

Fractional exhaled nitric oxide of at least 100 ppb and implications for future asthma research



Nitric oxide (NO) plays key roles in virtually all aspects of lung biology, both physiologic and pathophysiologic.¹ Although under normal physiologic conditions NO protects against airway hyperresponsiveness, under pathophysiologic conditions NO seems to act as a proinflammatory mediator predisposing to the development of airway hyperresponsiveness.² Patients with asthma have high levels of NO in their exhaled breath, and a close relation exists between fractional exhaled NO (FeNO) level and eosinophilic airway inflammation in asthma.^{3,4} There also is an association between elevated FeNO levels and risk of wheezing and asthma attacks.⁵ Furthermore, FeNO levels have been found to decrease in response to treatment with corticosteroids.⁵ Studies have shown that FeNO predicts the likelihood of steroid responsiveness more consistently than spirometry, bronchodilator response, peak flow variation, or airway hyperresponsiveness to methacholine.⁶

American Thoracic Society clinical practice guidelines strongly recommend the use of FeNO in the diagnosis of eosinophilic airway inflammation and in determining the likelihood of steroid responsiveness in individuals with respiratory symptoms suspected to be due to airway inflammation. Clinically significant “cut points” are recommended in the interpretation of FeNO levels.⁶

- Low FeNO: <25 ppb in adults, <20 ppb in children
- High FeNO: >50 ppb in adults, >35 ppb in children
- FeNO values of 25 to 50 ppb (adults) or 20 to 35 ppb (children) should be interpreted cautiously, with reference to the clinical context⁶

It is relatively uncommon for a patient to present with an FeNO of greater than 100 ppb. In a recent observational study of 825 children (4–18 years old) with asthma, only 40 children (4.5%) had an FeNO of greater than 100 ppb.⁷ To begin to characterize these patients who present with a very high FeNO (≥ 100), we conducted a small-scale observational study over a 6-month period (January 2013 to June 2013), which was strategically chosen to capture patients in and out of allergy season. Any new patient who presented to our practice during this period with respiratory complaints, and in whom an FeNO evaluation was performed, was included in this chart-review study. In total, we collected data on 40 patients.

All 40 patients underwent a standard new-patient evaluation including history, physical examination, spirometry, and prick skin test. The diagnosis of asthma was based on clinical history of recurrent cough, wheeze, and/or chest tightness. Not all patients had a history of short-acting β -agonist use, and those without had evidence of airway obstruction and bronchodilator response in the office. All others had a history of response to short-acting β -agonist bronchodilator and/or inhaled corticosteroid (ICS) with or without a long-acting bronchodilator.

Patients were grouped according to their forced expiratory volume in 1 second (FEV₁): the first group included patients with an FEV₁ of at least 90% of predicted, and the second group included patients with an FEV₁ lower than 90% of predicted. Data collected included age, spirometric values, Asthma Control Test (ACT) score, history of perennial or seasonal allergies, and ICS use. Data are presented in Table 1.

Through this small-scale observational study, we have perhaps identified a previously uncharacterized group of patients with apparently normal lung function (FEV₁ $\geq 90\%$) but very high FeNO values (> 100). As might be expected, these patients were found to be taking lower ICS doses than the patients with FEV₁ values lower than

90% of predicted. In the group with an FEV₁ of at least 90%, 10 of 13 patients were steroid naive, and the 3 patients using ICS were taking a low dose (average 153 μg of fluticasone propionate or its equivalent, range 100–200 μg). The ACT score of the steroid-naïve patients did not differ significantly from the rest of the group; patients had, on average, “well-controlled” asthma based on ACT score. However, these patients, despite appearing “normal,” could be at increased risk of asthma exacerbation, potentially requiring oral steroid courses and visits to their health care provider or the emergency department.

In the group with an FEV₁ lower than 90%, 14 of the 27 patients were steroid naive, and the average dose for the 13 patients using ICS was 506 μg of fluticasone propionate or its equivalent (range 80–1040 μg), which would be considered a medium dose. In patients treated with apparently adequate doses of ICS whose FeNO remains persistently high, the cause may be poor adherence to ICS therapy, poor medication administration technique, or continued exposure to allergens.⁸ We acknowledge that any of these factors could have contributed to our observation. More recent evidence has suggested that persistently high FeNO in ICS-treated patients also may reflect a highly reactive asthma phenotype characterized by greater airway reactivity, greater degree of airflow limitation, and more frequent emergency department use and intensive care unit admissions.⁹ In this subgroup of patients, steroid-resistant mechanisms may be driving airway inflammation, rather than the expected steroid-responsive disease.

Although this small pilot study is very limited in scope, we believe that patients of this type warrant further study and investigation. Epidemiologic studies have shown that patients with FeNO levels higher than 100 are at risk of a more severe clinical course, marked by increased asthma burden, repeated asthma exacerbations, and increased use of health care resources.⁴ However, because of the apparent disconnect between the impairment domain (FEV₁, ACT score) and the risk domain (of which FeNO is an indicator), these patients might not receive the treatment they need. A well-designed prospective study is needed to understand patients with a very high FeNO, in terms of their underlying, potentially unique pathophysiology and the treatment modalities

Table 1
Patient characteristics according to lung function

	FEV ₁ $\geq 90\%$ (n = 13)	FEV ₁ <90% (n = 27)
Age (y), average (range)	29.2 (9–68)	34.4 (12–79)
FeNO (ppb), average (range)	127 (119–180)	159 (107–284)
FEV ₁ , average (range)	105 (92–111)	74 (44–88)
FEV ₁ /FVC, average (range)	96.5 (87–109)	88.6 (65–107)
FEF25–75%, average (range)	91.5 (67–134)	57.6 (18–109)
ACT score (entire group), average (range)	18.8 (12–25)	15.5 (5–25)
ACT score (steroid-naïve patients), average (range)	20 (13–25)	14.2 (5–25)
Patients during allergy season, %	78	61
With perennial allergies	0	7
With seasonal allergies	23	11
With perennial and seasonal allergies	69	74
With neither perennial nor seasonal allergies	0	7
Steroid-naïve patients, n	10	14
Daily ICS dose for patients on ICS, ^{a,b} average (range)	153.3 (100–200)	506.15 (80–1,040)

Abbreviations: ACT, Asthma Control Test; FEF25–75%, forced expiratory flow of 25% to 75%; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid.

^aICS dose given as micrograms of fluticasone propionate or its equivalent.

^bOne patient in the FEV₁ <90% group also was on high-dose oral corticosteroid.

that will be most beneficial. Further studies would benefit from a larger sample, more precise characterization of asthma (to rule out other illnesses that can cause elevated FeNO levels, such as eosinophilic bronchitis), and an assessment of medication adherence.

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Contact hypersensitivity to triclosan



Triclosan is a broad-spectrum antibacterial and antifungal compound used extensively during the past decades to inhibit bacterial growth on skin and other surfaces. It is widely used in personal care products and in sportswear, beddings, and toys.^{1,2} Contact hypersensitivity to triclosan is a rare but recognized condition, with frequencies of sensitization usually reported below 1% of tested individuals.² Because triclosan is a high-volume production chemical that is widely used occupationally, with up to 10 million pounds produced annually in the United States alone³ and its use continuing to increase,² we investigated whether a change in prevalence rates of triclosan hypersensitization has occurred during the last 20 years.

Only recently, a new role for triclosan in IgE-mediated allergies has been described. Two independent studies found an association of increased urinary levels of triclosan in patients with aeroallergen and food sensitizations.^{1,4} The pathophysiologic features behind this observation remain unclear, but early studies point toward an immunomodulatory effect of this compound in atopy.^{3,5}

Atopy and contact hypersensitization are generally considered to be independent of each other.⁶ However, because triclosan is a rare cause of contact hypersensitivity and a putative augmentation factor for allergies, triclosan hypersensitivity and atopy may be associated. Thus, we investigated independent risk factors in our population with and without triclosan sensitization in addition to prevalence rates, focusing especially on associated atopic diseases.

We performed a retrospective analysis of data from the Information Network of Departments of Dermatology (IVDK) from 1993 to 2012. The IVDK stores patch test results and clinical data for 113,162 patients tested with triclosan, 2% pet.⁷ The IVDK receives patch test results and clinical data from 56 specialized departments of dermatology and allergology for contact allergy diagnostics in Germany, Switzerland, and Austria. A positive reaction was observed in 363 tested patients (0.32%). In 180 of 331 reported positive cases (54.4%), the results were clinically relevant. However, details were given in only a few patients, mentioning external drugs as sources in 33 patients and body care products in 27 patients.

In patch testing, not only (wanted) clear-cut positive reactions but also (unwanted) doubtful and irritant reactions occur. To measure the diagnostic quality of a distinct patch test preparation

in this concern, the reaction index (RI) was established, ranging from +1, if all nonnegative reactions observed are positive, to −1, if all reactions are doubtful or irritant.^{8,9} A good test preparation should have a positive RI. The positivity ratio (PR) indicates the percentage of weak positive reactions among all positive reactions. Ideally, it should be significantly less than 80%.^{8,9} The RI of triclosan, 2% pet, was −0.22, and its PR was 80.4%.

From 1993 to 2012, the percentage of positive reactions varied in a narrow range from 0.18% to 0.47%, without a uniform time trend. Patient numbers tested with triclosan among the total test population per year revealed constant proportions between 49.5% and 59.3%, with 3 exceptions: 1993 (40.0%), 2001 (64.0%), and 2004 (44.5%). Hence, a selection bias by a stricter or more deliberate indication for testing procedures seems rather improbable. Considering the unfavorable RI and PR, which marked triclosan, 2% pet, as a problematic allergen,⁹ it can be assumed that some positive reactions did not indicate contact sensitization but rather irritation. This assumption is supported by the low proportion of clinically relevant reactions.

Detailed analysis of patient characteristics (MOAHLFA [Male, Occupational dermatitis, Atopic dermatitis, Hand dermatitis, Leg ulcers, Facial dermatitis, and Age older than 40 years] index)¹⁰ and prognostic factors are given in Table 1. A closer look at the test population revealed that among patients 40 years or older, there were significantly more patients with leg dermatitis and fewer with atopic dermatitis, allergic rhinitis, hand dermatitis, and occupational dermatitis (data not shown). This is a common finding among patients with contact dermatitis. To disentangle interactions of these factors, we calculated a logistic regression analysis, using a positive reaction to triclosan as the target variable and all factors listed in Table 1 as explanatory variables. Only 3 of the explanatory variables had a significant independent effect on the outcome: leg dermatitis (odds ratio [OR], 1.7; 95% confidence interval [CI], 1.3–2.2), age of 40 years or older (OR, 1.5; 95% CI, 1.1–1.9), and hand dermatitis (OR, 0.5; 95% CI, 0.4–0.8). Of note, allergic rhinitis and asthma were not associated with triclosan hypersensitivity.

Summarizing our results of the largest available study of patients patch tested with triclosan, we found a continuously low prevalence and no increase in triclosan sensitization despite its increasing use. Furthermore, although the prevalence of allergies is