F_{ENO} as a biomarker guide for inhaled corticosteroid step down in patients with mild-to-moderate well-controlled asthma

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Reducing inhaled corticosteroid dose can be considered when F_{ENO} is less than 50 ppb in patients with well-controlled mild-to-moderate asthma. However, larger studies with longer follow-up are required in order to validate these preliminary data. https://bit.ly/2SckpnE

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Nitric oxide (NO) is an endogenous gaseous molecule synthesised by practically all living cells [1]. It has an impressive wide range of physiological properties, justifying both its recognition as "molecule of the year" in 1992 [2], and in the 1998 Nobel Prize being awarded for nitric oxide discoveries 6 years later [3]. The first reports on the detection of NO in the exhaled air of healthy humans was published in 1991 [4], followed 2 years later by the very first description of increased exhaled NO in asthmatic patients [5]. In 1997, the European Respiratory Society issued the first technical recommendations regarding exhaled and nasal NO measurements [6]. Two years later the American Thoracic Society (ATS) introduced the fractional concentration of NO in the exhaled air (F_{ENO}) as a noninvasive, reproducible and reliable online measurement of NO stemming from the large airways [7]. During the past two decades, numerous national and international societies have issued recommendations related to its practical measurement or clinical use in asthma [7–12]. Yet, some uncertainties or, at the very least, questions still remain regarding the utility of this simple point-of-care testing tool in asthma.

Asthma is a heterogeneous disease characterised by episodic reversible bronchial obstruction and chronic airway inflammation [13]. Asthma heterogeneity is based on both clinical and biological grounds, with type-2 inflammation being a recognisable immunological feature in a significant number of asthmatic patients [14–16]. Monitoring type-2 biomarkers, including blood eosinophils, serum periostin and F_{ENO}, to assess the underlying inflammatory processes seems therefore justified in type-2 high asthmatic patients [16]. It is, however, expected that any given type-2 biomarker candidate should be able to predict future exacerbations (*i.e.* as prognostic biomarker) and/or responsiveness to treatment (*i.e.* as theragnostic biomarker), especially with inhaled corticosteroids (ICS), to be qualified as a reliable and useful tool in clinical practice. Two papers recently published in the *European Respiratory Journal* have specifically addressed the clinical utility of F_{ENO} in severe asthma management [17], and ICS treatment guidance in subgroups of children with asthma [18]. In this issue of the journal, Wang *et al.* [19] have added another important piece of the puzzle to the broader picture of the role of F_{ENO} in asthma. These authors have

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TABLE 1 Risk factors for asthma attacks (exacerbations) in adults

Risks for asthma exacerbations		Low	Intermediate	High
A	Asthma **A**ttacks:			
	History of previous asthma **A**ttacks	None	1 exacerbation in past 12 months	⩾2 exacerbations in past 12 months
	Life-threatening asthma **A**ttack in medical history	None	Ever admitted to hospital for asthma	Ever intubated for asthma
B	**B**ehavioural risk factors:			
	SA**B**A use (canisters per year)	⩽1	2	⩾3
	Adherence to ICS	Good	Intermediate	Poor
	Smoking	Never-smoker	Ex-smoker	Current smoker
C	**C**omorbidities: **C**RS	Absent	Present (CRS+NP)	AERD; food anaphylaxis
D	Obesity: BMI	<30	⩾30	
E	**E**osinophil count in blood	Low to normal	Increased	
	F_{ENO} (while taking ICS)	Low to normal	Increased	
F	Lung **F**unction (**F**EV_1)	Normal	Low	
	Bronchodilator reversibility	Low	High	

SABA: short-acting β_2-agonist; ICS: inhaled corticosteroid; CRS: chronic rhinosinusitis; NP: nasal polyposis; AERD: aspirin-exacerbated respiratory disease; BMI: body mass index; F_{ENO}: fractional concentration of exhaled nitric oxide; FEV_1: forced expiratory volume in 1 s. Modified from [13].

addressed an important, but as yet unanswered, question related to the use of F_{ENO} to guide step down of ICS treatment in non-smoking patients with well-controlled mild-to-moderate asthma. The originality of this *post hoc* analyses study is three-fold. First the authors have extracted individual patient data from seven reports previously published from 2001 to 2016 [20–26]. Second, they have excluded studies whereby the decision to step down ICS was made on the basis of a predefined F_{ENO} threshold. Instead, the authors have prioritised and included results from patients whose asthma was sufficiently well-controlled to justify ICS step down, irrespective of their baseline F_{ENO}. Third, the authors have used multi-level logistic regression analysis to calculate the threshold of F_{ENO} below which ICS step down would be safe, *i.e.* not being associated with subsequent exacerbations. As a result, the F_{ENO} threshold found by the authors was 50 ppb, above which the authors advocate against ICS step down in asthmatic patients. Interestingly this figure is consistent with the one defined by the 2011 ATS clinical practice guideline as indicator of eosinophilic inflammation and responsiveness to ICS [8]. In other words, this analogy implies that it is not recommended to reduce ICS whilst type-2 inflammation is still high, even though current asthma symptoms seem to be clinically well-controlled. Conversely, if asthma control is achieved *and* F_{ENO} is below 50 ppb, WANG *et al.* [19] suggest that gradual ICS reduction may be initiated without increasing risk of exacerbations in the short-term. How does this F_{ENO} 50 ppb threshold relate to the 20 ppb threshold recommended by the Global Initiative for Asthma (GINA) in relation to patients with severe asthma and a possibly refractory type-2 inflammation [13]? Apparently at odds, those two thresholds are in fact consistent, as the F_{ENO} ⩾20 ppb threshold is suggestive of type-2 high asthma only in patients with severe asthma taking high dose ICS or daily oral corticosteroids [13]. The F_{ENO} 20 ppb threshold, therefore, is not applicable to the study in which patients had mild-to-moderate well-controlled asthma [19].

What are the limitations and strengths of the individual patient data meta-analysis by WANG *et al.* [19]? First, although the authors screened more than 24 000 records for the systematic review, after careful screening and selection they were able to include only seven studies, representing 384 patients, which is still a small number as compared with the more than 300 million subjects with asthma worldwide. Second, the follow-up time after decreasing the ICS dose (either halving the ICS dose, switching to ICS rescue treatment or withdrawal of ICS) was only 12 weeks, which is short for a lifelong disease such as asthma. Moreover, only 43 participants experienced one or more exacerbations after stepping down ICS therapy, limiting the robustness of risk prediction models. Finally, besides F_{ENO}, demographic data (age and gender), smoking status and body mass index, the authors could not investigate the impact of other risk factors for exacerbations, such as a history of previous asthma attacks, blood eosinophil counts, comorbidities (*e.g.* obesity, chronic rhinosinusitis), high short-acting β_2-agonist (SABA) use, poor adherence, incorrect inhaler technique and impaired lung function.

As mentioned earlier, NO has been synthesised by living organisms since the beginning of life on earth [27]. F_{ENO}, being now around for three decades [4], is also becoming an old-timer amongst asthma biomarkers [28]. Yet its role is still debated after extensive scrutiny, and two series of Cochrane analyses [29, 30]. The very first Cochrane analyses published in 2009 and summarised in 2012 concluded a lack of

added value of F_{ENO} in the management of asthma in adults and infants [29]. A second summary paper published in 2018 by the same group of authors have concluded that treatment tailored using F_{ENO} levels decreased the frequency of asthma exacerbations but did not impact on ICS dose [30]. The higher number of randomised controlled trials (RCTs) that has gradually increased over the years, thus improving the power of the meta-analyses, might explain the more favourable Cochrane summary report published in 2018 [30] as compared with the previous one [29]. Yet, marked differences including length of the study, F_{ENO} cut-off levels and definition of asthma exacerbations between the RCTs are weaknesses that will consistently reduce the strength of those meta-analyses. More importantly, with the knowledge that F_{ENO} is now considered as a biomarker of type-2 inflammation [14–17], any group analyses mixing asthmatic patients with high and low type-2 inflammation could be considered as biased. It is therefore laudable that the authors have decided to look at individual data and apply multi-level logistic regression to analyse these data. Using similar methodological approaches is probably the way to move forward in a disease with such a high degree of complexity, and interindividual differences, such as asthma.

In conclusion, in this meta-analysis the authors suggest that in non-smoking patients with well-controlled mild-to-moderate asthma, stepping down ICS treatment (by reducing ICS dose) could be considered when F_{ENO} is less than 50 ppb [19]. However, larger studies with longer follow-up are required in order to validate these preliminary data. Importantly, GINA guidelines highlight the need to assess the long-term risk of asthma in addition to the current control of asthma symptoms [13]. Indeed, beyond uncontrolled asthma symptoms, additional risk factors for exacerbations encompass not only elevated type-2 biomarkers, such as blood eosinophilia and increased F_{ENO}, but also a history of previous asthma attacks, behavioural risk factors (such as SABA overuse, non-adherence to ICS, incorrect inhaler technique and smoking), comorbidities and low lung function (table 1). The optimal management of asthma, including choosing the most appropriate dose of ICS for each unique individual, requires thus a careful holistic assessment.

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