# Azithromycin Is as Effective as and Better Tolerated Than Erythromycin Estolate for the Treatment of Pertussis

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**ABSTRACT.** *Objective.* **Although universal immunization against *Bordetella pertussis* (whooping cough) infection has resulted in dramatic reductions in the incidence of pertussis, outbreaks continue to occur in countries with excellent vaccine coverage. Treatment of infection may ameliorate symptom severity during the catarrhal phase of pertussis but has no effect on established paroxysms, emesis, or apnea if given during the paroxysmal or convalescent phases. Erythromycin, recommended for treatment of pertussis to prevent transmission of infection, is poorly tolerated because of gastrointestinal side effects. We compared the safety and efficacy of erythromycin with azithromycin for treatment of pertussis in a large, randomized, controlled trial that enrolled children from primary care practices in 1 American and 11 Canadian urban centers.**

*Methods.* **Children who were 6 months to 16 years of age and had cough illness that was suspected to be or was culture confirmed as pertussis were randomized to azithromycin (10 mg/kg on day 1 and 5 mg/kg on days 2–5 as a single dose) or erythromycin estolate (40 mg/kg/day in 3 divided doses for 10 days) with stratification by center. The primary outcome measure was bacteriologic cure of infection as determined by cultures of nasopharyngeal aspirates. Culture-positive participants had a second aspirate collected at the end of therapy (days 5–7 for azithromycin, days 10–12 for erythromycin) and 1 week after therapy. Bacteriologic cure was defined as negative cultures at the end of therapy. Bacteriologic relapse was defined as a positive culture 1 week after completion of therapy and after a negative end-of-therapy culture. Secondary outcomes were pertussis diagnosed by serology and polymerase chain reaction (PCR), treatment-associated adverse events, compliance, and presence of clinical symptoms at the end of the treatment course. Serology was performed using standard enzyme-linked immunosorbent assay methods. A participant was considered to have pertussis when the PCR was positive or a 4-fold increase in pertussis toxin antibody between baseline and follow-up visits was observed. PCR was performed using a 1046-bp ClaI DNA fragment from *B pertussis*.**

**Adverse events (nausea, vomiting, diarrhea, any gastrointestinal complaint, or other) were determined by a parent-completed diary that was reviewed with study personnel during study visits. Compliance was measured by review of the parent medication diary during study visits and observation of medication containers by the pharmacist at study completion. Symptoms were determined by history collected by study personnel at enrollment and subsequently from the diary. The design of the study was an equivalence trial, aimed at demonstrating that the bacteriologic failure rates with the 2 therapies did not differ by >8%. For the safety analysis, all participants who received at least 1 dose of study drug were included. In the per-protocol efficacy analysis, all culture-positive participants with end-of-treatment cultures were considered.**

*Results.* **A total of 477 children were enrolled and randomly assigned to either azithromycin (*n* = 239) or erythromycin (*n* = 238). Of these children, 114 (24%) grew *B pertussis* from nasopharyngeal specimens (azithromycin group: 58 of 239 [24%]; erythromycin group: 56 of 238 [23%]); these children composed the efficacy cohort for the per-protocol and intention-to-treat analyses. Serology and PCR added 52 children to the number considered to have pertussis for a total of 35% (166 of 477) of all children who presented with cough illness. In the safety analysis (antibiotic side effects, compliance) and comparison of cough symptoms after treatment, all randomized children are reported in their assigned treatment group. At end of therapy, bacterial eradication was demonstrated in all 53 patients in the azithromycin group and all 53 patients in the erythromycin group with follow-up cultures available (eradication 100%; 95% confidence interval [CI]: 93.3–100). No bacterial recurrence was demonstrated in children with 1 week posttreatment nasopharyngeal cultures available (51 and 53 participants in the azithromycin and erythromycin arms, respectively [0%, 95% CI: 0–7.0; and 0%, 95% CI: 0–6.7]). No serious adverse events attributable to study drug were observed. Gastrointestinal adverse events were reported less frequently in azithromycin (18.8%; 45 of 239) than in erythromycin estolate (41.2%; 98 of 238) recipients (90% CI on difference: −29.0% to −15.7%) as a result of less nausea (2.9% vs 8.4%; 95% CI: −8.9% to −2.0%), less vomiting (5.0% vs 13.0%; 95% CI: −4.9% to −1.4%), and less diarrhea (7.1% vs 11.8%; 95% CI: −9.0% to −0.3%). Children who were randomized to azithromycin were much more likely to have complied with antimicrobial therapy over the treatment period. In the azithromycin group, 90% of children took 100% of prescribed doses, whereas only 55% of children in the erythromycin group took 100% of prescribed doses.**

*Conclusions.* **In this large, multicenter, randomized trial, we found that azithromycin is as effective as erythromycin estolate for the treatment of pertussis in chil-**

**dren. Gastrointestinal adverse events were much more common with erythromycin treatment than azithromycin. Compliance with therapy was markedly better with azithromycin than with erythromycin in this study.** *Pediatrics* **2004;114:e96–e101. URL: http://www.pediatrics. org/cgi/content/full/114/1/e96; Bordetella pertussis,** *macrolides, respiratory tract infection.*

ABBREVIATIONS. PCR, polymerase chain reaction; CI, confidence interval.

Although universal immunization against *Bordetella pertussis* (whooping cough) infection has resulted in dramatic reductions in the incidence of pertussis,[1] outbreaks continue to occur in countries with excellent vaccine coverage[2–5] and are associated with morbidity and mortality.[6–8] Treatment given during the catarrhal phase of pertussis may ameliorate symptom severity[9] but has no effect on paroxysms, emesis, or apnea associated with cough illness if given during the paroxysmal or convalescent phases. The rationale for antibiotic treatment of suspected or proven pertussis is to prevent transmission of infection by eradicating the bacteria from the nasopharynx.

Erythromycin is recommended as the drug of choice for the prophylaxis and treatment of pertussis,[10] although it is poorly tolerated because of gastrointestinal side effects in up to 30% of patients,[11,12] which may lead to noncompliance with therapy.[13] Newer macrolide antimicrobials such as azithromycin and clarithromycin are better tolerated and offer the advantage of less frequent dosing and shorter duration of therapy, factors associated with improved antibiotic compliance.[14] We compared the safety and efficacy of azithromycin with erythromycin estolate in the treatment of pertussis in a large, randomized trial that enrolled children from 11 sites across Canada and 1 in the United States from 1995 to 1998.

## METHODS

The protocol was designed in 1995. Our main purpose was to determine whether azithromycin was as effective as erythromycin estolate in the treatment of pertussis, using bacterial eradication from the nasopharynx as the primary outcome measure.

### Participants

Eligible children were aged 6 months to 16 years and had either culture-proven *B pertussis* infection or a cough illness suspected by a physician to be pertussis that met the definition for a suspect case. A suspect case was a child with at least 1 of the following: 1) paroxysmal cough of any duration; 2) cough with inspiratory whoop; 3) cough ending in apnea, vomiting, or gagging with no other known cause; or 4) cough of any type in a child in contact with a culture-proven case of pertussis.

Children were not eligible when they had known allergy to any macrolide antimicrobial; immunodeficiency; had hepatic, renal, cardiovascular, or hematologic disease; had underlying lung disease with chronic symptoms; had gastrointestinal absorption disorder; had concomitant use of theophylline, digitalis, phenytoin, cyclosporin, carbamazepine, warfarin, triazolam, terfenadine, astemizole, ergot alkaloids, or zidovudine; or were already receiving macrolide, chloramphenicol, tetracycline, trimethoprim-sulfamethoxazole, or clindamycin.

Children were recruited through the primary care practices of physicians in 1 American and 11 Canadian urban centers. All participants or their parents gave written informed consent. The

study was approved by the local research ethics boards in all participating centers.

### Interventions

Children who were assigned to azithromycin received 10 mg/kg (maximum: 500 mg) by mouth on the first day of treatment and 5 mg/kg (maximum daily dose: 250 mg) once daily on the second to fifth days of treatment. In the erythromycin group, 3 doses of erythromycin estolate (40 mg/kg/day; maximum: 1 g) were given by mouth for 10 days.[15] Parents/guardians were instructed not to administer any medication other than acetaminophen or ibuprofen until after the last study visit had been completed.

### Randomization

Participants were randomly assigned to 2 parallel groups, the erythromycin and azithromycin groups, with stratification by center. A computer-generated randomization list was prepared by the statistician and provided to each center's pharmacy. The interventions were assigned by the pharmacist, and the allocation sequence was concealed from other study personnel until after the child was enrolled. Because of the differences in duration of therapy, dosing, and ease of product recognition, group assignment was not blinded after randomization.

### Outcomes

The primary outcome measure was bacteriologic cure of infection as determined by cultures of nasopharyngeal aspirates for *B pertussis*. Culture-positive participants had a second aspirate collected at the end of therapy (days 5–7 for azithromycin, days 10–12 for erythromycin) and 1 week after therapy. Collection of nasopharyngeal aspirates and inoculation of specimens for *B pertussis* culture were performed according to standard methods.[16–18] Bacteriologic cure was defined as negative cultures at the end of therapy. Bacteriologic relapse was defined as a positive culture 1 week after completion of therapy and after a negative end-of-therapy culture.

Secondary outcome measures were pertussis diagnosed by serology and polymerase chain reaction (PCR), treatment-associated adverse events, compliance, and presence of clinical symptoms at the end of the treatment course. Serology was performed using standard enzyme-linked immunosorbent assay methods.[19] A participant was considered to have pertussis when the PCR was positive or a 4-fold increase in pertussis toxin antibody between baseline (visit 1) and follow-up visits (visit 4) was observed. PCR using a 1046-bp ClaI DNA fragment from *B pertussis* was performed.[20] Adverse events (nausea, vomiting, diarrhea, any gastrointestinal complaint, or other) were determined by a parent-completed diary that was reviewed with study personnel during study visits. Compliance was measured by review of the parent medication diary during study visits and observation of medication containers by the pharmacist at study completion. Symptoms were determined by history collected by study personnel at enrollment and subsequently from the diary.

### Statistical Methods

The design of the study was an equivalence trial, aimed at demonstrating that the bacteriologic failure rates with the 2 therapies did not differ by >8%. For the safety analysis, all participants who received at least 1 dose of study drug were included. For the efficacy analysis, we performed intention-to-treat analysis and per-protocol analyses in culture-positive participants. In the per-protocol analysis, all culture-positive participants with end-of-treatment cultures were considered. In the intention-to-treat analysis, all culture-positive participants who received at least 1 dose of study drug were considered. We also report the prevalence of pre- and posttreatment cough-related symptoms in those who had laboratory-confirmed pertussis (culture and/or serology and/or PCR) in both treatment groups.

Baseline characteristics of treatment groups were compared using Fisher exact and *t* tests. Rates of bacteriologic failure were estimated by treatment group, together with exact binomial confidence intervals (CIs). Following Baughman et al,[21] the hypothesis of equivalence is rejected when a 90% 2-sided CI for the observed difference in rates is not contained in the equivalence interval (−8% to 8%). Unless otherwise specified, the intervals

reported are the simple asymptotic intervals.[22] Adverse events rates were estimated and compared in the same manner. The software program SAS Version 8.2 (SAS Institute Inc, Cary, NC) was used for these analyses.

## RESULTS

A total of 477 children were enrolled and randomly assigned to either azithromycin ($n$ = 239) or erythromycin ($n$ = 238; Fig 1). Of these children, 114 (24%) grew *B pertussis* from nasopharyngeal specimens (azithromycin group: 58 of 239 [24%]; erythromycin group: 56 of 238 [23%]); these children composed the efficacy cohort for the per-protocol and intention-to-treat analyses. Serology and PCR added 52 children to the number considered to have pertussis for a total of 35% (166 of 477) of all children who presented with cough illness. In the safety analysis (antibiotic side effects, compliance) and comparison of cough symptoms after treatment, all randomized children are reported in their assigned treatment group.

At enrollment, there were no differences between children who were assigned to erythromycin or azithromycin in the following characteristics: mean age (6.2 vs 6 years), gender (53% vs. 54% female), ethnicity (4.6% vs 5% nonwhite), previous number of pertussis vaccine doses received (mean 4.4 vs 4.1), or proportion having received antibacterial therapy within the previous 30 days (13.2% vs 15%). In the per-protocol cohort at baseline, there were no significant differences in the prevalence of cough-related symptoms between the azithromycin and erythromycin arms at baseline: paroxysmal cough (67% vs 73%), cough with vomiting (36% vs 34%), cough with whoop (66% vs 59%), and cough with apnea/and or cyanosis (48% vs 47%). There were no significant differences in the prevalence of cough-related symptoms in the intention-to-treat analysis: for paroxysmal cough (azithromycin 80.8% vs erythromycin 80.3%), cough with vomiting (29.3% vs 34%), cough

with whoop (68.6% vs 65.5%), or cough with apnea/cyanosis (34.3% vs 33.8%).

### Efficacy

At the end of therapy, bacterial eradication was demonstrated in all patients in the azithromycin and erythromycin groups for whom cultures were available (53 of 53 vs 53 of 53; eradication 100%; 95% CI: 93.3–100). No bacterial recurrence was demonstrated in the 51 patients in the azithromycin group (0%; 95% CI: 0–7.0) or the 53 patients in the erythromycin group (0%; 95% CI: 0–6.7) with 1 week posttreatment cultures available.

In the intention-to-treat analysis, the children who did not have cultures at the end of therapy ($n$ = 5 azithromycin, $n$ = 3 erythromycin) or 1 week after treatment ($n$ = 6 azithromycin, $n$ = 5 erythromycin) were assumed to be treatment failures. Participants with protocol deviations or violations were also assumed to have failed therapy. In this comparison, azithromycin was theoretically less effective than erythromycin in eradicating *B pertussis* at the end of treatment (93.2% vs 94.6% eradication; 95% CI: 83.5–98.1 vs 85.1–98.9; 90% CI on difference: −8.73 to 5.89) and may have had a higher recurrence rate at 1 week posttreatment (10.2% vs 5.4%; 95% CI: 3.9–20.8 vs 1.1–14.9; 90% CI on difference: 3.34–12.96). In the intention-to-treat cohort, exact 90% CI on the eradication rate was −16.2 to 12.1 and on the recurrence rate was −9.0 to 19.7.

At study completion, cough-related symptoms persisted in many children with laboratory-confirmed pertussis (culture and/or serology and/or PCR) and in those with undiagnosed cough illness (Fig 2). However, the prevalence of cough-related symptoms had decreased in all children, whether analyzed according to their treatment group or laboratory diagnosis. Equivalence testing of the prevalence of each symptom at study completion for the
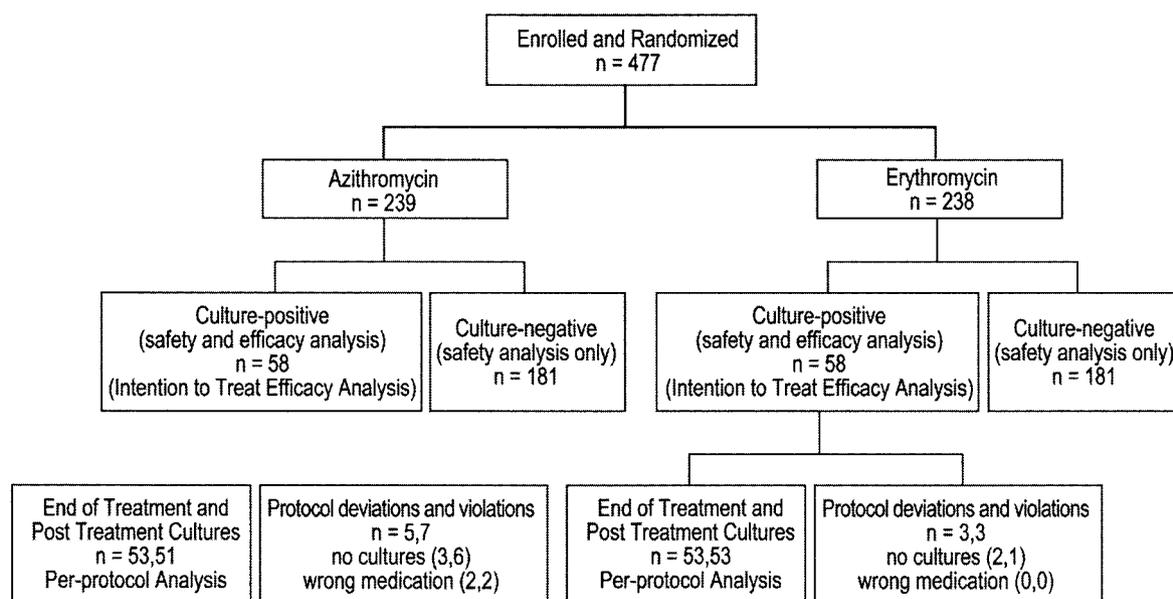


**Fig 1.** A randomized controlled trial of erythromycin compared with azithromycin for the treatment of pertussis: participant flow.
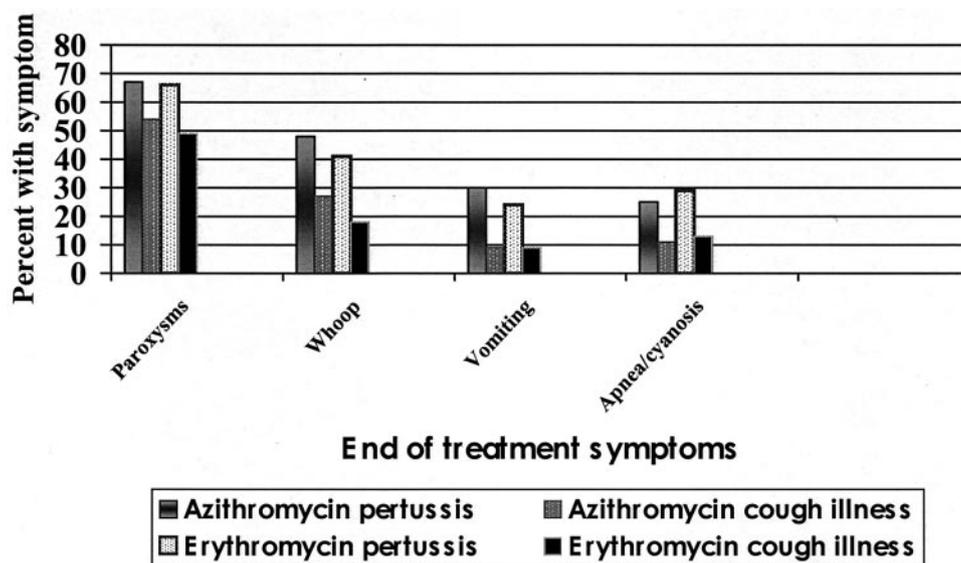
**Fig 2.** Prevalence of cough-related symptoms at the end of treatment. Children who were 6 months to 18 years of age and had suspected pertussis were randomized to erythromycin or azithromycin (*n* = 477). Within these 2 groupings, histogram bars show children who had pertussis confirmed in the laboratory with culture, PCR, or serology (azithromycin or erythromycin, pertussis) or children with cough illness in which pertussis was not diagnosed (azithromycin or erythromycin, cough illness).

azithromycin and erythromycin groups yielded the following results: paroxysmal cough (67.5% vs 66.3%; CI: −10.8% to 13.2%), vomiting (30% vs 24.4%; CI: −5.8% to 16.9%), and apnea/cyanosis (28.8% vs 25.6%; CI: −8.2% to 14.5%); prevalence of whoop was decreased (41.3% vs 48.8%; CI: −20.2% to 5.1%).

**Safety**

Gastrointestinal adverse events were reported less frequently in azithromycin (18.8%; 45 of 239) than in erythromycin estolate (41.2%; 98 of 238) recipients (90% CI on difference: −29.0% to −15.7%) as a result of less nausea (2.9% vs 8.4%; CI: −8.9% to −2.0%), less vomiting (5.0% vs 13.0%; CI: −4.9% to −1.4%), and less diarrhea (7.1% vs 11.8%; CI: −9.0% to −0.3%; Fig 3).

Four serious adverse events were reported, but none was designated as being related to the study drug. Three events occurred in recipients of erythromycin and 1 in a child randomized to azithromycin. The events were dehydration associated with a viral illness 2 weeks after completion of treatment, hospital admission for croup in 1 instance and for pneumonia in another, and progression of cough illness on the study drug.

Children who were randomized to azithromycin were much more likely to have complied with antimicrobial therapy during the treatment period (Fig 4). In the azithromycin group, 90% of children took 100% of prescribed doses compared with 55% of the erythromycin group.

**CONCLUSIONS**

In this large, multicenter, randomized trial, we found that azithromycin is as effective as and better tolerated than erythromycin estolate for the treatment of pertussis in children. We reported both intention-to-treat and per-protocol analyses, as is rec-
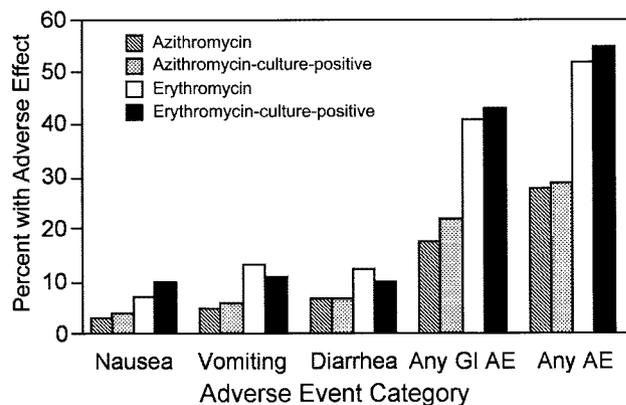


**Fig 3.** Adverse events in children who were 6 months to 18 years of age and had suspected pertussis and were randomized to erythromycin or azithromycin (*n* = 477). Children are presented according to the following groupings: Azithromycin, all children who were randomized to this treatment; Azithro culture-positive, all children who were randomized to azithromycin with *B pertussis* confirmed on culture; Erythromycin, all children who were randomized to this treatment; Erythro culture-positive, all children who were randomized to erythromycin with *B pertussis* confirmed on culture. AE, adverse event; GI, gastrointestinal.

ommended for the reporting of randomized clinical trials.[23] In our per-protocol analyses, we evaluated only children who had nasopharyngeal cultures after treatment, because bacterial eradication was our primary outcome measure, and no children failed therapy in either group. In the intention-to-treat analysis in which children who did not get their culture to assess bacterial eradication were assumed to have failed therapy, the estimates of bacterial eradication were high (93.1% for azithromycin and 94.6% for erythromycin). We suggest that this is strong evidence that azithromycin is as effective as erythromycin estolate for the treatment of pertussis in children.

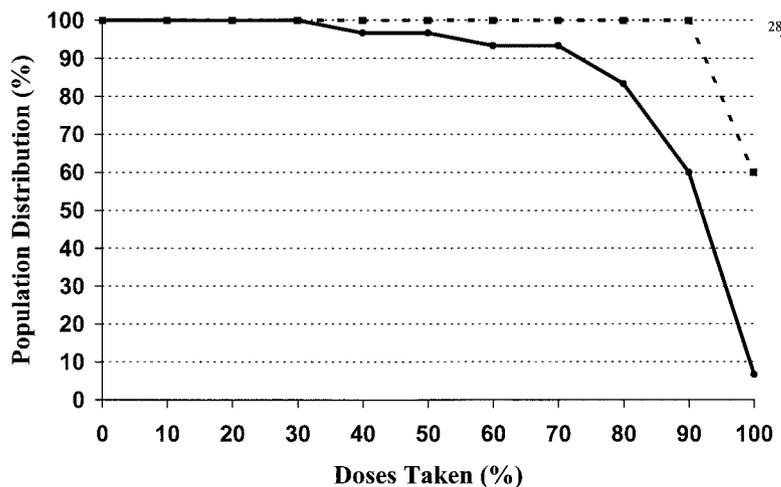Nasopharyngeal cultures were also obtained 1

**Fig 4.** Compliance with prescribed therapy (expressed as percentage of doses taken) in children who were randomized to azithromycin or erythromycin for treatment of pertussis.

week after completion of therapy to assess disease relapse, and no relapses occurred in the 91% (104 of 114) of children who had this outcome measure ascertained. In the intention-to-treat analyses, however, in which the 2 participants who had protocol violations were assumed to have failed therapy in a "worst-case scenario," 89% of azithromycin recipients and 94.6% of erythromycin recipients would have remained culture negative. The CIs around these point estimates indicate that as many as 15% of children on erythromycin could have positive cultures 1 week after therapy and as many as 21% of children on azithromycin. We suggest that these are extraordinarily high estimates that are not consistent with clinical experience with macrolides and indicate that the intention-to-treat analysis is overly conservative in this instance. In case series, erythromycin failures are reported to occur in 10% ($n = 1$ of 10)[24] to 11% ($n = 2$ of 18)[25] of patients and in randomized controlled trials in 1% ($n = 2$ of 168),[11] 4.3% ($n = 1$ of 23),[26] and 6% ($n = 1$ of 17)[9] of patients on erythromycin. Relapse did not occur in patients who were treated with azithromycin in 2 case series[25,27] but has been reported in 1 case report.[28] Relapse of infection with clarithromycin is equally uncommon.[25,26] The only randomized controlled trials of pertussis treatment other than this report are of 7 compared with 14 days of erythromycin[11] and clarithromycin compared with erythromycin.[26]

Compliance with therapy was markedly better with azithromycin than with erythromycin in this study, with 95% of children taking >90% of doses compared with only 60% of children on erythromycin. The gastrointestinal side effects of erythromycin are widely known[26,29,30] and thought to be attributable to the agonist effect of the drug on intestinal motilin receptors. We hypothesize that inability to comply with therapy may actually account for some erythromycin failures in the treatment and prophylaxis of pertussis. However, it is noteworthy that no treatment failures were observed on a 10-day course of erythromycin, even with poor compliance. We have previously shown that a 7-day course of erythromycin is as effective as a 14-day course.[11] In the absence of evidence of a clear treatment benefit, it seems unreasonable to recommend erythromycin as the drug of choice,[10] because up to 30% of patients will have significant gastrointestinal side effects. A course of azithromycin is considerably more expensive than erythromycin, however, and this must be considered when an antimicrobial choice is made.

Only ~24% of participants who were enrolled in this study ultimately had culture-proven *B pertussis* infection, although this was suspected by their primary care clinician as the cause of their infection; serologic and PCR diagnosis increased this percentage to 35%. It is likely that the most common cause of infection in these children, 65% of those who presented with cough illness, was viral. *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*[31] may also present with cough illness but are susceptible to macrolides. Alternatively, infection may have initiated airway damage leading to cough, and antimicrobial therapy would be unlikely to alter these symptoms. The cause of cough illness is difficult if not impossible to diagnose clinically, and this is even more difficult in the earlier nonspecific catarrhal stage of pertussis. This leads to late treatment of children with pertussis and accounts for the long period of enrollment in this multicenter trial. Accurate and early diagnosis would be possible only with easy access to rapid diagnostic tests. When such tests are available, it is possible that early treatment of pertussis will reduce transmission and potentially interrupt development of prolonged cough illness.

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