

Investigation of the tendency to wheeze in pollen sensitive patients

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Summary

We have undertaken a double blind placebo controlled study of the effect of nasal beclomethasone on the tendency to wheeze in 20 unselected hay fever sufferers, half with a history of previous seasonal wheezing. We found no difference between either bronchial hyperresponsiveness, as measured by methacholine challenge, home-monitored PEF, nor recorded wheeze nor cough between treated and placebo groups although the numbers were small. All were allowed the antihistamine cetirizine hydrochloride 10 mg daily. Eighteen out of the 19 patients had either bronchial hyperresponsiveness (PD₂₀ methacholine < 8 µmol or a > 2 doubling dose change in their PD₂₀ during the pollen season). We have shown a significant positive correlation between a hay fever score (HFS) (created by taking the sum of the home scored; nasal discharge, nasal blockage, eye irritation, sneeze and antihistamine use) and peak seasonal specific IgE to mixed grass pollen (Spearman correlation coefficient 0.5 $P < 0.02$). There was also a positive correlation between the rise in specific IgE from pre to peak season and the HFS, correlation coefficient 0.6 $P = 0.03$).

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Introduction

It has been known since Victorian times that exposure to pollen may produce symptoms in susceptible people. Hay fever is common, probably having a cumulative prevalence of 10% [1] and causes much morbidity. Although it is known to be related to atopy, which is genetically determined [2], it is not known why some patients have more symptoms than others, why they vary with time or why some patients have predominantly nasal symptoms and others respiratory symptoms and some a combination.

It was recently suggested [3] that adequate treatment of nasal symptoms during the ragweed season in Canada reduced the tendency to develop respiratory symptoms (reported cough, wheeze and shortness of breath) and the workers concerned postulated that this was due to restoration of normal nasal function with filtration of, and reduction in, allergen load to the lung. Others have also noted the improvement in asthma related to treatment of nasal and sinus disease which may involve the

same mechanism [4]. We have conducted a double-blind placebo controlled study of inhaled nasal steroids in a group of hay fever patients during the grass pollen season to see whether we could demonstrate any effect on the tendency to wheeze as measured by home peak flow measurements, numerical scoring of wheeze at home and bronchial reactivity to methacholine measured at regular intervals during the pollen season.

Using the opportunity that this investigation allowed, we have also tried to throw light on the causes of the different manifestations of hay fever between individuals. There has been some debate [5,6,7] about the relationship between symptoms and levels of specific IgE with some indicating a link and others being unable to verify this. We therefore also measured specific IgE levels to grass pollen and have correlated levels with the intensity of symptoms as measured by created scores.

Method

Patients

Patients with a history of hay fever were recruited from the Churchill Hospital allergy and chest clinics and local

Table 1. Showing some patient characteristics and specific IgE levels before, during and after the pollen season

History of wheeze	Smoking status	Skin prick test (alt, clad, asp, cat)	Specific IgE to grass (p.r.u./ml)				IgE to tree and rape	
			Mar	May	June	Jan	Tree	Rape
<i>Beclomethasone</i>								
PW	NS	All negative	1.5	1.4	2.4	1.7	0	0
SW	NS	All negative	11.8	10.7	75.0	15.3	0	0
NW	NS	All negative	4.0	3.2	6.8	—	0	0
PW	NS	All negative	0	0	0	0	0	0
SW	ES	All negative	23.0	23.0	35.0	21.0	1.5	3
SW	ES	All negative	7.6	8.0	21.4	10.0	0	0
NW	NS	Cat 3 mm, asp 3 mm	4.6	5.6	15.4	7.2	11.5	0
SW	CS	All negative		2.6	3.2	4.0	0	0
NW	NS	All negative		1.1	1.2	1.1	0	0
<i>Placebo</i>								
SW	NS	All negative	1.7	1.5	1.6	2.1	0	0
NW	ES	All negative	0.5	0.3	0.7	—	0	0
NW	NS	All negative	17.0	17.7	43.0	18.0	0.4	0.5
NW	NS	Cat 3 mm	54.0	60.0	93.0	66	0	0
PW	CS	Cat 4 mm	38.0	45.0	38.0	54.0	3.4	4.5
SW	NS	Alt 6 mm, cat 5 mm	28.0	36.0	56.0	50.0	1.7	1.7
NW	NS	Cat 4 mm	10.4	29.0	34.0	—	0.4	0
SW	NS	All negative	22.0	19.0	35.0	21.0	0	0
NW	NS	All negative	—	6.6	10.6	6.5	0	0
SW	NS	Cat 4 mm	—	12.4	14.8	11.2	0	0
NW	NS	All negative	—	6.7	21.0	12.0	0.5	0

NS, non-smoker. ES, ex-smoker. CS, current smoker. PW, perennial wheeze. SW, previous seasonal wheeze. NW, never wheezes. Alt, alternaria. Clad, cladosporium. Asp, aspergillus.

GP practices. They were included if they had a positive skin prick test (SPT) with a $>$ or $=$ 3 mm weal to mixed grass pollen and no reaction to house dust mite. Skin sensitivities to other common allergens and other characteristics of the patients are shown in Table 1.

Design of study

Patients were first seen between March and May 1989, the last patient entered in the middle of May (Julian day 141), and answered a detailed questionnaire about their respiratory and allergic history. Circulating specific IgE levels to mixed grass pollen, baseline lung function tests and bronchial reactivity to methacholine were measured. Randomization was double blind and stratified by whether or not they had a history of asthma or wheeze. Patients received either twice daily inhaled nasal beclomethasone or matching placebo from the beginning of May (or from randomization) until the end of July.

Antihistamine tablets in the form of cetirizine hydrochloride (Zirtek) and a salbutamol (Ventolin) inhaler were supplied to all patients for use as required. The recommended dose of Zirtek was one tablet (10 mg) daily. Patients were asked to take no other antihistamine, inhaled respiratory steroids or sodium cromoglycate. Topical eye preparations were permitted though only one patient took any.

From the beginning of May or from randomization (five patients) patients were asked to take their nasal spray (beclomethasone aqueous solution, 50 μ g per squirt or matching placebo) two squirts into each nostril twice daily. They also completed diary cards recording in the morning three peak expiratory flow rate (PEFR) measurements before any medication and in the evening three PEFR measurements, three peak nasal inspiratory flow (PNIFR) measurements and a 0–3 score for the following symptoms for that particular day; nasal blockage, nasal discharge, sneezing, eye irritation, cough and

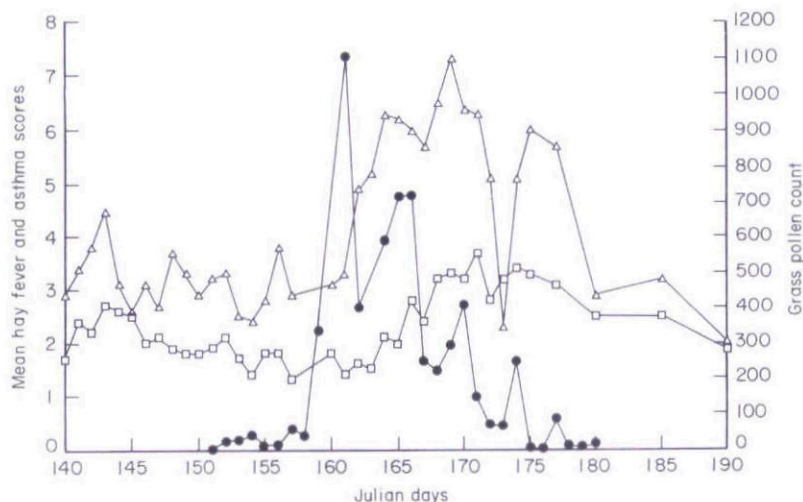


Fig. 1. Graph showing mean hay fever and asthma scores (see text for explanation) for the whole group in relation to the grass pollen count. Δ, hay fever score. □, asthma score. ●, grass pollen count.

wheeze where: 0=no symptoms; 1=few symptoms but not troublesome; 2=intermittent troublesome symptoms; 3=persistent symptoms interfering with activities. They also recorded how many Zirtek or puffs of Ventolin were taken. PEFs at home were measured using mini Wright's peak flow meters and PNIFRs using a Youlten Nasal Inspiratory Peak Flow meter; the latter are similar to expiratory flow meters but have a mask which is applied firmly over the nose and are adapted to measure inspiratory flow rates (i.e. the sniff-rate). Patients were taught how to use them at the beginning of the study until reproducible measurements were obtained. Patients were then seen every 2 weeks until the end of July, to check on compliance, take blood for specific IgE and measure their bronchial reactivity. They were asked to take no salbutamol in the morning of the days when bronchial reactivity was being measured.

Bronchial reactivity measurements

Bronchial reactivity was measured according to the method of Yan *et al.* [8] adapted to use methacholine. This was diluted in buffered saline and inhaled in increasing doses from De Vilbiss hand held nebulizers according to one of two schedules. For asthmatic subjects a reduced starting dose of 0.04 μmol was used, whilst in others this dose was 0.15 μmol increasing on each schedule to a maximum cumulative dose of 64 μmol . Forced expiratory volume in one second was measured using a dry bellows spirometer (Vitalograph, Buckingham, England). The dose required to reduce the FEV_1 by 20% from the post-saline FEV_1 (PD20) was calculated by logarithmic interpolation between the last two doses. Prior repeatability studies showed that >90% results lay within two doubling doses for all three people making measurements.

Pollen counts

Grass pollen counts in grains per cubic metre were recorded during June, 6 miles north of Oxford, using a Hirsch trap. For simplicity and ease of comparison dates are all expressed as Julian days (i.e. numbered from January 1). The grass pollen count started to rise at the beginning of June (Julian day 152) and peaked on June 11 (Julian day 161).

Specific IgE assay

A clotted blood sample was taken for specific IgE estimation, the serum was separated and stored at -20°C until required for the assay. A solid phase enzyme immunoassay (Phadezym RAST, Pharmacia Ltd) was used to measure the specific IgE to grass pollen mix ($g \times 3$), tree pollen mix ($t \times 8$) and rape pollen. Serum with high levels of specific IgE to grass pollen mix were diluted in IgE free horse serum and reassayed. Results are expressed in p.r.u./ml.

Statistical analysis

Serially collected data was analysed by calculating and comparing areas under the curve and using non-parametric statistical tests on this data. For all analyses the maximum of the three recorded PEF and PNIFR were used. Peak flow measurements were assumed to be normally distributed but for all other data this assumption was not made and non-parametric tests used. All the analyses were done using SAS (SAS Institute Inc., Box 800, Cary, North Carolina, U.S.A.) on a mainframe VAX computer.

Results

Patients

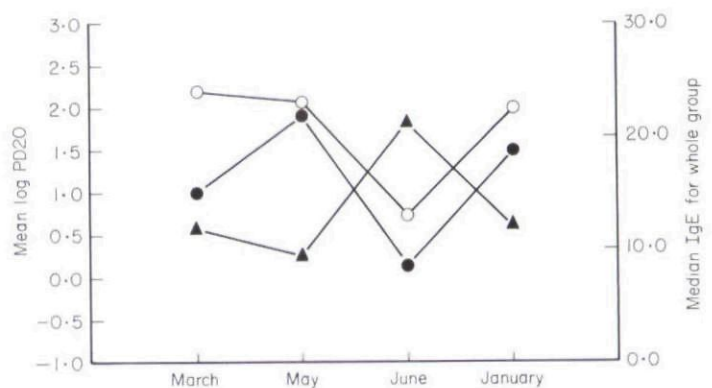
Twenty-three patients were recruited of whom 20 patients were randomized into and completed the study. The

Table 2. Showing median (5–95% range) individual hay fever symptom scores and mean peak nasal inspiratory flow rates (PNIFR) over the 15 days at the height of the pollen season (Julian days 160–175)

	HFS (baseline period)	HFS (peak season)	Nasal blockage	Nasal discharge	Sneeze	Eye irritation	PNIFR (peak nasal inspiratory flow rate)	Antihistamine use
Beclomethasone ($n=8$)	1.5 (0–4)	2.5 (0–4)	0.5 (0–2)	0.5 (0–2)	0.75 (0–2)	1 (0–2)	154 (s.e. = 27)	0.5 (0–1)
Placebo ($n=11$)	3 (0–13)	7 (2–13)	2 (0–3)	1 (0–3)	1 (0–3)	1 (1–3)	126 (s.e. = 19)	0.75 (0–1)
<i>P</i> value (for the difference)	0.1	0.09	0.13	0.04	0.04	0.04	0.4	0.24

Using Wilcoxon score rank sums test.

Fig. 2. Graph showing Log PD₂₀ values for beclomethasone and placebo groups and median specific IgE levels for the whole group to grass pollen for measurements taken before pollen season in March and April 1989, in May and at peak season in June 1989, then in January 1990. ○, placebo group. ●, beclomethasone group. ▲, median specific IgE to grass pollen.



remaining three attended the initial visit but, because of a slipped disc in one case and difficulties attending regularly in the other two, declined to enter the study. One patient who had a 4 mm weal on SPT and an equivocal history was subsequently found to have no specific IgE to grass pollen. Analyses were performed both including and excluding her data and results were not substantially different. In the report, data from this patient is included. The patients had had hay fever for a mean of 19 seasons of variable severity, ranging from symptoms on 60–100 days out of a season of 100 days. Twelve patients had undergone previous desensitization to grass pollen, from 2 to 20 years previously. Other skin sensitivities and specific IgE to mixed tree pollens and to rape seed pollen are shown in Table 1. Patients with a history of previous wheezing were approximately equally divided between the treatment groups (see Table 1). Their mean age was 35 years (range 20–49), two were current and two ex-smokers. All except one patient had a baseline FEV₁ > 85% predicted. The exception had an FEV₁ 76% predicted with no history of smoking or wheezing. The mean baseline predicted FEV₁ was similar in the two groups, 95% and 97% in the beclomethasone and placebo groups respectively.

Treatment

Of the 20 patients completing the study, nine received active nasal beclomethasone and eleven matching placebo. One patient receiving beclomethasone had an episode of viral meningitis at the height of the pollen season and failed to collect data during this time. Although baseline and IgE data are included, her diary card data was insufficient for analysis.

Hay fever symptoms

As a group as expected there was an increase in recorded symptoms of nasal discharge, nasal blockage, eye irritation and sneezing during the grass pollen season. A hay fever score was created by taking the sum of the scores for nasal discharge, nasal blockage, sneeze, eye irritation and antihistamine use for each individual (Fig. 1). For the purposes of comparison two periods of 15 days were selected; a baseline period (J days 140–155) which were the first 15 days for which data was available for all patients and high season (Julian days 160–175) when the pollen count was at its highest (see Fig. 1). During the baseline period, i.e. the middle 2 weeks of May there

would be no grass pollen around but other tree and flower pollens may have been present in the air.

For the high season the median hay fever score (HFS) for the whole group was 5.0 (5–95% range 2–7.5) this compared with a score of 2.5 (5–95% range 1.5–3.5) for the baseline period. Table 2 shows the median of the median individual score by treatment group for the different measures of hay fever symptoms during the height of the pollen season and the results of a significance test for the difference. As expected in high season patients taking nasal beclomethasone recorded less hay fever symptoms (see Table 2) and took less antihistamine. This was also true for the baseline period although the scores were all higher during the pollen season, there was no significant difference between the rise in scores from baseline to high season in the two groups. This suggests there was some allergen around during the baseline period to which the patients were already reacting possibly tree pollen or rape pollen. Specific IgE levels to a mixed tree pollen and rape seed pollen are shown in Table 1, the groups were not well balanced in this respect (2/9 in the treatment group compared with 5/11 in the placebo group having specific IgE to mixed tree pollen). There was no significant difference between treatment groups in their PNIFR measurements as analysed by area under the curve comparisons (see Table 2).

From a visual inspection of graphs of individual maximum PNIFR throughout the season only seven patients (five on placebo and two on beclomethasone) showed an obvious fall at the height of the pollen season. However, when looking at the correlation coefficients (Kendall tau b) between both maximum PNIFR and % fall in PNIFR (from the maximum recorded for that individual) and perceived nasal blockage, 14 showed highly significant figures.

Asthma symptoms and measurements

An asthma score created by taking the sum of scores for each individual for wheeze and cough and number of puffs of Ventolin taken is plotted for the whole group in

Figure 1. We did not demonstrate any significant differences in home recorded PEFR, score for wheeze and cough nor change in bronchial reactivity between the nasal beclomethasone and the placebo groups either in high season nor throughout the whole season (see Table 3). However there was a trend towards less reporting of chest symptoms and toward higher PEFR measurements in the beclomethasone group and there was a suggestion that allocated treatment modified evening PEFR measurements (difference in evening PEFR between treatment groups 19 l/min 95%CI 1–18 $P=0.05$) when variability due to pollen count was accounted for during a multivariate analysis. Those taking beclomethasone started with greater bronchial reactivity, despite similar baseline FEV₁, than those on placebo, and they remained more reactive throughout the season although the differences were not significant. In both treatment groups there was a significant increase in bronchial reactivity during the pollen season as shown graphically in Fig. 2. Mean areas under the curve for log PD₂₀ covering the Julian days 140 to 186 for beclomethasone patients compared with placebo were 18 (s.d. 76) and 62 (s.d. 87) respectively ($P>0.2$).

All except one of the subjects with a history of seasonal wheezing showed a greater than two doubling dose decrease in their PD₂₀ to methacholine between baseline and peak pollen season and all had minimum PD₂₀ values below 6 μ mol methacholine, the accepted range for asthmatics being below 8 μ mol. The one patient whose PD₂₀ did not significantly change had a persistently low value and was one of the smokers. Of the nine subjects who reported no previous seasonal wheezing only one had a consistently unobtainable PD₂₀ >64 μ mol and his PEFR variability for all measurements throughout the season was $<10\%$. Two of the remaining eight altered their PD₂₀ from being unobtainable to 16 and 13 μ mol respectively. For one this occurred at the peak of the pollen season (J day 167) in the absence of symptoms and the other who was the most tree sensitive of the group (patient 7 see Table 1) had PD₂₀ levels of 16 to 48 from April through till the end of June when they became

Table 3. Median (5–95% range) individual symptom scores for cough, wheeze and asthma score and mean morning and evening peak flow rate and log PD₂₀ for Julian days 160–175

	<i>Asthma score</i>	<i>Cough</i>	<i>Wheeze</i>	<i>Log PD₂₀</i>	<i>Morning PEFR</i>	<i>Evening PEFR</i>	<i>Ventolin use</i>
Beclomethasone ($n=8$)	3 (0–7)	1 (0–2)	0.5 (0–2)	62.7	452 (s.e. = 47)	461 (s.e. = 44)	1 (0–2)
Placebo ($n=11$)	7 (2–13)	0 (0–3)	1 (0–3)	64.1	433 (s.e. = 23)	430 (s.e. = 23)	0 (0–8)
<i>P</i> value (for difference)	0.8	0.5	0.9	0.8	0.7	0.5	0.6

Using Wilcoxon score rank sums test.

unobtainable at $>64 \mu\text{mol}$. The remaining six subjects with no history of wheezing all reduced their PD20 by more than two doubling doses, all having minimum levels at the peak season of less than $3 \mu\text{mol}$, and all showed PEFR variability of greater than 10%. Only one recorded no wheeze in the diary card.

Specific IgE

The results of the specific IgE levels to grass pollen are shown in Table 1. There were no differences between the specific IgE to grass pollen results between the beclomethasone and placebo patients either before or on nasal steroid treatment. Taking the group as a whole there was no difference between the March/April sample and the level in May but an approximate doubling of the level by the end of June. For the difference between March and May IgE, $P=0.2$ (95% CI for the difference -19 to 3). For the increase between March and the end of June (Julian days 171–184) ($P=0.003$ 95% CI for the difference in IgE 0.1 – 63 by Wilcoxon's signed rank test). By January the following year the levels had fallen back to similar values as obtained in March and May ($P=0.06$, 95% CI for the difference between January and March samples -22 to 2). There was no correlation between the per cent rise in specific IgE and pre-seasonal or peak season levels but there was a strong correlation between the absolute increase in IgE and both the pre-seasonal and peak seasonal values. Using a Spearman correlation gives a coefficient of 0.8 ($P=0.0007$) between the rise in IgE and the peak June level and a coefficient of 0.5 ($P=0.05$) for both the March and May IgE values and the rise. There was no effect of age on baseline specific IgE levels but there was a slight negative correlation between the maximum IgE level in June and age ($r=-0.15$, $P=0.04$ using Spearman rank correlation). Approximately half the subjects had undergone previous desensitization to grass pollen although none had in the previous 2 years. The peak IgE levels were higher in those desensitized in the past, medians 34.5 compared with 15.4 respectively although this did not reach statistical significance ($P=0.09$ by Wilcoxon's rank sums scores).

There was a positive correlation between the hay fever score (HFS) and IgE level on each set of values which was statistically significant for those done in June and January. Spearman correlation coefficients for March/April, May, June and January IgE levels with HFS were 0.4 $P=0.17$, 0.4 $P=0.06$, 0.5 $P=0.02$ and 0.6 $P=0.03$ respectively. There was also a correlation between the HFS and the rise in IgE from pre to peak season (Spearman correlation coefficient 0.6 $P=0.03$). Since insufficient numbers of subjects took Ventolin or recorded wheeze we have not correlated asthma score

with IgE. Taking the per cent variability of PEFR over the whole study as a measure of asthma severity there was no significant correlation with any measure of specific IgE.

Discussion

In our study we have shown no effect of inhaled nasal steroids on the tendency to develop seasonal asthma, neither looking at measured PEFR, nor perceived wheeze nor at changes in bronchial reactivity to methacholine. This is in contrast to the study reported by Reed *et al.* who found a reduction in asthma symptoms in patients on nasal flunisolide and beclomethasone compared with placebo and sodium cromoglycate during the ragweed pollen season. They did not measure BHR or lung function. This lack of an effect may be either because there is no effect or because we have failed to demonstrate it having only a small sample size. Our results did show a trend toward a reduction in both reported and measured pulmonary symptoms which might have become significant with greater numbers but the differences were very small. The lack of a statistically significant effect of nasal steroid on nasal blockage is also likely to be due to small numbers in the study and the fact that the inter-individual variation is of similar magnitude to the between group variability. It has been shown by others [9] that the combination of the antihistamine astemizole and nasal beclomethasone is significantly better at relieving sneezing, nasal blockage and discharge than the antihistamine alone. We used a relatively new antihistamine, cetirizine hydrochloride, which is a highly selected H1 blocker without sedative properties and which has been shown to be effective in hay fever at a dose of 10 mg daily [11,12]. It was well tolerated by all subjects and no side-effects were documented.

Like others [13,14] we have shown an increase in bronchial reactivity during the grass pollen season in this group of unselected hay fever sufferers. It occurred in more individuals than admit to symptoms. In answer to the question 'Do you have seasonal asthma?' six out of 19 (32%) replied affirmatively, although 10 of 19 (52%) admitted to previous seasonal wheezing. However, we have shown that 18 out of the 19 (95%) had either bronchial hyperreactivity or a >2 doubling dose change in their PD20 to methacholine in relation to the pollen season. This suggests at least some change in airway reactivity in most of our patients with hay fever perhaps representing a continuum of airway inflammation due to pollen exposure. This is supported by small changes (10–15%) in PEFR which coincide with days of high pollen counts in subjects who otherwise have little variability of their peak flows.

Four patients who had never reported asthma or seasonal wheeze before recorded some wheeze in their diary cards. This may reflect a heightened awareness because of the study, unrecognized previous asthma or simply the development of asthma in susceptible subjects [15] during a bad hay fever season. All four had PD20 below 2 μ mol but only two showed >15% variability in their home PEFR and all had significant correlations between their fall in PEFR and wheeze score suggesting that they were not poor perceivers of their asthma.

Unlike others [7] we have been able to show a positive correlation between peak seasonal specific IgE to grass pollen and hay fever symptoms though not with a peak flow variability measure of asthma. As others have recently described [6] we have shown a relationship between the absolute increase in circulating IgE and both the baseline and the peak IgE levels. We have also been able to demonstrate that the specific IgE levels fall back by the beginning of the following year to levels characteristic for that individual before the previous season.

Although only seven patients looked from their individual charts that PNIFR was a useful indicator of hay fever symptoms we found surprisingly good correlations (not shown) in 14 of our 19 subjects between their perceived nasal blockage and PNIFR. These results compare favourably with figures relating perceived wheeze and fall in PEFR where it is well recognized that up to 30% are poor perceivers. It may be that nasal blockage as measured by PNIFR in allergic rhinitis is a much more variable phenomenon, as suggested by the lack of a significant fall for the whole group during the season, and is therefore a less useful measure than PEFR in asthma. However it does appear from our data that PNIFR is a reasonably good indicator of nasal blockage as perceived by the subject.

Acknowledgment

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