Variables Influencing Penicillin Treatment Outcome in Streptococcal Tonsillopharyngitis

Michael E. Pichichero, MD; William Hoeger, MD; Steven M. Marsocci, MD; A. Marie Lynd Murphy, MD; Anne B. Francis, MD; Vladimir Dragalin, PhD

Objective: To examine whether penicillin treatment success for group A β-hemolytic streptococcal tonsillopharyngitis is influenced by patient age, number of days ill prior to initiation of treatment, number of prior episodes, season, total dosage (milligrams per kilogram), and frequency of administration (2 vs 3 times daily).

Methods: Four hundred seventy-eight children, adolescents, and young adults aged 2 to 21 years with acute symptoms compatible with the clinical diagnosis of group A β-hemolytic streptococcal tonsillopharyngitis and a positive streptococcus rapid antigen detection test result were enrolled (intent-to-treat group). Patients were randomly assigned to receive penicillin V potassium, 250 mg 3 times daily (n = 239) or 500 mg 2 times daily (n = 239). Randomization was independent of patient body weight and treatment was for 10 days with both regimens. Follow-up examinations occurred, and cultures were obtained at 14 to 21 days after the initiation of antibiotic therapy; those with group A β-hemolytic streptococcus isolated from a throat culture and who returned for follow-up were assessed for outcome (n = 359).

Results: Using a logistic regression analysis with a stepwise variable selection, we found the major variables associated with penicillin treatment success to be the number of days ill prior to initiation of treatment (P = .001; odds ratio, 1.55 [95% confidence interval, 1.2-2.1]) and the age of the child when infected (P = .004; odds ratio, 1.14 [95% confidence interval, 1.05-1.25]). The number of prior episodes within the preceding year, the season, the total daily penicillin dose (range, 8-76 mg/kg), and 2 vs 3 times daily dosing did not significantly alter treatment outcome.

Conclusion: Treatment after 2 days of illness and of adolescent patients increases penicillin treatment success for group A β-hemolytic streptococcal tonsillopharyngitis.


Editor’s Note: So, is the message that penicillin is OK for treating group A β-hemolytic streptococcal tonsillopharyngitis in adolescents or anyone with 2 days or less of illness and all others should receive [fill in the blank]?

Catherine D. DeAngelis, MD

We have noted a rising incidence of penicillin treatment failure in group A β-hemolytic streptococcal (GABHS) tonsillopharyngitis since the early 1980s1-2 and have suggested explanations for its occurrence.3-4 Kaplan5 also recognized a definite temporal trend toward an increased number of penicillin treatment failures from the 1960s to the 1980s, although Markowitz et al5 and Shulman et al6 have offered an alternative view. There is less disagreement that over the years penicillin has had diminished efficacy in recurrent GABHS tonsillopharyngitis6 and in eradication of GABHS from asymptomatic carriers.9 Nevertheless, penicillin will produce a cure in most sporadic, primary episodes of GABHS throat infection, and it remains the treatment of choice for most patients.

The variable success of penicillin treatment of GABHS tonsillopharyngitis,1-7 the recent increased appreciation of dosage frequency as a compliance determinant,10-11 and the recent reports of better treatment outcome with amoxicillin,12-13 which may reflect more prolonged antibiotic levels above the minimum inhibitory concentration for GABHS compared with penicillin,14-16 prompted us to undertake a contemporary reexamination of several variables that might influence penicillin treatment outcome. In this study, we sought to determine whether patient age, the number of days ill prior to initiation of antibiotic treatment, the number of prior episodes of GABHS throat in-
PATIENTS, MATERIALS, AND METHODS

STUDY POPULATION AND ENROLLMENT CRITERIA

This study was conducted at the Elmwood Pediatric Group, a private pediatric practice in suburban Rochester, NY, serving a patient population consisting primarily of middle-class and upper middle-class families. Prospective enrollment commenced in February 1, 1995, and concluded on June 30, 1997. Identification of patients for recruitment occurred according to the flow of the daily office routine and with consideration of the responsibilities of our study nurse staff to other projects.

Patients aged 2 to 21 years with acute symptoms compatible with the clinical diagnosis of GABHS tonsillopharyngitis and with a positive streptococcus rapid antigen detection test result were eligible for enrollment. Only patients for whom GABHS was isolated from the throat swab plated on sheep blood agar were included in the outcome group. Patients were excluded from enrollment if they had a history of hypersensitivity to penicillin, if they were suspected GABHS carriers based on review of the medical record, or if they had an apparent acute upper respiratory tract viral infection.

PRETREATMENT EVALUATION

After informed consent was obtained, the patient’s demographic, history, and physical examination findings were recorded. Data collection included patient age, weight, sex, date of visit, and number of acute GABHS tonsillopharyngitis episodes in the preceding 12 months. The medical history sought symptoms of sore throat, fever, headache, nausea, vomiting, and the day of illness onset. The physical examination assessed temperature, pharyngeal redness, pharyngeal exudate, anterior cervical lymph-node swelling and tenderness, and palatal petechiae.

TREATMENT

Patients were randomly assigned to receive penicillin V potassium, either 250 mg 3 times daily or 500 mg 2 times daily. Dosing randomization was done independently of patient body weight. Randomization was 1:1 and the duration of therapy for both regimens was 10 days.

BACTERIOLOGIC AND CLINICAL EVALUATION

All patients were scheduled to return to the office practice 14 to 21 days after the initiation of antimicrobial therapy (ie, 4-7 days after completion of therapy). At that visit, a history and physical examination were completed to collect information identical to that obtained at the pretreatment visit.

The outcome group included only patients who returned for follow-up. Outcome was defined as bacteriologic and clinical success if the patient had a negative throat culture and absence of symptoms, bacterial and clinical failure if the patient had a positive throat culture and the presence of any symptom associated with streptococcal tonsillopharyngitis (fever, sore throat, pharyngeal redness, exudate, or anterior cervical adenopathy/tenderness), or possible carrier if the patient had a positive culture of any colony count but no symptoms or signs of GABHS throat infection.

LABORATORY

Throat swabs were obtained and cultured on 5% sheep blood agar in our office laboratory (Clinical Laboratory Improvement Amendments level 3), and culture plates were incubated aerobically (35°C), with readings on 2 successive days. Using a latex agglutination test (Streptex; Murex Diagnostics Ltd, Dartford, England), β-hemolytic streptococci were identified as belonging to group A. The GABHS colony counts were graded as follows: 1+ for 1 to 10 colony-forming units, 2+ for 11 to 50 colony-forming units, 3+ for 51 to 100 colony-forming units, and 4+ for 100 or more colony-forming units. Rapid antigen detection tests were used according to the manufacturer’s instructions.

COMPLIANCE

Approximately 5 days after the initiation of therapy, parents collected a urine specimen from the patient, dipped a filter paper provided by our group in the urine, sealed the filter paper in a Ziploc bag, and mailed the specimen to us. Presence of antibiotic activity in urine was detected by placing the dipped filter paper on sheep blood agar along with a lawn of GABHS; any zone of inhibition was considered evidence for the presence of antibiotic. In addition, the medication administered was documented on record cards completed by the patients’ parents, and medication bottles were brought to the office at the follow-up visit for documentation of remaining suspension or tablets.

STATISTICAL ANALYSIS

The intent-to-treat and outcome groups were compared for enrollment variables by the Student t test or χ² test, as appropriate. Treatment outcome for the 2 vs 3 times daily penicillin VK groups was compared using the χ² test. Logistic regression analysis was used to investigate the relationship between penicillin treatment response and age, sex, weight, number of episodes of GABHS tonsillopharyngitis in the past year, number of days ill prior to treatment of current episode, and penicillin dose administered (milligrams per kilogram). The stepwise variable selection method was used to select the best prognostic factors for penicillin treatment success. Potential predictors of penicillin treatment success were added to the logistic regression model if they made a statistically significant contribution to fit (P≤.05), and a significance level of P≤.1 was required for a variable to stay in the model. For the best prognostic factors, the Cochran-Armitage test was also performed to test for trend in treatment success proportions across the ordered levels of the identified predictive factors. The extreme categories for the variables (days ill prior to treatment and patient age) that contained few observations were combined in one category for this analysis.
Table 1. Epidemiologic Data

<table>
<thead>
<tr>
<th></th>
<th>Intent-to-Treat Group† (n = 478)</th>
<th>Outcome Group‡ (n = 359)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BID (n = 239)</td>
<td>TID (n = 239)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>8.04 ± 2.88</td>
<td>7.86 ± 3.19</td>
</tr>
<tr>
<td>Median (range)</td>
<td>8 (2-17)</td>
<td>7 (3-19)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>36.7 ± 18.0</td>
<td>33.8 ± 15.4</td>
</tr>
<tr>
<td>Median (range)</td>
<td>32 (13-126)</td>
<td>30 (13-90)</td>
</tr>
<tr>
<td>Male, %</td>
<td>54</td>
<td>48</td>
</tr>
<tr>
<td>GABHS tonsillopharyngitis episodes in past year, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>71</td>
<td>67</td>
</tr>
<tr>
<td>1</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>≥3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Days ill prior to treatment, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>56</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>≥5</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

* BID indicates twice daily; TID, 3 times daily; GABHS, group A β-hemolytic streptococcus.
† The intent-to-treat group consisted of all enrolled patients with tonsillopharyngitis who had GABHS clinically and a positive rapid antigen detection test result.
‡ The outcome group was a subset of the intent-to-treat group with a culture positive for GABHS who returned for a follow-up visit 4 to 7 days after completion of a 10-day regimen of penicillin BID or TID. Patients with positive rapid antigen detection test results and negative cultures were excluded, as were patients who were carriers at follow-up (n = 45).

Results

Four hundred seventy-eight children were enrolled in the study and composed our intent-to-treat population; 119 failed to return for the follow-up visit, had initial throat cultures that were negative, or were considered carriers at the end of therapy, leaving 359 children in the outcome analysis group. There were no statistically significant differences between the intent-to-treat and outcome groups with respect to enrollment epidemiologic characteristics, symptoms and signs of acute GABHS tonsillopharyngitis at the initial visit, degree of culture positivity, or compliance at day 5 of treatment (Table 1 and Table 2). Compliance as measured by completion of diary cards and return of empty medication bottles in the outcome group was not significantly different from the results of mid-treatment urine-compliance assays.

Group A β-hemolytic streptococcus was eradicated in 131 (71.6%) of 183 patients receiving penicillin V 2 times daily and 126 (71.6%) of 176 patients receiving penicillin V 3 times daily; there was no significant difference attributable to dose frequency with respect to outcome. Therefore, all subsequent analyses examined differences in outcome without regard to dose frequency.

The best predictor of penicillin treatment success selected by the stepwise logistic analysis and model fitting was number of days ill prior to treatment (P = .001). Patient age was the second most significant variable in predicting treatment success with penicillin (P = .004). Other variables that were examined as possible predictors of penicillin treatment outcome included the number of episodes of GABHS tonsillopharyngitis in the preceding year, month during the year when the patient was enrolled and treated (season effect), sex, and penicillin dosage (milligrams per kilogram). None of these variables proved to have a significant effect on outcome in the model. The estimated odds ratio for penicillin treatment success increased 1.55 times (95% confidence interval, 1.2-2.1) when the number of days ill prior to the start of treatment increased by 1 day. The estimated odds ratio for penicillin success increased by 1.4 times (95% confidence interval, 1.05-1.25) when the age of the patient increased by 1 year.

The Cochran-Armitage trend test was performed to further verify the results. An increasing trend in the probability of treatment success from 1 day ill prior to treatment to 6 days ill prior to treatment was confirmed (right-sided P = .001) (Figure 1). Similarly, with the age variable, an increasing trend for treatment success with increasing age was confirmed (right-sided P = .001) (Figure 2). However, the overlapping 95% confidence intervals for probability of treatment success for the number of days ill prior to treatment and patient age (Figures 1 and 2) demonstrates that our data do not provide sufficient evidence that the increasing trends are statistically significant at all time points. Only the increase from 1 to 2 in the number of days ill prior to treatment was significant (P = .001 by χ² test, Figure 1). No discrete difference in age was significant.

We have previously published observations suggesting that a delay in treatment from onset of symptoms for 48 hours influences penicillin treatment out-
In the current study, the difference in the success of treatment between patients ill less than 2 days and patients ill 2 days or longer was highly significant (\(P = .001\) by \(x^2\) test and right-sided \(P = .001\) by trend test) (Table 3).

We have previously reported greater penicillin success in adolescent and young adult patients compared with younger children,\(^2\) and the epidemiology of streptococcal tonsillopharyngitis demonstrates a peak occurrence during the grade school years (ages 6-12 years). This suggests the classification of the patients in this study into 3 age categories: ages 2 to 5 years, 6 to 12 years, and 13 to 21 years; the proportions of treatment success for these 3 age categories were 42 of 71, 187 of 254, and 29 of 34, respectively (\(P = .01\) by \(x^2\) test). The trend test had a significant right-sided result (\(P = .001\)). Furthermore, there was a statistically significant (right-sided \(P = .009\)) increase in the proportion of treatment success in the group aged 6 to 12 years compared with the group aged 2 to 5 years. The increasing trend from the group aged 6 to 12 years to the group aged 13 to 21 years approached significance (right-sided \(P = .07\)) (Table 3).

**COMMENT**

Not all patients treated with penicillin for GABHS tonsillopharyngitis have a successful outcome,\(^1\)\(^-\)\(^9\) and the frequency of treatment failure with penicillin seems to be rising.\(^1\)\(^-\)\(^2\)\(^,\)^\(^4\) This study sought variables that might ex-

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**Table 2. Symptoms, Signs, and Laboratory Results at the Enrollment Visit and Compliance at Day 5 of Penicillin Treatment**

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Intent-to-Treat Group (n = 478)</th>
<th>Outcome Group (n = 359)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BID (n = 239)</td>
<td>TID (n = 239)</td>
</tr>
<tr>
<td>Oral temperature (\geq 38.0°C)</td>
<td>84</td>
<td>82</td>
</tr>
<tr>
<td>Sore throat</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>Tonsillopharyngeal redness</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>Tonsillopharyngeal exudate</td>
<td>67</td>
<td>68</td>
</tr>
<tr>
<td>Swollen anterior cervical lymph nodes</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td>Tender anterior cervical lymph nodes</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>Headache</td>
<td>41</td>
<td>44</td>
</tr>
<tr>
<td>Nausea</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Palatal petechiae</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>White blood cell count, (\times 10^9/L)</td>
<td>18.7</td>
<td>16.9</td>
</tr>
<tr>
<td>Throat culture, %</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>4+</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>3+</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>2+</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Negative</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Compliance</td>
<td>90</td>
<td>87</td>
</tr>
</tbody>
</table>

* BID indicates twice daily; TID, 3 times daily.  
† Values are means.

**Figure 1.** Observed and predicted treatment success by the number of days ill prior to initiation of treatment. The dots indicate observed proportions, with the vertical lines showing 95% confidence intervals. The curve is the logit-fitted line, with an intercept of 0.211 and a slope of 0.436. Numbers in parentheses indicate numbers of subjects.

**Figure 2.** Observed and predicted treatment success by patient age. The dots indicate observed proportions, with the vertical lines showing 95% confidence intervals. The confidence interval for age 15 years was calculated combining the 12 observations for patients aged 15 years and older. The curve is the logit-fitted line, with an intercept of −0.067 and a slope of 0.131. Numbers in parentheses indicate numbers of subjects.

**Table 3. Penicillin Treatment Successes Failures Total Successes, %**

<table>
<thead>
<tr>
<th>No. of prior days ill</th>
<th>Successes</th>
<th>Failures</th>
<th>Treated</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>123</td>
<td>70</td>
<td>193</td>
<td>64</td>
</tr>
<tr>
<td>(\geq 2)</td>
<td>133</td>
<td>29</td>
<td>162</td>
<td>82</td>
</tr>
<tr>
<td>Total</td>
<td>256</td>
<td>99</td>
<td>355†</td>
<td>72</td>
</tr>
</tbody>
</table>

†Values are means.

**COMMENT**

Not all patients treated with penicillin for GABHS tonsillopharyngitis have a successful outcome,\(^1\)\(^-\)\(^9\) and the frequency of treatment failure with penicillin seems to be rising.\(^1\)\(^-\)\(^2\)\(^,\)^\(^4\) This study sought variables that might ex-
plain differences in observed penicillin treatment success. During a 2.5-year prospective study of 478 patients, we found the major predictors of penicillin treatment outcome to be the number of days ill prior to the start of therapy and patient age.

We and others have noted an increase in the likelihood of treatment failure and of recurrent streptococcal GABHS tonsillopharyngitis when penicillin treatment is initiated at the time of diagnosis compared with patients treated after a 2-day symptomatic interval; however, not all studies have produced similar findings. There is increased acquisition of antibody to streptococcal antigens with a longer illness prior to treatment; this immunity has been suggested as one possible explanation for the higher success rate with penicillin in patients ill longer before therapy is started. It may also be that penicillin treatment is more often successful in patients who have been ill longer prior to treatment because such patients have a greater degree of tonsillopharyngeal inflammation, which permits better penetration of penicillin.

The peak incidence of GABHS tonsillopharyngitis is in the group aged 6 to 12 years. This has been thought to reflect increased exposure in children of this age as they enter school and experience gradual acquisition of GABHS type–specific immunity. In a previous study, we found that penicillin treatment success is greater in adolescents and young adults than in younger children. Perhaps the immune response in adolescents and adults differs from that in younger patients. We assessed as a variable the number of GABHS episodes in patients in the year prior to study enrollment (which should affect GABHS immunity), but this variable was not a predictor of outcome.

Our results and those of others consistently suggest that penicillin is equally effective whether administered 2, 3, or 4 times daily. Although not an important factor under study conditions, poor compliance with the 3 or 4 times daily administration of penicillin may account for treatment failures in clinical practice. Less-frequent dosing improves compliance. Our data, the data of others, and the review by Bass encourage the recommendation of the least-frequent daily dosing possible: 2 times daily.

No dose-related effect was observed with penicillin in a range of 8 to 76 mg/kg per day. Recent reports suggest that amoxicillin may be more effective than penicillin in GABHS tonsillopharyngitis since it can be administered for a shorter treatment duration than penicillin and on a once-a-day schedule, while for penicillin a once-a-day schedule reduces the likelihood of treatment success. The difference between amoxicillin and penicillin could be attributed to levels of antibiotic in tonsillar tissue, which would imply a possible dose-related effect. Our results suggest that increasing the dosage of penicillin above the usual recommended dose for GABHS tonsillopharyngitis will not improve the chance for cure.

We examined season as a possible variable associated with penicillin treatment outcome. We hypothesized that in late winter to spring, the number of cumulative GABHS episodes in patients might be increased and the number of prior treatments with antibiotics might be increased. These events might cause an increase in the prevalence of β-lactamase–producing copathogens or a decrease in the prevalence of patients colonized with potentially protective normal flora (α-streptococci). However, we found no influence on penicillin treatment outcome of the season in which the patient was enrolled in the study. The sex of the patient also made no significant difference.

Most patients treated with penicillin for GABHS tonsillopharyngitis will experience bacteriologic eradication and a clinical cure, although the relative frequency of that success varies from study to study, from more than 90% to just over 60%. Two variables that emerge from our study that might have contributed to differences in penicillin treatment success in prior studies are patient age and number of days ill prior to treatment; these may be relevant variables in clinical practice as well. Penicillin treatment failure occurs in about one third of our patient population with acute GABHS throat infections. Milder symptoms occur during relapses within 30 days of the index infection with the same serotype. We continue to perform follow-up examinations on patients who have had GABHS tonsillopharyngitis to carefully solicit a history, examine the child, and take a throat culture if appropriate. We advocate this approach despite recommendations to the contrary to avoid missing patients in whom penicillin treatment failed but who are only mildly symptomatic. This study suggests that such follow-up visits might not be needed in adolescents and young adults and in those who have been ill with acute symptoms for 2 or more days.

<table>
<thead>
<tr>
<th>Investigator</th>
<th>No. of Trials</th>
<th>Penicillin G or V Dosage, mg</th>
<th>Bacteriologic Success Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>BID TID/QID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breese et al</td>
<td>444</td>
<td>500 BID (n = 228) vs 250 QID (n = 216)</td>
<td>84 (BID) 84 (TID)</td>
</tr>
<tr>
<td>Spitzer and Harris</td>
<td>327</td>
<td>500 BID (n = 173) vs 250 TID (n = 154)</td>
<td>83 (BID) 84 (TID)</td>
</tr>
<tr>
<td>Gerber et al</td>
<td>99</td>
<td>250 BID (n = 48) vs 250 TID (n = 50)</td>
<td>73 (BID) 82 (TID)</td>
</tr>
<tr>
<td>Krober et al</td>
<td>142</td>
<td>500 BID (n = 48) vs 250 QID (n = 46)</td>
<td>94 (BID) 89 (QID)</td>
</tr>
<tr>
<td>Fyllingen et al</td>
<td>206</td>
<td>660 BID (n = 101) vs 440 TID (n = 105)</td>
<td>82 (BID) 88 (TID)</td>
</tr>
<tr>
<td>Current study</td>
<td>359</td>
<td>500 BID (n = 183) vs 250 TID (n = 176)</td>
<td>72 (BID) 72 (TID)</td>
</tr>
</tbody>
</table>

*BID indicates twice daily; TID, 3 times daily; QID, 4 times daily.
†Seven days of drug therapy.
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We thank John L. Green, MD, Ann Sorrento, PNP, and Carmen Noriega, MD, for their assistance in the implementation of this study.

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