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Azithromycin treatment in children hospitalized with asthma: a retrospective cohort study

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ABSTRACT

Objective: Azithromycin has anti-inflammatory properties in the lungs and decreases the duration of asthma-like episodes in children. We sought to evaluate length of stay (LOS) and readmission rates of children receiving azithromycin therapy during hospitalization for acute asthma exacerbations.

Methods: This was a retrospective cohort study at an urban, quaternary-care children's hospital including patients under 18 years old hospitalized for asthma, without concurrent infection, from 2002 to 2011. The primary predictor was azithromycin therapy administered within 48 hours of admission. The primary outcome was LOS and the secondary outcomes were 7, 30, and 90-day hospital readmission rates for asthma.

Results: Azithromycin therapy was administered to 174 (3%) of 5335 unique patients admitted for asthma, without concurrent infection, over the 10-year period. The overall median LOS was 2.3 days [Interquartile range, 1.8–3.1] and 9% (480) were readmitted for asthma within 90 days of discharge. Azithromycin therapy was associated with a 20% (11 hour) longer LOS (adjusted beta coefficient for log-transformed LOS, 0.18; 95% Confidence Interval (CI): 0.11–0.26), less than the 29% (16 hour) difference determined a priori as clinically relevant. Azithromycin therapy was not associated with 90-day readmission for asthma (adjusted odds ratio, 0.89; 95% CI: 0.46–1.72). The limited number of 7 and 30-day readmissions in the azithromycin treated group precluded adjusted analysis.

Conclusions: Azithromycin therapy was not associated with a clinically relevant difference in hospital LOS or with readmission rates for children hospitalized with asthma. Prospective trials are needed to determine the clinical effects of azithromycin therapy in children with asthma.

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Introduction

Asthma is a bronchospastic and inflammatory chronic lung disease that often presents in childhood. One in ten children in the United States has asthma and medical expenses for asthma account for over fifty billion dollars annually [1]. In the Bronx, a borough of New York City reported to have one of the highest prevalence's of asthma in the country, nearly 10 per 1000 children are hospitalized for asthma per year [2].

Macrolide antibiotics, including the most commonly prescribed, azithromycin, have potent anti-inflammatory properties in the lungs [3–5]. Macrolides also have primary anti-bacterial activity against atypical pathogens, including *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*, which have been implicated both in predisposing to the

development of chronic asthma [6] and triggering acute asthma exacerbations [3,7–12].

Previous studies of azithromycin therapy for asthma in adults and children have consistently shown improved inflammatory profiles, but have been inconclusive regarding clinical outcomes. Long-term use of azithromycin for adults and children with asthma is not recommended [13], yet a recent study found that when treated with azithromycin for 48 weeks, adults with asthma had fewer asthma exacerbations (1.86 per patient-year vs. 1.07 per patient year) and improved quality of life. Treatment in the acute setting with a short-course is less studied. Children treated with a short-course of macrolide therapy in a randomized prospective trial of clarithromycin involving 43 patients showed reduction of TNF- α , IL-1 β , and IL-10

levels, but no Repeat of work clinical differences in clinical asthma symptoms [3]. In preschool children 1–3 years old, azithromycin reduced the length of an asthma-like episode from 7.7 days to 3.4 days [14]. Young children 1–6 years old treated with azithromycin had a 36% decrease in risk of progression to a severe lower respiratory tract infection [15]. These findings were less prominent in adult populations. Treatment with telithromycin, a macrolide similar to azithromycin, in adults with acute asthma found a statistically significant, but perhaps not clinically relevant, one-third of a point reduction in a 7-point asthma score. Adults treated with azithromycin within 48 h of presentation to medical care for an acute asthma exacerbation had no differences in asthma score, quality of life, or lung function when compared to placebo [16].

A Cochrane review in 2015 found that when compared to placebo, macrolides did not affect clinical outcomes including: hospital admission, oral steroids use, symptom scales, asthma control, quality of life, lung function, and rescue inhaler use [13]. The review did not include short-term use of macrolides for asthma in children. Although current recommendations do not support the routine use of macrolides in the treatment of children with asthma [17,18], almost half a million prescriptions for macrolides were written over a 10-year period studied for children presenting for ambulatory asthma visits, without concurrent documented infection [19]. Little is known about clinical outcomes of macrolide therapy for acute exacerbations of pediatric asthma, particularly in the inpatient setting.

We sought to examine the hospital-based clinical outcomes of length of stay (LOS) and 7, 30, and 90-day readmission rates in a cohort of children admitted for asthma who received the most commonly prescribed macrolide, azithromycin, with no known concurrent infection. We hypothesized that azithromycin therapy would reduce hospital LOS by 16 h or more, in children hospitalized for acute asthma, without concurrent infection. We further hypothesized that this LOS reduction would not affect 7, 30, or 90-day readmission rates for asthma and that patients with intensive care stays would have different outcomes due to indication bias of the azithromycin receipt and increased severity of their asthma exacerbation.

Methods

Study design

Data for this retrospective cohort study included de-identified electronic records at an urban, quaternary

children's hospital. We extracted data from clinical and administrative datasets by means of Looking GlassTM Clinical Analytics (Streamline Health, Atlanta, Georgia), a user-friendly interactive software application unique to our hospital system. This study was reviewed and deemed exempt by our Institutional Review Board.

Primary diagnosis of asthma for admission was determined by using Internal Classification of Diseases, Ninth Revision (ICD-9) billing codes for asthma (493.00, 493.01, 493.02, 493.10, 493.11, 493.20, 493.21, 493.22, 493.90, 493.91 and 493.92). For inclusion, the code for asthma was the primary billing code, as used in similar retrospective studies [20,21]. If a patient was admitted more than once in the time period from 2002 to 2011, only the first admission was analyzed.

Patients were excluded if their admission had secondary billing codes for infection requiring antibiotics consistent with a previous study of antibiotic use in the pediatric outpatient asthma population [19]. Exclusion for infection requiring antibiotics included sinusitis, pharyngitis, tonsillitis, acute otitis media, mastoiditis, diphtheria, pertussis, streptococcal sore throat, peritonsillar abscess, non-viral pneumonia (including mycoplasma pneumonia), tuberculosis, skin infections, and urinary tract infections (ICD-9 codes: 461-463, 381-382, 383, 033, 034, 035, 475, 481-486, 010-018, 680-686, 035, 595.0, 595.9, 599.0.)

Setting and population

The study was conducted at a 132-bed quaternary-care children's hospital in the Bronx borough of New York City. Children less than 18 years of age admitted with a primary diagnosis of asthma were included in the analysis. Children with infection requiring antibiotics were excluded.

Primary predictor and outcome measures

The primary predictor in our model was azithromycin administration, as determined by nursing administration time, within the first 48 h of an admission for asthma. The primary outcome for this analysis was the hospital LOS and the secondary outcomes were 7, 30, and 90-day hospital readmission for asthma.

Data analysis

Descriptive analysis was performed of the baseline demographic and clinical characteristics of study

participants. Bivariate associations of categorical variables with azithromycin therapy receipt were evaluated by the Chi-square or Fisher's exact tests. Continuous variables were compared between azithromycin treated and untreated patients with the Mann-Whitney test.

Multivariable linear regression models were used to investigate the association of azithromycin therapy with primary outcome, LOS, while adjusting for possible confounders. LOS data were not normally distributed, so a log transformation was applied and the results are reported as a percent change in LOS (anti-log of the beta coefficient) for ease of interpretation, as well as a change in the log-transformed LOS (beta coefficient), similar to prior studies with log-LOS as an outcome [20]. Starting from the full model with azithromycin therapy status as the primary predictor and including all potential confounders and their two-way interactions, a backward-stepwise approach was considered for variable selection. Variables that were not associated with the outcome at a significance level of 0.05 and did not change the beta coefficient of the treatment effect by more than 15% were eliminated from the model. An unadjusted linear regression model with only treatment status was fitted for the purpose of comparison to the final model. The data was also analyzed by propensity score matching to verify that the azithromycin therapy effect estimated by multivariable linear regression was consistent with the propensity score adjusted estimate. The propensity score model for receiving azithromycin therapy included the same covariates considered in the multivariable linear regression analysis. Each azithromycin treated patient was matched to the nearest untreated patient who was within 0.05 calipers of the treated patient's propensity score.

A secondary analysis was conducted to assess the effect of azithromycin therapy on the likelihood of 7, 30, and 90-day readmission for asthma by fitting multivariable logistic regression models with the backward-stepwise method described above. Results of the adjusted and unadjusted logistic regression models are reported as odds ratios. Unadjusted comparisons of 7 and 30-day readmissions between azithromycin treated and untreated patients were performed by Fisher's exact test.

Power analysis

A power analysis was performed using a preliminary estimate of the cohort size and the LOS. We assumed a mean LOS of 2.8 days in the untreated comparison group, and standard deviation of 1.6 days, with a total cohort size of 8700 patients and 250 subjects in the

azithromycin therapy group. *A priori*, a clinically relevant difference in LOS was determined to be 16 h (0.67 days) as it would lead to one less calendar day in hospital stay and its associated costs, as well as one less day missed of school for the patient and work for a parent/guardian. With the sample sizes and assumptions stated above, the study had more than 99% power to detect a difference of 16 h in LOS between the two groups at a 5% significance level using a two-sided Mann-Whitney Test. In addition, with 80% power we could detect an effect size of 0.2 days using the same sample size.

Results

Patient characteristics

There were 10 729 admissions for asthma between 2002 and 2011. Among the 5335 unique patients with asthma meeting inclusion criteria, azithromycin therapy was administered to 174 (3%) of patients, all others were considered the non-treated group (Figure 1). The proportion of patients administered azithromycin without infection indication varied ten-fold over the study period, with nadir of 3 (0.6%) patients in 2005, to a peak of 32 (5.8%) patients in 2008. Patient characteristics were significantly different across groups, including age, gender, pediatric intensive care stay, terbutaline

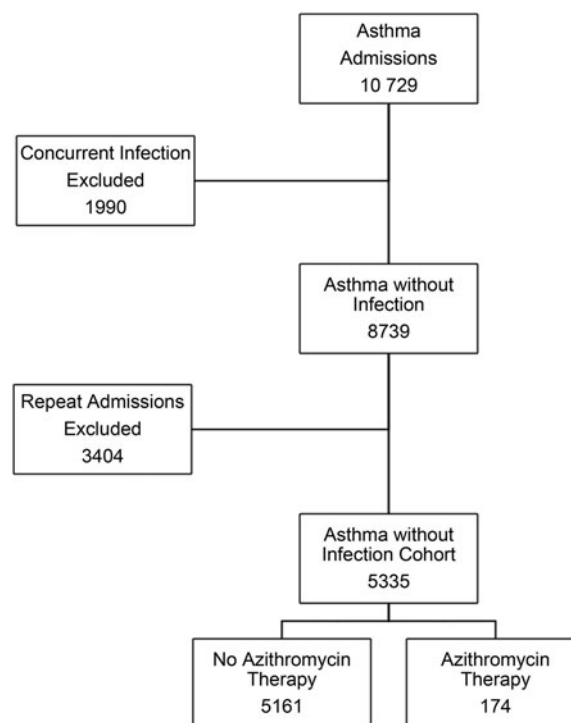


Figure 1. Asthma admissions and cohort enrollment, 2002–2011.

Table 1. Demographic and clinical characteristics for children hospitalized with asthma.

Table 1. Demographics and clinical characteristics for children hospitalized with asthma				
Variable ^a	All patients <i>n</i> = 5335	Azithromycin therapy		<i>p</i> -value
		No <i>n</i> = 5161	Yes <i>n</i> = 174	
Demographic characteristics				
Age, years median [Interquartile range]	4.1 [1.9, 8.5]	4.0 [1.9, 8.3]	7.6 [4.4, 11.8]	<0.001
Female	38% (2045)	38% (1972)	42% (73)	0.32
Race ^b				0.71
White	5% (214)	5% (209)	4% (5)	
Black	46% (2019)	46% (1951)	49% (68)	
Other	49% (2138)	49% (2073)	47% (65)	
Hispanic ethnicity ^b	57% (2667)	57% (2581)	53% (86)	0.33
Clinical characteristics				
Pediatric intensive care stay	8% (450)	8% (410)	23% (40)	<0.001
Magnesium sulfate therapy	3% (137)	3% (135)	1% (2)	0.33 ^c
Terbutaline therapy	0.8% (45)	0.6% (29)	9% (16)	<0.001
Intubation	0.07% (4)	0.06% (3)	0.6% (1)	0.12 ^c
Prior year asthma admission	7% (356)	7% (345)	6% (11)	0.85
Admission timing				
Admission in 2007–2011 (compared to 2002–2006)	49% (2606)	48% (2484)	70% (122)	<0.001
Season				0.09
Summer	13% (669)	13% (654)	9% (15)	
Fall	35% (1848)	35% (1796)	30% (52)	
Winter	24% (1280)	24% (1228)	30% (52)	
Spring	29% (1538)	29% (1483)	32% (55)	

^aValues listed as percent (number), unless otherwise noted.^bFor Race the *n* = 4371, and for Hispanic ethnicity *n* = 4692.^cDenotes Fisher's Exact Test used.

administration, prior admission for asthma, and admission in second half of the decade studied (Table 1).

Length of stay

The overall median LOS was 2.3 days [Interquartile range (IQR), 1.8–3.1 days], and 99% of patients had a LOS less than 8.2 days. The median LOS was 3.0 days [IQR, 2.2–4.2 days) for azithromycin recipients, and 2.3 days [IQR, 1.8–3.1 days] for non-recipients ($p < 0.001$). When adjusted for confounders, azithromycin therapy in children hospitalized with asthma was associated with a longer LOS of 20% (11 h) which was less than the *a priori* determined clinically relevant difference of 29% (16 h). Propensity score matching analysis confirmed a similar increase of 19% in LOS but showed wider 95% confidence intervals (Table 2). The concordance statistic of the propensity score was 0.76, indicating reasonably good ability of the propensity score model to predict treatment status in this cohort. Distributions of patient characteristics appeared to be balanced between azithromycin treated and untreated samples matched by the propensity score.

We conducted a post-hoc power analysis using the primary outcome of LOS, since our sample size was less than expected. With a sample size of 174 treated and 5000 untreated patients, we found we had 99% power to detect a 0.67 day (16 h) difference in LOS between the two groups, assuming a standard deviation for LOS of 1.6 days for both groups and 5% significance level using two-sided Mann-Whitney test.

We also calculated that with 80% power, we could detect a 0.3 day (7.2 h) difference in LOS.

Readmission

Overall, 48 (0.9%), 193 (4%), and 480 (9%) children were readmitted for asthma within 7, 30, and 90 days of discharge from the index admission, respectively. Azithromycin therapy was not significantly associated with the odds of 90-day readmission (Table 2). There was only one readmission (0.5%) in 7 days and three readmissions (1.7%) within 30 days in the azithromycin treatment group while there were 47 (0.9%) and 190 (3.7%) respectively in untreated group. The unadjusted readmission rate was not significantly different between azithromycin treated and untreated groups by Fisher's exact test for both 7 and 30 days ($p > 0.99$ and 0.22, respectively). Due to the limited numbers of readmissions at 7 and 30-days for the treatment group, the multi-variable logistic regression model was unstable and therefore this analysis was not feasible.

Discussion

In this retrospective cohort study of children hospitalized with asthma, azithromycin receipt was associated with a statistically significant, but not clinically relevant, increase in hospital LOS. Hospital LOS was 20% (11 h) longer for children receiving azithromycin compared to those that did not receive the therapy in the

Table 2. Unadjusted and adjusted association of azithromycin therapy with outcomes.

Association of azithromycin therapy with outcome	
Length of stay (days)	
Unadjusted beta coefficient (95% CI)	0.29 (0.22, 0.36)
Unadjusted percent change (95% CI)	34% (24%, 44%)
<i>p</i> -value, unadjusted	<0.001
Multivariable adjusted beta coefficient (95% CI) ^a	0.18 (0.11, 0.26)
Multivariable adjusted percent change (95% CI) ^a	20% (11%, 29%)
<i>p</i> -value, multivariable adjusted*	<0.001
Propensity score adjusted beta coefficient (95% CI) ^b	0.17 (0.05, 0.29)
Propensity score adjusted percent change (95% CI) ^b	19% (6%, 33%)
<i>p</i> -value, propensity score adjusted**	0.006
90-day readmission for asthma	
Unadjusted odds ratio (95% CI)	0.74 (0.41, 1.35)
<i>p</i> -value, unadjusted	0.33
Multivariable odds ratio (95% CI) ^c	0.89 (0.46, 1.72)
<i>p</i> -value, multivariable adjusted ^c	0.72

^aMultivariable linear regression models adjusted for possible confounders selected among age, gender, race, ethnicity, pediatric intensive care stay, magnesium sulfate therapy, terbutaline therapy, intubation, previous year asthma admission, admission year in second half of the decade studied, and season of admission. The final model included treatment status as well as age, ethnicity, intensive care stay, terbutaline administration, prior admission for asthma, admission in second half of the decade studied (2007–2011 vs. 2002–2006), and admission season.

^bMatching by propensity score of azithromycin therapy modeled with the same confounders included in the multivariable linear regression models.

^cMultivariable logistic regression models adjusted for possible confounders selected among age, gender, race, ethnicity, pediatric intensive care stay, magnesium sulfate therapy, terbutaline therapy, intubation, previous year asthma admission, admission year in second half of the decade studied, and season of admission. The variables included with azithromycin treatment status in the final model for 90-day readmission were age, race, and prior admission for asthma.

CI: confidence interval.

first 48 h of an admission for asthma. This difference was less than the *a priori* definition of a clinically relevant difference in LOS of 29% (16 h). Azithromycin receipt was not associated with 90-day readmission rates for asthma.

The azithromycin treated and untreated groups were very similar in demographic characteristics, except for age. Azithromycin treated patients had a median age nearly twice that of untreated patients (7.6 years vs. 4.0 years). Although we carefully attempted to exclude patients with infection requiring antibiotics, we surmise that this age difference may reflect treatment for *Mycoplasma pneumoniae*. This atypical pneumonia is more common after 5 years of age and has been implicated as a cause [6] and trigger of asthma [3,7–12]. We did not see that the groups were different in seasonality, however, which would support this theory since atypical pneumonia is more common in the fall and winter.

One of our hypotheses was that the effect of azithromycin therapy in patients with intensive care unit stays would differ from that in those without stays, but it was not supported by statistical evidence in our analyses. Intensive care unit stay was only a confounder, and not an effect modifier, of azithromycin therapy on LOS and was not associated with readmission. Since azithromycin is not a standardly recommended treatment, we thought that it was given more often in children in the PICU who had failed standard treatment, which was supported by our study – of the

174 patients treated with azithromycin, 23% (40 patients) had a PICU stay. However, the treatment with azithromycin did not modify the effect of azithromycin on the primary outcome of LOS. Although this was a small subset of patients, only 8% of our cohort (450 patients) had a PICU stay, this data suggests that azithromycin is not beneficial in patients even with more severe asthma evidenced by need for intensive care.

In addition to age and PICU stay, in bivariate analysis and included in the final model, treatment in the second half decade studied was both different between the two groups and an independent predictor of the primary outcome LOS. The increased use in the second half of the decade coincides with the known increased use in the outpatient setting in children with asthma [19] and underscores the relevance of our results – although there is no evidence that there are clinical benefits of azithromycin for asthma in hospitalized children, physicians continue and increasingly prescribe azithromycin for this population.

Our findings are consistent with the most recently published data on azithromycin for children with asthma; however they are inconsistent with studies in the past few years. In 2017, a study of a 5 day course of azithromycin vs. placebo for children 1–5 years of age found no difference in respiratory symptoms or time to exacerbations after an emergency room visit for asthma [22]. This study had the advantage of prospective enrollment and randomization, yet

enrollment was not complete and therefore the study was underpowered for the outcomes. Although not randomized, yet our study's 174 treated patients exceeded the number of patient treated in that study by 15% and we had over 5,000 untreated patients in comparison. Our findings, however, contrast with other studies showing reduction in respiratory symptoms [14,15]. These studies were also in very young children all under 6 years of age, differing from our cohort including children up to age 18 years. We also had a stricter definition of asthma as the primary diagnosis of admission as opposed to "asthma-like symptoms" [14] and "severe lower respiratory tract infection" [15] used in the other studies in young children.

Our large retrospective cohort of children with asthma has several advantages compared to prior studies [14–16,23]. We analyzed the largest cohort of children treated with azithromycin during a hospitalization for asthma to date (174 treated inpatients). We included children up to age 18 years, while prior pediatric studies included only children less than 6 years of age. We used a more reproducible and generalizable definition of asthma, the primary ICD-9 billing classification code for admission to the hospital. We excluded patients with billing codes for infections requiring antibiotics, including *Mycoplasma pneumoniae*. Finally, we report inpatient clinically-relevant, patient-centered, hospital-based outcomes on the use of macrolide therapy for children with asthma that have not previously been described.

We acknowledge several limitations of this study. First, this study was conducted at a single center; and the Bronx borough of New York City has one of the highest rates of asthma in the country, therefore the results of this study may not be generalizable to other populations with different race, ethnicity, asthma prevalence, and environmental exposure profiles. It is possible that we may have missed readmissions to nearby hospitals. However, we postulate that this difference in readmission to outside hospitals would be non-differential between treatment groups and therefore unlikely to affect results of the study. Second, due to the retrospective and de-identified nature of our study design, we were unable to identify the indication for azithromycin therapy for each patient. Indication bias by provider may have existed, however we did adjust for several measures of severity of asthma illness to ameliorate this bias, including intensive care unit stay and critical asthma medication administration including magnesium sulfate and terbutaline intravenously. Additionally, there may have

been other unmeasured confounders, for severity of illness and clinical or epidemiological characteristics that would obscure the effect of azithromycin therapy. The use of instrumental variables may have been an alternative to account for the unmeasured confounders, but we were unable to identify a valid instrumental variable predictive of receipt of azithromycin therapy with only indirect effect on the outcome, LOS, through azithromycin therapy. Third, we used ICD-9 billing classification to identify our patients. While this method has been validated by open chart review in previous studies [20,21], we used de-identified records, which precluded an internal chart review. Fourth, we did not exclude other patient populations that could overlap with our asthma population and would benefit from azithromycin therapy including patients with cystic fibrosis, human immunodeficiency virus (HIV), and sexually transmitted infections (STI). The single center studied is not a Cystic Fibrosis Center, and the nearest one is approximately 5 miles away so few patients are admitted to this study center. The center also has low rates of HIV and STI admissions. Finally, azithromycin therapy exposure was limited to treatment within the first 48 h of admission; therefore patients who received the medication after 48 h were classified as non-recipients. This misclassification would tend to bias the results toward the null, strengthening our results of no clinical difference found between groups.

Conclusions/key findings

In conclusion, we found that azithromycin therapy was not associated with a clinically relevant difference in hospital LOS or statistically significant difference in readmission rates for children hospitalized with asthma. Further studies, including prospective randomized controlled trials, are needed to address whether macrolide therapy affects clinical outcomes for acute asthma exacerbations in children.

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Disclosure statement

No potential conflict of interest was reported by the authors. The authors alone are responsible for the content and writing of the paper.

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