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Nebulized Inhaled Corticosteroids in Asthma Treatment in Children ≤ 5 Years of Age:
A Systematic Review and Global Expert Analysis

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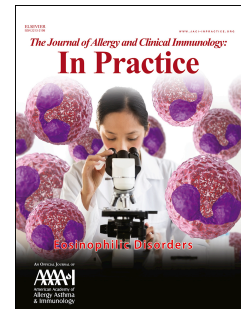
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ABSTRACT

Although nebulized corticosteroids (NebCS) 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 aims to clarify the role of NebCS in children aged ≤ 5 years for the management of acute asthma exacerbations, asthma maintenance therapy and for the treatment of VIW.

Electronic databases were used to identify relevant English language articles with no date restrictions. Studies reporting efficacy data in children aged ≤ 5 years, with a double-blind, placebo- or open-controlled, randomized design, and inclusion of ≥ 40 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 NebCS to be at least as efficacious as oral corticosteroids in the emergency room (ER) 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, NebCS are effective and well tolerated in patients aged ≤ 5 years 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

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77 **Abbreviations used**

78 *b.i.d. - twice a day*

79 *CI - confidence interval*

80 *ER - emergency room*

81 *ED - emergency department*

82 *GINA - Global Initiative for Asthma*

83 *ICS - inhaled corticosteroid*

84 *NebCS - nebulized corticosteroids*

85 *PEF - peak expiratory flow*

86 *pMDI - pressurized metered-dose inhaler*

87 *PRISMA-P - Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols*

88 *q.d. - once a day*

89 *q.i.d. - 4 times a day*

90 *RTI - respiratory tract infection*

91 *t.i.d. - 3 times a day*

92 *VIW - viral-induced wheezing*

93

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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.^{1,2} 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.¹ Wheezing, however, is common among children aged 5 years and younger, typically occurring in association with viral respiratory tract infections (RTIs).¹ 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.^{1,3} 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 as it must be made mainly on symptoms and clinical context (for example personal and family history of atopy, 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.¹

The Global Initiative for Asthma (GINA) 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.¹ Subsequent therapy recommendations follow a stepwise approach, based on symptom pattern, risk of exacerbations, medication side effects, and response to initial therapy (Figure 1).^{1,4}

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 GINA for young children is a pressurized metered-dose inhaler (pMDI) plus a spacer, with a facemask in individuals aged 0–3 years and without one in those aged 4–5 years.^{1,5} 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.^{6,7} Tidal breathing can be used with both delivery systems.⁸ Advantages of nebulized corticosteroids (NebCS) include the potential to administer multiple medications simultaneously and the ability to modify the dose of inhaled corticosteroid (ICS).⁴ Primary disadvantages of nebulizers can include lack of portability, length of time required for administration, and cost.⁴ As shown in Table I, 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.^{1,4,9,10}

Despite the important role of NebCS 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 NebCS relative to oral corticosteroids that are frequently included as part of standard-of-care treatment for the management of acute asthma exacerbations in young children.¹ This has resulted in local and regional variability in the use of NebCS around the world.^{7,11} In order to clarify issues surrounding the use of NebCS in young children, a Pediatric Expert Panel Meeting, organized and funded by AstraZeneca, was convened on January 20, 2018 in London, UK. 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 NebCS. 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 for the treatment of VIW in children aged ≤ 5 years.

METHODS

This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines.¹² PRISMA-P 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 employed 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 papers 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, with a double-blind, placebo-controlled or open-controlled randomized design, or meta-analysis, with ≥ 40 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 NebCS 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.L-L. and K.R.M. assessed those relating to VIW. S.E.P. provided an overall review. In cases where the reviewers could not determine whether an article met the eligibility criteria from the abstract alone, a full-text copy of the paper 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 papers had been identified.

RESULTS

Asthma

The literature searches yielded a total of 499 articles on the use of NebCS in asthma. After examination of study abstracts, 135 were deemed appropriate for full-text review. The complete PRISMA flow diagram is shown in Figure 2A. Studies eligible for inclusion were separated into those describing the use of NebCS 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 criteria specified only studies that reported efficacy

data in children aged ≤ 5 years some studies including children aged >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 as 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 1,018 children.^{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 (b.i.d.) 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; $P = .01$).¹³ 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.¹⁴ 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% confidence interval [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 endpoints, including respiratory rate, heart rate, oxygen saturation, or use of a bronchodilator.^{15,16} However, 1 study showed that budesonide-treated patients were discharged from the hospital ED significantly faster than placebo-treated patients ($P = .02$).¹⁵ Taken together, these results suggest that a single dose of NebCS is insufficient for treatment of asthma exacerbations but that repeated doses can be effective as add-on therapy to systemic steroids in the setting of acute exacerbation.

As systemic corticosteroids are frequently included as part of standard-of-care treatment for the management of acute asthma exacerbations in young children,¹ it is critical to evaluate the efficacy and safety of NebCS 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 b.i.d. or intravenous prednisolone 0.5 mg/kg 3 times a day (t.i.d.), with the dose of each medication gradually reduced and ultimately discontinued after the disappearance of wheezing.¹⁷ 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 <3 years of age. A study in children presenting at a pediatric emergency service compared 3 doses of budesonide 800 µg at 30-minute intervals with a single oral dose of prednisolone 2 mg/kg.¹⁸ 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 >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 (q.i.d.) or oral methylprednisolone 1 mg/kg/day.¹⁹ Both treatments were associated with significant decreases in pulmonary index score, total symptom scores, 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. One report suggested a rapid onset of action for nebulized dexamethasone 1.5 mg/kg, with 23% of children discharged from the ER within 2 hours, compared with only 7% with oral prednisone 2 mg/kg ($P = .02$).²⁰ Additionally, fewer patients were hospitalized with dexamethasone than with prednisone (21% vs 31%, respectively; $P = .26$). Together, these results suggest that NebCS are at least as efficacious as oral corticosteroids for the management of young children attending the ER with mild-to-moderate asthma exacerbations.

Two studies compared budesonide with other NebCS in an outpatient setting. The first study compared budesonide 500 µg b.i.d. with fluticasone 250 µg b.i.d., each for 10 days.²¹ Mean patient age was 7.8 years, and the overall results favored fluticasone in terms of morning PEF. However, when patients were stratified by age, children aged 4–6 years treated with budesonide had a greater improvement than those receiving fluticasone in morning PEF (34 L/minute vs 20 L/minute, respectively) and evening PEF (44 L/minute vs 24 L/minute, respectively), but these differences were not statistically significant. A second study compared budesonide with flunisolide in children aged 3–5 years.²² 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.

NebCS were generally well tolerated in these studies and no significant adverse events (AE) were reported.^{16,17,21,22} This included studies comparing budesonide with placebo in which there were no important differences in the incidence of AEs between treatment groups. Additionally, studies measuring serum cortisol levels found no change with NebCS relative to pretreatment/baseline levels,^{17,21–23} and relative to placebo¹⁹ following the short courses of treatment employed in this setting. One investigation found a significant decrease in serum cortisol level following intravenous prednisolone treatment ($P = .0036$), highlighting one of the key advantages of nebulized administration of corticosteroids in acute asthma therapy.¹⁷

Asthma maintenance

Nine papers from 8 studies published between 1996 and 2013, and including a total of 1,681 children, were identified (Table III).^{9,24-31} Nebulized budesonide was the focus in all of 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.²⁴

Three separate double-blind, randomized placebo-controlled trials have been conducted, one each in children with mild, moderate, or severe asthma. In 1 study, infants <30 months of age with severe asthma were randomized to receive 12 weeks of nebulized budesonide 1 mg b.i.d. or placebo.²⁵ 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 following 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.^{26,27} In the study of moderate persistent asthma, there was a significantly greater mean change from baseline in night-time ($P \leq .01$) and daytime ($P \leq .05$) asthma symptom scores for all doses of budesonide versus placebo.²⁷ A similar pattern was observed in children with mild persistent asthma, with the mean change from baseline in both night-time and daytime asthma symptom scores being significantly better for all doses of budesonide versus placebo (all $P \leq .05$).²⁶ 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 asthmatic children aged 4–8 years also demonstrated superiority of budesonide over placebo in improving night-time and daytime asthma symptom scores.¹⁰ These results demonstrate that 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 2–6 years with persistent asthma, the mean rate of asthma exacerbations was 1.23/year with budesonide, significantly less than the 2.41/year reported with cromolyn sodium ($P < .001$).²⁸ 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.²⁹ A second study showed a marked improvement in night-time asthma symptom scores within 1–2 weeks with both treatments, as well as improvements in daytime asthma symptom scores, cough scores, and night-time awakening during the 12-week study period.³⁰ Budesonide 0.5 mg once a day (q.d.) was compared with montelukast 4 mg q.d. in children aged 2–4 years with mild persistent asthma, in a 52-week study,⁹ which found no significant difference in the primary endpoint 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 endpoints 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. Additionally, 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, one open-label, randomized controlled trial compared budesonide 750 µg/day b.i.d. with beclomethasone 800 µg/day b.i.d. 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/day, 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 NebCS 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

NebCS and comparators.^{9,24–28,30,31} Hypothalamic-pituitary-adrenal axis suppression and the potential for growth retardation is of particular concern in young children taking long-term corticosteroids, even when medication is administered directly to the lungs. However, basal and adrenocorticotrophic 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 b.i.d. than in those receiving budesonide 0.25 mg b.i.d., 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/day group and 7.55 cm in the cromolyn sodium group over the course of the 52-week study period ($P < .001$).²⁷ 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/year vs 7.39 ± 2.52 cm/year, respectively; $P = .002$).³² However, most studies,^{24,25,27,31, 32} have shown no impact on growth.

VIW

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

The 7 studies were published between 1986 and 2014 and included a total of 1,184 children (Table IV).³³⁻³⁹ 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 >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 µg b.i.d. 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 endpoints, 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 al. 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.³⁶ Results with budesonide were not significantly different from those with montelukast for any of these measures. Durmaz et al. 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.³⁷

One study compared the effect of daily budesonide (0.5 mg q.d. increasing to 0.5 mg b.i.d. for 7 days during RTI) and intermittent treatment in which patients were treated with budesonide 1 mg b.i.d. 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.³⁹ Patients were treated with either budesonide 0.25 mg b.i.d. or budesonide 1 mg b.i.d., titrating down every second day until the dose had reached 0.25 mg b.i.d. 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 β_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 of the VIW studies, with few AEs 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.^{39,40} Two additional studies found no effect of NebCS on growth parameters.^{38,42}

DISCUSSION

Placebo-controlled studies in patients with acute asthma attacks/exacerbations failed to show any benefit for NebCS in terms of asthma or pulmonary index scores, as well as on respiratory rate, heart rate, oxygen saturation, or bronchodilator use. However, NebCS were associated with more rapid discharge from hospital and shorter lengths of stay. NebCS were also found to be noninferior to systemic corticosteroids in treating acute asthma attacks/exacerbations. Nebulized β_2 -agonist treatment was used as background therapy in all of 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. Since nebulized β_2 -agonists are the standard of care in this setting, addition of NebCS does not impose an additional burden as both drugs can be dosed together.¹ The demonstrated safety of a short course of relatively high-dose NebCS indicates that there is little risk to young patients when NebCS 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.⁹

This is consistent with recommendations in the GINA guidelines that low-dose ICS should be used as an initial controller medication with montelukast as an alternative.¹ The results of 1 further comparative study with no placebo arm indicated that nebulized beclomethasone was as effective as budesonide in asthma treatment.³¹

This review exposes a key limitation in our understanding of the role of NebCS in young children in that no studies were found that compared the efficacy and safety of NebCS 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;⁴³ 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 6–16 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 NebCS 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 (ED) visits for young children (63% of whom were ≤ 4 years) after initiation of nebulized budesonide as a controller medication (hazard ratio: 0.55; 95% CI: 0.41, 0.76; $P < .001$), while other classes of controller medications, including other ICS, oral corticosteroids, leukotriene receptor antagonists, and short- and long-acting β_2 -agonists showed no reduction in risk of subsequent exacerbation.⁴⁵ In a second analysis of a similar population, nebulized budesonide therapy initiated following an asthma-related ED visit was

associated with a 29% lower risk of a subsequent event 31–180 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.⁴⁶ Of note, in children aged ≤ 4 years, there was a 62% lower risk of recurrent asthma exacerbations with nebulized budesonide compared with budesonide delivered via non-nebulized routes, primarily by pMDI, equating to a 28% chance of further exacerbation with nebulized budesonide versus a 72% chance with non-NebCS. It should be noted, however, that higher fill rates were recorded for nebulized budesonide inhalation suspension compared with non-nebulized ICS, which, while 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 one 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 one study showed that pre-emptive 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 NebCS 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 one 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.⁴¹ 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, 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 6–8 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 of age 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 NebCS are well tolerated during both short- and long-term treatment. The majority of studies reviewed here included budesonide, with the drug being administered to 1,711 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.⁴⁸ Growth data for other NebCS is lacking.

CONCLUSIONS

NebCS are effective for the treatment of acute asthma and for asthma maintenance in children aged ≤ 5 years. 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 NebCS improves outcomes while adding little or no risk. In maintenance therapy, continuous NebCS has 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 NebCS 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 NebCS are effective and well tolerated for the management of asthma in young children.

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FIGURE LEGENDS

FIGURE 1. The Pediatric Asthma Yardstick flow chart for pre-school children (aged ≤ 5 years). A stepwise approach to long-term management of asthma. Figure adapted from Chipps et al.⁴ and reproduced with permission. *Prior to stepping up therapy, confirm that the increased level of symptoms is due to asthma. The patient should be assessed for non-adherence 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. *ED*, emergency department; *FP*, fluticasone; *ICS*, inhaled corticosteroids; *LABA*, long acting β_2 -agonist; *LTRA*, leukotriene receptor antagonist; *mo*, month; *OCS*, oral corticosteroids; *SABA*, short acting β_2 -agonist; *TRACK*, Test for Respiratory and Asthma Control in Kids; *wk*, week.

FIGURE 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram: (A) asthma; (B) viral-induced wheezing. *A study may have been rejected for more than one reason. *ICS/SABA FDC*, inhaled corticosteroid/short acting β_2 -agonist fixed-dose combination.

674 **TABLE I.** Recommendations for delivery of inhaled corticosteroids in infants and children.

675 Adapted from Chipps et al.⁴

Patient	Nebulizer	pMDI plus spacer	Dry powder inhaler
Infant (<2 years)	• Reliable • Easy to use • Mask, tight seal not required	• Unpredictable • Requires training • Mask, tight seal required	• Never appropriate
Preschool (2–5 years)	• Effective • Easy to use • Mask, tight seal not required • Breath-enhanced mouthpiece	• Effective • Requires training • Mask, tight seal required • Mouthpiece	• Not appropriate
School age (>5 years)	• Effective • Breath-enhanced mouthpiece	• Effective • Mouthpiece • Requires training and practice	• Effective • Easy to use • Deposition varies by device

676

677 **TABLE II.** Summary of acute asthma studies

Study	Design	Population	Intervention	Number of patients (intervention 1 vs intervention 2)	Duration of treatment	Outcome (key efficacy endpoint)
Razi et al ¹³ 2015	Double-blind, randomized controlled trial	Children aged 7–72 months hospitalized with asthma exacerbation	BUD 1 mg b.i.d. vs PBO	50 vs 50	Up to 5 days	Length of hospital stay was 44 hours BUD vs 80 hours PBO ($P = .01$)
Papi et al ¹⁴ 2011	Double-blind, randomized controlled trial	Children aged 1–4 years with acute wheezing episode and history of recurrent wheezing	BDP 400 µg b.i.d. vs PBO	110 vs 56	7 days	Significantly more symptom-free days in BDP group vs PBO group (54.7% vs 40.5%, respectively; $P = .012$)
Sung et al ¹⁵ 1998	Double-blind,	Children aged 6	BUD 2 mg vs PBO	24 vs 20	Single dose	Median PIS after 1

	randomized controlled trial	months to 18 years with moderate-to-severe asthma presenting at emergency department				hour was 5.0 in the BUD group vs 6.0 in the PBO group ($P =$.07)
Upham et al ¹⁶ 2011	Double-blind, randomized controlled trial	Children aged 2–18 years with moderate-to-severe acute asthma	BUD 2 mg vs PBO	91 vs 88	Single dose	Asthma score -3 in both groups ($P =$.64). No significant difference in respiratory rate, heart rate, oxygen saturation, or number of hospital admissions
Saito et al ¹⁷ 2017	Randomized controlled trial	Children aged <3 years with history of expiratory wheezing and mild	BUD 1 mg b.i.d. vs PDL 0.5 mg/kg i.v. t.i.d.	30 vs 20	As needed	Wheezing and steroid therapy continued for 5 days in both groups

		asthma				
		exacerbation				
Devidayal et al ¹⁸	Double-blind,	Children aged 2–12	BUD 800 µg dose at	41 vs 39	3 doses	Significantly
1999	randomized	years with	half-hour intervals (3			greater
	controlled trial	moderate asthma	doses) vs oral PDL 2			improvement in
		attack (39% and	mg/kg			mean respiratory
		49% were aged 2–5				rate, heart rate,
		years in				PIS, and respiratory
		budesonide and				distress assessment
		prednisolone				scores (all $P < .05$)
		groups,				for BUD vs PDL.
		respectively)				Significantly more
						BUD-treated
						patients had
						oxygen saturation
						>95% than PDL-
						treated patients
						(40% vs 19%,
						respectively; $P <$

						.01)
Demirca et al ¹⁹	Double-blind,	Children aged 1–16	FP 500 µg q.i.d. vs	39 vs 41	7 days	Mean PIS
2015	randomized	years with	oral methyl-PDL 1			decreased from 8
	controlled trial	moderate asthma	mg/kg/day (4 days)			to 1 in both groups
		attack	→ 0.5 mg/kg/day (3			(both $P < .0001$)
			days)			
Scarfone et al ²⁰	Double-bind,	Children aged 1–17	DEX 1.5 mg/kg vs 2	56 vs 55	Single dose	21% and 31% in the
1995	randomized	years with	mg/kg oral PDN			DEX and PDN
	controlled trial	moderate asthma				groups,
		exacerbation				respectively,
						required
						hospitalization ($P =$
						.26); 23% and 7% in
						the DEX and PDN
						groups,
						respectively, were
						discharged home
						within 2 hours ($P =$
						.02)

De Benedictis et al ²¹ 2005	Single-blind, randomized controlled trial	Children aged 4–15 years with asthma exacerbations	BUD 500 µg b.i.d. vs FP 250 µg b.i.d.	87 vs 81	10 days	Morning PEF increased 44 L/minute with FP and 39 L/minute with BUD ($P = .032$)
Decimo et al ²² 2009	Randomized controlled trial	Children aged 3–5 years with acute moderate asthma attack	BUD 0.5 mg b.i.d. for 7 days → 0.25 mg b.i.d. for 14 days vs FLUN 40 µg b.i.d. for 7 days → 20 µg b.i.d. for 14 days	20 vs 20	21 days	Oscillometric resistance and total symptom scores significantly better with FLUN than with BUD at day 7 ($P < .05$), but not at day 21

BDP, beclomethasone; *b.i.d.*, twice a day; *BUD*, budesonide; *DEX*, dexamethasone; *FLUN*, flunisolide; *FP*, fluticasone; *i.v.*, intravenous; *PBO*, placebo; *PDL*,

prednisolone; *PDN*, prednisone; *PEF*, peak expiratory flow; *PIS*, pulmonary index score; *q.i.d.*, 4 times a day; *t.i.d.*, 3 times a day.

681 **TABLE III.** Summary of asthma maintenance studies

Study	Design	Population	Intervention	Number of patients	Duration of treatment	Outcome (key efficacy endpoint)
Szeffler et al ⁹ 2013	Open-label, randomized controlled trial (<i>post hoc</i> analysis of younger patient cohort)	Children aged 2–4 years with mild persistent asthma	BUD 0.5 mg q.d. vs MON 4 mg q.d.	105 vs 87	52 weeks	Time to use of additional asthma medication was 183 days for BUD and 86 days for MON ($P = .128$). Significantly fewer BUD-treated patients than MON-treated patients required OCS at 52 weeks (21.9% vs 37.1%; $P = .022$)
Wennergren et al ²⁴	Double-blind,	Children aged ≥ 6	Starting dose: BUD	52 vs 50	18 weeks	Minimum effective

1996	randomized controlled trial	months to <4 years with uncontrolled moderately severe- to-severe asthma	0.25 mg b.i.d. vs BUD 1.0 mg b.i.d., followed by down- titration			dose of BUD was 0.25 mg b.i.d. in 48/102 patients. Healthcare utilization decreased from 50% during run-in to 15-20% after randomization
de Blic et al ²⁵ 1996	Double-blind, randomized controlled trial	Infants aged <30 months with severe asthma	BUD 1 mg b.i.d. vs PBO	20 vs 18	12 weeks	40% of BUD- treated patients vs 83% of PBO-treated patients had 1 exacerbation ($P <$.01)
Kemp et al ²⁶ 1999	Double-blind, randomized controlled trial	Children aged 6 months to 8 years with mild persistent asthma	BUD 0.25, 0.5, and 1.0 mg q.d. vs PBO	91 vs 83 vs 93 vs 92	12 weeks	Mean change from baseline in night- time 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)
Baker et al ²⁷ 1999	Double-blind, randomized controlled trial	Children aged 6 months to 8 years with moderate persistent asthma	BUD 0.25 mg q.d., 0.25 b.i.d., 0.5 mg b.i.d., and 1.0 mg q.d. vs PBO	94 vs 99 vs 98 vs 95 vs 95	12 weeks	Mean change from baseline in night-time asthma symptom scores was -0.28, -0.49 ($P \leq .0001$ vs placebo),

-0.42 ($P \leq .01$), -
 0.40 ($P \leq .01$), and -
 0.13 for BUD 0.25
 mg q.d., 0.25 mg
 b.i.d., 0.5 mg b.i.d.,
 and 1.0 mg q.d.,
 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

Leflein et al ²⁸ 2002;	Open-label,	Children aged 2–6	BUD 0.5 mg/day vs	168 vs 167	52 weeks	The mean rate of
Murphy et al ²⁹	randomized	years with	CROM 20 mg q.i.d.			asthma
2003	controlled trial	persistent asthma				exacerbations was

						1.23/year for BUD and 2.41/year for CROM ($P < .001$ for difference)
Nagakura et al ³⁰ 2012	Open-label, randomized controlled trial	Children aged 6 months to 5 years with mild-to- moderate persistent asthma	BUD 0.5 mg/day vs CROM 20 mg b.i.d. or t.i.d.	21 vs 23	12 weeks	Night-time asthma symptom scores occurred in both groups, with marked reductions within 1-2 weeks
Delacourt et al ³¹ 2003	Open-label, randomized controlled trial	Children aged 6 months to 6 years with severe persistent asthma	BDP 800 µg/day b.i.d. vs BUD 750 µg/day b.i.d.	62 vs 68	14 weeks	40.4% of BDP- treated patients and 51.7% of BUD- treated patients had no asthma exacerbations ($P =$.22 for difference)

682 *BDP*, beclomethasone; *b.i.d.*, twice a day; *BUD*, budesonide; *CROM*, cromolyn sodium; *MON*, montelukast; *OCS*, oral corticosteroids; *PBO*, placebo; *q.d.*, once a
683 day; *q.i.d.*, 4 times a day; *t.i.d.*, 3 times a day.

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686 **TABLE IV.** Summary of VIW studies

Study	Design	Population	Intervention	Number of patients	Duration of treatment	Outcome (key efficacy endpoint)
Clavenna et al ³³ 2014	Double-blind, randomized controlled trial	Children aged 1–5 years with a history of VIW	BDP 400 µg b.i.d. vs PBO	264 vs 261	10 days	Wheezing diagnosed in 6.8% of patients with BDP and 11.1% of patients with PBO (<i>P</i> = .09)
Maayan et al ³⁴ 1986	Double-blind, randomized, controlled cross- over trial	Children aged 15– 36 weeks who experienced recurrent persistent tachypnea, dyspnea, and expiratory wheezing during	BDP 100 µg t.i.d. vs PBO	9	2 weeks	Clinical score with BDP was 0.8 vs 3.2 at baseline and PBO (<i>P</i> < .001 for difference). Respiratory rate fell from 48 breaths/minute at

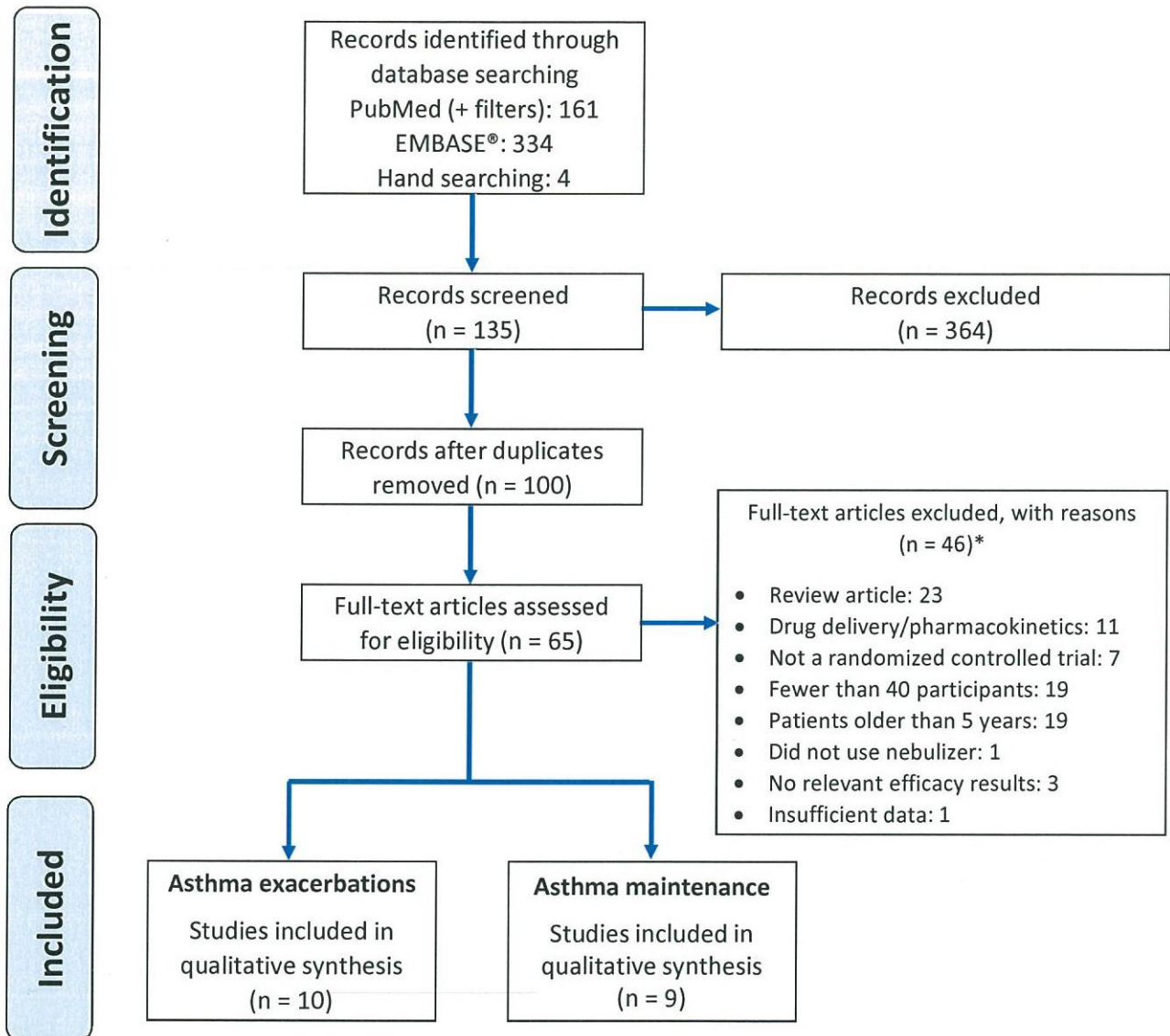
		the first 3 months of life				baseline to 34 breaths/minute with BDP ($P < .01$)
Ghirga et al ³⁵ 2002	Randomized controlled trial	Children aged 7–12 months with a history of recurrent wheezing during upper RTI	BDP 400 µg t.i.d. for 5 days vs no intervention	13 vs 13	4 study periods	1 BDP vs 4 control had ER visits; 2 BDP and 4 control received OCS
Bacharier et al ³⁶ 2008	Double-blind, randomized controlled trial	Children aged 12– 59 months with ≥2 episodes of wheezing in the context of RTI within past year	BUD 1 mg b.i.d. vs MON 4 mg q.d. vs PBO (all for 7 days)	96 vs 95 vs 47	12 months	Proportion of episode-free days was 0.76, 0.73, and 0.74 in BUD, MON, and PBO groups, respectively
Durmaz et al ³⁷ 2011	Randomized controlled trial	Children aged 6–36 months with intermittent VIW	BUD 500 µg/day vs control	36 vs 30	3 months	No difference in number of ER visits or use of systemic corticosteroids
Zeiger et al ³⁸ 2011	Double-blind,	Children aged 12–	BUD 0.5 mg q.d. →	139 vs 139	52 weeks	Rescue oral

	randomized	53 months with ≥ 4	0.5 mg b.i.d. for 7			glucocorticoid use
	controlled trial	episodes of	days during RTI			0.97/patient-year in
		wheezing, positive	(daily regimen) vs			daily regimen vs
		values on modified	PBO q.d. plus BUD 1			0.95/patient-year
		API, and at least 1	mg b.i.d. for 7 days			for intermittent
		exacerbation	during RTI			regimen ($P = .60$)
		requiring systemic	(intermittent			
		corticosteroids,	regimen)			
		emergency care, or				
		hospitalization				
Volovitz et al ³⁹ 1998	Double-blind,	Children aged 6	BUD 1 mg b.i.d.	21 vs 21	10 weeks	In high-dose group,
	randomized	months to 3 years	followed by 25%			wheezing improved
	controlled trial	with recurrent	decrease every 2			by 59.5% ($P =$
		wheezing	days until dose is			.0001), diurnal
			0.25 mg b.i.d. (high			cough improved by
			dose) vs 0.25 mg			38.3% ($P = .036$),
			BUD b.i.d. (regular)			nocturnal cough
						improved by 39.4%
						($P = .04$), and total

symptom scores
improved by 45.5%
($P = .004$); β_2 -
agonist use was
reduced by 66.9%
($P = .002$).
Improvements in
regular treatment
group were 2.4%,
11.3%, 14.7%, 2.9%,
and 43.7%,
respectively

687 API, Asthma Predictive Index; BDP, beclomethasone; *b.i.d.*, twice a day; BUD, budesonide; ER, emergency room; MON, montelukast; OCS, oral corticosteroids;

688 PBO, placebo; *q.d.*, once a day; RTI, respiratory tract infection; *t.i.d.*, 3 times a day; VIW, viral-induced wheezing.



Young Children

Stepping up from GINA STEP 1 to STEP 2 - PATIENT PROFILE:

Wheezing with or without coughing $\geq 2x/wk$ or who wakes due to wheezing $\geq 1x/mo$, or has a ≥ 10 point decrease in TRACK score, and/or ≥ 2 exacerbations requiring OCS, ED visit, or hospitalization in past year despite using as-needed ICS or LTRA (given at same time as SABA) for intermittent asthma.*

*Referral to
pediatric
asthma
specialist*

Daily low-dose ICS
OR LTRA
OR intermittent high-dose ICS

3-month therapeutic trial with
reassessment at 2-5 weeks

Stepping up from GINA STEP 2 to STEP 3 - PATIENT PROFILE:

Wheezing with or without coughing $\geq 2x/wk$ or who wakes due to wheezing $\geq 1x/mo$, or has a ≥ 10 point decrease in TRACK score after 3 mo of treatment with low-dose ICS and/or has had ≥ 2 exacerbations requiring OCS, ED visit, or hospitalization in past year.*

*Referral to
pediatric
asthma
specialist*

Double low-dose ICS
OR add LTRA to low-dose ICS

3-month therapeutic trial with
reassessment at 2-5 weeks

Stepping up from GINA STEP 3 to STEP 4 - PATIENT PROFILE:

Wheezing with or without coughing throughout most days or who wakes due to wheezing $> 1x/wk$ and has a ≥ 10 point decrease in TRACK score after 3 mo of treatment with double low-dose ICS (with or without LTRA) and/or whose daily activity is limited by symptoms and/or has had ≥ 3 exacerbations requiring OCS, ED visit, or hospitalization in past year.*

*Referral to
pediatric
asthma
specialist*

Continue to optimize medication:

- Increase to higher dose ICS with or without LTRA
- Consider ICS/LABA (FP/salmeterol is approved down to age 4 years)

3-month therapeutic trial with
reassessment at 2-5 weeks

Identification

Screening

Eligibility

Included

