9 studies there was no explanation for the subjects who did not complete the study. The marked heterogeneity of the 35 studies is apparent in the 11 different cephalosporins and 1 carbacephem used in these treatment trials.

The authors have applied the Jadad scale, a well-established instrument for assessing the quality of the individual studies included in a meta-analysis, to their own meta-analysis. The Jadad scale assigns each individual study a score of 1–5, with studies "of higher quality" (as defined by Casey and Pichichero) having a score >2, and the highest quality studies having a Jadad score of 5.[11] It is noteworthy that more than two-thirds of the studies included in Casey and Pichichero's meta-analysis had Jadad scores ≤ 2. This objective measure clearly indicates that the great majority of the analyzed studies were poorly designed. It is no coincidence that few of these studies were published in highly selective journals with a strict peer review process.

Casey and Pichichero support their conclusion that cephalosporins should be added "as a treatment of choice for GABHS tonsillopharyngitis…" with the concluding statement that cephalosporins "are 3 times more likely to produce *bacteriologic eradication* and 2 times as likely to produce a *clinical cure* compared to penicillin." However, this is clearly not the case. All of the odds ratios in the analyses are based on clinical and bacteriologic *failure* rates. The conclusion in the abstract is that "the likelihood of bacteriologic *failure* is 3 times higher and clinical *failure* 2 times higher in treatment of GABHS tonsillopharyngitis if oral penicillin is prescribed compared to an oral cephalosporin" (our italics for emphasis). Throughout the meta-analysis report, the concepts of clinical and bacteriologic cure are inappropriately interchanged with clinical and bacteriologic failure. It should be obvious that, when therapy A has a failure rate of 15% and therapy B has a failure rate of 5%, therapy A has a failure rate that is 3 times (15/5) the failure rate of therapy B, but therapy B does <u>not</u> have a *success* rate that is 3 times (95/85) the success rate of therapy A; it is misleading to state otherwise.

There is, however, a more fundamental problem that permeates the vast majority of the studies included in the current meta-analysis as well as those included in an earlier, also flawed, meta-analysis by Pichichero[12] upon which we have commented previously.[13] This problem is the inevitable "contamination" of streptococcal pharyngitis trials by patients who are chronic pharyngeal streptococcal carriers with intercurrent viral pharyngitis. Because cephalosporins are clearly more active than penicillin for eradication of the chronic carrier state, this "contamination" of treatment groups by carriers often contributes to an appearance of superior activity of cephalosporins compared to penicillin in groups of enrollees thought to have *bona fide* streptococcal pharyngitis. We recently showed this in an article in this journal.[14] We found equal bacteriologic eradication rates with penicillin and cefadroxil (94% and 95%, respectively) in those thought to have *bona fide* streptococcal pharyngitis, but 73% and 92%, respectively, in those thought likely to be streptococcal carriers.[14]

Casey and Pichichero attempt to deal with the carrier issue in their meta-analysis. They state that "where the published data allowed, an attempt was made to identify and eliminate GABHS carriers and recalculate the bacteriologic and clinical cure rates. For this purpose GABHS carriers were defined as those patients who had isolation of GABHS on early or late follow-up cultures without GABHS tonsillopharyngitis symptoms," while those with bacteriologic failure after therapy all had symptomatic pharyngitis at the time of follow-up culture. Streptococcal pharyngitis is a self-limited illness with resolution within a few days even without therapy. Therefore, attempting to classify treated patients with positive follow-up cultures as bacteriologic failures or carriers on the basis of the presence or absence, respectively, of symptoms of pharyngitis is inappropriate.

Actually, Casey and Pichichero dismiss streptococcal carriage as the explanation for differences between cephalosporin and penicillin failure rates because they observed an increase in this difference in recent years and indicate that this would imply that there has been an increase in streptococcal carriers in the studied populations during the same time period. We believe that this is precisely what has happened. Many of the studies included in the meta-analysis were funded by pharmaceutical companies. In their zeal to promote their latest cephalosporin, the inclusion criteria for these kinds of studies have often become very broad, resulting in the inadvertent enrollment of increasing numbers of streptococcal carriers into trials intended to evaluate therapy of acute streptococcal pharyngitis.

For all of these reasons, we believe that the claimed superiority of cephalosporins over penicillin for treatment of *bona fide* streptococcal pharyngitis remains unproven. Because chronic streptococcal carriage is ordinarily a benign condition and eradication of carriage is not necessary except in unusual circumstances, superiority of cephalosporins over penicillin in this specific regard (eradication of carriage) is not sufficient to warrant a change in the long-standing recommendation favoring penicillin as the drug of choice for streptococcal pharyngitis. Such a change would have major consequences.

While Casey and Pichichero acknowledge that injudicious use of antimicrobials and the resulting increase in antimicrobial resistance among bacteria "is a growing concern," they apparently do not believe that formal validation of cephalosporins as a treatment of choice for GABHS pharyngitis would contribute to this problem and to rising healthcare costs. Their belief is based, to a large extent, on the somewhat naïve assumption that only first generation cephalosporins with costs and antimicrobial spectra not dramatically different from those of penicillin would be used to treat streptococcal pharyngitis. In current practice, however, expensive broad-spectrum cephalosporins and macrolides are prescribed frequently for adults with acute respiratory tract infections despite many recommendations that these infections (usually viral in origin) not be treated with any antimicrobial.[1–4] These expensive broad-spectrum cephalosporins and macrolides are also currently prescribed for many adults with acute pharyngitis despite the recommendations noted above that penicillin is the agent of choice for streptococcal pharyngitis.[1–4] Recommending cephalosporins as a treatment of choice for GABHS pharyngitis undoubtedly would lead to aggressive marketing and increased prescriptions of all groups of cephalosporins for GABHS pharyngitis, including those that are 20–30 times the cost of penicillin and that have broad spectra of antimicrobial activity, thus greatly increasing the selection pressure upon flora that results in resistant organisms. We believe the situation is analogous to current efforts to preserve amoxicillin as the drug of choice for acute otitis media and sinusitis in children in the face of mounting marketing pressure to switch to more expensive, broad spectrum cephalosporins and macrolides.

Although the use of cephalosporins for group A streptococcal pharyngitis could reduce the number of patients (mostly merely chronic carriers) who continue to harbor the organism in their throats after completing therapy, the economic and ecologic costs involved would make this a Pyrrhic victory for those who advocate a cephalosporin as a drug of choice for streptococcal pharyngitis. Penicillin has stood the test of time satisfactorily for 5 decades, and there are compelling reasons to continue to recommend it as the drug of choice. Its narrow antimicrobial spectrum, inexpensive cost and impressive safety profile all offer substantial benefits to our patients and to society.

Casey and Pichichero advocate a major change in the treatment of streptococcal pharyngitis. We believe that, as observed by Bertrand Russell, change is not necessarily progress, and in this instance, it certainly would not be.

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