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**Aerocrine statement on article by de Jongste *et al* in
American Journal of Respiratory and Critical Care Medicine (January 15, 2009)**

In the 15 January (2009) issue of *The American Journal of Respiratory and Critical Care Medicine*, de Jongste *et al* published a study of the use of exhaled nitric oxide (NO) in telemonitoring anti-inflammatory therapy in 151 children with asthma that were randomized into two groups and followed for 30 weeks [1]. The authors concluded that, in this setting, there was no added value in daily monitoring of exhaled NO in addition to symptom monitoring compared to daily symptom monitoring only. This conclusion is similar to one by Szeffler *et al* in an article published in the *Lancet* in September 2008, also evaluating the role of exhaled NO in monitoring the therapy of children with asthma in a randomized controlled trial (RCT) [2].

Health technology assessment groups worldwide advocate that the added value of new medical methods must be demonstrated in RCTs. However, one inherent problem of the RCT environment is that control groups may not represent real-life clinical practice—and that this problem may be especially significant in patients with asthma, who are generally subject to poor treatment adherence. Rather, inclusion in an RCT *per se* causes significant improvement in asthma patients, primarily because of the far better treatment adherence induced by a clinical trial environment. This was observed during the run-ins or initial weeks of observation in both the aforementioned studies, which leave very little scope for exhaled NO to improve outcomes further, even less when exhaled NO is used in addition to symptom monitoring, since exhaled NO will be more powerful when used as an *alternative* to symptom monitoring. Despite this general problem with the exhaled NO-guided therapy monitoring studies published so far (six in total), they have demonstrated a significant improvement in many important outcome measures by incorporating exhaled NO in treatment decisions. For example, reduced use of inhaled corticosteroids (ICS) [3, 4], reduced airway hyperresponsiveness [5], improved small airway function [6], reduced need for peroral courses of corticosteroids [2], and a trend towards fewer hospitalisations, as in the latest study by de Jongste *et al* [1], have been reported.

The telemonitoring approach described in the article by de Jongste *et al* [1] may not be entirely feasible in real-life clinical environments. The intensive patient support in this study and in the study by Szeffler *et al* [2] would be too costly and demanding for healthcare providers. Instead, the role of exhaled NO as a guide for the titration of ICS doses could be evaluated in an asthma self-management strategy. One way forward might be to compare self-management based on relatively frequent NO measurements at home with a self-management strategy based on symptoms, and possibly peak flow measurements, with a minimum of clinic visits to maintain real-world asthma management.

While the above RCTs on exhaled NO-guided therapy monitoring were designed in 2004 and earlier, a more basal use of exhaled NO in the clinic has emerged as evidenced consistently in a multitude of studies. These basal applications include designating the patients likely to respond to ICS—patients with elevated exhaled NO levels when off anti-inflammatory treatment [7]. Thus, symptomatic patients with normal exhaled NO off treatment may have diagnoses other than asthma. Furthermore, the effect of introducing or stepping up anti-inflammatory treatment on exhaled NO levels themselves would indicate the level of success of the treatment [8]. If exhaled NO is *not* clearly reduced by high amounts of ICS, poor treatment adherence [2] or intense environmental exposure (allergens, traffic pollution) are indicated to the treating doctor, and an ICS-related improvement of symptoms may not be expected. Surprisingly, so far, no-one has commented on the simple fact that the lack of difference in symptom scores between the treatment strategy groups in the above ICS titration studies was generally mirrored by similar exhaled NO values in the two groups! In fact, the most successful inflammatory marker-guided ICS titration study so far, by Green *et al* [9], is the only study where exhaled NO was clearly separated between the groups, even though sputum eosinophil count was used to guide treatment.

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The use of exhaled NO to designate the patients likely to respond to steroids is much more convenient, and can be performed at a lower cost and risk than available alternatives: provocation tests and induced sputum collection. Furthermore, exhaled NO is more convenient and has a higher sensitivity than a bronchodilator reversibility test. Finally, trials of ICS treatment, when patients are followed up after a month or more, may be falsely positive since symptom improvement may not be related to the ICS treatment *per se* but may merely reflect the resolution of an infection or changes in the environment. Additionally, revealing NO values to patients who are aware of the significance of elevated NO values would be likely to improve treatment adherence.

It is important to acknowledge that *neither* of the aforementioned ICS titration studies incorporated *any* of these basal clinical applications of exhaled NO. Nevertheless, based on the vast literature, introducing the measurement of an objective marker of inflammation—exhaled NO—in the routine clinical management of asthma to improve initial patient assessment including short-term response to anti-inflammatory treatment, and improve treatment adherence, should be obvious.

**Kjell Alving, Director of Scientific and Medical Affairs
Aerocrine AB, Sweden**

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