Primary Care Respiratory Journal (2008); 17(2): 90-96

Primary Care RESPIRATORY JOURNAL
www.thepcrj.org

ORIGINAL RESEARCH

Implementation of an asthma guideline for the management of childhood asthma in general practice: a randomised controlled trial

***Wanda Hagmolen of ten Have[a,c], Norbert J van den Berg[a,c], Job van der Palen[b], Wim MC van Aalderen[c], Patrick JE Bindels[d]**

[a] Department of Paediatrics, Flevohospital, Almere, The Netherlands
[b] Department of Epidemiology, Medical Spectrum Twente, Enschede
[c] Department of Pediatric Pulmonology, Emma Children's Hospital, Academic Medical Center, University of Amsterdam
[d] Department of General Practice, Academic Medical Center, University of Amsterdam

Received 18th June 2007; revised version received 25th November 2007; accepted 9th January 2008

Abstract

Aim: The aim of the study was to assess, in a randomised, controlled design, the efficacy of different strategies to improve childhood asthma management.

Method: Three interventions directed to three groups of general practitioners were compared: Group A – dissemination of a guideline; Group B – guideline dissemination plus an educational session; Group C – guideline dissemination, educational session, plus individualised treatment advice based on airway hyperresponsiveness (AHR) and symptoms. Efficacy of the three strategies was assessed by evaluating change in AHR in 362 children after one year.

Results: The overall between-group effect of the severity of AHR was not significantly different (P=0.09). In Groups A and C an improvement was seen in nocturnal symptoms (P=0.02) and in Group C an improvement was seen in the prescription of inhaled corticosteroids (P=0.03).

Conclusion: In this study, the combined implementation strategy did not show a clear improvement in the management of children with asthma in general practice.

W Hagmolen of ten Have, *et al. Prim Care Resp J* 2008; **17**(2): 90-96.
doi:10.3132/pcrj.2008.00011

Keywords bronchial hyperreactivity, asthma, child, paediatric, general practice, guideline adherence

See Appendix A, B and C, at www.thepcrj.org

Introduction

In 2006, the revised Global Initiative for Asthma (GINA) guideline was published, which specified the overall goal of achieving and maintaining clinical control in patients with asthma.[1] Recent studies show that a substantial proportion of asthmatic children are still inadequately treated.[2,3]

The majority of children with asthma in the Netherlands are treated by the general practitioner (GP). A smaller group is treated by a paediatrician or a paediatric pulmonologist. In 1998, the Dutch College of General Practitioners developed a national guideline for children with asthma treated in general practice,[4] which was updated in 2006.[5] Among all children presenting with persistent respiratory symptoms, it is the GP's task to select those with persistent mild to severe asthma who, according to asthma guidelines, require treatment with an inhaled corticosteroid (ICS). Diagnosis and monitoring of asthma in general practice are primarily based on symptom severity and, less frequently, the level of airflow limitation. However, assessment of asthma severity and the level of control is difficult when based on symptoms alone.[6] Airway hyperresponsiveness (AHR) reflects the severity of asthma,[7] is a tool for monitoring asthma treatment,[8] and predicts its

* Corresponding author: Medical Spectrum Twente, Department of Pulmonology, Haaksbergerstraat 55, 7513 ER Enschede, The Netherlands
Tel: +31 (0)53 4872610 E-mail: wandahoth@hotmail.com

outcome.[9] However, in real-life general practice, therapeutic decisions are not based on the degree of severity of AHR because AHR assessment is not readily available.

This study investigates whether written treatment advice to the GP – based on symptoms, medication use, lung function, and the severity of AHR – resulted in an improvement in children's asthma after one year.

Methods

Setting

In Almere, the Netherlands, a centralised health care organisation with 18 health care centres (HCC) and approximately 100 GPs was approached. All agreed to participate in the study. The medical ethics committee of the Flevohospital in Almere approved the study.

Patient selection

Children from the HCCs, 7 to17 years old, were eligible for this study if at least two prescriptions of β_2-agonists or ICS were prescribed in the year before invitation. All GPs and pharmacies gave official permission to search in a joint data registration system for the selection of patients. Names and addresses of 1549 eligible children were thus obtained. Children and their parents were invited by their GP to participate in the study. After obtaining written consent we obtained the medication lists to calculate medication usage of the participants. Children who were also treated by a pediatrician or pulmonologist were excluded, as were children who had a disability, other relevant diseases, conductive disorders, or disturbing psychological problems. Informed consent was obtained from 539 children (Figure 1). Children were recruited from December 2000 until April 2002. Follow-up finished in August 2003.

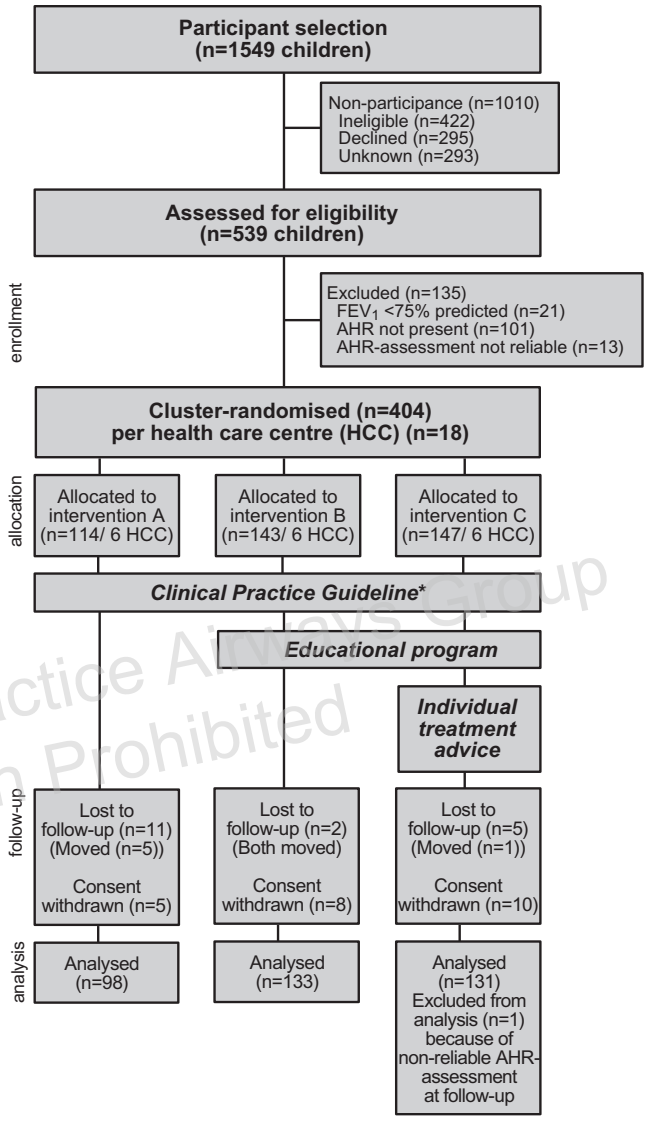
Randomisation

Randomisation of the intervention was on the HCC level. The main argument for randomising the HCCs (n=18) instead of GPs (n=±100) was the possibility of contamination bias due to collaboration between GPs working within one HCC, and also the possibility that patients within one HCC might visit other GPs within that same HCC. The procedure of randomisation was performed by JvdP who was not familiar with the location of the HCCs or the GPs working in those centres. Randomisation took place before children were invited. The studied strategies could not be blinded.

Sample size

The sample size was calculated such that a difference in the degree of AHR equal to one doubling dose could be detected assuming a standard deviation in PD_{20} (Provocative Dose of methacholine which gives a 20% fall in forced expiratory volume in one second [FEV_1] compared to baseline) of 2.5 doubling doses with a power of 80% and a significance level of 0.05. We assumed that the intra-cluster correlation coefficient (ICC) was very low (0.01), mainly because we assumed that GPs do not often consult each other about the treatment of asthma in children. With 18 clusters (HCCs) we needed 20 children in each cluster, making a total number of 360 children. We planned to recruit a total of 600 children.

Figure 1. Design of the study and flow diagram of participants in accordance with CONSORT (Consolidated Standards of Reporting Trials). HCC = Health Care Centre.



patients) were randomised by HCC to one of three study strategies – Groups A, B, and C. An extract of the latest updated version of the Dutch College of General Practitioner's clinical practice guideline (CPG) concerning the treatment of childhood asthma was sent to all GPs (see Appendices A and B at www.thepcrj.org). An invitation for a 2-hour educational session on asthma and inhalation technique was sent to GPs in groups B and C. In addition to the CPG and the educational session, GPs in group C received written individualised treatment advice based on symptoms, the use of medication, lung function, and the severity of AHR. This advice was standardised and based on the treatment algorithm used by Sont *et al*.[7] If the child had moderate to severe AHR (PD_{20} ≤300 mcg) independent of asthma symptoms, GPs of group C were advised to intensify the current treatment strategy. There were three options: start with an ICS twice daily; increase the dose; or add a long-acting β_2-agonist. GPs of children with mild AHR and frequent symptoms (> 3 days/2 weeks) also received the advice to intensify therapy. In the remaining cases GPs were advised to maintain current treatment policy or to decrease medication if possible. All children and their parents were informed about the result of the inhalation challenge test, but they were not given treatment advice. We encouraged parents to consult their GP in order to give the GP the opportunity to optimise asthma treatment according to the current guidelines. Primary and secondary outcomes were re-assessed one year after the primary evaluation in those children who had responded positively to the inhalation challenge test at baseline.

Primary outcome parameter

The primary study outcome was the change in AHR in children after one year. Spirometric tests were performed according to the Spirometry Flow/Volume program (version 4.34, Jaeger, Würzburg, Germany). The best result of three FEV_1 attempts was used for analysis. A single concentration methacholine challenge test was performed when FEV_1% predicted was ≥75%. Methods, validity and reliability of the test are described elsewhere.[10] The degree of AHR was expressed as a PD_{20}, a provocation dose that induces a 20% fall in FEV_1 from baseline. Moderate to severe AHR was defined as a PD_{20} ≤300 mcg as per Sont[7], Sterk,[11] *et al*.

Secondary outcome parameters

Secondary outcome parameters were changes in asthma symptom scores, peak expiratory flow (PEF) variability, FEV_1, and usage of asthma medication. The frequency of asthma-related symptoms, cough, wheeze, and shortness of breath were scored twice daily ('0' (no complaints), '1' (once a day), '2' (more than once a day), '3' (whole day)) in a two-week diary. The symptoms were scored by the child, sometimes with the help of a parent. We calculated total symptom score (range 0-18), night symptom score (range 0-9), and the number of symptom-free days (range 0-14). Children were provided with a 'Personal Best' PEF Meter and instructed to perform three measurements of PEF in the morning and in the evening, prior to the use of salbutamol. PEF variability was calculated as the best evening PEF value minus the best morning PEF value divided by their mean value. The number of prescribed inhalers for ICS and β_2-agonists was obtained from electronic medication lists.

Table 1. Baseline characteristics of 362 children with asthma treated in general practice.

	Cohort A	Cohort B	Cohort C
Number of participants	98	133	131
Age, years	10.8 (2.5)	10.6 (2.5)	11.0 (2.5)
M/F ratio	1.4	1.3	1.1
Duration of astma, years	6.5 (3.4)	6.4 (3.3)	6.4 (3.6)
Age at onset asthma, years	4.3 (3.4)	4.2 (3.3)	4.6 (3.8)
Lung function			
AHR, log transformed PD_{20}	8.0 (5-12)	7.8 (5-12)	7.7 (5-12)
Severe AHR	24 (24)	28 (21)	31 (24)
Moderately severe AHR	33 (34)	52 (39)	44 (34)
Mild AHR	21 (21)	26 (20)	26 (20)
Borderline response	20 (20)	27 (20)	30 (23)
FEV_1, % of predicted	96.2 (10)	96.5 (11)	96.6 (12)
PEF variability, %	8.8 (5.0)	9.4 (5.4)	8.5 (5.2)
Asthma symptoms			
Symptom score, day + night	0.8 (0-9)	1.0 (0-8)	0.8 (0-10)
Nocturnal symptom score	0.2 (0-5)	0.3 (0-3)	0.2 (0-5)
Symptom free days	8.4 (0-14)	6.0 (0-14)	8.0 (0-14)
Asthma medication			
ICS from medication list, puffs/day	0.3 (0-3)	0.3 (0-2)	0.4 (0-2)*
β_2-agonist from medication list, puffs/day	0.3 (0-3)	0.5 (0-6)	0.5 (0-5)
β_2-agonist score in diary, puffs/day	0.07 (0-4)	0.04 (0-4)	0.08 (0-5)
Atopic symptoms			
Eczema (%)	42	38	42
Allergy (%)	70	70	71
Rhinitis (%)	52	52	57
Asthma in 1st degree relatives (%)	65	66	60

Data are presented as numbers of children with percentages of subgroup, as median values with range, or as means with ± SD. * p<0.05.

Statistical analysis

If FEV_1 was <75% of predicted before the challenge test, PD_{20} was set at 14 mcg. If the FEV_1 fell ≥20% within the first provocation step, PD_{20} was set to 27 mcg, the sensitivity of the Masterscope. If PD_{20} was not reached within the provocative range, it was set at the maximal provocative dose of 1920 mcg. For the ANOVA mixed model analyses PD_{20} was log transformed.

Table 2. Results of re-implementation of the guideline.

	End of study (baseline adjusted)			Overall treatment effect
	A	B	C	P-value
Log PD_{20}	8.3 (0.2) 0.3	8.2 (0.2) 0.2	8.7 (0.2) 0.7 **	0.09
FEV_1 % of predicted	96.7 (1.0) 0.1	95.6 (0.9) -1.0	96.8 (0.9) 0.2	0.5
PEF variability %	7.5 (0.5) -1.3 *	7.2 (0.4) -1.7 **	7.2 (0.4) -1.6 **	0.4
Total Symptom Score	0.9 (0.2) -0.6 *	1.2 (0.2) -0.3	1.0 (0.2) -0.5 *	0.08
Nocturnal Symptom Score	0.3 (0.1) -0.24 *	0.5 (0.1) -0.07	0.4 (0.1) -0.15 *	0.02
Number of symptom free days	8.6 (0.5) 1.5 *	8.5 (0.5) 1.3 *	9.1 (0.5) 1.9 **	0.1
ICS, ppd (prescribed in 1 year)	0.4 (0.05) -0.1	0.5 (0.05) 0.01	0.6 (0.05) 0.1 *	0.03
β_2-agonist, ppd (GP, 1 yr)	2.6 (0.3) 0.06	2.3 (0.3) -0.2	2.1 (0.3) -0.4	0.4
β_2-agonist, ppd (diary)	0.45 (0.1) -0.07	0.43 (0.08) -0.09	0.29 (0.08) -0.24*	0.2

Data are presented as means (adjusted for baseline) with the standard error between brackets and the difference between means (end of study minus baseline) presented in the row below. Significant changes within the cohort are indicated: * = p<0.05; **= p<0.001. Significant effects between the cohorts are presented in the last column. Log PD_{20} is the logarithm of the provocation doses methacholine provoking a 20% fall in FEV_1. Total Symptom Score is the mean score per day for cough, wheezing and dyspnoea in diary. The Overall Nocturnal Symptom Score is the mean score during the night. The Asthma Nocturnal Symptom Score includes dyspnoea and wheezing only (without coughing). Inhalation Corticosteroids (ICS) and β_2-agonists are presented in number of puffs per day (ppd). For β_2-agonists two different assessments are included: the first obtained from data files of the health care centre (prescriptions during one year prior the start of the study and one year during study); the second is the mean number of puffs per day used during the diary period.

Results were analysed on an intention-to-treat basis. Mixed model ANOVA analyses were performed in SAS (Table 2 and 3). The analyses accounted for the effects of clustering. Except for the mixed model analyses, all other statistics were performed in SPSS version 10.5 (Table 1).

In a post-hoc analysis, we aggregated Groups A and B because we failed to reach the calculated sample size in Group A. Another reason was that in this way the additional effect of the individual treatment advice could be studied.

Table 3. Results of re-implementation of the guideline (second analysis).

	End of study (baseline adjusted)		Overall treatment effect
	A & B	C	P-value
Log PD_{20}	8.3 (0.2) 0.27 *	8.7 (0.2) 0.7 **	0.03
FEV_1 % of predicted	96.0 (0.7) -0.5	96.8 (0.9) 0.2	0.5
PEF variability %	7.3 (0.3) -1.5 **	7.2 (0.4) -1.6 **	0.5
Total Symptom Score	1.1 (0.1) -0.4 *	1.0 (0.2) -0.5 *	0.6
Nocturnal Symptom Score	0.4 (0.1) -0.14 *	0.4 (0.1) -0.15 *	0.2
Number of symptom free days	8.6 (0.4) 1.4 **	9.1 (0.5) 1.9 **	0.3
ICS, ppd (prescribed in 1 year)	0.4 (0.03) -0.03	0.6 (0.05) 0.1 *	0.02
β_2 sympaticomimetic, ppd (GP,1 yr)	2.5 (0.2) -0.1	2.1 (0.3) -0.4	0.3
β_2 sympaticomimetic, ppd (diary)	0.44 (0.06) -0.09	0.29 (0.08) -0.24 *	0.2

Data are presented as means (adjusted for baseline) with the standard error between brackets and the difference between means (end of study minus baseline) presented in the row below. Significant changes within the cohort are indicated: * = p<0.05; **= p<0.001. Significant effects between the cohorts are presented in the last column. Log PD_{20} is the logarithm of the provocation doses methacholine provoking a 20% fall in FEV_1. Total Symptom Score is the mean score per day for cough, wheezing and dyspnoea in diary. The Overall Nocturnal Symptom Score is the mean score during the night. The Asthma Nocturnal Symptom Score included dyspnoea and wheezing only (without coughing). Inhalation Corticosteroids (ICS) and β_2-agonists were presented in number of puffs per day (ppd). For β_2-agonists two different assessments were included: the first obtained from data files of the health care centre (prescriptions during one year prior the start of the study and one year during study); the second is the mean number of puffs per day used during the diary period.

Results

Implementation strategies

One hundred and five GPs received an update of the CPG. Of the 68 GPs invited, 21 GPs from Group B (62%) and 19 from Group C (56%) attended the educational session. The 38 GPs of group C received 197 individualised treatment advices for their patients: the median number of treatment advices per GP was 5 (range: 1-13).

General characteristics

Of 539 children, 404 with a positive inhalation challenge test were included in the study. The study was completed by 362

children (90%; 202 boys (56%); median age 10 years). There were no significant differences in baseline characteristics between the three study groups, except for the number of prescribed puffs of inhaled corticosteroids (ICS) which was higher in patients in group C (Table 1). Only 13% of the children (n=53) were prescribed a mean of one or more puffs ICS per day.

Results of implementation strategies on primary and secondary outcomes

Results of the three intervention strategies are presented in Table 2. For the primary outcome measure, AHR, the overall effect between the groups did not reach significance (P=0.09). Also, the overall asthma symptom score was not significantly different (P=0.08). We show a significant difference between groups in nocturnal symptoms (P=0.02) and the use of ICS (P=0.03). Nocturnal symptoms were significantly decreased in Groups A and C. However, the largest absolute improvement was seen in Group A. The use of ICS was statistically significantly increased in Group C only.

Despite the fact that we did not show a significant difference in our primary outcome between Group A, B and C, there were striking within-group differences. Group C was the only group in which AHR improved significantly during the study year. Moreover, this improvement in AHR coincided with an increased mean use of ICS from 0.55 to 0.63 puffs per day (P=0.04), and improvements in PEF variability, all symptom scores, and medication usage. Although improvements in PEF variability and symptom scores were also seen in Groups A and B, these improvements were not associated with improvements in AHR and ICS usage.

At the end of the study the use of ICS was only slightly improved as compared to the start of the study, with 64 children (17.5%) using one or more puffs ICS per day. Within the three groups, the number of children who were prescribed regular ICS treatment (mean > 1 puff per day) decreased in Group A from 11 to 9%, increased in Group B from 11 to 13%, and increased in Group C from 16 to 25%.

Post-hoc analysis

Table 3 shows the results of the post-hoc analysis in which we aggregated Groups A and B. There were no statistical differences at baseline between these two groups. In this analysis the between-group difference reached significance for the primary outcome (P=0.03). The between-group difference remained significant for the use of ICS (P=0.02). Other secondary outcomes were not different.

Discussion

The aim of the study was to evaluate whether the introduction of a national guideline for the treatment of asthma in children with three different implementation programs was effective with regard to the level of asthma control in children. The general hypothesis was that a combined strategy including the distribution of the guideline, a single educational session, and individualised treatment advice, would be superior in improving asthma control in general practice compared to the distribution of the guideline and the educational session alone. We did not achieve our study aim: there was no significant difference between the three strategies with respect to the primary outcome (AHR). There was a significant difference in two secondary outcomes; groups A and C performed best with respect to the nocturnal symptoms score and Group C with respect to the use of ICS.

These results might suggest that asthma treatment guided by the assessment of AHR does not benefit control of asthma in children – an explanation that is supported by a recently published study by Nuijsink *et al*.[12] However, the outcome of this study is not satisfactory because the 'combined strategy' intervention had positive and consistent (but not significant) effects towards improved asthma control in the participating children. This consistency was not seen in the other two groups.

It is possible that we dealt with a type-2 error, which means that we rejected the hypothesis falsely due to sample sizes being too small. This is supported by a secondary analysis of our data, in which we aggregated the data from Groups A and B (Group AB) because we did not reach the calculated sample size in Group A in the primary analysis. In this analysis the improvement in AHR in Group C differed significantly from Group AB.

Methodological issues and considerations

The study is a randomised controlled trial, which is the best method (by consensus) to investigate a hypothesis as formulated in our study. Cluster-randomisation restricted the statistical power of the analysis. The intervention in Group C in our study was controlled but could not be blinded, which is a disadvantage of the study. In addition, the result of the challenge test could not be blinded to the parents who were interested in the outcome. Both facts may have positively influenced the level of asthma control in Groups A and B and subsequently reduced the contrast with Group C.

In addition, improvement of asthma control is a highly conditional event: participants had to visit their GP during the study year (which was strongly advised, but voluntary); the GP had to adhere to the asthma guideline, and in Group C the GP had to agree with the treatment advice given; and the child (or parent) had to adhere to asthma therapy as initiated by the GP. The chain of steps, the number of involved individuals (participant, parent, GP) and the subsequent accumulation of uncertainties decreased the probability of achieving improved asthma control in the child. However, these conditions were applicable to all three study groups.

Each GP in group C received, dependent on the number of participants, a median number of five treatment advices during the study year (one per child). The learning effect of such a small number of treatment advices will be too low and not enough to influence effectively and persistently the knowledge and skills of the GP. It is therefore likely that continuation of the implementation strategies, with repeated attention to treatment plans, would be more effective in the long term.

Treatment strategy

The treatment advice given to GPs in Group C was based on a treatment strategy introduced by Sont and colleagues that was aimed at reducing AHR.[7] They showed convincingly that their AHR-guided strategy led to better control of asthma in adults by means of a more accurate increased dosage of ICS, resulting in a 1.8-fold decrease in exacerbation rate (P=0.03), an increased FEV_1, and a reduction of the thickness of the subepithelial reticular layer, as compared with a control group who were treated according to an asthma guideline similar to the GINA guideline. In children, we expected that an AHR-driven treatment approach would also be superior to a symptom-driven treatment approach in reaching optimal asthma control in children because symptoms of asthma are often difficult to judge in children.[13] Also, other studies in adults and in children have shown that treatment based on symptoms only is inferior to treatment based on an additional "inflammatory" marker. Green *et al*. demonstrated that treatment based on sputum eosinophils resulted in a decrease of asthma exacerbations compared to treatment based on symptoms alone.[14] Nuijsink *et al*. demonstrated that an AHR-driven asthma treatment, as compared with the conventional symptom-driven strategy, prevented long-term worsening of pre-bronchodilator FEV_1, specifically in a large subgroup of children who showed AHR and low symptom scores.[12] Smith *et al*. in adults,[15] and Pijnenburg *et al*. in children,[16] showed beneficial effects when information about exhaled nitric oxide was used in addition to treatment based on symptoms alone. However promising, the feasibility of using exhaled nitric oxide as guidance for asthma treatment in general practice has only just begun to be studied.[17]

Implementation techniques

We introduced three cumulative strategies. The first two strategies were only aimed at transferring information, one by means of the dissemination of the guideline and the other by means of a single educational session. Information transfer is an essential component of any implementation strategy, but additional techniques are usually needed to achieve changes in clinical practice.[18] With the development of the Dutch asthma guideline in 1998 no efforts at all were made to implement the guideline in general practice. Therefore, two 'control' groups (A and B) were created in this study to be able to observe carefully the effects of dissemination (Group A) and dissemination and implementation of the guideline through education (Group B). In Group C we provided very specific, individualised information on the level of asthma control and the degree of AHR, and additionally we gave feedback on current asthma therapy (inhalation technique and current medication usage). In addition, the latter implementation strategy promoted communication between the GP and the paediatrician and subsequently, it might have increased the social influence occurring between the two fields. Furthermore, the implementation strategy is a dynamic method and therefore suitable for adaptation when new insights in asthma therapy based on new studies become available. Finally, with the implementation of the combined strategy (guideline, educational session and individual treatment advice), the knowledge and skills of the GP on asthma treatment should increase in the long run. Two main conditions are necessary for the implementation of the strategy: firstly, a working network between paediatricians and GPs; and secondly, availability of a lung function laboratory. Furthermore, it is necessary to evaluate and to deal with local barriers and settings.[18]

In the literature, randomised and controlled studies investigating the implementation of asthma guidelines are scarce and have shown varying levels of success.[19-21] Jans and colleagues set up a non-randomised but controlled before-and-after implementation study to evaluate the implementation of a national guideline on the management of adult patients with asthma or chronic obstructive pulmonary disease (COPD) in general practice.[21] The comprehensive implementation program included the identification of barriers, feedback, multiple education sessions, and peer review. The implementation strategy had a positive effect on PEF variability after one year as compared to the reference group, especially amongst patients with asthma or allergy or a high educational level. Improvement of respiratory symptoms was only found in the intervention group.

Conclusions

This study was set up to improve the level of asthma control in children in general practice by means of the implementation of a current asthma guideline. The implementation of the combined strategy did not succeed in improving AHR and asthma symptoms as compared to both control groups. However, a trend towards improved asthma control was present in the 'combined strategy' group. We conclude that, to improve asthma management in children in general practice, even more efforts are needed than those explored in our study. Key messages and recommendations for the future are:

- Because of the lack of significance, this randomised controlled study shows no benefit from a combination of strategies, as compared to single strategies – focused on GPs – which aimed to achieve improved control of asthma in children.
- New randomised and controlled studies are needed in order to investigate extended or new strategies for improving asthma control in children.

Funding

This study was sponsored by an unrestricted research grant from GlaxoSmithKline.

Acknowledgements

We would like to express our gratitude to all patients and their parents, and to the Health Care Organization 'Zorggroep Almere', for their participation in the study. We would like to thank Paul Mulder separately, for his statistical assistance.

Conflict of interest statement

There are no competing interests for any of the authors.

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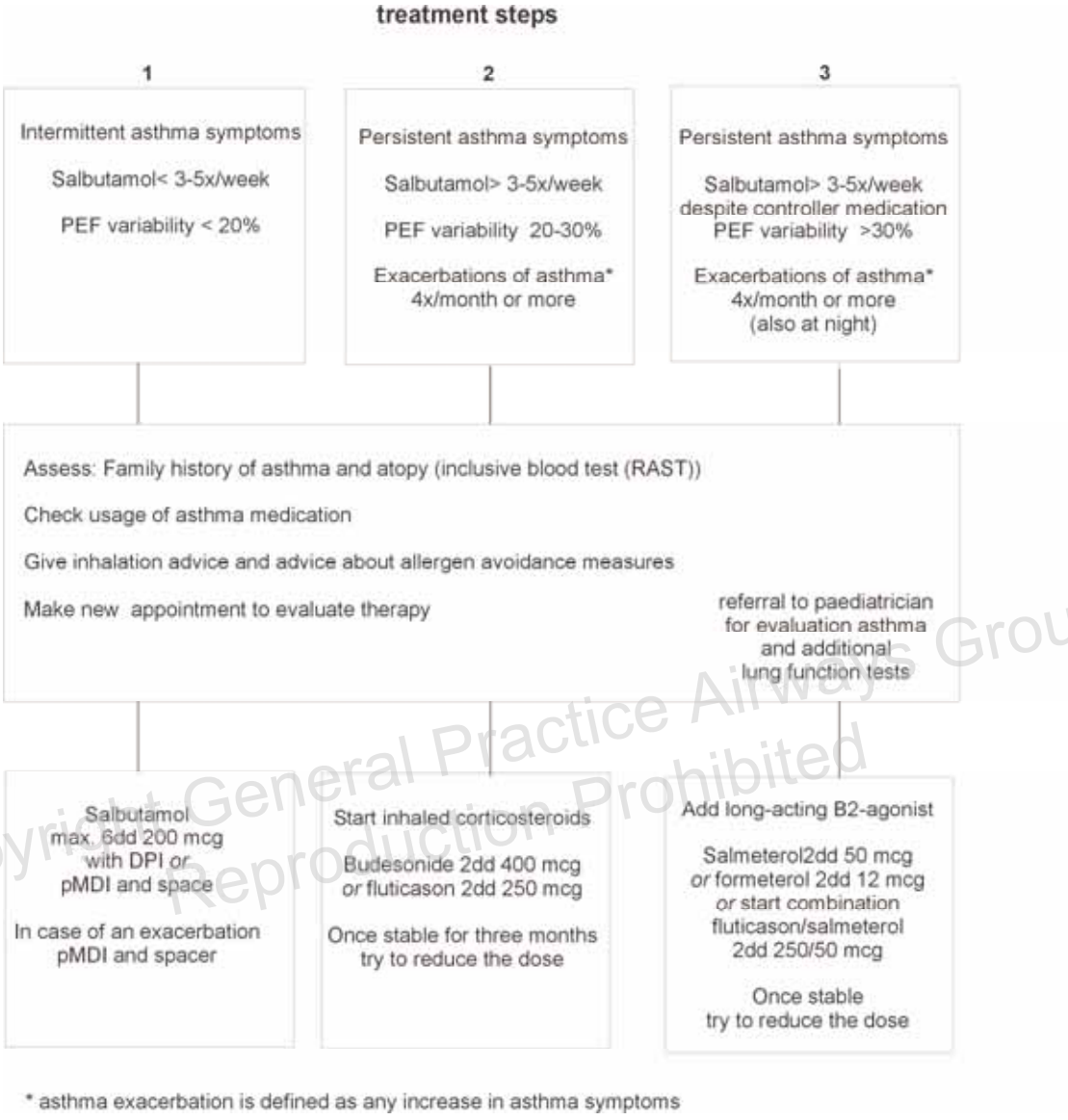
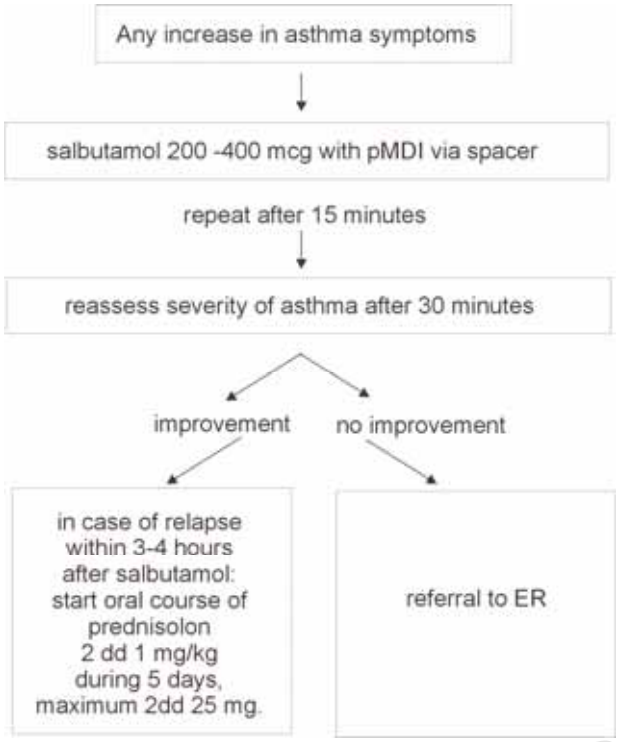
Appendix A: Management of recurrent childhood asthma



Flowchart 1. Presentation of clinical pathway for general practitioners for the management of recurrent childhood asthma as recommended in the distributed asthma CPG. Drawn for publication. For more detailed information see guideline.[4] PEF variability is defined as percentage of change in PEF before and after salbutamol.

Appendix B: Acute asthma guideline for children



Flowchart 2. Presentation of clinical pathway for general practitioners for children with an exacerbation of asthma as recommended in the distributed asthma CPG. Drawn for publication. For more detailed information see guideline.[4]

Appendix C: Paper contents as per CONSORT recommendations

PAPER SECTION And topic	Item	Descriptor	Reported on Page #
TITLE & ABSTRACT	1	How participants were allocated to interventions (*e.g.*, "random allocation", "randomized", or "randomly assigned").	Figure 1, page 2
INTRODUCTION Background	2	Scientific background and explanation of rationale.	Page 1-2
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	Page 2
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	Page 2 and 3
Objectives	5	Specific objectives and hypotheses.	Page 2
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors).	Page 3 and 4
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	Page 2
Randomization -- Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (*e.g.*, blocking, stratification)	Page 2
Randomization -- Allocation concealment	9	Method used to implement the random allocation sequence (*e.g.*, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	Page 2
Randomization -- Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	Page 2
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	Not applicable
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.	Page 3 and 4
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	Page 2
Recruitment	14	Dates defining the periods of recruitment and follow-up.	Page 2
Baseline data	15	Baseline demographic and clinical characteristics of each group.	Table 1, page 3
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (*e.g.*, 10/20, not 50%).	Page 3 and 4
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (*e.g.*, 95% confidence interval).	Page 4 and 5
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	Page 4 and 5
Adverse events	19	All important adverse events or side effects in each intervention group.	Not applicable
DISCUSSION Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	Page 5 and 6
Generalizability	21	Generalizability (external validity) of the trial findings.	Page 6
Overall evidence	22	General interpretation of the results in the context of current evidence.	Page 6