

Practical Applications of FeNO Measurement and Inhaler Monitoring Technologies in the Management of Difficult Asthma



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A startlingly high proportion of people with asthma—perhaps as many as one in five—have difficulty to treat asthma, which is characterized by persistent troublesome symptoms despite prescriptions of high-dose inhaled corticosteroids (ICS) and long-acting β_2 -agonists.¹ For most patients and clinicians, asthma should be a relatively straightforward disorder to treat; only around 4% of patients have genuinely severe asthma for which appropriately used inhaled therapies are unable to suppress airway inflammation adequately and control symptoms.¹ Hence, much of the task in the asthma clinic is to tease out which patients with difficult asthma have genuinely severe underlying disease. In some cases, these patients have been misdiagnosed and are consequently unlikely to benefit from asthma therapy, whereas others have symptoms attributed to the asthma that are primarily driven by comorbidities such as obesity or chronic rhinosinusitis. However, a critical factor limiting adequate disease control in many patients with difficult asthma is that they do not use the inhaled medication as prescribed.²

Perhaps counterintuitively, bad asthma does not beget good adherence. Rather, poor adherence to ICS is common in patients attending difficult asthma clinics, including among those considered for or receiving high-cost biologic therapy.^{2,3} Non-adherence can be broadly classified as unintentional (for example, when a patient is unable to use the inhaler device effectively or forgets to use it) or intentional (in which the patient actively decides not to undergo the treatment), although the boundary between them is not as well-defined as it may initially appear.⁴ Regardless, the first step toward addressing either is the successful identification of suboptimal adherence. Historically, assessment of adherence was based on a combination of patient interviews and/or an appraisal of prescription or dispensing records, but these are notoriously blunt tools.⁵ Instead, technological developments facilitate a more sophisticated approach, such as through the use of remote monitoring to assess

inhaler use to determine adherence accurately in a dynamic fashion over time.⁶ Ideally, an inhaler monitoring device will measure not just attempted use of the device but also the successful delivery of medication. An example of this is the inhaler compliance assessment (INCA) device, which records audio from the inhaler priming, patient exhalation, and dose inhalation to breath hold, and thus can evaluate both inhaler use frequency and technique.⁷

Nitric oxide production is upregulated as a by-product of type 2 inflammation, in particular by interleukin-13 signaling. Although it is also influenced by other endogenous and exogenous factors, such as comorbid chronic rhinosinusitis, smoking, and dietary nitrate intake, measurement of fractional exhaled nitric oxide (FeNO) can be used to estimate levels of type 2 inflammation in the lower airway. Measurement of FeNO has been used to help diagnose asthma and guide ICS dosage in patients with problematic asthma, but arguably its most useful clinical application is as an adherence assessment and monitoring tool.⁸ As initially validated, FeNO suppression testing (FST) involved difficult asthma patients who attended a clinic for 7 days to receive high-dose ICS under direct observation, in parallel with having the FeNO measured daily.⁹ A reduction in FeNO level from baseline of >42% by day 5 was indicative of poor prestudy adherence to the usual maintenance ICS.

While instinctively it seems unlikely that an intentionally nonadherent patient would engage with home inhaler monitoring, FeNO measurement has more recently been successfully coupled with the use of the INCA monitoring device.¹⁰ In a multicenter UK study of patients with poorly controlled asthma and elevated baseline FeNO, participants were prescribed high-dose, INCA-monitored fluticasone propionate (INCA-FP) alongside the usual ICS regimen and asked to measure FeNO levels daily at home for 7 days. This methodology effectively provided remotely observed ICS therapy, and subsequently identified probable prestudy ICS nonadherence in 65% of participants. Although conceptually elegant, performing clinic-based or domiciliary FST outside clinical trials demands significant logistical, resource and time commitment from both patients and asthma clinicians. Thus, a less resource-intensive method would be highly desirable if it were capable of providing comparable information regarding adherence.

In this issue of the *Journal*,¹¹ Boddy et al describe their experience using a combination of home INCA monitoring and clinic FeNO measurement. Patients attending the asthma service with a baseline FeNO level ≥ 45 ppb were given twice-daily, INCA-enabled, high-dose fluticasone propionate–salmeterol xinafoate (INCA-FP/SX) with FeNO measurement performed in the clinic after 28 days, or the 7-day INCA-FP FST described

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earlier (with the option to transfer to the extended 28-day INCA-FP/SX group afterward). In both groups, participants with a reduction of $\Delta\log_{10}$ FeNO value of ≥ 0.24 , equivalent to an approximately 42% fall from baseline, were considered to have a positive FST (ie, presumed to be nonadherent to the ICS prestudy). Of 23 patients offered participation in the 28-day INCA-FP/SX arm, 21 managed to complete the protocol, with wearily familiar results: 66% had significant FeNO suppression, and as a consequence of better adherence, exhibited improvements in lung function and asthma control, thus confirming ICS-responsive disease. In parallel, 74 of 80 people completed the 7-day INCA-FP phase, 48 of whom had a positive FST (65%), and 29 of whom subsequently agreed to participate in the follow-up INCA-FP/SX monitoring phase (25 suppressors and 4 nonsuppressors).

In a nice apparent demonstration of the Hawthorn effect, 91% of participants had excellent adherence to the inhalers while undergoing INCA monitoring, although longer-term disease control for those patients is likely contingent on persistent optimal inhaler use. Although follow-up FeNO levels in that cohort, measured on average 4.75 months later, remained encouragingly similar to those on day 28 (suggesting maintenance of satisfactory adherence), this is in contrast to the behavior exhibited by 14 of the 18 patients with a positive 7-day INCA-FP FST, who experienced a delay of more than a week between 7- and 28-day monitoring phases and reverted back to the pretest nonadherence. Moreover, across the entire group, although patients received intensive education and demonstrated optimal technique in the clinic, they still missed significant numbers of doses and made critical inhaler technique errors. This underlines that education is not a panacea for nonadherence, and that inhaler technique should be checked regularly despite previous competence.

Although prospective, randomized controlled data are needed to validate properly the approach described by Boddy and colleagues,¹¹ this work suggests that remotely confirmed adherence using the INCA device, coupled with clinic FeNO measurement, can help differentiate between patients who will achieve asthma control with improved inhaler use and those who are likely to remain uncontrolled despite adequate adherence to inhaled treatment and may require escalation to advanced asthma therapies. It also confirms our suspicions that some patients will

relapse into nonadherence when they are not monitored, despite education to the contrary.

Taken as a whole, the available evidence suggests that the combination of FeNO measurement and remote inhaler monitoring allows the effective assessment of ICS adherence. Identifying nonadherence is, of course, only the first step: future trials should examine how asthma control can be influenced by the long-term use of remote monitoring technology and evaluate the impact of patient-centered technological approaches, in which patients with asthma are given full access to and control of clinical and adherence data.⁶ In addition, the development and application of evidence-based techniques to improve adherence in chronic airways disease will be critical. A combination of these measures may allow care of patients with previously difficult asthma to be moved decisively from the asthma clinic to the home.

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