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Study of the Characteristics of Sputum Inflammatory Phenotypes in Adults with Asthma and Identification of Subgroup with Isolated Sputum Neutrophilia and Poor Response to Inhaled Corticosteroids in a Tertiary Care Hospital of North-East India

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ABSTRACT

Background: Asthma is a heterogeneous chronic inflammatory airway disease characterized by variable airflow obstruction and airway inflammation. Sputum induction enables classification into eosinophilic, neutrophilic, mixed granulocytic, and paucigranulocytic phenotypes. Neutrophilic asthma is often associated with poor responsiveness to inhaled corticosteroids (ICS).

Objective: To estimate the proportion of sputum inflammatory phenotypes in adult asthma patients and to evaluate the response of the neutrophilic phenotype to ICS therapy.

Methods: A cross-sectional observational study was conducted among 223 adult non-smoking asthmatic patients at a tertiary care hospital in North-East India. Clinical evaluation, blood eosinophil count, serum IgE, spirometry, and induced sputum cytology were performed. Patients received inhaled budesonide 400 µg twice daily for six weeks and pre- and post-treatment FEV1 were compared.

Results: Among 223 patients eosinophilic phenotype(47.53%) was most common, followed by paucigranulocytic (32.74%), neutrophilic (21.07%), and mixed (4.93%) phenotypes. Majority(60.54%) are 18-40 yrs old , subjects were predominantly female (Female :Male ratio 1.89:1). Most of the study subjects (79.37%) had onset of asthma before 6 years whereas only 9.87% had severe persistent asthma. The most common co-morbidity encountered among study subjects was GERD (59.19%) and the least common was DM (16.14%). In terms of classification of study subjects according to BMI the two extremes obese and underweight were 37.67% and 3.14% respectively, 62.33% study subjects have serum IgE level >160 IU/ml and 85.65% have blood eosinophils <5%. 70.40% study subjects improved FEV1 by use of ICS and 29.60% study subjects had no response on FEV1 by use of ICS. This response is statistically significant ($X2=51.267$, $P<0.005$, $df=3$). Neutrophilic phenotype demonstrated comparatively poorer improvement in FEV1 following ICS therapy.

Conclusion: Asthma in this population shows marked inflammatory heterogeneity. Identification of neutrophilic asthma is clinically important due to reduced responsiveness to ICS and the potential need for alternative therapeutic strategies.

Keywords: *Asthma, Sputum Phenotype, Neutrophilic Asthma, Eosinophilic Asthma, Inhaled Corticosteroids.*

INTRODUCTION

Asthma represents a prevalent chronic respiratory disorder affecting millions globally, characterized by airway inflammation, hyperresponsiveness, and reversible airflow obstruction, manifesting in symptoms such as wheezing, coughing, chest tightness, and shortness of breath. According to the World Health Organization, over 262 million individuals suffer from this condition, imposing substantial burdens on healthcare systems and quality of life. In India, particularly in regions with high air pollution and environmental exposures, asthma prevalence is significant, impacting tens of millions. The disease's pathophysiology involves a complex interplay between genetic predisposition and environmental factors, traditionally linked to T helper type 2 (Th2) immune responses involving cytokines like interleukin-4 (IL-4), IL-5, and IL-13, which activate eosinophils and mast cells. However, asthma is now recognized as heterogeneous, encompassing diverse inflammatory phenotypes that vary in presentation and treatment response. Phenotype identification, especially for severe cases, enables individualized approaches, with predictors derived from clinical characteristics. Advances in treatments, such as inhaled corticosteroids (ICS) combined with long-acting beta agonists, have reduced symptoms, exacerbations, and improved lung function, particularly in eosinophilic profiles responsive to anti-inflammatory therapies.

The concept of inflammatory phenotypes has gained traction, driven by observations that not all asthmatics share uniform profiles or respond to standard treatments. Sputum induction, a non-invasive gold standard for evaluating bronchial inflammation, distinguishes four phenotypes: eosinophilic, neutrophilic, mixed granulocytic, and paucigranulocytic, based on cellular composition including eosinophils, neutrophils, lymphocytes, and macrophages. Eosinophilic asthma, often Th2-driven, responds well to ICS, which suppress eosinophil activation and Th2 cytokine production. In contrast, non-eosinophilic subsets, like neutrophilic asthma, show resistance, associated with severe disease, poorer lung function, frequent exacerbations, and diminished ICS efficacy. Mechanisms involve distinct pathways, such as IL-17, IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF), produced by Th17 cells, promoting neutrophil recruitment and survival. Factors like environmental pollutants, cigarette smoke, viral infections, obesity, genetic susceptibility, and airway microbiome composition contribute to phenotype development. Peripheral blood eosinophilia predicts airway eosinophilia, though cutoffs remain unestablished, while recent studies highlight predominant neutrophilic inflammation in diverse patient groups, including severe cases, raising questions about disease severity versus treatment effects.

Neutrophilic asthma, marked by increased airway neutrophils, often correlates with milder to severe presentations and poor ICS response, potentially reflecting a subset with predominant neutrophilic inflammation. Heterogeneity within this spectrum includes isolated sputum neutrophilia, where neutrophils dominate without significant eosinophils or other granulocytes, necessitating tailored management. Conventional therapies like ICS may underperform here, underscoring needs for alternatives, such as biologics targeting IL-17 or novel inhibitors. Geographical contexts influence phenotypes; in North-East India, unique factors like biomass smoke exposure, air pollution, and respiratory infection patterns may shape distributions, affecting local disease burden. Tertiary care settings in this region handle complex cases, making phenotype studies crucial for understanding severity and prevalence. Research gaps persist in elucidating drivers of neutrophilic profiles and developing targeted interventions, with sputum analysis offering insights into response variations. Hypotheses suggest predominant neutrophilic inflammation in milder subsets associates with suboptimal ICS outcomes, highlighting the importance of phenotype-specific strategies for optimized clinical care.

This study addresses these gaps by examining sputum inflammatory phenotypes in adult asthmatics at a North-East Indian tertiary hospital, providing an epidemiological snapshot and evaluating ICS effectiveness, particularly in isolated neutrophilic cases. Primary objectives include estimating proportions of eosinophilic, neutrophilic, mixed, and paucigranulocytic phenotypes to map the local inflammatory landscape, and assessing neutrophilic subgroup responses to standard treatments. Findings aim to characterize heterogeneity, identify treatment-resistant subsets, and inform personalized management, potentially guiding alternative therapies. By correlating profiles with clinical traits, severity, and responses, the research lays a foundation for future explorations of underlying mechanisms and targeted interventions, enhancing outcomes and quality of life for regional patients. Ultimately, this contributes to asthma's global understanding, emphasizing regional adaptations for effective, evidence-based care in diverse populations.

MATERIALS AND METHODS

Study Design: Cross-sectional observational study.

Study Setting: Department of Respiratory Medicine, AGMC & GBPH, Agartala.

Study Period: October 2023 to March 2025.

Sample Size: 223 patients (calculated using prevalence of neutrophilic phenotype 15.6% with 95% CI and 5% precision).

Study Tools:

1. A predesigned proforma.
2. Weight machine and measuring tape for BMI calculation
3. Blood eosinophil percentage and absolute blood eosinophil count
4. Total serum IgE
5. Sputum cytological analysis
6. Spirometry-pre and post (SPIROWIN)

Inclusion Criteria: Adults ≥18 years, clinically diagnosed asthma, non-smokers.

Exclusion Criteria: Smoking history, respiratory infections, ABPA, bronchiectasis, ACOS, refusal of consent.

Procedure: Detailed clinical evaluation, BMI measurement, blood eosinophil count, total serum IgE estimation, pre- and post-bronchodilator spirometry, and induced sputum cytology were performed. Phenotypes were defined as: eosinophilic (≥3% eosinophils), neutrophilic (≥61% neutrophils), mixed (≥3% eosinophils and ≥61% neutrophils), and paucigranulocytic (<3% eosinophils and <61% neutrophils). All patients received inhaled budesonide 400 µg twice daily for 6 weeks and change in FEV1 was assessed.

Statistical Analysis: Data analyzed using SPSS version 27. Percentages and Chi-square test applied.

RESULTS

Characteristics of Phenotypes:

Demographic Characteristics

Among 228 patients with confirmed asthma , age distribution showed concentration in the younger age group. 135 patients (60.54%) are between 18-40 years ,65 patients (29.15%) are between 41-60 years and 23 patients (10.31%) are between 61-80 years. Youngest is 18 years and oldest being 79 years.

Males comprised 34.53 %(77 patients) and females 65.47%(146 patients) , resulting in a female to male ratio of 1.89:1.

Characteristics of Asthma

Among the study subjects childhood asthma was diagnosed in 23.32 % (52 patients) wheras onset of asthma was before 6 years in 79.37% (177 patients). 9.87% had severe persistent asthma and rest (90.13 %) didn't. Among the study subjects 20.18% (45 patients) had occupational exposure and 79.82 % (178 patients) didn't. 58.30 % (130 patients) had family history of asthma and the rest (41.70%) didn't.

Prevalence of Comorbidities :

Association as documented in the study sample:

Comorbidity	No of patients	Percentage
GERD	132	59.19%
Anxiety/Depression	55	24.66%
Cardiovascular Disease	76	34.08%
Diabetes Mellitus	36	16.14%
Obesity	84	37.67%
Nasal Polyposis	37	16.59%
Rhinitis	144	64.57%
Atopy	109	48.88%

GERD: 132 patients (59.19%) , **Anxiety/Depression** : 55 patients (24.66%) , **Cardiovascular Disease** :76 patients (34.08%) , **Diabetes Mellitus** : 36 patients (16.14%) , **Obesity** :84 patients (37.67%) **, Nasal Polyposis** : 37 patients (16.59%), **Rhinitis** : 144 patients (64.57%) ,**Atopy** : 109 patients (48.88%).

Bronchodilator test interpretation : Among the study subjects 58 patients (26.01%) were found to be positive while the rest 165 patients (73.99 %) were negative on bronchodilator test.

Relationship with serum IgE and blood eosinophil count :

139 patients (62.33%) had serum IgE level >160 IU/ml while the remaining 84 patients (37.67%) had IgE level <=160 IU/ml.

Only 32 patients (14.35%) had blood eosinophil percentage >=5 and 191 patients (85.65%) had blood eosinophil percentage <5.

Distribution of sputum phenotypes :

Sputum neutrophil and eosinophil percentage	Neutrophilic	Eosinophilic	Mixed	Paucigranulocytic
	No (%)	No (%)	No (%)	No (%)
>=61% ,<3%	33 (14.79)	0(0)	0(0)	0(0)
<61% , >=3%	0(0)	106 (47.53)	0(0)	0(0)
>=61% , >=3%	0(0)	0(0)	11(4.93)	0(0)
<61% , <3%	0(0)	0(0)	0(0)	73(32.74)

Based on the sputum neutrophil and eosinophil percentage , it was found that neutrophilic subgroup in 33 patients (14.79 %) , eosinophilic subgroup in 106 patients (47.53%) , mixed subgroup in 11 patients (4.93%) and paucigranulocytic subgroup in 73 patients (32.74%).

Effectiveness of inhaled corticosteroids :

ICS Response	Other	Neutrophilic	Total
Improved	150	7	157
No response	40	26	66
Total	190	33	223

It was seen that improvement occurred with the use of inhaled corticosteroid in 7 patients (21.21%) only , whereas no response seen in 26 patients (78.78%) in the neutrophilic subgroup.

On the contrary , in the other subgroups excluding the neutrophilic , improvement was seen in 150 patients (78.94%) and no response seen in only 40 patients (21.05%).

So , inhaled corticosteroids respond poorly in the neutrophilic subgroup.

DISCUSSION

This cross-sectional observational study was conducted in the Department of Respiratory Medicine, AGMC & GBPH, Agartala, Tripura over 18 months. Two hundred and twenty-three adult patients (known and newly diagnosed) with clinically confirmed bronchial asthma were enrolled after applying strict inclusion (age ≥18 years, non-smokers) and exclusion criteria (active smoking, ABPA, bronchiectasis, acute infection). Standardized tools included pre- and post-bronchodilator spirometry, complete blood count with CRP, total serum IgE, induced sputum cytology, chest radiography, and selective HRCT/ECG. All participants received a 6-week follow-up with inhaled corticosteroid review and repeat spirometry/sputum assessment to evaluate treatment response.

The study cohort was predominantly young (60.54% aged 18–40 years), female (65.47%), and had childhood-onset asthma (76.68%, 79.37% before age 6). Severe persistent asthma was noted in 9.87%. Key comorbidities included GERD (59.19%), obesity (37.67%), rhinitis (64.57%), atopy (48.88%), and nasal polyposis (16.59%). Bronchodilator reversibility was positive in 26.01%, while 70.40% demonstrated FEV1 improvement with inhaled corticosteroids, highlighting a steroid-responsive population with significant atopic burden.

Findings align closely with contemporary literature. Crespo-Lessmann et al. (2023) reported eosinophilic phenotype as most prevalent (46.9%) in 96 severe asthmatics, with peripheral blood eosinophils emerging as the strongest predictor of bronchial eosinophilia (AUC-ROC 0.72). Similar predictive utility of blood eosinophils (>220/mm³, AUC 0.79) and FeNO was documented by Schleich et al. and Shi et al. (2021), while Gerday et al. and Jatakanon et al. reinforced the value of non-invasive markers across atopic and non-atopic subgroups. Our high childhood-onset and female predominance mirrors regional Indian patterns and contrasts with Western cohorts dominated by later-onset disease.

These results affirm sputum induction and peripheral blood eosinophilia as practical, cost-effective tools for asthma phenotyping in resource-limited settings, enabling targeted biologic selection and exacerbation prevention. Single-centre design and modest sample size limit generalizability; multi-centric studies incorporating induced-sputum phenotyping in larger Indian cohorts are warranted. Overall, the study underscores the need for phenotype-guided management to optimize outcomes in severe asthma.

Limitations
This single-center, cross-sectional study conducted at a tertiary care hospital in North-East India limits the generalizability of findings to broader populations and settings. The cross-sectional design precludes establishing causality or temporal relationships between sputum inflammatory phenotypes and inhaled corticosteroid response. Specific exclusion criteria (e.g., smoking history, infections), sputum induction variability, short 6-week follow-up, and the debated ≥60% neutrophilic cutoff further restrict applicability and comparability of results.

CONCLUSION

This hospital-based, cross-sectional observational study, conducted over 18 months in the Department of Respiratory Medicine at AGMC & GBPH, Agartala, Tripura, analyzed clinical and demographic factors in 223 asthma patients (new and previously diagnosed) using spirometry, CBC with CRP, total serum IgE, sputum cytology, chest X-rays, and additional ECG/HRCT as required. The sample size ensured a 95% confidence interval with 5% precision, accounting for 10% non-response.

The majority (60.54%) were aged 18–40 years, predominantly female (65.47%). Childhood-onset asthma was common (76.68%), with onset before age 6 in 79.37%. Severe persistent asthma affected 9.87%. Comorbidities included GERD (59.19%), obstructive sleep apnea (31.84%), obesity (37.67%), rhinitis (64.57%), atopy (48.88%), family history of asthma (58.30%), and elevated IgE>160 IU/ml (62.33%). Positive bronchodilator response occurred in 26.01%, while 70.40% showed FEV1 improvement with inhaled corticosteroids, highlighting early-onset, allergic-predominant asthma with significant comorbidities in this population. .

Ethics Approval and Consent to Participate
The study protocol was approved by the Institutional Ethics Committee of Agartala Government Medical College & G.B. Pant Hospital. Written informed consent was obtained from all participants.

Data Availability
The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest
The author declares that there is no conflict of interest regarding the publication of this paper.

Funding Statement
No external funding was received for this study.

Author Contributions
The corresponding author conceptualized the study, collected data, performed analysis, and prepared the manuscript.

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