Treatment of Streptococcal Pharyngitis With Once-Daily Compared With Twice-Daily Amoxicillin

A Noninferiority Trial

Herbert W. Clegg, MD, Amy G. Ryan, MD,* Steven D. Dallas, PhD,† Edward L. Kaplan, MD,‡ Dwight R. Johnson, BS,‡ H. James Norton, PhD,§ Oliver F. Roddey, MD,* Edward S. Martin, MD,* Raymond L. Swetenburg, MD,* Elizabeth W. Koonce, MD,* Mary M. Felkner, MD,* and P. Michael Giftos, MD**

Background: Two relatively small previous studies comparing once-daily amoxicillin with conventional therapy for group A streptococcal (GAS) pharyngitis reported similar rates of bacteriologic success for each treatment group. The purpose of this study was to further evaluate once-daily amoxicillin for GAS pharyngitis in a larger study.

Methods: In a single pediatric practice, from October through May for 2 consecutive years (2001–2003), we recruited children 3 to 18 years of age who had symptoms and signs suggestive of GAS pharyngitis. Patients with a positive rapid test for GAS were stratified by weight (<40 kg or ≥40 kg) and then randomly assigned to receive once-daily (750 mg or 1000 mg) or twice-daily (2 doses of 375 mg or 500 mg) amoxicillin for 10 days. We determined bacteriologic failure rates for GAS in the pharynx from subsequent swabs taken at 14 to 21 (visit 2) and 28 to 35 (visit 3) days after treatment initiation. We conducted a randomized, controlled, investigator-blinded, noninferiority trial to evaluate whether amoxicillin given once daily would have a bacteriologic failure rate no worse than that of amoxicillin given twice daily within a prespecified margin of 10%. GAS isolates were characterized to distinguish bacteriologic failures from new acquisitions. Adverse events were described and adherence was evaluated by review of returned daily logs and dosage bottles.

Results: Of 2139 potential study patients during the 2-year period, we enrolled 652 patients, 326 into each treatment group. Children in the 2 groups were comparable with respect to all demographic and clinical characteristics except that children <40 kg more often presented with rash in each treatment group. At visit 2, failure rates were 20.1% (59 of 294) for the once-daily group and 15.5% (46 of 296) for the twice-daily group (difference, 4.53%; 90% confidence interval [CI], −0.6 to 9.7). At visit 3, failure rates were 2.8% (6 of 216) for the once-daily group and 7.1% (16 of 225) for the twice-daily group (difference, −4.33; 90% CI, −7.7 to −1.0). Gastrointestinal and other adverse events occurred in the once-daily treatment group with a frequency comparable to that in the twice-daily treatment group. Presumed allergic reactions occurred in 0.9% (6 of 635). More than 95% (516 of 541) of patients complied with 10 days of therapy with no significant differences between groups.

Conclusions: We conclude that amoxicillin given once daily is not inferior to amoxicillin given twice daily. Gastrointestinal and other events did not occur significantly more often in the once-daily treatment group. From the data in this large, investigator-blinded, controlled study, once-daily amoxicillin appears to be a suitable regimen for treatment of GAS pharyngitis.

Key Words: group A streptococcus, *Streptococcus pyogenes*, streptococcal, pharyngitis, tonsillopharyngitis, amoxicillin, once-daily therapy, noninferiority trial

(*Pediatr Infect Dis J* 2006;25: 761–767)

Penicillin has been the recommended treatment of group A streptococcal (GAS) pharyngitis since the American Heart Association recommendations were first published in 1953.[1] Guidelines developed for the Infectious Diseases Society of America in 1997[2] and again in 2002[3] included the recommendation that penicillin is the antimicrobial agent of choice for GAS pharyngitis. However, the panel also stated that "Amoxicillin is often used in place of oral penicillin V in young children; the efficacy appears to be equal. The choice is primarily related to acceptance of the taste of the suspension."

Further refinement of the treatment of GAS pharyngitis may lead to added convenience for parents and caregivers and also to improved patient adherence to the regimen. In a meta-analysis of clinical trials comparing dosing frequencies of 10-day courses of penicillin or amoxicillin for GAS pharyngitis, Lan and Colford[4] concluded that twice-daily penicillin was as efficacious as more frequent dosing regimens but that once-daily dosing with penicillin was less efficacious than more frequent dosing regimens. Once-daily dosing regimens with other drugs (eg, cephalosporins, azithromycin) as well as shorter length of treatment courses for GAS pharyngitis have been studied, but these drugs have a broader spectrum

Accepted for publication June 1, 2006.

From *Eastover Pediatrics, Charlotte, NC; †Presbyterian Laboratory Services, Microbiology Department, Presbyterian Hospital, Charlotte, NC; ‡World Health Organization Collaborating Center for Reference and Research on Streptococci, Department of Pediatrics, University of Minnesota Medical School, Minneapolis, MN; and the §Department of Biostatistics, Carolinas Medical Center, Charlotte, NC.

This study was supported by grants from the American Academy of Pediatrics Research in Pediatric Practice Fund and from the Foundation for the Carolinas.

Address for correspondence: Herbert W. Clegg, MD, Eastover Pediatrics, 2600 E. 7th St., Charlotte, NC 28204. E-mail: hwclegg@novanthealth.org.

ISSN: 0891-3668/06/2509-0761
DOI: 10.1097/01.inf.0000235678.46805.92

of coverage and are more expensive or are in the macrolide group in which resistance occurs.[5] Bass et al,[6] in a commentary on Lan and Colford's meta-analysis, suggested that amoxicillin, with its longer serum half-life, should be considered in once-daily doses. Two published studies to date have addressed this issue. Shvartzman et al[7] compared once-daily amoxicillin (50 mg/kg per day; maximum, 750 mg) with penicillin (250 mg per dose 3 or 4 times a day) for 10 days and found amoxicillin given once daily was as effective as conventional penicillin therapy for GAS pharyngitis. Feder et al[8] compared treatment of GAS pharyngitis with 3 daily doses of penicillin (250 mg per dose) and once-daily amoxicillin (750 mg) for 10 days. The 2 treatment methods were equally effective in eradication. Small numbers of patients in each of these studies (fewer than 80 subjects in each treatment arm for each study were included) preclude definitive conclusions. We decided to conduct a larger study in an effort to demonstrate that amoxicillin given once daily is not inferior to amoxicillin given twice daily for treatment of GAS pharyngitis.

METHODS

Study Participants. Patients were 3 to 18 years of age presenting with sore throat to an office of 8 pediatricians and 2 nurse practitioners during the months of October through May for the 2 consecutive years 2001 to 2003. Criteria for inclusion in the study included clinical symptoms and signs consistent with GAS pharyngitis (fever, sore throat, pain on swallowing, pharyngeal erythema, tonsillar exudate, soft palate petechiae and/or tender cervical nodes), the absence of findings making viral illness more likely (primary symptoms of cough, coryza and hoarseness; diarrhea; conjunctivitis; and viral exanthem/enanthem),[9] and a positive rapid test for GAS, always confirmed by a conventional culture positive for GAS. Patients were excluded if there was a history of penicillin or amoxicillin allergy, treatment with an oral antimicrobial in the past week, treatment with a long-acting parenteral penicillin in the past 4 weeks, 3 or more culture-confirmed episodes of GAS pharyngitis in the previous year, known streptococcal carriage or immune suppression. The study protocol was approved by the Institutional Review Board of Presbyterian Healthcare, Novant Health, Charlotte, NC. Written informed consent was obtained from a parent (and assents from those patients who were over 12 years of age) before enrollment.

Study Design. Patients were stratified on the basis of weight ($<$40 kg or $\geq$40 kg) and then, within each weight group, randomly assigned by the study nurse on a 1:1 basis to receive either once- or twice-daily amoxicillin by sequential selection from a computer-generated set of random numbers. The investigators and clinicians providing care for children and enrolling patients as well as the microbiologists were blinded to treatment assignment for the duration of the study. A study nurse collected the baseline information, made the assignments, provided the study drugs, and collected the follow-up information and throat swabs.

Because there are no published recommended dosages for once- or twice-daily amoxicillin for GAS pharyngitis, we derived a treatment regimen by examining: 1) the 2 studies evaluating once-daily amoxicillin for GAS pharyngitis (Shvartzman[7] used once-daily amoxicillin at 50 mg/kg per day, maximum 750 mg, and Feder[8] used once-daily amoxicillin at 750 mg for all children), 2) the Red Book's suggestion of using penicillin for GAS pharyngitis of 500 mg 2 or 3 times per day for adolescents and adults,[10] and 3) the suggestion in the *Physicians' Desk Reference* (PDR) of using amoxicillin for mild/moderate ear, nose and throat infections at 500 mg every 12 hours or 250 mg every 8 hours for adults and 25 mg/kg per day divided every 12 hours or 20 mg/kg per day divided every 8 hours for children. The PDR suggests also that the "The children's dosage is intended for individuals whose weight is less than 40 kg. Children weighing 40 kg or more should be dosed according to the adult recommendations."[11] A weight, rather than an arbitrary age, criterion was used because this is also closer to common practice. Patients were allowed to select a liquid or tablet/capsule formulation.

Thus, for children $<$40 kg, the dosage for amoxicillin was 750 mg once daily or 375 mg twice daily. For children $\geq$40 kg, the dosage for amoxicillin was 1000 mg once daily or 500 mg twice daily. All treatment courses were for 10 days. In the event of clinical recurrence, bacteriologic failure at the follow-up visits, or allergy to amoxicillin during the course of therapy, the patient was treated with an alternative, standard antibiotic for GAS pharyngitis[10] as requested by the Institutional Review Board. The patient was then discontinued from further study.

At the initial visit (visit 1), the following data were obtained: patient name, date of visit, sex, weight, ethnicity, underlying illness, daycare attendance and history of concurrent illness in the family. Symptoms and signs of disease were documented. Parents were given a study log for recording daily the doses given and any symptoms or signs present, including the occurrence of sore throat, fever, headache, abdominal pain, nausea, vomiting, diarrhea and rash. They were asked to write in the log by day the occurrence of any other symptom. They were also asked to return for an early posttherapy visit at 14 to 21 days (visit 2) and a late posttherapy visit at 28 to 35 days (visit 3) after initiation of treatment. These visits included a brief evaluation (when symptoms and signs of pharyngitis were sought) by the study nurse, and a single throat swab was obtained for culture of GAS organisms. At visit 2, daily logs were collected and medication bottles were inspected. Additional posttreatment throat cultures were obtained at any time clinical symptoms suggestive of GAS pharyngitis warranted.

Laboratory Studies. We obtained material from the patient's posterior pharynx and each tonsillar area using a single sterile Dacron swab (for visits 1, 2 and 3), which was plated for recovery of GAS organisms by using the standard technique.[12] A rapid test for GAS organisms was then performed with the Signify Strep A Test (Abbott Labs, Abbott Park, IL). This test has sensitivity 88% and specificity 99% (unpublished data) in our pediatric office laboratory, a Clinical Laboratory Improvement Act-approved laboratory for complex testing. Isolation of GAS organisms on blood agar plates was confirmed by testing beta-hemolytic organisms with the PathoDX Strep Grouping Kit (Remel, Lenexa, KS). Pure culture isolates of GAS organisms recovered at the initial and subsequent visits were frozen in Microbank beads (Pro-Lab Diagnostics, Austin, TX) according

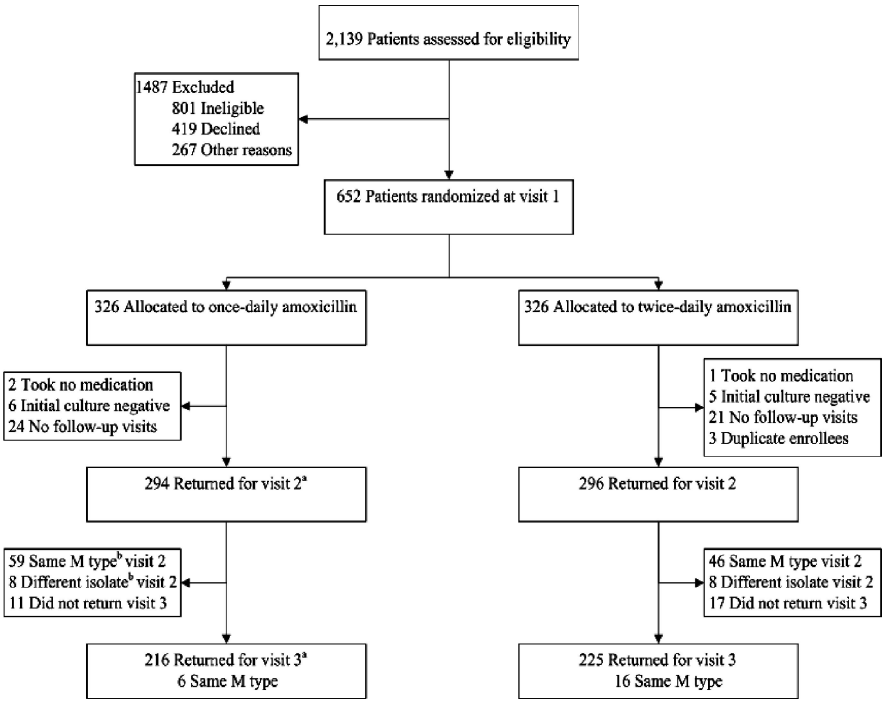

FIGURE 1. Flow of participants through trial. [a]Visit 2 was 14 to 21 days and visit 3 was 28 to 35 days after visit 1. [b]Compared with visit 1 isolates.

to the manufacturer's instructions and stored at −70°C. If a study patient had a positive follow-up swab for GAS organisms, the baseline and subsequent isolates were sent to the World Health Organization Collaborating Center for Reference and Research on Streptococci at the University of Minnesota for further testing for strain relatedness (T agglutination, M typing, SOF determination and *emm* genetic sequencing, if necessary).[13]

Outcome Assessment. The primary outcome measure was bacteriologic failure at visit 2, which included those with bacteriologic persistence (the presence of the same M type of GAS organisms as for the initial throat culture for visit 1) and clinical recurrence (clinical cure, defined as resolution of symptoms and signs of GAS pharyngitis, followed by recurrence of symptoms and signs of GAS pharyngitis associated with recovery from a throat swab of the same M type of GAS as on visit 1). Secondary outcome measures were bacteriologic failure and clinical recurrence at visit 3 and bacteriologic failure for visits 2 and 3 combined. For visit 3, bacteriologic failure included those patients with bacteriologic relapse (eradication of GAS at visit 2 followed by recovery in culture of the same M type of GAS at visit 3 as at visit 1) and clinical recurrence (defined as for visit 2). Bacteriologic eradication was defined by lack of recovery in a throat swab at visit 2 or 3 of GAS of the same M type as visit 1. Recovery of a GAS M type different from visit 1 on a visit 2 or 3 culture was regarded as a new acquisition. Streptococcal antibody titers were not determined.

Statistical Analysis. The study was designed as a noninferiority trial using an a priori equivalence or noninferiority margin of 10%. This margin was selected based on bacteriologic failure rates of 3% to 16% after amoxicillin treatment of GAS pharyngitis reported by various authors,[14–20] including 4% to 5% rates found in the 2 previous studies of once-daily amoxicillin[7,8] and the U.S. Food and Drug Administration's suggestion of the use of a noninferiority margin of 10% if trial success rates were ≥90% (failure rates ≤10%).[21] We assumed a dropout rate of 20%, power of 90% and the use of 2-sided testing with the 90% confidence interval (CI) for the difference in efficacy between treatment groups as suggested in an extension of the Consolidated Standards of Reporting Trials statement recently.[22] A sample size of 650 patients was estimated based on an expected bacteriologic failure rate of 15%. The differences in rates were calculated as rates once daily minus rates twice daily. Because we calculated bacteriologic failure rates, noninferiority could be shown if the upper one-sided 95% (2-sided 90%) confidence limit did not exceed +10%.

For evaluation of clinical and demographic variables in the 2 treatment groups, data measured on the interval scale (eg, weight, age) were compared with a Student *t* test. The χ^2 or Fisher exact test was used for data measured on the nominal scale (eg, gender, daycare attendance). A *P* value of less than 0.05 was considered statistically significant. SAS software (version 8.2; Cary, NC) was used for all analyses.

Baseline clinical and demographic characteristics at the time of enrollment were compared in randomized patients. The main outcome analyses were based on the evaluable patient population defined as those patients who completed both follow-up visits or who had a positive culture at visit 2 with the same M type as visit 1. We also performed an intention-to-treat analysis, including all 326 randomized patents in each treatment group. For this analysis, we assigned an outcome of bacteriologic failure to children who took no medication, were duplicate enrollees, had an initial culture that was negative after a positive rapid test, and/or did not keep either visit 2 or 3 in follow up (see Fig. 1). Interim analyses were performed by a 3-member independent data and safety monitoring committee after 100 and then 250 patients had undergone

randomization. The committee approved continuation of the study at each evaluation.

Adverse Events and Adherence. Adverse events were described for patients eligible for visit 2 from whom a study log was received at visit 2. The symptoms and signs of GAS pharyngitis in untreated patients resolve in approximately 50% of patients by the fourth day of illness and approximately 1 day earlier in treated patients.[23] Thus, new symptoms noted on the log, starting on day 4 of treatment, were considered possible amoxicillin-related adverse events.

Adherence to the treatment regimen was evaluated by review, at visit 2, of the returned daily log on which parents were asked to document dosages given and by comparison of the dispensed doses with the returned dosage bottle.

RESULTS

Patient Population. We assessed 2139 patients who had suspected GAS pharyngitis and who had a positive rapid antigen detection test during the 2-year period. We randomized 652 (30%) patients and excluded 1487 patients. Of those excluded, 801 did not meet study entry criteria, 419 declined participation, and 141were not recruited because they were seen on weekends or after hours when a study nurse was unavailable. Of the randomized patients, 3 took no study medication, 11 (2%) had positive rapid tests but subsequent negative cultures for GAS, 3 were enrolled twice and had only their first enrollment included and 45 (7%) did not return for either follow-up visit 2 or visit 3. Thus, the evaluable population for visit 2 consisted of 590 (90%) patients, 294 in the once-daily and 296 in the twice-daily treatment groups (Fig. 1).

Patients who were culture-positive at visit 2 included 105 who had identical M types to those of visit 1 (59 of 294 [20%] in the once-daily and 46 of 296 [16%] in the twice-daily groups). There were 15 patients with different M types (7 in the once-daily and 8 in the twice-daily groups) and one (in the once-daily group) with a different serogroup. Because each of these 121 culture-positive patients received a second course of antibiotic, they were counted, for the visit 3 analysis, as not returning for visit 3 along with 28 patients (11 in the once-daily and 17 in the twice-daily groups) who came for visit 2 but did not come for visit 3. Thus, the evaluable population for visit 3 was reduced and consisted of 441 patients, 216 in the once-daily and 225 patients in the twice-daily treatment groups (Fig. 1).

Patients in the once- and twice-daily treatment groups were similar for all demographic and clinical characteristics, with the exception noted subsequently, when stratified by weight and when the 2 weight groups were combined within each treatment group (Table 1). Our patient population was 89% (582 of 652) white, had 76% (494 of 652) college-educated parents and included 97% (634 of 652) with private, commercial insurance (only 3% of patients enrolled had Medicaid or no insurance. Although rash was present in 10% (33 of 326) of patients in both once- and twice-daily treatment groups, rash was present more often in children weighing <40 kg than in those ≥40 kg in each treatment group ($P = 0.015$ for the once-daily group and $P = 0.074$ for the twice-daily group).

TABLE 1. Demographic and Clinical Characteristics of Randomized Patients With Group A Streptococcal Pharyngitis by Treatment Group and Weight

Characteristic	Once-Daily Amoxicillin		Twice-Daily Amoxicillin	
	<40 kg (n = 267)	≥40 kg (n = 59)	<40 kg (n = 269)	≥40 kg (n = 57)
Age, years				
Mean ± SD	6.9 ± 2.2	12.1 ± 2.0	6.8 ± 2.2	12.1 ± 2.6
Median	6.6	11.8	6.5	12.1
Range	2.9–13.6	7.9–17.3	3.0–13.1	7.0–18.0
Weight				
Mean ± SD	24.6 ± 6.5	51.4 ± 11.0	24.6 ± 6.7	54.1 ± 16.1
Range	12.3–39.5	38.2–99.0†	13.0–40.0	40.0–102.7
Female sex*	133 (50)	31 (53)	135 (50)	27 (47)
Race/ethnicity				
White	244 (91)	55 (93)	235 (87)	48 (84)
Black	18 (7)	3 (5)	25 (9)	8 (14)
Hispanic/other	5 (2)	1 (2)	9 (3)	1 (2)
Form of medication				
Chewable	105 (39)	12 (20)	110 (41)	11 (19)
Liquid	162 (61)	10 (17)	159 (59)	14 (25)
Capsule/pill	0 (0)	37 (63)	0 (0)	32 (56)
Symptoms/signs other than sore throat				
Fever	206 (77)	44 (75)	210 (78)	43 (75)
Pain with swallowing	132 (49)	39 (66)	139 (52)	44 (77)
Pharyngeal erythema	239 (90)	52 (88)	237 (88)	52 (91)
Tonsillar exudate	61 (23)	12 (20)	53 (20)	13 (23)
Soft palate petechiae	72 (27)	13 (22)	79 (29)	10 (18)
Cervical adenitis	95 (36)	19 (32)	102 (38)	15 (26)
Skin rash	32 (12)	1 (2)	31 (12)	2 (4)
Other symptoms	31 (12)	5 (8)	22 (8)	3 (5)

*Values are no. (%) of patients unless otherwise specified.

†One patient weighing 38.2 kg was inadvertently randomized to the ≥40-g group and given the higher dosage.

SD indicates standard deviation.

Bacteriologic Outcomes. For all evaluable patients at visit 2, 18% (105 of 590) had a positive throat culture for GAS of the same M type as for visit 1. As shown in Table 2, bacteriologic persistence rates for all evaluable patients at visit 2 were comparable for the 2 treatment groups. All patients achieved clinical cure. For visit 2, the clinical recurrence rates for the 2 treatment groups were also comparable (Table 2) with a mean for clinical recurrence of 13.7 days after therapy was begun for the once-daily group and of 13.0 days for the twice-daily group. These differences were also small (difference, 2.09%; 90% CI, −1.6 to 5.8). For visit 3 in evaluable patients (see Table 2), rates of bacteriologic relapse and clinical recurrence in all patients were small. However, there was a greater bacteriologic failure rate (including patients with bacteriologic relapse and clinical recurrence) in the twice-daily group (7.1% [16 of 225]) compared with the once-daily group (2.8% [6 of 216]). Only 2 late clinical recurrences occurred in each treatment group (0.9% for each).

For symptomatic patients with concordant GAS isolates (clinical recurrences), 96% reported sore throat and 60% had fever with no differences between treatment groups for either symptom. A clinical recurrence occurred in 9% (52 of 590) of all evaluable patients, 10% (29 of 294) in the once-daily group and

TABLE 2. Bacteriologic and Clinical Outcomes in Evaluable Children Treated With Once- or Twice-Daily Amoxicillin for Group A Streptococcal Pharyngitis

Bacteriologic and Clinical Outcomes	No. (%) of Patients by Treatment Group		Percent Treatment Difference (90% confidence interval)
	Once Daily	Twice Daily	
Visit 2, all patients, n	294	296	
Bacteriologic failure	59 (20.1)	46 (15.5)	4.53 (−.6 to 9.7)
Bacteriologic persistence	32 (10.9)	25 (8.4)	2.44 (−1.6 to 6.4)
Clinical recurrence	27 (9.2)	21 (7.1)	2.09 (−1.6 to 5.8)
Visit 3, all patients, n	216	225	
Bacteriologic failure	6 (2.8)	16 (7.1)	−4.33 (−7.7 to −1.0)
Bacteriologic relapse	4 (1.9)	14 (6.2)	−4.37 (−7.4 to −1.3)
Clinical recurrence	2 (0.9)	2 (0.9)	0.04 (−1.4 to 1.5)

8% (23 of 296) in the twice-daily group (difference, 2.07%; 90% CI, −1.8 to 5.9).

We calculated bacteriologic failure rates in each treatment group for patients who kept both follow-up visits 2 and 3. As required by the Institutional Review Board, all patients with a positive culture at visit 2 for GAS received a second course with an alternative antibiotic. For this analysis of both visits, we considered these patients as positive for both follow-up visits. As noted in Figure 1, 105 patients had a concordant positive culture for GAS at visit 2 (59 in the once-daily group and 46 in the twice-daily group). In addition, 216 patients in the once-daily group and 225 in the twice-daily group returned for visit 3. Thus, for both visits 2 and 3, in the once-daily group, 24% (59 + 6 of 216 + 59) were positive for GAS and 23% (46 + 16 of 225 + 46) were positive in the twice-daily group (difference, 0.76%; 90% CI, −5.2 to 6.7).

TABLE 3. Possible Amoxicillin-Related Adverse Events Reported in Daily Logs by Parents of Children With Group A streptococcal pharyngitis

Number of Patients	Amoxicillin Treatment Group	
	Once Daily	Twice Daily
Returning for visit 2/eligible for visit 2* (%)	294/318 (92)	296/317 (93)
Returning with log at visit 2/returning for visit 2 (%)	271/294 (92)	270/296 (91)
With any adverse event after day 3/returning with log at visit 2 (%)	45/271 (17)	39/270 (14)†
Abdominal pain	16 (5.9)	16 (5.9)
Diarrhea	13 (4.8)	13 (4.8)
Nausea/vomiting	9 (3.3)	4 (1.5)
Fever	8 (3.0)	4 (1.5)
Rash, nonspecific	7 (2.6)	4 (1.5)
Cough	3 (1.1)	2 (0.7)
Rhinorrhea	1 (0.4)	1 (0.4)
Headache	1 (0.4)	0 (0.0)
With allergic reaction	1/318 (0.3)	5/317 (1.6)‡

*Includes only those who took medication for more than a day.
†Difference, 2.2%; 90% confidence interval, −3.0 to 7.3.
‡Difference, −1.3%; 90% confidence interval, −2.5 to 0.0.

The intention-to-treat analysis assumed that all children with missing data had positive cultures. Combining both weight categories, for visits 2 and 3, bacteriologic failure rates in all randomized patients were compared for patients with bacteriologic failure or with missing data (patients who were duplicate enrollees, did not receive medication, whose initial culture was negative and/or did not keep follow-up visits). Bacteriologic failure rates for patients in the once-daily amoxicillin group were 33% (108 of 326) and 33% (109 of 326) for those in the twice-daily amoxicillin group (difference, −0.3%; 90% CI, −6.4 to 5.8).

No risk factors for bacteriologic failure could be identified by univariate analysis.

Safety. Adverse events were recorded by parents on daily logs kept while medication was administered. Overall, 93% of patients returned for the first follow-up evaluation (visit 2). Of these patients, 92% (541 of 590) returned logs and are the basis for evaluation of possible adverse events (Table 3). No symptoms or signs occurred significantly more frequently in the once-daily group compared with the twice-daily group (17% vs 14%; difference, 2.2%; 90% CI, −3.0 to 7.3).

In addition, charts were reviewed and patients were asked to call or be reevaluated for any possible allergic reaction. Physician-diagnosed allergic reactions were seen in 0.9% (6 of 635) of these patients. Each had diffuse urticaria or erythema multiforme on days 2 through 10 (mean, 7 days) of amoxicillin treatment. Five were in patients receiving twice-daily amoxicillin and one was the in once-daily group (difference, −1.3%; 90% CI, −2.5 to 0.0). Of note, 2 of these occurred in siblings enrolled on the same day with onset of diffuse urticaria on the same day (day 7) of treatment.

Adherence. Daily logs were returned at follow-up visit 2 by 92% (271 of 294) in the once-daily and 91% (270 of 296) of those in the twice-daily groups, respectively (Table 3). Medication bottles were returned by 84% (247 of 294) and 86% (256 of 296) in the once- and twice-daily groups. Of children whose parents returned with follow-up daily log data, only 4% (12 of 271) and 5% (13 of 270) did not receive all 10 days of prescribed treatment in the once- and twice-daily groups, respectively. For these 25 patients, the once-daily group received a mean of 6.8 days and the twice-daily group a mean of 8.2 days of treatment. Also for these 25 patients, 7 failures (28%) occurred, 4 in the once-daily group and 3 in the twice-daily group.

DISCUSSION

In this study, we compared amoxicillin given once daily and twice daily for GAS pharyngitis by measuring bacteriologic failure rates. We found, in this prospective, controlled, investigator-blinded study, a difference of only 4.53% between the 2 treatment groups for the early posttherapy visit 2 and −4.33% for the late posttherapy visit 3. In addition, we also demonstrated similar bacteriologic failure rates for the 2 treatment groups for visits 2 and 3 combined (difference, 0.76%) and in an intention-to-treat analysis (difference, −0.3%).

Our bacteriologic failure rates of 15% to 20% for visit 2 were higher than in some previous studies of amoxicillin treatment of GAS pharyngitis.[14–20] In the 2 studies that

evaluated once-daily treatment,[7,8] low rates for bacteriologic failure were found for both amoxicillin and penicillin (given 3 times daily). These rates were 4% and 5% for amoxicillin and 6% and 11% for penicillin, respectively. In the 3 studies that examined twice-daily amoxicillin, bacteriologic failure rates were 5%,[20] 16%[17] and 24%.[24] Six studies of amoxicillin given 3 times daily found rates of 3% to 15%.[14–16,18–20]

Possible explanations for these varying rates include differences in design (including microbiologic techniques), sample size, and rates of carriage of GAS organisms in the populations studied. With our enrollment criteria, we attempted to exclude possible GAS carriers and include only those with clinical findings suggestive of GAS pharyngitis; however, inclusion of a high percentage of GAS carriers in treatment groups could inflate failure rates.[25] Studies evaluating GAS carriage in the throat have noted rates of 2.5% to 7% in children in practice settings[26] and higher in school settings.[27]

We also noted clinical recurrence rates of 10% and 8% for the once-daily and twice-daily treatment groups, respectively. The Elmwood Pediatric Group retrospectively evaluated patients treated for GAS pharyngitis for clinical recurrences and found that up to 17% of 140 episodes treated with amoxicillin were followed by a recurrence within 30 days.[28] Compared with these reported rates of clinical recurrence and for GAS pharyngeal carriage, the rates found in the 2 prior studies of once-daily amoxicillin are notably low.

Two design features of our study are noteworthy. First, we used a noninferiority design and our study had sufficient power to detect a difference of 10% between the 2 treatment groups for bacteriologic failure rates. Second, we stratified our treatment groups by weight so that patients ≥40 kg were given a higher dosage than those <40 kg. This approach has not been taken for previous studies of penicillin or amoxicillin treatment of GAS pharyngitis, but a similar dosing approach is often used in practice.

Adverse events possibly related to amoxicillin occurred in 16% (84 of 541) of patients in this study. Gastrointestinal symptoms were most common. The 2 treatment groups had comparable frequencies of gastrointestinal and other events. The rate of presumed drug-associated allergic reactions was less than 1%. Similar rates were found by Bass et al[29] for urticarial skin eruptions after orally administered ampicillin (0.8% [3 of 400]) and for allergic rash in 7 previous studies of amoxicillin treatment of GAS pharyngitis (0.4% [4 of 955]).[14–20,24]

This study has 3 potential limitations. First, we did not directly compare once-daily amoxicillin with the standard comparator, namely penicillin, given 3 times daily. There are likely different bacteriologic failure rates with different antibiotics, so we used amoxicillin as the comparator to eliminate this source of variation. Second, stratification of patients by weight for dosing may not represent standard practice for the use of amoxicillin for GAS pharyngitis. For visit 2, we demonstrated noninferiority when both weight subgroups were considered together, but we cannot be confident of noninferiority in subgroup analyses by weight because this study was not powered for subgroup analyses. Third, our study subjects were drawn from a single pediatric practice with similar demographic characteristics, and this may limit the generalizability of our findings somewhat.

We found that for treatment of GAS pharyngitis, amoxicillin given once daily is not inferior to amoxicillin given twice daily with respect to the prespecified margin of 10%. We conclude that amoxicillin given once daily is a suitable regimen for treatment of GAS pharyngitis, especially in circumstances when once-daily dosing would improve adherence.

ACKNOWLEDGMENTS

The authors acknowledge the data collection contributions and technical help of Elaine Nishioka, Mary Beth Forcina, Diane Strawn, Gale Atkins, Kim Ardrey, Amy Cunningham, Judith Osborn, Jan Rapisardo, Felecia Ferrell, Frances Lewis, and Kristine Ellison. The authors thank David H. Moore, MD, and David G. Rupar, MD, for help with data monitoring; Stanford T. Shulman, MD, for advice with study design; and Michele Jonsson Funk, PhD, Andrew L. Baughman, PhD, MPH, and Steven B. Thacker, MD, MSc, for manuscript review and analysis suggestions. The authors especially thank Jane Moss for study coordination.

REFERENCES

1. Breese BB, Bellows MT, Fischel EE, et al. Statements of the American Heart Association Council on rheumatic fever and congenital heart disease. Prevention of rheumatic fever. *JAMA*. 1953;151:141–143.
2. Bisno AL, Gerber MA, Gwaltney JM, Kaplan EL, Schwartz RH. Diagnosis and management of group A streptococcal pharyngitis: A practice guideline. *Clin Infect Dis*. 1997;25:574–583.
3. Bisno AL, Gerber MA, Gwaltney JM, Kaplan EL, Schwartz RH. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. *Clin Infect Dis*. 2002;35:113–125.
4. Lan AJ, Colford JM. The impact of dosing frequency on the efficacy of 10-day penicillin or amoxicillin therapy for streptococcal tonsillopharyngitis: a meta-analysis. *Pediatrics*. 2000;105:e19. Available at: http://www.pediatrics.org/cgi/content/full/105/2/e19.
5. Freeman AF, Shulman ST. Macrolide resistance in group A *Streptococcus*. *Pediatr Infect Dis J*. 2002;21:1158–1160.
6. Bass JW, Person DA, Chan DS. Twice-daily oral penicillin for treatment of streptococcal pharyngitis: Less is best. *Pediatrics*. 2000;105:422–423.
7. Shvartzman P, Tabenkin H, Rosentzwaig A, Dolginov F. Treatment of streptococcal pharyngitis with amoxycillin once a day. *BMJ*. 1993;306:1170–1172.
8. Feder HM, Gerber MA, Randolph MF, Stelmach PS, Kaplan EL. Once-daily therapy for streptococcal pharyngitis with amoxicillin. *Pediatrics*. 1999;103:47–51.
9. Dajani A, Taubert K, Ferrieri P, et al. Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: A statement for health professionals. *Pediatrics*. 1995;96:758–764.
10. American Academy of Pediatrics, Committee on Infectious Diseases. *2000 Red Book. Report of the Committee on Infectious Diseases,* 25th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2000:530–531.
11. *Physicians' Desk Reference*, 54th ed. Montvale, NJ: Medical Economics Co, Inc; 2001:2969–2971.
12. Wannamaker LW. A method for culturing beta hemolytic streptococci from the throat. *Circulation*. 1965;32:1054–1058.
13. Johnson DR, Kaplan EL, Sramek J, et al. *Laboratory Diagnosis of Group A Streptococcal Infections.* Geneva: World Health Organization; 1996.
14. Stillerman M, Isenberg HD, Facklam RR. Treatment of pharyngitis associated group A *Streptococcus*: Comparison of amoxicillin and potassium phenoxymethyl penicillin. *J Infect Dis*. 1974;129:S169–177.
15. Breese BB, Disney FA, Talpey WB, Green JL. Treatment of streptococcal pharyngitis with amoxicillin. *J Infect Dis*. 1974;129:S178–180.
16. Breese BB, Disney FA, Green JL, Talpey WB. The treatment of beta hemolytic streptococcal pharyngitis. Comparison of amoxicillin, erythromycin estolate, and penicillin V. *Clin Pediatr*. 1977;16:460–463.
17. Cohen R, Levy C, Doit C, et al. Six-day amoxicillin vs ten-day penicillin V therapy for group A streptococcal tonsillopharyngitis. *Pediatr Infect Dis J*. 1996;15:678–682.

18. Kearsley NL, Campbell A, Sanderson AAF, Weir RD, Kamdar MK, Coles SJ. Comparison of clarithromycin suspension and amoxicillin syrup for the treatment of children with pharyngitis and/or tonsillitis. *Br J Clin Pract*. 1997;51:133–137.
19. Gopichand I, Williams GD, Medendorp SV, et al. Randomized, single-blinded comparative study of the efficacy of amoxicillin (40 mg/kg/day) versus standard-dose penicillin V in the treatment of group A streptococcal pharyngitis in children. *Clin Pediatr*. 1998;37:341–346.
20. Aguilar A, Tinoco JC, Macias M, et al. Clinical and bacteriologic efficacy of amoxycillin bd (45 mg/kg/day) versus amoxycillin tds (40 mg/kg/day) in children with group A beta-hemolytic streptococcal tonsillopharyngitis. *J Chemother*. 2000;12:396–405.
21. Powers JH, Ross DB, Brittain E, Albrecht R, Goldberger MJ. The United States Food and Drug Administration and noninferiority margins in clinical trials of antimicrobial agents. *Clin Infect Dis*. 2002;34:879–881.
22. Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJW, for the CONSORT group. Reporting on noninferiority and equivalence randomized trials. *JAMA*. 2006;295:1152–1160.
23. Shulman ST, Tanz RR, Gerber MA. Streptococcal pharyngitis. In: Stevens DL, Kaplan EL, eds. *Streptococcal Infections. Clinical Aspects, Microbiology, and Molecular Pathogenesis*. New York: Oxford University Press; 2000:76–101.
24. Curtin-Wirt C, Casey JR, Murray PC, et al. Efficacy of penicillin vs. amoxicillin in children with group a beta hemolytic streptococcal tonsillopharyngitis. *Clin Pediatr*. 2003;42:219–225.
25. Gerber MA, Tanz RR, Kabat W, et al. Potential mechanisms for failure to eradicate group A streptococci from the pharynx. *Pediatrics*. 1999; 104:911–917.
26. Pichichero ME, Marsocci SM, Murphy ML, Hoeger W, Green JL, Sorrento A. Incidence of streptococcal carriers in private pediatric practice. *Arch Pediatr Adolesc Med*. 1999;153:624–628.
27. Breese BB. Carriers. In: Breese BB, Hall CB, eds. *Beta Hemolytic Streptococcal Diseases*. Boston: Houghton Mifflin Professional Publishers; 1978:143–153.
28. Pichichero ME, Green JL, Francis AB, et al. Recurrent group A streptococcal tonsillopharyngitis. *Pediatr Infect Dis J*. 1998;17:809–815.
29. Bass JW, Crowley DM, Steele RW, Young FSH, Harden LB. Adverse effects of orally administered ampicillin. *J Pediatr*. 1973;83:106–108.