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Daily or intermittent budesonide in preschool children with recurrent wheezing

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Daily or Intermittent Budesonide in Preschool Children with Recurrent Wheezing


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*Other investigators in the Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers (MIST) trial from the Childhood Asthma Research and Education (CARE) Network are listed in the Supplementary Appendix, available at NEJM.org.


ABSTRACT

BACKGROUND
Daily inhaled glucocorticoids are recommended for young children at risk for asthma exacerbations, as indicated by a positive value on the modified asthma predictive index (API) and an exacerbation in the preceding year, but concern remains about daily adherence and effects on growth. We compared daily therapy with intermittent therapy.

METHODS
We studied 278 children between the ages of 12 and 53 months who had positive values on the modified API, recurrent wheezing episodes, and at least one exacerbation in the previous year but a low degree of impairment. Children were randomly assigned to receive a budesonide inhalation suspension for 1 year as either an intermittent high-dose regimen (1 mg twice daily for 7 days, starting early during a predefined respiratory tract illness) or a daily low-dose regimen (0.5 mg nightly) with corresponding placebos. The primary outcome was the frequency of exacerbations requiring oral glucocorticoid therapy.

RESULTS
The daily regimen of budesonide did not differ significantly from the intermittent regimen with respect to the frequency of exacerbations, with a rate per patient-year for the daily regimen of 0.97 (95% confidence interval [CI], 0.76 to 1.22) versus a rate of 0.95 (95% CI, 0.75 to 1.20) for the intermittent regimen (relative rate in the intermittent-regimen group, 0.99; 95% CI, 0.71 to 1.35; P = 0.60). There were also no significant between-group differences in several other measures of asthma severity, including the time to the first exacerbation, or adverse events. The mean exposure to budesonide was 104 mg less with the intermittent regimen than with the daily regimen.

CONCLUSIONS
A daily low-dose regimen of budesonide was not superior to an intermittent high-dose regimen in reducing asthma exacerbations. Daily administration led to greater exposure to the drug at 1 year. (Fundied by the National Heart, Lung, and Blood Institute and others; MIST ClinicalTrials.gov number, NCT00675584.)
RECURRENT WHEEZING EPISODES IN PRE-SCHOOL-AGE CHILDREN ARE USUALLY TRIGGERED BY RESPIRATORY TRACT INFECTIONS, which often progress to severe exacerbations requiring systemic glucocorticoids and frequent use of health care services. In children under the age of 5 years who had at least four wheezing episodes during the previous year and positive values on the modified asthma predictive index (API) (indicating an increased likelihood of persistent asthma in the future), the National Asthma Education and Prevention Program Expert Panel Report 3 (EPR-3) recommends the initiation of long-term daily inhaled glucocorticoid therapy on the basis of the results of the Childhood Asthma Research and Education (CARE) Network Prevention of Early Asthma in Kids (PEAK) trial (ClinicalTrials.gov number, NCT00272441). In a post hoc analysis, investigators in the PEAK trial found that daily therapy with inhaled glucocorticoids most benefited children who had had at least one exacerbation requiring emergency or hospital care during the previous year.

Daily use of inhaled glucocorticoids in the PEAK trial was associated with a small but significant reduction in height growth, as compared with placebo, a reduction that was only partially reversed during a 1-year observation period after the discontinuation of study treatments. Concern about growth retardation and parental resistance to a daily regimen of inhaled glucocorticoids for young children, who usually have only episodic but often severe symptoms, stimulated a search for alternative strategies — specifically, intermittent therapy with inhaled glucocorticoids. Intermittent 7-day courses of high-dose nebulized budesonide, as compared with placebo, a reduction that was only partially reversed during a 1-year observation period after the discontinuation of study treatments. Concern about growth retardation and parental resistance to a daily regimen of inhaled glucocorticoids for young children, who usually have only episodic but often severe symptoms, stimulated a search for alternative strategies — specifically, intermittent therapy with inhaled glucocorticoids. Intermittent 7-day courses of high-dose nebulized budesonide, as compared with placebo, a reduction that was only partially reversed during a 1-year observation period after the discontinuation of study treatments.

In confirmation of these findings, preemptive use of intermittent high-dose fluticasone during upper respiratory illness reduced exacerbations requiring oral glucocorticoids in young children with moderate-to-severe, virus-induced wheezing.

We conducted the Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers (MIST) trial to determine whether a daily low-dose regimen of budesonide would be superior to an intermittent high-dose regimen in young children who had positive values on the modified API, along with recurrent wheezing, high-risk asthma (≥1 exacerbation in the previous year), and low impairment (infrequent use of albuterol and infrequent night awakenings between episodes).

METHODS

STUDY PATIENTS
We enrolled children between the ages of 12 and 53 months who met all the following criteria: during the previous year, they had at least four episodes of wheezing (or three episodes of wheezing and controller use for ≥3 months), positive values on the modified API, and at least one exacerbation requiring the use of systemic glucocorticoids, urgent or emergency care, or hospitalization, and during a 2-week run-in period, they had fewer than 3 days per week of albuterol use and fewer than 2 nights with awakening. Children were excluded from the study if they had received more than six courses of oral glucocorticoids or had been hospitalized more than two times for wheezing during the previous year. (For additional details on inclusion and exclusion criteria, see the Supplementary Appendix, available with the full text of this article at NEJM.org.)

STUDY DESIGN
The study, which was conducted at seven sites, was a randomized, double-blind, parallel-group trial. During a 2-week run-in period, all patients received nightly placebo doses of budesonide inhalation suspension (Pulmicort Respules, AstraZeneca) and as-needed albuterol, followed by a 52-week treatment period. The full protocol and statistical analysis plan are available at NEJM.org. We compared the use of budesonide inhalation suspension given in a daily low-dose regimen with an intermittent high-dose regimen, with matching placebos (Fig. 1A). Specific procedures that were performed at all visits are detailed in Figure S1 in the Supplementary Appendix. The institutional review boards at each center approved the study. Parents or guardians (hereafter referred to as parents for simplicity, unless otherwise noted) provided written informed consent.

Intermittent high-dose treatments were started for an identified respiratory tract illness on the basis of a published education program (see the Supplementary Appendix). Parents began a 7-day course of intermittent study medication...
Outcome Measures

The primary outcome measure was the frequency of exacerbations, which was defined as the number of courses of an oral glucocorticoid (prednisolone) started for acute wheezing after consultation with a physician (by telephone or in person) on the basis of a specific published protocol during the 12-month treatment period (see the Supplementary Appendix). About 30% of courses of an oral glucocorticoid were not initiated by the study team.

Secondary prespecified risk outcomes included the number of exacerbations, which was defined as the number of courses of an oral glucocorticoid (prednisolone) started for acute wheezing after consultation with a physician (by telephone or in person) on the basis of a specific published protocol during the 12-month treatment period (see the Supplementary Appendix). About 30% of courses of an oral glucocorticoid were not initiated by the study team.

Secondary prespecified outcome measures included the number of exacerbations, rate of exacerbation, rate of wheezing-related health care utilization, and growth effects. Secondary prespecified impairment outcomes included the number of episode-free days, symptom severity during a respiratory tract illness, absences related to respiratory symptoms, albuterol use, quality of life according to the Infant Toddler Quality of Life questionnaire, and levels of fractional exhaled nitric oxide (Fig. S1 in the Supplementary Appendix). Adherence was determined by means of diary recordings of budesonide use. Analyses also examined the relationship between specific nasal respiratory viruses and respiratory tract illnesses.

Study Oversight

The study was funded by the National Heart, Lung, and Blood Institute and was approved by its protocol review committee and data and safety monitoring board. AstraZeneca donated budesonide and matching placebo and reviewed the protocol with minor comments and the manuscript without commenting; the company had no other role in the study. The authors are fully responsible for the study design and data (collection, analysis, completeness, accuracy, and interpretation), as well as for the fidelity of the report to the study protocol.

Statistical Analysis

The study was designed as a superiority trial of a daily low-dose regimen of budesonide, as compared with an intermittent high-dose regimen, since previous CARE trials had shown the efficacy of both regimens versus placebo in similar high-risk, low-improvement cohorts. Baseline characteristics were summarized with the use of descriptive statistics. We used the exact Wilcoxon–Mann–Whitney test, stratified according to study center and age group, to determine statistical significance.

Although the determination of statistical significance for the treatment comparison was based on a nonparametric test, the primary research question was framed in terms of the annual rate of exacerbations. For the primary parametric anal-
For counted outcomes, such as unscheduled health care visits, a similar model was applied. We used analysis of covariance for outcomes that were measured on a continuous scale, such as linear growth, and appropriate transformations were applied for
any outcome that had a skewed distribution. We used a proportional-hazards regression model for time-to-event outcomes, such as the time to the first exacerbation. The total exposure to budesonide in an intention-to-treat model is described in the Supplementary Appendix.

For sample-size determination, we used the results of the PEAK\textsuperscript{7} and AIMS\textsuperscript{11} trials to estimate exacerbation rates. The sample size that was required for a power of 90% was determined for a range of exacerbation rates, from 0.6 to 1.2 per year. On the basis of a 10% dropout rate, we calculated that a sample of 250 children would provide a power of 90% (225 total patient-years) if the relative exacerbation rate for one treatment group was at least 40% lower than the rate in the other group. During the course of the trial, it became evident that the actual noncompletion rate might be as high as 20%. With approval from the data and safety monitoring board and the institutional review boards, 28 additional patients underwent randomization, which preserved a power of 90%, since data from 235 patient-years would be available for the intention-to-treat analysis.

All analyses were performed with the use of SAS statistical software, version 9.1, and were adjusted for the randomization strata. A two-sided P value of less than 0.05 for between-group comparisons was considered to indicate statistical significance, with no adjustment for multiple testing of secondary outcomes.

RESULTS

STUDY PATIENTS

Of the 450 children who were originally enrolled in the study, 172 were excluded during the run-in period. A total of 278 children underwent randomization, and 213 completed the study (Fig. 1B). The two study groups had similar demographic and clinical characteristics (Table 1). The noncompletion rate was 23.3%, with no significant differences between the two groups (Tables S1 and S2 in the Supplementary Appendix). Reported rates of adherence to treatment and diary entries were high and similar in the two groups (Table 2). Of the reports of treatments for respiratory tract illness, 95.6% were made by mothers, 3.9% by fathers, 0.4% by grandparents, and 0.1% by legal guardians.

PRIMARY OUTCOME

There was no significant difference between a daily regimen of budesonide and an intermittent regimen with respect to the frequency of exacerbations requiring the use of rescue oral glucocorticoids, with a rate per patient-year of 0.97 (95% confidence interval [CI], 0.76 to 1.22) in the daily-regimen group versus a rate of 0.95 (95% CI, 0.75 to 1.20) in the intermittent-regimen group (relative rate in the intermittent-regimen group, 0.99; 95% CI, 0.71 to 1.35; P=0.60) (Fig. 2A and Table 2). There was also no significant between-group difference with respect to the time to the first exacerbation (hazard ratio, 0.97; 95% CI, 0.76 to 1.22; P=0.87) (Fig. 2B), the time to the second exacerbation (hazard ratio, 0.79; 95% CI, 0.49 to 1.32; P=0.38), or the frequency of treatment failure (P=0.12).

SECONDARY PRESPECIFIED OUTCOMES

The distribution of the type of symptoms (e.g., coughing or wheezing) that led caregivers to recognize a respiratory tract illness and initiate treatment was similar in the two study groups (P=0.60) (Table S3 in the Supplementary Appendix). There were also no significant differences in the rates of respiratory tract illness per patient-year (3.27 with the daily regimen and 3.61 with the intermittent regimen, P=0.30), respiratory tract illnesses in which prednisolone was administered (0.26 with the daily regimen and 0.24 with the intermittent regimen, P=0.50) (Table 2), the frequency of treatments for respiratory tract illnesses (P=0.30) (Fig. 2C), and the time to the first treatment for respiratory tract illness (P=0.16) (Fig. 2D). Most exacerbations occurred during treated respiratory tract illnesses, with 102 of 111 exacerbations during treated illnesses (91.9%) in the daily-regimen group and 105 of 115 exacerbations during treated illnesses (91.3%) in the intermittent-regimen group. Similarly, there were no significant between-group differences in symptom scores during respiratory tract illnesses (Fig. 3, and Table S4 in the Supplementary Appendix) or during exacerbations (Fig. S3 in the Supplementary Appendix).

The proportion of episode-free days across the study was 78%, and the rate of wheezing-related unscheduled physician visits was approximately 2.40 visits per patient-year in the two study groups (Table 2). The rate of absences for children and parents (from day care and work, respectively), the proportion of days with albuterol use (Table 2), and changes in most quality-of-life measures (Table S4 in the Supplementary Appendix) were similar in the two study groups. Given that measurements of fractional exhaled nitric oxide were unsuccessful in 36% of chil-
Table 1. Demographic and Asthma Characteristics of the Patients.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 278)</th>
<th>Intermittent Regimen (N = 139)</th>
<th>Daily Regimen (N = 139)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of 12–32 mo — no. (%)</td>
<td>127 (45.7)</td>
<td>64 (46.0)</td>
<td>63 (45.3)</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>192 (69.1)</td>
<td>102 (73.4)</td>
<td>90 (64.7)</td>
</tr>
<tr>
<td>White race — no. (%)†</td>
<td>173 (62.2)</td>
<td>91 (65.5)</td>
<td>82 (59.0)</td>
</tr>
<tr>
<td>Height — cm</td>
<td>94.2±9.1</td>
<td>94.0±9.1</td>
<td>94.5±9.0</td>
</tr>
<tr>
<td>Weight — kg</td>
<td>15.2±3.1</td>
<td>15.0±3.0</td>
<td>15.5±3.1</td>
</tr>
<tr>
<td>Head circumference — cm</td>
<td>50.0±1.9</td>
<td>50.1±2.0</td>
<td>49.9±1.9</td>
</tr>
<tr>
<td>Physician diagnosis of asthma — no. (%)</td>
<td>198 (71.2)</td>
<td>99 (71.2)</td>
<td>99 (71.2)</td>
</tr>
<tr>
<td>No. of wheezing episodes in past year</td>
<td>6.7±5.4</td>
<td>7.0±5.9</td>
<td>6.4±4.7</td>
</tr>
<tr>
<td>No. of urgent or emergency visits in past year</td>
<td>4.8±4.2</td>
<td>4.6±4.2</td>
<td>5.0±4.1</td>
</tr>
<tr>
<td>Hospitalizations in past year — no. (%)</td>
<td>53 (19.1)</td>
<td>26 (18.7)</td>
<td>27 (19.4)</td>
</tr>
<tr>
<td>Tobacco-smoke exposure from birth — no. (%)</td>
<td>114 (41.0)</td>
<td>55 (39.6)</td>
<td>59 (42.4)</td>
</tr>
<tr>
<td>Medication use in past year — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma controller</td>
<td>194 (69.8)</td>
<td>100 (71.9)</td>
<td>94 (67.6)</td>
</tr>
<tr>
<td>Inhaled glucocorticoid</td>
<td>189 (68.0)</td>
<td>96 (69.1)</td>
<td>93 (66.9)</td>
</tr>
<tr>
<td>Oral glucocorticoid</td>
<td>210 (75.5)</td>
<td>110 (79.1)</td>
<td>100 (71.9)</td>
</tr>
<tr>
<td>Allergy — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food sensitivity</td>
<td>95/273 (34.8)</td>
<td>50/135 (37.0)</td>
<td>45/138 (32.6)</td>
</tr>
<tr>
<td>Any aeroallergen sensitivity</td>
<td>161/276 (58.3)</td>
<td>82/137 (59.9)</td>
<td>79/139 (56.8)</td>
</tr>
<tr>
<td>IgE — IU/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>58</td>
<td>50</td>
<td>61</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>21–186</td>
<td>20–195</td>
<td>25–179</td>
</tr>
<tr>
<td>Eosinophils ≥4% — no./total no. (%)</td>
<td>123/260 (47.3)</td>
<td>61/132 (46.2)</td>
<td>62/128 (48.4)</td>
</tr>
<tr>
<td>Eczema — no. (%)</td>
<td>146 (52.5)</td>
<td>76 (54.7)</td>
<td>70 (50.4)</td>
</tr>
<tr>
<td>Allergic rhinitis — no. (%)</td>
<td>105 (37.8)</td>
<td>50 (36.0)</td>
<td>55 (39.6)</td>
</tr>
<tr>
<td>Parental asthma — no./total no. (%)</td>
<td>171/266 (64.3)</td>
<td>85/131 (64.9)</td>
<td>86/135 (63.7)</td>
</tr>
<tr>
<td>Exhaled nitric oxide ≥10 ppb — no./total no. (%)</td>
<td>78/178 (43.8)</td>
<td>36/82 (43.9)</td>
<td>42/96 (43.8)</td>
</tr>
<tr>
<td>Episode-free days during run-in period — %</td>
<td>67±30</td>
<td>66±30</td>
<td>68±29</td>
</tr>
<tr>
<td>Diary scores during run-in period:‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughing</td>
<td>0.4±0.4</td>
<td>0.4±0.5</td>
<td>0.4±0.4</td>
</tr>
<tr>
<td>Wheezing</td>
<td>0.1±0.3</td>
<td>0.2±0.3</td>
<td>0.1±0.3</td>
</tr>
<tr>
<td>Trouble breathing</td>
<td>0.1±0.3</td>
<td>0.1±0.3</td>
<td>0.1±0.3</td>
</tr>
<tr>
<td>Interference with activities</td>
<td>0.1±0.2</td>
<td>0.1±0.2</td>
<td>0.1±0.3</td>
</tr>
<tr>
<td>General health perceptions from ITQOL§</td>
<td>59.2±14.1</td>
<td>59.0±14.8</td>
<td>59.4±13.5</td>
</tr>
<tr>
<td>Any nasal virus identified — no. (%)</td>
<td>148 (53.2)</td>
<td>72 (51.8)</td>
<td>76 (54.7)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. There were no significant differences between the two groups.
† Race was determined by parents or guardians.
‡ Scores range from 0 to 5, with higher scores indicating more severe symptoms. Scores were calculated from diaries as means ±SD for the 2-week run-in period.
§ The scores on the Infant Toddler Quality of Life (ITQOL) questionnaire range from 0 to 100, with higher scores indicating better health.

dren at baseline, particularly in the youngest children, changes in values for fractional exhaled nitric oxide were not reported. The frequency and distribution of respiratory viruses in nasal secretions during two regularly scheduled clinic visits and during respiratory tract ill-
eses were similar in the two groups (Table 2, and Table S5 in the Supplementary Appendix).

SAFETY
The total exposure to budesonide over the course of the study was less in the intermittent-regimen
Table 2. Outcomes at 1 Year.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intermittent Regimen (N = 139)</th>
<th>Daily Regimen (N = 139)</th>
<th>Treatment Effect†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of prednisolone courses for asthma‡</td>
<td>Event Rate/Person-Yr (95% CI)</td>
<td>Relative Rate (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.95 (0.75 to 1.20)</td>
<td>0.97 (0.76 to 1.22)</td>
<td>0.99 (0.71 to 1.35)</td>
</tr>
<tr>
<td>No. of treatments for respiratory tract illness‡</td>
<td>3.61 (3.13 to 4.16)</td>
<td>3.27 (2.82 to 3.79)</td>
<td>1.10 (0.91 to 1.35)</td>
</tr>
<tr>
<td>No. of urgent care visits for asthma‡</td>
<td>2.37 (1.89 to 2.97)</td>
<td>2.40 (1.91 to 3.02)</td>
<td>0.99 (0.72 to 1.35)</td>
</tr>
<tr>
<td>No. of days absent from work, school, or day care‡</td>
<td>2.72 (2.00 to 3.70)</td>
<td>3.02 (2.22 to 4.12)</td>
<td>0.90 (0.59 to 1.37)</td>
</tr>
<tr>
<td>Respiratory tract illnesses in which prednisolone was administered‡</td>
<td>0.24 (0.19 to 0.29)</td>
<td>0.26 (0.21 to 0.32)</td>
<td>0.90 (0.68 to 1.19)</td>
</tr>
<tr>
<td>Respiratory tract illnesses with virus detected in nasal sample</td>
<td>0.83 (0.74 to 0.92)</td>
<td>0.83 (0.74 to 0.93)</td>
<td>1.00 (0.85 to 1.17)</td>
</tr>
<tr>
<td>Respiratory tract illnesses with exacerbations and nasal virus</td>
<td>0.79 (0.61 to 1.02)</td>
<td>0.78 (0.61 to 1.01)</td>
<td>1.00 (0.70 to 1.44)</td>
</tr>
<tr>
<td>Episode-free days — %</td>
<td>Mean Value (95% CI)</td>
<td>Mean Difference (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>78 (75 to 80)</td>
<td>−0.7 (−4.0 to 2.0)</td>
<td></td>
</tr>
<tr>
<td>Episode-free days, excluding days during treatment for respiratory</td>
<td>85 (82 to 87)</td>
<td>84 (82 to 86)</td>
<td>0.5 (−3.0 to 4.0)</td>
</tr>
<tr>
<td>tract illness — %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days with albuterol use — %</td>
<td>6 (5 to 7)</td>
<td>5 (4 to 6)</td>
<td>0.4 (−1.0 to 2.0)</td>
</tr>
<tr>
<td>Annualized days of treatment with budesonide — no.</td>
<td>24 (21 to 27)</td>
<td>337 (330 to 344)</td>
<td>−314 (−322 to −306)</td>
</tr>
<tr>
<td>Cumulative dose of budesonide — mg</td>
<td>46 (39 to 53)</td>
<td>150 (140 to 160)</td>
<td>−104 (−116 to −92)</td>
</tr>
<tr>
<td>Change in height from baseline</td>
<td>Value — cm</td>
<td>8.01 (7.71 to 8.30)</td>
<td>0.26 (−0.17 to 0.68)</td>
</tr>
<tr>
<td></td>
<td>Percentile</td>
<td>4.04 (2.07 to 6.00)</td>
<td>1.65 (−1.34 to 4.63)</td>
</tr>
<tr>
<td></td>
<td>z score</td>
<td>0.12 (0.04 to 0.20)</td>
<td>0.02 (−0.10 to 0.13)</td>
</tr>
<tr>
<td>Change in weight from baseline</td>
<td>Value — kg</td>
<td>2.54 (2.37 to 2.71)</td>
<td>0.16 (−0.08 to 0.41)</td>
</tr>
<tr>
<td></td>
<td>Percentile</td>
<td>4.11 (2.07 to 6.16)</td>
<td>3.38 (0.43 to 6.33)</td>
</tr>
<tr>
<td></td>
<td>z score</td>
<td>0.15 (0.07 to 0.22)</td>
<td>0.10 (−0.01 to 0.21)</td>
</tr>
<tr>
<td>Change in head circumference from baseline</td>
<td>Value — cm</td>
<td>0.92 (0.79 to 1.05)</td>
<td>0.05 (−0.14 to 0.23)</td>
</tr>
<tr>
<td></td>
<td>Percentile</td>
<td>−1.20 (−3.45 to 1.04)</td>
<td>2.39 (−1.43 to 6.20)</td>
</tr>
<tr>
<td></td>
<td>z score</td>
<td>−0.07 (−0.17 to 0.03)</td>
<td>0.06 (−0.09 to 0.21)</td>
</tr>
<tr>
<td>Days with diary-card adherence — %‡</td>
<td>83 (78 to 88)</td>
<td>88 (84 to 92)</td>
<td>−5 (−11 to 2)</td>
</tr>
<tr>
<td>Days with adherence to budesonide or placebo — %‡</td>
<td>Daily</td>
<td>94 (93 to 96)</td>
<td>−1 (−2 to 1)</td>
</tr>
<tr>
<td></td>
<td>During respiratory tract illness</td>
<td>81 (75 to 87)</td>
<td>−1 (−10 to 8)</td>
</tr>
</tbody>
</table>

* All outcomes have been adjusted for age and clinical center. Growth was measured in 113 children in the intermittent-regimen group and 110 in the daily-regimen group. All other outcomes included data from the entire cohort.
† The treatment effect was calculated as the value in the intermittent-regimen group divided by the value in the daily-regimen group.
‡ Models were also adjusted for sex, race, and atopy, since results were similar with adjustment for age and clinical center only.
§ Treatment adherence was evaluated on days for which diary data were available.

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DISCUSSION

We report that a daily low-dose regimen of budesonide inhalation suspension was not superior to an intermittent high-dose regimen, administered for 7 days during a predefined respiratory tract illness, with respect to the frequency of exacerbations (the primary outcome) in preschool-age children at risk for asthma and future exacerbations. In addition, there was no significant between-group difference in respiratory symptoms (symptom severity during respiratory tract illnesses, episode-free days, and bronchodilator use) or quality of life. These findings occurred in the context of similar rates of reported adherence and identification of nasal viruses in the two study groups.

The treatment of preschool-age children with recurrent wheezing is complex, since most of these children do not have persistent asthma, as defined by regular symptoms, and the diagnosis is difficult to confirm. U.S. guidelines recognize this complexity in regard to diagnosis and management and recommend daily therapy with inhaled glucocorticoids as the preferred option for young chil-

There were no deaths. The proportions of patients with serious adverse events (including all hospitalizations) and nonserious adverse events did not differ significantly in the two study groups (Table S6 in the Supplementary Appendix). Four children in the daily-regimen group and five in the intermittent-regimen group were hospitalized for asthma exacerbations. Other reasons for hospitalization were pneumonia, gastroenteritis, and diarrhea (one patient each) in the daily-regimen group and concussion, gastroenteritis, influenza, tonsillectomy, and motor-vehicle accident (one patient each) in the intermittent-regimen group.
Children with recurrent wheezing and risk factors for persistent asthma (i.e., positive values on the modified API), although this treatment does not alter the course of the disease after the inhaled glucocorticoids are discontinued. Guidelines of the Global Initiative for Asthma (GINA) also recommend daily controller therapy, including the use of inhaled glucocorticoids, for young children with intermittent wheezing, a history suggestive of asthma, and at least three wheezing episodes in the previous year. The guidelines caution against the use of daily high-dose therapy with inhaled glucocorticoids for prolonged periods, given the reported effect of such use on growth, and advise using the lowest dose necessary for asthma control. In this context, the inability to show the superiority of a daily low-dose regimen of budesonide over an intermittent high-dose regimen may be important in the preparation of future guidelines.

The efficacy of daily low-dose inhaled glucocorticoids, as compared with placebo, has been documented in studies ranging from 1.5 to 12 months and involving preschool-age children with positive values on the modified API, risk factors for asthma, frequent recurrent wheezing or asthma symptoms, or physician-diagnosed asthma. A recent meta-analysis and both the EPR-3 national guidelines and GINA guidelines for infants and preschool-age children support these findings. In the PEAK trial, the daily low-dose inhaled glucocorticoid that was shown to be efficacious was fluticasone administered in a metered-dose inhaler, but there has been no evidence that efficacy differs when other inhaled glucocorticoids are used in clinically similar doses.

Figure 3. Profiles of Symptom Severity during Respiratory Tract Illness.
Day zero corresponds to the start of treatment for a respiratory tract illness. P values are for comparisons of symptom levels during the first 14 days after the initiation of treatment for respiratory tract illness, with adjustment for baseline symptom levels (on days 13 to 7 before the initiation of treatment). Plotted values are means for the indicated day. Scores range from 0 to 5, with higher scores indicating more severe symptoms.
glucocorticoids than among those receiving placebo, but the comparison between daily use and as-needed use was not significant. On the other hand, the use of intermittent high-dose inhaled glucocorticoids for specified periods was more effective than placebo in preschool-age children with intermittent, recurrent wheezing\(^2\,\,^3\,\,^4\) and in those at high risk for asthma but with low levels of respiratory impairment.\(^5\) Thus, we determined that a placebo group was not indicated for our study, which involved children who had low impairment but were at high risk for emerging, persistent asthma and recurrence of an asthma exacerbation, a decision that was approved by the independent oversight boards.

Budesonide inhalation suspension was selected for the daily low-dose inhaled glucocorticoid since it was the only such drug approved by the Food and Drug Administration for daily use in children between the ages of 1 and 4 years at recommended starting daily doses of 0.5 to 1.0 mg on the basis of pivotal trials of budesonide versus placebo in children between the ages of 1 and 8 years.\(^1\,\,^3\,\,^5\) In post hoc analyses, daily doses of 0.5 and 1.0 mg of budesonide were similarly effective in children under the age of 4 years and in those 4 years of age or older.\(^6\) Budesonide in a daily dose of 0.5 mg was also associated with fewer exacerbations and less impairment than was cromolyn\(^7\) or montelukast\(^8\) in young children. The efficacy of once-daily budesonide by nebulization (including a dose of 0.5 mg) has been summarized previously.\(^9\) In addition, guidelines recommend a daily dose of 0.5 mg of budesonide as a low-dose inhaled glucocorticoid.\(^10\,\,^11\) As compared with placebo, budesonide was efficacious without retarding growth when used in an intermittent high-dose regimen of 1 mg twice daily for 7 days with each respiratory tract infection in preschool-age children.\(^12\)

Our findings may not be applicable to young children whose asthma was different from or more severe than that of the children in our study. Daily\(^13\) or intermittent\(^14\) use of inhaled glucocorticoids or even short courses of oral glucocorticoids started at the onset of wheezing episodes\(^15\,\,^16\) may not be efficacious in preschool-age children with a first episode, with transient or infrequent wheezing, or without an asthma diagnosis or a high risk of asthma.

Although the observed exacerbation rates in the two study groups were numerically similar, our results do not show with certainty that the two treatments were equally effective. The uncertainty is reflected in the confidence interval for the relative rate of exacerbations, which extends from approximately 0.7 to 1.35, so our data do not rule out the possibility that either treatment could be up to 35% more effective than the other. The advantage of the intermittent regimen over the daily regimen cannot be based on differential effects on growth, but rather on a reduced exposure to inhaled glucocorticoids (approximately 100 mg less during the course of a year, or a reduction in exposure by a factor of 3.3). The non-completion rate was higher than anticipated but similar in the two groups, as were the characteristics of the children who did not complete the study.

A major advantage of an intermittent regimen of inhaled glucocorticoids is that its initiation occurs early during a predefined respiratory tract illness on the basis of individualized symptoms that historically have occurred before the onset of wheezing.\(^11\) This strategy avoids the use of inhaled glucocorticoids for each upper respiratory tract illness and thus allows for the benefits of the regimen at considerably lower cumulative levels of exposure. In our study, intermittent budesonide was initiated on average once every 3.5 months, in contrast to a monthly rate when such therapy was started preemptively with each upper respiratory tract infection.\(^12\) This finding may explain the adverse effects on growth in the latter study,\(^12\) as compared with our approach.\(^11\) Nevertheless, parents require careful, individualized instruction on when to start budesonide in order to ensure that this intermittent approach is used appropriately, as detailed previously\(^11\,\,^17\) (Fig. S2 in the Supplementary Appendix).

In summary, our trial compared the efficacy of an early intermittent high-dose regimen of budesonide for respiratory tract illness with that of a daily low-dose regimen, with the latter recommended by current guidelines for preschool-age children with recurrent wheezing episodes and positive values on the modified API. We conclude that for such children who have had one or more exacerbations requiring the use of systemic glucocorticoids, urgent or emergency medical visits, or hospitalizations during the previous year but a documented history of low impairment from asthma, the daily low-dose regimen of budes-
onide was not superior to an intermittent high-
dose regimen initiated during a predefined res-
piratory tract illness in reducing exacerbations.
Moreover, the daily low-dose regimen was as-
associated with more frequent administration of
and greater exposure to budesonide.

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APPENDIX

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