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Effectiveness of Nebulized Beclomethasone in Preventing Viral Wheezing: An RCT

AUTHORS: Antonio Clavenna, MD, PhD, Marco Sequi, StatSc, Massimo Cartabia, StatSc, Filomena Fortinguerra, PharmD, Marta Borghi, PharmD, and Maurizio Bonati, MD, on Behalf of the ENBe Study Group

Laboratory for Mother and Child Health, Department of Public Health, IRCCS—Istituto di Ricerche Farmacologiche “Mario Negri,” Milan, Italy

KEY WORDS

beclomethasone, physicians, preschool-aged child, primary care, randomized controlled trial

ABBREVIATIONS

CI—confidence interval

RCT—randomized controlled trial

RR—relative risk

URTI—upper respiratory tract infection

Dr Clavenna conceptualized and designed the study, and drafted the initial manuscript; Drs Sequi and Cartabia conducted the statistical analyses, and reviewed and revised the manuscript; Drs Borghi and Fortinguerra were involved in the data management and reviewed and revised the manuscript; and Dr Bonati contributed to defining the protocol, supervised the study, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted.

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Address correspondence to Antonio Clavenna, MD, PhD, Laboratory for Mother and Child Health, Department of Public Health, IRCCS—Istituto di Ricerche Farmacologiche “Mario Negri,” via Giuseppe La Masa 19, 20156, Milan, Italy. E-mail: antonio.clavenna@marionegri.it

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WHAT'S KNOWN ON THIS SUBJECT: Viral wheezing is common in preschool-aged children. The efficacy of inhaled steroids in preventing viral wheezing is debated. Despite this debate, nebulized beclomethasone is widely prescribed (particularly in a few countries) to children with upper respiratory tract infections.



WHAT THIS STUDY ADDS: Findings from this study confirm that inhaled steroids are not effective in preventing viral wheezing. Moreover, no differences were found in the persistence of symptoms (eg, runny nose, sore throat) or in the parental perception of asthma-like symptom severity.

abstract

OBJECTIVE: The goal of this study was to evaluate the effectiveness of nebulized beclomethasone in preventing the recurrence of viral wheezing.

METHODS: The study was designed as a randomized, double-blind, placebo-controlled trial. Outpatient children aged 1 to 5 years with at least 1 episode of viral wheezing in the last 12 months, presenting to any of 40 Italian pediatricians for an upper respiratory tract infection, were randomly allocated to receive beclomethasone 400 μ g or placebo twice daily for 10 days. Medications were administered through a nebulizer. A clinical evaluation was performed by the pediatrician at the start and end of the treatment period. A subjective evaluation of symptoms and efficacy of treatment was performed by the parents. The primary endpoint was the incidence of viral wheezing diagnosed by the pediatricians during the 10-day treatment period.

RESULTS: A total of 525 children were enrolled in the study, 521 of whom were visited at the end of the treatment period. Wheezing was diagnosed by the pediatricians in 47 children (9.0% [95% confidence interval: 6.7 to 11.3]), with no statistically significant differences between treatment groups (beclomethasone versus placebo relative risk: 0.61 [95% confidence interval: 0.35 to 1.08]). The treatment was considered helpful by 63% of parents (64% in the beclomethasone group vs 61% in the placebo group). In all, 46% of children still had infection symptoms at the end of the treatment period, with no differences between groups.

CONCLUSIONS: The findings from this study confirm that inhaled steroids are not effective in preventing recurrence of viral wheezing. Moreover, no benefits were found in reducing symptoms of respiratory tract infections. *Pediatrics* 2014;133:e505–e512

According to population studies, 1 in 3 children aged <3 years has at least 1 episode of wheezing, and 50% experience such an episode by the age of 6 years.^{1–3} In most preschool-aged children, wheezing occurs only during upper viral respiratory tract infections (URTIs).⁴

A prospective study reported that 19% of children aged <18 months had had at least 1 episode of wheezing associated with a URTI. In 40% of cases, the wheezing recurred in the subsequent episodes of URTI.⁵ In a telephone survey involving 7251 households in the United States and Europe, a prevalence of 32% of children aged 1 to 5 years with recurring cough, wheeze, or breathlessness in the preceding 6 winter months was reported.¹ Viral wheezing, however, is different from atopic asthma, in that in 60% of cases, symptoms disappear before the age of 6 years.³ The efficacy of drug treatments in the prevention and/or treatment of viral wheezing is controversial, and short-acting β_2 -agonists are considered the first choice for symptomatic treatment of acute episodes.⁴ The usefulness of inhaled steroids is a matter of debate: no benefits are documented for maintenance with low doses, whereas their episodic use at a high dose may lead to a modest improvement in symptoms.^{6–10} A systematic review by the Cochrane Collaboration regarding the use of episodic, high-dose inhaled steroids in viral wheezing prevention concluded, on the basis of the results of 2 crossover, randomized controlled trials (RCTs), that children's parents preferred inhaled steroids to placebo (relative risk [RR]: 0.64 [95% confidence interval (CI): 0.48 to 0.87]) and observed a trend for a reduced requirement of oral corticosteroids (RR: 0.53 [95% CI: 0.27 to 1.04]).^{11,12} No differences were observed concerning hospitalization rate or bronchodilator

use.⁹ A prospective RCT included in the Cochrane Review reported that episodic, high-dose budesonide reduced the asthma symptom score (as rated by parents) but found no difference in emergency department attendance, hospitalization rate, or bronchodilator use.¹³ Despite the scant evidence, nebulized steroids are widely prescribed, especially in a few countries such as Italy, for the symptomatic treatment of URTIs and/or prophylaxis of viral wheezing.^{1,14,15} Beclomethasone is the second most prescribed drug in Italian children among the medications reimbursed by the National Health Service, with a prevalence estimated ~15% (9%–22%, depending on the setting), without changes across time.^{16,17} Beclomethasone prevalence is highest in children 1 to 4 years old (23%). In 60% of cases, it is prescribed occasionally (1 box per patient per year), and in 98%, it is prescribed as a nebulized suspension.¹⁶ Moreover, an analysis of the prescriptions dispensed by 1165 pediatricians found that all pediatricians had prescribed nebulized beclomethasone at least once during the 1-year observation period.¹⁸

A rigorous evaluation of current practices is fundamental in such a context. In this regard, a trial was planned with the goal of evaluating the effectiveness of nebulized beclomethasone in preventing viral wheezing in children with URTIs. The study was designed as a 2-phase trial: an RCT (phase 1) followed by a 6-month prospective observational study (phase 2). This latter phase had the objective of monitoring the incidence of viral wheezing recurrence in preschool-aged children and the different therapeutic approaches used by physicians. Only the results concerning the RCT are reported in the present article.

METHODS

Patients

Subjects recruited were preschool-aged children with a history of viral wheezing who were visited by any of 40

participating Italian family pediatricians for a URTI between October 2010 and March 2012. Pediatricians worked in a total of 9 Italian local health units: 3 located in the north, 3 in the center, and 3 in the south of Italy.

Children were considered for inclusion if they were 1 to 5 years old, had any viral URTI symptoms, had had at least 1 episode of viral wheezing (diagnosed by a physician) in the preceding 12 months, and had no or minimal asthma-like symptoms between distinct airway infections. Children were excluded if they had at least 1 of the following criteria: steroid hypersensitivity; inhaled and/or oral corticosteroid use in the preceding month; chronic respiratory disease (eg, cystic fibrosis, bronchopulmonary dysplasia); and presence of wheezing at the entry visit.

Study Design

A randomized, double-blind, parallel-group design was used. Children were allocated in a 1:1 ratio to receive beclomethasone or placebo according to a computer-generated randomization list. A central randomized block randomization procedure stratified by pediatricians was performed with a block size of 4. Each pediatrician received 8 to 16 medication packs, each identified according to a code. Pediatricians were instructed to give the enrolled patient the medication pack with the lowest available number.

Treatment

Children were randomly assigned to receive beclomethasone suspension 400 μg (Clenil, Chiesi Farmaceutici SpA, Parma, Italy) or placebo, twice daily, for 10 days. The duration of the treatment was chosen based on the Summary of Product Characteristics and previous trials.¹³

Active drug and placebo were administered by parents through a pneumatic nebulizer (Nebula, Air Liquide Medical

System, Bovezzo, Italy), in the morning and in the evening. In administering the drug, 1 mL of suspension was diluted with 1 mL of saline solution. The nebulizer and the saline solution (20-mL vials) were provided as part of the study and given to parents by the pediatricians at the entry visit along with the medication package.

Paracetamol use for the symptomatic treatment of fever and/or pain was allowed. Nasal saline irrigation and antibiotics were also allowed if needed.

If viral wheezing occurred during the 10-day treatment period, pediatricians were allowed to prescribe nebulized salbutamol, nebulized beclomethasone, or oral steroids as rescue medications.

Blinding

The packaging, labeling, schedule of administration, and appearance of active and placebo treatments were identical. Each medication pack contained a total of 20 identical 1-mL ampoules and was identified by a code. A person not involved in the study evaluation labeled the medication packages. The statistical analyses were performed by investigators unaware of the treatment allocation.

Study Plan

Two visits were scheduled: the entry visit (visit 1, day 0), and the end of treatment visit (visit 2, day 11, with a tolerance of +2 days). In addition to the scheduled visits, pediatricians were requested to visit the children, within 24 hours of the parent's request, in case of wheezing and/or lack of improvement within 72 hours of the start of therapy.

Data Collection

At the entry visit (visit 1), pediatricians completed a Web-based electronic case report form collecting demographic, anamnestic, and clinical data of the child, as well as information regarding

familiarity for asthma or allergy (Table 1). At the end of the treatment period (visit 2), pediatricians visited the patient and collected information concerning treatment compliance through an interview with the parents. Parents were requested to return to the pediatrician any remaining drug doses.

In case of wheezing and/or lack of improvement within 72 hours of the start of therapy, pediatricians were asked to visit the child, evaluate the presence of wheezing, and rate it. A wheezing score was assigned as follows: 0 = no wheezing, 1 = end-expiratory wheeze only (mild), 2 = wheeze during entire expiratory with or without inspiratory phase, audible with stethoscope only

(moderate), and 3 = inspiratory and expiratory wheezing audible without stethoscope (severe).⁵

During the 10-day treatment period, symptoms were recorded by parents on a daily diary. The parents scored the asthma-like symptoms subjectively. Symptoms were divided into cough, wheeze, noisy breathing, and breathlessness and were scored daily along a 4-point scale (none = 0; mild = 1; moderate = 2; severe = 3) that has been used in previous clinical trials.^{11–13} The presence (yes/no) of airway infection symptoms (fever, blocked nose, runny nose, sore throat, and watery eyes) and the number of doses administered were also recorded daily. At the end of the

TABLE 1 Baseline Patient Characteristics According to Group

Characteristic	Beclomethasone (n = 264)	Placebo (n = 261)	P
Age, y	2.1 ± 1.0	2.1 ± 1.0	.73
Male gender	161 (61)	158 (60)	.92
Delivery			
Natural	154 (58.3)	147 (56.3)	.64
Cesarean	110 (41.7)	114 (43.7)	
Gestational age, wk			
≤37	58 (21.6)	43 (16.5)	.13
>37	206 (78.0)	218 (83.5)	
Atopic dermatitis (yes)	64 (24.2)	68 (26.1)	.63
Allergic rhinitis (yes)	13 (4.9)	8 (3.1)	.28
At least 1 case with allergy in family (yes)	136 (51.5)	130 (49.8)	.70
At least 1 case with asthma in family (yes)	67 (25.4)	59 (22.6)	.46
At least 1 smoker in family (yes)	107 (40.5)	97 (37.2)	.43
Enrollment period			
October–December	129 (48.9)	129 (49.4)	.91
January–March	100 (37.9)	101 (38.7)	
April–September	35 (13.2)	31 (11.9)	
No. of URTIs in the last 12 mo	3.1 ± 2.0	3 ± 1.9	.66
No. of wheezing episodes in the last 12 mo	2.1 ± 1.1	2.0 ± 1.1	.10
No. of wheezing episodes in the last 6 mo			
0	91 (34.5)	77 (29.5)	.40
1	98 (37.1)	110 (42.1)	
>1	75 (28.4)	74 (28.4)	
Time from the last wheezing episode, mo			
1–3	137 (51.9)	137 (52.5)	.74
4–6	46 (17.4)	51 (19.5)	—
7–9	45 (17.0)	45 (17.2)	—
10–12	36 (13.6)	28 (10.7)	—
Children taking drugs in the preceding month	72 (27.3)	95 (36.4)	.02
Kind of infection at baseline visit			
Rhinitis	233 (88.3)	230 (88.1)	.51
Pharyngotonsillitis	85 (32.2)	73 (28.0)	
Laryngitis	41 (15.5)	40 (15.3)	
Otitis	25 (9.5)	37 (14.2)	
Other	74 (28.0)	70 (26.8)	
Fever in the last 12 h (yes)	58 (22.0)	69 (26.4)	.23

Data are presented as mean ± SD or n (%).

treatment period, the parents expressed a judgment on the treatment (helpful versus not helpful). Adverse events were also recorded by the parents.

Ethics

The study protocol and all informed consent documents were approved by the ethics committees of each of the 9 local health units. Written informed consent was obtained from parents of each subject after a thorough explanation of the study details, and subjects were free to withdraw from the study at any time, without consequence to their care or treatment. The study was supervised by an external, independent research monitoring committee.

At the end of the study, a formal letter reporting the main findings was sent to participating parents.

Outcome

The primary outcome measure was the percentage of children with wheezing (diagnosed by the pediatrician) during the URTI episode. Secondary outcome measures included the percentage of patients with the following: moderate/severe wheezing (score ≥ 2 rated by pediatrician), needing medical care during the treatment period, receiving rescue medication during the treatment period, admitted to an emergency department during the treatment period, having an asthma-like symptom score (rated by parents) totaling ≥ 7 , and being fully adherent to therapy. Other secondary outcome measures included duration of the respiratory tract infection episode; mean asthma-like symptom score for each child; and percentage of parents who considered the treatment helpful.

Sample Size Estimate

The risk of recurrent viral wheezing in children who had ≥ 1 episode was estimated at $\sim 40\%$.⁵ At least 260 children per group were therefore needed to

detect a 30% reduction in the risk of viral wheezing (from 40% to 28%), with a statistical power of 0.8 and a 2-sided α error of 0.05.

Hypothesizing a 10% dropout rate, a total of 578 randomized children were needed.

Statistical Analysis

Analyses included all randomized children (intention-to-treat population). The primary outcome measure, as well as the other categorical variables, was compared by using the χ^2 test. For the main outcome measure analyses, patients were stratified according to the number of viral wheezing episodes in the previous 6 months (≤ 1 vs > 1).

The proportion of children with no respiratory tract infection symptoms was compared by using the Kaplan-Meier method. Repeated measures analysis of variance was performed to analyze changes in the daily asthma-like symptom score. The last-observation-carried-forward-method was used to deal with the missing data, when applicable.

A P value $< .05$ was considered statistically significant.

RESULTS

From October 2010 to March 2012, a total of 1371 children with a history of viral wheezing were visited by pediatricians for a URTI. In all, 714 were not eligible (Fig 1), mainly for the presence of wheezing at the baseline visit (63% of not eligible children) and/or the use of steroids in the 30 days before the visit (53%). Of the 657 provisionally eligible children, the parents of 132 (20%) declined participation, and 525 children were enrolled; 264 were randomized to the beclomethasone group and 261 to the placebo group.

Table 1 reports the characteristics of the enrolled children according to treatment group. No differences were found between the 2 groups, with the

exception of the percentage of children treated with drugs in the 30 days preceding the baseline visits (36% in the placebo group vs 27% in beclomethasone group; $P = .02$), but similar rates were found when comparing single drug classes.

A total of 521 patients were visited at the end of the treatment period. The parents of 2 children withdrew consent after randomization, and 2 children were lost to follow-up.

The number of children visited at the end of the treatment period was consistent with the estimated sample size ($n = 520$).

Primary and Secondary Outcome Measures

Wheezing was diagnosed by pediatricians in 47 children (9.0% [95% CI: 6.7 to 11.3]), with no statistically significant differences between treatment groups: 18 children (6.8% [95% CI: 4.2 to 10.4]) received beclomethasone and 29 (11.1% [95% CI: 7.7 to 15.4]) received placebo (Table 2). For 26 children, the wheezing was diagnosed during the 10-day treatment period, and for 21 children, after its end. No statistically significant differences were found even after stratification for the number of wheezing episodes in the 6 months preceding the entry visit (Mantel-Haenszel RR: 0.61 [95% CI: 0.35 to 1.08]). In 40 cases, the wheezing was scored by the pediatrician as mild and as moderate in 7. No differences were found for the secondary outcome measures (Table 3).

Parental Perception of Symptom Severity and Treatment Efficacy

In all, 62.7% of parents rated the treatment as useful, with no differences between beclomethasone and placebo (Table 3). At day 1, the overall mean \pm SD score was 2.85 ± 2.04 in the beclomethasone group and 2.94 ± 2.06 in the placebo group. At the end of the therapy (day 10), these scores decreased

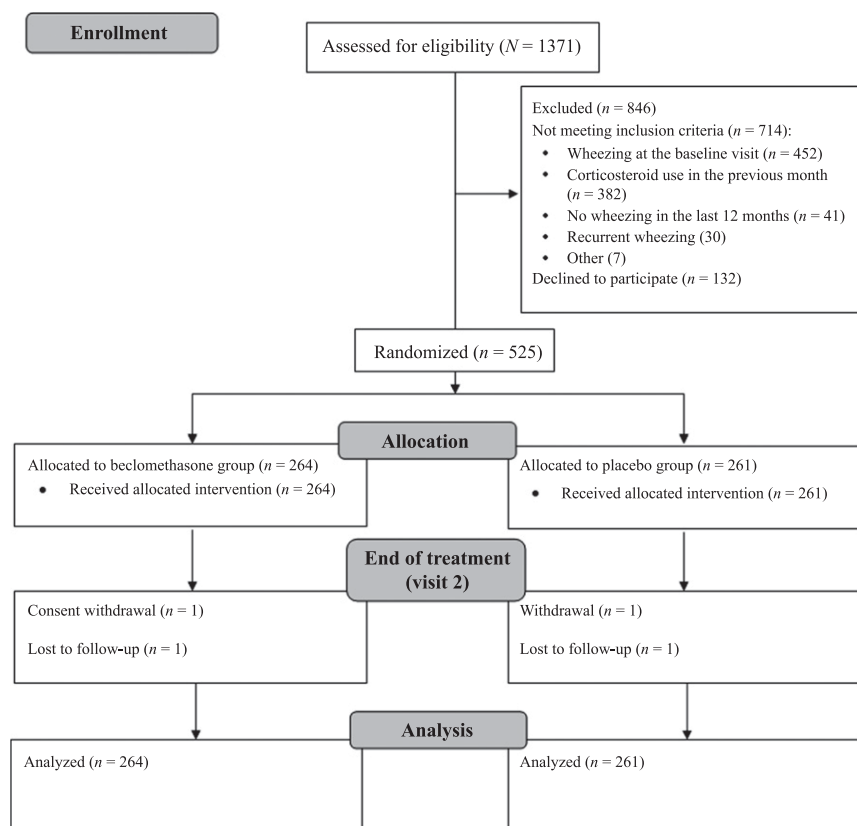


FIGURE 1
Flow diagram.

to 1.20 ± 1.66 and 1.53 ± 2.01 in the beclomethasone and placebo groups, respectively (Fig 2). No statistically significant differences were found when evaluating individual symptoms (cough, noisy breathing, breathlessness, wheezing) separately. A slightly higher percentage of children had a total score >6 for ≥ 1 day in the placebo group compared with the beclomethasone group (14.9% vs 11.7%; $P = .34$).

At the end of the treatment period, parents reported URTI symptoms for 46% of children. No differences were found in the distribution of the proportion of symptom-free children according to

group during the treatment period (beclomethasone versus placebo hazard ratio: 1.02 [95% CI: 0.86 to 1.22]) (Fig 3).

Safety

No differences were found in the incidence of adverse events reported by parents at the end of the therapy (Table 4).

Two serious adverse events were reported by pediatricians: 1 hospital admission for urinary tract infection in the beclomethasone group and 1 hospitalization for adenoidectomy and tonsillectomy in the placebo group. Neither adverse event was drug related.

DISCUSSION

This is the first National Health Service–funded, double-blinded, RCT performed in the pediatric primary care setting in Italy and, to the best of our knowledge, one of the few performed anywhere. Some difficulties arose, in terms of time spent for ethics committee approval, enrollment of the children, and adherence to the protocol, especially regarding the timing of the scheduled visits. However, the study can be considered a pragmatic trial because it evaluated the efficacy of beclomethasone in the real-life context. The prescription of beclomethasone in children with URTIs is a widespread “approach,” particularly in Italy, and the study consequently tried to address a relevant topic.

One of the main strengths of this study was its combination of the clinical evaluation of pediatricians with the perception of parents. Previous studies regarding the prevention of episodic viral wheezing used outcome measures almost exclusively based on parental scores and/or symptoms recorded in a diary.^{11–13} Because scores depend greatly on subjective perception, and differences exist in parents’ understanding of what wheezing means,^{19,20} a stronger primary endpoint was used: the incidence of wheezing diagnosed by pediatricians. Wheezing occurred less frequently in the beclomethasone group, in particular when taking into account children with a recent history of recurrent episodes, but with no statistically significant differences.

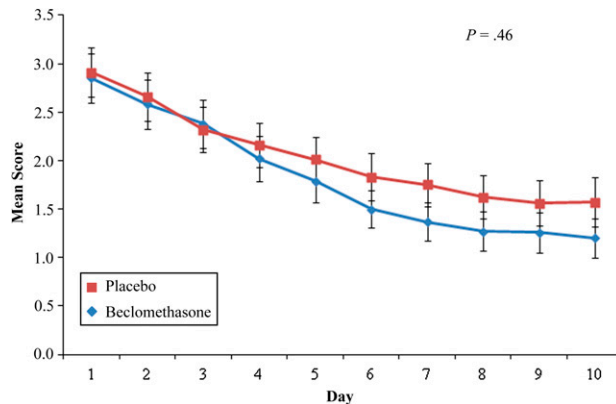
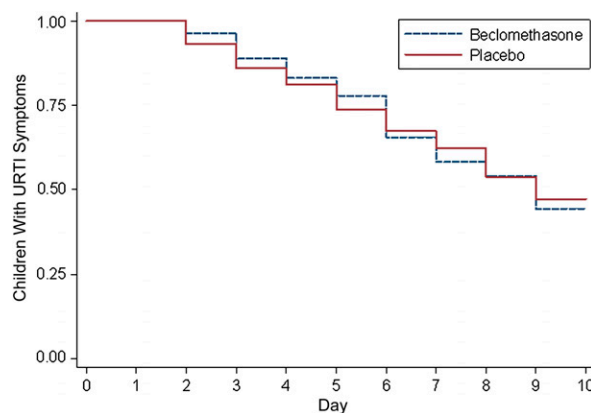
A lower than expected incidence of wheezing was observed. In a previous observational study, a risk of recurrence

TABLE 2 Children With an Occurrence of Viral Wheezing During the Study Period

Wheezing Episode	Beclomethasone	Placebo	P	RR (95% CI)	Risk Difference (95% CI)
Episodes in the preceding 6 mo					
≤1	13/189 (6.9%)	20/187 (10.7%)	.19	0.64 (0.33 to 1.26)	−3.8 (−9.5 to 1.9)
>1	5/75 (6.7%)	9/74 (12.2%)	.25	0.54 (0.19 to 1.56)	−5.5 (−11.8 to 3.8)
Overall	18/264 (6.8%)	29/261 (11.1%)	.09	0.61 (0.35 to 1.08)	−4.3 (−9.1 to 0.6)

TABLE 3 Secondary Outcome Measures

Outcome Measure	Beclomethasone (n = 264)	Placebo (n = 261)	P	RR (95% CI)	Risk Difference (95% CI)
Extra visits	34 (12.9%)	41 (15.7%)	.35	0.82 (0.54 to 1.25)	−2.8 (−8.8 to 3.1)
Wheezing moderate/severe	2 (0.8%)	5 (1.9%)	.43	0.40 (0.08 to 2.02)	−1.1 (−3.1 to 0.8)
Prescription of rescue drugs	11 (4.2%)	17 (6.5%)	.23	0.64 (0.31 to 1.34)	−2.3 (−6.2 to 1.5)
Emergency department attendance	6 (2.3%)	4 (1.5%)	.76	1.48 (0.42 to 5.19)	0.8 (−1.6 to 3.0)
Children fully adherent to therapy	162 (61.4%)	155 (59.4)	.68	1.03 (0.90 to 1.19)	2.0 (−6.4 to 10.3)
Children with URTI symptoms at visit 2	108 (40.9%)	115 (44.1%)	.46	0.93 (0.76 to 1.13)	−3.2 (−11.6 to 5.3)
Parents who rated the treatment as helpful	170 (64.4%)	160 (61.3%)	.46	1.05 (0.92 to 1.20)	3.1 (−5.2 to 11.4)
Parental score ≥ 7	31 (11.7%)	39 (14.9%)	.34	0.79 (0.51 to 1.22)	−3.2 (−9.0 to 2.6)

**FIGURE 2**
Day-by-day overall asthma-like symptom score (mean and 95% CI).**FIGURE 3**
Proportion of children with symptoms of URTI during the 10-day treatment period.

of 40% was reported in infants who had had at least 1 episode of viral wheezing.⁵ In the present study, only 11% of children in the placebo group developed wheezing. The sample size was calculated on the basis of a 40% risk of wheezing recurrence with the aim to detect at least a 30% RR reduction (from 40% to 28%), and it is possible that the study was not adequately powered

for this scope. Given a rate of 11%, and a sample of 525 children, the minimum detectable RR difference was 45%.

A significant proportion of children were not enrolled because these children still had wheezing at the baseline visit (33% of the screened population), and this exclusion can explain the lower prevalence of wheezing occurrence. The fact that, during the experimental

phase, only a single episode of a URTI was monitored should also be taken into consideration. When looking at the 6-month observation period, the rate of recurrence was 30% (data not presented here). From this point of view, children enrolled in this study were no different from children at risk for viral wheezing.¹

It is possible that some cases of wheezing were missed because children were not visited by pediatricians, but this same possibility occurs in daily practice. In this regard, it should be emphasized that 21 (45%) of 47 cases of wheezing were not recognized by parents and were detected by pediatricians at the end of treatment. Nevertheless, a small (4.3%) absolute risk reduction was observed, and according to our results, the number needed to treat with beclomethasone for obtaining an additional benefit was estimated at 23. The effectiveness of the drug prophylaxis therefore seems small, independently of the statistical significance. The scant effectiveness is confirmed by the fact that no differences were found in the additional care (pediatrician visits, emergency department admissions, and drug prescriptions) needed by the 2 groups. Moreover, the parental perception of the severity of asthma-like symptoms and of the helpfulness of the treatment was similar in the beclomethasone and placebo groups.

In addition to wheezing prevention, many Italian pediatricians routinely prescribe beclomethasone as treatment of URTI symptoms (eg, cough, sore throat).¹⁴ In this regard, this study's findings prove that the duration of symptoms is similar

TABLE 4 AEs Reported by Parents

AE	Beclomethasone (n = 264)	Placebo (n = 261)	P
Any AEs	97 (38)	98 (39)	.86
Hoarseness	34 (13)	34 (13)	.97
Diarrhea	27 (10)	35 (14)	.30
Skin rash	19 (8)	22 (8)	.69
Vomiting	19 (7)	20 (8)	.95
Candidosis	12 (5)	15 (6)	.65
Others	25 (10)	26 (11)	.94

Data are presented as n (%).

in children receiving beclomethasone and those receiving placebo, and that 46% of children had ≥ 1 symptom after 10 days of treatment, independently of the treatment.

Results of ENBe (Efficacy of Nebulised Beclomethasone in Viral Wheezing Prophylaxis) study should stimulate pediatricians in improving rational drug prescribing, also through further clinical trials in the pediatric primary care setting.²¹

Finally, low compliance was observed. Only 6 of every 10 children completed all 10 days of therapy. In nearly one-half of the cases, incomplete adherence was due to difficulties in performing nebulization, mainly because of the child's lack of cooperation. This possible issue should be taken into account by pediatricians when prescribing drugs to be administered through a nebulizer.

CONCLUSIONS

The findings of this study confirm that inhaled steroids have little benefit in preventing viral wheezing and no effect in reducing URTI symptoms. These drugs may have greater efficacy in children with recurrent episodes of viral wheezing, but this possibility needs to be investigated further. Despite some limitations, clinical trials

performed in the primary care setting can provide useful evidence for health professionals, regulatory agencies, and National Health Service officers, with the goal of improving rational drug use in children.

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