Assessment of Controversial Pediatric Asthma Management Options Using GRADE

abstract

OBJECTIVES: To develop explicit and transparent recommendations on controversial asthma management issues in children and to illustrate the usefulness of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach in rating the quality of evidence and strength of recommendations.

METHODS: Health care questions were formulated for 3 controversies in clinical practice: what is the most effective treatment in asthma not under control with standard-dose inhaled corticosteroids (ICS; step 3), the use of leukotriene receptor antagonist for viral wheeze, and the role of extra fine particle aerosols. GRADE was used to rate the quality of evidence and strength of recommendations after performing systematic literature searches. We provide evidence profiles and considerations about benefit and harm, preferences and values, and resource use, all of which played a role in formulating final recommendations.

RESULTS: By applying GRADE and focusing on outcomes that are important to patients and explicit other considerations, our recommendations differ from those in other international guidelines. We prefer to double the dose of ICS instead of adding a long-acting β-agonist in step 3; ICS instead of leukotriene receptor antagonist are the first choice in preschool wheeze, and extra fine particle ICS formulations are not first-line treatment in children with asthma. Recommendations are weak and based on low-quality evidence for critical outcomes.

CONCLUSIONS: We provide systematically and transparently developed recommendations about controversial asthma management options. Using GRADE for guideline development may change recommendations, enhance guideline implementation, and define remaining research gaps. Pediatrics 2012;130:e658–e668

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KEY WORDS guidelines, asthma, drug therapy, child, evidence-based medicine, glucocorticoids, leukotriene antagonists, bronchodilator agents

ABBREVIATIONS CIC—ciclesonide FEV1—forced expiratory volume in 1 second GRADE—Grading of Recommendations Assessment, Development and Evaluation HFA—hydrofluoroalkane ICS—inhaled corticosteroids LABA—long-acting β-agonist LTRA—leukotriene receptor antagonist RCT—randomized controlled trial

www.pediatrics.org/cgi/doi/10.1542/peds.2011-3559

doi:10.1542/peds.2011-3559

Accepted for publication May 11, 2012

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2012 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: Dr Rottier has received a travel grant to attend the European Respiratory Society in Vienna (2009) from TEVA Pharmaceuticals and his institution has received a speakers fee for Motivational Interviewing for a Glaxo Smith Kline organized symposium (2010); in the past 5 years, Dr Brand has received funds for performing research, attending conferences, lectures, and consulting, from Astra Zeneca, Glaxo Smith Kline, Boehringer Ingelheim, Mersk, and Nycomed; the other authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by the Quality Funding Medical Specialists.
Evidence-based guidelines for the management of pediatric asthma provide comprehensive and up-to-date overviews on asthma management in children. Although they may serve as a basis to develop local recommendations and to guide individual patient care, controversy remains because different guidelines contain different recommendations, using the same body of evidence.1–3 For example, if school-age children with asthma remain symptomatic despite treatment with inhaled corticosteroids (ICS), some guidelines specifically recommend adding a long-acting β-agonist (LABA),1,2 whereas others propose doubling the ICS dose or adding a leukotriene receptor antagonist (LTRA).3 The justification for these differing choices often remains unclear, although all guidelines provide levels of evidence to support each recommendation. The systems usually applied to rate levels of evidence and strength of recommendations are limited by their lack of transparency about judgments, values and preferences, and lack of separation between quality of evidence and strength of recommendations.4–6 Grading of Recommendations Assessment, Development and Evaluation (GRADE) was launched as a highly structured and more transparent methodology to rate the quality of evidence and strength of recommendations in clinical practice guidelines.7 GRADE specifies how to frame structured clinical questions, choose outcomes of interest and rate their importance, evaluate the evidence, and incorporate other important values (such as safety and resources) and preferences to arrive at recommendations (Fig 1). Today, >50 influential professional organizations, including the Cochrane Collaboration and the American Thoracic Society (ATS), have adopted the GRADE system.8

In 2007, the Dutch Pediatric Respiratory Society, including all board-certified pediatric pulmonologists in the Netherlands, updated its national guideline on pediatric asthma management.9 Because a number of recommendations remained controversial, the group decided to examine these controversial issues using the GRADE methodology. In this article, we describe how the GRADE process helped us to summarize the evidence, weigh preferences and values, and arrive at final recommendations for these controversial asthma management issues that differ from other guidelines based on the same evidence.

### METHODS

#### Controversial Recommendations

There was controversy regarding 3 recommendations in the 2007 revision of the Dutch national asthma guideline (Table 1).

#### Framing Relevant Questions and Deciding on Important Outcomes

A working group consisting of 4 pediatric pulmonologists and a pediatrician epidemiologist experienced in evidence-based guideline development framed these controversial recommendations into structured clinical questions using the PICO acronym (Patient/Intervention/Comparison/Outcome; Table 2). Outcomes were categorized according to GRADE as “critical” (outcomes 1 and 2), “important” (3 and 4), or “of limited importance” (5–7) as a basis for making decisions regarding the overall quality of evidence supporting a recommendation (Table 3).
TABLE 1 Controversial Recommendations on Pediatric Asthma Management

<table>
<thead>
<tr>
<th>Step</th>
<th>Asthma Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>ICS with extra-fine particles should be considered in preschool children (&lt;6 y of age). LTRAs are recommended in preschool children with episodic viral wheeze.</td>
</tr>
<tr>
<td>3</td>
<td>In case of symptoms despite ICS treatment, it is recommended to add a LABA in case of airway reversibility (≥4 y of age) and to double the dose of ICS or add a LTRA in children with signs of airway inflammation (eg, elevated exhaled nitric oxide levels).</td>
</tr>
</tbody>
</table>

TABLE 2 Structured Clinical Questions (PICO format)

| Question 1: In preschool and school-age children with wheeze/asthma (P), are ICSs with extra-fine particles (I) more effective and/or safer (O) than ICS with normal particle size (C)?
| Question 2: In young children with viral induced wheeze/asthma (P), are LTRA (I) more effective and/or safer (O) than ICS (C)?
| Question 3: In children with asthma symptoms despite ICS (P), what is the most effective and safe (O) treatment option (doubling the ICS dose, adding a LABA or a LTRA) (I, C)?

PICO, patient, intervention, comparison, outcome.

TABLE 3 Relevant Outcomes

<table>
<thead>
<tr>
<th>Critical</th>
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</thead>
<tbody>
<tr>
<td>Asthma symptoms (number of days without symptoms)</td>
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<tr>
<td>(Severe) asthma exacerbations (hospital admission, visit to emergency department and/or need for systemic corticosteroids)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Important</th>
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<tbody>
<tr>
<td>Quality of life</td>
</tr>
<tr>
<td>Adverse effects (with clinical relevance): reduced growth and local side effects</td>
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</table>

<table>
<thead>
<tr>
<th>Limited importance</th>
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<tbody>
<tr>
<td>Changes in lung function (FEV₁, MEF 75–25)</td>
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<tr>
<td>Airway inflammation assessed by exhaled nitric oxide (FeNO)</td>
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<tr>
<td>Costs</td>
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</table>

MEF, midexpiratory flow.

RESULTS

Question 1: In preschool and school-age children with wheeze/asthma, are ICS with extra-fine particles more effective and/or safer than ICS with normal particle size?

Rationale

ICS treatment with extra-fine particles aims to treat the entire bronchial tree including the small airways. Extra-fine particles penetrate better into small airways, leading to higher and more homogeneously distributed lung deposition. This might result in asthma control using lower daily doses with fewer side effects. Particle size may be of particular importance in young children because of their smaller airways and different breathing patterns, with higher breathing frequency and relatively small tidal volume. There are 2 ICSs with extra-fine particle size: extra-fine hydrofluoroalkane (HFA) beclomethasone dipropionate (licensed in Europe for children aged ≥5 years) and ciclesonide (licensed for children aged ≥12 years). Ciclesonide, a prodrug that is converted in the airways into the active metabolite desisobutyryl-ciclesonide (CIC), is thought to have a reduced potential for local and systemic side effects. Because of its binding to protein and slow release, it is licensed for once-daily use, which may improve adherence.

Evidence

We did not find any systematic reviews in children specifically addressing this question. However, 7 RCTs were found: 2 using extra-fine HFA beclomethasone and 4 CIC. Because these agents have different pharmacokinetic and pharmacodynamic properties, they are discussed separately.

No clinical studies examined efficacy or safety of extra-fine beclomethasone in...
preschool children with asthma; both available studies were conducted in children >5 years of age.\textsuperscript{15,16} Pooling of data were not possible, but both studies showed no statistically significant or clinically relevant difference between HFA beclomethasone and fluticasone for symptom-free days, exacerbations, or adverse effects. Growth and quality of life were not reported.

All studies on ciclesonide were conducted in children >6 years and older and used a noninferiority design with a surrrogate primary endpoint, forced expiratory volume in 1 second (FEV$_1$).\textsuperscript{13,14,17,18} There were no significant differences between ciclesonide and other ICS (budesonide or fluticasone) in asthma symptom score and exacerbations, except for 1 study showing significantly more exacerbations in the CIC group (Table 4). Side effects (such as oropharyngeal candidiasis and hoarseness) occurred with similar frequency in both groups. One study showed a significant improvement in height in the CIC group compared with the BUD group (1.18 cm vs 0.70 cm respectively) after 12 weeks of intervention, but measurements were only performed in a subset of patients.\textsuperscript{18} Some studies showed significantly less suppression of 24-hour urinary cortisol levels adjusted for creatinine in the CIC group compared with other ICS, no suppression in the CIC group or even an increase in the CIC group. Adherence was not assessed in the studies.

The quality of evidence for our critical outcomes was rated down by 3 levels (Table 4). We concluded that there is no evidence that ICS with small particles are more effective or safer than ICS with normal particle size in preschool or school-age children (very low-quality evidence).

Other Key Factors

A relatively high value was placed on the consideration that new medications should either be more effective or safer before they can be recommended for clinical practice. The long-term safety of treatments for asthma has been identified as being of particular importance to patients and clinicians.\textsuperscript{16} Because older medications have been used for longer periods of time, more knowledge is available on their long-term safety, and they are usually cheaper than new drugs. Another argument against the use of “me too” preparations with only a slightly different pharmacokinetic or pharmacodynamic profile is that they increase the complexity of treatment, as for inhaled medication, additional and repeated instruction may then again be required to ensure correct inhalation.

The trade-off between benefits and harms of using CIC compared with other ICS is unclear. Ciclesonide has not been proven to be more effective or safer compared with fluticasone and budesonide for relevant outcomes but is noninferior on short-term lung function and asthma symptom score end points. Potentially more severe exacerbations in the CIC group cannot be excluded because of wide confidence intervals. For relevant adverse effects, such as growth and adrenal insufficiency, a follow-up period of 12 weeks is too short; and adequate duration should be at least 6 to 12 months. The clinical significance of lower 24-hour urinary cortisol levels is limited. The measurement is often unreliable and/or invalid and unable to detect partial hypothalamic-pituitary-adrenal axis suppression.\textsuperscript{20} Much more relevant is the ability of the adrenal cortex to be able to respond to stressful stimuli. The most appropriate test would then be the more invasive low-dose corticotropin (Synacthen) stimulation test, which is more sensitive in detecting adrenal impairment.\textsuperscript{21–23}

One study was published assessing the long-term safety of ciclesonide.\textsuperscript{24} This RCT was not included in this review because it compared CIC only with placebo. Mean linear growth velocity and 24-hour urinary cortisol levels were comparable between the groups after 1 year. However, this study could not provide enough reassurance about safety, and considerable concern was expressed about compliance of the children because the study failed to show any benefit of CIC in terms of lung function or asthma control.\textsuperscript{25,26}

Although once-daily dosing (CIC) may improve adherence, this did not lead to better asthma control and was therefore not considered a significant point.

Recommendation

We proposed that ICS with extra-fine particles were not to be recommended as first choice ICS in school-age children with wheezing/asthma (weak recommendation). Specific evidence for clinical superiority of ICS with extra-fine particles in preschool children is lacking. Hence we do not recommend these as first choice for this age group (weak recommendation).

Question 2: In Preschool Children With Viral Induced Wheeze/Asthma, Are LTRAs More Effective (and/or Safer) Than ICS?

Rationale

There is no consensus on how to diagnose asthma in preschool children.\textsuperscript{27} Most preschool children with recurrent wheeze grow out of their symptoms and do not develop chronic persistent asthma.\textsuperscript{28} Although ICSs are universally recommended as the treatment of choice for older children with asthma because ICSs have been shown to be more effective than an LTRA in this age group, some guidelines propose LTRAs as the preferred treatment in preschool children with viral-induced wheezing.\textsuperscript{27}

Evidence

Two RCTs compared budesonide to montelukast in preschool children with recurrent wheezing.\textsuperscript{29,30} The number of symptom-free days and exacerbations...
<table>
<thead>
<tr>
<th>Study, N</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Overall Quality of Evidence per Outcome</th>
<th>Effect Size&lt;sup&gt;b&lt;/sup&gt; for CIC versus other ICS (BUD or FP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical outcome: asthma symptom score</td>
<td>1 (Serious risk of bias: Patients and personnel not blinded)</td>
<td>0 (No serious inconsistency)</td>
<td>1 (Serious indirectness: different inhalers for CIC and comparator ICS)</td>
<td>0 (No pooled estimate)</td>
<td>1 (Serious risk of publication bias: sponsoring/coauthorship of pharmaceutical companies)</td>
<td>⊝⊝⊝ (Very low)</td>
<td>Change from baseline: -1.21 vs -1.21 (difference 95% CI -0.14 to 0.21)</td>
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<td>Von Berg,&lt;sup&gt;18&lt;/sup&gt; N = 621</td>
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<td></td>
<td>Vermeulen,&lt;sup&gt;17&lt;/sup&gt; N = 403</td>
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<td>Pedersen,&lt;sup&gt;13&lt;/sup&gt; N = 511; Pedersen,&lt;sup&gt;14&lt;/sup&gt; N = 704</td>
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<tr>
<td>Critical outcome: exacerbations</td>
<td>1 (Serious risk of bias: Patients and personnel not blinded; Follow-up too short [12 wk])</td>
<td>0 (No serious inconsistency)</td>
<td>1 (Serious indirectness: no definition of exacerbations; different inhalers for CIC and comparator ICS)</td>
<td>1 (Serious imprecision: Wide confidence intervals including important benefit and harm)</td>
<td>1 (Serious risk of publication bias: Sponsoring/coauthorship of pharmaceutical companies)</td>
<td>⊝⊝⊝ (Very low)</td>
<td>CIC vs BUD (dose ratio 1:2) pooled estimate from 2 studies&lt;sup&gt;17,18&lt;/sup&gt;: RR 2.2; CI 0.75–6.43</td>
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<td>Von Berg,&lt;sup&gt;18&lt;/sup&gt; N = 621</td>
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BUD, budesonide; CI, 95% confidence interval; FP, fluticasone; RR, relative risk.

<sup>a</sup> RCTs start as “high” and can be downgraded a maximum of 3 levels to “very low.” Downgrading: no, serious (−1 level), very serious (−2 levels).

<sup>b</sup> Pooling of data was only possible for exacerbations; results for asthma symptom score are presented per study.
defined as hospital admissions were not significantly different between the 2 groups, but in 1 study, the percentage of children requiring oral corticosteroids or additional asthma medication was significantly lower in the budesonide group than in the montelukast group (Table 5). 30 There were no significant differences in quality of life, growth, and side effects.

The quality of evidence for our critical outcomes was rated down by 3 levels (Table 5). We concluded thatLTRAs are not more effective (or safer) than ICS in preschool children with recurrent wheeze (very low-quality evidence).

Other Key Factors

Although the ERS Task Force recommended distinguishing episodic viral from multiple trigger wheeze in preschool children, it recognized that the evidence base for this recommendation was limited.27 Since the publication of the Task Force Report, it has been shown that the clinical phenotype in preschool children may vary over time.31 In addition, a systematic review of ICS studies in preschool wheezing showed that ICS were effective in these patients irrespective of their clinical phenotype.32 The distinction between episodic viral and multiple trigger wheeze does not take severity and frequency of episodes into account, although this is the main driver for starting maintenance therapy.33 Finally, it has been shown that 90% of wheezing episodes in preschool children are associated with viral infection.34 According to the working group, this invalidates the concept of viral versus multiple trigger wheeze to an important extent, and it was felt that making the difference on clinical grounds is probably not feasible.

A relatively high value was placed on the fact that ICSs have proven benefits and are more effective than LTRAs in older (>6 years) children with asthma.35 Several as have shown effectiveness of ICSs compared with placebo in preschool children when wheezing is severe, with a family history of asthma and/or atopy.36–38 A relatively low value was placed by the guideline panel on the potential short-term growth delay in children using an ICS, because this is unlikely to influence final height.39 However, this will depend on dose and duration of ICS use.

Recommendation

In preschool children with mild intermittent (viral) wheeze, we suggest not starting any medication. In preschool children with recurrent (severe) wheeze and/or a family history of asthma and/or atopy, we propose starting daily low-dose ICS (up to 250 μg of fluticasone equivalent per day) as the preferred first-line therapy. Daily LTRA therapy is second-line therapy that can be used when inhalation technique is poor or long-term higher dose ICS is necessary (weak recommendation).

Question 3: In Children With Asthma Symptoms Despite ICS, What Is the Most Effective and/or Safe Treatment Option: Doubling the ICS Dose, Adding an LABA, or Adding an LTRA?

Rationale

Asthma management now focuses on clinical control rather than severity. In children whose asthma remains uncontrolled despite adequate ICS use, step-up treatment is advised. However, the most effective step-up strategy is still unclear.

Evidence

We found 1 Cochrane review and 2 more recently published RCTs.40–45 The Cochrane review included 5 studies in children aged 2 to 18 years with persistent asthma and daily ICS use for at least 28 days. Because asthma symptoms despite ICS were not a prerequisite for inclusion, 3 of the studies in the Cochrane review could not answer our question.45–47 Four RCTs (2 from Cochrane review and 2 more recently published trials) were included.40,42,46,47 Children with ongoing symptoms during ICS use were randomized to either a double dose of ICS or adding an LABA. Only 1 study included a third arm: adding an LTRA to ICS.40 The primary outcome after 16 weeks of treatment was a composite endpoint comprising exacerbations, asthma-control days, and the surrogate end point FEV1 (change of 5%). Asthma control days were not separately reported. Pooling of results was impossible because of clinical heterogeneity. There were no significant differences between the double-dose ICS group and the adding an LABA group for asthma symptoms (except for 1 study) and exacerbations (Table 6). Two studies looked at a difference in treatment effect between subgroups based on FEV1 or FeNO; no difference was found.40,42

The quality of evidence for our critical outcomes was rated down by 3 levels (Table 6). We concluded that both adding an LABA and doubling ICS are effective in children with symptoms despite ICS, irrespective of airway reversibility of airway inflammation (very low-quality evidence). Only 1 study compared LTRA with ICS and LABA with ICS and provided insufficient evidence (compared with ICS and LABA) to position LTRA prominently in step 3 asthma management.

Other Key Factors

A relatively high value was placed on safety. The US Food and Drug Administration recently issued a black box warning and label changes for LABAs because of an excess of severe asthma exacerbations in adults treated with them.48 A systematic review and a recently published meta-analysis expressed the same concern in children.41,49 In children, long-term safety studies on LABA are lacking, and existing trials were underpowered to exclude relevant differences in (severe) exacerbations.
A low value was placed on short-term and surrogate growth outcome parameters, as described earlier.39 High-dose ICS (400 mg per day fluticasone equivalent) is associated with adrenal insufficiency, and therefore 400 mg fluticasone equivalent is the maximum allowed dose.50–52 In addition, convenience and cost (resources) played a role in our final recommendation: we considered it easier to double the dose of ICS than to write a new prescription (with LABA/ICS), and ICSs are generally cheaper than LABA/ICS combinations.

**Recommendation**

In children with asthma and symptoms despite a low to moderate dose of ICS (up to 250 mg of fluticasone equivalent per day), we propose first doubling the ICS dose (weak recommendation). If insufficient improvement of symptoms is achieved after 6 to 12 weeks or a maximum ICS dose (weak recommendation) is reached, we recommend adding a LABA (for children <4 to 6 years; children with asthma control <4 to 6 years or children with exacerbations needing additional asthma medication: 123 vs 1.63 (P = .034). Patients requiring oral steroids: 25.5% vs 32.0%)

**DISCUSSION**

We have described the value of applying GRADE methodology to resolve controversial issues in the Dutch childhood asthma guideline. We have changed the recommendation regarding the use of LABAs in children with asthma control >4 to 6 years and asthma exacerbations in the context of viral-induced wheezing. The use of LABAs in children with asthma control >4 to 6 years and asthma exacerbations in the context of viral-induced wheezing has been increased from weak to moderate recommendation. The use of LABAs in children with asthma exacerbations needs additional asthma medication has been increased from very low to low recommendation.

**TABLE 5 GRADE Evidence Profile for Question 2: In Preschool Children With Viral-Induced Wheeze/Asthma, Are LTRAs More Effective (and/or Safer) Than ICS?**

<table>
<thead>
<tr>
<th>Study, N</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Overall Quality of Evidence per Outcome</th>
<th>Effect Size for ICS vs LTRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical outcome: symptom-free days</td>
<td>−1 (Serious risk of bias: uncertainty about several risk of bias items and high loss to follow-up)</td>
<td>0 (No serious inconsistency)</td>
<td>−1 (Serious indirectness: children with very mild symptoms; children with wheezing, but not viral wheeze; ICS via nebulizer and in high dosage)</td>
<td>0 (No pooled estimate)</td>
<td>−1 (Serious risk of publication bias: sponsoring/coauthorship of pharmaceutical companies)</td>
<td>☬ ☬ ☬ (Very low)</td>
<td>79% (95% CI, 70% to 81%) vs 73% (95% CI, 66%–79%) P = .86</td>
</tr>
<tr>
<td>Bacharier, N = 238</td>
<td>−1 (Serious risk of bias: uncertainty about several risk of bias items and high loss to follow-up)</td>
<td>−1 (Serious indirectness: one study showing no difference and the other showing more exacerbations in LTRA group)</td>
<td>0 (No pooled estimate)</td>
<td>−1 (Serious risk of publication bias: sponsoring/coauthorship of pharmaceutical companies)</td>
<td>☬ ☬ ☬ (Very low)</td>
<td>Hospital admissions: 2 (2.1%, 95% CI 0.25–7.3) vs 6.63%, 95% CI 2.4–15.4) P = .22</td>
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<tr>
<td>Szefer, N = 395</td>
<td>−1 (Serious risk of bias: uncertainty about several risk of bias items and high loss to follow-up)</td>
<td>−1 (Serious indirectness: children with very mild symptoms; children with wheezing, but not viral wheeze; ICS via nebulizer and in high dosage)</td>
<td>0 (No pooled estimate)</td>
<td>−1 (Serious risk of publication bias: sponsoring/coauthorship of pharmaceutical companies)</td>
<td>☬ ☬ ☬ (Very low)</td>
<td>Exacerbations needing additional asthma medication: 123 vs 1.63 (P = .034). Patients requiring oral steroids: 25.5% vs 32.0%</td>
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</table>

0, 95% confidence interval.

* RCTs start as "high" and can be downgraded a maximum of 5 levels to "very low." Downgrading: no, serious (−1 level), very serious (−2 levels).

* Pooling of data was only possible for exacerbations; results for asthma symptom score are presented per study.
<table>
<thead>
<tr>
<th>Study, N</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Overall Quality of Evidence per Outcome</th>
<th>Summary of Findings</th>
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<tr>
<td><strong>Critical outcome:</strong> symptom-free days</td>
<td></td>
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<tr>
<td>Gappa,44 N = 283</td>
<td>−1 (Serious risk of bias: uncertainty in risk of bias; follow-up too short [8–12 wk] and incomplete in 1 study)</td>
<td>−1 (Serious inconsistency: no significant differences in 2 studies—significantly more symptom-free days in add LABA group in 1 study)</td>
<td>−1 (Serious indirectness: children in trials do not resemble clinical practice [mild asthma, airway reversibility without symptoms])</td>
<td>−1 (No pooled estimate)</td>
<td>−1 (Serious risk of publication bias: sponsoring/coauthorship of pharmaceutical companies)</td>
<td>⊝⊝⊝ (Very low)</td>
<td>41.5 ± 34.5 vs 33.3 ± 31.4 difference 8.7 (95% CI 1.2–16.3)</td>
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<td>De Blic,45 N = 231</td>
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<td>19% vs 19%, P = .389 (% of weeks totally controlled) Difference 0.4% (95% CI –0.1 to 9.9, P = .93)</td>
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<tr>
<td>Vaessen,39 N = 257</td>
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<td><strong>Critical outcome:</strong> exacerbations</td>
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<tr>
<td>Gappa,44 N = 283</td>
<td>−1 (Serious risk of bias: Uncertainty in risk of bias Follow-up too short [8–16 wk] and incomplete in 1 study)</td>
<td>−1 (Serious inconsistency: Severe exacerbations in LABA/ICS group in 2 studies, no difference in 1 study and less oral steroid in LABA/ICS in 1 study)</td>
<td>−1 (Serious indirectness: children in trials do not resemble clinical practice [mild asthma, airway reversibility without symptoms])</td>
<td>−1 (No pooled estimate)</td>
<td>−1 (Serious risk of publication bias: sponsoring/coauthorship of pharmaceutical companies)</td>
<td>⊝⊝⊝ (Very low)</td>
<td>1 child in LABA/ICS severe tachycardia requiring hospitalization</td>
</tr>
<tr>
<td>De Blic,45 N = 231</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1% vs 1% Moderate/ severe: difference 5%, 95% CI –3% to 14%, P = .34); both severe in LABA/ICS</td>
</tr>
<tr>
<td>Vaessen,39 N = 257</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Oral steroids in LABA/ICS 30 compared with 47 in ICS and 43 in LTRA</td>
</tr>
<tr>
<td>Lemanske,37 N = 165</td>
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</table>

O, 95% confidence interval.

a RCTs start as “high” and can be downgraded a maximum of 3 levels to “very low.” Downgrading: no, serious (−1 level), very serious (−2 levels).

b Pooling of data was only possible for exacerbations; results for asthma symptom score are presented per study.
Evidence, imprecision, and publication bias. As a consequence, the overall quality of evidence for important outcomes will generally be lower with GRADE than with other grading systems. Indeed, the quality of evidence for our 3 controversial pediatric asthma management issues was “very low,” although they were all based on RCTs.

According to GRADE, guideline developers should start by specifying and ranking the most important outcomes. This helps guideline panels to focus attention on studies assessing the most important outcomes instead of those measuring surrogate end points. Instead of ranking the quality of each individual study, GRADE uses a rating of quality for each important outcome across studies. Symptom-free days and exacerbations were considered the most important (“critical”) outcomes. Although lung function is commonly used as a primary outcome parameter in studies on pediatric asthma management, we considered this to be of limited importance because there is no evidence that measuring lung function improves asthma outcomes and it is of limited value to patients and parents. Our selected outcomes are in keeping with a recommended set of outcomes by an American Thoracic Society/European Respiratory Society task force relating to pediatric asthma control for clinical trials and clinical practice, except for lung function end points. A systematic review of RCTs in children with asthma concluded that short-term disease activity (eg, lung function) is the most frequently measured outcome and that those endpoints that may be more relevant to patients (quality of life, side effects, and long-term consequences of asthma) are rarely taken into account. Choosing relevant outcomes helps us to weigh the evidence in a more clinically relevant manner.

Going from evidence to recommendations, GRADE recognizes that, in addition to quality of evidence, other key factors determine the strength of a recommendation. Desirable and undesirable consequences (benefits vs harm and burden) of the treatment options should be balanced by guideline panels, and patient and clinician values and preferences should be taken into account. For these preferences and values, evidence is often lacking, and not all statements and choices made can be answered by evidence. However, they do play an important role in clinical decision-making and should therefore not be disregarded. Quality of evidence and strength of recommendations are thus separated in the GRADE approach; low-quality evidence can lead to a strong recommendation and vice versa. For the majority of pediatric illneses, high-quality evidence for important outcomes is scarce. Treatment decisions in daily practice are therefore mainly based on other considerations, which are often not explicitly mentioned. We specifically describe the other key factors underlying our final recommendations. For example, we specifically considered the balance between benefits and harms, and this led to the recommendation to first double the dose of ICS in step 3 because safety was considered crucial. As a result, this recommendation differs from the recommendations in most other guidelines. We do recognize that for guideline panels in other countries, the preferences and values can be different, leading to different recommendations.

A weakness of our guideline development process was the fact that we did not include patient representatives in our guideline panel. Preferences and values that patients assign to the outcomes of interest can be different from those of clinicians. We did place a high value on long-term safety because we know this is of particular importance to patients. Although clinical practice guidelines can facilitate translation of research into effective clinical care, they are commonly not followed in clinical practice. One of the main concerns hampering the implementation of guidelines in clinical practice is that there is no explicit link between the recommendations and the supporting evidence. The GRADE approach, by transparently defining each essential step in recommendation development, facilitates understanding of how recommendations are being derived. That this may indeed enhance implementation was recently illustrated by a randomized trial comparing 4 methods of presenting recommendations to clinicians based on the same evidence. The GRADE system was most effective in provoking change in the pediatrician’s decision on a hypothetical clinical case. Therefore, future updates of guidelines on asthma management should preferably be developed according to GRADE methodology.

GRADE does not eliminate the need for judgments in interpreting the evidence, and there are no fixed criteria for downgrading the quality of evidence by 1 or 2 levels. However, GRADE does offer an explicit account of the judgments involved. It is likely that this facilitates the adaptation of guidelines for local use. Despite a range of published studies, the lack of high-quality evidence supporting decisions about asthma treatment in children remains considerable. The GRADE approach can help to identify remaining research gaps and specify the design of studies to fill these gaps. By applying these additional factors influencing the quality of evidence, we identified a number of

<table>
<thead>
<tr>
<th>TABLE 7</th>
<th>Main Weaknesses of Studies on Pediatric Asthma Management</th>
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<tbody>
<tr>
<td>Noninferiority design with surrogate end points</td>
<td>Children included in the studies are different than those seen in clinical practice</td>
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<tr>
<td>Studies underpowered to detect differences in critical outcomes</td>
<td>Too short follow-up time for critical outcomes and adverse effects</td>
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<tr>
<td>Sponsoring/ coauthorship of pharmaceutical companies</td>
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</table>
weaknesses in the studies on the controversial asthma management issues (Table 7).

We think that future randomized trials in pediatric asthma management should consider GRADE criteria from the design of the trial onwards, to ensure that the study results will generate high-quality evidence to guide clinical decision-making. Ideally, such trials should not be designed by pharmaceutical industry but by independent agencies. Studies should be powered to be able to detect differences in critical outcomes. Relevant patient characteristics, extending beyond the diagnosis of “asthma” and a lung function criterion should be defined in detail. Designing and running such high-quality clinical trials requires international collaboration. The large multinational clinical trial recently launched to resolve the uncertainty regarding the safety of LABAs, initiated by the Food and Drug Administration, is an example of such a high-quality study fulfilling all GRADE criteria and is therefore likely to provide the high-quality evidence needed to resolve this controversial issue.

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Pediatrics; originally published online August 27, 2012;
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