

Randomized Controlled Trial of Fluticasone in Preschool Children with Intermittent Wheeze

Caroline S. Pao and Sheila A. McKenzie

Department of Respiratory Paediatrics, The Royal London Hospital, Whitechapel, London, United Kingdom

Preschool children with intermittent wheeze are often prescribed inhaled corticosteroids, although there is no proven benefit. Measurement of airway resistance by the interrupter technique can be used to objectively assess response to treatment. If lung function improves, treatment may be justified. Children with intermittent wheeze aged 2 to ≤ 5 years of age completed a 6-week randomized controlled crossover trial of fluticasone propionate (100 μg , twice daily), followed by a 10-week parallel extension. The relationships between changes in resistance, serum immunoglobulin E and sensitization measured by skin prick testing were investigated. Sixty-one children completed the crossover trial and 44 (72%) completed the extension. After 6 weeks, geometric mean change in resistance was -16.0% (95% confidence interval, -7.0 to -25.0% , $p = 0.003$) in sensitized children and -3.5% (95% confidence interval, $+0.7$ to -7.6% , $p = 0.1$) in nonsensitized children. Changes in resistance were unrelated to immunoglobulin E. Sixteen weeks after stopping fluticasone, resistance returned to baseline. This is the first study of preschool children with intermittent wheeze that has related changes in lung function on treatment to aeroallergen sensitization. Lung function improved in sensitized children and deteriorated after stopping treatment. Treatment with inhaled steroids may be justified in sensitized children.

Keywords: asthma; child, preschool; airway resistance; skin test

The prevalence of preschool asthma has increased (1, 2). Childhood asthma guidelines recommend prescribing inhaled corticosteroids (ICS) for children with daily asthmatic symptoms (3), but their benefit in preschool children with episodic wheeze without interval symptoms is controversial (4, 5). Approximately 65% of preschool wheeze is episodic and only one-third of wheezy preschool children will have persistent wheeze in later childhood (6). In 1999, almost 60% of UK asthmatic preschool boys were prescribed ICS by their family doctor (7). However, a Cochrane review found no evidence to support maintenance ICS in episodic mild virally induced wheeze of childhood (8).

Different mechanisms for wheeze in early childhood have been proposed (9, 10). Nonatopic children who wheeze have been shown to have impaired premorbid lung function, suggesting they have smaller than normal airways, predisposing them to wheeze. Atopic children with early-onset asthma have normal premorbid lung function, suggesting normal airway caliber. Persistent inflammation may lead to airway nar-

rowing with persistence of symptoms. It is proposed that early treatment with ICS may prevent permanent loss of pulmonary function (11) and prevent persistence of bronchial hyperresponsiveness (BHR) and chronic asthma (12). These are compelling reasons to prescribe ICS.

Previous intervention studies of preschool children with intermittent wheeze have used subjective outcome measures, such as change in reported symptoms and use of bronchodilator drugs. A clinical trial powerful enough to detect a change in symptoms in children with episodic wheeze would be too long to be realistic, especially as adherence is poor (13). Moreover, parental reports of children's respiratory symptoms may be inaccurate (14). Measurements of airway resistance (R_{int}) and bronchodilator responsiveness (BDR), using the interrupter technique, are suitable for lung function testing in young children (15). Airway resistance is inversely proportional to airway caliber and therefore children with narrow airways would be expected to have high airway resistance. Using R_{int} , it should be possible to demonstrate whether lung function improves in children taking ICS. If this is so, prescription of ICS to these children may be justified.

Older subjects with wheeze are more likely to be sensitized to aeroallergens, and ICS are known to reduce allergic airway inflammation. Infants with both persistent and intermittent wheeze whose parents report a personal history consistent with atopy have benefited symptomatically from treatment with ICS (16). Will change in lung function in preschool children with recurrent intermittent wheeze treated with ICS be related to atopic status?

Published data show improvement in lung function and symptoms after 4 weeks of ICS (17–19) and a return to pretreatment values 4 weeks after stopping ICS (20). These observations suggest that a 6-week crossover study would be likely to provide meaningful results, providing adequate wash-in and washout periods.

PURPOSE OF STUDY

1. To compare changes in R_{int} , BDR, and symptom scores in preschool children with recurrent intermittent wheeze treated with ICS and placebo.
2. To relate changes in lung function at 6 weeks to atopic status.
3. To measure changes at 16 weeks of ICS compared with 6 weeks of ICS. This extension was included to investigate whether a longer period of treatment would be effective.
4. To measure changes on placebo 16 weeks after stopping ICS.

METHODS

This was a single-center, randomized, double-blind, 6-week crossover trial of fluticasone propionate (FP), 100 μg twice daily, compared with placebo with a 10-week parallel extension. Primary outcomes were changes in R_{int} and BDR. Lung function changes were related to serum total immunoglobulin E (IgE) and skin prick test (SPT) positivity. A secondary outcome was change in symptom scores.

(Received in original form March 28, 2002; accepted in final form June 22, 2002)

Supported by an NHS R&D grant supervised by the National Asthma Campaign. Inhalers supplied by GlaxoSmithKline.

Correspondence and requests for reprints should be addressed to Sheila A. McKenzie, M.D., Department of Respiratory Paediatrics, Fielden House, The Royal London Hospital, Whitechapel, London E1 1BB, United Kingdom. E-mail: s.a.mckenzie@qmul.ac.uk

This article has an online data supplement, which is accessible from this issue's table of contents online at www.atsjournals.org

Am J Respir Crit Care Med Vol 166, pp 945–949, 2002

DOI: 10.1164/rccm.200203-265OC

Internet address: www.atsjournals.org

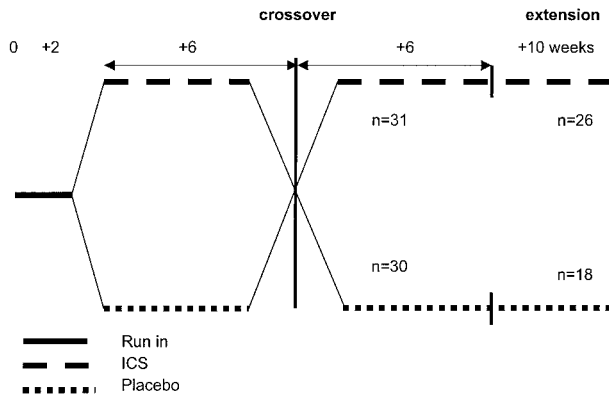


Figure 1. Study protocol.

R_{int} was measured as previously described (21) before (baseline) and 20 minutes after administration of 400 μ g of salbutamol. BDR was defined as the ratio of baseline to postsalbutamol R_{int} . Drug and placebo were administered via unmarked metered-dose inhaler and spacer (Volumatic; Allen and Hanburys, Uxbridge, UK).

After recruitment there was a 2-week run-in period to ensure that parents understood how to fill in the symptom diary. Subjects were retested 2 weeks later and randomized, using random number generation, to receive ICS or placebo. Crossover was at 6 weeks. R_{int} , BDR, and height were measured at each visit. IgE was measured and SPT was performed at the end of crossover. Willing families also completed a 10-week parallel extension of the second crossover arm to ensure that any longer term benefit was not missed. These children ended the study having had either 16 weeks of ICS or 16 weeks of placebo (Figure 1). If a child had signs of a respiratory infection testing was deferred for 1 week.

As "wheeze" is poorly understood by our population (14), a pictorial symptom diary was designed and successfully piloted for use throughout the study (see Figure E1 in the online data supplement). Parents scored 1 each for daytime and nighttime cough, and daytime and nighttime difficulty in breathing (wheezing) and relief by salbutamol scored 1 for one to four puffs for persistent cough and 2 for more than four puffs for wheeze/difficulty in breathing (maximum daily score, 6). Scores were calculated for 2 weeks before visits to allow time for therapeutic effect and washout. The washout period was therefore 4 weeks.

SPT was to house dust mite, cat and dog dander, grass, and *Aspergillus*, with positive (histamine) and negative (saline) controls (ALK-Abelló, Hørsholm, Denmark). Using a standard lancet prick, wheals 2 mm or more than the negative control in children 4 years of age or younger, or 3 mm or more for the others, were considered positive (22).

Consecutive referrals of children aged 2 to 5 years of age or less with recurrent (2 or more episodes in the last 6 months), intermittent (with no interval symptoms), and previously doctor-observed wheeze were recruited between January 1999 and February 2000. Baseline demographic data were recorded. Eligible children had no wheeze or corticosteroids for 4 weeks before recruitment. Those unable to complete the tests or with a coefficient of variation of greater than 20% for a R_{int} measurement or with other respiratory or otolaryngeal pathology were excluded. Written informed consent was obtained and local ethics board approval was granted.

Subjects needed were estimated on the basis of earlier data (15). To detect a decrease in R_{int} of 15% with 85% power and $p = 0.02$ would require 60 wheezy children to complete the crossover. Interim analysis would be at 1 year. If a clear result was obtained, one way or the other, the trial would be stopped. If the result was unclear the trial would continue.

To encourage adherence (13), families were contacted regularly. Adherence was assessed by direct questioning and by weighing inhalers before and after the study. Adherence was considered acceptable if the inhalers weights dropped by 70% or more of the expected amount.

Data were analyzed on an intention-to-treat basis. R_{int} and BDR data were transformed ($\log_{10}$) for analysis and results were expressed

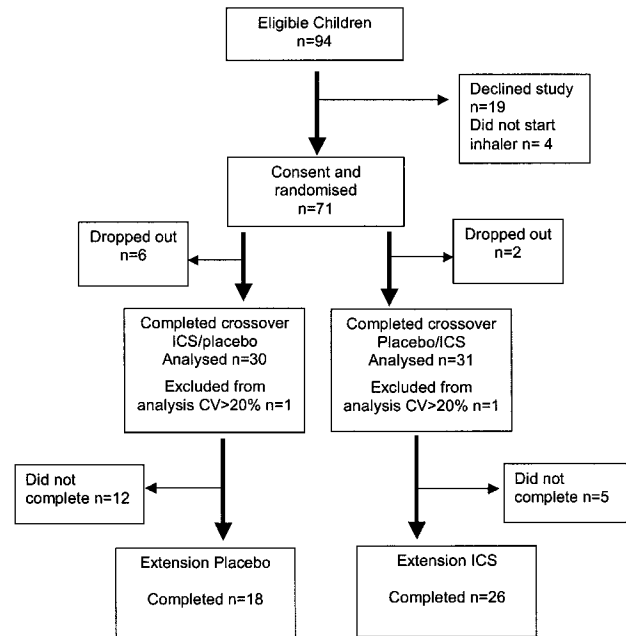


Figure 2. Flow chart of progress through the study. CV = Coefficient of variation of R_{int} measurement; ICS = inhaled corticosteroids.

after back-transformation. Changes in lung function were expressed as ratios of pretreatment to posttreatment R_{int} and BDR, transformed for analyses, and compared by paired and unpaired t testing. The relationships between change in R_{int} , log IgE, SPT positivity and treatment given were examined by multiple regression. Spearman rank correlation and χ^2 testing were used as appropriate.

RESULTS

Subjects

At 1 year, the time of the planned interim analysis, 94 children had been invited to participate and 61 (65%) had been successfully recruited (Figure 2). The interim analysis suggested a clear response in the 46 children who had completed the crossover, and so recruitment was stopped. Children continued until they had completed the study. Forty-four children completed the 10-week extension, 18 taking placebo and 26 taking ICS. Children who did not complete did not differ significantly from those who completed (Table 1). A family history of asthma was present in 25 children, and 18 had a history of eczema. Nine children had previously wheezed without respiratory infection but not within 6 months of recruitment.

TABLE 1. DEMOGRAPHIC DATA OF SUBJECTS

	Completed (n = 61)	Declined/Dropped Out (n = 33)	p Value
Median age, yr	3.5	3.2	0.11
Male, %	67.2	54.5	0.24
Median gestation, wk	40	40	0.67
Median birth weight, kg	3.22	3.22	0.5
Smoking in pregnancy, %	14.8	30.3	0.11
Damp, %	27.9	36.4	0.41
Smoking at home, %	62.3	75.8	0.17
Pets, %	18	12.1	0.35

TABLE 2. EFFECT OF SENSITIZATION ON PERCENT CHANGE FROM BASELINE IN AIRWAY RESISTANCE AND BRONCHODILATOR RESPONSIVENESS OF INHALED CORTICOSTEROIDS*

	SPT Positive	SPT Negative	p Value
Percent change in R_{int} , % (95% CI)	-16.0 [†] (-25.0 to -7.0)	-3.5 (-7.6 to +0.7)	0.01
Percent change in BDR, % (95% CI)	-10.6 [†] (-20.7 to -0.4)	-1.6 (-7.0 to +3.7)	0.1

Definition of abbreviations: BDR = bronchodilator responsiveness; CI = confidence interval; R_{int} = airway resistance; SPT = skin prick test.

* Positive change denotes deterioration and negative change denotes improvement.

[†] Significant to $p < 0.05$.

Atopic Status

Serum total IgE. Median serum total IgE ($n = 60$) was 141.5 kU/L (range, <2 to 2,324 kU/L). Measurements among those who started ICS were similar to those of children who started on placebo, $p = 0.50$.

Skin prick tests. Of 60 children who had SPT, 14 were positive to at least 1 allergen.

Lung Function

At recruitment. Geometric mean baseline R_{int} was $1.19 \text{ kPa} \cdot \text{L}^{-1} \cdot \text{second}$ (estimated quartiles, 0.99 to $1.43 \text{ kPa} \cdot \text{L}^{-1} \cdot \text{second}$); geometric mean BDR was 1.28 (estimated quartiles, 1.12 to 1.46).

Using normative data obtained in our laboratory for the local population (23), baseline R_{int} was equivalent to a mean Z score of +0.99 (quartiles, +0.25 to +1.72) for age. The baseline measurements of those children randomized to ICS initially did not differ from those randomized to placebo (geometric mean baseline R_{int} for ICS = +0.80 Z score [quartiles, +0.14 to +1.46]; for placebo = +1.16 Z score [quartiles, +0.37 to +1.95]; $p = 0.20$).

Adherence. For the 6-week crossover period, adherence was 80% for placebo and 73% for FP ($p = 0.29$). During the 10-week extension, adherence was 83% for placebo and 84% for FP ($p = 0.79$). Analysis excluding data from five children who returned more than 90% inhaler by weight did not significantly alter the results.

After the 6-week crossover ($n = 61$). Compared with placebo, geometric mean R_{int} changed by -7.6% after 6 weeks of treatment with ICS (95% confidence interval [CI] of -3.4 to -11.5%, $p < 0.001$) and geometric mean BDR changed by -5.6% (95% CI, -0.6 to -10.4%, $p = 0.03$).

Symptom scores on ICS during the crossover were unchanged (median total scores in 2 weeks: on placebo = 3.5, with an interquartile range [IQR] of 0 to 15; on FP = 3.0 [IQR, 0 to 16]). Improvements in R_{int} on ICS were not related to initial symptoms (correlation coefficient $r = 0.0003$). There were no significant period or crossover effects for either symptoms or lung function ($p = 0.47$ and 0.11 for lung function).

Relationship of response to atopic status. Multiple regression analysis showed that changes in R_{int} were unrelated to log IgE ($p = 0.70$) but were strongly related to SPT positivity ($p = 0.007$).

Baseline R_{int} Z scores did not differ between SPT-positive and SPT-negative children before ICS (mean Z score for SPT-positive children = +0.41 [IQR, -0.29 to +1.11] and mean Z score for SPT-negative children = +0.6 [IQR, +0.03 to +1.17], $p = 0.7$) or placebo (mean Z score for SPT-positive children = +0.52 [IQR, -0.18 to +1.22] and mean Z score for SPT-negative children = +0.96 [IQR, +0.32 to +1.6], $p = 0.31$).

BDR did not differ between SPT-positive and SPT-negative children before ICS (mean for SPT-positive children = 1.35 [IQR, 0.95 to 1.76] and mean for SPT-negative children = 1.27 [IQR, 0.86 to 1.68], $p = 0.4$) or placebo (mean for SPT-positive children = 1.20 [IQR, 0.81 to 1.62] and mean for SPT-negative children = 1.22 [IQR, 0.78 to 1.61], $p = 0.8$).

SPT-positive children demonstrated a geometric mean change in R_{int} on ICS compared with placebo of -16.0% (95% CI, -7.0 to -25.0%; $p = 0.003$) compared with -3.5% (95% CI, -7.6 to +0.7%; $p = 0.1$) for SPT-negative children ($p = 0.01$) (Table 2 and Figure 3).

SPT-positive children taking ICS compared with placebo demonstrated a geometric mean change in BDR of -10.6% (95% CI, -20.7 to -0.4%, $p = 0.04$) compared with -1.6% (95% CI, -7.0 to +3.7%, $p = 0.5$) for SPT-negative children ($p = 0.1$) (Table 2).

After the 10-week extension ($n = 44$). Because of the increased frequency of wheeze, one child taking placebo was withdrawn from the extension.

There was no additional improvement in R_{int} at 16 weeks compared with 6 weeks of ICS: mean change, -1.7% (95% CI, -11.0 to +9.4%; $p = 0.75$). BDR was also unchanged (mean percent change, +5.8%; 95% CI, -0.8 to +12.4%; $p = 0.25$) (Table 3).

Sixteen weeks after stopping treatment, R_{int} on placebo (i.e., after stopping ICS) increased by +5.3% (95% CI, -2.7 to +14.1%; mean expected change with age, -7.6%; $p = 0.004$) (Table 3). Only four SPT-positive children completed the extension on placebo. For these children, there was a significantly greater ($p < 0.02$) mean change in R_{int} of +25.0% (95% CI, -8.1 to +70.0%) compared with SPT-negative children ($n = 14$; mean change in R_{int} , +1.1%; 95% CI, -5.8 to +8.5%).

At the end of the extension there was no difference in the 2-week symptom score between ICS and placebo (median score on ICS, 0.55 [IQR, 0.1 to 10]; on placebo, 2 [IQR, 0.1 to 32]; $p = 0.33$).

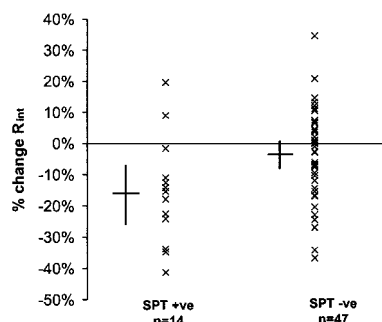


Figure 3. Effect of SPT positivity on change in R_{int} on ICS compared with placebo at 6 weeks.

TABLE 3. OVERALL PERCENT CHANGE IN R_{int} AND BRONCHODILATOR RESPONSIVENESS ON ADMINISTRATION OF INHALED CORTICOSTEROID COMPARED WITH PLACEBO*

	Percent Change in R_{int} , % (95% CI)	Percent Change in BDR, % (95% CI)
Overall benefit of ICS over placebo, 6 wk	-7.6 [†] (-3.4 to -11.5)	-5.6 [‡] (-0.6 to -10.4)
From randomization to placebo	+2.7 (-3.3 to +8.9)	+2.2 (-4.2 to +9.0)
From 6 to 16 wk ICS	-1.7 (-11.0 to +9.4)	+5.8 (-0.8 to +12.4)
On stopping ICS for 16 wk (compared with mean expected change = -7.6% with age)	+5.3 [‡] (-2.7 to +14.1)	+7.7 (0.0 to +16.9)

Definition of abbreviations: BDR = bronchodilator responsiveness; CI = confidence interval; ICS = inhaled corticosteroid; R_{int} = airway resistance.

* Positive change denotes deterioration and negative change denotes improvement.

[†] Significant to $p < 0.001$.

[‡] Significant to $p < 0.05$.

DISCUSSION

Our study demonstrates that on the recommended dose of ICS, mean R_{int} improves by 16% and BDR is reduced in preschool children with recurrent intermittent wheeze who are sensitized to common aeroallergens. SPT-negative children as a group did not benefit, and serum total IgE was unrelated to changes in lung function. Thus, if a patient is aeroallergen positive they have a better chance of improving with treatment than if they have no treatment. Some subjects in the treatment group will not benefit and some subjects in the nontreatment group may improve. Between-occasion repeatability of R_{int} in children is poor (24) and change of this magnitude will not be picked up in the individual. However, this group study has shown that if a sensitized patient belongs to the treatment group they will stand a better chance of benefiting. Total IgE reflects atopic tendency and is not a sensitive indicator of sensitization to aeroallergens. Our results are consistent with the well-described effect of corticosteroids on airways with allergic inflammation. The proportion of SPT-positive children in our cohort was not dissimilar to that demonstrated in a group that included children with persistent wheeze who would be expected to be more atopic (25). SPT was undertaken at the end of crossover so that researchers were blinded as far as possible to atopic status. In this study, we have shown no change in symptoms, probably reflecting low initial symptom scores with little room for improvement. To assess the effect of ICS on the frequency of exacerbations in children with intermittent symptoms only would require a much longer study. Lung function deteriorated on stopping treatment as others have shown in older subjects (11).

Our results are in keeping with a study (26) showing that a positive family history of asthma and frequent symptoms in preschool children with recurrent wheeze are predictive of a beneficial response to ICS, although these subjects did not have skin prick tests performed.

Although the 6-week crossover design may not be considered long enough to show a change in lung function on ICS, the length of treatment was selected to optimize adherence and there was no additional benefit at 16 weeks compared with 6 weeks of treatment.

After stopping treatment, R_{int} increased significantly in the SPT-positive subjects. In adults with mild asthma, ICS may prevent deterioration in lung function (11). Agertoft and Pedersen demonstrated a decline in FEV₁ in children with mild/moderate asthma and not taking ICS. In their study, children who started ICS soon after diagnosis had better lung function, which persisted after 3 years of treatment (12). It would be interesting to know how many of these children were sensitized to aeroallergens.

It is known that children with persistent wheeze improve symptomatically when treated with ICS and that lung function

also improves (4, 12, 27, 28). Improvement in FEV₁ on FP is reported to be 10% to 27% (29). Our improvement was 16% in SPT-positive subjects taking the recommended dose of FP. Nielsen and Bisgaard have demonstrated that in preschool children with persistent moderate/severe asthma, baseline lung function is abnormal, improving with inhaled high-dose budesonide (800 µg daily; a dosage above that recommended), and deteriorating off treatment (28). The authors did not relate their findings to aeroallergen sensitization. In studies of older children with mild disease, changes are less impressive. In schoolchildren with mild asthma treated with budesonide (200 µg twice daily), Waalkens and coworkers demonstrated no change in FEV₁, although improvements were seen in other variables (30). In another study, a small improvement in FEV₁ of 5.2% was demonstrated (31).

When considering treatment with ICS for preschool children, their classification as sensitized or nonsensitized to aeroallergens would be helpful. Skin prick testing is relatively noninvasive, acceptable to most children and parents, and results (available within minutes) can be used to target treatment more precisely.

In summary, this is the first study that has shown that ICS in recommended doses improves lung function in aeroallergen-sensitized preschool children with recurrent intermittent wheeze. We suggest that skin prick testing be undertaken in this group of children if treatment with ICS is considered.

Acknowledgment: The authors thank all the families involved in the study and all the staff who referred them. The authors also thank Peter Bridge for technical help and assistance with data collection; Rachel Cane for help in designing the symptom diary; and Professor Michael Healy, who advised about data analysis.

References

1. Kuehni CE, Davis A, Brooke AM, Silverman M. Are all wheezing disorders in very young (preschool) children increasing in prevalence? *Lancet* 2001;357:1821-1825.
2. National Asthma Campaign. National asthma audit 1999/2000. Cookham, Berkshire, UK: Direct Publishing Solutions, on behalf of the National Asthma Campaign; 2000.
3. British Thoracic Society, General Practitioners in Asthma Group, British Association of Accident and Emergency Medicine, British Paediatric Respiratory Society, Royal College of Paediatrics and Child Health. British guidelines on asthma management: 1995 review and position statement. *Thorax* 1997;52(Suppl. 1):S2-S21.
4. Bisgaard H, Gillies J, Groenewald M, Maden C. The effect of inhaled fluticasone propionate in the treatment of young asthmatic children: a dose comparison study. *Am J Respir Crit Care Med* 1999;160:126-131.
5. Wilson N, Sloper K, Silverman M. Effect of continuous treatment with topical corticosteroid on episodic viral wheeze in preschool children. *Arch Dis Child* 1995;72:317-320.
6. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. Group Health Medical Associates. *N Engl J Med* 1995;332:133-138.
7. Majeed A, Moser K. Prescribing for patients with asthma by general practitioners in England and Wales 1994-96. *Health Stat Q* 1999;1:16-20.

8. McKean M, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood. *Cochrane Database Syst Rev* 2000;2:CD001107.
9. Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig LM. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med* 1988;319:1112–1117.
10. Dezateux C, Stocks J, Dundas I, Fletcher ME. Impaired airway function and wheezing in infancy: the influence of maternal smoking and a genetic predisposition to asthma. *Am J Respir Crit Care Med* 1999;159:403–410.
11. Hahtela T, Jarvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, Nikander K, Persson T, Selroos O, Sovijarvi A, *et al.* Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994;331:700–705.
12. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88:373–381.
13. Gibson NA, Ferguson AE, Aitchison TC, Paton JY. Compliance with inhaled asthma medication in preschool children. *Thorax* 1995;50:1274–1279.
14. Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by “wheeze”? *Arch Dis Child* 2000;82:327–332.
15. McKenzie SA, Bridge PD, Healy MJ. Airway resistance and atopy in preschool children with wheeze and cough. *Eur Respir J* 2000;15:833–838.
16. Chavasse RJ, Bastian-Lee Y, Richter H, Hilliard T, Seddon P. Persistent wheezing in infants with an atopic tendency responds to inhaled fluticasone. *Arch Dis Child* 2001;85:143–148.
17. Hoekx JC, Hedlin G, Pedersen W, Sorva R, Hollingworth K, Efthimiou J. Fluticasone propionate compared with budesonide: a double-blind trial in asthmatic children using powder devices at a dosage of 400 $\mu\text{g} \times \text{day}^{-1}$. *Eur Respir J* 1996;9:2263–2272.
18. Sheffer AL, LaForce C, Chervinsky P, Pearlman D, Schaberg A. Fluticasone propionate aerosol: efficacy in patients with mild to moderate asthma. Fluticasone Propionate Asthma Study Group. *J Fam Pract* 1996;42:369–375.
19. MacKenzie CA, Weinberg EG, Tabachnik E, Taylor M, Havnen J, Crescenzi K. A placebo controlled trial of fluticasone propionate in asthmatic children. *Eur J Pediatr* 1993;152:856–860.
20. Hoekstra MO, Grol MH, Bouman K, Stijnen T, Koeter GH, Kauffman HF, Gerritsen J. Fluticasone propionate in children with moderate asthma. *Am J Respir Crit Care Med* 1996;154:1039–1044.
21. Bridge PD, Ranganathan S, McKenzie SA. Measurement of airway resistance using the interrupter technique in preschool children in the ambulatory setting. *Eur Respir J* 1999;13:792–796.
22. Brydon MJ. Procedure and results. In: Skin prick testing in clinical practice. Oxford: Blackwell Science; 2000. p. 39.
23. McKenzie SA, Chan E, Dundas I, Bridge PD, Pao CS, Mylonopoulou M, Healy, MJR. Airway resistance measured by the interrupter technique: normative data for 2–10 year olds of three ethnicities. *Arch Dis Child* 2002;87:248–251.
24. Lombardi E, Sly PD, Concutelli G, Novembre E, Veneruso G, Frongia G, Bernardini R, Vierucci A. Reference values of interrupter respiratory resistance in healthy preschool white children. *Thorax* 2001;56:691–695.
25. Wilson NM, Phagoo SB, Silverman M. Atopy, bronchial responsiveness, and symptoms in wheezy 3 year olds. *Arch Dis Child* 1992;67:491–495.
26. Roorda RJ, Mezei G, Bisgaard H, Maden C. Response of preschool children with asthma symptoms to fluticasone propionate. *J Allergy Clin Immunol* 2001;108:540–546.
27. Calpin C, Macarthur C, Stephens D, Feldman W, Parkin PC. Effectiveness of prophylactic inhaled steroids in childhood asthma: a systemic review of the literature. *J Allergy Clin Immunol* 1997;100:452–457.
28. Nielsen KG, Bisgaard H. The effect of inhaled budesonide on symptoms, lung function, and cold air and methacholine responsiveness in 2- to 5-year-old asthmatic children. *Am J Respir Crit Care Med* 2000;162:1500–1506.
29. Jarvis B, Faulds D. Inhaled fluticasone propionate: a review of its therapeutic efficacy at dosages $\leq$ or $=$ 500 $\mu\text{g}/\text{day}$ in adults and adolescents with mild to moderate asthma. *Drugs* 1999;57:769–803.
30. Waalkens HJ, Gerritsen J, Koeter GH, Krouwels FH, van Aalderen WM, Knol K. Budesonide and terbutaline or terbutaline alone in children with mild asthma: effects on bronchial hyperresponsiveness and diurnal variation in peak flow. *Thorax* 1991;46:499–503.
31. Jonasson G, Carlsen KH, Blomqvist P. Clinical efficacy of low-dose inhaled budesonide once or twice daily in children with mild asthma not previously treated with steroids. *Eur Respir J* 1998;12:1099–1104.