# The anti-inflammatory effect of prophylactic macrolides on children with chronic lung disease: a double blinded RCT

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**PROTOCOL**

# The anti-inflammatory effect of prophylactic macrolides on children with chronic lung disease: a double blinded RCT


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**Research Aims**
**Primary Aims:**

1. To determine if prophylactic use of azithromycin will reduce the total number of unscheduled face-to-face physician visit for respiratory related illness in a clinic, urgent care, emergency room or hospital setting during the 3-6 month study period, and subsequent 2 months follow-up.

**Secondary Aim:**

1. To determine if the administration of azithromycin will have similar number of adverse side effects, or adverse events leading to unscheduled clinic, urgent care, emergency room or hospital visit as compared to placebo during the 3-6 month study period and the following 2 months.
2. To determine if the use of azithromycin will reduce healthcare cost associated with respiratory illness during the 3-6 month study period and 2 month follow-up period.

**Exploratory Outcomes:**

1. Using a standardize nasal wash procedure, respiratory samples will be collected at enrollment, at end of study, and during acute respiratory illness requiring face-to-face provider interaction. Children with a tracheostomy will have both a nasal wash sample and a tracheal aspirate sample collected. The respiratory samples will be stabilized with a universal transport media, processed and stored at -80 C for future testing. Testing will be performed for cytokines/chemokines; other biomarkers of disease such as LDH, MPO, and caspase; viral and bacterial respiratory pathogens; and microbiome.

2. To determine if prophylactic use of azithromycin will reduce level of airway resistance as measured by an Airwave Oscillometry System in subjects above 2 years of age, at the time of respiratory illnesses, during the 3-6 months intervention.

*3.* To determine if prophylactic use of azithromycin will reduce the total number of unscheduled face-to-face physician visit for respiratory related illness in a clinic, urgent care, emergency room or hospital setting during the following 12 months after the intervention.

**Background**

For the past 3 years, the High Risk Children's Clinic at UTP (HRCC) has been providing a medical home for medically complex children. We have demonstrated major benefits (e.g., 50% fewer serious illnesses & 55% fewer hospital days) and savings (~$10K/child/year) from the comprehensive care provided in our enhanced medical home to high-risk chronically ill children--including patients with chronic lung disease (CLD). These benefits have not been previously shown for medical homes for patients of any kind or age.[1,2] These benefits result primarily from 24/7 access by phone to dedicated and experienced caregivers directed by a pediatric pulmonologist. The clinic offers same day appointments and provides comprehensive coordination of care for this population. We now aim to further cut morbidity rates by developing specific outpatient interventions to augment comprehensive care for each major disorder that we treat.

A significant portion (44%) of our patients in the High Risk Children clinic are chronically ill children who have some form of CLD including patients with bronchopulmonary dysplasia (BPD). Chronic lung disease, as defined by the ATS statement from 2002, is "a heterogeneous group of respiratory diseases of infancy that usually evolves from an acute respiratory disorder experienced by a newborn infant." Specifically, infants with bronchopulmonary dysplasia, defined as the need for supplemental oxygen therapy in children past 28 days born under 32 weeks gestation.[3] These infants often incur long-term pulmonary function abnormalities, including oxygen dependency after discharge, recurrent respiratory infections, and other reactive airway diseases. From our data, we have learned that many of the hospital admissions in our group of patients were related to respiratory infections (37%) during the winter season. Despite vaccination rates of nearly 100%, administration of Palivizumab to all of those eligible patients and access to our comprehensive care clinic, viral respiratory illnesses continue to cause considerable

morbidity and high healthcare costs. Innovative new prophylactic treatments are needed.

Macrolides have received considerable attention for their anti-inflammatory and immunomodulatory actions beyond the antibacterial effect. Such properties may ensure some efficacy against a wide spectrum of respiratory viral infections.[4] Recent studies, including a study performed in our lab with elderly BALB/c mice infected with RSV, have shown that the high mortality rate of respiratory virus infections is a result of a neutrophilic overactive inflammatory response.[5] A recently published study examined the inflammatory response in hospitalized infants with RSV and evaluated the predictive value of cytokines in nasopharyngeal aspirate in comparison to disease severity and found an increase in Th1 and Th2 cytokines.[6] Respiratory viral infections are characterized by the appearance of cytokine storms which are an extreme production and secretion of numerous pro-inflammatory cytokines. Severity of infection is closely related to virus-induced cytokine dysregulation, which is responsible for the development of fatal clinical symptoms, such as massive pulmonary edema, acute bronchopneumonia, alveolar hemorrhage, and acute respiratory distress syndrome.[4] Macrolides down-regulate the inflammatory cascade, attenuate excessive cytokine production in viral infections, and may reduce virus-related exacerbation. Clinical trials have demonstrated controversial results in the effects of macrolides in respiratory viral infections.[7] To date, studies have only evaluated macrolide use as a treatment, not as a prophylactic therapy. Long-term therapy with the macrolide antibiotic erythromycin was shown to alter the clinical course of diffuse pan bronchiolitis in the late 1980s.[8] Since that time, macrolides have been found to have a large number of anti-inflammatory properties in addition to being antimicrobials. These observations provided the rationale for many studies performed over the last decade to assess the usefulness of macrolides in other inflammatory airways diseases, such as cystic fibrosis, asthma, COPD, and bronchiolitis obliterans syndrome.[9] One RCT looked at the daily use of macrolides for up to six weeks to prevent bronchopulmonary dysplasia in premature infants in a NICU setting and found the neonates to have better outcomes without an increase in adverse effects.[10] However, chronic use of macrolides

has not been studied to prevent respiratory infection complications in patients with CLD of infancy. We will test the hypothesis that prophylactic macrolides are effective in reducing the severity of respiratory viral illness and that this is associated with the prevention of the full activation of an inflammatory cascade.

**Study Design and Methods**

*Overview*:

This pilot randomized control trial (RCT) will enroll 92 children from 6 months to <6 years of age that have chronic lung disease (CLD) such as bronchopulmonary dysplasia during two seasons of respiratory illnesses defined as 1st October to 31st March of each year (2015-2016 Season and 2016-2017 Season). If the minimum number of patients (n=92) in Season 1 is achieved, we will then perform an interim analysis of the data. These children will all be patients who receive their primary medical care from either the High Risk Children Clinic or the similar High Risk Infant Clinic that cares for premature infants from discharge until age 2. Clinic records will be screened to determine eligibility. Patients that have parental consent will be given a baseline EKG, a nasal aspirate, an oscillometer reading (over 2 years of age only), and a three to six month supply of either the medication or the placebo at an initial study visit. Both medications will be taken once a day for three days a week: Monday, Wednesday and Friday. The azithromycin medication will be dosed at 5 mg/kg/day. Adjustments in dosage amount will be made with any new weights obtained during the trial period. Any child that is eligible to receive Palivizumab will be given this every 28-30 days in clinic as per usual care. Patients will be followed on a monthly basis and closely monitored for adverse reactions; this will occur by phone, in clinic during their regularly scheduled appointments, and/or during any necessary illness visits. Any children with adverse reactions will discontinue the medication, but will continue to be followed clinically. At any clinic visit in which a child presents with respiratory infections, including pneumonia,

upper respiratory illness, bronchiolitis, etc., he/she will have an additional nasal aspirate and/or tracheal aspirate if applicable and an oscillometer reading (only for children >2 years) performed. At the completion of the 3-6 months treatment phase, each child will have a final nasal aspirate and/or tracheal aspirate if applicable, and an oscillometer reading performed. Data will continue to be collected for the following 2 months (April 1st to May 31st), to monitor for respiratory illnesses and possible side effects.

*Study Population:*

High risk children between the chronological age of 6 months and 6 years who attend either the High Risk Children's Clinic or the High Risk Infant Clinic at UTP will be screened by the research nurse, and additional help will be provided by the clinic providers. The high risk infant clinic follows premature infants born before 32 weeks gestation for their first 2 years of life; the high risk pediatric clinic follows medically complex children who have had at least 3 ED visits, 2 hospitalizations, and/or 1 PICU visit within the last year for a chronic health condition.

*Inclusion/Exclusion Criteria:*

Children who belong to either the High Risk Infant Clinic or the High Risk Children's Clinic and that have been diagnosed with a chronic lung disease as defined by ATS by a medical provider will be included.[3] Chronic lung disease (CLD) is the final common pathway of a heterogeneous group of pulmonary disorders that start in the neonatal period. Often the inciting factor is bronchopulmonary dysplasia (BPD), a chronic condition that can develop after premature birth and respiratory distress syndrome due to surfactant deficiency. Myriad other conditions can also cause airway and parenchymal inflammation that leads to chronic airflow obstruction, increased work of breathing, and airway hyper reactivity. Usually the inciting factors are not only the underlying disorders, but also the effects of the supportive treatment, including mechanical ventilation, barotrauma, and oxygen toxicity. These aggressive interventions for serious neonatal and infant lung diseases are often responsible for much of the chronic pulmonary abnormalities that follow. [3]Exclusion criteria include

children with cystic fibrosis or bronchiectasis,[11] because the prophylactic use of macrolides has already demonstrated value and become usual care for these patients. Children with cardiac arrhythmias will be excluded, due to the potential increase in cardiovascular death that has been shown in the adult population[12]. Patients with cyanotic heart disease would be excluded. Children with colitis will also be excluded due to the potential effects to the gastrointestinal flora. In addition, any child with a known macrolide allergy or child who is taking any medication that has a known interaction with macrolides, and any child with kidney or liver failure will also be excluded. Patients with short-bowel syndrome would also be excluded due to malabsorption of medication.

Once patients are screened for eligibility, families will be approached, either over the phone or at a regularly scheduled office visit. Informed written consent will be obtained in the clinic from the parent or legal guardian of each eligible child by any of the co-investigators or the research nurse at the time of enrollment. Either the research nurse or another clinical member of the HRCC team will then collect a nasal aspirate sample at the first study visit (description in Laboratory section). The nasal aspirate will be stored and studied after the conclusion of the treatment phase for its levels of myleoperoxydase, cytokines, respiratory virology, and micro biome. In addition, all patients 2 and older will have a spirometry reading performed using a TremoFlo airway oscillometry system (iOS) manufactured by Thorasys. With the iOS, the child breathes normally into the machine and lung function is measured by a gentle multi-frequency airway against the patient's respiratory airflow. A baseline EKG will be obtained on all patients.

*Study Procedures:*

Patients will be randomized by the REDCap statistical program in a double blind manner. Parents will then be provided with a medication or placebo for the duration of the study. Patients would be recruited for this study on a rolling basis from October 1st to December 31st, and all patients completing the intervention part of the protocol on 31st March at the end of the season. Half of the patients will receive azithromycin at a

dose of 5 mg/kg to be given once a day on Monday, Wednesday, and Friday. The other half, the control group, will be provided with a placebo medication of similar taste, color, texture, and consistency, also to be taken once a day on Monday, Wednesday, and Friday. Both the study medication and the placebo will be dispensed from Corner Compounding Pharmacy, mixed with a fish-oil base to ensure a shelf life of more than six months, and flavored with citrus to improve palatability. Parents will be contacted biweekly, either in clinic or by phone, to monitor for any adverse reactions, including rash, nausea, vomiting, diarrhea, or abdominal cramping. If a significant adverse reaction occurs, the medication will be discontinued. If an allergic reaction (such as rash or shortness of breath) is noted, the blind will be broken by Research Coordinator Ana Gomez-Rubio, who is not involved with the project. This un-blinding will be done to note if it is an allergy to the medication.

After the initial appointment, at any face to face encounter (unscheduled sick visit or hospital admission Monday through Friday) in which the patient presents with respiratory symptoms, the patient will be evaluated by the research nurse or one of the co-investigators. Specifically, if a patient presents with the following symptoms: cough, wheeze, tachypnea, rhinorrhea, increased respiratory secretions, hypoxemia, and/or an increased oxygen requirement, an additional nasal aspirate sample/and tracheal aspirate if applicable, and an oscillometry reading (for patients over 2 years of age) will be performed. These samples will also be stored in the office of Dr. Piedra. At the conclusion of the 3-6 months treatment phase, a final nasal aspirate/and tracheal aspirate if applicable sample. Oscillometer reading will also be performed for those above 2 years of age while the patients are in clinic for an office visit at the end of the study visit and during each sick clinic visit for respiratory illness. There will be no expected/additional study visits and no compensation will be provided for parents or patients.

*Risks*:

Potential risks include an allergic reaction or adverse reaction to the medication or placebo. Examples of potential side effects include nausea, vomiting, diarrhea, and skin

reactions. In addition, there may be an increased risk of diaper rash and/or oral thrush with the increased use of antibiotics. Another adverse outcome of azithromycin has been an increase in pyloric stenosis with both prenatal and infant exposure for the first 4 months of life, and benefit in this age group must outweigh this potential risk. [13] However, our population for this project will begin at 6 months of age. Each of these risks and any other unexpected outcomes will be monitored at any visits to the clinic, or with biweekly phone calls if no visits have been scheduled in the previous two weeks. The primary benefit we hope to see is a reduction in the number of respiratory illness related office visits. With the anti-inflammatory properties of the macrolide, we predict an overall reduction in the severity of respiratory illnesses during the study period. Additionally, we will monitor data for a 2 month period following last azithromycin administration. This reduction may lead to a decrease in the number of unscheduled office visits, emergency room visits, and hospital admissions. With less face to face provider encounters, there will be less opportunity for potential exposure to other viruses, as well as less time away from home or work for the patients' parents and, potentially, decreased health care related costs.

**Study Outcomes**

1. In the treatment group, we expect a 20% total reduction in face to face encounters (defined as unscheduled sick visits, emergency room visits, and hospital admissions) for respiratory symptoms with the prophylactic use of azithromycin, as compared to the control group.
    a. In the treatment group, we expect to have a 20% decrease in the number of unscheduled sick visits due to respiratory illness during the 3-6 month study period with the prophylactic use of azithromycin, as compared to the control group .
    b. In the treatment group, we expect to have a 20% decrease in the number of Emergency Room visits due to respiratory illness during the 3-6 month study period with the prophylactic use of azithromycin, as compared to the control group.

c. In the treatment group, we expect to have a 20% reduction in the number of hospital admissions due to respiratory illness during the 3-6 month study period with the prophylactic use of azithromycin, as compared to the control group.

2. In the treatment group, we expect a 10% total reduction (as compared to baseline) in the level of myeloperoxidase in the nasopharyngeal secretions collected during respiratory illnesses that require a face to face provider encounter, as compared to the control group.

3. In the treatment group, we expect a 10% total reduction in the level of pro-inflammatory cytokines in the nasopharyngeal secretions collected during respiratory illnesses that require a face to face provider encounter, as compared to the control group.

4. In the treatment group, we expect a 10% reduction from baseline in the level of airway obstruction as measured by a tremoFlo Airwave Oscillometry System during the 3-6 month study period, respiratory illness and at the conclusion of the intervention phase.

5. We expect no significant difference in adverse side effects between the treatment group receiving the macrolide and the control group receiving the placebo during the 4 month study.

6. We expect the intervention to be cost-effective from a healthcare system perspective.

**Laboratory Evaluation**

Microbiologic studies for the secondary hypotheses will be conducted under the direction of Dr. Pedro A. Piedra, the Clinical Director of the Respiratory Virus Diagnostic

Laboratory at Baylor College of Medicine in Houston, Texas. The study involves collecting 2-8 nasal aspirates from each patient. Nasal aspirate samples will be tested to measure the levels of myeloperoxidase; we will also use ELISA tests to measure the levels of specific pro-inflammatory cytokines, including IL-8 and IL-6, and PCR, in order to screen for several major respiratory viral pathogens.

Nasal aspirate specimens will be collected at the first visit, the final visit, and during any episodic respiratory sick visits at clinic or at Children Memorial Hermann Hospital. These samples will all be frozen and stored until the completion of the trial. For the collection, the child will be placed supine, 2 ml of normal saline will be instilled into one nostril, and then an 8 or 10 French suction catheter (depending on the size of the patient) will be used to remove the mucus. This procedure will be performed once on each nostril. After the specimen collection from both nostrils, 2 ml of normal saline will be suctioned through the catheter to clear the tubing and to insure that a standard volume of aspirate is obtained. All specimens will be placed on ice in a bio-hazard bag and then collected by study personnel. After collection by study personnel, the specimen will be immediately diluted (1:1 solution) with viral transport medium (15% glycerol in Iscove's media). The final solution (aspirated specimen mixed with viral transport medium) will contain a maximum of 9 mls (with a range of 3-9 mls). After dilution, the specimens will be immediately refrigerated in the HRCC refrigerator at 37 degrees, until transportation to the freezers at the Department of Pathology at Baylor, where they will be stored at -80$^{o}$C.

*Specimen Handling / Storage*

Nasal aspirate specimens will be transported by study personnel from the HRCC refrigerators to Dr. Piedra's laboratory. Once received, the dilution will be separated into 0.5 – 1 ml aliquots and snap frozen to -80º C. Samples will be thawed and centrifuged at 1,000g for 10 minutes at room temperature. This clarified nasopharyngeal lavage fluid supernatant will be used to measure the levels of myeloperoxidase, will undergo cytokine analysis, and will be screened for up to 5-6 major respiratory viruses. Remaining volumes will be stored for future studies,

including studies for additional biomarkers, such as Flu A, Flu B or other viruses All specimens will be transported to Dr. Piedra's laboratory Monday – Thursday between 8am and 3pm and Friday between 8am and 1pm by involved research personnel walking to the laboratory. Specimens received Friday afternoon will be stored in clinic freezer until Monday morning. For during the weekend episodes, samples will be collected on Monday and properly marked with date and time of ER/Hospital visit and date and time of sample collection. Samples will be stored for one year after the completion of the study at Dr. Piedra's laboratory, and will be destroyed after the one-year period. Neither samples nor data will be shared outside of the University of Texas.

*Labeling*

Specimens collected for this study must be easily distinguishable from other laboratory specimens stored in the Department of Pathology refrigerators and laboratory freezers. ID numbers will be pre-assigned and pre-printed on a label for each specimen. The date (mm/dd/yr) and time (hh:mm) of specimen collection must be written on the label. The ID number used for the case report form must match the ID number used on the specimen (eg, first patient 001 should be typed on the specimen labels and case report form). Specimens will also be labeled with date (mm/dd/yr) and time (hh:mm) of symptoms onset.

*Laboratory Procedures*

The level of myeloperoxidase will be measured using reagent tests, and several cytokines that are markers of inflammation will be tested using ELISA tests. These tests are routinely performed in Dr. Piedra's laboratory and details of the primers and probes to be used are found in a 2005 article by Beckham et al. [14] In addition, RT-PCR assays will be performed using TaqMan-based primers and probes to detect the presence of 5-6 major respiratory viruses, and the remaining volume of aspirate will be stored for future studies of additional biomarkers. Nasal aspirate samples will be collected for assay of up to 4 cytokines and chemokines. Samples will be tested according to the

manufacturer's instructions. Samples and serial dilutions of the cytokine standards will be incubated with anti-human cytokine-coated beads in a 96-well filtration plate.

**Data Analysis Plan**

Patients will be randomized to one of two different branches by the REDCap data base randomization program. This will be a double-blind placebo controlled study. Standard frequentist and Bayesian analyses will be performed using an intent-to-treat approach. Total hospital days, total ER visits (counting one day for each ER visit), and unscheduled clinic visits (counting one day for each visit) for respiratory symptoms will be analyzed and related to treatment (Azithromycin vs Placebo), with logistic regression models and the treatment group as a covariate and random intercept to account for within patient correlation (due to multiple ED visits). To assess the probability of benefit, we will use Bayesian hierarchical models with interaction terms between treatment groups (Azithromycin vs Placebo) and predefined potential moderators. The groups will be stratified by palivizumab use and by tracheostomy on chronic mechanical ventilation. The conservative Bayesian approach of Dixon and Simon allows us to shrink the subgroup estimates to the overall mean treatment effect. For all Bayesian analyses, prior distributions for main effects will be neutral ~N(0,1000), and Uniform (0,1000) for SD parameters. Neutral and skeptical priors will be used for interaction terms. Point estimates of treatment effect and 95% credible intervals will be reported along with probability of treatment benefit.

**Sample size and power**

Based on data from our HRCC, we expect the control group to have 1.6 encounters per child-year (SD=1.66). Assuming a two-sided alpha = 0.05, a sample size of 90 (45/group) will have 80% power to detect a difference of 1 in the encounter rate between placebo and azithromycin groups (i.e., 1.6 vs 0.6 in encounter rate or 38% reduction). Power will be more limited for secondary outcomes but Bayesian analyses will provide an estimate of the probability of benefit in these outcomes.

**Limitations**

Parents may opt out of allowing their child to participate in the study due to the extent of the sampling. The standard of care for respiratory illnesses may include a nasal aspirate, but the additional sampling at the baseline and conclusion of the study is a deviation from standard procedure. We will, however, emphasize the ease and low-invasive nature of both the nasal aspirate specimen collections and the oscillometer readings. In addition, parents may opt out of participating if their child's medical diagnosis or current health status is too emotionally overwhelming, or if they have concerns regarding the prophylactic administration of an antibiotic for 3-6 months. We will obtain respiratory samples from patients that are admitted Monday through Friday during business hours, but it will be difficult to obtain nasal samples from the Emergency Department, on weekend admissions, and afterhours. For sick episodes occurring weekends and afterhours we will collect samples on the next business day morning. Parents may also not adhere to the administering the medication/placebo three days a week.

**Confidentiality**

Every effort will be made to protect the privacy of the subjects. Unique identifiers will not be stored in the final database that will be used for analytic purposes. Information such as age, sex, and race will be collected to examine the patterns of interaction in different demographic subgroups.

Specimens will be sent to Baylor College of Medicine for processing and testing. Specimens will be coded with study ID numbers and will not have any personal information.

Upon completion of the study, electronic data will be retained by the principal investigator (R. Mosquera) at his University of Texas Medical School office. All data

forms will be kept in a locked file cabinet and electronic files will be password protected. Subjects will not be directly identifiable. The PI, co-investigators, and designated study staff will use the information for data analysis and manuscript preparation.

**Interpretation and Potential Importance of Findings**

A substantial portion of our high risk chronically ill children have some form of chronic lung disease, including patients with tracheostomies, bronchopulmonary dysplasia, and chronic respiratory failure requiring mechanical ventilation. Most of the hospital admissions in this group of patients were related to respiratory infections in children less than 6 years of age (37% during the winter season for the previous 3 years). Despite vaccination rates of nearly 100% and 24/7 access to our clinic, viral respiratory illnesses continue to cause considerable morbidity and high healthcare costs. Innovative new prophylactic treatments are needed.

With this proposal, we will determine if the prophylactic use of azithromycin will 1) reduce the number of days when unscheduled medical treatment health care related encounters was given outside the home, 2) reduce the number of emergency room visits, hospitalizations and clinic visits due to respiratory illness, 3) reduce the level of myeloperoxydase and pro-inflammatory cytokines during viral illnesses requiring face to face physician interaction, 4) demonstrate a reduction in airway obstruction as measured by an oscillometer 5) have a similar safe profile compared to the placebo, and 6) demonstrate cost-effectiveness of macrolides use. Understanding the anti-inflammatory effects of azithromycin when used as a prophylactic drug will provide important insight into the prevention of more serious sequelae of respiratory infections. In particular, this proposal will contribute to understanding disease in children ages 6 months to 6 years with chronic lung disease, a population that has a higher rate of hospitalizations for respiratory symptoms.

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