

ORIGINAL ARTICLE

Azithromycin for Preschoolers with Wheezing in the Emergency Department

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ABSTRACT

BACKGROUND

Wheezing illnesses are a leading cause of hospitalization for preschool-age children and are frequently treated with antibiotics. Observational studies have shown more frequent isolation of three pathogenic bacteria (*Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*) from nasopharyngeal samples from children with recurrent episodes of wheezing than from those without such illnesses.

METHODS

In this multicenter trial, we randomly assigned patients 18 to 59 months of age who presented to an emergency department with a moderate-to-severe episode of wheezing to receive azithromycin once daily at a dose of 12 mg per kilogram of body weight or matching placebo for 5 days. The primary outcome was the sum of scores on the Asthma Flare-up Diary for Young Children (ADYC) over 5 days. Primary-outcome scores could range from 5 to 35, with higher scores indicating more severe wheezing-related symptoms. Efficacy was assessed separately in patients who tested positive for pathogenic bacteria (the positive cohort) and in those who tested negative (the negative cohort). Secondary outcomes were length of stay in the emergency department, length of hospital stay, and return emergency department visits or hospitalizations within 72 hours. Bacterial clearance and antimicrobial resistance were measured at follow-up visits 1 to 3 weeks after randomization.

RESULTS

Among 840 patients who underwent randomization, 521 tested positive for pathogenic bacteria. The trial was stopped for futility by the data and safety monitoring board after a planned interim analysis. ADYC scores did not differ significantly between the azithromycin and placebo groups in either the positive cohort (median, 9.59 [interquartile range, 7.29 to 12.60] vs. 9.72 [interquartile range, 7.66 to 12.17]; $P=0.70$) or the negative cohort (median, 9.30 [interquartile range, 6.97 to 11.62] vs. 9.10 [interquartile range, 7.19 to 11.45]; $P=0.69$). In the positive cohort, bacterial clearance was 58.7% in the azithromycin group and 11.4% in the placebo group. Secondary outcomes appeared to be similar in the two groups for both cohorts, as did the development of bacterial resistance and the incidence of adverse events.

CONCLUSIONS

Azithromycin did not lead to a greater reduction in the severity of wheezing-related symptoms than placebo in preschool-age children who presented to the emergency department with moderate-to-severe acute wheezing. (Funded by the National Heart, Lung, and Blood Institute and others; AZ-SWED ClinicalTrials.gov number, NCT04669288.)

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LOWER RESPIRATORY ILLNESSES THAT present with wheezing are a major cause of respiratory distress and health care utilization in early life. Rates of hospitalization with a diagnosis of asthma are highest in children less than 5 years of age, with approximately 30,000 such admissions in the United States in 2019.¹ Most young children with acute episodes of wheezing after the first year of life have concomitant viral infections caused predominantly by rhinovirus.² Recently, several studies have shown a high incidence of isolation of three pathogenic bacteria (*Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*) from nasopharyngeal samples from preschool-age children with recurrent episodes of wheezing.³⁻⁵ These findings suggested that the bacteria may have a role in the pathogenesis of acute lower respiratory illnesses in this age group.

On the basis of this assumption, several randomized, placebo-controlled trials have assessed the effectiveness of azithromycin for the treatment of preschool children with lower respiratory illnesses of different levels of severity, and the results have been mixed. Stokholm et al.⁶ found that azithromycin, initiated early in the course of illness, was associated with a shorter duration of symptoms than placebo in children with recurrent wheezing, and Bacharier et al.⁷ found that azithromycin was associated with lower use of oral glucocorticoids than placebo. However, a trial performed in an emergency department showed that azithromycin did not lead to a shorter duration of symptoms than placebo in children 12 to 60 months of age with wheezing.⁸

Azithromycin has both antiinflammatory and antibacterial effects,⁹ and its potential role in treating wheezing illnesses in preschool-age children could be attributable to one or both of these properties. None of the studies described above assessed efficacy in association with nasopharyngeal bacterial colonization, which may help to elucidate the mechanism of action of azithromycin in the treatment of wheezing illnesses.

Given that up to one fourth of wheezing episodes among preschoolers are treated with antibiotics,¹⁰ we conducted the Azithromycin Therapy in Preschoolers with a Severe Wheezing Episode Diagnosed at the Emergency Department (AZ-SWED) trial to evaluate whether a 5-day course of azithromycin decreases the severity of illness in young children presenting to the emergency

department with wheezing, with separate analyses according to the presence or absence of nasopharyngeal colonization with *S. pneumoniae*, *M. catarrhalis*, or *H. influenzae*.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this randomized, placebo-controlled, clinical trial at eight pediatric emergency departments in the United States that are affiliated with the Pediatric Emergency Care Applied Research Network. Written permission was obtained from the children's parents or guardians. An institutional review board at the University of Utah functioned as the single institutional review board for all the sites. Each participating site established a reliance agreement with the single institutional review board, and this board approved the trial protocol (available with the full text of this article at NEJM.org). The National Heart, Lung, and Blood Institute (NHLBI) appointed a data and safety monitoring board to periodically review enrollment, the conduct of the trial, safety, and efficacy. The funders had no role in the trial design; in the collection, analysis, or interpretation of the data; in the writing of the manuscript; or in the decision to submit the manuscript for publication. The role of each author is described in the Supplementary Appendix (available at NEJM.org). The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PATIENTS

The target population was children 18 to 59 months of age who presented to the emergency department with a moderate-to-severe episode of expiratory wheezing (as ascertained by emergency department care providers). Children were assessed according to the Pediatric Respiratory Assessment Measure (PRAM)¹¹ by trained care providers (e.g., physicians, nurse practitioners, and nurses) as soon as possible after arrival in the emergency department, and assessments were periodically updated. PRAM scores range from 0 to 12, with higher scores indicating greater severity of the acute wheezing episode. Children were eligible for the trial if they had a PRAM score of 4 or higher, which indicates moderate-to-severe symptoms, at any time during the visit to the emergency department. The most important exclusion

criterion was receipt of antibiotics for any reason within the previous 2 weeks or presentation to the emergency department with an acute infection that warranted systemic antibiotics. Additional exclusion criteria were the use of a systemic glucocorticoid for wheezing or suspected foreign-body aspiration within the previous 2 weeks, premature birth, known systemic illness other than allergies, known sensitivity or allergy to azithromycin, and active coronavirus disease 2019 (Covid-19). A complete list of exclusion criteria is provided in the protocol.

RANDOMIZATION, INTERVENTIONS, AND PROCEDURES

Patients were randomly assigned to receive one dose (12 mg per kilogram of body weight) of azithromycin or placebo orally each day for 5 days. Formulations of azithromycin and placebo were prepared by Sharp Services to be similar in taste, color, and smell and were provided in masked bottles. Randomization was performed through a built-in module of the Research Electronic Data Capture (REDCap) system with the use of permuted blocks with random block sizes. Randomization was stratified according to the clinical site and the qualifying PRAM score (4 through 7 vs. ≥ 8). Nasopharyngeal samples were obtained before the administration of azithromycin or placebo and were later tested for respiratory viruses and for *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae* (see the Supplementary Appendix). Randomization could not be stratified according to the presence of the three pathogenic bacteria because these test results were not available at the time of assessment for eligibility. All the patients were expected to receive their first dose of azithromycin or placebo in the emergency department, or shortly thereafter in the inpatient unit if admitted, and all were prescribed oral or systemic glucocorticoids along with albuterol treatment in accordance with the guidelines of the NHLBI.

OUTCOME MEASURES

The primary outcome was the sum of scores on the Asthma Flare-up Diary for Young Children (ADYC) over the 5 days after randomization, as reported by caregivers. The ADYC is a previously validated Web-based measure with 17 questions, each of which is scored on a scale from 1 to 7, with higher scores indicating more severe wheezing-related symptoms. Daily ADYC scores were calcu-

lated as the average score per question, and the primary outcome was the sum of the five daily scores. The range of possible primary-outcome values was 5 to 35.¹²

The three prespecified secondary outcomes were length of stay in the emergency department, length of hospital stay, and return visits (emergency department visits or hospital admissions, excluding admissions that resulted from the initial emergency department visit) within 72 hours after randomization. Data regarding adherence to the trial regimen were also collected. A safety-related follow-up survey was completed on day 8.

Before randomization, caregivers were asked whether the child would participate in optional follow-up visits. If the caregiver agreed to participate and the child was subsequently found to be positive for pathogenic bacteria, the caregiver was contacted to bring the child back to the site for follow-up visits between 5 and 8 days after randomization and again between 14 and 21 days. Nasopharyngeal swab samples were collected at these follow-up visits to test for the presence of bacteria and, when tests were positive, for antimicrobial resistance.

Patients who were found to be positive for at least one of the three bacterial species were classified into the positive cohort, whereas those who tested negative for all three bacteria were classified into the negative cohort. Trial outcomes were compared separately in the positive and negative cohorts.

Antimicrobial resistance in any of the three pathogenic bacteria was a safety outcome assessed in the subgroup of patients in the positive cohort who returned for at least one follow-up visit. All adverse events were also reported.

STATISTICAL ANALYSIS

The full statistical analysis plan is available with the protocol. In brief, the target sample size was 1476 patients. The sum of ADYC scores was compared between trial groups with a Van Elteren test, which was stratified according to site and PRAM category on presentation (4 through 7 vs. ≥ 8). A Bonferroni-adjusted significance level of 0.025 was used for each of the two primary comparisons (i.e., those between the two trial groups in the positive and negative cohorts). To account for missing data, we applied multiple imputation. On the basis of this analysis plan, 10 full datasets were generated with fully conditional expectation,

with backward selection to choose sufficiently predictive models for each variable given the others. A complete-case analysis was also performed, which was limited to patients with no missing data.

Two secondary outcomes, length of stay in the emergency department and hospital length of stay, were analyzed in the same manner as the primary outcome, whereas return visits were analyzed with a Mantel–Haenszel test, with stratification according to site and PRAM category. Because the number of data points missing for secondary outcomes was small, a complete-case analysis was used. Significance thresholds for secondary outcomes were adjusted for multiple comparisons with the use of the Holm procedure.¹³ Bacterial resistance was analyzed with standard methods (see the Supplementary Appendix).

Significance levels were adjusted for multiple subgroups (stratified according to sex and race or ethnic group). The consistency of results was also analyzed across sites and PRAM categories on presentation. We used IVEware software (University of Michigan) for imputation and SAS software, version 9.4 (SAS Institute), for all other analyses. Results are presented according to the 2010 Consolidated Standards of Reporting Trials (CONSORT) guidelines.¹⁴

In December 2024, as specified in the protocol, the data and safety monitoring board reviewed the results of a futility analysis and determined that the conditional power of the trial in both cohorts was less than 16%, even with the assumption that the sum of ADYC scores was truly lower with azithromycin than with placebo by as much as 1.3 points. On the basis of this finding, the NHLBI, on the recommendation of the data and safety monitoring board, stopped the trial for futility.

RESULTS

PATIENTS AND ADHERENCE TO TRIAL INTERVENTION

From the initiation of the trial in September 2021 through December 2024, a total of 840 patients were enrolled, among whom 521 (62.0%) tested positive for one or more of the three pathogenic bacteria, 312 (37.1%) tested negative, and 7 (0.8%) had an unknown bacterial status. Randomization and follow-up are summarized in Figure 1. In each cohort and assigned trial group, at least 80% of

the patients had all the daily surveys completed, and at least 94% had at least one survey completed.

The demographic and baseline characteristics of the children who underwent randomization are shown in Table 1. The patients were generally representative of similarly affected children in the United States (Table S1 in the Supplementary Appendix).

Respiratory viruses were isolated from the nasopharynx in 86.1% of the patients. The most frequently isolated virus was rhinovirus (72.5%), followed by respiratory syncytial virus (9.2%), bocavirus (4.6%), and metapneumovirus (3.7%). The incidence of isolation of rhinovirus was similar in the positive and negative cohorts (Table S2). Adherence to the assigned trial regimen (defined as caregiver report of the patient receiving at least four of five daily doses) was 78.3% in the positive cohort and 80.4% in the negative cohort.

PRIMARY OUTCOME

The sum of ADYC scores over 5 days did not differ significantly between the azithromycin and placebo groups in either the positive cohort or the negative cohort (Table 2 and Fig. 2). Only 11.7% of ADYC questionnaire data points from the positive cohort and 11.2% from the negative cohort were missing and required imputation, with similar missingness in all the trial groups. The results of the complete-case analysis and per-protocol analysis were similar to those of the primary analysis (Table S3 and Fig. S1).

SECONDARY OUTCOMES AND SUBGROUPS

Approximately half the patients who had undergone randomization (416 of 840; 49.5%) were hospitalized, and the percentages were similar in all the trial groups: in the positive cohort, 123 of 257 patients (47.9%) in the azithromycin group and 138 of 263 (52.5%) in the placebo group were hospitalized, as were 77 of 158 (48.7%) and 78 of 154 (50.6%), respectively, in the negative cohort. The length of stay in the emergency department and the length of the hospital stay appeared to be similar in the two trial groups in both cohorts (Table 2 and Fig. S2). The incidence of return visits also appeared to be similar in the trial groups. Prespecified subgroup analyses of the primary and secondary outcomes according to sex and race or ethnic group, as well as exploratory

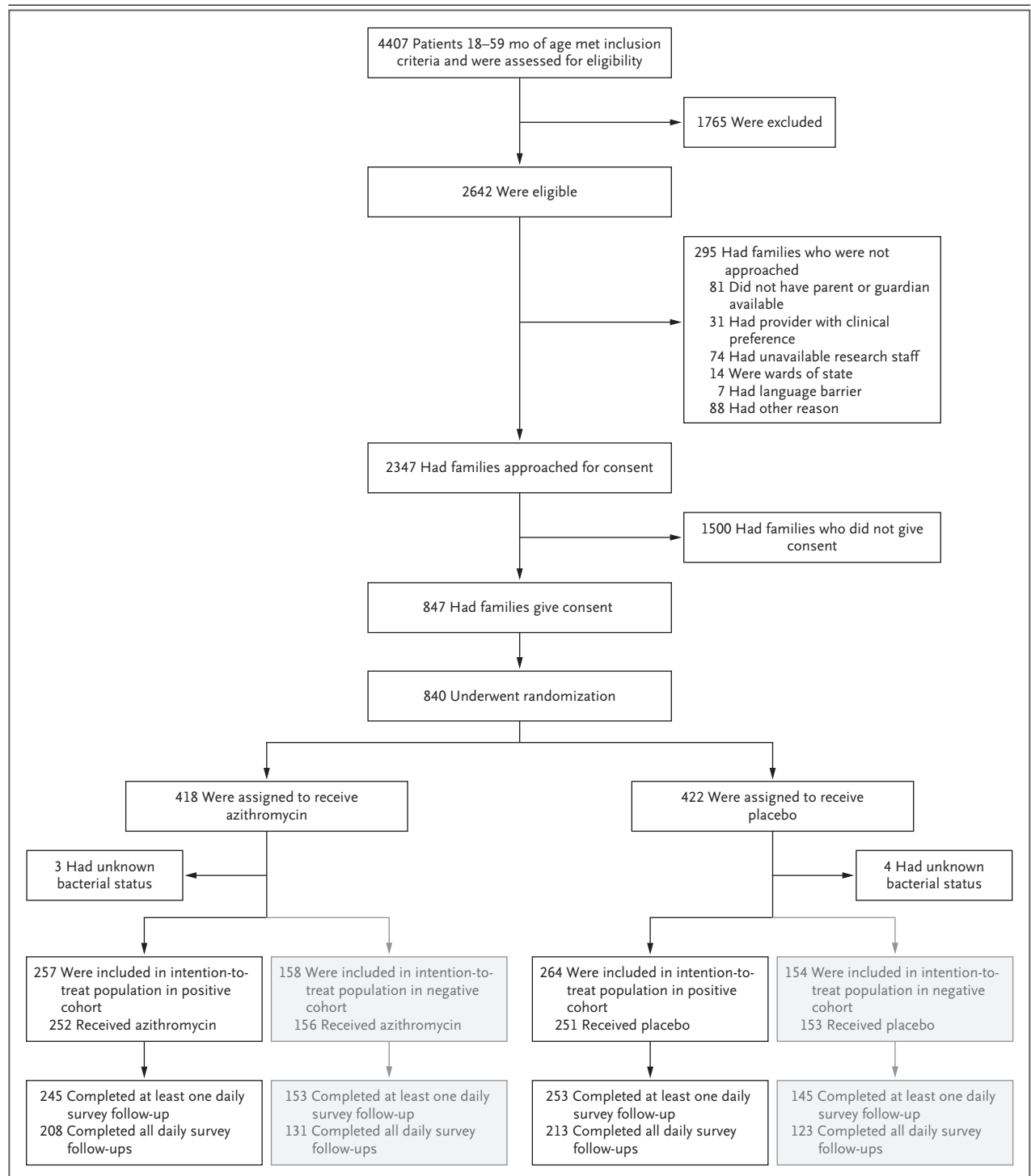


Figure 1. Screening, Randomization, and Follow-up.

Among the patients who underwent randomization, those who tested positive for any of three pathogenic bacteria — *Streptococcus pneumoniae*, *Moraxella catarrhalis*, or *Haemophilus influenzae* — were included in the positive cohort. Those who tested negative for all three bacteria were included in the negative cohort.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Positive Cohort			Negative Cohort		
	Azithromycin (N = 257)	Placebo (N = 264)	Overall (N = 521)	Azithromycin (N = 158)	Placebo (N = 154)	Overall (N = 312)
Demographic characteristics						
Male sex — no./total no. (%)	155/257 (60.3)	164/263 (62.4)	319/520 (61.3)	102/158 (64.6)	91/154 (59.1)	193/312 (61.9)
Age group — no. (%)						
18 to <24 mo	44 (17.1)	59 (22.3)	103 (19.8)	18 (11.4)	21 (13.6)	39 (12.5)
24 to <36 mo	102 (39.7)	91 (34.5)	193 (37.0)	40 (25.3)	44 (28.6)	84 (26.9)
36 to <48 mo	69 (26.8)	66 (25.0)	135 (25.9)	54 (34.2)	51 (33.1)	105 (33.7)
48 to <60 mo	42 (16.3)	48 (18.2)	90 (17.3)	46 (29.1)	38 (24.7)	84 (26.9)
Race or ethnic group — no. (%)†						
American Indian or Alaska Native	0	1 (0.4)	1 (0.2)	2 (1.3)	0	2 (0.6)
Asian	6 (2.3)	3 (1.1)	9 (1.7)	1 (0.6)	2 (1.3)	3 (1.0)
Black or African American	109 (42.4)	124 (47.0)	233 (44.7)	84 (53.2)	80 (51.9)	164 (52.6)
Native Hawaiian or other Pacific Islander	1 (0.4)	0	1 (0.2)	1 (0.6)	0	1 (0.3)
White	96 (37.4)	91 (34.5)	187 (35.9)	46 (29.1)	47 (30.5)	93 (29.8)
Multiracial	13 (5.1)	12 (4.5)	25 (4.8)	9 (5.7)	8 (5.2)	17 (5.4)
Unknown	32 (12.5)	33 (12.5)	65 (12.5)	15 (9.5)	17 (11.0)	32 (10.3)
Hispanic or Latino ethnic group — no. (%)†						
Yes	49 (19.1)	53 (20.1)	102 (19.6)	28 (17.7)	35 (22.7)	63 (20.2)
No	201 (78.2)	206 (78.0)	407 (78.1)	129 (81.6)	116 (75.3)	245 (78.5)
Unknown or not reported	7 (2.7)	5 (1.9)	12 (2.3)	1 (0.6)	3 (1.9)	4 (1.3)
Clinical characteristics						
Admitted to the hospital — no./total no. (%)‡	123/257 (47.9)	138/263 (52.5)	261/520 (50.2)	77/158 (48.7)	78/154 (50.6)	155/312 (49.7)
Received other antibiotics in emergency department — no./total no. (%)	4/257 (1.6)	3/263 (1.1)	7/520 (1.3)	3/158 (1.9)	2/154 (1.3)	5/312 (1.6)
PRAM score for eligibility§						
Mean	6.0±1.78	6.2±1.81	6.1±1.80	6.5±1.91	6.6±1.97	6.5±1.94
Category — no. (%)						
4–7	202 (78.6)	205 (77.7)	407 (78.1)	116 (73.4)	114 (74.0)	230 (73.7)
8–12	55 (21.4)	59 (22.3)	114 (21.9)	42 (26.6)	40 (26.0)	82 (26.3)
Fever — no./total no. (%)¶	32/256 (12.5)	50/262 (19.1)	82/518 (15.8)	13/157 (8.3)	17/153 (11.1)	30/310 (9.7)

Primary care visits for wheezing in past year — no./total no. (%)						
0	74/237 (31.2)	77/242 (31.8)	151/479 (31.5)	47/146 (32.2)	41/143 (28.7)	88/289 (30.4)
1	36/237 (15.2)	50/242 (20.7)	86/479 (18.0)	23/146 (15.8)	43/143 (30.1)	66/289 (22.8)
>1	127/237 (53.6)	115/242 (47.5)	242/479 (50.5)	76/146 (52.1)	59/143 (41.3)	135/289 (46.7)
Emergency department or urgent care visits for wheezing in past year — no./total no. (%)						
0	68/243 (28.0)	70/248 (28.2)	138/491 (28.1)	38/145 (26.2)	38/145 (26.2)	76/290 (26.2)
1	59/243 (24.3)	54/248 (21.8)	113/491 (23.0)	34/145 (23.4)	48/145 (33.1)	82/290 (28.3)
>1	116/243 (47.7)	124/248 (50.0)	240/491 (48.9)	73/145 (50.3)	59/145 (40.7)	132/290 (45.5)
Wheezing-related hospitalizations in past year — no./total no. (%)						
0	144/241 (59.8)	157/248 (63.3)	301/489 (61.6)	93/147 (63.3)	93/144 (64.6)	186/291 (63.9)
1	59/241 (24.5)	48/248 (19.4)	107/489 (21.9)	31/147 (21.1)	30/144 (20.8)	61/291 (21.0)
>1	38/241 (15.8)	43/248 (17.3)	81/489 (16.6)	23/147 (15.6)	21/144 (14.6)	44/291 (15.1)
Antibiotics taken in past year — no./total no. (%)						
Inhaled glucocorticoids taken in past year — no./total no. (%)						
Oral glucocorticoids taken in past year — no./total no. (%)						
Positivity of nasopharyngeal swab sample — no. (%)						
Human rhinovirus	176 (68.5)	203 (76.9)	379 (72.7)	116 (73.4)	109 (70.8)	225 (72.1)
Human respiratory syncytial virus	27 (10.5)	33 (12.5)	60 (11.5)	10 (6.3)	7 (4.5)	17 (5.4)
Bocavirus	19 (7.4)	11 (4.2)	30 (5.8)	5 (3.2)	3 (1.9)	8 (2.6)
Human metapneumovirus	16 (6.2)	6 (2.3)	22 (4.2)	4 (2.5)	5 (3.2)	9 (2.9)
Human parainfluenza virus	8 (3.1)	9 (3.4)	17 (3.3)	3 (1.9)	4 (2.6)	7 (2.2)
Any combination of viruses	19 (7.4)	20 (7.6)	39 (7.5)	10 (6.3)	7 (4.5)	17 (5.4)
Negative for all tested viruses — no. (%)	37 (14.4)	23 (8.7)	60 (11.5)	26 (16.5)	30 (19.5)	56 (17.9)

* Plus-minus values are means $\pm$ SD. Percentages may not total 100 because of rounding.

† Race and ethnic group were reported by the patients' caregivers.

‡ The decision to admit to the hospital may have been made before or after randomization. Thus, these data do not represent a true baseline measure for all the patients.

§ The Pediatric Respiratory Assessment Measure (PRAM) is a tool to assess the severity of an acute wheezing episode. Scores range from 0 to 12, with higher scores indicating greater severity. Patients were eligible for the trial if they had a score of 4 or higher.

¶ Fever was defined as a temperature of 38°C or higher.

|| Data were reported by the patients' caregivers.

subgroup analyses, are shown in Figures S3 through S6.

BACTERIAL CLEARANCE AND RESISTANCE

Of the 521 patients in the positive cohort, 444 (85.2%) had caregivers who agreed to participate in follow-up visits. Of those patients, 116 (26.1%) returned for the 1-week follow-up visit and 188 (42.3%) returned for the follow-up visit at 2 to 3 weeks, for a total of 209 patients (47.1%; 99 in the azithromycin group and 110 in the placebo group) with at least one follow-up visit to assess bacterial clearance and resistance. Clearance of the three pathogenic bacteria from the upper airway was 58.7% in the azithromycin group and 11.4% in the placebo group (Table S4). The effect of azithromycin on the ADYC score appeared to be similar in those found to be positive for bacteria and those found to be negative at the 1-week follow-up (Table S5).

Among patients with at least one follow-up visit, antimicrobial resistance in at least one of the three pathogenic bacteria at baseline was found in 16 (16.2%) in the azithromycin group and 19 (17.3%) in the placebo group, and these patients were thus excluded from the analysis of the development of bacterial resistance. Bacterial resistance at follow-up was present in 21.7% of the samples from the azithromycin group and in 22.0% of those from the placebo group (Table S6).

ADVERSE EVENTS AND SIDE EFFECTS

In the positive cohort, three patients in the azithromycin group and five in the placebo group had at least one serious adverse event. Serious adverse events in this cohort consisted of respiratory distress, bronchospasm, increased work of breathing, and respiratory syncytial virus infection. In the negative cohort, three patients in the azithromycin group and one in the placebo group had at least one serious adverse event; events consisted of Covid-19 pneumonia, respiratory distress, respiratory failure, septic shock, and worsening cough (Table S7). Nonserious adverse events were evenly distributed between the two trial groups in both cohorts (Table S8). No deaths were reported.

DISCUSSION

An important finding of our trial was that approximately 50% of preschool-age children who presented to the emergency department with

wheezing and a PRAM of 4 or higher were admitted to the hospital for treatment. This result confirms our initial assumption that, notwithstanding recent advances in our understanding of the pathogenesis and heterogeneity of acute wheezing illnesses,¹⁵ these illnesses remain a substantial cause of respiratory distress and a driver of health care costs, and new approaches are needed to prevent and treat them.

Respiratory viruses are frequently isolated from preschool children with wheezing episodes; in our trial, 72.5% of the patients tested positive for rhinoviruses, and only 13.9% tested negative for all the viruses covered in our assays of nasopharyngeal swabs. Several studies have shown that at least one of three pathogenic bacterial taxa, *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae*, was more likely to be present in children with a history of recurrent wheezing illnesses than in controls.³⁻⁵ These findings suggested the hypothesis that the bacteria could have a role in the pathogenesis of these illnesses and, therefore, that antibiotics such as azithromycin could decrease the severity of such illnesses.¹⁰ In our trial involving wheezing episodes for which care was sought in an emergency department, the severity and clinical outcomes of the wheezing episodes did not differ between children treated for 5 days with azithromycin and those treated with placebo. This finding was consistent regardless of whether any of the three bacteria were present or absent. The lack of efficacy met the pre-established conditional power threshold for both cohorts in the trial, and in accordance with the planned interim analysis, the data and safety monitoring board recommended stopping the trial early, after 840 patients had undergone randomization.

Findings in this trial are similar to those from a trial by Mandhane et al.⁸ that involved 222 preschoolers who presented to the emergency department with wheezing. That trial, which did not include stratification according to bacterial colonization status, showed no effect of azithromycin on the duration of symptoms. Our results differ from those of two outpatient trials involving children with milder wheezing episodes. Bacharier et al.⁷ compared the frequency of use of oral glucocorticoids in 607 preschool-age children who were given azithromycin or placebo at the first signs that preceded the development of a wheezing illness. The azithromycin group had a 36% lower risk of progression to

Outcome	Positive Cohort		Negative Cohort	
	Azithromycin (N = 257)	Placebo (N = 264)	Azithromycin (N = 158)	Placebo (N = 154)
				Difference in Means or Risk Ratio (97.5% CI)†
Primary outcome				
Sum of scores on ADYCI‡				
Median (IQR)	9.59 (7.29 to 12.60)	9.72 (7.66 to 12.17)	9.30 (6.97 to 11.62)	9.10 (7.19 to 11.45)
Mean	10.34±3.82	10.39±3.69	9.76±3.40	9.83±3.41
				−0.05 (−0.80 to 0.69)§
Secondary outcomes 				
Length of stay in emergency department — hr				
Median (IQR)	5.2 (4.1 to 6.8)	4.9 (3.9 to 7.0)	4.9 (3.9 to 6.2)	4.9 (3.8 to 6.4)
Mean	6.0±3.4	6.0±3.9	5.7±3.8	6.5±7.5
				−0.0 (−0.7 to 0.7)
Hospital length of stay — hr				
Median (IQR)	7.7 (4.5 to 28.4)	15.8 (4.3 to 29.6)	13.1 (4.3 to 29.5)	16.9 (4.3 to 29.5)
Mean	20.0±20.5	20.8±21.1	20.8±23.3	20.9±20.7
				−0.8 (−4.9 to 3.3)
Return visit to emergency depart- ment or hospitalization — no. (%)**	3/256 (1.17)	5/264 (1.89)	2/158 (1.27)	2/153 (1.31)
				0.6 (0.1 to 3.1)
				−0.1 (−5.8 to 5.5)
				0.9 (0.1 to 8.4)

* Plus-minus values are means ±SD. Data on the length of stay in the emergency department and hospital length of stay were missing for one patient in the placebo group of the positive cohort. The widths of the confidence intervals (CIs) have not been adjusted for multiplicity and should not be used in place of hypothesis testing. IQR denotes interquartile range. † Values are differences in means for all the outcomes except for return visits, for which the risk ratio is shown. Return visits were analyzed with a Mantel-Haenszel test with stratification according to site and baseline severity (as indicated by PRAM category).

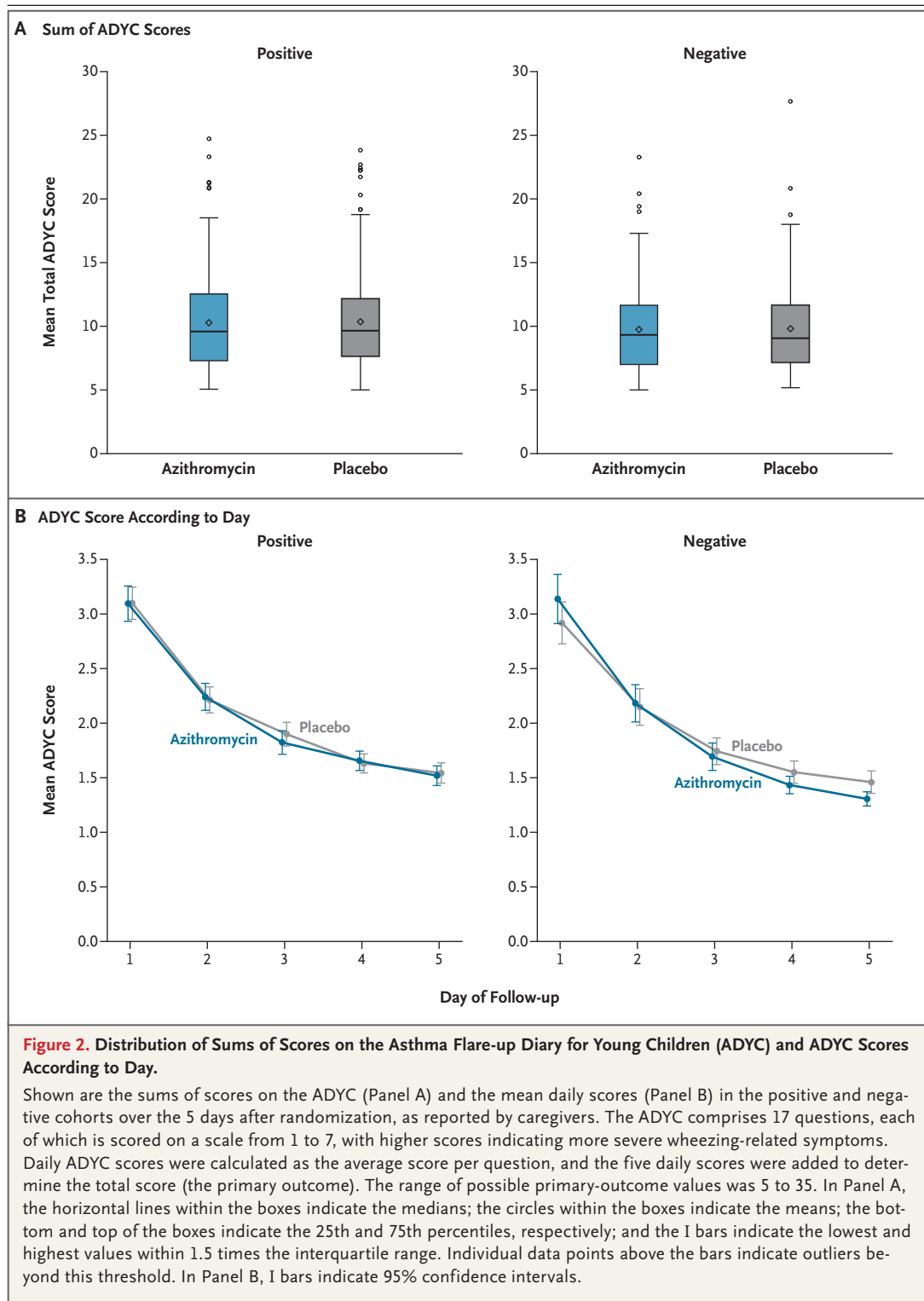
‡ The primary outcome was the sum of five daily scores on the Asthma Flare-up Diary for Young Children (ADYC). The ADYC includes 17 questions, each scored on a scale from 1 to 7, with higher scores indicating greater severity of wheezing-related symptoms. Each daily score was equal to the average score per question.

§ P = 0.70 by a Van Elteren test with stratification according to site and baseline severity.

|| P = 0.69 by a Van Elteren test with stratification according to site and baseline severity.

** No P values for secondary outcomes met the first threshold of the hierarchical testing procedure.

Data include return visits to the emergency department or hospitalizations within 72 hours after randomization but exclude hospital admissions resulting from the initial visit to the emergency department.



severe illness than the placebo group. The number needed to treat to prevent one severe illness was higher for the first respiratory tract infection (33) than for the fourth respiratory tract infection (7), a finding that indicates justification for this approach in children with a history of

severe recurrent illnesses. Stokholm et al.⁶ compared the duration of asthma-like episodes in 72 children and found that the episodes were 63.3% shorter in the azithromycin group than in the placebo group. In our trial involving children who received treatment in an emergency department, we found that the severity of illness decreased substantially after the first day of treatment and generally became relatively mild by the fifth day (Fig. 2B), with similar trajectories among the trial groups.

One potential explanation for the discrepancy in the results between clinical settings (i.e., emergency departments vs. outpatient care) is the severity of the illness, with azithromycin having an effect when the respiratory infection has not yet caused severe lower-airway obstruction. In support of this explanation is the fact that in the trial by Bacharier et al., azithromycin was given before any clinical signs of airway obstruction were observed, and in the trial by Stokholm et al., the effect of azithromycin was stronger if the drug was taken early in the course of the illness.

Azithromycin is known to have antiinflammatory effects in addition to its defining antibacterial effects.¹⁶ Our large trial did not show benefit from azithromycin in children with colonization by *S. pneumoniae*, *M. catarrhalis*, or *H. influenzae*, despite substantial bacterial clearance from the nasopharynx in the azithromycin group. On the basis of that observation, we speculate that azithromycin may have been more effective in the outpatient setting than in our emergency department cohort with more severe illness owing to the preventive antiinflammatory effects of the drug, and we suggest that azithromycin should not be used to treat children with established respiratory distress.

Our trial has some limitations. Although the decision to stop the trial early was justified, given the results of the interim analysis, stopping early limited the sample size, decreased the precision of estimated differences, and greatly reduced the power of the trial. However, the results show that a moderate or large true effect is implausible. Owing to sample-size constraints and the preliminary evidence that supported azithromycin, we did not test the effectiveness of other antibiotics, but as noted, the differences in bacterial clearance between the groups do not support a role for antibacterial agents in these episodes.

In our trial, azithromycin was not associated

with a greater reduction in the severity of wheezing-related symptoms than placebo in preschool-age children who presented to the emergency department with moderate-to-severe acute wheezing.

The content and conclusions are those of the authors and should not be construed as the official position or policy of, nor should any endorsements be inferred by, the Health Resources and Services Administration, the Department of Health and Human Services, or the U.S. Government.

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REFERENCES

1. Binney S, Flanders WD, Sircar K, Idubor O. Trends in US pediatric asthma hospitalizations, by race and ethnicity, 2012–2020. *Prev Chronic Dis* 2024;21:E71.
2. Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008;178:667-72.
3. Bisgaard H, Hermansen MN, Buchvald F, et al. Childhood asthma after bacterial colonization of the airway in neonates. *N Engl J Med* 2007;357:1487-95.
4. Zhu Z, Camargo CA Jr, Raita Y, et al. Nasopharyngeal airway dual-transcriptome of infants with severe bronchiolitis and risk of childhood asthma: a multicenter prospective study. *J Allergy Clin Immunol* 2022;150:806-16.
5. Teo SM, Mok D, Pham K, et al. The infant nasopharyngeal microbiome impacts severity of lower respiratory infection and risk of asthma development. *Cell Host Microbe* 2015;17:704-15.
6. Stokholm J, Chawes BL, Vissing NH, et al. Azithromycin for episodes with asthma-like symptoms in young children aged 1-3 years: a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2016;4:19-26.
7. Bacharier LB, Guilbert TW, Mauger DT, et al. Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: a randomized clinical trial. *JAMA* 2015;314:2034-44.
8. Mandhane PJ, Paredes Zambrano de Silbernagel P, Aung YN, et al. Treatment of preschool children presenting to the emergency department with wheeze with azithromycin: a placebo-controlled randomized trial. *PLoS One* 2017;12(8):e0182411.
9. Kanoh S, Rubin BK. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. *Clin Microbiol Rev* 2010;23:590-615.
10. de Benedictis FM, Carloni I, Guidi R. Question 4: Is there a role for antibiotics in infantile wheeze? *Paediatr Respir Rev* 2020;33:30-4.
11. Chalut DS, Ducharme FM, Davis GM. The Preschool Respiratory Assessment Measure (PRAM): a responsive index of acute asthma severity. *J Pediatr* 2000;137:762-8.
12. Ducharme FM, Jensen ME, Mendelson MJ, et al. Asthma Flare-up Diary for Young Children to monitor the severity of exacerbations. *J Allergy Clin Immunol* 2016;137(3):744-749.e6.
13. Guilbaud OJM. Note on a stepwise procedure for rejecting at least k out of m hypotheses: a simple Holm-type formulation and proof. *Biom J* 2022;64:377-83.
14. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
15. Bush A, Schaub B. Approaches to reduce the risk of severe asthma in children with preschool wheeze. *Expert Rev Respir Med* 2025;19:535-50.
16. Pollock J, Chalmers JD. The immunomodulatory effects of macrolide antibiotics in respiratory disease. *Pulm Pharmacol Ther* 2021;71:102095.

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