

## Effect of Different Doses of Inhaled Corticosteroids on the Isolation of Nasopharyngeal Flora in Children with Asthma

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**Objectives:** To find the effects of inhaled corticosteroids and the impact of different doses of inhaled corticosteroids on the isolation of nasopharyngeal flora in asthmatic children aged 1-15 years. **Methods:** The study included 75 children with asthma and 25 age-matched controls. Nasopharyngeal swabs were obtained. Bacteria were identified by standard techniques. **Results:** Pathogenic organisms were isolated from 36% of asthmatic children and 20% of controls, the difference was not significant statistically (OR=2.25, 95% CI=0.75-6.67,  $P=0.13$ ). There was no statistically significant association of using a high dose of inhaled corticosteroids with the isolation of pathogenic organisms. Usage of biomass fuel for cooking in the household of asthmatic children increases the risk of colonization (OR=3.4, 95% CI= 1.26-9.10,  $P=0.03$ ). **Conclusion:** Inhaled corticosteroids are safe in the treatment of asthma and there is no association between different doses of Inhaled corticosteroids and isolation of the pathogenic organism.

**Keywords:** Biomass fuels, Management, Pneumococcus.

Inhaled corticosteroids (ICS) form the cornerstone of treatment of asthma. Local side-effects associated with ICS use include oropharyngeal candidiasis, dysphonia, reflex cough, bronchospasm, and pharyngitis due to the weakening of local immunity [1]. In children, the nasopharyngeal flora becomes established within the first 12 months of their life including both commensal bacteria and potential pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenza* [2].

Deposition of ICS in the oropharynx may alter the local mucosal immune response through their immunosuppressive effects which have been considered responsible for oropharyngeal candidiasis [3]. Arocha-Sandoval, *et al.* [4] found a higher rate of oropharyngeal bacterial colonization in asthmatic children as compared with healthy individuals. As colonization with potential pathogens can lead to the development of respiratory or even invasive infections, recognition of the risk factors for such colonization is important. Thus, the main objective of the study was to investigate the effects of steroids on bacterial colonization and to analyze the impact of different doses of ICS on nasopharyngeal isolation of a pathogenic organism.

### METHODS

The study was carried out over a period of one year (September 2015 to July 2016) in the outpatient

department of Pediatrics, and department of Microbiology of a tertiary-care referral teaching Institute of Northern India after obtaining ethical clearance from the institutional ethics committee.

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All diagnosed cases of asthma according to GINA guidelines were enrolled [5]. We excluded the children who received antibiotics or got hospitalized in the last 15 days. For children aged 1-5 years, spirometry was not possible. Thus, cases were recruited that had a presence of two or more of the following symptoms: current presence of wheeze in any child with a history of more than two episodes of documented wheeze or use of bronchodilator in the preceding 12 months; on any regular medication for asthma such as corticosteroids,  $\beta$ -2 agonist, methylxanthines, leukotriene modifiers, and cromones; and, presenting with symptoms of asthma along with positive family history of asthma or other allergic disease (allergic rhinitis or eczema).

Controls were enrolled from the children attending the immunization clinic or siblings of children attending the OPD, from the same locality/ community for some other ailments. Inclusion criteria for controls included no past or present diagnosis of asthma and other pulmonary diseases; no history of wheezing, shortness of breath, and other symptoms of allergic diseases such as nasal and skin

symptoms; no use of immunosuppressant or medications for asthma and, absence of first-degree relatives with a history of asthma.

Almost all the patients were taking inhaled budesonide in our study, only two patients used inhaled fluticasone. A dose of 100-200 µg was considered as low dose, >200-400 µg was considered as moderate dose and >400 µg dose was considered as a high dose of inhaled budesonide in the children aged 6-11 years while the children who were 12 years and older, an inhaled dose of 200- 400 µg, >400-800 µg, and >800 µg were considered as low dose, moderate dose, and high dose, respectively [5]. A predesigned data collection form was filled and a nasopharyngeal swab was taken. After obtaining the consent and explaining the procedure to parents and child, the patient's head was tilted back to 70 degrees. The distance from ala of the nose to tragus was measured and marked on the swab. The swab was inserted horizontally into nostril up to a point equivalent to half the distance measured or until resistance is met. The swab was rotated and hold in place for 5-10 seconds. Tip of the swab was placed into a sterile tube and immediately transported to the laboratory (transport media was not used).

The swab was cultured on sheep blood agar, Mc Conkey agar and chocolate agar and a direct smear were prepared and the gram stain was made. Plates were immediately incubated at 37°C in 5% CO<sub>2</sub> incubator for overnight. After that, culture growth was reported and colonies were identified. Colony morphology was identified as per standard protocol [6]. The bacteria were divided into two groups: potentially pathogenic bacteria mainly *S. aureus*, *S. pneumoniae*, *M. catarrhalis* and gram-negative rods like *Acinetobacter*, *Enterobacter* and *E. coli*. Bacteria other than them were included in non-pathogenic group/commensals, which mainly includes Coagulase-negative *S. aureus*, *S. viridans*, and Diptheroids. Subjects in whom, both potentially pathogenic and nonpathogenic bacteria were present, were included in the potentially pathogenic group.

**Statistical analysis:** The analysis was performed on SPSS software (Windows version 17.0) and Epi Info 7. Categorical groups were compared by the chi-square (-2) test and Fisher exact test. We calculated odd's odds ratio with a 95% confidence interval. A two-tailed *P*-value less than 0.05 was considered statistically significant.

## RESULTS

Out of 86 patients screened, 11 patients were excluded as per the exclusion criteria. Included were 75 asthma cases and 25 age-matched healthy controls. The baseline

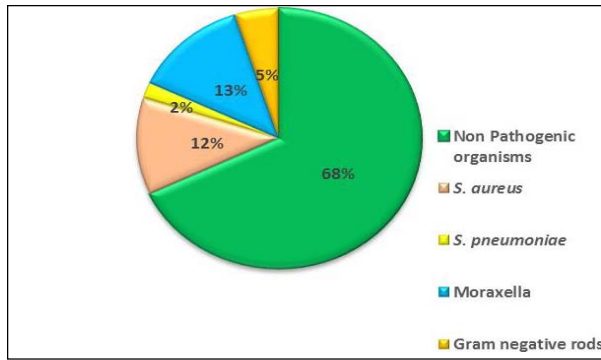
characteristics of the study population are given in **Table I**. There was a statistically significant difference between the smoking status of father and the usage of biomass fuel for cooking among cases and controls. Pneumococcal vaccines were taken by 25.3% of asthmatic children and 20% of controls (information on influenza vaccine was not collected). Among recruited cases, 40 (53.3%) had well controlled, 23 (30.7%) had partially controlled and 12 (16%) had uncontrolled asthma. Out of 75 children with asthma, 33 (44%), 33 (44%) and 9 (12%) were using low dose, moderate dose and the high dose of ICS, respectively. Sixty-two (82.7%) asthmatic children were using a spacer and 46 (61.3%) children were washing the mouth after administration of ICS. In the present study, the overall carriage rate of potential pathogens was 36% for asthmatic children and 20% for controls (OR=2.25, 95% CI=0.75-6.67, *P*=0.13). **Fig. 1** illustrates an overview of the carriage rate of pathogenic organism. No significant age-wise (1-5 years *versus* 6-15 years) differences have been observed in the isolation rates of the pathogens in the present study. We did not find any association between the level of control of asthma and carriage rates.

The pathogenic organisms were isolated in 30.3%, 33.3% and 66.7% of asthmatic children taking a low dose, medium dose and high dose ICS, respectively. There was no statistically significant association of using a high dose of inhaled corticosteroids with the isolation of pathogenic organisms (OR=4.6, 95% CI=0.95-22.1,

**TABLE I** BASELINE CHARACTERISTICS OF CHILDREN WITH ASTHMA AND NON-ASTHMATIC CONTROLS

Social Characteristics	Cases (n=75)	Control (n=25)
<i>Age category</i>		
12-60 mo	21 (28)	7 (28)
61-180 mo	54 (72)	18 (72)
Mean (SD) age, mo	89.9 (36.98)	84.6 ( 35.47)
Male gender	51 (68)	14 (56)
Rural residence	42 (56)	15 (60)
Use of biomass for cooking*	33 (44)	5 (20)
Overcrowding	23 (30)	9 (36)
Joint family	51 (68)	14 (56)
Smoker father*	38 (50.7)	7 (28)
<i>Immunization status</i>		
Not immunized	39 (52)	17 (68)
Completely immunized	19 (25.3)	5 (20)
Partially immunized	16 (21.3)	3 (12)
Status unknown	1 (1.3)	0

\**P*<0.05; All values in n (%) except \*mean (SD).



**FIG. 1** Bacterial isolate from nasopharynx in children (aged 1- 15 years) with (n=75) and without asthma (n=25)

*P*=0.05). Colonization with pathogenic organism was found in 44% of asthmatic children who were taking inhaled corticosteroids for more than 1 year as compared to 25% of asthmatic children who were on inhaled corticosteroids for less than 1 year duration which was not statistically significant (OR=2.3, 95% CI 0.87-6.46, *P*=0.08). **Table II** depicts the isolation of pathogenic organisms among asthmatic children stratified by various characteristics. Exposure to biomass fuel was associated with higher colonization rates of pathogenic organisms among asthmatic children (OR=3.4, 95% CI= 1.26-9.10, *P*=0.03).

**DISCUSSION**

The present study showed the lack of association between the use of ICS and nasopharyngeal colonization by pathogenic bacteria in asthmatics. Similar findings were also reported by another study conducted in China in 2013

**TABLE II** NASOPHARYNGEAL ISOLATION OF PATHOGENIC ORGANISM AMONG CHILDREN WITH ASTHMA

	Pathogenic organisms	
	Present, n (%)	OR (95% CI)
<i>Dose of ICS</i>		
Low dose	10 (30.3)	
Moderate dose	11 (33.3)	1.1 (0.4-3.24)
High dose	6 (66.7)	4.6 (0.95-22.10)
<i>Level of control</i>		
Well controlled	11 (27.5)	
Moderately controlled	10 (43.5)	2.0 (0.69-5.90)
Uncontrolled	6 (50)	2.6 (0.69-9.94)
Mouth wash after ICS use	13 (28.3)	3.1 (0.89-6.25)
Use of spacer	24 (38.7)	1.1 (0.07-2.12)
*Child in exacerbation	12 (57.1)	5.7 (0.10-0.82)

\**P*=0.01.

[7]. They found no significant differences in bacterial isolation rates among controls and children with asthma treated with ICS after 3, 6 and 12 months. Although in our study, we did not do a longitudinal follow up. We could not find a statistically significant association between the different doses of ICS and carriage rate of the pathogenic organisms. Our results were also in concordance with another similar study from Turkey [8].

We observed that children receiving higher doses of ICS were more likely to be carriers of potentially pathogenic bacteria than those receiving low and medium doses, although there was no statistical effect on the carriage of pathogenic bacteria tested. This could be because the number of children receiving high dose ICS was small. Children in exacerbation had increased colonization with the pathogenic organism as compared to children without exacerbations. Although, evidence linking acute asthma exacerbations to bacterial infections are limited. However, respiratory viruses may facilitate the emergence of bacterial infections by impairing the anti-bacterial defenses by human alveolar macrophages [9]. But, testing for viral pathogens in nasopharyngeal swab was not done in the present study. Usage of biomass fuel is a potential risk factor for colonization of pathogenic organisms in asthmatic children.

There were some limitations in our study. We did not follow up cases of asthma taking ICS for change in colonization patterns. Skim milk, tryptone, glucose, and glycerin (STGG) medium was not used for transport of nasopharyngeal swab, hence there was low isolation of *S. pneumoniae*. Majority of the cases were taking one pharmacological preparation of ICS, hence we could not assess the effect of different types of ICS on nasopharyngeal colonization.

We conclude that ICS do not increase the colonization of potentially pathogenic organisms and high doses of ICS are safe in the treatment of asthma. We should avoid biomass fuels for cooking in households as it increases the risk of colonization.

**Contributors:** GN: enrolled the patients, collected the data, performed data analysis, drafted the initial manuscript and approved the final manuscript as submitted; SA: conceived the idea of this the study, supervised data collection, helped in data analysis. reviewed it critically and approved the final manuscript as submitted; SG: supervised data collection, and approved the final manuscript as submitted; JA: supervised microbiological testing and approved the final manuscript as submitted.

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**REFERENCES**

1. Dubus JC, Marguet C, Deschildre A, Mely L, Le Roux P, Brouard J, *et al*. Local side effects of inhaled

**WHAT THIS STUDY ADDS?**

- Inhalational corticosteroids do not appear to increase the risk of nasopharyngeal colonization of potential pathogenic organisms in children with asthma.

corticosteroids in asthmatic children: influence of the drug, dose, age, and device. *J Allergy Clin Immunol.* 2001;56:944-8.

- Garcia-Rodriguez J, Fresnadillo M. Dynamics of NP colonization by potential respiratory pathogens. *J Antimicrob Chemother.* 2002;50:59-73.
- Fukushima C, Matsuse h, Tomari S, Obase Y, Miyazaki Y, Shimoda T, *et al.* Oral candidiasis is associated with inhaled corticosteroid use: Comparison of fluticasone and beclomethasone. *Ann Allergy Asthma Immunol.* 2003;90:646-51.
- Arocha-Sandoval F, Parra-Quevedo K. Oropharyngeal bacteria in asthmatic patients in the city of Maracaibo, Venezuela. *Invest. Clin.* 2002;43:145-55.
- Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma (GINA), National Heart, Lung and Blood Institute, US Department of Health and Human Services: National Institute of Health (NIH); 2015.
- Collee JG, Marmion BP, Fraser AG, Simmons A. Mackie & Mc Cartney Practical Medical Microbiology, 14th ed. India; Elsevier; 2006.
- Lin H, Sun Y, Lin RJ, Xv J, Li N. Influence of inhaled corticosteroids on distribution of throat flora in children with bronchial asthma. *Chin J Otorhinolaryngol Head Neck Surg.* 2010;45:656-9.
- Talay F, Karabay O, Yilmaz F, Kocoglu E. Effect of inhaled budesonide on oropharyngeal, Gram-negative bacilli colonization in asthma patients. *Respirology.* 2007;12:76-80.
- Oliver BG, Lim S, Wark P, Laza-Stanca V, King N, Black JL, *et al.* Rhinovirus exposure impairs immune responses to bacterial products in human alveolar macrophages. *Thorax.* 2008;63:519-25.