



## EDITORIAL

# High inhaled corticosteroids adherence in childhood asthma: the role of medication beliefs

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For two decades, maintenance inhaled corticosteroids have been recommended by international guidelines as the mainstay of treatment in children and adults with persistent asthma. As asthma control criteria have become increasingly more stringent, an even larger proportion of individuals are labelled as having “uncontrolled persistent” asthma. Indeed, while in 1996, we accepted as criteria for acceptable control as up to 10 doses per week of rescue  $\beta_2$ -agonists, that is to say one dose per day for the prevention of exercise-induced asthma and three doses per week for the relief of symptoms [1], they were progressively reduced to two doses per week since 2006 [2]. An expanding proportion of individuals with mild asthma now qualify for maintenance controller therapy. The preference for daily inhaled corticosteroids over leukotriene receptor antagonists and placebo is solidly supported by systematic reviews of the efficacy of randomised controlled trials [3, 4] in children and adults [5–7].

However, most patients with mild persistent asthma do not use maintenance inhaled corticosteroids and most individuals remain poorly controlled [8–10]. Insufficient use of inhaled corticosteroids may be due to suboptimal medical prescriptions and to limited patient access to healthcare and medications [11, 12]. However, even in settings where patients have free access to medications, adherence remains suboptimal; many discontinue asthma controllers when asymptomatic and restart therapy when deemed required [11–13]. Reasons for poor patient adherence include: side effects, fear of side effects, forgetfulness, inconvenience of medication use, the erroneous conception that no symptoms equate to no disease, and negative beliefs about always having asthma, having airway inflammation, and about the importance of using inhaled corticosteroids [10, 13, 14]. Yet, suboptimal adherence to daily controller is clearly associated with poor asthma control [15].

A large body of literature has explored solutions to overcome these barriers. A comprehensive approach, which includes a regular medical review, asthma education, and provision of a written self-management plan, has consistently been shown to be effective in improving compliance and asthma control [16–18]. Recently, studies on pragmatic effectiveness trials

have reported a lower compliance with maintenance inhaled corticosteroids when compared with leukotriene receptor antagonists and a lower compliance with long-acting  $\beta_2$ -agonist compared to leukotriene receptor antagonists as adjunct therapy to inhaled corticosteroids, such that the superiority of first-line therapies appeared annihilated by poor compliance; indeed, leukotriene receptor antagonists looked equivalent or superior to inhaled corticosteroid as monotherapy and to long-acting  $\beta_2$ -agonist as adjunct therapy [19, 20]. Some individuals have questioned the wisdom of the increasingly stringent asthma control criteria, wondering if some patients with mild persistent asthma could be treated without daily controller therapy [21]. These data have opened new approaches to the demanding task of coaching our patients to take daily inhaled corticosteroids; the “giving-up to poor compliance” strategies.

The popular debate had changed from compliance-enhancing educational interventions, to accepting defeat by adapting our prescription to patients’ poor compliance. One option is to systematically opt for second-choice controller. Another option, first tested by BOUSHEY *et al.* [22] in 2005, advocated what patients do naturally, that is, intermittent inhaled corticosteroids initiated at the onset of exacerbations. To date, six published trials have compared intermittent with maintenance inhaled corticosteroids in adults [22, 23], school-aged children [24, 25], and preschool-aged children [26, 27]. In three trials [22, 24, 27], intermittent inhaled corticosteroids were prescribed at a fixed predefined high dose; while three trials [23, 25, 26] tested the strategy of combining inhaled corticosteroids with short-acting  $\beta_2$ -agonist, such that whenever a patient took a  $\beta_2$ -agonist a dose of inhaled corticosteroid was also taken. With one exception, trials have uniformly concluded that maintenance inhaled corticosteroids offered superior asthma control than intermittent therapy, the latter being either similar or superior to placebo. The only exception was a study in preschool-aged children with recurrent wheezing who may have had intermittent, rather than persistent, asthma [27]. Yet, these approaches appeal to physicians’ discouragement over never-ending efforts to convince patients to benefit from the most effective strategy. It is tempting to prescribe second-rate no-effort solutions, either by selecting medications patients want to take or by recommending that inhaled corticosteroids be taken on the patients’ own terms. Compared to first-line therapy [21], these alternatives are not as good, but they are also not that bad, in the short and medium term, at least in selected patients with very mild asthma. Of note, no studies have examined the long-term impact on lung growth and lung function decline of these “no-effort” strategies that are gaining popularity.

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The study by KLOK *et al.* [28] is a welcome reminder that physicians do not need to give up on poor compliance: a concerted multidisciplinary approach can achieve amazing compliance and asthma control. In this cohort of preschool-aged children who had been followed for over a year in a specialised asthma paediatric centre, the median adherence to maintenance inhaled corticosteroids was sustained at 92% over a 3-month period.

KLOK *et al.* [28] explored the parental determinants of compliance *via* questionnaires. Adherence was objectively documented with dose counters fitted on inhalers, a major advantage over diaries in which adherence is consistently overestimated [29]. Defining high adherence as the intake of  $\geq 80\%$  of the prescribed medication, bivariate analyses depicted a positive association between adherence and parental beliefs about the child's need for, and benefit from, maintenance medication, but not with parental beliefs about asthma. In turn, associations between adherence and several markers of asthma control were identified including physician global assessment of control, asthma control questionnaire score, and change in respiratory resistance. It is thus feasible to achieve high adherence to inhaled corticosteroids in preschool-aged children in the context of routine specialised care. Although a multidisciplinary approach has shown clear benefit in various populations including patients with difficult-to-treat asthma [30], the study by KLOK *et al.* [28] is probably unique in the magnitude of adherence achieved. The clinic's routine care included patient management according to the Dutch national guidelines on paediatric asthma, which were adapted from the Global Initiative for Asthma's Global Strategy for Asthma Management and Prevention update 2010 [31] and involved: education using a collaborative approach between the paediatric asthma specialist, a dedicated paediatric asthma nurse, and the parents; with frequent follow-up visits with open discussion at each visit about parental perceptions of asthma, treatment, goals, and importance of adherence to inhaled corticosteroids. The findings would suggest that it is possible to change not only parental beliefs but also their behaviour, using repeated tailored education and close follow-up in a specialised asthma clinic.

As an observational study with no control group, the study was subject to several biases. The cohort represented 75% of those eligible for the study. Non-participants were similar in age, sex, dose of inhaled corticosteroids, and duration of follow-up; however, they differed in the lower number of attended visits in the year preceding enrolment, with fewer hospitalisations and fewer atopic children, suggesting perhaps that less compliant parents who perceived a lower need for asthma care failed to participate. Parental awareness of adherence monitoring may have increased adherence. In other words, it is possible that the selection criteria and monitoring biases would have contributed to overestimating adherence, the magnitude of which is not known.

Unfortunately, the study was not designed to explore the key determinants of success factors. Admittedly, the combination of regular medical review, asthma education and self-management plan has been consistently shown to improve control and decrease healthcare resources in adults [16] and children [17, 32]. Whether and how important were other motivators to adherence, such as a healthcare professional's feedback on

observed clinical improvement and objective measures of lung function in these preschool-aged children, remains unclear. Presumably, something would have changed parental misconceptions concerning inhaled corticosteroids. An observational study that selected patients at the first consultation, ascertained parental perception of disease and treatment beliefs at baseline, monitored the change in beliefs and adherence over time, and enquired from parents the key elements that changed their perception towards a positive risk-benefit ratio of maintenance inhaled corticosteroids for their child, would have provided some dearly needed information.

Despite several unanswered questions, KLOK *et al.* [28] have demonstrated that it is possible to achieve optimal management in preschool-aged children, at least after a year of intensive education, close monitoring, and partnership. The strategy works; one must now define what works and prove that it is exportable and replicable. Could the results be replicated in school-aged children and adolescents in whom the physician must deal with a dyad including the child and parents and not only convince, but also modify the behaviour of the increasingly independent child as he/she grows up. As the authors reported a positive association between maternal educational level and adherence, what is the best approach for children of less educated parents? More importantly, does one need a specialised clinic or can this be achieved by community specialists and general practitioners? In other words, how implementable is the proposed approach to physicians who may not have the aura of a paediatric asthma specialist in the eyes of parents and who are unlikely to have similar access to paediatric evaluation tools, including lung function tests, at each visit and dedicated asthma nurses, which are available in a specialised asthma clinic. One must define the key elements of success and test their impact in general or community practice, as well as in differing populations and other healthcare settings.

One wonders if guideline recommendations should be setting, rather than patient, specific? In other words, should optimal management remain as maintenance inhaled corticosteroids for patients managed in settings organised to provide optimal guided self-management, while second-best options using second-line therapy or intermittent corticosteroids be recommended for other practice settings? KLOK *et al.* [28] demonstrated that we can achieve high adherence and good asthma control in preschool-aged children. Let's encourage them and others to explore the key elements of their success that could be generalised to all patients and practice settings.

#### STATEMENT OF INTEREST

A statement of interest for F.M. Ducharme can be found at [www.erj.ersjournals.com/site/misc/statements.xhtml](http://www.erj.ersjournals.com/site/misc/statements.xhtml)

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