The Azithromycin for Acute Exacerbations of Asthma (AZALEA) Randomized Clinical Trial

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Mary Cross: design of study, analysis and interpretation of data, drafting/revising report, approval of report

Christopher Brightling, Rekha Chaudhuri, Timothy Harrison, Adel Mansur, Christopher Corrigan, Bernard Higgins, Philip Ind, Dave Singh, Neil Thomson, Anoop Chauhan: conception and design of study, analysis and interpretation of data, drafting/revising report, approval of report

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Abstract

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 of asthma attacks in adults resulted in clinical benefit.

Design: The AZithromycin Against pLacebo in Exacerbations of Asthma (AZALEA) randomized, double-blind, placebo-controlled clinical trial ran from September 2011 to April 2014.

Setting: UK-based multi-center study in adults requesting emergency care for acute asthma exacerbations.

Participants: Adults with a history of asthma for >6 months, recruited within 48 hours of presentation to medical care with an acute deterioration in asthma control requiring a course of oral/systemic corticosteroids.

Intervention: Azithromycin 500mg daily or matched placebo for 3 days.

Main Outcomes: The primary outcome was diary card symptom score 10 days after randomization, with an hypothesized treatment effect size of -0.3. Secondary outcomes were diary card symptom score, quality of life questionnaires and lung function changes between exacerbation and day 10, and time to 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 non-recruitment was receiving antibiotics (2044, 44.6% of screened subjects). Median time from presentation to drug administration was 22 hours. Exacerbation characteristics were well balanced across treatment arms and centers. The primary outcome asthma symptom scores in this likely underpowered study were: mean (SD) 4.14 (1.38) at exacerbation and 2.09 (1.71) at 10 days for azithromycin; 4.18 (1.48) and 2.20 (1.51) for placebo.

Using multilevel modeling, there was no significant difference in symptom scores between azithromycin and placebo at day 10 (difference -0.166 [95% confidence interval -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:** In this randomized population, azithromycin resulted in no statistically or clinically significant benefit. For each patient randomized, >10 failed screening because they had already received antibiotics.

**Trial Registration:** ClinicalTrials.gov Identifier: NCT01444469, https://clinicaltrials.gov/ct2/show/NCT01444469?term=AZALEA&rank=1

Word count: 347 words (including headings)
List of abbreviations

AZALEA  AZithromycin Against pLacebo for acute Exacerbations of Asthma

FEF$_{25-75\%}$  Forced mid-expiratory flow

FEF$_{50\%}$  Forced expiratory flow at 50% expiration

FEV$_1$  Forced expiratory volume in one second

FEV$_1$/FVC  Ratio of forced expiratory volume in one second to forced vital capacity

FVC  Forced vital capacity

LRTI  Lower respiratory tract infection

PCR  Polymerase chain reaction

PEF  Peak expiratory flow

AQLQ  Asthma quality of life questionnaire
Background

Asthma morbidity, mortality and major health care costs result from acute attacks (exacerbations)\(^1\). The majority of asthma patients report an exacerbation in the last year, with >1/3 children and >1/4 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 (\textit{Mycoplasma} and \textit{Chlamydophila (C.) pneumoniae}) infection/reactivation is also associated, with serologic positivity rates of 40-60\% in some studies\(^8-12\), indicating 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 culture\(^16\) and molecular techniques\(^17\) and impaired interferon/Th\(_1\) responses to bacterial polysaccharides\(^18,19\). Viral infection impairs antibacterial innate immune responses\(^20\) and increases bacterial adherence to bronchial epithelium\(^21\). Thus, bacterial infections are more common and more severe in asthma, viruses increase susceptibility to bacterial infection and acute wheezing episodes in children aged <3 years were associated with both bacterial and virus infection\(^22\).

Asthma exacerbations treated with telithromycin had greater reductions in asthma symptoms, improvement in lung function and faster recovery compared to placebo\(^12\). However, liver toxicity limits telithromycin to life threatening infections and guidelines recommend antibiotics should NOT be administered routinely in asthma exacerbations\(^23,24\).

The AZALEA study investigated the effectiveness of azithromycin 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, anti-inflammatory properties\(^25\) and azithromycin, but not telithromycin, was anti-viral\(^26\) augmenting production of interferons that are deficient in asthma\(^19,27\). A mechanistic/exploratory aim of AZALEA was to determine whether treatment benefitted patients with these infections.
Methods

Study design

This United Kingdom-based multi-center, double-blind, placebo-controlled study randomized eligible patients to azithromycin 500mg daily or placebo for 3 days on day 1 (Visit 1), with post-therapy assessments/visits on days 5 (Visit 2) and 10 (Visit 3) and for serum sampling at six weeks (Visit 4).

The main inclusion criteria were adults aged 18-55 years with any smoking history, aged 56-65 with <20 pack year smoking history or >65 years with <5 pack year smoking history with a documented history of asthma for >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) requiring a course of oral/systemic corticosteroids (based on clinical judgement by attending physicians) and a peak expiratory flow (PEF) or forced expiratory volume in one second (FEV$_1$) 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/systemic antibiotics within 28 days of enrolment, need for intensive care, significant lung disease other than asthma, chronic use of >20mg oral corticosteroid daily, known QT-interval prolongation, history of brady/tachy arrhythmias or uncompensated heart failure and patients on 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). Secondary outcomes included the acute Asthma Quality of Life Questionnaire (AQLQ), the mini AQLQ, FEV$_1$, forced vital capacity (FVC), FEV$_1$/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 sub-group analyses were planned in relation to initial standard/atypical bacteriologic and virologic status.
Spontaneous or induced sputum was taken where possible at exacerbation and sent for quantitative bacteria culture. A nasal mucus sample, nasal and throat swabs were taken where possible at exacerbation and these and spontaneous/induced sputum were analyzed by viral and atypical bacterial PCRs and acute and convalescent sera for atypical bacterial serology.

The trial received Research Ethics Committee approval and all patients gave written informed consent. Additional methods are available in the Online Supplement.

Statistical analyses

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

All patients who returned at least one diary card and received study drug were included in the intention-to-treat analyses. As the timing of greatest magnitude of any treatment effect was not known, multilevel modelling was used to calculate the estimated differences in primary and secondary outcomes between treatment arms 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 Online Supplement. 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 September 2011 to April 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, 199 were randomized, 97 to active treatment, 102 to placebo (Figure 1). The major reason for non-recruitment was already receiving antibiotics (2044, 44.6% of screened patients).

Clinical characteristics of randomized patients are summarized in Table 1. Study participants’ mean age was 39.9 years, gender 69.8% female, 30.2% male. Underlying asthma severity, smoking status, exacerbation severity and median time from presentation to trial drug administration are in Table 1.

Pulmonary function at baseline (exacerbation, Visit 1) are in Table 2 and include PEF 74.8% predicted, FEV1 64.8% predicted, and FEV1/FVC 69.2% (all means). Baseline characteristics were well balanced across treatment arms and centers.

Of the 199 patients randomized, all attended visit 1 (randomization), 21 (11%) missed Visit 2, 28 (14%) missed Visit 3 and 39 (20%) missed Visit 4, 80% of patients attended all follow-up visits. Missing visits/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 azithromycin and 4.18 (1.48) and 2.20 (1.51) respectively for placebo. Using multilevel modeling, there was no statistically significant difference in symptom scores between groups at day 10 (difference -0.166 [95% CI: -0.670; 0.337], Figure 2 and Online Supplement eTable 3).

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 Online Supplement eTable 3).

No significant between group differences were seen in acute AQLQ, mini AQLQ (Figure 3a and 3b and Online Supplement eTables 7-10) nor in any measure of lung function (Online Supplement eTables 11 and 12) 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

105 (52.7%) patients provided sputum for bacterial culture, 191 (96.0%) nasal/throat mucus/swabs for virus/atypical bacterial PCR and 158 (79.4%) acute (IgM) and acute and convalescent (IgG, IgA) sera for atypical bacterial serology.

A bacterial/atypical bacterial test positive occurred in 10.6% of patients (9.3% active, 11.8% placebo). Nasal/throat swab/mucus and/or sputum virus PCRs were positive in 18.1% of patients (16.5% active, 19.6% placebo).

Subgroup analyses

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

Safety

Adverse events were infrequent (Online Supplement eTables 16-22), with more gastrointestinal adverse events in the azithromycin group compared to placebo (35 vs 24 events respectively Online Supplement eTable 16). There was an increased frequency of cardiac adverse events (4 vs 2 respectively) in the azithromycin group compared to placebo and a reduced frequency of respiratory, thoracic and mediastinal (63/64 respiratory) adverse events (27 vs 37 respectively) Online Supplement eTables 16 and 20), suggesting antibiotic therapy possibly reduced respiratory adverse events in this population.
Discussion

In the patients with asthma exacerbations randomized to treatment/placebo in this study, addition of azithromycin to standard medical care resulted in no statistically or clinically significant therapeutic benefit. The findings were consistently negative across three different symptom and quality of life scores, including one previously reporting statistically and clinically significant benefit with telithromycin\textsuperscript{12}. The findings were also negative for all measures of lung function, including FEV\textsubscript{1} which was significantly improved in the previous study\textsuperscript{12} and for time to a 50\% reduction in asthma symptoms, which was significantly improved in the previous study\textsuperscript{12}. Recruitment proved extremely challenging; initially there were 10 centers each aiming to recruit 38 subjects over one 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)\textsuperscript{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 usage, a total of 31 centers were enrolled, inclusion criteria were relaxed to change eligibility criteria from $<$24 to $<$48 hours from time of presentation, to include older subjects with low smoking histories and recruitment was extended to 2 years and 7 months. However, despite all these efforts only 199 subjects 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 study\textsuperscript{12}, which employed closely related therapies in very similar study designs, requires interpretation/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, as azithromycin has a very long tissue half-life and
is likely to have remained at therapeutic doses in the lung for around 10 days\textsuperscript{28}. Azithromycin, but not telithromycin has anti-viral activity\textsuperscript{26}, so this is an unlikely explanation. In terms of anti-bacterial activity against relevant respiratory bacteria, telithromycin is reportedly more active than azithromycin against \textit{S. pneumoniae}, but has similar activity against both \textit{M. catarrhalis} and \textit{H. influenzae}\textsuperscript{29-31}. Since the present study only detected 3 \textit{S. pneumoniae}, 1 \textit{M. catarrhalis} and no \textit{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\textsuperscript{25}.

A remarkable finding of this study was the number of patients (2044) excluded as they were already receiving antibiotic therapy for their asthma exacerbation, despite treatment guidelines recommending such therapy should not be routinely given\textsuperscript{23,24}. For each patient randomized, more than 10 were excluded for this reason. This important finding has obvious and worrying implications regarding antibiotic stewardship\textsuperscript{32}, in addition, such high antibiotic usage may also have directly influenced study outcome as 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 as patients being screened had often been seen by their primary care practitioner, by emergency room medical staff and by a member of the on call respiratory/medical team, so in many instances three independent doctors/teams had assessed them, including their suitability for antibiotics. It is likely therefore that those not prescribed antibiotics were negatively selected against, for suitability for antibiotics. This interpretation is supported by the very low bacterial/atypical bacterial positivity rate found in this study: only 9.3% of azithromycin treated subjects. It is also possible that the population randomized were in other ways not representative of the larger population screened, as over 2000 other patients were excluded from the study for other reasons.
(Figure 1). The telithromycin study did not report numbers of patients screened\textsuperscript{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/systemic corticosteroid treatment, while in the telithromycin study only 34.1\% of patients randomized to active treatment required corticosteroid therapy\textsuperscript{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 subjects, 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 to 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), gender (30.2\% male vs 32\%), smoking status (mean of 3.44 pack years vs 2.15), exacerbation symptom score severity (4.16 vs 2.9) and lung function at exacerbation (PEF 74.8\% predicted vs 55.2\%, FEV\textsubscript{1} 64.8\% predicted vs 67.2\%, FEV\textsubscript{1}/FVC 69.2\% vs 72\%)\textsuperscript{12}. Differences in clinical characteristics do not seem a likely explanation for the difference in outcome of the two studies.

The studies differed strikingly in one regard: 61\% of telithromycin-treated but only 5.2\% of azithromycin-treated patients had a positive test for current atypical bacterial infection\textsuperscript{12}. Both studies used similar sampling and detection methods, though the laboratories performing the analyses differed (GR Micro, London UK for telithromycin, Prof Johnston’s laboratory for this study). PCR detection rates were very low in both studies (3 positive in the telithromycin study and 0 positive in this study). In contrast, serological positives differed markedly: the telithromycin study positives were almost all \textit{C. pneumoniae} IgM positives, while in our study only one sample was IgM positive for this organism. Both studies used the same assay (Medac \textit{C. pneumoniae} IgM sandwich ELISA, Medac, Hamburg, Germany) so the discrepancy between the results of this assay is difficult to explain. This major difference in frequency of \textit{C. pneumoniae} IgM positivity may have contributed to the difference in clinical outcomes between the two studies.
Sputum culture for standard bacteria was not performed in the telithromycin study\textsuperscript{12}. In the present study 105 (52.8\%) subjects provided sputum 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 non-infectious 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\textsuperscript{12}, azithromycin treatment during bronchiolitis in infancy was reported to reduce nasal lavage IL-8, the occurrence of post-bronchiolitic wheezing\textsuperscript{33} and the duration of acute episodes of asthma-like symptoms in 1-3 year old children\textsuperscript{34}. Furthermore, in 1-6 year old children with histories of recurrent severe lower respiratory tract infections (LRTIs), azithromycin early during an apparent RTI reduced the likelihood of severe LRTI\textsuperscript{35}. Finally low-dose azithromycin prophylaxis for 6 months in subjects with exacerbation-prone severe asthma did not reduce the primary outcome (rate of severe exacerbations and LRTIs requiring treatment with antibiotics) however in a predefined subgroup analysis according to inflammatory phenotype, azithromycin benefitted subjects with non-eosinophilic severe asthma\textsuperscript{36}. We therefore carried out a similar post hoc analysis, but found no evidence of benefit in this subgroup (\textbf{Online Supplement}). Thus further study of azithromycin in acute exacerbations of asthma in adults and children in settings of low antibiotic usage and stratifying on blood/sputum cell counts seems justified.

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

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The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all raw data and the corresponding author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
References


Figure legends

Figure 1. CONSORT diagram of the AZALEA trial.

Figure 2: Primary outcome symptom diary scores from randomization to day 10.
Data are mean with standard error (SE) bars.

Figure 3: Secondary outcome acute and mini AQLQ scores from randomization to day 10 and time to 50% reduction in symptom diary score.
(a) Acute AQLQ and (b) mini AQLQ mean scores and standard error (SE) bars by visits for each treatment arm and (c) Kaplan-Meier curves of time to a 50% reduction in symptom diary score for each treatment arm (truncated at 10 days).
<table>
<thead>
<tr>
<th>Table 1: Baseline characteristics of patients by treatment group</th>
<th>Active</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>97</td>
<td>102</td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td>39.1 (28.9, 49.5)</td>
<td>36.15 (25.4, 49.3)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>64 (66.0%)</td>
<td>75 (73.5%)</td>
</tr>
<tr>
<td>Male</td>
<td>33 (34.0%)</td>
<td>27 (26.5%)</td>
</tr>
<tr>
<td>Asthma Severity (N = 198)††</td>
<td></td>
<td></td>
</tr>
<tr>
<td>step 1: mild intermittent asthma</td>
<td>7 (7.2%)</td>
<td>13 (12.9%)</td>
</tr>
<tr>
<td>step 2: regular preventer therapy</td>
<td>30 (30.9%)</td>
<td>26 (25.7%)</td>
</tr>
<tr>
<td>step 3: initial add-on therapy</td>
<td>31 (32.0%)</td>
<td>27 (26.7%)</td>
</tr>
<tr>
<td>step 4: persistent poor control</td>
<td>22 (22.7%)</td>
<td>22 (21.8%)</td>
</tr>
<tr>
<td>step 5: continuous/frequent oral steroids</td>
<td>7 (7.2%)</td>
<td>13 (12.9%)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>never smoked</td>
<td>60 (61.9%)</td>
<td>61 (60.4%)</td>
</tr>
<tr>
<td>former smoker</td>
<td>26 (26.8%)</td>
<td>19 (18.8%)</td>
</tr>
<tr>
<td>current smoker</td>
<td>11 (11.3%)</td>
<td>21 (20.8%)</td>
</tr>
<tr>
<td>Pack years, median (IQR) (min/max) (N=75)*</td>
<td>5 (1, 15)</td>
<td>5 (2, 12)</td>
</tr>
<tr>
<td>(current/former smokers)</td>
<td>(0/127)</td>
<td>(0/22)</td>
</tr>
<tr>
<td>Asthma Exacerbation (N = 198)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild Asthma Exacerbation</td>
<td>5 (5.2%)</td>
<td>3 (3.0%)</td>
</tr>
<tr>
<td>Moderate Asthma Exacerbation</td>
<td>26 (26.8%)</td>
<td>35 (34.7%)</td>
</tr>
<tr>
<td>Acute Severe Asthma</td>
<td>61 (62.9%)</td>
<td>56 (55.4%)</td>
</tr>
<tr>
<td>Life Threatening Asthma</td>
<td>4 (4.1%)</td>
<td>7 (6.9%)</td>
</tr>
<tr>
<td>Near-Fatal Asthma</td>
<td>1 (1.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Time from presentation to study drug, median (IQR) (N = 192)</td>
<td>21 (12, 29)</td>
<td>22 (14, 28)</td>
</tr>
</tbody>
</table>
Table 2: Baseline (exacerbation) pulmonary function by treatment arm

<table>
<thead>
<tr>
<th>Pulmonary function</th>
<th>Active</th>
<th></th>
<th></th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>P25</td>
<td>Median</td>
<td>P75</td>
</tr>
<tr>
<td>FEV₁ (liters)</td>
<td>95</td>
<td>1.9</td>
<td>0.7</td>
<td>1.4</td>
<td>1.8</td>
<td>2.5</td>
</tr>
<tr>
<td>FEV₁ %predicted (%)</td>
<td>93</td>
<td>63.2</td>
<td>21.8</td>
<td>48</td>
<td>63</td>
<td>79</td>
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<tr>
<td>FVC (liters)</td>
<td>96</td>
<td>2.8</td>
<td>1.0</td>
<td>2.0</td>
<td>2.7</td>
<td>3.5</td>
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<tr>
<td>FEV₁/FVC ratio</td>
<td>94</td>
<td>69.7</td>
<td>13.3</td>
<td>62.0</td>
<td>70.0</td>
<td>79.0</td>
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<tr>
<td>FEF₂₅-₇₅% (liters/sec)</td>
<td>80</td>
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<td>0.9</td>
<td>1.4</td>
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<td>FEF₅₀% (liters/sec)</td>
<td>76</td>
<td>1.9</td>
<td>1.1</td>
<td>1.1</td>
<td>1.7</td>
<td>2.6</td>
</tr>
<tr>
<td>PEF (liters/min)</td>
<td>95</td>
<td>288</td>
<td>108</td>
<td>211</td>
<td>283</td>
<td>361</td>
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<tr>
<td>PEF %predicted (%)</td>
<td>94</td>
<td>76.6</td>
<td>108.6</td>
<td>47.0</td>
<td>67.5</td>
<td>79.0</td>
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<th>Pulmonary function</th>
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<tr>
<td></td>
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<td>Mean</td>
<td>SD</td>
<td>P25</td>
<td>Median</td>
<td>P75</td>
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<td>FEV₁ (liters)</td>
<td>96</td>
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<td>0.8</td>
<td>1.5</td>
<td>2.0</td>
<td>2.6</td>
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<td>52.5</td>
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<td>FEV₁/FVC ratio</td>
<td>96</td>
<td>68.8</td>
<td>13.7</td>
<td>58.0</td>
<td>69.0</td>
<td>79.5</td>
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<tr>
<td>FEF₂₅-₇₅% (liters/sec)</td>
<td>87</td>
<td>1.7</td>
<td>1.1</td>
<td>0.9</td>
<td>1.4</td>
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<tr>
<td>FEF₅₀% (liters/sec)</td>
<td>84</td>
<td>2.0</td>
<td>1.3</td>
<td>1.1</td>
<td>1.7</td>
<td>2.8</td>
</tr>
<tr>
<td>PEF (liters/min)</td>
<td>97</td>
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<td>247</td>
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<td>21.4</td>
<td>56.5</td>
<td>74.0</td>
<td>90.0</td>
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SD = standard deviation, P25 = 25th percentile, P75 = 75th percentile
Figure 1. CONSORT diagram of the AZALEA trial

Assessed for eligibility (n = 4582)

Excluded (n = 4383):
- Antibiotics (n = 2044)
- Other (n = 660)
- Underlying health condition (n = 417)
- Discharged (n = 315)
- Age (n = 259)
- <48-hour presentation (n = 220)
- Declined (n = 191)
- Not known (n = 130)
- No requirement for steroids (n = 110)
- No English (n = 30)
- No Asthma Exacerbation (n = 7)

Randomized (n = 199)

Allocated to Azithromycin (n = 97)
- Symptom diary scores analyzed (n = 87)
- Acute and Mini AQLQ scores analyzed (n = 96)
- Pulmonary functions analyzed (n = 97)

Allocated to Placebo (n = 102)
- Symptom diary scores analyzed (n = 89)
- Acute and Mini AQLQ scores analyzed (n = 100)
- Pulmonary functions analyzed (n = 101)
Figure 2: Primary outcome symptom diary scores from randomization to day 10.
Figure 3: Secondary outcome acute and mini AQLQ scores from randomization to day 10 and time to 50% reduction in symptom diary score.

(a)

(b)

(c)