A retrospective observational study on pheno-endotypes of severe asthma among adults attending asthma clinic in a tertiary care centre in India

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ABSTRACT

Background and Objective: Severe asthma phenotyping based on invasive and non-invasive bio-markers assists in a better understanding of heterogeneity of clinical presentations and thereby using targeted therapies. Therefore, the current study was conducted to evaluate phenotypes based on non-invasive bio-markers of severe asthma patients attending a tertiary care hospital in North India. Methods: This was a retrospective, observational study conducted on the patients who visited the respiratory department of a tertiary care hospital in North India. Patients aged 18 years and above diagnosed with severe asthma were classified into distinct phenotypes, namely, atopic asthma, eosinophilic asthma, and Type 2 low asthma. Patients with their clinical and functional parameters were classified based on the levels of bio-chemical and hematological results [such as total/specific IgE, blood absolute eosinophil count (AEC)], skin prick tests, history of allergy, and the presence of allergic symptoms. Results: Out of total 100 severe asthmatics, the majority of the patients had an eosinophilic asthma (49%) phenotype, followed by atopic (allergic) asthma (36%) and Type 2 low asthma (15%) phenotypes. However, it was found that 29% of these patients had overlap of both atopy and eosinophilia. The atopic phenotype showed allergic symptoms, positive skin prick tests, and elevated IgE levels. The eosinophilic phenotype had high AEC (≥300 cells/µL) and low IgE (<30 IU/ml) levels. The Type 2 low phenotype showed low AEC and IgE levels along with the absence of allergic symptoms. However, among these 100 patients, overlapping traits of both atopy and eosinophilia were labelled as overlap phenotypes. 50% of type 2 low severe asthma cases had eosinophils >150 cells/cmm and were eligible for mepolizumab. Conclusions: Identification of severe asthma pheno-endotypes based on simple non-invasive bio-markers is feasible in Indian settings, and it is of utmost importance for future treatment planning in these patients with available biologicals. Overlap of eosinophilic and atopic endotypes in one-third cases would challenge physicians to choose upfront appropriate biologicals in our country. Type 2 low asthma was least common with only <10% cases of severe asthma being ineligible for any biological.

KEY WORDS: Endotypes, phenotype, severe asthma

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INTRODUCTION

Severe asthma is an augmented form of inflammatory lung disease which requires treatment with a high dose of inhaled corticosteroids along with a second controller and/or systemic corticosteroids to prevent it from further worsening or which remain uncontrolled despite this therapy.[1] According to the World Health Organisation, 235 million individuals suffer from asthma, globally. Asthma is a public health concern for all the countries as it occurs regardless of the development status of the country.[2] Asthma has been increasing since the early 1980s in all age, sex, and racial groups.[3] Over 80% of asthma deaths occur in low- and lower-middle-income countries.[4] The burden of asthma across Asia and India is considerable, but it remains under-diagnosed and under-treated. Among India’s 1.4 billion people, 2.4% has asthma and severe asthma is reported in less than 10% of adults; hence, around 20 million Indians are expected to have severe asthma.[4]

Severe asthma leads to re-occurrence exacerbations, hospitalisations, oral steroid use, and poor quality of life and needs special attention. The concept of asthma phenotyping and endotyping has emerged as a tool for an understanding of heterogeneity behind its clinical presentations and development and use of targeted therapies to overall improve outcomes in severe asthma. Phenotyping/endotyping requires integration of biological and clinical features ranging from morphological, cellular, molecular, functional, and patient-related clinical characteristics with an aim of choosing appropriate therapies.[5] Unfortunately, such identification till date remains imperfect.

The Severe Asthma Research Program (SARP), primarily utilising clinical characteristics, recognised five clusters of asthma amongst adult patients having mild, moderate, and severe asthma.[6] Similarly, the Leicester group performed another adult asthma cohort analysis and identified four clusters on the basis of sputum eosinophil counts.[7] Furthermore, a SARP study carried out on children also identified four clusters of asthmatic patients.[8] Interestingly, these phenotypes have significant overlap with those previously identified clinical phenotypes such as late onset eosinophilic and early onset atopic/allergic asthma.[9]

Although severe asthma can be classified into distinct pheno-endotypes based on the age of onset, atopy, and several other parameters defined by clinical, immunological, and molecular assessments, the stability and natural history of these clinical types remain poorly understood. In addition to this, there is also a significant overlap amongst inflammatory profiles and mechanisms across diverse phenotypes.[10-13] Severe asthma seems to be severe from the beginning, whereas in most cases, an event such as viral infection can change the mild asthma phenotype to a more severe type.[14]

Across the past decade, multiple international cohort studies[6,13,16] have demonstrated pathophysiological significance of various pheno-endotypes of severe asthma. This is important as it allows to offer targeted therapies including biologicals (Anti IgE, Anti IL5, Anti IL4/13) and bronchial thermoplasty as per GINA guidelines[10] for Step 5 treatment before starting maintenance oral steroids. Reliable non-invasive tests are being used to diagnose different endotypes of severe asthma. However, there are a dearth of studies on profiling of severe asthmatics from India based on non-invasive bio-markers. The current study was conducted to evaluate pheno-endotypes based on non-invasive bio-markers in severe asthma patients in North India.

METHODS

This was a retrospective observational study wherein data of 2 years (June 2017 to June 2019) were analysed. Ethical committee approval was taken and the date for the same was 15th June 2017. The study was conducted at the Metro Centre for Respiratory Diseases, Noida, in Uttar Pradesh with prior ethics approval according to the Declaration of Helsinki. All patients were on GINA Step 5 treatment (biologics naive) seen in a severe asthma clinic referred from the respiratory out-patient department (OPD). High-dose ICS use was reported in 5 patients. All patients had used ≥2 bursts oral steroids to treat exacerbations in the previous year, and use of maintenance OCS (oral corticosteroids) was reported in five patients.

Inclusion criteria were severe asthma as mentioned above and age ≥18 years with no history of use of biologics. Hundred consecutive patients were evaluated for severe asthma pheno-endotypes based on the pre-formed proforma (containing details of all co-morbidities, questionnaires, investigations, and treatments). Based on the proforma, all the patients in the clinic underwent a complete evaluation and management of addressable factors. The highest bio-marker values were taken of absolute eosinophil count (AEC) and exhaled breath nitric oxide (FeNO) during 1 year of the follow-up period in the clinic for assessments if performed more than once. Only those patients that fulfilled all the criteria were included in the study. Reports of blood AEC, serum IgE total, FeNO, and skin prick test (SPT) or Immunocap assay for specific IgE were collected for analysis, which are performed routinely in all the cases of severe asthma in our clinic. Further, data with respect to demographics, clinical presentation (history of allergy symptoms and co-morbidities), pulmonary function tests, and so on were also collected using the pre-formed standard proforma.
used in the severe asthma clinic after written informed consent from the patients.

Based on the data, criteria for pheno-endotyping severe asthma were obtained. Patients were classified into Type 2 or Non-type 2 severe asthma based on Type 2 inflammatory bio-markers, and Type 2 were further sub-typed into atopic or eosinophilic as follows:

1. **Type 2 high atopic asthma**: The presence of allergic symptoms and other allergic co-morbidities, positive SPT/specific IgE to aeroallergens, and elevated total serum IgE levels (>30 IU/ml) [16]
2. **Type 2 high eosinophilic asthma**: The presence of nasal polyposis or sinusitis and elevated AEC, that is, more than ≥300/μl in the past 1 year [15]
3. **Type 2 low asthma**: Low total serum IgE levels (<30 IU/ml) and the absence of allergic symptoms and persistent AEC <300/μl for 1 year.

The Type 2 high group with overlapping features of both atopy and eosinophilia was found on analysis in patients with Type 2 high eosinophilic asthmatics where SPT/specific IgE against aeroallergens was positive.

**Statistical analysis**
Data management was performed using Microsoft Excel, 2019. Data analysis was executed using IBM SPSS (Statistical Package for Social Sciences) statistical program version 20. The descriptive analysis included generation of a descriptive table. For continuous variables, measures of central tendency, that is, mean and median along with the measures of dispersion [standard deviation and inter-quartile range (IQR)], were used. Categorical variables were presented using values and proportions. Different groups were compared using Chi square test (for proportions) and ANOVA (for means), and the level of significance was a P value less than 0.05.

**RESULTS**
A total of 100 consecutive patients with severe asthma were studied. The severe asthma patients were categorised into three asthma pheno-endotypes, namely, atopic asthma, eosinophilic asthma, and Type 2 low asthma. However, another group with features of both atopic and eosinophilic overlap was identified based on the levels of bio-chemical and hematological parameters (such as total/specific IgE, AEC, SPTs, and history of atopy). The cut-offs used for low serum IgE were <30 IU/ml and high eosinophils ≥300 IU/ml. **Type 2 high asthma** was seen in 85% of severe asthmatics in our clinic, and the predominant phenotype was eosinophilic (49%), followed by atopic (IgE mediated) (36%), and the least common phenotype was Type 2 low (15%). However, 29% of these Type 2 high patients exhibited features of both atopy and eosinophilia, that is, overlap phenotype [Table 1].

**Phenotypes of severe asthma**
The distribution of various clinical, functional, and bio-marker parameters of different phenotypes of severe asthmatics is presented in Figure 1.

**Atopic (allergic) asthma**
There were 36 severe asthma patients (36%) who were characterised as Type 2 high atopic asthma and had a mean age of 35.4 years with an average body mass index (BMI) of 25.7 kg/m². These patients had allergic symptoms on exposure to aeroallergens and/or associated other allergic co-morbidities, for example, allergic rhinitis or allergic dermatitis. These atopic asthmatics had a median total serum IgE level of 628.5 IU/ml and a median AEC of 200 cu/mm³. All atopic asthmatics showed positive SPT or specific IgE positive to common aeroallergens. Other major co-morbidities in this group were GERD (22) and hypertension (20).

**Eosinophilic asthma**
Nearly half (49) of severe asthma patients (49%) were categorized into Type 2 high eosinophilic asthma and had a mean age of 43.8 years with a mean BMI of 25 kg/m². All asthmatics in this group had eosinophil count ≥300/mm³, and the median eosinophil count was 440 cu/mm³. The median total serum IgE level was 142 IU/ml. Major co-morbidities were hypertension (24) and OSA (22). However, 56.9% had a family history of allergy, and nearly one third of the patients had h/o allergic rhinosinusitis (39).

**Type 2 low asthma**
Fifteen patients (15%) belonged to the Type 2 low asthma phenotype (neither atopic nor eosinophilic) with a mean age of 48 years and a mean BMI of 28.6 kg/m². None had allergic symptoms. The median total serum IgE level was 22.7 IU/ml, and the median blood eosinophil count was 170/mm³(107.50 to 207.50). Other co-morbidities were GERD (6) and hypertension (6).

**Type 2 high overlap asthma (atopic and eosinophilic)**
Interestingly, among 85 Type 2 high severe asthmatics, one third (29) had overlapping features with blood eosinophils ≥300/mm and serum IgE >30 IU/ml and had...
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Hence, this overlap group was eligible for both biologicals, that is, anti IgE and Anti IL-5. This group had a mean age of 36 years and a mean BMI of 25.6 kg/m². Half of them had a family history of allergy within this group when analysed separately and revealed a median AEC of 394/mm³ and a total serum IgE of 216 IU/ml. Allergic rhinosinusitis was reported in 80% (24), and other co-morbidities were GERD (25) and OSA (17).

Clearly, the age of onset of severe asthma was 10 years early in the atopic group as compared to Type 2 low asthma, whereas eosinophilic asthma had the onset of severe asthma in the middle age. Associated allergic rhinitis as well as nasal polyposis was seen in both atopic and eosinophilic asthma with no statistically significant difference between two groups. Pulmonary functions (measured as FEV₁ % predicted) were similar in all phenotypes [Table 1], and similarly, IOS parameters had no statistically significant difference between various groups. Exhaled breath nitric oxide (FeNO) was the highest in the eosinophilic group (mean 44.7 ppb), followed by the atopic group (18.7 ppb), and the lowest in Type 2 low asthma (12.5 ppb). The overlap group had a mean FeNo of 41 ppb, more than 2 times higher as compared to the atopic group.

On reviewing the eligibility for available biologicals, we found that as per label indication of bio-marker threshold, 63 were eligible for omalizumab and 49 were eligible for Anti IL-5 biologicals (mepolizumab and benralizumab) [Figure 2]. However, one of the eligibility criteria for mepolizumab is AEC >150 cells/cm³ at initial visit. In the Type 2 low asthma group, seven patients had AEC >150. Hence, the total number of patients eligible for mepolizumab therapy in our study group was 56. Overall, only 8% severe asthma cases in our clinic were ineligible for any biological for management [Figure 3].

**DISCUSSION**

Severe asthma is a heterogeneous disease which makes it complex to define the various clinical asthma phenotypes/endotypes. An observed overlapping amongst the clinical clusters, inflammatory profiles, and imperative mechanisms makes the task even more challenging. The extent of overlap of these clinical pheno-endotypes is poorly understood (17). Understanding the characteristics of different pheno-endotypes will help to guide treatment to improve outcomes in severe asthma patients. Very few studies have been conducted in Indian patients to determine the prevalence of different severe asthma types.

Thus, to fill the gap, an observational study was conducted to evaluate the pheno-endotypes of severe asthma patients who may benefit from biological treatment.
asthma patients attending the severe asthma clinic in a tertiary care hospital in North India. This study identified three pre-defined pheno-endotypes among 100 consecutive severe asthma patients. Besides atopic (allergic) asthma, eosinophilic asthma, and Type 2 low asthma (non-allergic, non-eosinophilic), we found significant overlap in some patients with high eosinophils who also exhibited some features of atopy, that is, the overlap phenotype. This was found in one third of Type 2 high severe asthma in our series. Similar multiple cross-sectional and cohort studies have been performed in different countries such as US (10), UK (11), Korea (18), and so on. GINA 2020 also mentions about phenotypic differences in allergic versus non-allergic, late onset asthma with fixed airway obstruction, and asthma with obesity (19). Similar results from Brazil (20), Germany (21), and Netherlands (22) for the identification of severe asthma pheno-endotypes have been reported in their respective populations.

A multi-center network SARP in US focused on the biological and clinical traits for the categorisation of the phenotypes (23) in children on the basis of duration of asthma, lung functions, and the use of asthma control medications. The most significant factors for differentiating phenotypes were the age of the onset of asthma and FEV₁ % predicted in adults. The main phenotypes summarised recently in a review by Kaur et al. (24) include (1) early-onset allergic asthma, (2) early-onset allergic moderate-to-severe remodeled asthma, (3) late-onset non-allergic eosinophilic asthma, and (4) late-onset non-allergic non-eosinophilic asthma. However, terminologies used are frequently overlapping and individual characteristics may be shared among various phenotypes and hence require large studies to refine phenotypes.

Advances in immunobiology have led to endotyping of asthma based on drivers of airway inflammation in asthma, that is, IgE or eosinophils and other Type 2 cytokines IL 4, IL 5, and IL 13 with an aim to personalise therapy in severe asthma using monoclonal antibodies to target these mediators. It would be of even greater importance in India as biologicals are very expansive and one needs to choose the most suitable candidate for every patient. The most robust bio-marker is eosinophil in blood or respiratory tract secretions as its predictor of Type 2 inflammation and other tests, for example, FeNO and SPT or specific IgE for aeroallergens, help in refining endotyping to IgE atopic versus eosinophilic inflammatory endotypes to choose wisely anti-IgE versus anti eosinophilic (anti-IL-5 or IL4/13 drugs) biologicals. Total serum IgE is not a bio-marker but is required to calculate the dose of anti-IgE therapy. These monoclonal antibodies targeting IgE, IL 5, IL 4, and IL13 have shown significant reduction in asthma exacerbations and decrease or eliminate the need for oral corticosteroids but require evaluation of severe asthma pheno-endotypes to choose the ‘best fit’ biological.

In our study, we used clinical, functional, and non-invasive investigative bio-markers, for example, blood AEC, FeNO, IgE total, SPT, and/or specific IgE against aeroallergens, to categorise pheno-endotypes of severe asthmatics. Blood eosinophils were significantly higher (>300/mm³) in eosinophilic phenotypes. In our atopic severe asthma group, the serum IgE levels were substantially elevated (>400 IU/ml) with atopic symptoms and positive SPT or specific IgE against aeroallergens, whereas the eosinophilic group had significantly elevated blood eosinophils (median 440). Studies conducted by Khusial et al. (25) and Zedan et al. (26) showed similar results wherein the patients of eosinophilic and allergic phenotypes indicated the elevated levels of AEC and IgE, respectively. The age of the patients having allergic asthma was the lowest (35.41 ± 17.63) amongst all the other identified phenotypes (40–50 years of age) in our patients. A recent study (27) was performed to study the age-specific incidence of allergic and non-allergic asthma. The results of the study indicated that allergic asthma has higher incidence in childhood, whereas non-allergic asthma peaks in late adulthood (after approximately 40 years of age). Our study also showed similar findings with the atopic asthmatic group having a lower age of onset than the eosinophilic group. Another finding of our study shows that the severe asthmatics had higher BMI. Multiple studies (28, 29) on identification of severe asthma phenotypes reported a similar presence of obesity in severe asthmatics. Sutherland et al. (30) while conducting cluster analysis of obesity and asthma phenotypes, have also found BMI to be a significant determinant of asthma in adults.

Our study showed that the least common endotype was Type 2 asthma with low blood eosinophils and low serum IgE. This type 2 low asthma has been reported relatively in a small number of patients by others too. (31) These patients were older with the mean age being higher as compared to other endotypes. A recent review conducted by Robinson et al. (2017) (32) summarised the clinical features of Type 2 low asthma with the absence of airway eosinophilia and allergic sensitization, with the age of onset being toward...
late life. Our findings confirm equivalence and indicate
Type 2 low severe asthma being uncommon in India. In
our study, Type 2 high asthma accounted for 85% of severe
asthma in India, whereas the eosinophilic group was the
most common seen in 49%, followed by atopic severe
asthma in 36%.

However, overlap of allergic and eosinophilic endotypes
was seen in nearly one third of the total severe asthmas.
This patient group had an elevated blood eosinophil
count (≥300) with the presence of atopy defined by
symptoms and sensitisation to aeroallergens. Tran et al.\[30\]
studied the overlap of atopic and eosinophilic Type 2 high
asthma using National Health and Nutrition Examination
Survey (NHANES) data and found that substantial overlap
exists among Type 2 high severe asthma patients. These
patients show elevated levels of both eosinophils and
high allergen specific and total serum IgE levels. Our
study showed similar results in our population too. This
overlap group is eligible for both anti-IgE and anti-IL-5
monoclonal antibodies [Figure 1], and hence, we need to
incorporate clinical and functional parameters to improve
endotyping prior to choosing biologics in severe asthma.
A German study[21] also showed results very similar to those
of our study [Table 2]. In our study, the overlap group was
split from the eosinophilic group with patients having
both blood eosinophilia and atopy (under Type 2 high
asthma), and this group becomes the second most common
pheno-endotype of severe asthma in India.

The overlapping group seen in one third of severe asthmas is very important as these patients are eligible for
both anti-IgE and Anti-IL-5 biologicals and need judicious
treatment decisions to choose the appropriate biological
in India. In our study, we tried to evaluate this group further and found that two patients had IgE >1500 IU/ml
and hence were not eligible for omalizumab, and hence,
27 patients were eligible for omalizumab, but all 29 had
blood eosinophils >300 cells/cmm, hence eligible for
anti-IL-5 (mepolizumab as well as benralizumab) in all
29 cases. The Type 2 low group had 15 patients with
AEC <300 cells/cmm, but seven patients had AEC between
150 and 300 cells/cmm and were eligible for mepolizumab
as it requires AEC >150 cells/cmm at initial visit. Hence,
only eight severe asthma patients remained ineligible
for any available biologicals. These eight patients were
given the option of bronchial thermooplasty. Out of these,
five underwent the procedure. Hence, there is significant
overlap in eligibility of available biologicals in Indian
patients with severe asthma, and clinicians need to
incorporate predictors of response of each biological to
choose appropriately [Figure 3].

Studies of asthmatic patients have shown that persistence
of eosinophils predisposes these patients to increase the
risk of severe asthma exacerbations.\[30\] Therefore, it is best
that we target these particular phenotypes with available
modalities. The benefits of use of these biologicals are
better asthma control, decreased exacerbation frequency,
hospitalisation, reduction in steroid use, improvement
in lung functions, and overall quality of life, and this
has already been shown by various meta-analyses.\[32,33\]
Adverse effects associated with the use of these agents are
minor, such as headache, myalgia, and local site reactions.
Rarely (<1%) cases may experience hyper-sensitivity
reactions such as anaphylaxis. The most important
drawback of use of these agents is their cost as far as
developing countries are concerned.

Our study brings some clarity on these largely unrecognized
categories of severe asthma. There is a dearth of studies
in India regarding severe asthma pheno-endotypes and
their clinical profile and etiological distribution. Two studies conducted in India\[34,35\] based on sputum cellularity
analysis are not feasible, and clinicians would need inputs
using simple diagnostic tools in making therapeutic
decisions in management of severe asthma. Our study
would be a stepping stone for further larger multi-center
studies to elucidate severe asthma pheno-endotypic
profiles in severe Indian asthmatics based on these
simple clinical, functional, and bio-marker assessments.
Recent publication by the same authors has discussed a
stratified approach of using bio-markers for phenotyping
management of asthma.\[36\]

### Table 2: Summary of the results of comparative studies of severe asthma phenotyping

| Studies | No. of patients | No. of identified phenotypes | Study characteristics of the patients |
|---------|----------------|------------------------------|--------------------------------------|
|         |                |                              | Age (mean at diagnosis) | BMI (mean) | IgE levels (median) | Eosinophil count (median) | Other specific characteristics |
| Present Study (India)* | 100 | Atopic (allergic) (36%) | 35.41 | 25.69 | 628.5 | 200 | Allergy symptoms present and positive allergy tests and/or specific IgE against aeroallergens |
|         |                | Eosinophilic (20%) | 43.87 | 24.98 | 142 | 440 | Elevated eosinophils |
|         |                | Atopic and eosinophilic overlap (29%) | 36 | 25.64 | 216 | 394 | Atopy and elevated eosinophils |
|         |                | Allergic (121) (39%) | 21.9 | 28.4 | 222 | 128 | Allergic symptoms present, positive SPT, and/or specific IgE and low blood eosinophils |
| Holstege et al.\[1\] | 308 | Eosinophilic 50 (16%) | 38.7 | 25.9 | 156 | 586 | No signs of allergy and elevated eosinophils |
| 2015 (Germany) |                | Allergic and eosinophilic overlap 75 (24%) | 28.6 | 26.9 | 310 | 512 | Signs of allergy and elevated eosinophils |

Overlap group added to the type 2 high severe asthma group with re-arrangement from the eosinophilic group in our patients
However, there are certain limitations in our study, namely, 1. It is a single-centre study based on the tertiary care teaching facility where the patient’s inflow is from North India and cannot be representative of the whole country. 2. Patient selection bias as only patients who can afford expenses seek care in private facilities. 3. It is a retrospective study and hence lacks uniformity in labelling severe asthma prior to being seen at our centre. Also, the lack of follow-up and response to biologicals was not included in this study, and it would be interesting to evaluate responses of biologicals particularly in the overlap group in our country. However, the study was taken with an aim to stratify severe asthma into pheno-endotypes by using easily available diagnostic tools to identify right candidates for personalised therapies; further research can investigate these aspects. This study clearly highlights the need for urgent research in this area.

To conclude, severe asthma pheno-endotyping to enhance suitable treatment with biologicals is achievable using presently available bio-markers. Our study indicates the widely used clinical and available laboratory tests, for example, age of onset, H/O atopy and allergic co-morbidities, blood eosinophils, serum IgE total, SPT, or specific IgE to aeroallergens with FeNO, to evaluate drivers of inflammation in severe asthmatics are feasible and relevant in the Indian population. However, the overlap pheno-endotype of type 2 high cases is common and seen in 29% cases. Surprisingly, as per eligibility of the overlap group in our country. However, the study was taken with an aim to stratify severe asthma into pheno-endotypes by using easily available diagnostic tools to identify right candidates for personalised therapies; further research can investigate these aspects. This study clearly highlights the need for urgent research in this area.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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