A Double-Blind, Randomized, Placebo-Controlled Trial of Azithromycin in Children Hospitalized with Acute Asthma Exacerbations

AIMS

1. To determine the clinical efficacy of azithromycin in the treatment of children with persistent asthma hospitalized with acute asthma exacerbations.
2. To obtain preliminary data regarding the mechanisms of action of azithromycin in children with acute asthma exacerbations.

BACKGROUND

Asthma is a chronic lung condition in children and adults, characterized by bronchospasm and inflammation with clinical wheezing and dyspnea. Atypical pathogens, including *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, have been implicated both in predisposing to asthma diagnosis and triggering acute asthma exacerbations. Small, but promising, studies have shown improvement in lung inflammation and asthma symptoms in patients treated with macrolide antibiotics. This effect may be secondary to treatment of atypical pathogens or due to the anti-inflammatory effects of macrolides.

Macrolides and Atypical Pathogens

Macrolides have primary anti-bacterial activity against atypical pathogens, including *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. Multiple studies have shown higher prevalence of these organisms in patients with stable and acute asthma, implying that these organisms may play a role in the pathogenesis of the disease. *Mycoplasma pneumoniae* infection has been associated with recurrent wheezing and lower forced vital capacity even in asymptomatic patients.[1] Prevalence rates range from 18-56% for *Mycoplasma pneumoniae* and/or *Chlamydia pneumoniae* in serologic titers, serum polymerase chain reaction (PCR), nasopharyngeal aspirates, or sputum of patients with asthma, and tend to be higher during acute exacerbations.[2-8] In children with asthma and *Chlamydia pneumonia*, IL-8 levels and neutrophils numbers are increased in bronchoalveolar lavage (BAL) specimens.[9] In children with asthma and *Mycoplasma pneumoniae* infection, IgE levels are lower.[10] In addition, *Chlamydia pneumoniae* infection induces MUC5AC production and gene expression needed for mucous production, which is reduced after treatment with clarithromycin.[11]

Immunomodulatory Effects of Macrolides

In addition to direct inhibition of microbial growth, macrolides have a number of anti-microbial properties including inhibition of biofilm formation, bacterial adherence, and flagella mobility, especially in *Pseudomonas aeruginosa*. In addition, they suppress both bacterial quorum sensing and production of cytotoxic enzymes, and promote phagocytosis[12].
There have been a variety of anti-inflammatory properties associated with macrolides. This class of drugs consistently decreases interleukin-8 (IL-8), a pro-inflammatory chemokine that attracts neutrophils, in nasopharyngeal aspirates[8], sputum[13], and serum[14] of asthma patients. Other inflammatory markers have been shown to be modulated by macrolides including, TNF-α[8,15] IL-1β[8], IL-10[8], IL-5, IL-12[15], MUC5AC needed for mucin production[11], neutrophil elastase, MMP-9[13], superoxide production by neutrophils[16], and VEGF[14]. A decreased number of neutrophils has also been shown in patients with asthma treated with macrolides.[13,16,17] Macrolides decrease serum and sputum eosinophil counts.[18,19] Asthma models in mice have corroborated many of these findings, in addition to finding other anti-inflammatory cytokine and chemokine effects. [20-23] The clinical immunomodulatory effects of macrolides have been

postulated by some studies to be secondary to a reduction in steroid metabolism which results increased levels of circulating steroids – a "steroid-sparing" effect.[24]

Clinical Use of Macrolides in Lung Disease

Recognizing the above effects in lung tissue, many investigators have used macrolides in the treatment of various chronic respiratory illnesses including diffuse panbronchiolitis, cystic fibrosis, non-cystic-fibrosis bronchiectasis, chronic obstructive pulmonary disease, chronic rhinosinusitis, cryptogenic organized pneumonia, bronchopulmonary dysplasia, and asthma. The most impressive results have been seen in diffuse panbronchiolitis and cystic fibrosis. After erythromycin began being used widely three decades ago for diffuse panbronchiolitis, a chronic respiratory illness found almost exclusively in Japan, the five year survival rates improved from 30% to 90%.[25] A large trial in children with cystic fibrosis infected with *Pseudomonas* and treated for 24 weeks with azithromycin, found improvement in FEV1, fewer pulmonary exacerbations, and improved weight gain.[26]

Clinical Use of Macrolides in Asthma

In long-term therapy with macrolides, adult patients with asthma have shown improved bronchiolar hyperreactivity (measured by PC20, defined as a 20% fall in FEV1).[19,27,28] In addition, spirometry has improved in many patients with asthma treated with long-term macrolides,[15,29] while others have seen no change in spirometry[28]. Multiple studies found improvement in reported asthma symptoms[13,30,31] or improvement in quality of life scoring.[13,31] Reduced steroid use was also reported in some studies.[32,33] In pediatric patients, macrolides have been shown to improve cough, bronchoconstriction[34], PC20[34], FEV1[17], and steroid use.[35]

There is less data on the potential role of macrolides in the treatment of acute asthma exacerbations. The only clinical study in short-term use of macrolide was in adults receiving telithromycin; it showed a reduction in asthma scores, but no change in spirometry.[7] There has only been one study in short-term macrolide treatment in children, however, only chemokine concentrations were reported and clinical effects were not followed.[8]

A Cochrane review in 2005 concluded that considering the small number of patients, there was "insufficient evidence to support or to refute the use of macrolides in patients with chronic asthma".[36]

Azithromycin and Asthma at CHAM

At the Children's Hospital at Montefiore (CHAM), the macrolide azithromycin is currently being used by some practitioners for its presumed anti-inflammatory effects in patients with acute asthma exacerbations. In 2010, 14% of 895 pediatric patients with a primary diagnosis of asthma received azithromycin during their inpatient stay. (Data obtained from a Clinical Looking Glass preliminary search). The length of stay of patients who received azithromycin was longer (mean: 4.5 days, median 3.8 days) than those who did not receive azithromycin (mean: 3.2 days, median 2 days) which may suggest that the current practice includes administering azithromycin to more severe asthma patients or patients refractory to standard treatments. A similar search of patients admitted with a primary diagnosis of asthma from 2008-2010 and transferred at any time to a pediatric intensive care bed, revealed that even more received azithromycin – over 30%. However, the length of stay for the critical care patients was unchanged whether they received azithromycin or not (both groups had a mean: 5.0 days, and median: 4.0 days). Although currently 14-30% of children admitted with acute asthma to CHAM receive azithromycin, there is currently no evidence on the efficacy of this treatment practice.

We propose to conduct the first double-blind, randomized, placebo-controlled trial to determine whether azithromycin will effect inpatient length of stay in children with acute asthma exacerbations.

OBJECTIVES

Primary Objective:
To conduct a double-blind, randomized, placebo-controlled trial to determine the clinical efficacy of azithromycin treatment in hospitalized children with acute asthma exacerbations, as measured by length of stay.

Secondary Objectives in a Subset of Patients – "Mechanism Subset Study":
1. To quantify the relative prevalence of atypical infection in the inpatient pediatric asthma population.
2. To determine if atypical infection with *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* is associated with treatment effect, if found.
3. To determine immunomodulatory effects of azithromycin in children hospitalized with acute asthma exacerbations, as measured by neutrophil counts, eosinophil counts, and interleukin-8.

Hypothesis:
Azithromycin treatment will decrease length of stay in children with persistent asthma hospitalized with acute asthma exacerbation.

OUTCOME MEASURES

Primary Outcome:
Length of Stay

Secondary Outcomes:
Telephone follow-up at one week and one month:
1. Hospital readmission rate
2. Days missed of school for patient
3. Days missed of work for parent/guardian
4. Number of emergency room visits for asthma symptoms since discharge
5. Number of physician office visits for asthma symptoms since discharge
6. Number of recurrences of asthma symptoms since discharge
7. Number of courses of oral steroids since discharge (only at 1 month follow-up)

Also monitored: Respiratory viral panel or rapid viral testing results (if obtained as part of medical care), chest x-ray results (if obtained as part of medical care), medication side effects (diarrhea, abdominal pain, vomiting, flatulence), transfer to intensive care unit, time of wean of beta-agonists (q3h and q4h), and asthma severity (PASS score) at time of enrollment

"Mechanism Subset Study": A Pilot and Feasibility Study in the subset of patients who consent to sample retrieval:
- Nasopharyngeal aspirate samples on enrollment and at 48 hours – measure a set of select biomarkers associated with inflammation (including IL-8) via Bioluminex or ELISA technology, eosinophil and neutrophil count per high power field, Mycoplasma and Chlamydia PCR

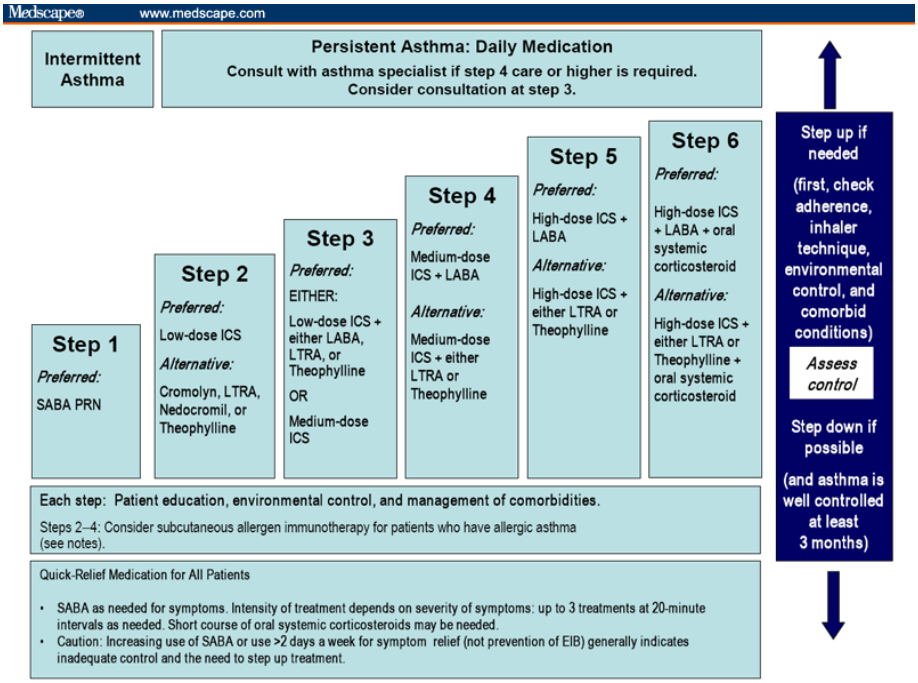
- Serum on enrollment and at 48 hours – measure same biomarkers of inflammation as in above aspirate, Mycoplasma and Chlamydia IgM and IgG, Mycoplasma and Chlamydia PCR, absolute neutrophil and eosinophil count

METHODS

Population

The study will include patients between the ages of 4-12 years of age admitted to the pediatric inpatient unit or pediatric intensive care unit at the Children's Hospital at Montefiore (CHAM).

Inclusion Criteria: Patients will be considered for enrollment if 4-12 years of age with an admission diagnosis of asthma and a history of persistent asthma (as defined by National Heart, Lung, and Blood Institute; see below and Eligibility Questionnaire).



Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** ICS, inhaled corticosteroid; LABA, inhaled long-acting beta$_2$-agonist, LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Theophylline is a less desirable alternative due to the need to monitor serum concentration levels.
- Step 1 and step 2 medications are based on Evidence A. Step 3 ICS + adjunctive therapy and ICS are based on Evidence B for efficacy of each treatment and extrapolation from comparator trials in older children and adults—comparator trials are not available for this age group; steps 4–6 are based on expert opinion and extrapolation from studies in older children and adults.
- Immunotherapy for steps 2–4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults. Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.

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- **Classifying severity in children who are not currently taking long-term control medication.**

Components of Severity		Classification of Asthma Severity (Children 5–11 years of age)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC >85%	• FEV_1 = >80% predicted • FEV_1/FVC >80%	• FEV_1 = 60–80% predicted • FEV_1/FVC = 75–80%	• FEV_1 <60% predicted • FEV_1/FVC <75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2 in 1 year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →			
		Relative annual risk of exacerbations may be related to FEV_1			

- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of the previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

- **Classifying severity in patients after asthma becomes well controlled, by lowest level of treatment required to maintain control.***

Lowest level of treatment required to maintain control (See figure 4–1b for treatment steps.)	Classification of Asthma Severity			
	Intermittent	Persistent		
		Mild	Moderate	Severe
	Step 1	Step 2	Step 3 or 4	Step 5 or 6

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in second; FVC, forced vital capacity; ICU, intensive care unit

*Notes:

- For population-based evaluations, clinical research, or characterization of a patient's overall asthma severity after control is achieved. For clinical management, the focus is on monitoring the level of control (See figure 3–5b.), not the level of severity, once treatment is established.
- See figure 3–5b for definition of asthma control.

Exclusion Criteria: Receiving albuterol every 4 hours (q4h) at the time of enrollment, concurrent bacterial infection requiring antibiotics, antibiotics received within previous 2 weeks, contraindication to azithromycin (including allergy to macrolides), chronic lung disease other than asthma (including bronchopulmonary dysplasia, cystic fibrosis, bronchiectasis), immunodeficiency (primary or acquired), chronic systemic steroid use, invasive or non-invasive mechanical ventilation required acutely as result of current asthma admission, significant cardiac co-morbidity (including hemodynamically significant cardiac disease or arrhythmia), liver disease (hepatitis), pregnancy, seizure disorder, currently on medication contraindication for use with azithromycin, and/or previous enrollment in study.

Withdrawal from study will occur for:

1. Parent/guardian preference
2. Primary attending preference
3. Worsening of clinical status requiring invasive or non-invasive ventilatory support
4. Diagnosis of infection requiring antibiotics during the 3-day course of azithromycin/ placeboso. (However, if the diagnosis of infection and initiation of antibiotics is after the

completion of the 3-day course of azithromycin/placebo, the antibiotic will be recorded and reported. Patients given antibiotics after the completion of the 3-day course of study drug will not be withdrawn from the study and their outcomes will be included in analysis.)

Safety Exit Criteria: Worsening of clinical status requiring invasive or non-invasive ventilatory support

Study Design

This is a double-blind, randomized, placebo-controlled trial. Patients between the ages of 4-12 years of age admitted to the Children's Hospital at Montefiore (CHAM) with an admission diagnosis of asthma exacerbation, as determined by the admitting physician, will be assessed for eligibility within 12 hours of admission by study personnel. Patients may be enrolled in the pediatric emergency room, pediatric inpatient units, or pediatric intensive care unit.

Potential study patients will be identified by the pediatric emergency room staff, pediatric housestaff who will page the research pager upon admission. In addition, attending physicians in the emergency room, pediatric units, and pediatric intensive care unit can refer patients by paging the research paper. Study personnel will review with primary care team any studies (including chest x-ray) that may alter the decision to start antibiotics prior to enrollment in the study. A member of the medical team caring for the patient will approach the parent/guardian and inquire if study personnel can discuss the study with him/her. If a parent/guardian is not available, the research personnel will return when one is available. If the parent/guardian agrees, study personnel will approach him/her and complete a standardized interview to determine if the patient meets eligibility requirements (see Eligibility Questionnaire). If eligibility requirements are met, the research personnel will obtain informed consent from the parent/guardian and assent from the child (if applicable) for participation in the study. If a female patient has achieved menarche, a pregnancy test will be administered with the consent of the parent/guardian and assent of the patient. Pregnant patients will be excluded from the study.

The research personnel will then conduct a standardized interview to obtain baseline demographic, clinical, and contact information from the parent/guardian (see Enrollment Questionnaire).

The enrolled patient will then be randomized by the Pharmacy Investigational Drug Services. Patients will either receive azithromycin suspension or indistinguishable placebo suspension once daily for three days at a dose of 10 mg/kg/dose with a maximum dose of 500 mg/dose. All research personnel, medical staff, patients, and parents/guardians will be blinded to the composition of suspension prepared in the research pharmacy. If the patient is discharged before the third dose of medication is administered, the pharmacy will provide any remaining suspension doses to be completed by patient as an outpatient.

The selection of the intervention dose of azithromycin (once daily dosing of 10 mg/kg/dose with a maximum dose of 500 mg) was made for several reasons. This dosing is shorter and more convenient to administer than the more commonly used 5 day course with 10 mg/kg/day for one day and 5 mg/kg/day for subsequent days. Since the average length of stay for patients 4-12 years old with asthma is 3 days, it is more likely that patients will complete this dosing during hospitalization. This dosing is currently recommended for other infectious indications including otitis media in penicillin allergic patients. In addition, this dosing is consistent with an open trial registered at clinicaltrials.gov in Denmark studying azithromycin treatment in children 1-3 years of age with recurrent asthma (planned enrollment November 2010 until November 2014).

At the time of enrollment, the patient will have an asthma severity score performed by research personnel via the Pediatric Asthma Severity Score (PASS), which has been validated in children 1-18 years old.[37,38] The score will be conducted within 30 minutes prior a scheduled beta-agonist treatment or at any time if patient is on continuous albuterol. This score will be used to determine severity of the patient's asthma exacerbation at the time of enrollment.

Pediatric Asthma Severity Scoring (PASS)

Signs	0	1	2
Wheezing (= expiratory sounds heard auscultation)	None/mild	Moderate	Severe or absent due to poor air entry
Respiratory work (= utilization of accessory muscles or retractions)	None/mild	Moderate	Severe
Prolongation of expiration (= ratio of the length of expiration over inspiration)	Normal/mild prolongation	Moderate prolongation	Severe prolongation

Other than the administration of azithromycin suspension or placebo, the medical treatment of the enrolled patients will be at the discretion of the medical team. The current standard of care for treatment of acute asthma exacerbations in hospitalized children includes inhaled beta-agonists and systemic steroids. The medical team often continues or initiates "controller" asthma medications during the inpatient stay (ie inhaled corticosteroids, leukotriene receptor antagonists). In addition, patients with severe asthma might receive intravenous medications (ie magnesium sulfate, terbutaline, aminophylline). No medical treatments will constitute exclusion from the study. However, invasive or non-invasive mechanical ventilatory support will be part of safety exit criteria.

At 7-10 days and again between 28 and 35 days after discharge, research personnel with contact the parent/guardian of enrolled patient for a follow-up interview. This interview will include questions about recurrence of asthma symptoms, days of work/school missed, hospital readmissions, emergency room visits, pediatrician visits, subsequent steroid courses, and medication side effects.

<u>Mechanism Subset Study: A Pilot and Feasibility Study in a Subset of Patients</u>

After enrollment, and at the time of the PASS asthma severity scoring, research personnel will ask parents/guardians if they would also be willing to participate in a separate subset study involving blood and nasal aspirate samples. If parents/guardians consent, they will be offered compensation for their time and inconvenience (if funding is available). If the parent/guardian is interested, the research personnel will obtain a separate, additional informed consent from the parent/guardian and assent from the child for the "Mechanism Subset Study". At that time, a nasal aspirate sample will be obtained by the research personnel (who will be trained on proper technique prior to the start of study). A blood sample will be obtained as soon as possible. A second sample of both blood and nasal aspirate will be obtained on the calendar day that is 48 hours from the first sample. Two samples will allow for baseline and post-treatment samples to be compared.

The blood samples will be obtained by the unit phlebotomist. As is unit policy, an effort will be made to apply a topical anesthetic before the blood sample is obtained. A maximum of three (3) trials will be made to obtain the blood. If unable to obtain first blood sample, the patient will still have attempt for blood sample in 48 hours.

The nasal aspirate samples will be obtained using the same protocol as a previous study in children 4-17 years old[8]. Study personnel will be trained on the technique of obtaining the

samples. The study personnel will instill 1.5mL of saline into each nostril and then using low-wall suction and an intransal catheter, will aspirate into a mucus trap.

If the enrolled patient is discharged before 48 hours or research personnel are not available, the second set of samples will not be obtained for that patient.

Laboratory

If patients enrolled in the study have a rapid viral testing, respiratory viral panel, or complete blood count performed as part of medical care and at the discretion of the primary medical team, the results will be recorded. A urine pregnancy test will be performed for all female patients that have achieved menarche; pregnant patients will be excluded.

For the "Mechanism Subset Study":

Blood samples will be tested for absolute neutrophil count, absolute eosinophil count, Mycoplasma pneumoniae IgM/IgG, Chlamydia pneumoniae IgM/IgG, Mycoplasma pneumoniae PCR, Chlamydia pneumoniae PCR, and a set of select biomarkers associated with inflammation including cytokines, chemokines, and other immune mediators via Bioluminex or ELISA technology.

Nasal aspirate samples will be tested for neutrophil count per high power field, eosinophil count per high power field, Mycoplasma pneumoniae PCR, Chlamydia pneumoniae PCR, and a set of select biomarkers associated with inflammation including cytokines, chemokines, and other immune mediators via Bioluminex or ELISA technology.

Neutrophil and eosinophil counts will be performed at the Montefiore Medical Center Lab. Biomarkers associated with inflammation via Bioluminex or ELISA will be performed at Albert Einstein College of Medicine in Dr. Betsy Herold's Laboratory. PCR and serology will be performed at the Microbiology Laboratory at University of Massachusetts, Amherst, by outside collaborator, Dr. Wilmore Webley.

STATISTICAL ANALYSIS

The primary outcome measure is hospital length of stay (LOS). Preliminary data obtained from a Clinical Looking Glass search reveals that in 2011, there were 410 children between the ages of 4-12 years admitted to CHAM with a primary diagnosis of asthma. During their admission, 237 patients received inhaled steroids, a marker of a persistent asthma diagnosis. Using this data, the mean length of stay was 3.0 days, median 2.5 days, and standard deviation 1.6. The distribution approximated normal distribution in this group. A clinically significant difference in length of stay would be 16 hours or 0.67 days (equivalent to 0.4 standard deviations).

Data analysis will be conducted with the assistance of a statistician. LOS between the two groups will be compared using independent samples t-test, if the data is normally distributed. If the data is not normally distributed, log transformation will be attempted and if the results of the transformation yield normal distribution for both groups, then t-test will be used for the logged values and reported as a geometric mean. If log transformation is not successful in yielding normal distribution, non-parametric Mann-Whitney U test will be used to report median and interquartile ranges. All tests will be two-tailed with an $\alpha = 0.05$ to denote clinical significance.

In order determine the number of patients needed to enroll to detect a 16 hour (0.67 day) difference in length of stay with a power of 80%, PASS software was utilized, with the assistance of a statistician, to model various types of adjustments for non-parametric distribution –normal distribution adjustment, uniform distribution adjustment, and logistic distribution adjustment. For each of these adjustments, the number of patients required for enrollment per

group ranged from 83 to 96 patients. Using the largest number, 96, and assuming a 10% attrition rate for parent/guardian preference, attending preference, or safety exit criteria, the sample size will need to be 107 patients in each group. We anticipate it will take approximately 15-18 months to enroll this number of patients.

The data from the interview questionnaire will be coded and descriptive statistics will be used to analyze the baseline characteristics of the two groups. If the parent characteristics are not balanced, multi-variable analysis will be utilized to adjust for variables not balanced by randomization. Secondary outcome measures will be compared using chi-squared test for categorical data and t-test or Mann-Whitney U test for continuous data, with statistical significance considered a p value < 0.05.

Due to the invasive nature of the sample collection in the "Mechansim Subset Study", only 25% of patients are expected to agree to submit to this portion of the study. These patients may not be representative of all patients in each arm of the study and will not be randomized. This subset study will be a pilot and feasibility study for future investigation into the potential mechanism of action of azithromycin in asthma. Data will be analyzed to compare the proportion of positive lab findings in each group using chi-squared analysis. There will not likely be sufficient power to find statistical significance, but the results will be used to estimate the effect size for subsequent study.

ETHICAL CONSIDERATIONS

Risks/Benefits

The potential risks are considered minimal. This study meets the category in the U.S. Department of Health and Human Services Code of Federal Regulations, Part 46, Subpart D (§46.405) for research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. The risks are deemed by the investigators to be justified by the anticipated benefit to the subjects; and the anticipated benefit is at least as favorable to the subjects as that presented by available alternative approaches.

The intervention medication, azithromycin, is a relatively commonly used antibiotic in the pediatric population for a variety of illnesses, including otitis media, atypical pneumonia, and pharyngitis. It is relatively well tolerated. The major side effects are gastrointestinal and temporary. Other side effects, including elevation of hepatic enzymes and prolonged QT syndrome, are rarely reported (less than 1%) and considered unlikely by the investigators. Patients will be monitored by the primary medical team for symptoms of rare and common side effects and will inform the PI of any concerns. Education will be conducted on pediatric units and in the critical care unit regarding side effects to ensure adequate monitoring by the primary medical teams. There is little clinical evidence on the use of azithromycin in children hospitalized with acute asthma, therefore it is possible that azithromycin will worsen the condition of some patients and increase length of stay. Previous studies in long-term macrolide use have shown either clinical improvement or no effect and none have reported any significant harm.

The alternative treatment for children hospitalized with acute asthma is the current standard of care: inhaled beta-agonists and systemic steroids. All patients enrolled, at the discretion of the attending physician and medical team, are expected to received these treatments in addition to the study medication.

The potential benefit of this study to research participants is that azithromycin may decrease length of stay in the hospital and days of symptoms. In addition, it may have longer-term effects and decrease rate of readmission to the hospital or subsequent medical visits or steroid courses in the month following administration.

Protections Against Risk

All patients will be hospitalized at the Children's Hospital at Montefiore (CHAM), a 120-bed tertiary level pediatric hospital well equipped for the management of children with acute respiratory illnesses, including severe asthma. Clinical risks to patients will be protected by close clinical monitoring for patients who meet exit criteria of mechanical ventilation. In the event of an adverse event to a patient enrolled in the study, the patient will be assessed by the attending physician, research investigator, and/or the Pediatric Rapid Response Team (PMET) or pediatric code team.

Privacy risks will be protected by allowing only study personnel access to confidential information and by assigning a study number that will be kept separate from medical record number and identifiers. Only research personnel will have access the individually identified private information. After enrollment, patient will receive a study number. A list of medical record numbers and study numbers will be kept by the PI separately. All written and digital data will be identified by study number and kept in locked cabinet or password protected computer.

For the "Mechanism Subset Study", all patients will be approached, and the investigators anticipate only a subset of patients will consent, as invasive blood and nasal sampling will be obtained in this group. This subset of patients will have blood and nasal aspirate samples obtained on two occasions during the inpatient stay. Samples will be sent to another institution for testing, and the investigator at that institution will comply with the same privacy protection protocols. Samples supplied to other institutions will be identified only by assigned study number, without other identifiers. IRB approval will be obtained by the collaborating institution (University of Massachsetts, Amherst, Dr. Wilmore Webley).

Identifiers will be destroyed at earliest possible time.

Importance of Knowledge Gained

Although some practitioners currently use azithromycin in the routine management of hospitalized children with acute asthma exacerbation, there is little data to support this practice. This study will be the first double-blind, randomized, placebo-controlled trial to determine if azithromycin has a clinical effect on children hospitalized with acute asthma. In addition, the "Mechanism Subset Study" will provide preliminary data to determine the mechanism of action of azithromycin in children with acute asthma exacerbations.

Recruitment and Informed Consent

Patients will be recruited after identification by pediatric emergency room staff, admitting physician, or pediatric residents of patient with admission diagnosis of acute asthma exacerbation in the age range of 4-12 years. After the medical staff has determined if the parent/guardian is willing to meet with research personnel, the parent/guardian of the admitted child will be approached and undergo a standardized interview to determine if the patient meets eligibility requirements. If eligibility requirements are met, the research personnel will obtain informed consent from the parent/guardian and assent from the child (if applicable) for participation in the study.

The details of the study will be explained by research personnel and all questioned will be answered before consent and assent are obtained. Potential risks and benefits will be discussed. The parent/guardian will need to be physically present at the bedside of the child and written confirmation of consent will be obtained via signature on a consent form. For children 7-12 years of age capable of assent, assent will be obtained after verbal confirmation via signature of the child on an assent form.

For the "Mechanism Subset Study": After enrollment, and at the time of the PASS asthma severity scoring, research personnel will ask parents/guardians if they would also be willing to participate in a subset study involving blood and nasal aspirate samples. If the parent/guardian is interested, the research personnel will obtain a second and separate informed consent from the parent/guardian and assent from the child (7-12 years) for the "Mechanism Subset Study".

Adverse Event Monitoring

Adverse events that will be monitored include: bronchospasm or worsening clinical status (as determined by the primary medical team), transfer to the intensive care unit, medication side effects (abdominal pain, diarrhea, flatulence, vomiting), and readmission for asthma within 30 days. Additional unanticipated adverse events will also be monitored. Adverse events will be standardly documented and reported to the IRB within 30 days. All co-investigators and research personnel will immediately report any serious adverse events to the PI who will report them to the IRB within 48 hours.

Withdrawal from the study will occur for parent/guardian preference, primary attending preference, or worsening of clinical status requiring invasive or non-invasive ventilatory support. Ventilatory support (invasive or non-invasive) will serve as the safety exit criteria.

Data and Safety Monitoring Plan

The PI will be continuously responsible for data and safety monitoring, including adverse events. The IRB will also be responsible for data and safety monitoring.

An internal Data and Safety Monitoring Board was created with three established clinical investigators with knowledge of clinical trials (Dr. Peter Belamarich, Dr. Tsoline Kogaoglanian, and Dr. H. Michael Ushay) and a biostatistician, Aileen McGinn, PhD. The PI will provide data to the Board every 3 months during the enrollment process, and they will meet to assess the safety of enrolled patients. The Board will report their findings to the PI and IRB every 3 months, and will have the authority to recommend termination of the trial if the rates of adverse events are deemed unsafe to study participants.

Inclusion of Women, Minorities, and Children

Female children and children of all minorities will be screened for eligibility after hospital admission for asthma. A urine pregnancy test will be performed for all female patients that have achieved menarche; pregnant patients will be excluded. Asthma affects both genders and has been described in nearly all minority groups; there are no anticipated exclusions of females or minorities. The population served by the Children's Hospital at Montefiore (CHAM) in Bronx borough of New York City is primarily Hispanic, Black/African American, and White patients with limited numbers of American Indian, Alaskan Native, Native Hawaiian, and Pacific Islander patients. However, if a patient from any of these underrepresented groups presents with acute asthma in the age range specified, the patient will be approached for eligibility and enrollment.

Children are included in this trial as asthma is a chronic lung condition common in childhood and the investigators will determine whether azithromycin will change the length of hospital stay for children hospitalized with acute asthma. Children between the ages of 4-12 years hospitalized for acute asthma will be included in the study. National Heart, Lung, and Blood Institute (NHLBI) has clear guidelines for classifying asthma in specific age ranges. We will use the guidelines for children aged 5-11 years in the eligibility questionnaire to determine and include only children with persistent asthma in the study. We expanded the age range by one year on each side of NHLBI guidelines to better capture children in the "school age" range.

ClinicalTrials.gov Requirements

- The trial will be registered with clinicaltrials.gov within 21 days of the first enrolled patient.

IRB revisions - 8/20/12
IRB amendment – 12/4/13
IRB amendment – 1/2/14

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