Higher Dosages of Azithromycin Are More Effective in Treatment of Group A Streptococcal Tonsillopharyngitis

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Background. Azithromycin has become a frequent choice for the treatment of group A streptococcal (GAS) tonsillopharyngitis. In this study, our objective was to determine the optimal dose of azithromycin for treatment of GAS tonsillopharyngitis in children and adults by analyzing trials that used different dose regimens.

Methods. We performed a meta-analysis of randomized, controlled trials that involved bacteriological confirmation of GAS tonsillopharyngitis, random assignment to receive either azithromycin or a 10-day comparator antibiotic, and assessment of bacteriological eradication by throat culture after therapy. The primary outcomes of interest were bacteriological and clinical cure rates.

Results. Nineteen trials involving 4626 patients were included in the analysis. One trial used 10-day course of 2 different comparator antibiotics, and 2 trials compared 2 dose regimens of azithromycin with a 10-day course of comparator antibiotic; all other trials compared 1 dose regimen of azithromycin with a single 10-day course of comparator antibiotic. In children, azithromycin administered at 60 mg/kg per course was superior to the 10-day courses of comparators \( (P < .00001) \), with bacterial failure occurring 5 times more often in patients receiving the 10-day courses of antibiotics. Azithromycin administered at 30 mg/kg per course was inferior to the 10-day courses of comparators \( (P = .02) \), with bacterial failure occurring 3 times more frequently in patients receiving azithromycin. Three-day regimens were inferior to 5-day regimens \( (P = .002) \). In adults, no studies compared dosages by weight. Three-day regimens of 500 mg/day showed a trend favoring azithromycin over the 10-day courses of comparators \( (P = .14) \); 5-day regimens were inferior to 3-day regimens \( (P = .006) \). Clinical cure rates were significantly different for the different azithromycin regimens, with differences that resembled those for bacterial cure rate.

Conclusion. This analysis suggests that azithromycin administered at a dosage of 60 mg/kg in children or administered for 3 days at a dosage of 500 mg/day in adults is more effective than other treatment regimens in producing eradication and clinical cure of GAS tonsillopharyngitis.

Streptococcus pyogenes (group A streptococcus [GAS]) is the most common bacterial cause of tonsillopharyngitis requiring treatment with antibiotics. Prevention of acute rheumatic fever is the principle goal of treatment, although antibiotic therapy may also relieve the signs and symptoms of infection, shorten the infective period, and prevent suppurative complications [1, 2]. Penicillin has been the recommended drug of choice for the treatment of GAS tonsillopharyngitis since the early 1950s [3–7]. Guidelines published by the Infectious Diseases Society of America recommend erythromycin as treatment for patients who have allergic reactions to penicillin [8]. Unfortunately, an estimated one-third of patients do not complete therapy with erythromycin because of drug-induced adverse events. The need for multiple daily doses and 10-day treatment regimens also compromises the efficacy of erythromycin therapy. Gastrointestinal adverse effects are frequent with erythromycin, and they limit its usefulness [9–11]. Because of the significant compliance barriers associated with erythromycin, azithromycin—with its convenient once-daily dosing for 3 or 5 days and its lower risk of gastrointestinal adverse events—has become a frequent choice for the treatment of GAS tonsillopharyngitis [12]. In the United States, azithromycin
is approved for treatment of GAS tonsillopharyngitis in children at a regimen of 12 mg/kg per day for 5 days; outside the United States, the approved treatment regimen for children is 10–12 mg/kg per day for 3 days. In the United States, a 5-day regimen of azithromycin is approved for treatment of GAS tonsillopharyngitis in adults; outside the United States, a 3-day regimen is approved. This study uses meta-analytic techniques to evaluate published, randomized, controlled trials involving GAS tonsillopharyngitis to determine the optimal treatment regimen for azithromycin. The results strongly suggest that regulatory agencies in the United States and Europe have licensed azithromycin for treatment durations and/or dosages that are suboptimal, compared with standard therapy.

METHODS

Randomized, controlled trials of azithromycin and a 10-day course of comparator antibiotic for the treatment of GAS tonsillopharyngitis in children and adults were identified from searches of the MEDLINE database (which contains citations from 1966 through 2004) and the Embase database (which contains citations from 1970 through 2004). The searches had no language restriction; the search terms used were "streptococcal pharyngitis," "streptococcal tonsillitis," "azithromycin," "macrolide," "cephalosporin," and "penicillin." Reference lists of included trials and relevant review articles were reviewed to identify additional trials. Abstracts from meetings of the Interscience Conference on Antimicrobial Agents and Chemotherapy, the Infectious Diseases Society of America, and the Society for Pediatric Research were searched to identify relevant trials that had not been published.

Trials comparing azithromycin therapy and a 10-day course of treatment with a comparator antibiotic for GAS tonsillopharyngitis infections were reviewed independently by the authors for inclusion according to the following criteria: bacterial confirmation of GAS tonsillopharyngitis at study enrollment; random assignment to azithromycin treatment or a 10-day course of treatment with a comparator antibiotic; and assessment of bacteriological outcome using a throat culture after therapy. The quality of the included trials was assessed using the Jadad scale. The scale assigns scores from 0 (lowest-quality trial) to 5 (highest-quality trial) on the basis of the following criteria: random allocation of treatment and specification of the appropriate method, such as a random-number table, in the text of the trial (2 points); double-blind trial design (2 points); and a complete accounting and description of study withdrawals (1 point) [13]

The primary outcome of interest was bacteriological cure, defined as the failure to isolate GAS from cultures of throat swab samples obtained after completion of the antibiotic course. Most trials had an “early” and “late” follow-up evaluation; when possible, the “early” follow-up result was used in this analysis. The secondary outcome of interest was clinical cure, defined as the absence of GAS on throat culture and the resolution of or improvement in the presenting signs and symptoms of GAS infection on completion of the antibiotic course and throughout follow-up.

This meta-analysis was conducted using Revman, version 4.2 (Cochrane). Differences in bacteriological cure rates after azithromycin treatment, compared with after 10-day courses of antibiotic treatment, were calculated and expressed as ORs with 95% CIs. An OR of >1 indicated a higher bacteriological cure rate for the azithromycin treatment than for the 10-day courses of antibiotic treatment. ORs were calculated for individual trial outcomes, and a summary OR was determined for trials grouped into pediatric and adult trials and further grouped by dose (30 mg/kg total treatment dose vs. 60 mg/kg total treatment dose) and by duration of azithromycin treatment (3 days vs. 5 days). Two methods were used to calculate ORs: the Peto fixed-effects model [14], which assumes trial homogeneity, and the DerSimonian and Laird random-effects model [15], which assumes trial heterogeneity. Statistical heterogeneity among the trials was assessed by χ² analysis [16, 17].

RESULTS

The MEDLINE and Embase searches yielded 56 citations, 38 of which were randomized, clinical trials that compared a short-course treatment (i.e., <10 days) with a 10-day treatment course for GAS tonsillopharyngitis. Six trials were identified from reference listings. Forty-four citations were further assessed according to the inclusion criteria. Twenty-five of these trials were excluded from the meta-analysis for the following reasons: the short-course treatment did not use azithromycin; the data presented were a re-publication of previous data already present in trials included in the meta-analysis; or the publication could not be obtained for review. This left 19 publications [18–36]; of these, 1 publication used 10-day courses of 2 different comparator antibiotics [24], 2 publications used 2 different dose regimens for azithromycin [22, 27], and 3 publications were abstracts presented at national conferences [29–31].

Fourteen of the 19 trials were pediatric studies, and 5 were adult trials (table 1). Six different antibiotics were used as comparator drugs, with penicillin being used most frequently (in 10 of the trials). The total dose of azithromycin was either 30 mg/kg (given as 10 mg/kg per day for 3 days or 10 mg/kg per day on day 1 and 5 mg/kg per day for days 2–5) or 60 mg/kg (given as 20 mg/kg for 3 days or 12 mg/kg /day for 5 days) in the pediatric trials. In the adult trials, the azithromycin dosage was either 500 mg on day 1 and 250 mg on days 2–5 (for 5-day regimens) or 500 mg on days 1–3 (for 3-day regimens). For the 19 trials of azithromycin, the duration of treatment was 3 days in 15 trials and 5 days in 4 trials.

Table 1 also details the methodological aspects of the in-
# Table 1. Methodological details of trials comparing azithromycin therapy with 10-day comparator antibiotic therapy for treatment of group A streptococcal (GAS) tonsillopharyngitis.

<table>
<thead>
<tr>
<th>Trial subjects, study</th>
<th>Azithromycin course (no. of subjects)</th>
<th>Comparator antibiotic (no. of subjects)</th>
<th>QS</th>
<th>Concealment of treatment allocation</th>
<th>Clinical status</th>
<th>Compliance monitoring</th>
<th>Serotyping performed</th>
<th>Test-of-cure day&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Pediatric</td>
<td></td>
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<tr>
<td>Hamill [18]</td>
<td>10 mg/kg per day for 3 days (41)</td>
<td>Penicillin V (44)</td>
<td>2</td>
<td>Open-label</td>
<td>No details</td>
<td>Not reported</td>
<td>Yes</td>
<td>9–11 days</td>
</tr>
<tr>
<td>Weippl [19]</td>
<td>10 mg/kg per day for 3 days (44)</td>
<td>Erythromycin estolate (46)</td>
<td>2</td>
<td>Open-label</td>
<td>No details</td>
<td>Not reported</td>
<td>No</td>
<td>10–11 days</td>
</tr>
<tr>
<td>Pacifico et al. [20]</td>
<td>10 mg/kg per day for 3 days (76)</td>
<td>Penicillin V (78)</td>
<td>3</td>
<td>Open-label</td>
<td>Detailed</td>
<td>TC, RC</td>
<td>Yes</td>
<td>12–14 days</td>
</tr>
<tr>
<td>Schaad and Heynen [21]</td>
<td>10 mg/kg per day for 3 days (160)</td>
<td>Penicillin V (160)</td>
<td>3</td>
<td>Open-label</td>
<td>Detailed</td>
<td>PQ</td>
<td>Yes</td>
<td>9–20 days</td>
</tr>
<tr>
<td>O’Doherty [22]</td>
<td>10 mg/kg per day for 3 days (123); 20 mg/kg per day for 3 days (103)</td>
<td>Penicillin V (132)</td>
<td>4</td>
<td>Double-blind</td>
<td>No details</td>
<td>TC</td>
<td>Yes</td>
<td>12–14 days</td>
</tr>
<tr>
<td>Padilla-Raygoza [23]</td>
<td>10 mg/kg per day for 3 days (112)</td>
<td>Clarithromycin (99)</td>
<td>1</td>
<td>Open-label</td>
<td>No details</td>
<td>Not reported</td>
<td>No</td>
<td>3 days</td>
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<tr>
<td>Garcia Callejo et al. [24]</td>
<td>10 mg/kg per day for 3 days (74)</td>
<td>Amoxicillin-clavulanate (19); Cefaclor (12)</td>
<td>2</td>
<td>Open-label</td>
<td>Detailed</td>
<td>No details</td>
<td>No</td>
<td>14 days</td>
</tr>
<tr>
<td>Venuta et al. [25]</td>
<td>10 mg/kg per day for 3 days (74)</td>
<td>Clarithromycin (63)</td>
<td>2</td>
<td>Investigator blinded</td>
<td>Detailed</td>
<td>No details</td>
<td>Yes</td>
<td>17–20 days</td>
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<td>Cremer et al. [26]</td>
<td>10 mg/kg per day for 3 days (52)</td>
<td>Cefaclor (46)</td>
<td>2</td>
<td>Open-label</td>
<td>No details</td>
<td>Not reported</td>
<td>Yes</td>
<td>7–25 days</td>
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<td>Cohen et al. [27]</td>
<td>10 mg/kg per day for 3 days (135); 20 mg/kg per day for 3 days (139)</td>
<td>Penicillin V (146)</td>
<td>3</td>
<td>Azithromycin; arms, double-blind</td>
<td>Detailed</td>
<td>TC, RS</td>
<td>Yes, DNA</td>
<td>4–11 days</td>
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<tr>
<td>Schaad et al. [28]</td>
<td>10 mg/kg per day for 3 days (141)</td>
<td>Penicillin V (130)</td>
<td>2</td>
<td>Open-label</td>
<td>No details</td>
<td>Not reported</td>
<td>Yes</td>
<td>4–9 days</td>
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<tr>
<td>Still [29]</td>
<td>10 mg/kg on 1 day and 5 mg/kg per day on days 2–5 days (81)</td>
<td>Penicillin V (87)</td>
<td>Abstract</td>
<td>Open-label</td>
<td>No details</td>
<td>Not reported</td>
<td>No</td>
<td>11 days</td>
</tr>
<tr>
<td>Still [30]</td>
<td>12 mg/kg per day for 5 days (176)</td>
<td>Penicillin V (190)</td>
<td>Abstract</td>
<td>Double-blind</td>
<td>No details</td>
<td>Not reported</td>
<td>No</td>
<td>14 days</td>
</tr>
<tr>
<td>Still [31]</td>
<td>12 mg/kg per day for 5 days (147)</td>
<td>Penicillin V (127)</td>
<td>Abstract</td>
<td>Double-blind</td>
<td>No details</td>
<td>Not reported</td>
<td>No</td>
<td>14 days</td>
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<tr>
<td>Adult</td>
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<td>Muller [32]</td>
<td>500 mg per day for 3 days (71)</td>
<td>Clarithromycin (73)</td>
<td>2</td>
<td>Open-label</td>
<td>No details</td>
<td>Not reported</td>
<td>No</td>
<td>10–14 days</td>
</tr>
<tr>
<td>Muller [33]</td>
<td>500 mg per day for 3 days (74)</td>
<td>Roxithromycin (63)</td>
<td>2</td>
<td>Open-label</td>
<td>No details</td>
<td>Not reported</td>
<td>No</td>
<td>11–15 days</td>
</tr>
<tr>
<td>O’Doherty [34]</td>
<td>500 mg per day for 3 days (117)</td>
<td>Cefaclor (119)</td>
<td>2</td>
<td>Open-label</td>
<td>No details</td>
<td>Not reported</td>
<td>No</td>
<td>11–15 days</td>
</tr>
<tr>
<td>Hooten [35]</td>
<td>500 mg on day 1 and 250 mg on days 2–5 (152)</td>
<td>Penicillin (90)</td>
<td>3</td>
<td>Open-label</td>
<td>No details</td>
<td>Not reported</td>
<td>No</td>
<td>11 days</td>
</tr>
<tr>
<td>Kaplan et al. [36]</td>
<td>500 mg on day 1 and 250 mg on days 2–5 (198)</td>
<td>Clarithromycin (194)</td>
<td>3</td>
<td>Investigator blinded</td>
<td>Detailed</td>
<td>TC</td>
<td>Yes</td>
<td>13–19 days</td>
</tr>
</tbody>
</table>

<sup>a</sup> Test-of-cure day is recorded as day after start of medication.

NOTE. PQ, patient/parent questioned; QS, Jadad quality score; RC, record card; TC, tablet count.
cluded trials. The mean Jadad quality score (± SD) for the trials, excluding the abstracts, was 2.5 (± .8), out of a maximum score of 5; 38% of the trials were of relatively high quality (Jadad score, >2). One trial [22] was double-blind, and another trial [27] had the azithromycin arms blinded. The investigators were blinded to treatment allocation in 2 other trials [25, 36]. Five of the trials [29–31, 35, 36] were conducted in multiple outpatient treatment sites in the United States. The remaining trials were conducted in 7 countries other than the United States. All trials required isolation of GAS from a throat culture for inclusion in the study. Most trials used rapid antigen testing at enrollment but excluded patients from the study if the throat culture did not grow GAS. Fifteen of the trials gave detailed descriptions of the clinical signs and symptoms of the study subjects at enrollment. Detailed compliance monitoring was performed in 7 of the trials; 2 trials [25, 27] reported a statistical difference in compliance favoring the azithromycin treatment. Serotyping or genotyping of GAS at enrollment and again if GAS was isolated at a follow-up visit was performed in 8 trials. True bacterial failure rates from these 8 trials were used in this meta-analysis. The timing of the test-of-cure follow-up culture varied among the trials; most trials had an early and a late follow-up visit and culture. When possible, bacteriological and clinical cure rates used in this meta-analysis were taken from the early follow-up test-of-cure visit.

The primary outcome analyzed was bacterial cure rate. The studies were grouped into pediatric trials and adult trials and were further classified by azithromycin dose (either 30-mg/kg total dose or 60-mg/kg total dose) and by duration of azithromycin treatment (either 3 or 5 days) (figures 1–3). When the pediatric trials were analyzed according to the total treatment dose of azithromycin, there was a striking difference in outcome. The summary OR for bacterial cure rate favored the comparator regimen when the total azithromycin dose was 30 mg/kg (OR, 0.47; 95% CI, 0.24–0.91; P = .02). Conversely, when the total azithromycin dose was 60 mg/kg, the summary OR for bacterial cure rate significantly favored azithromycin (OR, 5.27; 95% CI, 3.34–8.32; P < .00001) (figure 1). All 5 adult trials, involving a total of 1070 patients, evaluated only the 30-mg/kg total dose of azithromycin. In these trials, the bacterial cure rate favored neither azithromycin nor the comparators (summary OR, 0.86; 95% CI, 0.37–1.99; P = .73) (figure 2).

Results of the pediatric trials, analyzed according to the length of azithromycin treatment (3 or 5 days), are shown in figure 3. The bacterial cure rate favored neither the comparators nor azithromycin when the 3-day azithromycin trials were analyzed (summary OR, 0.62; 95% CI, 0.30–1.27; P = .19) but favored azithromycin when the 5-day trials were analyzed (summary OR, 4.37; 95% CI, 1.70–11.27; P = .002). In adults, the 3-day trials (all with 500 mg/day dosing) had bacterial cure rates favoring neither azithromycin nor the comparators (summary OR, 1.87; 95% CI, 0.81–4.27; P = .14). However, the 10-day courses of comparators were statistically superior to the 5-day course of azithromycin (known as the “Z Pak”) (OR, 0.41; 95% CI, 0.22–0.78; P = .006) (figure 2).

All trials reported clinical cure rates. The studies were grouped into pediatric trials and adult trials and were further divided according to dose (either 30-mg/kg total dose or 60-

![Figure 1. Bacterial cure rates in pediatric trials comparing azithromycin therapy with 10-day comparator antibiotic therapy (10-day comp) for treatment of group A streptococcal tonsillopharyngitis. Studies are grouped according to total treatment dose of azithromycin (30 mg/kg or 60 mg/kg).](image-url)
Figure 2. Bacterial cure rates in adult trials comparing azithromycin therapy with 10-day comparator antibiotic therapy (10-day comp) for treatment of group A streptococcal tonsillopharyngitis. All studies used a total treatment dose of azithromycin of 30 mg/kg. Comparisons are shown for all trials and for trials grouped according to whether a 3-day or 5-day course of azithromycin was used.

mg/kg total dose) and duration of treatment (either 3 or 5 days). When the pediatric trials were divided according to the azithromycin total treatment dose, there was a difference in outcome. The summary OR for clinical cure rate favored neither the comparator regimen nor the 30-mg/kg total azithromycin dose (summary OR, 0.92; 95% CI, 0.46–1.83; \( P = .80 \)), but the 60-mg/kg total azithromycin dose significantly favored azithromycin (summary OR, 7.51; 95% CI, 3.66–15.39; \( P < .00001 \)). The clinical cure rate favored neither azithromycin treatment nor the 10-day courses of comparators in adults (summary OR, 0.86; 95% CI, 0.37–1.99; \( P = .73 \)).

The clinical cure rate favored neither azithromycin nor the comparators when the 3-day azithromycin pediatric trials were analyzed (summary OR, 1.04; 95% CI, 0.51–2.13; \( P = .91 \)) and

Figure 3. Bacterial cure rates in pediatric trials comparing azithromycin therapy with 10-day comparator antibiotic therapy (10-day comp) for treatment of group A streptococcal tonsillopharyngitis. Studies are grouped according to whether a 3-day or 5-day course of azithromycin was used.
favored azithromycin when the 5-day pediatric trials were analyzed (summary OR, 6.80; 95% CI, 3.30–14.01; P < .00001). The 3-day (summary OR, 0.56; 95% CI, 0.22–1.46; P = .23) and 5-day (summary OR, 1.53; 95% CI, 0.69–3.38; P = .29) adult trial clinical cure rates favored neither azithromycin nor the comparators.

There was significant heterogeneity among the pediatric trials. To evaluate this heterogeneity further, the 7 pediatric trials using penicillin as a comparator were grouped and analyzed; the bacterial cure rate favored neither azithromycin nor the 10-day penicillin therapy (OR, 0.49; 95% CI, 0.20–1.17), and statistical heterogeneity persisted (P < .00001). With a jackknife analysis (in which studies are eliminated from the analysis one at a time and then in groups), statistical heterogeneity persisted until 3 of the studies with the widest 95% CIs [22, 24, 31] were excluded.

DISCUSSION

This paper examined the results of azithromycin trials involving children and adults with GAS tonsillopharyngitis. We found that, in pediatric trials, a total dose of 60 mg/kg (administered either as 20 mg/kg for 3 days or 12 mg/kg for 5 days) was superior to the 10-day comparator antibiotic therapy (with penicillin, erythromycin estolate, amoxicillin–clavulanate, cefaclor, or clarithromycin) in bacteriological eradication. In contrast, an azithromycin total dose of 30 mg/kg (administered as either 10 mg/kg for 3 days or 10 mg/kg for 1 day followed by 5 mg/kg for 4 days) resulted in bacteriological eradication that was inferior to that achieved with the 10-day comparator antibiotic therapy.

In adults, only the 30 mg/kg total azithromycin dose was compared with a 10-day antibiotic regimen, and we found bacteriological eradication rates favored neither azithromycin nor the comparators. However, results achieved with the US-approved 5-day azithromycin dose schedule (“Z Pak”) were significantly inferior to those achieved with the 10-day comparator therapy (P = .006). Paradoxically, the 3-day regimen approved outside the United States for azithromycin treatment (using the same total dose as the 5-day regimen) neared a significantly better outcome, compared with that for the 10-day comparator treatment. However, the width of the 95% CI makes it difficult to conclude superiority for either treatment regimen. The 3 trials involving 3-day treatment were conducted in Europe, and the 2 trials involving 5-day treatment were conducted in the United States. At the time the studies were conducted, macrolide-resistant GAS strains were not widely prevalent in Europe or the United States.

Patients with GAS tonsillopharyngitis experience clinical improvement over time, with or without antibiotic therapy. Therefore, measurement of clinical response during treatment is largely meaningless in antibiotic trials. However, after comple-

- Adverse events are a common reason for poor patient com-
pliance and for increases in overall treatment costs associated with additional physician visits, medications, and monitoring. Shortened-course treatment has been shown to reduce the number of adverse events associated with antibiotic therapy [52, 53]. Overall, the trials included in this analysis did not show a difference in the number of adverse events associated with the different treatment courses, and the 2 trials that compared 2 different dosages of azithromycin [22, 27] showed no association between an increase in adverse events and a higher dosage.

Although macrolide-resistant GAS was not prevalent when the azithromycin trials were conducted, it is a growing problem worldwide and in the United States [54–58]. An additional important advantage of shortened-course antibiotic treatment is the reduced impact on the development of antibiotic resistance and nasopharyngeal colonization with resistant bacteria. Guillemot et al. [59] showed that inappropriately low dosages of aminopenicillins or third-generation cephalosporins administered to children (such as might occur in the later half of a 10-day treatment course, when patient compliance decreases) is associated with an increased risk of penicillin-resistant Streptococcus pneumoniae nasopharyngeal carriage. In addition, their findings showed that a longer duration of treatment was associated with an increased risk of drug-resistant S. pneumoniae carriage. Cohen et al. [27] showed a lower rate of macrolide resistance among GAS isolates after administration of a 60-mg/kg total treatment dose than after a 30-mg/kg total treatment dose. Higher azithromycin doses for shorter treatment courses may result in higher concentrations of the drug in tonsillar tissue and could positively impact the development of macrolide resistance.

In conclusion, this analysis of—to the best of our knowledge—all published, randomized trials of azithromycin treatment for GAS tonsillopharyngitis shows that a total treatment dose of 60 mg/kg is needed to adequately eradicate GAS tonsillopharyngitis in children. Adults trials show that a 3-day, 500-mg/day regimen of azithromycin is superior to other regimens in eradicating GAS tonsillopharyngitis. Azithromycin therapy for GAS tonsillopharyngitis has the potential to result in better compliance, and because macrolides concentrate in nasopharyngeal tissues, including tonsillar tissues, higher dosages should result in higher bacterial eradication rates; this may have a positive impact on the emergence of macrolide resistance. The issue of macrolide resistance in GAS isolates may be the limiting factor in determining azithromycin’s usefulness for treating GAS tonsillopharyngitis in the future.

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References


