



## Immune Mediator Levels in the Upper Airways Predict Response to Azithromycin for Episodes with Asthma-like Symptoms in Young Children

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## ABSTRACTS

# Young Investigator's Oral Communications

### A-27 | Immune Mediator Levels in the Upper Airways Predict Response to Azithromycin for Episodes with Asthma-like Symptoms in Young Children

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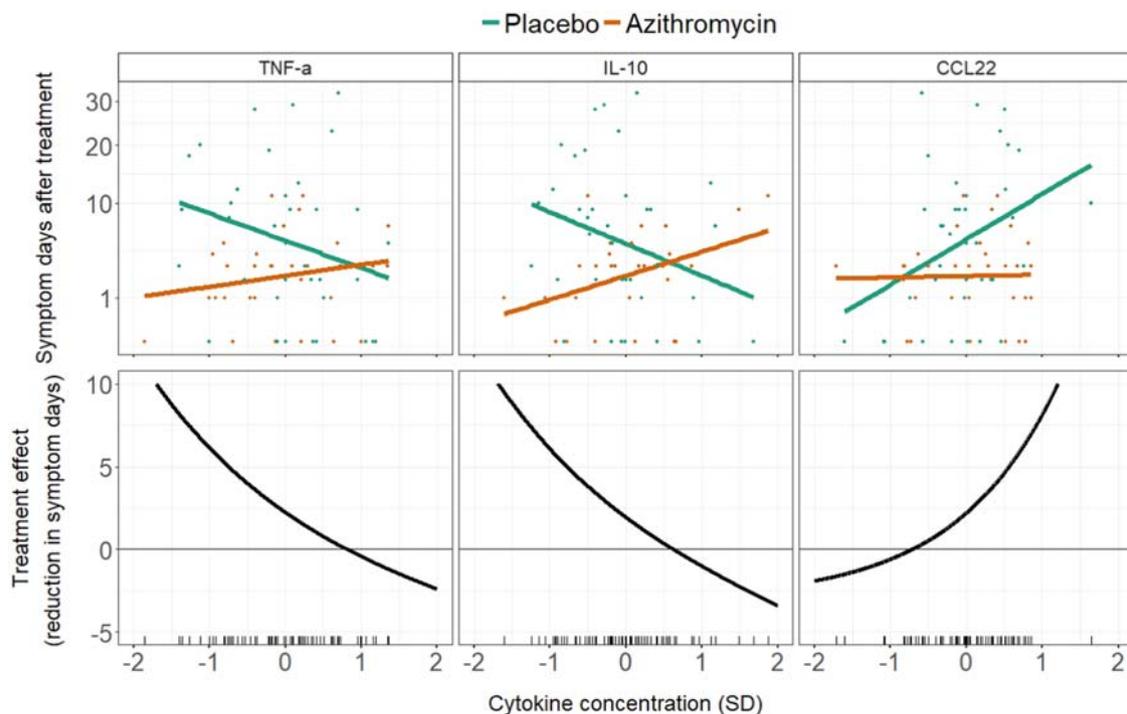
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**Background:** The immune response in the airways during episodes with asthma-like symptoms in young children is presumed to determine the clinical outcome, although current knowledge largely relies on in vitro airway models. Azithromycin has been shown to reduce the duration of episodes with asthma-like symptoms, though efficacy may depend on the individual child's immune response.

**Objective:** To investigate in vivo upper airway immune mediator levels during episodes with asthma-like symptoms in young children and their ability to predict the clinical response to azithromycin treatment.

**Methods:** Five hundred thirty-five children from the Copenhagen Prospective Studies of Asthma in Childhood-2010 mother-child cohort were examined for immune mediator levels in samples of upper airway epithelial lining fluid during episodes with asthma-like symptoms through ages 0 to 3 years as well as in the asymptomatic state at age 2 years. A subset of samples was also examined for CRP levels. In a sub-study, children aged 1 to 3 years with recurrent asthma-like symptoms were randomized to either a 3-day course of oral azithromycin (10 mg/kg) or placebo. In the current study, we compared the immune mediator levels before treatment and the clinical response to treatment with azithromycin.

**Results:** Four hundred ninety samples obtained during episodes with asthma-like symptoms and 434 samples obtained during asymptomatic periods were analyzed. The mediator concentrations during vs.



**FIGURE 1** Top panel: Duration of episodes with asthma-like symptoms at various immune mediator levels in episodes treated with azithromycin (N = 32) and placebo (N = 38). Bottom panel: Treatment effect of azithromycin for episodes with asthma-like symptoms with various immune mediator levels. Treatment effect is the calculated difference in symptom duration between the placebo and the azithromycin group for any immune mediator level. X-axis indicators signify observations

outside episodes were significantly upregulated for IFN- $\gamma$  (ratio 1.73), TNF- $\alpha$  (2.05), IL-1 $\beta$  (1.45), IL-10 (1.97), and CRP (1.74), while CCL22 (0.65) was downregulated. Low levels of TNF- $\alpha$  and IL-10 and high levels of CCL22 predicted better treatment response to azithromycin (p-values  $\leq$  0.05).

**Conclusion:** The immune mediator profile of the upper airways was altered during episodes with asthma-like symptoms in young children. TNF- $\alpha$ , CCL22 and IL-10 levels predicted the response to azithromycin treatment and may potentially be used in future point-of-care testing.

## A-85 | The Relation of Matrix Metalloproteinases 2 and 9 with Reticular Basement Membrane Thickening in Chronic Neutrophilic Airway Inflammation

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**Introduction:** Cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) are characterized by persistent or repeated neutrophilic airway inflammation. Reticular basement membrane (RBM) thickening of varying extent has been described in these conditions. Although not fully understood, matrix metalloproteinases 2 and 9 (MMP2 and MMP9) and their imbalance relative to tissue inhibitors of metalloproteinases are suspected to play an important role in airway remodeling. To date, MMP levels have only been studied in bronchoalveolar lavage fluid (BALF), sputum or blood, but not directly in the airway wall. Sparse data on their relationship to airway remodeling and lung function are available.

**Methods:** We performed a cross-sectional study to evaluate the expression of MMP2 and MMP9 in bronchial wall in patients with chronic neutrophilic airway inflammation. After excluding patients with incomplete data, 49 children aged 0.5 to 17 years (median 9.80 years) were included. The study group consisted of 16 patients with CF, 7 with PCD and 10 with other forms of chronic neutrophilic airway inflammation (6 with non-CF and non-PCD bronchiectasis (BE) and 4 with chronic suppurative lung disease (CSLD), as defined by Chang AB, 2016). The control group included 16 patients undergoing bronchoscopy for a large airway pathology with no signs of chronic respiratory disease or atopy. Anthropometric characteristics of both groups did not differ significantly. Bronchoscopy was performed in clinically stable patients. Endobronchial biopsies were stained with hematoxylin-eosin to assess RBM thickness (as validated by Sullivan P, 1998). The number of MMP2- and MMP9-positive cells in lamina propria mucosae was assessed using indirect immunohistochemical methods (rabbit polyclonal antibodies Abcam ab73734 and ab37150) in relation to the total

number of cells in the lamina propria (MMP2%, resp. MMP9%). Percentage of neutrophils and lymphocytes in BALF was assessed. Lung clearance index (LCI2.5) was measured using nitrogen multiple breath washout test in all patients before bronchoscopy. RBM thickness, MMP2%, MMP9%, BALF neutrophils and lymphocytes and LCI2.5 were compared between study and control groups and in three subgroups within the study group (CF, PCD and CSLD together with BE) using t-test. Spearman rank correlation (r) of MMPs% to RBM thickness, BALF cytology, LCI2.5 and anthropometry was tested in the study group (n = 33).

**Results:** RBM thickness, MMPs%, percentage of neutrophils in BALF and LCI2.5 were significantly higher in the study group than in controls ( $\Delta$ RBM = 1.66  $\mu$ m,  $P < 0.001$ ;  $\Delta$ MMP2% = 5.6%,  $P < 0.001$ ;  $\Delta$ MMP9% = 3.0%,  $P < 0.001$ ;  $\Delta$ LCI2.5 = 3.6,  $P < 0.001$ ;  $\Delta$ neuro = 36.1%,  $P < 0.001$ ). All of the differences remained significant when the three subgroups were compared separately to controls. Both MMP2% and MMP9% correlated with RBM thickness (Diagram 1 and 2). Only MMP2% correlated with LCI2.5 ( $r = 0.383$ ,  $P = 0.041$ ). No relationship was found between MMPs% and BAL cytology or anthropology.

**Conclusion:** MMP2 and MMP9 are upregulated in bronchial lamina propria mucosae in patients with CF, PCD, CSLD and BE. Their positivity is related to RBM thickness indicating their important role in airway remodeling. MMP2% is related to ventilation inhomogeneity but not to BALF neutrophilia.

Diagram 1. Correlation of MMP2% to RBM thickness:  $r = 0.427$ ,  $P = 0.021$ .

Diagram 2: Correlation of MMP9% to RBM thickness:  $r = 0.364$ ,  $P = 0.044$ .

## D-38 | Correlation between Body Mass Index and Optimal Continuous Positive Airway Pressure Level in Children with Obstructive Sleep Apnea

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**Background:** A subgroup of children with obstructive sleep apnea (OSA) requires treatment with Continuous Positive Airway Pressure (CPAP). When initiating CPAP, determining a priori the required optimal CPAP level remains a challenge in children. While the correlation between Body Mass Index (BMI) and optimal CPAP is well recognized in adults, it is uncertain if such a correlation exists in children. The clinical guideline<sup>1</sup> for manual titration of CPAP in patients with OSA acknowledges the