

Azithromycin for Acute Exacerbations of Asthma

The AZALEA Randomized Clinical Trial

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IMPORTANCE Guidelines recommend against antibiotic use to treat asthma attacks. A study with telithromycin reported benefit, but adverse reactions limit its use.

OBJECTIVE To determine whether azithromycin added to standard care for asthma attacks in adults results in clinical benefit.

DESIGN, SETTING, AND PARTICIPANTS The Azithromycin Against Placebo in Exacerbations of Asthma (AZALEA) randomized, double-blind, placebo-controlled clinical trial, a United Kingdom-based multicenter study in adults requesting emergency care for acute asthma exacerbations, ran from September 2011 to April 2014. Adults with a history of asthma for more than 6 months were recruited within 48 hours of presentation to medical care with an acute deterioration in asthma control requiring a course of oral and/or systemic corticosteroids.

INTERVENTIONS Azithromycin 500 mg daily or matched placebo for 3 days.

MAIN OUTCOMES AND MEASURES The primary outcome was diary card symptom score 10 days after randomization, with a hypothesized treatment effect size of -0.3 . Secondary outcomes were diary card symptom score, quality-of-life questionnaires, and lung function changes, all between exacerbation and day 10, and time to a 50% reduction in symptom score.

RESULTS Of 4582 patients screened at 31 centers, 199 of a planned 380 were randomized within 48 hours of presentation. The major reason for nonrecruitment was receipt of antibiotics (2044 [44.6%] screened patients). Median time from presentation to drug administration was 22 hours (interquartile range, 14-28 hours). Exacerbation characteristics were well balanced across treatment arms and centers. The primary outcome asthma symptom scores were mean (SD), 4.14 (1.38) at exacerbation and 2.09 (1.71) at 10 days for the azithromycin group and 4.18 (1.48) and 2.20 (1.51) for the placebo group, respectively. Using multilevel modeling, there was no significant difference in symptom scores between azithromycin and placebo at day 10 (difference, -0.166 ; 95% CI, -0.670 to 0.337), nor on any day between exacerbation and day 10. No significant between-group differences were observed in quality-of-life questionnaires or lung function between exacerbation and day 10, or in time to 50% reduction in symptom score.

CONCLUSIONS AND RELEVANCE In this randomized population, azithromycin treatment resulted in no statistically or clinically significant benefit. For each patient randomized, more than 10 were excluded because they had already received antibiotics.

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Asthma morbidity, mortality, and major health care costs result from acute attacks (exacerbations).¹ The majority of patients with asthma report an exacerbation in the past year, with more than one-third of children and more than one-fourth of adults requiring consequent urgent medical care.²

Respiratory viral infections are a frequent cause of asthma exacerbations in children^{3,4} and adults.⁵⁻⁷ Atypical bacterial (*Mycoplasma pneumoniae* and *Chlamydia pneumoniae*) infection and/or reactivation is also associated, with serologic positivity rates of 40% to 60% in some studies,⁸⁻¹² indicating that viral and atypical bacterial infections may interact in increasing asthma exacerbation risk.

People with asthma have increased susceptibility to streptococcal infections,¹³⁻¹⁵ increased carriage of bacterial pathogens identified by culture¹⁶ and molecular techniques,¹⁷ and impaired interferon and type 1 T helper cell responses to bacterial polysaccharides.^{18,19} Viral infection impairs antibacterial innate immune responses²⁰ and increases bacterial adherence to bronchial epithelium.²¹ Thus, bacterial infections are more common and more severe in patients with asthma, viruses increase susceptibility to bacterial infection, and acute wheezing episodes in children younger than 3 years were associated with both bacterial and viral infection.²²

Patients with asthma exacerbations treated with telithromycin had greater reductions in asthma symptoms, improvement in lung function, and faster recovery compared with placebo.¹² However, toxic effects to the liver limit telithromycin treatment to life-threatening infections, and guidelines recommend that antibiotics should not be administered routinely in patients with asthma exacerbations.^{23,24}

The Azithromycin Against Placebo in Exacerbations of Asthma (AZALEA) study investigated the effectiveness of azithromycin treatment when added to standard care for adult patients with asthma exacerbations, closely following the telithromycin study design, with the aim of providing confirmation or otherwise of those results.

Macrolide antibiotics might benefit asthma exacerbations through antimicrobial activity and/or anti-inflammatory properties²⁵; and azithromycin, but not telithromycin, has been shown to have antiviral properties,²⁶ augmenting production of interferons that are deficient in patients with asthma.^{19,27} A mechanistic and exploratory aim of AZALEA was to determine whether treatment benefited patients with these infections.

Methods

Study Design

This United Kingdom-based multicenter, double-blind, placebo-controlled study randomized eligible patients to azithromycin 500 mg daily or placebo for 3 days on day 1 (visit 1), with posttherapy assessments at visits on days 5 (visit 2) and 10 (visit 3) and for serum sampling at 6 weeks (visit 4) (see trial protocol in [Supplement 2](#)).

The main inclusion criteria were that participants be adults aged 18 to 55 years with any smoking history, aged 56 to 65

Key Points

Question Does addition of azithromycin to standard care improve outcomes in adults requesting acute medical care for asthma attacks?

Findings This randomized clinical trial found no statistically or clinically significant benefit in symptoms, lung function, or speed of recovery. For every 1 patient randomized, more than 10 had to be excluded because they had already received antibiotics.

Meaning Widespread use of antibiotics despite guideline recommendations limited interpretation of the results of this study.

years with a less than 20 pack-year smoking history, or older than 65 years with a less than 5 pack-year smoking history, with a documented history of asthma for more than 6 months, and recruitment within 48 hours of presentation to medical care with an acute deterioration in asthma control (increased wheeze, dyspnea, and/or cough) necessitating a course of oral and/or systemic corticosteroids (based on clinical judgement by attending physicians) and a peak expiratory flow (PEF) or forced expiratory volume in 1 second (FEV₁) less than 80% predicted or patient's best at presentation, at recruitment, or in the time elapsed between presentation and recruitment.

The main exclusion criteria were use of oral and/or systemic antibiotics within 28 days of enrollment, need for intensive care, substantial lung disease other than asthma, long-term use of more than 20 mg oral corticosteroid daily, known QT-interval prolongation, history of bradyarrhythmias and/or tachyarrhythmias or uncompensated heart failure, and patients taking drugs known to prolong the QT interval.

The primary outcome was diary card summary symptom score, with symptoms including wheezing, breathlessness, and coughing assessed at 10 days after randomization (as in the telithromycin study).¹² Secondary outcomes included the acute Asthma Quality of Life Questionnaire (AQLQ), the mini AQLQ, FEV₁, forced vital capacity (FVC), FEV₁/FVC, forced mid-expiratory flow (FEF_{25%-75%}), forced expiratory flow at 50% expiration (FEF_{50%}), PEF, and time to 50% reduction in symptom score. Primary and secondary outcomes were assessed over the time course of the exacerbation to 10 days, and subgroup analyses were planned in relation to initial standard and/or atypical bacteriologic and virologic status.

Spontaneous or induced sputum samples were obtained where possible at exacerbation and sent for quantitative bacteria culture. A nasal mucus sample and nasal and throat swab samples were obtained where possible at exacerbation, and these and spontaneous or induced sputum samples were analyzed by means of viral and atypical bacterial polymerase chain reactions (PCRs) and acute and convalescent serum samples were sent for atypical bacterial serologic analysis.

The trial received approval from the National Research Ethics Committee, Bloomsbury, London, England, and all patients gave written informed consent. Additional methods are available in the eMethods in [Supplement 1](#).

Statistical Analyses

The sample size calculations hypothesized a treatment mean (SD) effect size of -0.3 (0.783) based on the primary outcome of the telithromycin study¹² and used a significance level of 1% with 80% power, assuming a dropout rate of 15%.¹² We proposed to recruit 190 patients to each arm. To run the trial within the project funding 1-year timeline, we planned 10 centers, each recruiting roughly 38 patients.

All patients who returned at least 1 diary card and received study drug were included in the intention-to-treat analyses. Because the timing of greatest magnitude of any treatment effect was not known, multilevel modeling was used to calculate the estimated differences in primary and secondary outcomes between treatment groups for each day from randomization to day 10. A Cox model was used to calculate the hazard ratio for time to 50% reduction in symptom score. Details of the statistical model, model selection process, and treatment of missing data are in the eMethods in Supplement 1. All analyses were performed using Stata 13. A statistical analysis plan was prepared by the trial statistician prior to unblinding.

Results

Recruitment Details and Clinical Characteristics

Recruitment from 31 sites (30 secondary care hospitals, 1 primary care center) lasted 2.5 years, from October 12, 2011, to April 30, 2014. The recruitment period was longer than planned because of recruitment difficulties arising from the large numbers of patients excluded. A total of 4582 patients were screened, of whom 390 patients met eligibility criteria. A total of 199 were randomized, 97 to active treatment and 102 to placebo (Figure 1). The major reason for nonrecruitment was already receiving antibiotics (2044 [44.6%] screened patients).

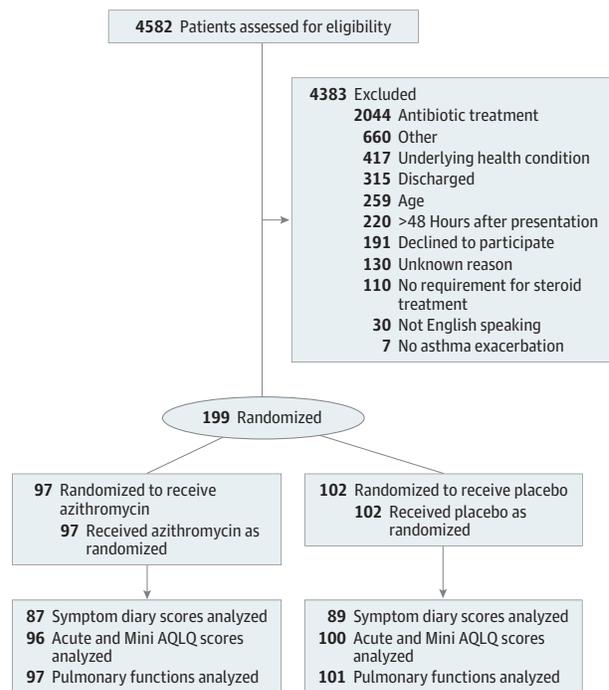
Clinical characteristics of randomized patients are summarized in Table 1. Study participants' mean (SD) age was 39.9 (14.82) years (median [interquartile range] age, 38.4 [26.7-49.5] years), with 69.8% female. Underlying asthma severity, smoking status, exacerbation severity, and median time from presentation to trial drug administration are presented in Table 1. Pulmonary function at baseline (exacerbation, visit 1) is presented in Table 2 and includes mean (SD) PEF, 69.4% (22.7%) of predicted; FEV₁, 64.8% (21.4%) of predicted; and FEV₁/FVC, 69.2% (13.5%). Baseline characteristics were well balanced across treatment arms and centers.

Of the 199 patients randomized, all attended visit 1 (randomization), 21 (10.6%) missed visit 2, 28 (14.1%) missed visit 3, and 39 (19.6%) missed visit 4; 159 (80%) patients attended all follow-up visits. Missing visits and/or data were balanced between the treatment arms. Day 1 was defined as the day of administration of study drug.

Primary Outcome Analysis

Mean (SD) asthma symptom scores (from 0 = no symptoms to 6 = severe symptoms) were 4.14 (1.38) at baseline (exacerbation) and 2.09 (1.71) at day 10 for the azithromycin group and 4.18 (1.48) and 2.20 (1.51), respectively, for placebo. Using mul-

Figure 1. Consolidated Standards of Reporting Trials Diagram of the Azithromycin for Acute Exacerbations of Asthma (AZALEA) Trial



AQLQ indicates Asthma Quality of Life Questionnaire.

tilevel modeling, there was no statistically significant difference in symptom scores between groups at day 10 (difference, -0.166 ; 95% CI, -0.670 to 0.337) (Figure 2 and eTable 3 in Supplement 1).

Secondary Outcome Analyses

Multilevel modeling revealed no significant between-group differences in symptom scores on any day between baseline and day 10 (Figure 2 and eTable 3 in Supplement 1). Significant between-group differences were seen in neither the acute AQLQ, the mini AQLQ (Figure 3A and B and eTables 7-10 in Supplement 1), nor in any measure of lung function (eTables 11 and 12 in Supplement 1) on any day from baseline to day 10, and there was no difference in time to 50% reduction in symptom score (hazard ratio, 1.03; 95% CI, 0.71-1.49) (Figure 3C).

Pathogen Detection Results

One hundred five (52.8%) patients provided sputum samples for bacterial culture, 191 (96.0%) nasal and throat swabs and/or nasal mucus samples for virus and atypical bacterial PCR, and 158 (79.4%) acute (IgM) and acute and convalescent (IgG, IgA) serum samples for atypical bacterial serologic analysis. A bacterial and/or atypical bacterial test positive result occurred in 21 (10.6%) patients (9 [9.3%] active, 12 [11.8%] placebo). Nasal and/or throat swab and/or mucus and/or sputum virus PCRs had positive results in 36 (18.1%) patients (16 [16.5%] active, 20 [19.6%] placebo).

Table 1. Baseline Characteristics of Patients by Treatment Group

Characteristic	Azithromycin (n = 97)	Placebo (n = 102)
Age, median (IQR), y	39.1 (28.9-49.5)	36.2 (25.4-49.3)
Sex, No. (%)		
Male	33 (34)	27 (26)
Female	64 (66)	75 (74)
Asthma severity (n = 198), No. (%) ²⁸		
Step 1: mild intermittent asthma	7 (7)	13 (13)
Step 2: regular preventer therapy	30 (31)	26 (26)
Step 3: initial add-on therapy	31 (32)	27 (27)
Step 4: persistent poor control	22 (23)	22 (22)
Step 5: continuous/frequent oral steroids	7 (7)	13 (13)
Smoking status, No. (%)		
Never	60 (62)	61 (60)
Former	26 (27)	19 (19)
Current	11 (11)	21 (21)
Smoking pack-years for current or former smokers (n = 75), median (IQR) [range]	5 (1-12) [0-20]	5 (2-12) [0-22]
Asthma exacerbation (n = 198), No. (%)		
Mild exacerbation	5 (5)	3 (3)
Moderate exacerbation	26 (27)	35 (35)
Acute severe asthma	61 (63)	56 (55)
Life-threatening asthma	4 (4)	7 (7)
Near-fatal asthma	1 (1)	0
Time from presentation to receipt of study drug (n = 192), median (IQR), h	21 (12-29)	22 (14-28)

Abbreviation: IQR, interquartile range.

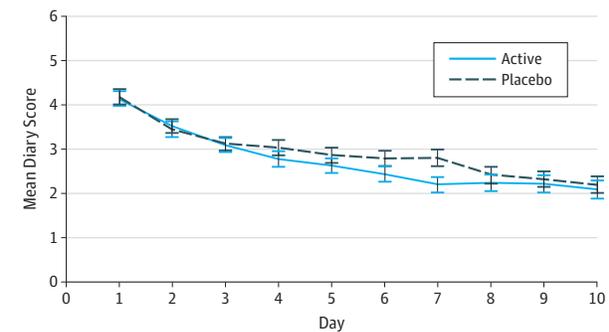
Subgroup Analyses

There were no differences in the primary outcome asthma symptom score between treatment groups in patients with positive sputum bacterial culture results, atypical bacterial PCR and/or serologic analysis results, or virus PCR test results (including any bacteria and/or virus positive test result) (eTables 13-15 and eFigures 6-8 in Supplement 1), although patient numbers for these analyses were low.

Safety

Adverse events were infrequent (eTables 16-22 in Supplement 1), with more gastrointestinal adverse events in the azithromycin group compared with placebo (35 vs 24 events, respectively) (eTable 16 in Supplement 1). There was an increased frequency of cardiac adverse events (4 vs 2, respectively) in the azithromycin group compared with placebo and a reduced frequency of respiratory, thoracic, and mediastinal

Figure 2. Primary Outcome Symptom Diary Scores From Randomization to Day 10



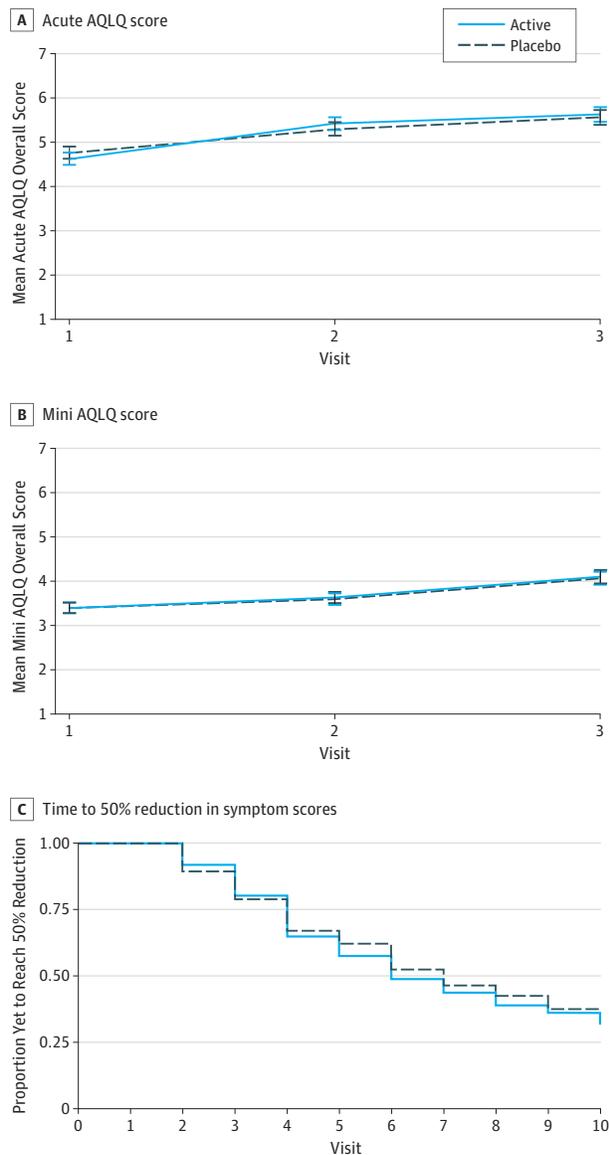
Error bars indicate standard error.

Table 2. Baseline (Exacerbation) Pulmonary Function by Treatment Arm

Pulmonary Function	Patients, No.	Mean (SD)	Percentile		
			25th	50th	75th
Azithromycin					
FEV ₁ , L	95	1.9 (0.7)	1.4	1.8	2.5
FEV _{1%} predicted, %	93	63.2 (21.8)	48	63	79
FVC, L	96	2.8 (1.0)	2.0	2.7	3.5
FEV ₁ /FVC ratio	94	69.7 (13.3)	62.0	70.0	79.0
FEF _{25%-75%} , L/s	80	1.6 (0.9)	0.9	1.4	2.1
FEF _{50%} , L/s	76	1.9 (1.1)	1.1	1.7	2.6
PEF, L/min	93	290 (104)	215	283	348
PEF % predicted, %	92	65.7 (23.4)	47.0	67.0	79.0
Placebo					
FEV ₁ , L	96	2.1 (0.8)	1.5	2.0	2.6
FEV _{1%} predicted, %	96	66.3 (21.0)	52.5	64.0	84.0
FVC, L	96	3.1 (1.0)	2.4	3.0	3.6
FEV ₁ /FVC ratio	96	68.8 (13.7)	58.0	69.0	79.5
FEF _{25%-75%} , L/s	87	1.7 (1.1)	0.9	1.4	2.4
FEF _{50%} , L/s	84	2.0 (1.3)	1.1	1.7	2.8
PEF, L/min	96	323 (98)	248	341	390
PEF % predicted, %	95	73.0 (21.5)	56.0	75.0	90.0

Abbreviations: FEF_{25%-75%}, forced mid-expiratory flow; FEF_{50%}, forced expiratory flow at 50% expiration; FEV₁, forced expiratory volume in 1 second; FEV₁/FVC, ratio of forced expiratory volume in 1 second to forced vital capacity; FVC, forced vital capacity; PEF, peak expiratory flow.

Figure 3. Secondary Outcome Acute and Mini Asthma Quality of Life Questionnaire (AQLQ) Scores From Randomization to Day 10 and Time to 50% Reduction in Symptom Diary Score



A and B, Acute and Mini AQLQ mean scores by visits for each treatment arm. Error bars indicate standard error. C, Kaplan-Meier curves of time to a 50% reduction in symptom diary score for each treatment arm (truncated at 10 days).

(63 of 64 respiratory) adverse events (27 vs 37, respectively) (eTables 16 and 20 in Supplement 1), suggesting that antibiotic therapy possibly reduced respiratory adverse events in this population.

Discussion

In the patients with asthma exacerbations randomized to treatment or placebo in this study, the addition of azithromycin to standard medical care resulted in no statistically or clinically sig-

nificant therapeutic benefit. The findings were consistently negative across 3 different symptom and quality-of-life scores, including 1 previously reporting statistically and clinically significant benefit with telithromycin treatment.¹² The findings were also negative for all measures of lung function, including FEV₁, which was significantly improved in the previous study,¹² and for time to a 50% reduction in asthma symptoms, which was significantly improved in the previous study.¹²

Recruitment proved challenging; initially there were 10 centers, each aiming to recruit 38 participants over 1 winter season, to recruit the planned 380 patients. Our power calculation deliberately mandated large patient numbers to provide statistically robust data to settle the important clinical question regarding antibiotic efficacy in this setting (for comparison, the telithromycin study randomized 270 patients).¹² We also desired larger patient numbers to enhance subgroup analyses aimed at potentially important mechanistic questions. Once recruitment obstacles became clear with such widespread antibiotic use, a total of 31 centers were enrolled, inclusion criteria were relaxed to change eligibility criteria from less than 24 to less than 48 hours from time of presentation, to include older participants with low smoking histories, and recruitment was extended to 2 years and 7 months. However, despite all these efforts, only 199 participants were recruited by medication expiry and funding end dates and the study was terminated despite not reaching its recruitment target. The study was therefore underpowered and a difference of 0.3 in mean symptom score between treatment arms at 10 days cannot be excluded.

The different outcomes of the present and previous studies,¹² which used closely related therapies in similar study designs, require interpretation and/or explanation. The antibiotics studied are different, albeit related. Both drugs were used at their standard recommended doses and durations of therapy. The shorter duration of treatment with azithromycin (3 days vs 10 days with telithromycin) is unlikely to explain the difference in outcome because azithromycin has a long tissue half-life and is likely to have remained at therapeutic doses in the lung for approximately 10 days.²⁹ Azithromycin but not telithromycin has antiviral activity,²⁶ so this is an unlikely explanation. In terms of antibacterial activity against relevant respiratory bacteria, telithromycin is reportedly more active than azithromycin against *Streptococcus pneumoniae* but has similar activity against both *Moraxella catarrhalis* and *Haemophilus influenzae*.³⁰⁻³² Because the present study only detected 3 *S pneumoniae*, 1 *M catarrhalis*, and no *H influenzae* infections in the active treatment arm, differences in activity against these organisms seem unlikely to explain the differing outcomes. In terms of anti-inflammatory activities, both drugs reportedly have similar activities when compared.²⁵

A remarkable finding of this study was the number of patients (2044) excluded because they were already receiving antibiotic therapy for their asthma exacerbation despite treatment guidelines recommending that such therapy not be routinely given.^{23,24} For each patient randomized, more than 10 were excluded for this reason. This important finding has obvious and worrying implications regarding antibiotic stewardship³³; in addition, such high antibiotic use rates may also have directly influenced the study outcome because it is

possible that patients who might potentially have benefitted from antibiotic therapy for their asthma exacerbation (through having sputum production, sputum purulence, fever) were excluded from the study through already having received them. The population remaining to be randomized could theoretically have been selected against for antibiotic responsiveness, through having no clinical indication that antibiotic therapy might be of benefit. This is possible because patients being screened had often been seen by their primary care practitioner, by emergency department medical staff, and by a member of the on-call respiratory and/or medical team, so in many instances 3 independent physicians and/or teams had assessed them, including their suitability for antibiotic therapy. It is likely therefore that those not prescribed antibiotics were negatively selected against, for suitability for antibiotics. This interpretation is supported by the low bacterial and/or atypical bacterial positivity rate found in this study: only 9.3% of azithromycin-treated participants.

It is also possible that the population randomized were in other ways not representative of the larger population screened because more than 2000 other patients were excluded from the study for other reasons (Figure 1). The telithromycin study did not report numbers of patients screened,¹² so it is not possible to determine to what extent these caveats may also have applied to that study.

A further difference is that all patients randomized to this study were required to be prescribed oral and/or systemic corticosteroid treatment, whereas in the telithromycin study only 34.1% of patients randomized to active treatment required corticosteroid therapy.¹² Requirement for corticosteroid treatment in this study was designed to reduce the number of milder exacerbations studied. However, if our study included largely non-bacterially infected participants, this could have resulted in us studying possible anti-inflammatory effects of azithromycin, in the face of the powerful anti-inflammatory effects of corticosteroids, with predictably negative results.

The clinical characteristics of the patients in our study compared with those in the telithromycin study were similar in terms of mean age (39.9 years in our study vs 39.5 in the telithromycin study), sex (30.2% male vs 32%), smoking status (mean of 3.44 vs 2.15 pack-years), exacerbation symptom score severity (4.16 vs 2.9), and lung function at exacerbation (PEF, 69.4% vs 55.2% of predicted; FEV₁, 64.8% vs 67.2% of predicted; FEV₁/FVC, 69.2% vs 72%).¹² Differences in clinical characteristics do not seem a likely explanation for the difference in outcome of the 2 studies.

The studies differed strikingly in one regard: 61% of telithromycin-treated but only 5.2% of azithromycin-treated patients had a positive test result for current atypical bacterial infection.¹² Both studies used similar sampling and detection methods, although the laboratories performing the analyses differed (GR Micro London, England, for telithromycin; S.L.J.'s laboratory for this study). Detection rates by PCR were low in both stud-

ies (3 positive in the telithromycin study and 0 positive in this study). In contrast, serological positive results differed markedly: the telithromycin study positive results were almost all *C pneumoniae* IgM positives, while in our study only 1 sample was IgM positive for this organism. Both studies used the same assay (Medac *C pneumoniae* IgM sandwich enzyme-linked immunosorbent assay, Medac) so the discrepancy between the results of this assay is difficult to explain. This major difference in frequency of *C pneumoniae* IgM positivity may have contributed to the difference in clinical outcomes between the 2 studies.

Sputum culture for standard bacteria was not performed in the telithromycin study.¹² In the present study, 105 (52.8%) participants provided sputum samples for bacterial culture and positivity was observed in 6.0% (4.1% active, 7.8% placebo). These results, together with the negative outcomes in relation to therapy, suggest that the role of standard bacterial infection in the population studied was unlikely to be important.

Interpretation of the outcome of this study must be considered in the light of prior knowledge that noninfectious agents can also trigger exacerbations, and of other randomized placebo-controlled studies investigating the effects of similar therapies in acute wheezing episodes. In addition to the telithromycin study reporting positive outcomes in asthma exacerbations in adults,¹² azithromycin treatment during bronchiolitis in infancy was reported to reduce nasal lavage interleukin 8 levels, the occurrence of postbronchiolitic wheezing,³⁴ and the duration of acute episodes of asthma-like symptoms in 1- to 3-year-old children.³⁵ Furthermore, in 1- to 6-year-old children with histories of recurrent severe lower respiratory tract infections (LRTIs), azithromycin treatment early during an apparent respiratory tract infection reduced the likelihood of severe LRTI.³⁶ Finally, low-dose azithromycin prophylaxis for 6 months in participants with exacerbation-prone severe asthma did not reduce the primary outcome (rate of severe exacerbations and LRTIs necessitating treatment with antibiotics); however, in a pre-defined subgroup analysis according to inflammatory phenotype, azithromycin treatment benefitted participants with noneosinophilic severe asthma.³⁷ We therefore carried out a similar post hoc analysis but found no evidence of benefit in this subgroup (eResults in Supplement 1). Thus, further study of azithromycin treatment in acute exacerbations of asthma in adults and children in settings of low rates of antibiotic use and stratifying on blood and/or sputum cell counts seems justified.

Conclusions

In the patients randomized to treatment or placebo in this study, addition of azithromycin to standard medical care resulted in no statistically significant or clinically important benefit. However, for each patient randomized, more than 10 were excluded because they had already received antibiotics.

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