Are Cephalosporins Superior to Penicillin for Treatment of Acute Streptococcal Pharyngitis?

Alan L. Bisno
University of Miami School of Medicine and Miami Veterans Affairs Medical Center, Miami, Florida

(See the article by Casey and Pichichero on pages 1526–34)

Penicillin has been the “gold standard” for treatment of acute pharyngitis due to group A streptococci (GAS) (i.e., “strep throat”) for 5 decades. It is effective not only for treating acute infection but also for preventing acute rheumatic fever. GAS have remained exquisitely and uniformly susceptible to penicillin in vitro, and the drug is notable for its safety, narrow spectrum, and low cost. For these reasons, it is considered to be the agent of choice in guidelines published by the American Heart Association, the Infectious Diseases Society of America (IDSA), the American College of Physicians, and the American Academy of Pediatrics.

Starting in the 1980s, there have been reports of increased bacteriologic and clinical failure rates associated with penicillin. In this issue of Clinical Infectious Diseases, Casey and Pichichero [1] present a meta-analysis of treatment of GAS tonsillopharyngitis in adults and conclude that the likelihood of bacteriologic and clinical failure associated with oral penicillin therapy is 2 times higher than that for oral cephalosporin therapy. Pichichero [2] previously published a similar meta-analysis in a study involving pediatric populations, but that analysis was severely criticized in some quarters because of methodological flaws [3]. Moreover, a careful analysis of older and more recent articles published during 1953–1979 and 1980–1993, respectively, that met scrupulous design criteria failed to find evidence of an increase in penicillin failures among patients with GAS pharyngitis [4].

Although Casey and Pichichero [1] have attempted to address many of the flaws criticized in the pediatric study, their efforts are inevitably deterred by the quality of the trials available for review. Although they excluded most of the published trials on methodological grounds, many of the 9 trials eventually included for analysis had appreciable deficiencies. For example, as they point out, 3 trials did not provide detailed descriptions of signs and symptoms required for enrollment, 3 did not provide adequate methods for monitoring treatment compliance, 2 did not perform follow-up cultures early enough to avoid confusion introduced by reacquisition, 3 did not specifically attempt to define and eliminate GAS carriers from the study, and 5 did not include typing of GAS strains recovered from patients in whom treatment apparently failed. The latter 2 deficiencies leave open the possibility that the patient groups under study may either have contained an increased number of patients with chronic streptococcal carriage or that the strains recovered during convalescence were not those that caused the initial acute infection. This issue is of particular importance because penicillin is ineffective in eradicating chronic pharyngeal carriage of GAS [5], whereas cephalosporins are likely to be more effective for this purpose. For example, in a study by Gerber et al. [6] comparing cefadroxil and penicillin, the former was superior to the latter for eradicating pharyngeal GAS in patients classified clinically as likely to be streptococcal carriers (eradication rate, 92% vs. 73% of patients). In contrast, the efficacy of the 2 antimicrobials was equivalent in patients clinically classified as likely to have bona fide GAS pharyngitis (95% vs. 94%).

The definition of “adults” in the current meta-analysis includes some subjects as young as 12 years of age, and 2 of the 9 listed trials are in reality a single trial in which groups that received 2 different cefdinir dosages (with identical total daily doses) were compared with a single comparator group of penicillin recipients [7]. The flaws enumerated above are not likely to be overcome by even the most rigorous analytic statistical techniques.

Data on clinical cure rates are often looked at askance by students of streptococcal disease because of the self-limited nature of GAS pharyngitis. Fever and constitutional disease are markedly improved
within 3–4 days after onset, even without antimicrobial therapy [8]. Antimicrobial therapy shortens the course of the illness by only ~1–2 days, making precise comparison of the clinical cure rates of 2 different regimens quite difficult. This problem may be partially overcome by double-blinding, which was done in 5 of the studies analyzed. In 2 of these, clinical cure rates favored penicillin over the comparator, whereas the opposite was true in 3 studies. Of interest, in 2 studies by the same senior author published in the same year using identical double-blinded protocols [9, 10], clinical cure rates favored penicillin in one and loracarbef in the other, although the magnitude of the differences in each study was trivial.

Bacteriologic eradication of pharyngeal GAS within the first few days after cessation of oral therapy is a much more easily documented end point, taking into consideration, of course, the variables introduced by inevitable contamination of any study group to some degree by patients with chronic pharyngeal streptococcal carriage (see above). Casey and Pichichero [1] note that “studies have shown an increase in the number of cases of GABHS [β-hemolytic GAS] infections that are not eradicated by penicillin treatment.” Although it is true that there is considerable variability in reported eradication rates, the issue is far from settled. In this regard, it is of interest to examine the reported rates of penicillin failure in the studies included in the meta-analysis. These vary from 0% to 16.6%, with a mean of 8.1%. Such “failure” rates, which are likely attributable to the inevitable inclusion of some streptococcal carriers, are precisely in the same range found in studies conducted in the 1950s through 1970s [4]. Nor are there reports of increases in local supplicative complications, such as cervical lymphadenitis or peritonsillar abscess, in penicillin-treated patients, as might be expected if treatment was failing. The life-threatening GAS infections reported in adults during the past 2 decades have been often associated with skin and soft-tissue infections and have not been attributable to the failure of penicillin to treat strep throat. When acute rheumatic fever has appeared in the United States, it has been associated with the introduction of a highly rheumatogenic streptococcal strain [11] and not with treatment failure associated with the antecedent pharyngeal infection.

The choice of the preferred antimicrobial agent for treatment of strep throat in adults is not a trivial matter. Between 1989 and 1999, there were an estimated 6.7 million annual visits to primary care physicians by adults complaining of sore throat [12]. GAS is the only commonly occurring cause of acute pharyngitis that requires antimicrobial therapy, and only ~10% of adult cases of acute pharyngitis would be expected to be streptococcal. Yet antibiotics were prescribed in 73% of these visits. Because of these numbers, the potential impact of selecting a broader-spectrum agent on antimicrobial resistance patterns of upper respiratory tract, gastrointestinal, and cutaneous flora needs serious consideration. Equally important are considerations of cost, both on an individual and societal basis. Currently, the average wholesale price for a 10-day course of penicillin V (500 mg b.i.d.) is one-sixth that for equivalent twice daily regimens of cefpodoxime or cefdinir. Even should the practitioner elect to use the 5-day regimens approved by the US Food and Drug Administration (but not the IDSA) for these 2 cephalosporins, the cost would be thrice that of the penicillin regimen. It must be admitted that this disparity can be largely eliminated by use of a generic first-generation cephalosporin, such as cephalaxin. Because of pharmaceutical detailing patterns, however, this option will rarely be exercised should cephalosporins be considered agents of choice for GAS pharyngitis.

Even if cephalosporins were truly superior—a proposition that is at best dubious—the question remains how important the 5.4% difference in eradication rates reported by Casey and Pichichero [1] might be in the adult population. This raises the fundamental question: what are we attempting to achieve with treatment of strep throat in adults? After all, in almost all areas in the United States at the present time, rheumatic fever is extremely uncommon even in school-aged children, and first attacks in adults are vanishingly rare. As alluded to above, treatment decreases the duration of symptoms only if started early in the course of the illness and then only by, at most, 1 or 2 days. (It is likely, although without corroborative data, that treatment of strep throat during the acute phase will minimize intrafamilial spread.) Antimicrobial treatment can prevent rare but serious supplicative complications such as peritonsillar or retropharyngeal abscess, but many patients with these illnesses present to the physician after the appearance of those symptoms, rather than at the time of acute pharyngitis [13, 14]. Indeed, the major public health issue related to the management of acute pharyngitis in adults is not the need for a more efficacious antimicrobial agent but, rather, the need to control the gross overprescribing of any agent to the 90% of such patients who do not have streptococcal infection [15, 16].

The efficacy of cephalosporins for treatment of strep throat is well-recognized, and indeed the use of first generation cephalosporins is endorsed by the IDSA for penicillin-allergic individuals whose hypersensitivity is not of the immediate type. This option may become even more frequent should the prevalence of GAS resistance to erythromycin increase in the United States. Nevertheless, penicillin at this time remains the drug of choice, and rightly so. Health care analysts apply a motto for judging “significant” differences: to be a difference it has to make a difference [17]. I believe that this aphorism applies in the present case.

References
1. Casey JR, Pichichero M. Meta-analysis of cephalosporins versus penicillin for treatment of group A streptococcal tonsillitis/pharyngitis in


