

Long-Term Adherence to Daily Controller Medication in Children With Asthma: The Role of Outpatient Clinic Visits

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Summary. Objective: To investigate changes in inhaled corticosteroids adherence, both before and after a scheduled follow-up visit, in young children in a comprehensive asthma management program. Study design: One-year prospective follow-up study in 104 asthmatic children (mean age 4.8 years). Adherence to inhaled corticosteroids was assessed using electronic (Smartinhaletm) devices. We assessed changes in adherence before and after clinic visits. A > 10% increase in adherence in the 3 days preceding a clinic visit was considered to reflect clinically relevant white coat adherence (WCA) if it exceeded background variation in adherence (median change >0, and increase larger than adherence changes after a clinic visit). Results: Overall adherence was high (median 85%). A pre-visit increase in adherence of >10% was demonstrated in 17 patients (22%), but the median change in adherence around a clinic visit was 0. There were no significant differences in changes in adherence between the days before or after a visit ($P > 0.2$). The median coefficient of variation in adherence was 9%, and did not significantly differ between children with and without a pre-visit increase in adherence ($P = 0.12$). Twelve patients (15.4%) showed an increase of adherence in the month following a clinic visit; their overall mean (SE) adherence was slightly lower (73% (4.6%)) than those without such an increase (80% (2.2%), $P = 0.054$). Conclusions: There was no WCA in children with asthma enrolled in a comprehensive asthma management program with high overall adherence. This suggests that WCA in pediatric chronic conditions primarily occurs against the background of low overall adherence. **Pediatr Pulmonol.** © 2014 Wiley Periodicals, Inc.

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INTRODUCTION

Adherence to inhaled corticosteroid (ICS) treatment is a major determinant of pediatric asthma control. Poor adherence results in poor asthma control with an increased risk of exacerbations; conversely, adherence rates $\geq 80\%$ are associated with good asthma control.^{1–5} Although, it has been well established that good adherence to ICS can be achieved by enrolling children with asthma into a comprehensive guideline-based asthma management program, including extensive asthma education and close follow-up,^{2,4} the effect of the clinic visit itself on ICS adherence in childhood asthma has not been examined to date. An increase in adherence in the days before a clinic visit, which disappears shortly after the visit, has been demonstrated in children with epilepsy, atopic dermatitis, and diabetes.^{6–8} This phenomenon has been termed white coat adherence (WCA), and is thought to reflect a conscious effort by patients or their parents to improve adherence behavior before visiting their doctor.^{6,8} Because adherence varies over time,^{8,9} particularly in patients with poor adherence, an

analysis of changes in adherence around a clinic visit should take the background level and variability of adherence into account. In our opinion, WCA should only be regarded as clinically relevant if it exceeds the usual background variation of adherence over time. In previous

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studies in which an increase in the days preceding a clinic visit was shown, the mean level of adherence was low,^{6–8} suggesting that the presence of WCA may depend on the overall level of adherence.

The purpose of the present study was to assess the presence and extent of WCA in children with asthma enrolled in a comprehensive guideline-based asthma management program in which the importance of adherence to ICS is emphasized at every follow-up visit. Because high overall ICS adherence has been demonstrated in this cohort,^{2,10} we expected variability of adherence to be low, and we expected to find little, if any, evidence of clinically relevant WCA.

METHODS

Design and Setting

For this paper, we used data from a prospective observational study in which adherence to ICS use was monitored over a 1-yr period in asthmatic children, aged 2–6 years, who were being followed up at our hospital-based pediatric asthma outpatient clinic. They followed a comprehensive asthma management program, details of which have been published previously.^{2,11} Briefly, after confirming the diagnosis of asthma, and agreeing with parents and patient on long-term daily controller therapy with ICS (and other controllers as needed), patients and parents receive comprehensive guideline-based self-management education and repeated inhalation instruction. Patients and parents visit the clinic four to six times during the first year of follow-up and two to four times a year afterwards. Follow-up focuses on maintaining a strong partnership with patients and parents, tailoring treatment if needed to the parents' and patient's views and preferences.¹¹

For the adherence monitoring study, we approached consecutive children with asthma who had been using ICS (fluticasone propionate 100–250 µg/day by metered dose inhaler/spacer combination) for at least 3 months, and had been enrolled in our asthma program for at least 3 months. Children with severe neurological or cardiovascular comorbidity, children of parents with insufficient understanding of Dutch language to allow participation in the study, and those using inhaler devices not compatible with the Smartinhaler[®] device (breath-actuated inhalers and dry powder inhalers) were excluded. For the current analysis, all patients who used ICS throughout the entire 1-yr study period were included if complete adherence data were available for the month preceding and following each visit.

Assessment of Adherence to ICS

Throughout the 1-yr follow-up, ICS adherence was recorded electronically with the Smartinhaler[®], a

validated electronic device logging the date and time of each ICS actuation.¹² At each follow-up visit, Smartinhaler[®] data were uploaded and proper recording function was checked.

Statistical Analysis

Adherence was calculated as the number of inhaled doses recorded by the Smartinhaler[®] expressed as a percentage of the number of doses prescribed and was censored at 100% of the prescribed dose.² We calculated individual average adherence rates over the month preceding and following a clinic visit, as well as the average adherence rates during the 7th to the 4th day preceding, 3rd to the 1st day preceding, 1st to the 3rd day following, and the 4th to the 7th day following a clinic visit.

In previous studies, WCA was defined as an average increase in adherence of more than 10% in the 3 days preceding a clinic visit, compared to the 4th to the 7th day preceding a clinic visit.^{6–8} Instead of using the term WCA, we described this phenomenon as “pre-visit increase in adherence”, because we wanted to reserve the term “clinically relevant WCA” to identify patients whose pre-visit increase in adherence exceeded the usual background variation of adherence. We analyzed this by calculating the median of the change in adherence in the 3 days preceding a clinic visit, compared to the change in the 7th–4th day preceding a clinic visit, and by comparing adherence changes in the 3 days before a clinic visit to those after a clinic visit. We reasoned that if a pre-visit increase in adherence of >10% truly reflected clinically meaningful WCA (i.e., a conscious effort to improve adherence behavior before a study visit), the mean change in adherence in those 3 days (as compared to the previous 4 days) should be >0, and should exceed the change in adherence in the days following a clinic visit. We therefore compared the difference in adherence in the days before a clinic visit to changes in adherence in the days following a clinic visit.

We also calculated differences in adherence between the month preceding and following a clinic visit, to assess the effect, if any, of reinforcing the importance of daily ICS use during the clinic visit (“post-visit increase in adherence”). Wilcoxon sign test was used to determine whether pooling of data from different visits for this purpose was justified, by assessing whether the individual variation in adherence around a clinic visit changed between different visits.

To assess the background variation in adherence throughout the study, we calculated coefficients of variation (CV) for each individual patient as the standard deviation expressed as a % of the mean of their individual adherence, and compared these between children with and without a pre-visit increase in adherence using Mann–Whitney *U* test.

Ethical Considerations

This study was approved by the hospital ethics review board and all parents provided written informed consent.

RESULTS

The patient flow chart is presented in Figure 1. Of the 104 children who entered the study after informed consent was obtained, complete adherence data were available in 78 (75%). The most common reason for incomplete adherence data (in 61% of cases) was withdrawal of ICS treatment because of apparent clinical remission (Figure 1). There was no significant difference in adherence rates between children with or without complete adherence data (data not shown). Clinical characteristics of the 78 patients in the final analysis are presented in Table 1. The majority of participants had well controlled asthma while on ICS maintenance therapy. Overall adherence was high, with a median interquartile range, (IQR) adherence rate of 85% (70% to 92%).

Because adherence was not significantly associated with increasing number of visits or duration of follow-up during the study (all P values >0.2), analyses of WCA and other changes of adherence around clinic visits were performed using pooled data from all visits in all patients. Figure 2 shows the change in adherence rates in the days preceding a clinic visit (191 visits). A pre-visit increase in adherence (difference in adherence between the 7th–4th day before a visit and that on the 3rd–1st day before a visit

TABLE 1—Characteristics of Study Patients at Baseline (n = 78)

Demographic and clinical characteristics	
Age (years, mean (SD))	4.8 (1.0)
Male gender (%)	47 (60%)
Parental asthma	26 (33%)
Household smoking (%)	25 (32%)
Maternal educational level (1 = low and 7 = high)	5 (4–6)
Positive specific IgE to inhalant allergens (n = 75)	42 (56%)
Hospitalisation ever for asthma exacerbation (n, %)	30 (38%)
Duration of asthma care before study (months)	18 (7–27)
Number of scheduled follow-up visits	4 (3–5)
ACQ at end of follow-up	0.5 (0.1–1.1)
PACQOL at end of follow-up	6.3 (5.3–6.8)
Baseline medication	
Long-acting bronchodilators (%)	9 (12%)
Daily fluticasone dose (mean; range; μ g)	250 (125–500)

Data are presented as median (interquartile range) unless otherwise stated.

IgE, immunoglobulin E; ACQ, asthma control questionnaire (<0.75 = well-controlled asthma, >1.5 = not well-controlled asthma); PACQOL, paediatric asthma caregiver quality of life questionnaire (1 is low and 7 is high quality of life).

$>10\%$) was found in 47/191 visits (25%) in 17/78 children (22%). The median change in adherence, however, was 0 (IQR -4.2 to 12.5%), and a decrease in adherence of $>10\%$ in the 3 days before a visit was equally common (41 visits, 21%) as an increase (Figure 2). When we calculated differences in adherence between the 7th–4th day before a clinic visit, the 3rd–1st day before a clinic visit, the 1st–3rd day after a clinic visit, and the 4th–7th day after a clinic visit, the median of all these differences was 0, and the frequency distributions were comparable to that presented in Figure 2. There were no significant differences between any of these adherence differences (all P values >0.2).

Difference in adherence rates in the month before and after a clinic visit was calculated in the 109 visits in 64 children with complete adherence data for all months preceding and following each clinic visit. The median (IQR) change in adherence was 0% (-6 to 5%). An increase in adherence of $>10\%$ in the month following the visit compared to the month preceding the visit was found in 17 visits (16%) in 12 patients (19%). Their overall mean (SE) adherence was slightly lower (73% (4.6%)) than those without such an increase (80% (2.2%)) although this failed to reach statistical significance ($P = 0.054$).

Overall variation of adherence throughout follow-up was low, with a median (IQR) CV of 9% (5% to 19%). Although the 17 children with WCA showed slightly higher CV (median 15%, IQR 6 to 24%) than those

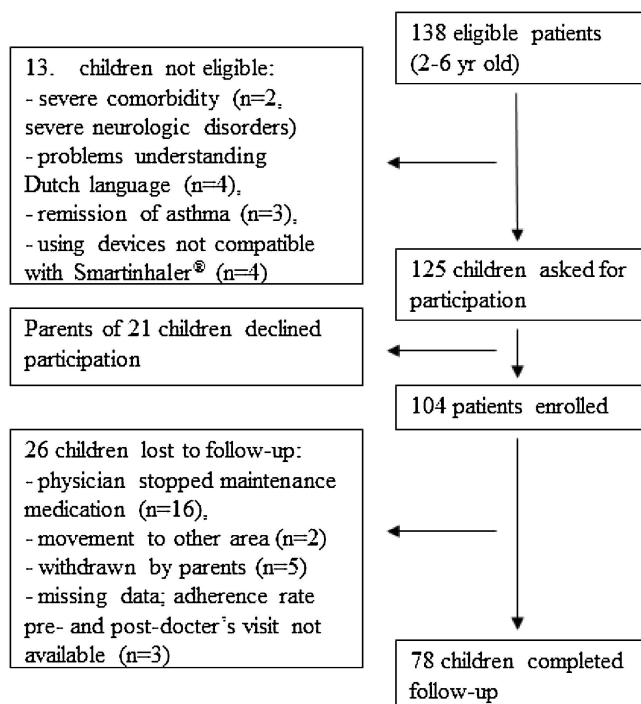


Fig. 1. Patient flow chart.

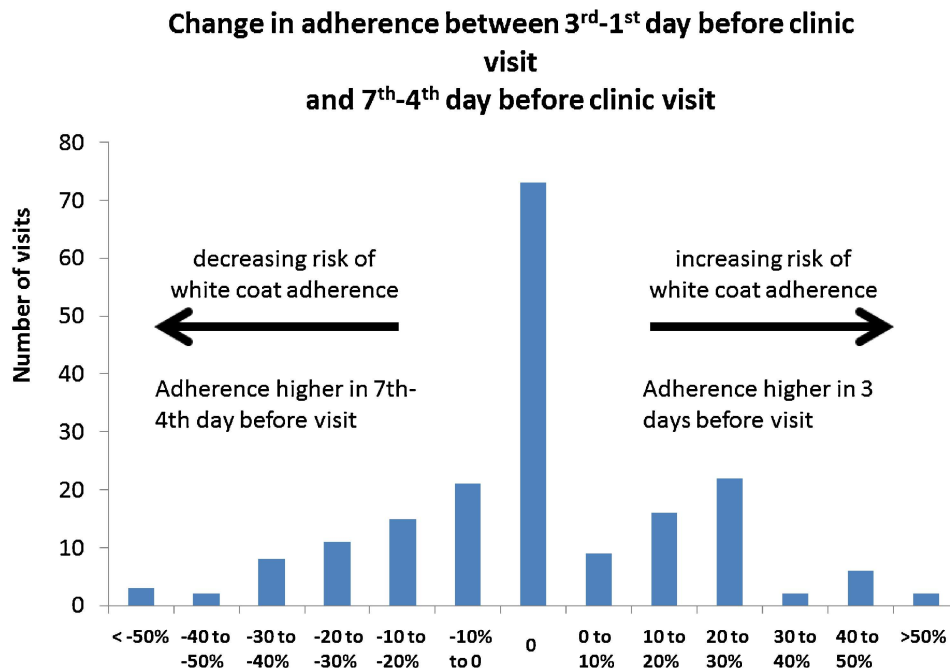


Fig. 2. Frequency distribution of the difference in adherence between the 3rd-1st day before a clinic visit and the 7th-4th day before a clinic visit (pooled data of all visits of all patients, see text). A difference >10% indicates WCA, by definition. Median difference was 0.

without WCA (9%, 4 to 17%), this difference was not significant ($P = 0.12$).

DISCUSSION

Main Findings

In this cohort of young children with asthma enrolled in a comprehensive guideline-based asthma management and follow-up program, there was no evidence of clinically relevant WCA. Although, a >10% increase of adherence in the 3 days prior to a clinic visit was found in 25% of visits in 22% of children, the median change of adherence in the days immediately before a study visit was 0, and there was a comparable number of children who showed a decrease in adherence of >10% during this time period (Figure 2). The same was the case for changes in adherence in the days after clinic visits, the week, and the month before and after clinic visits. This indicates that the pre-visit increase in adherence that we observed in a quarter of patients and visits in our study does not differ from the day-to-day and week-to-week background variation in adherence in this cohort. This was supported by the finding that the CV of adherence was comparable in children with and without a pre-visit increase in adherence.

Comparison With Earlier Work

The main difference between our study and earlier studies in which WCA was observed in children with

epilepsy, diabetes, and atopic dermatitis,⁶⁻⁸ is that overall adherence in our cohort was considerably higher. To our knowledge, the overall 1-yr adherence rate observed in our study (median 85%, IQR 70 to 92%) is the highest ever reported in a long-term study of adherence in a pediatric chronic condition. We previously demonstrated that adherence was the only significant determinant of the high level of asthma control observed in this cohort, and that the study cohort was not subject to selection bias recruiting parents with high adherence into the program.² Because studies in other settings have shown similarly good asthma control in children enrolled in comparable asthma management programs,^{4,13} the high adherence and good asthma control observed in our study are likely to be the result of the comprehensive, guideline-based, asthma management program we offered. The stability of adherence over time in this cohort suggests that after establishing successful self-management in children with asthma in such a program, follow-up visits have little additional value in increasing adherence further: a median adherence rate of 85% over a 1-yr period appears to be the maximum attainable level of adherence in these patients. There was a trend of borderline significance, however, that adherence improved after clinic visits in children with relatively poor adherence. Whether this is the result of the intervention during the clinic visit (reinforcing the importance of daily adherence to ICS use) or merely reflects regression to the mean cannot be distinguished in

this observational study. Because the number of follow-up visits in previous studies demonstrating clinically relevant WCA was comparable or higher than that in our study,^{6,8} it is unlikely that the frequent visits the patients made to our clinic prevented us from identifying clinically relevant WCA in this cohort.

Against the background of high overall rate and little variability of adherence over time, we found no evidence of clinically relevant WCA. In previous studies reporting WCA in children with epilepsy and atopic dermatitis, overall adherence rates and control of disease were considerably poorer,^{6,7} suggesting that WCA primarily occurs in children with low overall adherence to maintenance medication. Therefore, evidence of WCA in children on daily maintenance medication in pediatric chronic conditions could be regarded as a possible warning signal for low overall adherence rates.

Strengths and Limitations

The main strengths of this study are the use of long-term electronic assessment of adherence, and the setting of a clinic offering optimal, comprehensive, guideline-based asthma care. The Smartinhaler[®] has been validated for the assessment of adherence to daily inhaled medication use.¹² Such electronic adherence monitoring is far superior to parental report and pharmacy refill rates in reliably assessing adherence.^{14–16} The setting of our asthma clinic offering comprehensive, guideline-based asthma care allowed us to evaluate the importance of WCA in children receiving optimal care for their chronic condition.

We acknowledge the following limitations of our study. First, the relatively low proportion of children with poor adherence limited our power to detect a relationship between adherence levels and WCA. Second, because the overall level of asthma control in our cohort was high, our results may not be generalizable to children with severe, therapy-resistant asthma, or to children with other conditions receiving comprehensive care. Third, the observational nature of our study precludes causal inference. Finally, we have no data on adherence rates in our patients from the moment they were enrolled into our asthma management program.

In conclusion, this study shows no evidence of WCA in children with asthma receiving comprehensive, guideline-based asthma care. This is likely to be related to the high overall rate and limited background variability of adherence observed in such a setting. WCA may be a marker of poor overall adherence in chronic pediatric conditions.

REFERENCES

1. Drotar D, Bonner MS. Influences on adherence to pediatric asthma treatment: a review of correlates and predictors. *J Dev Behav Pediatr* 2009;30:574–582.
2. Klok T, Kaptein AA, Duiverman EJ, Brand PL. It's the adherence, stupid (that determines asthma control in preschool children). *Eur Respir J* 2014;43:783–791.
3. Jentzsch NS, Camargos P, Sarinho ES, Bousquet J. Adherence rate to beclomethasone dipropionate and the level of asthma control. *Respir Med* 2012;106:338–343.
4. Scott L, Morpew T, Bollinger ME, Samuelson S, Galant S, Clement L, O'Cull K, Jones F, Jones CA. Achieving and maintaining asthma control in inner-city children. *J Allergy Clin Immunol* 2011;128:56–63.
5. Stanford RH, Gilsenan AW, Ziemiecki R, Zhou X, Lincourt WR, Ortega H. Predictors of uncontrolled asthma in adult and pediatric patients: analysis of the Asthma Control Characteristics and Prevalence Survey Studies (ACCESS). *J Asthma* 2010;47:257–262.
6. Modi AC, Ingerski LM, Rausch JR, Glauser TA, Drotar D. White coat adherence over the first year of therapy in pediatric epilepsy. *J Pediatr* 2012;161:695–699.
7. Krejci-Manwaring J, Tusa MG, Carroll C, Camacho F, Kaur M, Carr D, Fleischer ABJ, Balkrishnan R, Feldman SR. Stealth monitoring of adherence to topical medication: adherence is very poor in children with atopic dermatitis. *J Am Acad Dermatol* 2007;56:211–216.
8. Driscoll KA, Johnson SB, Tang Y, Tang F, Deeb LC, Silverstein JH. Does blood glucose monitoring increase prior to clinic visits in children with type 1 diabetes. *Diab Care* 2011;34:2170–2173.
9. Modi AC, Rausch JR, Glauser TA. Patterns of nonadherence to antiepileptic drug therapy in children with newly diagnosed epilepsy. *JAMA* 2011;305:1669–1676.
10. Klok T, Kaptein AA, Duiverman EJ, Brand PL. High inhaled corticosteroids adherence in childhood asthma: the role of medication beliefs. *Eur Respir J* 2012;40:1149–1155.
11. Klok T, de Groot EP, Brouwer AFJ, Brand PLP. Follow-up of children with asthma. *Eur Respir Mon* 2012;56:210–223.
12. Burgess SW, Wilson SS, Cooper DM, Sly PD, Devadason SG. In vitro evaluation of an asthma dosing device: the smart-inhaler. *Respir Med* 2006;100:841–845.
13. Gruchalla RS, Sampson HA, Matsui E, David G, Gergen PJ, Calatroni A, Brown M, Liu AH, Bloomberg GR, Chmiel JF, et al. Asthma morbidity among inner-city adolescents receiving guidelines-based therapy: role of predictors in the setting of high adherence. *J Allergy Clin Immunol* 2009;124:213–221.
14. Burgess SW, Sly PD, Morawska A, Devadason SG. Assessing adherence and factors associated with adherence in young children with asthma. *Respirology* 2008;13:559–563.
15. Jentzsch NS, Camargos PA, Colosimo EA, Bousquet J. Monitoring adherence to beclomethasone in asthmatic children and adolescents through four different methods. *Allergy* 2009;64:1458–1462.
16. Schultz A, Sly PD, Zhang G, Venter A, Devadason SG, Le Souef PN. Usefulness of parental response to questions about adherence to prescribed inhaled corticosteroids in young children. *Arch Dis Child* 2012;97:1092–1096.