Nebulized Inhaled Corticosteroids in Asthma Treatment in Children 5 Years or Younger: A Systematic Review and Global Expert Analysis

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Although nebulized corticosteroids (NebCSs) are a key treatment option for young children with asthma or viral-induced wheezing (VIW), there are no uniform recommendations on their best use. This systematic review aimed to clarify the role of NebCSs in children 5 years or younger for the management of acute asthma exacerbations, asthma maintenance therapy, and the treatment of VIW. Electronic databases were used to identify relevant English language articles with no date restrictions. Studies reporting efficacy data in children 5 years or younger, with a double-blind, placebo- or open-controlled, randomized design, and inclusion of 40 or more participants (no lower patient limit for VIW) were included. Ten articles on asthma exacerbation, 9 on asthma maintenance, and 7 on VIW were identified. Results showed NebCSs to be at least as efficacious as oral corticosteroids in the emergency room for the management of mild to moderate asthma exacerbations. In asthma maintenance, nebulized budesonide, the agent of focus in all trials analyzed, significantly reduced the risk of further asthma exacerbations compared with placebo, cromolyn sodium, and montelukast. Intermittent NebCS treatment of VIW was as effective as continuous daily treatment. In summary, NebCSs are effective and well tolerated in patients 5 years or younger for the management of acute and chronic asthma.

Key words: Nebulization; Pediatric; Asthma; Viral-induced wheezing; Inhaled corticosteroids; Budesonide; Beclomethasone; Fluticasone; Asthma exacerbation; Asthma maintenance

INTRODUCTION

Asthma is one of the most common chronic diseases of childhood; it can be associated with a significant burden of disease, affecting normal sleep and activity levels, thereby influencing physical and social development. It is defined by a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough that vary in intensity and over time, and occur along with variable expiratory airflow limitation. Wheezing, however, is common among children aged 5 years and younger, typically occurring in association with viral respiratory tract infections (RTIs). Viral-induced wheezing (VIW) in young children is a heterogeneous condition that does not necessarily indicate asthma per se, although it may predict subsequent wheezing and asthma. Wheezing phenotypes have been proposed but none have been validated as identifying individuals responding to specific therapeutic approaches.

The differential diagnosis of VIW and asthma in young children is particularly challenging because it must be made mainly on symptoms and clinical context (eg, personal and family history of atopy, and frequency and duration of wheezing) owing to difficulties in obtaining high-quality test results for airflow limitation and bronchodilator responsiveness. In the absence of a clear diagnosis, a probability-based approach is often used.

The Global Initiative for Asthma and the Pediatric Asthma Yardstick give guidance for the initial treatment of preschool
children with wheezing regardless of whether the diagnosis of asthma has been made. Subsequent therapy recommendations follow a stepwise approach, based on symptom pattern, risk of exacerbations, medication side effects, and response to initial therapy (Figure 1).

Inhaled therapy is the cornerstone of asthma treatment among children aged 5 years and younger, with the choice of device based on the child’s age and capability. The preferred drug delivery system recommended by the Global Initiative for Asthma for young children is a pressurized metered-dose inhaler (pMDI) plus a spacer, with a facemask in individuals aged 0 to 3 years and without one in those aged 4 to 5 years. When a spacer is used, the delivery time is relatively short; however, many children are unable to use a pMDI even with a spacer, for instance, because they are too young, or too ill to use a handheld device. Nebulizers represent an important alternative to pMDIs, delivering a therapeutic dose of medicine over approximately 15 minutes, and permitting medication to be delivered to the lungs of patients of any age, with good distribution within the lungs. Tidal breathing can be used with both delivery systems.

Advantages of nebulized corticosteroids (NebCSs) include the potential to administer multiple medications simultaneously and the ability to modify the dose of inhaled corticosteroid (ICS). Primary disadvantages of nebulizers can include lack of portability, length of time required for administration, and cost. As shown in Table 1, nebulized therapy, with a breath-enhanced mouthpiece if appropriate, can be considered reliable, easy to use, efficacious, and efficient, especially for younger patients with asthma.

Despite the important role of NebCSs in the treatment of young children with asthma or VIW, there are no uniform recommendations on their most appropriate use beyond being an alternative to pMDIs. Also, there remain gaps in our understanding on the use of NebCSs relative to oral corticosteroids, which are frequently included as part of standard-of-care treatment for the management of acute asthma exacerbations in young children. This has resulted in local and regional variability in the use of NebCSs around the world. To clarify issues surrounding the use of NebCSs in young children, a Pediatric Expert Panel Meeting, organized and funded by AstraZeneca, was convened on January 20, 2018, in London, United Kingdom. Attendees who are locally recognized as experts in inhaled therapy were selected from different regions in the world. Discussions during the meeting highlighted the need for a systematic review and global expert analysis to form the basis of clinical recommendations that identify children who will benefit from the use of NebCSs. This review reports the outcomes of this analysis, with the specific aims of clarifying the role and correct use of NebCS for the management of acute asthma exacerbations, asthma maintenance therapy, and the treatment of VIW in children aged 5 years or younger.

METHODS

This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols guidelines. PRISMA Protocols consists of a 17-item checklist that is designed to facilitate the preparation and reporting of a robust protocol for the systematic review. Searches were initially conducted in November 2018 and repeated in October 2019 with no new records identified.

Literature search methods

Electronic databases, including EMBASE and PubMed, were used to identify relevant English language articles. Two separate searches were carried out. The first used terms such as “nebulized” (or “nebulizer”), “corticosteroid,” AND “asthma.” The second included the term “wheeze” or “wheezing” in place of “asthma.” Searches of PubMed used filters to identify studies of infants and children where possible. Inclusion of published abstracts was permitted if the primary outcomes of interest were reported. If 2 or more articles were published using results from the same cohort, the publication with the most complete data was included. Additional studies were identified through hand searching.

Inclusion criteria

To be eligible for inclusion, articles needed to be English language publications of studies on acute asthma, asthma maintenance therapy, or VIW that reported efficacy data in children aged 5 years or younger, with a double-blind, placebo-controlled or open-controlled, randomized design, or meta-analysis, with 40 or more patients (no lower subject limit was imposed in the VIW analysis).

Abstract review

Details of the studies meeting the inclusion criteria were then reviewed, summarized, and categorized according to whether they described the use of NebCSs in the management of acute asthma exacerbation, for maintenance asthma therapy, or for the management of VIW. Two authors independently reviewed each group of abstracts identified by the literature search: J.G.H. and O.V.Z. reviewed abstracts relating to acute asthma, G.W. and A.E.B. examined those relating to asthma maintenance, and D.I.-L. and K.R.M. assessed those relating to VIW. S.E.P. provided an overall review. In cases in which the reviewers could not determine whether an article met the eligibility criteria from the abstract alone, a full-text copy of the article was retrieved for review. The reviewers were not masked as to author or journal name. Meta-analyses were not used for data extraction but were included in the initial searches to validate that all articles had been identified.

RESULTS

Asthma

The literature searches yielded a total of 499 articles on the use of NebCSs in asthma. After examination of study abstracts, 135 were deemed appropriate for full-text review. The complete PRISMA flow diagram is shown in Figure 2, A. Studies eligible for inclusion were separated into those describing the use of NebCSs for the management of acute asthma exacerbations (n = 10) and those investigating asthma maintenance therapy (n = 9). It should be noted, however, that although the inclusion
FIGURE 1. The Pediatric Asthma Yardstick flowchart for preschool children (aged ≤5 years). A stepwise approach to long-term management of asthma. Figure adapted from Chipps et al.4 and reproduced with permission. ED, Emergency department; FP, fluticasone; ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting $\beta_2$-agonist; TRACK, Test for Respiratory and Asthma Control in Kids. *Before stepping up therapy, confirm that the increased level of symptoms is due to asthma. The patient should be assessed for nonadherence to the management plan, potential comorbidities, and other factors that might have a negative impact on response to therapy, including an age-appropriate understanding of asthma and the management plan as well as parent and/or caregiver knowledge.
criteria specified only those studies that reported efficacy data in children aged 5 years or younger, some studies including children older than 5 years were not excluded from the review. For example, studies involving children aged 6 months to 6 years and those with results stratified by age group were retained because they contributed relevant data on the population of interest.

**Asthma exacerbations.** The 10 included randomized controlled studies were published between 1995 and 2017, and included a total of 1018 children.\textsuperscript{13-22} The studies, summarized in Table II, included reports on budesonide (n = 7), fluticasone (n = 2), flunisolide (n = 1), beclomethasone (n = 1), and dexamethasone (n = 1). Three studies compared budesonide with control/placebo and 2 compared budesonide with oral corticosteroids; 1 study each compared dexamethasone and fluticasone with oral corticosteroid. One study compared beclomethasone with placebo, and 1 study compared budesonide with fluticasone and 1 with flunisolide. Addition of budesonide 1 mg twice a day for up to 5 days to standard treatment for children hospitalized for asthma
exacerbation resulted in a significantly shorter length of stay than placebo (44 hours vs 80 hours; $P = .01$). This improvement occurred despite the fact that the standard-of-care background therapy included intravenous methylprednisolone as well as salbutamol and ipratropium bromide. A post hoc analysis of a double-blind, randomized controlled study in children with recurrent wheezing, who were recruited at an outpatient pediatric special care unit during an acute wheezing episode, compared beclomethasone with placebo during the first week of treatment. The proportion of symptom-free days was 54.7% in the beclomethasone group and 40.5% in the placebo group ($P = .012$). The proportion of patients without asthma symptoms over this period was also higher in the beclomethasone group than in the placebo group (odds ratio, 2.65; 95% CI, 1.08-6.51; $P = .033$).

Two trials of single-dose budesonide initiated in the emergency room (ER) showed no significant improvements in asthma or pulmonary index scores compared with placebo; these studies also failed to demonstrate improvements in other end points, including respiratory rate, heart rate, oxygen saturation, or use of a bronchodilator. However, 1 study showed that budesonide-treated patients were discharged from the hospital emergency department significantly faster than placebo-treated patients ($P = .02$). Taken together, these results suggest that a single dose of NebCS is insufficient for the treatment of asthma exacerbations but that repeated doses can be effective as add-on therapy to systemic steroids in the setting of acute exacerbation.

Because systemic corticosteroids are frequently included as part of standard-of-care treatment for the management of acute asthma exacerbations in young children, it is critical to evaluate the efficacy and safety of NebCSs versus this approach, and 4 such studies were identified. In a recent investigation, children admitted to hospital owing to mild asthma exacerbation were randomized to receive either budesonide 1 mg twice a day or intravenous prednisolone 0.5 mg/kg 3 times a day, with the dose of each medication gradually reduced and ultimately discontinued after the disappearance of wheezing. The average time to elimination of wheezing was 5 days in both groups, with patients receiving a total of 5 days of corticosteroid treatment. Nebulized budesonide was at least noninferior to systemic corticosteroids in children younger than 3 years. A study in children presenting at a pediatric emergency service compared 3 doses of...
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Intervention</th>
<th>No. of patients (intervention 1 vs intervention 2)</th>
<th>Duration of treatment</th>
<th>Outcome (key efficacy end point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Razi et al, 2015</td>
<td>Double-blind, randomized controlled trial</td>
<td>Children aged 7-72 mo hospitalized with asthma exacerbation</td>
<td>BUD 1 mg bid vs PBO</td>
<td>50 vs 50</td>
<td>Up to 5 d</td>
<td>Length of hospital stay was 44 h with BUD vs 80 h with PBO ($P = .01$)</td>
</tr>
<tr>
<td>Papi et al, 2011</td>
<td>Double-blind, randomized controlled trial</td>
<td>Children aged 1-4 y with acute wheezing episode and history of recurrent wheezing</td>
<td>BDP 400 μg bid vs PBO</td>
<td>110 vs 56</td>
<td>7 d</td>
<td>Significantly more symptom-free days in the BDP group vs the PBO group (54.7% vs 40.5%, respectively; $P = .012$)</td>
</tr>
<tr>
<td>Sung et al, 1998</td>
<td>Double-blind, randomized controlled trial</td>
<td>Children aged 6 mo to 18 y with moderate to severe asthma presenting at emergency department</td>
<td>BUD 2 mg vs PBO</td>
<td>24 vs 20</td>
<td>Single dose</td>
<td>Median PIS after 1 h was 5.0 in the BUD group vs 6.0 in the PBO group ($P = .07$)</td>
</tr>
<tr>
<td>Upham et al, 2011</td>
<td>Double-blind, randomized controlled trial</td>
<td>Children aged 2-18 y with moderate to severe acute asthma</td>
<td>BUD 2 mg vs PBO</td>
<td>91 vs 88</td>
<td>Single dose</td>
<td>Asthma score –3 in both groups ($P = .64$). No significant difference in respiratory rate, heart rate, oxygen saturation, or number of hospital admissions</td>
</tr>
<tr>
<td>Saito et al, 2017</td>
<td>Randomized controlled trial</td>
<td>Children aged &lt;3 y with history of expiratory wheezing and mild asthma exacerbation</td>
<td>BUD 1 mg bid vs PDL 0.5 mg/kg IV tid</td>
<td>30 vs 20</td>
<td>As needed</td>
<td>Wheezing and steroid therapy continued for 5 d in both groups</td>
</tr>
<tr>
<td>Devidayal et al, 1999</td>
<td>Double-blind, randomized controlled trial</td>
<td>Children aged 2-12 y with moderate asthma attack (39% and 49% were aged 2-5 y in budesonide and prednisolone groups, respectively)</td>
<td>BUD 800 μg dose at half-hour intervals (3 doses) vs oral PDL 2 mg/kg</td>
<td>41 vs 39</td>
<td>3 doses</td>
<td>Significantly greater improvement in mean respiratory rate, heart rate, PIS, and respiratory distress assessment scores (all $P &lt; .05$) for BUD vs PDL. Significantly more BUD-treated patients had oxygen saturation &gt;95% than PDL-treated patients (40% vs 19%, respectively; $P &lt; .01$)</td>
</tr>
<tr>
<td>Demirca et al, 2015</td>
<td>Double-blind, randomized controlled trial</td>
<td>Children aged 1-16 y with moderate asthma attack</td>
<td>FP 500 μg qid vs oral methyl-PDL 1 mg/kg/d (4 d) → 0.5 mg/kg/d (3 d)</td>
<td>39 vs 41</td>
<td>7 d</td>
<td>Mean PIS decreased from 8 to 1 in both groups (both $P &lt; .0001$)</td>
</tr>
<tr>
<td>Scarfone et al, 1995</td>
<td>Double-blind, randomized controlled trial</td>
<td>Children aged 1-17 y with moderate asthma exacerbation</td>
<td>DEX 1.5 mg/kg vs 2 mg/kg oral PDN</td>
<td>56 vs 55</td>
<td>Single dose</td>
<td>21% and 31% in the DEX and PDN groups, respectively, required hospitalization ($P = .26$); 23% and 7% in the DEX and PDN groups, respectively, were discharged home within 2 h ($P = .02$)</td>
</tr>
<tr>
<td>De Benedictis et al, 2005</td>
<td>Single-blind, randomized controlled trial</td>
<td>Children aged 4-15 y with asthma exacerbations</td>
<td>BUD 500 μg bid vs FP 250 μg bid</td>
<td>87 vs 81</td>
<td>10 d</td>
<td>Morning PEF increased 44 L/min with FP and 39 L/min with BUD ($P = .032$)</td>
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</tbody>
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(continued)
budesonide 800 μg at 30-minute intervals with a single oral dose of prednisolone 2 mg/kg. Both treatments caused significant improvements in symptoms, but budesonide was associated with a significantly greater improvement in respiratory rate, heart rate, pulmonary index score, and respiratory distress assessment score (all \( P < .05 \)), and the proportion of patients with saturated oxygen level greater than 95% (\( P < .01 \)). Similar results were seen in a study of children with acute asthma exacerbations presenting at the ER who received fluticasone 500 μg 4 times a day or oral methylprednisolone 1 mg/kg/d. Both treatments were associated with significant decreases in pulmonary index score, total symptom scores, and total medication score, and a significant increase in peak expiratory flow (PEF) (all \( P < .001 \)). There were no significant differences between the 2 arms, suggesting that nebulized fluticasone has equal clinical efficacy to oral methylprednisolone for treating moderate asthma attacks. Although not widely used clinically, nebulized dexamethasone has been studied in younger children for the management of acute asthma attacks. One report suggested a rapid onset of action for nebulized dexamethasone 1.5 mg/kg, with 23% of children experiencing an improvement within 2 hours of treatment (\( P < .05 \)). In another study, patients were stratified by age, children aged 4 to 6 years treated with budesonide had a greater improvement than those receiving fluticasone in morning PEF (34 L/min vs 20 L/min, respectively) and evening PEF (44 L/min vs 24 L/min, respectively), but these differences were not statistically significant. A second study compared budesonide with flunisolide in children aged 3 to 5 years. Both treatments significantly improved oscillometric resistance and total symptom scores at days 7 and 21, with flunisolide giving significantly better results than budesonide at day 7 (\( P < .05 \)) but not at day 21.

NebCSs were generally well tolerated in these studies and no significant adverse events (AE) were reported. This included studies comparing budesonide with placebo in which there were no important differences in the incidence of AEs between treatment groups. In addition, studies measuring serum cortisol levels found no change with NebCSs relative to pretreatment/baseline levels, and relative to placebo after the short courses of treatment used in this setting. One investigation found a significant decrease in serum cortisol level after intravenous prednisolone treatment (\( P = .0036 \)), highlighting one of the key advantages of nebulized administration of corticosteroids in acute asthma therapy.

**Asthma maintenance.** Nine articles from 8 studies published between 1996 and 2013, and including a total of 1681 children, were identified (Table III). Nebulized budesonide was the focus in all these trials. Three studies compared budesonide with control/placebo, 1 with beclomethasone, and 3 with other agents: cromolyn sodium (\( n = 2 \)) and montelukast (\( n = 1 \)). One early study attempted to determine the minimal effective dose for budesonide. Three separate double-blind, randomized placebo-controlled trials have been conducted, 1 each in children with mild, moderate, or severe asthma. In 1 study, infants younger than 30 months with severe asthma were randomized to receive 12 weeks of nebulized budesonide 1 mg twice a day or placebo. Significantly fewer patients in the budesonide arm versus the placebo arm were treated for at least 1 asthma exacerbation (40% vs 83%; \( P < .01 \)). Overall, 28% of children in the budesonide group, compared with 0% in the placebo group, had no exacerbations during the 12 weeks after the end of treatment (\( P < .05 \)). Budesonide-treated patients also had a significantly shorter duration of oral corticosteroid exposure than those receiving placebo (\( P < .05 \)). The other 2 studies were dose-ranging trials of 12 weeks’ duration, the severity of asthma being the only substantial difference between them. In the study of moderate persistent asthma, there was a significantly greater mean change from baseline in nighttime (\( P < .01 \)) and daytime (\( P < .05 \)) asthma symptom scores for all doses of budesonide versus placebo. A similar pattern was observed in children with mild persistent asthma, with the mean change from baseline in both nighttime and daytime asthma symptom scores being significantly better for all doses of budesonide versus placebo (all \( P < .05 \)). When interpreting the findings from these studies, it is important to note that in the absence of a universally accepted definition, there were differences in the author-applied descriptions of asthma severity. Although excluded from this systematic analysis owing to a higher mean patient age, a further study of nebulized budesonide in steroid-dependent children with asthma aged 4 to 8 years also demonstrated superiority of budesonide over placebo in improving nighttime and daytime asthma symptom scores.

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### TABLE II. (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Intervention</th>
<th>No. of patients (intervention 1 vs intervention 2)</th>
<th>Duration of treatment</th>
<th>Outcome (key efficacy end point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decinno et al.,22 2009</td>
<td>Randomized controlled trial</td>
<td>Children aged 3-5 y with acute moderate asthma attack</td>
<td>BUD 0.5 mg bid for 7 d → 0.25 mg bid for 14 d vs FLUN 40 μg bid for 7 d → 20 μg bid for 14 d</td>
<td>20 vs 20</td>
<td>21 d</td>
<td>Oscillometric resistance and total symptom scores significantly better with FLUN than with BUD at day 7 (( P &lt; .05 ), but not at day 21)</td>
</tr>
</tbody>
</table>

**BDP:** Beclomethasone; **bid:** twice a day; **BUD:** budesonide; **DEX:** dexamethasone; **FLUN:** flunisolide; **FP:** fluticasone; **IV:** intravenous; **PEF:** peak expiratory flow; **PRO:** placebo; **PDL:** prednisolone; **PDN:** prednisone; **PIS:** pulmonary index score; **qid:** 4 times a day; **tid:** 3 times a day.
### TABLE III. Summary of asthma maintenance studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Intervention</th>
<th>No. of patients</th>
<th>Duration of treatment</th>
<th>Outcome (key efficacy end point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szefler et al, 2013</td>
<td>Open-label, randomized controlled trial (post hoc analysis of younger patient cohort)</td>
<td>Children aged 2-4 y with mild persistent asthma</td>
<td>BUD 0.5 mg qd vs MON 4 mg qd</td>
<td>105 vs 87</td>
<td>52 wk</td>
<td>Time to use of additional asthma medication was 183 d for BUD and 86 d for MON ($P = .128$). Significantly fewer BUD-treated patients than MON-treated patients required OCS at 52 wk (21.9% vs 37.1%; $P = .022$)</td>
</tr>
<tr>
<td>Wennergren et al, 1996</td>
<td>Double-blind, randomized controlled trial</td>
<td>Children aged ≥6 mo to &lt;4 y with uncontrolled moderately severe to severe asthma</td>
<td>Starting dose: BUD 0.25 mg bid vs BUD 1.0 mg bid, followed by down titration</td>
<td>52 vs 50</td>
<td>18 wk</td>
<td>Minimum effective dose of BUD was 0.25 mg bid in 48 of 102 patients. Health care utilization decreased from 50% during run-in to 15%-20% after randomization</td>
</tr>
<tr>
<td>de Blic et al, 1996</td>
<td>Double-blind, randomized controlled trial</td>
<td>Infants aged &lt;30 mo with severe asthma</td>
<td>BUD 1 mg bid vs PBO</td>
<td>20 vs 18</td>
<td>12 wk</td>
<td>40% of BUD-treated patients vs 83% of PBO-treated patients had 1 exacerbation ($P &lt; .01$)</td>
</tr>
<tr>
<td>Kemp et al, 1999</td>
<td>Double-blind, randomized controlled trial</td>
<td>Children aged 6 mo to 8 y with mild persistent asthma</td>
<td>BUD 0.25, 0.5, and 1.0 mg qd vs PBO</td>
<td>91 vs 83 vs 93</td>
<td>12 wk</td>
<td>Mean change from baseline in nighttime asthma symptom scores was −0.49, −0.42, −0.42, and −0.16 for BUD 0.25 mg, 0.5 mg, and 1.0 mg, and PBO, respectively (all $P \leq .05$ vs PBO). Mean change in daytime asthma symptom scores was −0.26, −0.57, −0.46, and −0.50, respectively (all $P \leq .05$ vs PBO)</td>
</tr>
<tr>
<td>Baker et al, 1999</td>
<td>Double-blind, randomized controlled trial</td>
<td>Children aged 6 mo to 8 y with moderate persistent asthma</td>
<td>BUD 0.25 mg qd, 0.25 mg bid, 0.5 mg bid, and 1.0 mg qd vs PBO</td>
<td>94 vs 99 vs 98</td>
<td>12 wk</td>
<td>Mean change from baseline in nighttime asthma symptom scores was −0.28, −0.49 ($P \leq .001$ vs placebo), −0.42 ($P \leq .01$), −0.40 ($P \leq .01$), and −0.13 for BUD 0.25 mg qd, 0.25 mg bid, 0.5 mg bid, and 1.0 mg qd, and PBO, respectively. Mean change in daytime asthma symptom scores was −0.28, −0.40 ($P \leq .05$ vs PBO), −0.46 ($P \leq .01$), −0.37 ($P \leq .05$), and −0.13, respectively</td>
</tr>
<tr>
<td>Leflein et al, 2002; Murphy et al, 2003</td>
<td>Open-label, randomized controlled trial</td>
<td>Children aged 2-6 y with persistent asthma</td>
<td>BUD 0.5 mg/d vs CROM 20 mg qid</td>
<td>168 vs 167</td>
<td>52 wk</td>
<td>The mean rate of asthma exacerbations was 1.23/y for BUD and 2.41/y for CROM ($P &lt; .001$ for difference)</td>
</tr>
<tr>
<td>Nagakura et al, 2012</td>
<td>Open-label, randomized controlled trial</td>
<td>Children aged 6 mo to 5 y with mild to moderate persistent asthma</td>
<td>BUD 0.5 mg/d vs CROM 20 mg bid or tid</td>
<td>21 vs 23</td>
<td>12 wk</td>
<td>Nighttime asthma symptom scores occurred in both groups, with marked reductions within 1-2 wk</td>
</tr>
<tr>
<td>Delacourt et al, 2003</td>
<td>Open-label, randomized controlled trial</td>
<td>Children aged 6 mo to 6 y with severe persistent asthma</td>
<td>BDP 800 µg/d bid vs BUD 750 µg/d bid</td>
<td>62 vs 68</td>
<td>14 wk</td>
<td>40.4% of BDP-treated patients and 51.7% of BUD-treated patients had no asthma exacerbations ($P = .22$ for difference)</td>
</tr>
</tbody>
</table>

**Note:** BDP: Beclomethasone; bid: twice a day; BUD: budesonide; CROM: cromolyn sodium; MON: montelukast; OCS: oral corticosteroid; PBO: placebo; qd: once a day; qid: 4 times a day; tid: 3 times a day.
nebulized budesonide is clinically effective for the control of asthma in young children.

Nebulized budesonide has been compared with cromolyn sodium and the leukotriene receptor antagonist montelukast, both of which have been used for maintenance treatment of mild persistent asthma in children. In a 52-week study in children aged 2 to 6 years with persistent asthma, the mean rate of asthma exacerbations was 1.23 per year with budesonide, significantly less than the 2.41 per year reported with cromolyn sodium \((P < .001)\).25 There was also a significantly longer time to the first asthma exacerbation with budesonide than with cromolyn sodium \((P < .001)\). This study also showed that budesonide inhalation suspension provided better overall child health status, as well as greater caregiver quality of life and caregiver satisfaction, convenience, ease of use, and treatment compliance.27 A second study showed a marked improvement in nighttime asthma symptom scores within 1 to 2 weeks with both treatments, as well as improvements in daytime asthma symptom scores, cough scores, and nighttime awakening during the 12-week study period.30 Budesonide 0.5 mg once a day was compared with montelukast 4 mg once a day in children aged 2 to 4 years with mild persistent asthma, in a 52-week study,1 which found no significant difference in the primary end point of time to first use of additional asthma medication for mild or severe asthma exacerbation \((P = .128)\), although the median was numerically greater for budesonide than for montelukast (183 days vs 86 days, respectively). A number of secondary end points favored budesonide, with significantly fewer patients requiring oral corticosteroids at 12, 26, and 52 weeks \((P < .05)\) at all timepoints, resulting in a 50% reduction in oral corticosteroid exposure. In addition, physicians reported a statistically significant greater improvement in asthma symptom scores with budesonide than with montelukast at week 12 \((P = .021)\); similarly, caregivers reported a greater ability to manage the child’s symptoms and health compared with baseline at week 12 and at end of study \((P < .05)\).

Finally, 1 open-label, randomized controlled trial compared budesonide 750 \(\mu\)g/d twice a day with beclomethasone 800 \(\mu\)g/d twice a day in children aged 6 months to 6 years.31 The study met its primary objective of demonstrating similar efficacy for nebulized beclomethasone and nebulized budesonide, with no significant difference in the proportion of patients who did not experience at least 1 major asthma exacerbation during the study \((P = .22)\). Other parameters, including the number of major plus minor exacerbations, the total number of exacerbations/patient/d, the time to first major exacerbation, bronchodilator use, and oral corticosteroid use, were also not significantly different in the 2 treatment groups, suggesting that both interventions were efficacious.

The long-term safety of NebCSs is of greater concern in the context of chronic use for asthma maintenance than for the treatment of asthma exacerbations. The studies reported here found no important treatment-emergent AEs, and no significant difference in this respect between NebCSs and comparators.5,24-28,30,31 Hypothalamic-pituitary-adrenal axis suppression and the potential for growth retardation is of particular concern in young children taking long-term corticosteroids, even when the medication is administered directly to the lungs. However, basal and adrenocorticotropic hormone-stimulated plasma cortisol levels, as well as urinary and salivary cortisol levels, were unchanged in most of these studies with nebulized budesonide.26-28,30,31 One investigation found morning serum cortisol levels below the level of detection in more patients taking budesonide 1 mg twice a day than in those receiving budesonide 0.25 mg twice a day, suggesting a possible dose-response relationship.24 A second study reported a change in growth, with a mean increase in height of 6.69 cm in the budesonide 0.5 mg/d group and 7.55 cm in the cromolyn sodium group over the course of the 52-week study period \((P < .001)\).25 A 52-week open-label extension to another study26 showed a small but statistically significant reduction in growth velocity between budesonide and placebo groups (6.55 ± 2.08 cm/y vs 7.39 ± 2.52 cm/y, respectively; \(P = .002)\). However, most studies24,25,27,31,32 have shown no impact on growth.

Viral-induced wheezing

The literature searches yielded a total of 102 relevant articles on the use of NebCSs in VIW. After examination, 28 articles were deemed appropriate for full-text review. The complete PRISMA flow diagram is shown in Figure 2, B. Ultimately, 7 articles met all the search criteria and were included in the systematic review.

The 7 studies were published between 1986 and 2014 and included a total of 1184 children (Table IV).3-39 Budesonide \((n = 4)\) and beclomethasone \((n = 3)\) were the only corticosteroids included in these trials. Three studies compared beclomethasone with control/placebo and 2 compared budesonide with control/placebo. Some studies included comparisons of different formulations or treatment regimens for budesonide \((n = 2)\) or compared budesonide with montelukast \((n = 1)\).

Three studies included nebulized beclomethasone. In a large study of more than 500 children with a history of VIW and at least 1 episode of viral wheezing in the preceding 12 months, there was no significant difference in the rate of wheezing between those treated for 10 days with beclomethasone 400 \(\mu\)g twice a day and those receiving placebo (6.8% vs 11.1%; \(P = .09)\).33 Two small pilot studies in this population yielded results consistent with those of the larger study.34,35

Two studies of nebulized budesonide failed to meet their primary end points, with no differences being found in terms of ER utilization, systemic steroid use, or episode-free days compared with control or montelukast.36,37 However, Bacharier et al38 reported significant reductions in breathing difficulty scores \((P = .003)\), interference with activity area under the curve \((P = .01)\), and total symptom score \((P = .02)\) with nebulized budesonide compared with placebo. Results with budesonide were not significantly different from those with montelukast for any of these measures. Durmaz et al39 observed that the duration of wheezing during upper RTIs was shortened in subjects treated as needed with budesonide and salbutamol during episodes compared with salbutamol therapy only, but no statistical significance was given.

One study compared the effect of daily budesonide (0.5 mg once a day increasing to 0.5 mg twice a day for 7 days during RTI) and intermittent treatment in which patients were treated with budesonide 1 mg twice a day for 7 days during RTI only, on the frequency of exacerbations requiring rescue therapy with oral corticosteroids.38 No difference between the 2 approaches was found, with a relative rate of prednisolone courses of 0.99 (95% CI, 0.71-1.35) for intermittent compared with daily treatments;
similar results were reported for the number of RTIs, number of urgent care visits, and number of days absent from school/day care. However, the lack of a placebo arm in this study limits its value. Another study compared different nebulized budesonide treatment strategies for the management of VIW in children with recurrent wheezing episodes. Patients were treated with either budesonide 0.25 mg twice a day or budesonide 1 mg twice a day, titrating down every second day until the dose had reached 0.25 mg.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Intervention</th>
<th>No. of patients</th>
<th>Duration of treatment</th>
<th>Outcome (key efficacy end point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clavenna et al, 2014</td>
<td>Double-blind, randomized controlled trial</td>
<td>Children aged 1-5 y with a history of VIW</td>
<td>BDP 400 μg bid vs PBO</td>
<td>264 vs 261</td>
<td>10 d</td>
<td>Wheezing diagnosed in 6.8% of patients with BDP and 11.1% of patients with PBO (P = .09)</td>
</tr>
<tr>
<td>Maayan et al, 1986</td>
<td>Double-blind, randomized, controlled cross-over trial</td>
<td>Children aged 15-36 wk who experienced recurrent persistent tachypnea, dyspnea, and expiratory wheezing during the first 3 mo of life</td>
<td>BDP 100 μg tid vs PBO</td>
<td>9</td>
<td>2 wk</td>
<td>Clinical score with BDP was 0.8 vs 3.2 at baseline and PBO (P &lt; .001 for difference).</td>
</tr>
<tr>
<td>Ghirga et al, 2002</td>
<td>Randomized controlled trial</td>
<td>Children aged 7-12 mo with a history of recurrent wheezing during upper RTI</td>
<td>BDP 400 μg tid for 5 days vs no intervention</td>
<td>13 vs 13</td>
<td>4 study periods</td>
<td>Respiratory rate fell from 48 breaths/min at baseline to 34 breaths/min with BDP (P &lt; .01)</td>
</tr>
<tr>
<td>Bacharier et al, 2008</td>
<td>Double-blind, randomized controlled trial</td>
<td>Children aged 12-59 mo with ≥2 episodes of wheezing in the context of RTI within past year</td>
<td>BUD 1 mg bid vs MON 4 mg qd vs PBO (all for 7 d)</td>
<td>96 vs 95 vs 47</td>
<td>12 mo</td>
<td>Proportion of episode-free days was 0.76, 0.73, and 0.74 in BUD, MON, and PBO groups, respectively</td>
</tr>
<tr>
<td>Durmaz et al, 2011</td>
<td>Randomized controlled trial</td>
<td>Children aged 6-36 mo with intermittent VIW</td>
<td>BUD 500 μg/d vs control</td>
<td>36 vs 30</td>
<td>3 mo</td>
<td>No difference in the number of ER visits or use of systemic corticosteroids</td>
</tr>
<tr>
<td>Zeiger et al, 2011</td>
<td>Double-blind, randomized controlled trial</td>
<td>Children aged 12-53 mo with ≥4 episodes of wheezing, positive values on modified API, and at least 1 exacerbation requiring systemic corticosteroids, emergency care, or hospitalization</td>
<td>BUD 0.5 mg qd → 0.5 mg bid for 7 d during RTI (daily regimen) vs PBO qd plus BUD 1 mg bid for 7 d during RTI (intermittent regimen)</td>
<td>139 vs 139</td>
<td>52 wk</td>
<td>Rescue oral glucocorticoid use 0.97/patient-year in daily regimen vs 0.95/patient-year for intermittent regimen (P = .60)</td>
</tr>
<tr>
<td>Volovitz et al, 1998</td>
<td>Double-blind, randomized controlled trial</td>
<td>Children aged 6 mo to 3 y with recurrent wheezing</td>
<td>BUD 1 mg bid followed by 25% decrease every 2 d until dose is 0.25 mg (high dose) vs 0.25 mg BUD bid (regular)</td>
<td>21 vs 21</td>
<td>10 wk</td>
<td>In the high-dose group, wheezing improved by 59.5% (P = .0001), diurnal cough improved by 38.3% (P = .036), nocturnal cough improved by 39.4% (P = .04), and total symptom scores improved by 45.5% (P = .004); β2-agonist use was reduced by 66.9% (P = .002). Improvements in the regular treatment group were 2.4%, 11.3%, 14.7%, 2.9%, and 43.7%, respectively</td>
</tr>
</tbody>
</table>

API, Asthma Predictive Index; BDP, beclomethasone; bid, twice a day; BUD, budesonide; MON, montelukast; OCS, oral corticosteroid; PBO, placebo; qd, once a day; tid, 3 times a day.
twice a day. Compared with the run-in period, wheezing in the high-dose group improved by 59.5% \((P = .0001)\), diurnal cough by 38.3% \((P = .036)\), nocturnal cough by 39.4% \((P = .04)\), and total symptom score by 45.5% \((P = .004)\), and the number of inhalations of \(\beta_2\)-agonists reduced by 66.9% \((P = .002)\); these values for the lower-dose group were 2.4%, 11.3%, 14.7%, 2.9%, and 43.7%, respectively.

Budesonide \((n = 4)\) and beclomethasone \((n = 3)\) were well tolerated in all the VIW studies, with few AEIs being reported, and no differences found between treatment arms.\(^{33,35,38-41}\) Two studies determined that treatment was not associated with changes in serum cortisol levels, even in patients receiving high initial doses of budesonide.\(^{35,40}\) Two additional studies found no effect of NebCSs on growth parameters.\(^{38,42}\)

**DISCUSSION**

Placebo-controlled studies in patients with acute asthma attacks/exacerbations failed to show any benefit for NebCSs in terms of asthma or pulmonary index scores, as well as on respiratory rate, heart rate, oxygen saturation, or bronchodilator use. However, NebCSs were associated with more rapid discharge from hospital and shorter lengths of stay. NebCSs were also found to be noninferior to systemic corticosteroids in treating acute asthma attacks/exacerbations. Nebulized \(\beta_2\)-agonist treatment was used as background therapy in all these studies; however, the minimum detectable improvements that can be demonstrated by asthma and pulmonary index scores are unknown, so the lack of differences observed may be due to insufficient sensitivity to measure any incremental benefit. Because nebulized \(\beta_2\)-agonists are the standard of care in this setting, addition of NebCSs does not impose an additional burden because both drugs can be dosed together.\(^1\) The demonstrated safety of a short course of relatively high-dose NebCSs indicates that there is little risk to young patients when NebCSs are used in acute asthma.

Nebulized budesonide was the ICS in all asthma maintenance studies identified. Budesonide was shown to be superior to both placebo and cromolyn sodium.\(^{25-30}\) Budesonide did not reach statistical significance relative to montelukast in terms of time to first use of additional medication for asthma exacerbation, but was superior in a number of secondary outcomes.\(^3\) This is consistent with recommendations in the Global Initiative for Asthma guidelines that low-dose ICS should be used as an initial controller medication, with montelukast as an alternative.\(^5\) The results of 1 further comparative study with no placebo arm indicated that nebulized beclomethasone was as effective as budesonide in asthma treatment.\(^1\)

This review exposes a key limitation in our understanding of the role of NebCSs in young children in that no studies were found that compared the efficacy and safety of NebCSs with that of ICS delivered via pMDI or other devices. Although data in young children are available comparing delivery via different inhalation techniques for bronchodilators,\(^{45}\) it would not be correct to extrapolate the results from such studies to ICS due to differences in particle size. Furthermore, although data are available indicating comparable efficacy and safety between ICS given by nebulization or pMDI in children aged 6 to 16 years with asthma exacerbations, the capabilities of older children are markedly different to those of young children, so again, the results may not be transferrable.\(^{44}\) In the absence of directly comparative data in young children, support for the use of NebCSs can be gained from results from real-world analyses, particularly in asthma maintenance therapy. For example, data from managed care claims have shown a reduced risk of hospitalization or emergency department visits for young children (63% of whom were aged \(\leq 4\) years) after initiation of nebulized budesonide as a controller medication (hazard ratio, 0.55; 95% CI, 0.41-0.76; \(P < .001\)), whereas other classes of controller medications, including other ICSs, oral corticosteroids, leukotriene receptor antagonists, and short- and long-acting \(\beta_2\)-agonists, showed no reduction in the risk of subsequent exacerbation.\(^{45}\) In a second analysis of a similar population, nebulized budesonide therapy initiated after an asthma-related emergency department visit was associated with a 29% lower risk of a subsequent event 31 to 180 days after the index event compared with no prescribed nebulized budesonide; no other controller medication was associated with a significant reduction in the risk of ER visit/hospitalization recurrence.\(^\) Of note, in children 4 years or younger, there was a 62% lower risk of recurrent asthma exacerbations with nebulized budesonide compared with budesonide delivered via nonnebulized routes, primarily by pMDI, equating to a 28% chance of further exacerbation with nebulized budesonide versus a 72% chance with non-NebCSs. It should be noted, however, that higher fill rates were recorded for nebulized budesonide inhalation suspension compared with nonnebulized ICS, which, although suggesting better adherence with nebulization, may also have influenced the results.\(^{46}\)

Concerns about the overuse of ICS and resulting adverse effects have led to the study of intermittent therapy for VIW. Intermittent treatment regimens can substantially decrease the cumulative exposure to corticosteroid. In 1 study, intermittent budesonide inhalation suspension was found to be comparable to daily budesonide inhalation suspension in terms of managing exacerbations, but with a total budesonide exposure approximately 100 mg, or 3.3-fold, lower over the 1-year study period.\(^{38}\) However, only 1 study showed that preemptive ICS reduced the incidence of wheezing episodes requiring treatment with systemic corticosteroids in children with a history of VIW,\(^{47}\) limiting the conclusions that can be drawn about the efficacy of intermittent therapy, and of NebCSs in VIW overall.

A potential weakness of this review is that it does not evaluate the relative efficacy of different nebulizer devices. The literature search identified a number of articles describing the drug deposition, exposure, and pharmacokinetics of ICS with different devices, but only 1 study investigated efficacy. This study showed that although drug delivery was different among nebulizer devices, there was no apparent difference in efficacy, as measured by the minimal effective dose.\(^{48}\) Other weaknesses include the fact that a number of the acute asthma studies enrolled a mixed population of children, younger and older than 5 years. Only 3 of 10 acute asthma studies were restricted to children 5 years or younger, and 1 of these was a post hoc analysis in patients with recurrent wheezing who were recruited during an acute episode.\(^{14,17,22}\) Some asthma maintenance studies also allowed older children to participate, but the upper age limit was 6 to 8 years in these cases. In addition, many of the studies in all 3 pathological entities included enrolled small numbers of patients, limiting the statistical power and strength of their individual conclusions; the 2 acute asthma studies involving only patients 5 years or younger included 40 and 50
patients, respectively.17,22 Finally, the doses and treatment regimens used, and the duration of study, varied among different reports; this was particularly the case for VIW (Table IV).

The results of this review indicate that NebCSs are well tolerated during both short- and long-term treatment. Most studies reviewed here included budesonide, with the drug being administered to 1711 children in 19 separate studies across all 3 indications, compared with the next most widely studied NebCS, beclomethasone (n = 458, in 5 studies). Importantly, nebulized budesonide resulted in no significant reduction in growth velocity compared with other asthma therapies, including ICS delivered via pMDI.32 In addition, treatment with inhaled budesonide has been shown to have no effect on final adult height.9 Growth data for other NebCSs are lacking.

CONCLUSIONS

NebCSs are effective for the treatment of acute asthma and for asthma maintenance in children aged 5 years or younger. Results of real-world studies suggest that nebulized therapy is both effective and easy to use. In acute asthma, nebulized therapy is already routine, and the addition of NebCSs improves outcomes while adding little or no risk. In maintenance therapy, continuous NebCSs have been shown to be effective in clinical studies, and in real-world data analyses nebulized budesonide has been found to be superior to other treatments, including ICS delivered by pMDI. Intermittent high-dose treatment of VIW with NebCSs is as effective as daily treatment while reducing overall corticosteroid exposure; however, data from well-controlled studies are lacking and among studies that have been conducted, not all were able to show efficacy for all measures. Taken together, evidence from double-blind, placebo-controlled, and randomized controlled trials and from real-world studies indicates that NebCSs are effective and well tolerated for the management of asthma in young children.

ACKNOWLEDGMENTS

Medical writing support, in accordance with Good Publications Practice and International Committee of Medical Journal Editors guidance, was provided by Darwin Healthcare Communications (London, UK) and funded by AstraZeneca.

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