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Introduction: Ethnicity may influence response to treatment of asthmatic patients, but this is controversial

Objectives: To determine if ethnicity influences the response to intramuscular steroid (eliminating adherence as an issue).

Methods: Children with severe therapy resistant asthma were admitted for assessment of steroid response. Asthma Control Test (ACT), exhaled nitric oxide (FENO), spirometry and sputum eosinophils were measured before and 4 weeks after intramuscular triamcinolone. Definitions of responsiveness: symptom response, ACT ↑ to ≥20 or by ≥5; inflammatory response, if paired induced sputum samples available, sputum eosinophil count ↓ to ≤2.5%, or if unavailable, FENO ↓ to <24 parts per billion (ppb); lung function response, FEV₁ ↑ to ≥-1.96 Z-score or by ≥15%. Non-responder, improvement in 0 domain; partial response, ≥1 domains; complete response, all 3 domains.

Results: 79 subjects were identified (Caucasian = 54, Black = 16, Asian = 5, Mixed Caucasian/Black = 4). There were no ethnic differences in the proportion of non-responders, partial responders and complete. After triamcinolone, there was a significant drop in mean FENO in Caucasians (49.6 to 26.3 ppb, $p < 0.0001$) but not in black (55.5 to 54.1 ppb, $p = 0.87$). More Black than Caucasian were FENO non-responders (86.7 vs. 45.3%, $p < 0.05$) and had exacerbations despite triamcinolone (61 vs. 17%, $p < 0.05$). There was no ethnic difference in ACT, FEV₁ and sputum eosinophil responders.

Conclusions: Black asthmatic children were less likely to have a FENO response and had more exacerbations when compared to Caucasians. Further research is needed to understand the mechanisms of these differences.

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Inhaled corticosteroids and bone mineral density in children: A prospective 12-year follow-up study after early-life wheezing

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Background: Inhaled corticosteroids (ICS) are the drugs of choice for asthma. Corticosteroids can have many detrimental effects on bone mineralization and growth, despite of inhaled administration.

Aims and objectives: To evaluate the association between the long-term use of ICS in childhood and bone mineral density (BMD) in teenagers.

Methods: Ninety-one children hospitalized for wheezing at age <24 months were prospectively followed until 12.2 (median) years of age. Data on ICS use were collected by interviewing the parents, supplemented by data from patient records. Cumulative doses, the duration of ICS use and systemic steroid doses were calculated. At the last check-up, BMD (BMDareal, g/cm²) was measured by dual energy X-ray absorptiometry (DXA) in 89 children, and apparent volumetric BMDs (aBMDvol, g/cm³) were calculated for the lumbar spine and femoral neck. Weight, height and pubertal stage were recorded.

Results: The regular use of ICS at age <6 years was associated with a lower BMDareal of the lumbar spine (mean 0.76, 95%CI 0.71-0.81 vs. 0.88, 0.84-0.92; $p = 0.006$). A lower BMDareal and aBMDvol of the femoral neck were associated with higher cumulative doses of ICS at 0-12.2 (median) years of age. Pearson's correlation coefficients were $r(r^2) = -0.320 (0.10)$ for BMDareal and $r(r^2) = -0.291 (0.08)$ for aBMDvol. Age, sex and pubertal stage were significantly associated with both BMDareal and aBMDvol, but did not confound the results.

Conclusion: The use of ICS during childhood may be related to a decrease in BMD at early teenage, though the clinical manifestations of reduced BMD usually occur later in adulthood.

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Inhaled corticosteroids and risk of oropharyngeal colonization by streptococcus pneumoniae in children with asthma

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Introduction: Recent epidemiological studies have raised concerns about possible link between use of inhaled corticosteroids (ICS) and risk of pneumonia in patients with chronic obstructive pulmonary disease. This cross-sectional study aimed to investigate association between ICS and oropharyngeal colonization by Streptococcus pneumoniae (S. pneumoniae) among children (up to 18 years old) with asthma.

Methods: Two age-matched groups of patients were consecutively recruited: 1) Exposed group: children who had persistent asthma and were being treated with daily ICS for at least 30 days; 2) Non-exposed group: children who had asthma and were not being treated with ICS. Oropharyngeal specimens from the tonsillar area and posterior pharyngeal wall were collected.

Results: A total of 192 patients (96 in each group) were included in the study. In

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Ethnic variation in response to intramuscular triamcinolone in children with severe therapy resistant asthma

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the exposed group, the mean daily dose of ICS was 400 mcg of beclomethasone or equivalent and the mean duration of treatment was 8.6 months. The prevalence of oropharyngeal colonization by *S. pneumoniae* was higher among children exposed to regular use of ICS than among those not exposed to ICS (27.1% vs. 8.3%, $p=0.001$). After adjusting for potential confounders, regular use of ICS was an independent risk factor for oropharyngeal carriage of *S. pneumoniae*, with an adjusted prevalence ratio of 3.76 (95% confidence interval: 1.73–8.18, $p=0.001$).

Conclusions: Regular use of ICS is associated with an increased risk of having oropharyngeal colonization by *S. pneumoniae* in children with asthma. These findings highlight the need to further investigate the association between ICS therapy and risk of pneumonia among asthmatic children.

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Barriers to adherence to inhaled corticosteroids in a high adherent population of children with asthma

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Introduction: Although reasons for nonadherence to inhaled corticosteroids (ICS) have been widely studied, an in-depth understanding of barriers to adherence in children is lacking.

Methods: We measured ICS adherence electronically for 1 year in children (2-12 yr) with asthma who received comprehensive care and strict follow-up in our hospital-based asthma clinic. After completion of this study, we performed in-depth interviews with parents of children with the lowest and highest adherence rates. Verbatim transcripts were analyzed with standard qualitative research methods.

Results: Parents of 20 children (median age 5.9 yrs, range 4-13 yrs) were interviewed. All parents had the intention to use ICS on a regular basis. Two patterns of low adherence were identified. One group of (highly educated) parents deliberately did not use the ICS according to doctor's advice, but adjusted the ICS dose based on their perception of asthma control in their child, leading to regular use of ICS, but at a dose lower than prescribed. The other group of parents (most with lower educational levels) were faced with barriers impeding regular ICS use. These barriers included chaotic family life and parenting problems. A common and striking finding was the low adherence rate in children 8-12 yrs of age, who were given full responsibility for taking their ICS without parental support or supervision.

Conclusion: Although comprehensive asthma care prevents intentional non-adherence, family driven barriers remain an important cause of non-adherence. The excessive responsibility put on school-aged children to organize their own ICS medication taking is a common and possibly modifiable barrier.

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Pulmonary immunoglobulin E levels and the response to anti-immunoglobulin E antibody therapy in paediatric severe therapy resistant asthma

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Background: Omalizumab is used in children with atopic, moderate to severe persistent asthma, but predictors of response are unknown. Broncho-alveolar lavage (BAL) or endobronchial biopsy (EB) immunoglobulin E (IgE) has not been reported. It has been proposed that pulmonary IgE levels may predict response to therapy. Hypothesis: there is no relationship between serum and pulmonary IgE; and pulmonary IgE levels predict response to omalizumab.

Methods: We measured IgE levels in serum, induced sputum (IS), BAL and EB in 70 children (6-16 yr) with severe asthma. 15 underwent an omalizumab trial. IgE expression was determined in EB by immunohistochemistry and levels in IS and BAL were quantified using ELISA. Haematoxylin and eosin stained EB were used to quantify airway remodelling and eosinophilic inflammation was quantified using the Congo red stain.

Results: 54 subjects had at least one evaluable biopsy. There was no relationship between total serum IgE and EB IgE+ cells, Spearman $r=0.4739$. Non-responders had higher serum IgE (failed trial: median 1582 IU/ml, range [1324 - 11355] vs. successful trial: 386 IU/ml, range [105-2438], $p<0.05$). EB IgE+ cells did not predict omalizumab response. There was no association between EB IgE expression and airway remodelling or eosinophilic inflammation.

Conclusions: There was no relationship between serum and pulmonary IgE. Very high serum IgE levels predicted a failed response to omalizumab, but EB IgE expression was not useful in predicting a response. There was no relationship between airway remodeling, eosinophilic inflammation and EB IgE+ cells.

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Hypertonic saline and acute wheezing in pre-school children

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Background: Most acute wheezing episodes in preschool children are associated with viral respiratory tract infections, most commonly rhinovirus. Rhinovirus, like RSV, decreases extra-cellular ATP, leading to airway surface liquid dehydration. This, along with sub-mucosal edema, mucus plaques and inflammation cause failure of mucus clearance (MC). Such preschool children do not respond well to available treatments, including oral steroids. This calls for pro-MC and pro-hydration treatment like hypertonic saline.

Methods: Randomized, controlled, double-blind study. Forty one children (mean age 31.9 ± 17.4 months, range 1-6 years) presented with wheezing to the emergency department (ED) were randomized after one albuterol inhalation to receive either 4 ml of Hypertonic Saline 5% (HS), ($n=16$) or 4 ml of Normal saline (NS), ($n=25$) both with 0.5 ml albuterol, twice every 20 minutes in the ED and four times a day thereafter if hospitalized. Primary outcome measured was length of stay (LOS) and secondary outcomes were admission rate (AR) and clinical severity score (CS).

Results: LOS was significantly shorter in the HS than in the NS group: median (range) 2 (0-6) days, versus 3 (0-5) days ($P=0.027$). AR was significantly lower in the HS than the NS group: 62.2% versus 92%. CS improved significantly in both groups but did not reach significance between them.

Hospitalization rate

Outcomes	HS, N=16	NS, N=25	P value: HS v NS	All, N=41
Admission rate (%)	10 (62.2)	23 (92)	$P<0.05$	33 (80)
Discharged home (%)	6 (38.8)	2 (8)		8 (20)
Length of stay, Median (range)	2 (0-5)	3 (0-6)	$P<0.03$	2.7 (0-6)

Conclusions: Using HS inhalations significantly shortens LOS and lowers AR in preschool children presenting with acute wheezing episode to the ED.

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The prevention of virus-induced exacerbation of bronchial asthma in children

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Background: The viral infection is the most common trigger of bronchial asthma. The role of antiviral therapy in prevention of virus-induced bronchial asthma exacerbations in children is still unknown.

Aim: To evaluate the efficacy and safety of ultralow doses of antibodies to interferon- γ (ULD AB IFN- γ) - IFN-inducer ("Anaferon") in treatment of patients with virus-induced phenotypes of bronchial asthma.

Methods: A comparative, randomized, double-blind placebo-controlled trial of ULD AB IFN- γ (anaferon for children) efficacy in prevention of acute respiratory viral infections (ARVI) and bronchial asthma exacerbations in a 100 children of 1-5 years with virus-induced phenotype of mild and moderate bronchial asthma. 52 patients of the treatment group obtained ULD AB IFN- γ (anaferon) for children in preventive regimen (1 pill 1 time per day for 3 months) and 48 patients of the comparison group took placebo in the same way.

Results: During 3-months follow-up period the mean number of acute respiratory viral infections in treatment group was 0.6 ± 0.14 and duration was 4.4 ± 0.4 days; in comparison group children suffered from 1.32 ± 0.18 ARVI episodes with mean duration 8.9 ± 0.9 days. The percent of children with exacerbation of bronchial asthma induced by ARVI was 11.5% and 27% of children in treatment and comparison groups respectively. Side effects were not registered during the trial.

Conclusions: The preventive administration of ULD AB IFN- γ (anaferon) affords to decrease the number of virus-induced bronchial asthma exacerbations, episodes and duration of acute respiratory viral infection. This fact considerably improves the quality of patients' life and decrease economic costs for exacerbation treatment.

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Modified mRNA encoding Foxp3 protects against allergic asthma in mice by rebalancing T helper cell responses through an IL-23/IL-17A-dependent mechanism

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Chemically modified mRNA has recently shown life-saving efficacy in a murine model of a rare, genetic lung disease, Surfactant Protein-B deficiency, by inducing therapeutic levels of protein expression while circumventing the threat of genomic integration often associated with viral vectors (Korman et al, Nat Biotechnol. 2011 Feb; 29(2):154-7). To translate this novel therapeutic tool into a high prevalence disease model, we investigated whether modified mRNA could restore immune balance and alleviate disease severity in Th2-driven allergic asthma. We show that intratracheal delivery of modified mRNA coding for the regulatory T cell factor Foxp3 rebalanced pulmonary T helper cell responses, modulated innate immune

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cell recruitment, and protected from allergen-induced tissue inflammation and goblet cell metaplasia. Protection against asthma was achieved following delivery of modified mRNA either before or after the onset of allergen challenge, demonstrating its potential as both a preventative and a therapeutic. Mechanistically, Foxp3 upregulation was critical in downregulating IL-23 and IL-17 production, and recombinant IL-23 or IL-17 expression during challenge abolished protection conferred by Foxp3 mRNA. Taken together, our results provide evidence that chemically modified Foxp3 mRNA protects against allergic asthma in vivo, which may pave the way for considering modified mRNA as a safe therapeutic tool for the treatment of asthma, allergy and beyond.