Practical recommendations for home-nebulized corticosteroid use in children aged ≤ 5 years with asthma: A review and advisory group consensus

Chalerat Direkwattanachai,[1] Jitladda Deerojanawong,[2] Chalermthai Aksilp,[3] Orathai Jirapongsananuruk,[4] Harutai Kamalaporn,[1] Wasu Kamchaisatian,[5] Sorasak Lochindarat,[3] Lina Ngamtrakulpanit,[6] Orapan Poachanukoon,[7] Mongkol Lao-Araya,[8] Jamaree Teeratakulpisarn,[9] Kanokporn Udomittipong,[4] Mukda Vangveeravong,[3] Kanokpan Ruangnapa,[10] Pantipa Chatchatee[11]

Abstract

Background: Despite nebulized budesonide being identified by the Global Initiative for Asthma report as a viable alternative to inhaled corticosteroids (ICS) delivered by pressurized metered-dose inhalers (pMDIs) with spacers, practical guidance on nebulized corticosteroid use in the pediatric population remains scarce.

Objective: To review the current literature and provide practical recommendations for nebulized budesonide use in children aged ≤ 5 years with a diagnosis of asthma.

Methods: A group of 15 expert pediatricians in the respiratory and allergy fields in Thailand developed Delphi consensus recommendations on nebulized budesonide use based on their clinical expertise and a review of the published literature. Studies that evaluated the efficacy (effectiveness) and/or safety of nebulized budesonide in children aged ≤ 5 years with asthma were assessed.

Results: Overall, 24 clinical studies published between 1993 and 2020 met the inclusion criteria for review. Overall, results demonstrated that nebulized budesonide significantly improved symptom control and reduced exacerbations, asthma-related hospitalizations, and the requirement for oral corticosteroids compared with placebo or active controls. Nebulized budesonide was well tolerated, with no severe or drug-related adverse events reported. Following a review of the published evidence and group consensus, a treatment algorithm as per the Thai Pediatric Asthma 2020 Guidelines was proposed, based on the availability of medications in Thailand, to include nebulized budesonide as the initial treatment option alongside ICS delivered by pMDIs with spacers in children aged ≤ 5 years.

Conclusion: Nebulized budesonide is an effective and well-tolerated treatment option in children aged ≤ 5 years with asthma.

Key words: asthma, budesonide, corticosteroid, nebulization, young children

Affiliations:
[1] Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[2] Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[3] Department of Pediatrics, Queen Sirikit National Institute of Child Health, Ministry of Public Health, Bangkok, Thailand
[4] Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand
[5] Pediatric Allergy and Immunology Division, Samitivej Children's Hospital, Bangkok, Thailand
[6] Allergy and Asthma Center, Bangkok Hospital, Bangkok, Thailand
[7] Center of Excellence for Allergy, Asthma and Pulmonary Diseases and Department of Pediatrics, Thammasat University, Pathum Thani, Thailand

Affiliations (Continued):
[8] Department of Pediatrics, Faculty of Medicine,
  Chiang Mai University, Chiang Mai, Thailand
[9] Department of Pediatrics, Faculty of Medicine,
  Khon Kaen University, Khon Kean, Thailand
[10] Department of Pediatrics, Faculty of Medicine,
  Prince of Songkla University, Songkhla, Thailand
[11] HAUS IAQ Research Unit, Division of Allergy and Immunology,
  Department of Pediatrics, Faculty of Medicine,
  Chulalongkorn University, King Chulalongkorn Memorial Hospital,
  the Thai Red Cross Society, Bangkok, Thailand

Corresponding author:
Pantipa Chatchatee
HAUS IAQ Research Unit, Division of Allergy and Immunology,
Department of Pediatrics, Faculty of Medicine,
Chulalongkorn University, King Chulalongkorn Memorial Hospital,
the Thai Red Cross Society, Bangkok, Thailand
E-mail: pantipa.c@chula.md

Introduction

Asthma is a chronic inflammatory respiratory disease that affects approximately 339 million patients worldwide across all age groups.[1] The global prevalence of childhood asthma has significantly increased over the past 40 years, although substantial variations in the prevalence of asthma symptoms in children have been reported worldwide, with up to 13 fold differences between countries.[2] Notably, the prevalence of childhood asthma in Thailand stands at over 10%, which is comparable to the global prevalence at 11.2%.[1]

Childhood asthma exerts a substantial financial burden on healthcare systems, especially from direct costs associated with exacerbations and subsequent hospitalizations.[3] Indeed, a retrospective study in Thailand reported that annual direct medical costs were the highest in patients diagnosed with asthma before 5 years of age.[3] Furthermore, treatment costs increased significantly for patients who had at least one exacerbation compared with those without an exacerbation.[3] A population-based cohort study investigating over 0.4 million patients in the United Kingdom (UK) showed that children aged < 5 years had more severe asthma with higher exacerbation rates compared with adolescents and adults aged < 55 years.[4] Moreover, the National Health Interview Survey conducted in the United States (US) between 2001 and 2010 revealed that children aged ≤ 4 years had the highest rate of asthma-related hospitalization (5.2 per 100 persons with asthma) of any age group.[5] Consequently, the management of pediatric asthma, the goal of which is to achieve good symptom control, maintain normal activity levels, and minimize the future risk of exacerbations, requires particular attention.[6] Importantly, relative risks and benefits of treatments require careful consideration, especially in young children, to ensure normal physical and psychosocial development.[6]

The "Global Strategy for Asthma Management and Prevention 2021" report developed by the Global Initiative for Asthma (GINA) recommends a daily inhaled corticosteroid (ICS) for maintenance treatment of asthma in children aged ≤ 5 years at GINA treatment steps 2–4 (mild to moderate-to-severe asthma).[6] As young children are unable to use dry powder inhalers or pressurized metered-dose inhalers (pMDIs) without assistance,[7] ICS can be delivered via pMDIs with spacers or nebulizers.[6] However, aerosol delivery using pMDIs in infants and young children can present significant challenges, including a lack of cooperation, inability to breathe through the mouth and hold one's breath, rejection of masks, small tidal volume, and crying. All these factors can affect the breathing patterns of infants and adequacy of the seal between the mask and the face and consequently the drug dosage delivered to the lungs.[8] Notably, crying reduces the proportion of the drug deposited in the lungs (non-crying infant, 21.9% vs crying infant, 4%).[9] Crucially, nebulized inhalation therapy can overcome some of these challenges inherent to pMDIs (**Figure 1**).[10-12] Nebulizers provide more consistent and less error-prone drug delivery compared with pMDIs with spacers,[12]
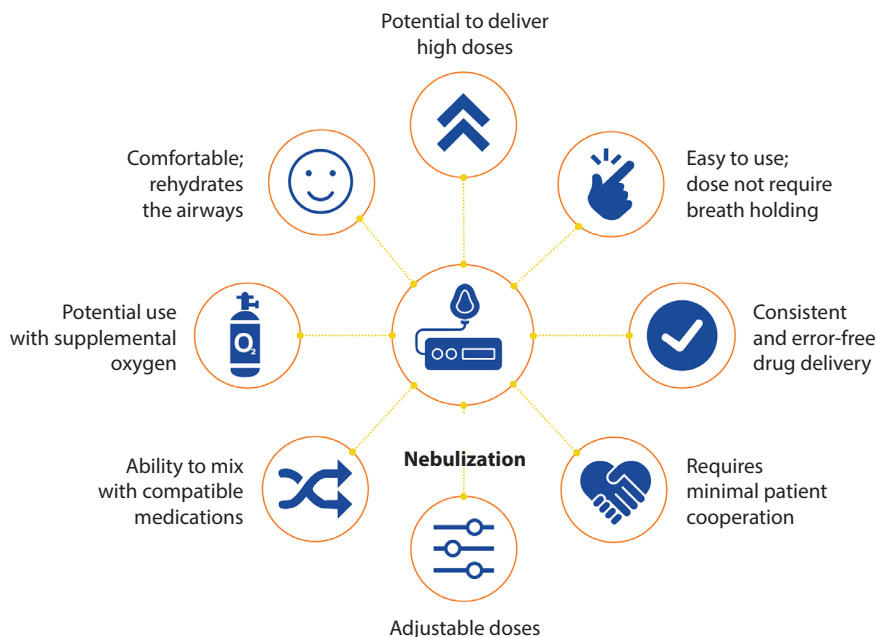

Figure 1. Advantages of nebulization.

require minimal patient cooperation,[11] are easy to use as they do not require breath-holding,[11] and offer adjustable doses[11] with the potential to mix with other compatible nebulized drugs, such as bronchodilators.[11,13] Moreover, nebulizers cause less irritation because of their hydrating effect on the airways[10] and can be used with supplemental oxygen.[11]

Budesonide, a second-generation ICS, provides fast onset of local action, dissolves rapidly in human bronchial fluid,[14] and has a strong bronchial vasoconstrictive effect.[15] Additionally, the unique esterification of budesonide prolongs its anti-inflammatory action and improves airway selectivity,[16] resulting in low systemic exposure and side effects with favorable long-term tolerability.[17] Notably, a systematic review in children aged ≤ 5 years, which included nine articles on asthma maintenance therapy, confirmed that nebulized budesonide significantly reduced the risk of further asthma exacerbations compared with placebo, cromolyn sodium, and montelukast in randomized controlled trials (RCTs).[18] Additionally, nebulized budesonide is well tolerated, without significantly impacting growth velocity or cortisol levels in infants and young children.[19-21] Although pMDIs with spacers are generally used to deliver corticosteroids in pediatric patients with asthma, the latest GINA report[6] has identified nebulized budesonide as the only effective and viable alternative for patients who may be unwilling or unable to use a pMDI with the correct inhaler technique.[7] However, although expert consensus recommendations on asthma management using nebulized corticosteroids in children and adolescents with acute asthma exacerbations in the hospital setting have been previously published,[7] practical guidance on the use of nebulized budesonide in young children remains scarce. Therefore, we present expert consensus recommendations on the use of nebulized corticosteroids in multiple settings specifically in children aged ≤ 5 years with a diagnosis of asthma based on published evidence and clinical experience.

Methods

A steering committee comprising 15 hospital-based pediatric pulmonologists and allergists treating asthma at public and private tertiary medical centers across Thailand was convened in Bangkok, Thailand, on November 27, 2020, to discuss the role of nebulized corticosteroids in asthma management in children aged ≤ 5 years. Committee members were jointly selected by AstraZeneca and a group of pediatric advisors who had worked collaboratively with the Pediatric Medical Association in Thailand (Pediatric Society of Thailand) as guideline committee members and were invited to participate in the current study based on a relevant publication history and their clinical experience and expertise in pediatric asthma. A narrative review of published studies on nebulized budesonide in children aged ≤ 5 years with asthma was undertaken to evaluate the evidence and develop expert recommendations through panel discussions for implementation in clinical practice. PubMed was interrogated with the following search terms: (asthma [title] OR asthmatic [title] OR asthmatics [title]) AND budesonide [title/abstract] AND (nebulization [title/abstract] OR nebulized [title/abstract] OR nebulizer

[title/abstract] OR suspension [title/abstract]) AND (pediatric [title/abstract] OR paediatric [title/abstract] OR children [title/abstract] OR infants [title/abstract]) NOT (review OR case series OR case report). Additional studies were identified via a Google scholar search. The PubMed search was updated prior to final submission of the manuscript to include publications up to 25 January, 2023. All 15 committee members participated in the inclusion/exclusion of retrieved articles from all literature search results. Studies were restricted to clinical studies, including RCTs, observational studies, and real-world studies, that were published in English and that assessed the efficacy (effectiveness) and/or safety of nebulized budesonide either as maintenance therapy or in the management of acute exacerbations in children aged ≤ 5 years with an asthma diagnosis. Case reports/series, review articles, systematic reviews, and meta-analyses were a priori excluded from the study: case reports, because they represent low quality evidence;[22] the latter three article types, because they are not primary data sources. Based on the review of published studies and the opinions of clinicians, an algorithm on asthma management in children aged ≤ 5 years was developed to provide health care providers (HCPs) with simplified practical recommendations to ensure seamless transition of evidence-based medicine into routine clinical practice.

In addition to the literature review, the Delphi technique[23] was used to gain consensus on a questionnaire comprising 11 questions related to asthma management in children aged ≤ 5 years, that was developed through verbal discussions prior to the steering committee meeting and completed in one round during the meeting. Statements from the Delphi technique that obtained a mean consensus score of at least four out of five were concluded to be expert recommendations.

Results
Overview of published studies

The literature search retrieved a total of 88 articles. After excluding 64 articles that did not meet the inclusion criteria, 24 relevant clinical studies were identified that examined the efficacy and/or safety of nebulized budesonide either as maintenance therapy or in the management of acute exacerbations (**Figure 2**) in a total of 16,261 young children with asthma. These 24 studies were published between 1993 and 2020 across eleven countries,[20,21,24-45] comprising 20 RCTs,[20,21,24-30,32-34,36,38-40,42-45] three retrospective analyses,[35,37,41] and one observational study[31] (**Table 1**). In total, seven studies evaluated patients with mild, mild-to-moderate, or mild-to-severe asthma,[20,27,28,31,33,39,42] six evaluated patients with moderate or moderate-to-severe asthma,[21,29,30,36,41,43] whereas four studies evaluated patients with severe asthma.[24-26,38] Three studies assessed the effect of intermittent high-dose nebulized steroids during an exacerbation.[21,28,43] Assessments included a wide range of endpoints, including lung function, asthma symptoms, use of reliever medications, pulmonary index scores, exacerbations, hospitalizations, emergency department (ED) visits, requirements for oral corticosteroid (OCS) therapy,
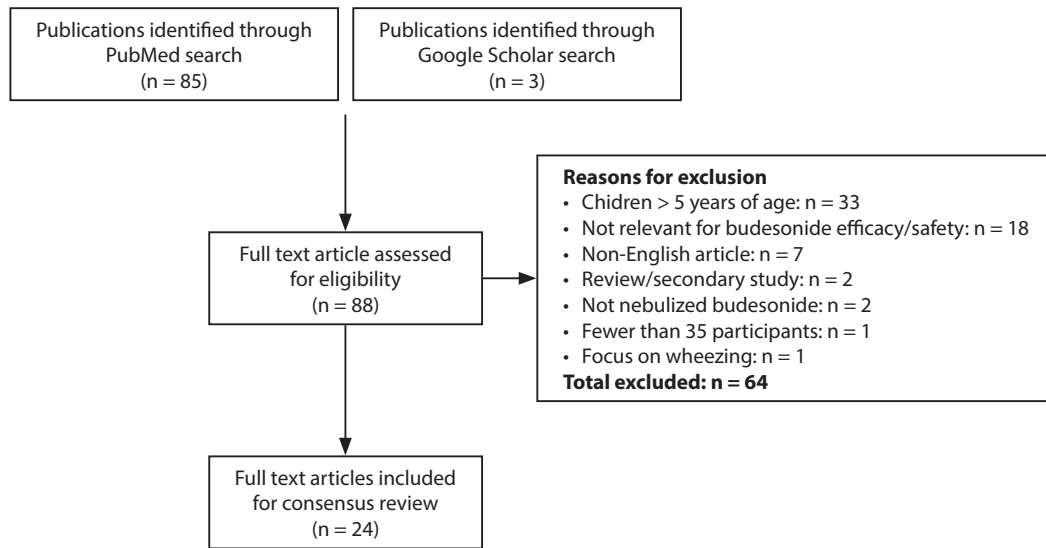
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┌─────────────────────────┐   ┌─────────────────────────┐
│ Publications identified  │   │ Publications identified  │
│ through PubMed search    │   │ through Google Scholar   │
│ (n = 85)                 │   │ search (n = 3)           │
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Reasons for exclusion
- Chidren > 5 years of age: n = 33
- Not relevant for budesonide efficacy/safety: n = 18
- Non-English article: n = 7
- Review/secondary study: n = 2
- Not nebulized budesonide: n = 2
- Fewer than 35 participants: n = 1
- Focus on wheezing: n = 1

Total excluded: n = 64

Full text article assessed for eligibility (n = 88)

Full text articles included for consensus review (n = 24)

Figure 2. PRISMA diagram summarizing the literature search process.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Clinical studies assessing the efficacy and/or safety of nebulized budesonide in children aged ≤ 5 years with asthma.

Publication	Country	Design	Duration	Patients, n	Asthma severity	Age	Treatment	Control (comparator)
Connett, 1993	UK	Double-blind, placebo-controlled RCT	6 months	40	Severe	1–3 years	400–800 µg budesonide/day	Placebo
Ilangovan, 1993	UK, Israel, Denmark	Double-blind, placebo-controlled RCT followed by open follow-up	16 weeks	36	Severe	< 5 years	2 ml budesonide twice daily (2 mg/day)	Placebo
Wennergren, 1996	Sweden	Double-blind, parallel-group RCT	18 weeks	102	Moderate-to-severe	< 4 years	0.25 or 1 mg budesonide twice daily	None
De Blic, 1996	France	Double-blind, placebo-controlled RCT followed by open follow-up	24 weeks	40	Severe	< 2.5 years	1 mg budesonide twice daily	Placebo
Kemp, 1999	USA	Double-blind, placebo-controlled RCT	12 weeks	359	Mild persistent	< 8 years	Budesonide inhalation suspension once daily (0.25 mg, 0.50 mg, or 1 mg)	Placebo
Baker, 1999	USA	Double-blind, placebo-controlled RCT	12 weeks	480	Moderate persistent	< 8 years	Budesonide inhalation suspension 0.25 mg once daily, 0.25 mg twice daily, 0.5 mg twice daily, or 1 mg once daily	Placebo
Mellon, 2000	USA	Retrospective analysis of a double-blind, placebo-controlled RCT	12 weeks	481	Moderate persistent	< 8 years	Budesonide inhalation suspension 0.25 mg once daily, 0.25 mg twice daily, 0.5 mg twice daily, or 1 mg once daily	Placebo

Table 1. (Continued)

Publication	Country	Design	Duration	Patients, n	Asthma severity	Age	Treatment	Control (comparator)
Leflein, 2002	USA	Randomized, parallel-group, open-label study	52 weeks	335	Persistent	2–6 years	Budesonide inhalation suspension (0.5 mg daily)	Cromolyn sodium nebulizer solution, 20 mg 4 times daily for 8 weeks followed by dose titration
Murphy, 2003	USA	Randomized, parallel-group, open-label study	52 weeks	335	Mild-to-moderate persistent	2–6 years	Budesonide inhalation suspension 0.5 mg once or twice daily	Cromolyn sodium nebulizer solution, 20 mg 4 times daily for 8 weeks followed by dose titration
Delacourt, 2003	France	Randomized, controlled, parallel-group, open-label study	14 weeks	120	Severe persistent	< 6 years	Budesonide nebulization suspension 750 µg/day in a twice-daily regimen	Beclometasone dipropionate nebulization suspension 800 µg/day in a twice-daily regimen
Berger, 2005	USA	Double-blind, placebo-controlled, parallel-group RCT	12 weeks	141	Mild-to-moderate persistent asthma or recurrent wheeze	6 to <12 months	0.5 or 1.0 mg budesonide once daily	Placebo
Zielen, 2006	Germany	Prospective, double-blind, parallel-group, active-controlled RCT	9 months	78	-	6–36 months	Nebulized budesonide 0.5 mg twice daily	Disodium cromoglycate 20 mg three times daily
Camargo, 2007	USA	Retrospective analysis of claims from the Florida Medicaid database	-	10,976	-	≤ 8 years	Budesonide inhalation suspension	None
Decimo, 2009	Italy	Parallel-group, simple blind, RCT	21/22 days	40	Moderate asthma exacerbation	3–5 years	Nebulized budesonide 0.5 mg twice daily for 7 days then 0.25 mg twice daily for 15 days	Nebulized flunisolide 40 µg/kg twice daily for 7 days and then 20 µg/kg twice daily for 14 days
Zeiger, 2011	USA	Randomized, double-blind, parallel-group study	52 weeks	278	At risk of developing persistent asthmaa	12–53 months	Budesonide inhalation suspension as either an intermittent high-dose regimen (1 mg twice daily for 7 days) or a daily low-dose regimen (0.5 mg nightly) with corresponding placebos	
Nagakura, 2012	Japan	Randomized, parallel-group, open-label study	12 weeks	53	Mild or persistent asthma	0.5–4 years	Budesonide inhalation suspension (0.5 mg/day)	Cromolyn sodium inhalation suspension (40–60 mg/day)

Table 1. (Continued)

Publication	Country	Design	Duration	Patients, n	Asthma severity	Age	Treatment	Control (comparator)
Szefler, 2013	USA	Randomized, active-controlled, open-label study	52 weeks	203	Mild persistent asthma	2–4 years	Budesonide inhalation suspension once daily (0.5 mg/day)	Montelukast 4–5 mg once daily
Yanagida, 2015	Japan	Randomized, active-controlled study	3–6 days (or until discharge)	40	Moderate bronchial asthma attacksb	≤ 5 years	Procaterol hydrochloride (0.01%; 0.3 ml) and budesonide inhalation suspension (0.5 mg) TID	Procaterol hydrochloride (0.01%; 0.3 ml), disodium cromoglycate (1%; 2 ml) and methylprednis-olone (1 mg/kg) TID
Zhou, 2016	China	Secondary analysis of prospective, observational study	7 weeks	897	Mild and severe cough-variant asthma	≤ 5 years	Nebulized budesonide inhalation suspension	None
Bian, 2017	China	Randomized, active-controlled study	N/R	60	Acute asthmatic bronchitis	1–5 years	0.5–1.0 mg budesonide plus 2.5 mg terbutaline (body weight < 20 kg) or 5.0 mg terbutaline (body weight > 20 kg) once or twice daily	Dexamethasone (0.1–0.3 mg/kg/day)
Saito, 2017	Japan	Randomized, active-controlled study	5 days	50	Mild asthma exacerbations	< 3 years	Budesonide inhalation suspension (1 mg) twice a day	Intravenous prednisolone (0.5 mg/kg) TID
Razi, 2017	Turkey	Randomized, double-blind, placebo-controlled, parallel-group study	1 day	100	Moderate-to-severe acute wheezing episodes	0.5–6 years	Budesonide inhalation suspension (3 mg) in addition to standard treatment (salbutamol and a single 1 mg/kg dose of methyl-prednisolone)	Placebo (preservative-free normal saline) in addition to standard treatment (salbutamol and a single 1 mg/kg dose of methyl-prednisolone)
Ding, 2019	China	Randomized, active-controlled study	1 year	239	Capillary bronchitis, asthmatic bronchitis, or asthmatic bronchial pneumonia	< 5 years	Inhaled budesonide suspension liquid, 500 µg twice daily	Oral montelukast 4 mg once daily, inhaled fluticasone propionate 100 µg twice daily
Wu, 2020	China	Retrospective cohort study	12 weeks treatment; up to 2 years follow-up	778	Treatment-naïve asthma	≤ 2 years	500 µg budesonide twice daily for 6 weeks followed by 250 µg budesonide twice daily for 6 weeks	250 µg fluticasone twice daily for 6 weeks followed by 125 µg fluticasone twice daily for 6 weeks

aPositive values on the modified API scale, recurrent wheezing episodes, and ≥ 1 exacerbation in the previous year.
bDefined by the JPGL 2008 as the presence of apparent wheezing, retractive breathing, prolonged expiration orthopnea, or increased respiratory rate.
API, asthma predictive index; JPGL, Japanese pediatric guidelines for the treatment and management of bronchial asthma; N/R, not reported; RCT, randomized controlled trial; TID, three times a day; UK, United Kingdom; USA, United States of America.

cortisol levels, and hospital discharge rates. Most studies assessed a twice-daily nebulized budesonide regimen, with a total daily dose ranging between 400 µg and 2 mg per day. In terms of reference groups, nine studies were placebo-controlled,[24-26,33,36,39,41,43,44] disodium cromoglycate was used as an active comparator in four studies,[27,32,40,42] whereas flunisolide,[30] fluticasone,[35,45] dexamethasone,[34] beclomethasone dipropionate,[38] prednisolone,[28] montelukast,[20,45] and a combination of disodium cromoglycate and methylprednisolone[21] were used as active comparators in one study each.

Overall, in addition to providing symptom control,[20,21,24,25,28-32,34-36,39-41,45] nebulized budesonide reduced asthma exacerbations[25,32,38] and subsequent hospitalizations,[21,37,43,45] and had an OCS-sparing effect.[20,21,25,26,28] Importantly, nebulized budesonide did not negatively impact adrenocortical function in children aged ≤ 5 years in clinical studies,[21,27,28] suggesting that it can be used clinically in young children without significant effects on growth or development.[27] **Table 2** provides an overview of efficacy and safety outcomes for each of the 24 included studies.

Table 2. Efficacy and safety outcomes in clinical studies assessing the efficacy and/or safety of nebulized budesonide in children aged ≤ 5 years with asthma.

Publication	Efficacy outcomes	Safety outcomes
Connett, 1993	Cough scores improved significantly with budesonide ($p < 0.05$)	One child developed a facial skin rash, which resolved after parents were reminded to wipe their child's face after drug administration
Ilangovan, 1993	Requirement for treatment with oral steroids reduced and overall health as scored on a visual analog scale improved with nebulized budesonide ($p < 0.05$ for both)	Two children developed an eczematous rash in the area of the face mask. Treatment was not stopped and the rash was controlled by applying a barrier cream before nebulization and washing the face afterwards
Wennergren, 1996	Although an overall minimal effective maintenance dose could not be demonstrated, 47% of patients achieved symptom control on 0.25 mg twice daily, i.e., fulfilled the criteria for further dose reduction	Transient candidiasis was recorded in 6 children in the 0.25-mg group and in 4 in the 1-mg group. Facial skin irritation was transiently observed in 5 children in each group. During the first dose reduction there was a difference in the number of children below morning plasma cortisol reference values, with 10 children in the 1 mg and 4 in the 0.25 mg group after corrections for betamethasone use.
De Blic, 1996	Patients receiving nebulized budesonide needed a shorter duration of oral corticosteroid therapy and had a lower incidence of asthma symptoms (both $p < 0.05$) Fewer patients in the budesonide group experienced exacerbations compared with those in the placebo group ($p < 0.01$)	Facial skin reactions were not observed in either group. One child in the budesonide group had transient hyperexcitability, and one child had oral candidiasis. Coughing or bronchoconstriction or were not reported after nebulized budesonide administration.
Kemp, 1999	All budesonide inhalation suspension doses produced significant improvements in nighttime/daytime symptoms and decreases in reliever medication use, while improvements in FEV(1) were observed in the 0.5 mg and 1 mg budesonide inhalation suspension groups ($p < 0.05$).	Treatment was discontinued by 4 children because of AEs: bronchospasm (1 child each in the 0.25 mg and 0.5 mg budesonide groups), meningitis (1 in the 0.25 mg budesonide group), and cellulitis (1 in the 0.5 mg budesonide group). No significant differences between placebo and any budesonide group in basal and ACTH-stimulated cortisol levels were reported.
Baker, 1999	All budesonide inhalation suspension doses produced statistically significant improvements in lung function and daytime and nighttime symptoms compared with placebo ($p \leq 0.05$).	The incidence of AEs deemed possibly or probably related to treatment was similar between placebo and budesonide groups. Mean height and weight changes were similar between the treatment groups. No clinically relevant changes in basal cortisol levels were found in any treatment group.
Mellon, 2000	Budesonide inhalation suspension via a face mask or mouthpiece resulted in clinical improvements in nighttime and daytime asthma symptoms compared with placebo ($p < 0.05$).	The overall incidence, type, and severity of non-asthma–related AEs were similar in the placebo and budesonide groups. The overall incidence of any AEs among budesonide-treated children was slightly higher in those who received treatment with face masks (85%) than mouthpieces (78%).
Leflein, 2002	The budesonide group had a mean (median) asthma exacerbation rate of 1.23 (0.99) per year compared with 2.41 (1.85) for the cromolyn group, significantly longer times to the first exacerbation and first use of additional long-term asthma medication, greater improvements in asthma symptom scores, reduced use of reliever medication, and fewer urgent care visits.	There were no clinically relevant differences in the incidence or type of AEs between groups. Levels of basal and ACTH-stimulated plasma cortisol were similar between groups.
Murphy, 2003	Improvements from baseline in domain-specific (activities and emotional function), and total PACQLQ scores were greater at each time point (weeks 8, 28, and 52) for caregivers of patients treated with budesonide compared with caregivers of patients receiving cromolyn sodium.	In the budesonide group no discontinuations were attributable to AEs or disease deterioration. Other safety parameters were not assessed or reported.

Table 2. (Continued)

Publication	Efficacy outcomes	Safety outcomes
Delacourt, 2003	Overall, 51.7% and 40.4% of patients on budesonide and beclometasone dipropionate treatments, respectively, did not experience major exacerbations ($p = 0.28$). Both treatments were also associated with marked reductions in the number of nights with wheezing and the number of days of oral steroid use.	The incidence and AE profile were equivalent between the groups. Urinary cortisol and urinary cortisol/creatinine ratios were not significantly affected.
Berger, 2005	Compared with patients receiving placebo, the mean percentage of symptom-free days was numerically greater for patients receiving 0.5 and 1.0 mg budesonide (37.5%, 48.8%, and 43.4%, respectively). Treatment-related differences in physicians' global assessments of patient health status did not reach statistical significance, but physicians rated 90% and 85% of patients in the 0.5-mg budesonide and 1.0-mg BIS groups, respectively, a "great deal better" or "somewhat better" compared with 67% of patients in the placebo group. Budesonide treatment resulted in a greater reduction in daytime and nighttime symptoms compared with placebo.	The safety profile of budesonide was similar to that of placebo, with no suppressive effect on adrenal function.
Zielen, 2006	Patients treated with budesonide had a lower exacerbation rate than cromoglycate-treated patients after 3 months of treatment (5.4% vs 31.7%; $p = 0.003$) and towards the end of follow-up (30% vs 49%; $p = 0.062$). Days without cough were 80% and 65% for budesonide and cromoglycate, respectively ($p = 0.014$), and nights without cough were 89% and 78%, respectively ($p = 0.016$).	Adverse events were mild and of similar frequency in both groups.
Camargo, 2007	Patients who had a claim for budesonide inhalation suspension had a lower risk of a subsequent hospitalization or an ED visit (HR, 0.55; 95% CI, 0.41–0.76; $p < 0.001$) than patients who did not have budesonide inhalation suspension claims.	N/R
Decimo, 2009	Airway resistances were significantly reduced at day 7 ($p < 0.01$ flunisolide; $p < 0.05$ budesonide) and day 21 ($p < 0.05$ flunisolide; $p < 0.05$ budesonide) versus baseline in both groups, although at day 7 the reduction occurred faster in the flunisolide group than in the budesonide group ($p < 0.01$). During the first 7 days of treatment, symptom scores decreased in both groups; however, the decrease was greater in the flunisolide group ($p < 0.05$).	Morning serum cortisol level after 21 days of treatment did not differ versus baseline ($p = 0.5$) (**Table IV**). The other blood parameters evaluated were within normal limits in both groups. There were no cases of oral Candida infection or dysphony.
Zeiger, 2011	The daily regimen of budesonide did not differ significantly from the intermittent regimen with respect to the frequency of exacerbations, with a relative rate per patient-year of 0.99 (95%CI, 0.71–1.35; $p = 0.60$).	There were no significant differences in the proportions of children with serious AEs (including all hospitalizations) and nonserious AEs between groups. Five children in the intermittent-regimen group and four in the daily-regimen group were hospitalized for asthma exacerbations.
Nagakura, 2012	N/R	No significant differences in salivary cortisol levels were seen from baseline for budesonide and cromolyn sodium inhalation suspensions, suggesting that they are safe and without any inhibitory effects on adrenocortical function. There were no drug-related adverse reactions recorded in any group.
Szefler, 2013	No difference was observed between the budesonide inhalation suspension and montelukast groups in median time to the first additional asthma medication over 52 weeks (183 vs 86 days). Statistically significant differences were observed in favor of budesonide inhalation suspension over montelukast in the percentage of patients requiring oral steroids at 52 weeks (21.9% vs 37.1%; $p = 0.022$), the rate (number/patient/year) of additional courses of medication (1.35 vs 2.30; $p = 0.003$), the rate of additional oral steroid therapy (0.44 vs 0.88; $p = 0.008$), and caregivers' ability to manage patients' symptoms ($p = 0.026$)	The incidence of most commonly reported adverse events was similar in both groups and mostly mild. No discontinuations due to adverse events were reported with budesonide, versus 4 discontinuations with montelukast (asthma [n = 2], upper respiratory tract infection, and pneumonia). Other safety parameters were not assessed or recorded.
Yanagida, 2015	There were no significant differences between the two groups in terms of the severity of attacks and duration of management or in terms of therapeutic efficacy, duration of wheezing, or period of hospitalization. The frequency of inhalations on days 3 to 6 of hospitalization was lower in the budesonide inhalation suspension group than in the methylprednisolone group, and the cortisol level at discharge was significantly higher in the budesonide inhalation suspension group (13.9 ± 6.1 µg/dL) than in the methylprednisolone group (8.0 ± 2.1 µg/dL) ($p = 0.008$)	A significantly higher number of children in the methylprednisolone group (5 of 15) versus budesonide group (0 of 18; Fisher exact test, $p = 0.013$) had cortisol levels below the reference value of 4 mg/dL. Other safety parameters were not assessed or recorded.

Table 2. (Continued)

Publication	Efficacy outcomes	Safety outcomes
Zhou, 2016	Symptom scores in the severe disease group were higher than those in the mild group at weeks 1, 3, and 5 ($p < 0.05$), but not at week 7 ($p > 0.05$). Further, more patients in the mild group achieved disease control at any time point (98.6% at 3 weeks and 99.7% at 7 weeks), compared with the patients in the severe group ($p < 0.001$). The proportion of patients requiring bronchodilators differed between the groups until week 5 ($p < 0.001$).	No severe or drug-related adverse events were reported.
Bian, 2017	The overall effective rate of treatment in the control group was 73.33% (40% with marked improvement, 33.33% with some improvement and 26.67% with no improvement) and that in the treatment group was 96.67% (73.73% with marked improvement, 23.33% with some improvement and only 3.33% with no improvement); $p < 0.05$. Overall improvement in FEV(1), FVC, FEV(1)/FVC and PEF was higher in the treatment group than the control group ($p < 0.05$). ESR and CRP levels in the treatment group were improved to a greater degree than in the control group ($p < 0.05$).	There were only minor adverse reactions in two patients in the treatment group, and the overall rate of adverse reactions was not significantly different between the two groups.
Saito, 2017	Wheezing disappeared after an average of 5 days, with no significant difference in days of oxygen use.	Serum cortisol levels remained unchanged in the budesonide inhalation suspension group and were significantly decreased in the prednisolone group compared with the budesonide inhalation suspension group ($p = 0.0036$). On the 4th day of hospitalization serum cortisol levels were 17.0 µg/dL and 10.9 µg/dL in the budesonide and prednisolone groups, respectively, with significant suppression in the prednisolone group. No adverse events were reported in either group.
Razi, 2017	The discharge rate in the budesonide inhalation suspension group was significantly higher than that in the placebo group ($p < 0.001$). Expected mean discharge times were 200.4 (95%CI, 185.3–215.5) minutes in the placebo group and 164.4 (95%CI, 149.4–179.4) minutes in the budesonide group. The median (25th–75th percentile) pulmonary index score at the 120th minute was significantly lower in the budesonide group than in the placebo group (5 [4–8] vs 8 [5–9] respectively; $p = 0.006$).	N/R
Ding, 2019	All treatments were found to be equally effective as assessed by the number of wheezing episodes and emergency room visits.	N/R
Wu, 2020	Budesonide treatment achieved a reduced sRaw (1.28 ± 0.11 vs 1.21 ± 0.10 kPa/sec; $P < 0.0001$) and improved FEV(1) (0.977 ± 0.068 vs 0.997 ± 0.085 L/sec; $P < 0.0001$) vs baseline. The efficacy of budesonide to reduce sRaw ($P = 0.008$) and improve FEV(1) ($P < 0.0001$) was greater than that of fluticasone. The budesonide treatment group had more post-treatment symptom-free days than the fluticasone treatment group (165.56 ± 23.15 vs 112.21 ± 9.45 days; $P < 0.0001$).	In the budesonide group, sneezing (33 vs 12 cases in the fluticasone group; $p = 0.002$), runny nose (45 vs 13 cases; $p < 0.0001$) and watering of eyes (11 vs 1 case; $p = 0.009$) were the most frequent adverse effects in infants during the follow up period.

AE, adverse event; CI, confidence interval; ED, emergency department; FEV(1), forced expiratory volume in 1 second; FVC, forced vital capacity; HR, hazard ratio; N/R, not reported; PACQLQ, Pediatric Asthma Caregiver's Quality of Life Questionnaire; PEF, peak expiratory flow; sRaw, specific airway resistance.

Summary of expert consensus and clinical recommendations included in the proposed treatment algorithm

Summary of expert consensus

The following statements received an average score of at least four out of five using the Delphi technique and were therefore considered to be expert recommendations:

1. The goal of asthma treatment in children is to achieve symptom control; therefore, patients should be categorized by their level of control (controlled vs uncontrolled).
2. Education of children's families and healthcare workers is a key factor in achieving asthma control in children.
3. ICS are recommended as the preferred maintenance medication for recurrent wheezing in children aged ≤ 5 years, especially in those experiencing frequent symptoms, using relievers more than twice a month, or with a history of ≥ 3 exacerbations per year or ≥ 2 severe exacerbations in 6 months.
4. As reported by GINA,[6] adequate efficacy and safety data in children are available for nebulized budesonide (≥ 1 year) and fluticasone propionate pMDI (≥ 4 years).
5. Nebulization requires minimal patient cooperation and results in fewer errors in drug delivery in young children with asthma when compared with other inhalation methods.

6. Nebulized budesonide is a viable ICS treatment option along with budesonide delivered by pMDIs with spacers in children with asthma aged ≤ 5 years.
7. Should a nebulized mode of delivery be selected, jet nebulizers may be the preferred delivery devices for nebulizing ICS.
8. The use of nebulizers should be recommended for pediatric patients who are unwilling or unable to use a pMDI with a spacer properly.

9. Referral to a specialist should be considered for patients aged ≤ 5 years who are not well controlled with regular medium-dose ICS.
10. Home nebulization can be implemented in the following scenarios.
   10.1. ICS maintenance treatment for 1–3 months to prevent an acute exacerbation[6]
   10.2. Intermittent high-dose ICS treatment at the onset of a respiratory infection[46]
   10.3. Management of an acute exacerbation[7]
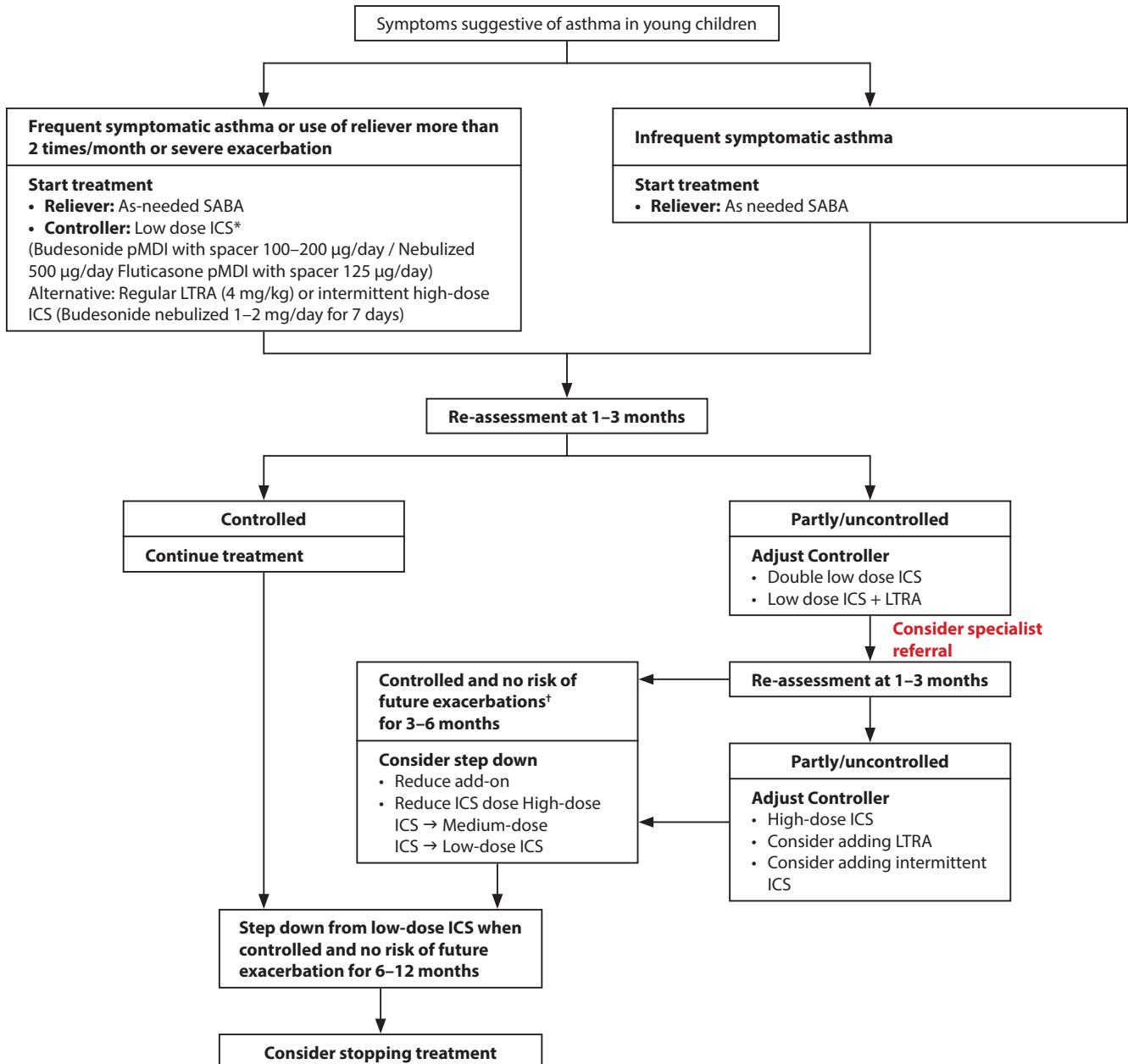
Figure 3. Practical treatment algorithm for children aged ≤ 5 years with a diagnosis of asthma. This treatment algorithm is adapted from the Thai Pediatric Asthma 2020 Guideline[47] and based on available medications in Thailand.

*Based on the drugs available in Thailand

†Future risk of exacerbations is characterized by uncontrolled symptoms, > 1 severe exacerbation in the past 12 months, exposure to tobacco smoke, pollution, and aeroallergens especially in those with respiratory tract infections, low adherence, and inaccurate inhaler technique.

ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; pMDI, pressurized metered-dose inhaler; SABA, short-acting β_2-agonist.

Based on the review of 24 published clinical studies and the consensus reached by the expert panel, a treatment algorithm was proposed (**Figure 3**). This algorithm was adapted from the Thai Pediatric Asthma 2020 Guidelines[47] as per the availability of drugs in Thailand and included nebulized budesonide as the initial treatment option alongside ICS delivered by pMDIs with spacers in children aged ≤ 5 years. The algorithm proposes that young children who have frequent symptoms, experience a severe exacerbation, or require the use of reliever medications more than twice a month should be prescribed low-dose ICS (0.5 mg nebulized budesonide/day, 0.1–0.2 mg budesonide/day delivered via pMDI with a spacer, or 0.125 fluticasone/day delivered via pMDI with a spacer) with as-needed reliever medications. Alternatively, a regular leukotriene receptor antagonist (LTRA; 4 mg/day) or intermittent high-dose nebulized budesonide (1–2 mg/day for 7 days after the first sign of acute respiratory tract infection) can be prescribed. The initial recommended dosage for nebulized budesonide during periods of severe asthma exacerbations or while tapering off OCS is 0.5–1 mg twice daily, whereas the dosage for maintenance treatment is 0.25–0.5 mg twice daily. The recommended oxygen flow for nebulization is 6–8 liters. Home nebulization can also be used to administer multiple drugs simultaneously, i.e., budesonide with albuterol or ipratropium bromide together in one dose. As-needed reliever medication is usually sufficient for children with non-severe, infrequent symptoms.

As recommended by GINA,[6] symptoms should be reassessed at intervals of 1–3 months. Patients with well-controlled symptoms can continue treatment and step down their ICS doses when there is no risk of future exacerbations in the next 6–12 months. Once full asthma control is achieved, HCPs can consider stopping ICS treatment altogether. However, in patients whose symptoms are not fully controlled, HCPs should either increase the ICS dose or add another maintenance medication, such as an LTRA. Upon periodic reassessment at 1–3 months, HCPs should consider further increasing the ICS dose, adding an LTRA, or prescribing intermittent high-dose ICS. Finally, HCPs should consider referring patients with uncontrolled asthma to specialists to ensure optimal asthma management.

Discussion

Unmet needs in asthma management in children aged ≤ 5 years

In recent years, the prevalence of asthma has increased globally in children and adolescents, particularly in low- and middle-income countries.[48] Moreover, asthma-related hospitalizations are particularly common in children aged < 5 years, with a rising prevalence over the past two decades.[48] There are several unique challenges pertaining to pediatric asthma management that require urgent attention. Notably, adherence to inhaled medication is generally poor among children with asthma; indeed, a systematic review conducted in the US, Canada, and the UK reported adherence rates ranging from 28% to 67%,[49] emphasizing the need for educational initiatives to improve adherence

to asthma medications. Additionally, in non-specialist practices in rural areas of Thailand, most of the burden of pediatric asthma results from underdiagnosis or misdiagnosis (cross-diagnosis with pneumonia, virus-induced wheezing, and bronchiolitis) and underuse of and limited adherence to maintenance medications. This indicates the need for accurate and timely diagnosis and management aligned with evidence-based recommendations. Notably, adherence to maintenance medications remains problematic across practice types, particularly in non-specialist practices. Therefore, while several guidelines recommend the referral of pediatric patients with asthma to a specialist to minimize the burden on healthcare systems,[50] simplified treatment algorithms that focus on inhaled ICS treatment with the correct inhaler technique are warranted. Thus, an expert consensus on the optimal use of nebulized budesonide in young children was urgently required.

Implementation of budesonide nebulization in maintenance therapy in pediatric asthma

Since the goal of asthma treatment in children is to achieve symptom control, pharmacological management of children should focus on age-specific treatments according to clinical severity and the level of asthma control; this is determined by the interaction between a patient's ongoing treatment, environment, and psychosocial factors.[51]

Nebulized budesonide is the only nebulized ICS recommended for children aged ≤ 5 years in the 2021 GINA report[6] due to its broad evidence base in childhood asthma. Several trials in young children have shown that nebulized budesonide significantly improves asthma symptoms, including exacerbations, when compared with placebo[24-26,39] and disodium cromoglycate[32,40,42] in RCTs. In a double blind, placebo-controlled study of 100 children aged 7–72 months hospitalized for asthma exacerbations, Razi et al.[52] showed that 2 mg/day of nebulized budesonide added to standard treatment significantly reduced the length of stay in hospital. Another study by Razi and colleagues,[43] which included 100 preschool children aged ≤ 6 years who presented to an ED with acute wheezing attacks, reported that addition of nebulized budesonide significantly decreased hospital readmission rates and increased discharge rates. Although a 52-week, open-label, randomized, active-controlled, multicenter study in 203 children aged 2–4 years showed no significant differences between nebulized budesonide and montelukast in median time to first additional asthma medication (183 vs 86 days), statistically significant differences were observed in favor of nebulized budesonide over montelukast in the proportion of patients requiring oral steroids at 52 weeks (21.9% vs 37.1%; $p = 0.022$) and caregivers' ability to manage patients' symptoms ($p = 0.026$).[20] Moreover, in two separate RCTs in young children (aged ≤ 5 years) with asthma exacerbations, nebulized budesonide was therapeutically equivalent to the systemic corticosteroids prednisolone and methylprednisolone for symptom control[21,28] and period of hospitalization.[21] However, in contrast to systemic corticosteroid treatments, nebulized budesonide did not suppress adrenocortical function.[21,28]

A real-world analysis of claims data from > 10,000 patients aged ≤ 8 years with ≥ 1 asthma exacerbation requiring hospitalization or ED visit from the Florida Medicaid database revealed that patients treated with nebulized budesonide had a 71% lower risk of repeat asthma exacerbations than those receiving other ICS medications delivered through other modes (hazard ratio [HR], 0.29; 95% confidence intervals [CI], 0.18–0.48; $p < 0.001$).[37] Moreover, treatment with nebulized budesonide in the first 30 days after hospitalization or an ED visit for asthma was associated with a 45% reduction in the risk of subsequent asthma-related hospitalizations or ED visits (HR, 0.55; 95%CI, 0.41–0.76; $p < 0.001$).[37]

A retrospective analysis of three randomized, double-blind, placebo-controlled, 12-week studies[36,39,53] showed that all nebulized budesonide dosage regimens (0.25–1 mg once daily; 0.25–1 mg twice daily) were effective in improving asthma control days, symptom-free days, and rescue medication-free days in pediatric patients aged 6 months to 9 years with mild to moderate persistent asthma.[54] Two meta-analyses have also confirmed the efficacy of nebulized budesonide in children with asthma. A meta-analysis of nine studies (n = 1,473) reported that addition of nebulized budesonide to systemic corticosteroids decreased the length of hospital stay by more than 1 day and significantly improved the acute asthma score among children (birth to 18 years) with acute asthma in ED settings.[55] Another meta-analysis of 21 RCTs reported that nebulized budesonide reduced the hospitalization rate (random effects-odds ratio [RE OR], 0.34; $p = 0.003$) and worsening of symptoms (RE-OR, 0.38; $p = 0.001$) compared with conventional treatments in 12,787 patients, including pediatric patients (6 months to 18 years) with asthma who were admitted to an ED.[56]

Overall, nebulized budesonide is well tolerated; an analysis of three pooled randomized, double-blind, placebo-controlled, multicenter, short-term (12 weeks) studies[36,39,53] revealed that the incidence, type, and severity of nonasthma-related adverse events were similar between nebulized budesonide and placebo in infants and young children (6 months to 8 years of age) with persistent asthma.[19] Furthermore, long-term treatment with nebulized budesonide, as assessed in 52-week extension studies of the 12-week double-blind trials, was well tolerated, with the incidence of reported adverse events comparable between nebulized budesonide and other conventional asthma therapies.[19] Moreover, the OCS-sparing effects observed with nebulized budesonide[20,21,25,26,28] may improve the overall safety of asthma therapy in patients with persistent asthma and during acute exacerbations.[57] However, to date, no study has directly compared the efficacy and safety of nebulized budesonide with those of budesonide delivered using pMDIs with spacers. Therefore, additional clinical studies are warranted to examine the comparative efficacy or effectiveness of these two modes of budesonide delivery in children aged ≤ 5 years.

Based on the results of published studies, daily low-dose ICS is recommended for optimal clinical benefits in children with asthma. While increasing evidence shows that ICS are effective and well tolerated at recommended doses in young children with asthma, long term studies have suggested that chronic ICS use at intermediate-to-high doses may affect growth in prepubertal children in the initial years of treatment, resulting in reduced final height at adulthood.[58-60] Higher doses of ICS have been associated with an increased risk of local and systemic adverse effects, including the risk of adrenal suppression in some children;[61] therefore, ICS must be carefully titrated and considered for their benefits and risks.[6] However, poorly controlled asthma itself may affect patients' growth;[62] consequently, it is essential that ICS therapy be gradually tapered to the lowest effective dose once the desired symptom control is achieved.[51]

Role of home nebulization and practical recommendations

In instances where HCPs, patients' families, or caregivers deem nebulized therapy to be more effective than inhalers, home nebulization may be continued for a short period following discharge from a healthcare facility and after a demonstrable improvement in clinical status following an acute asthma exacerbation.[7] Moreover, children may be more compliant with treatment when at home in a familiar environment. The nebulizer should be used in a room that is isolated from other household members to minimize the risk of transmission of respiratory viral infections. Crucially, parents and caregivers should be educated that failure to protect the skin or eyes during ICS delivery using a nebulizer may result in local side effects, such as steroid rashes;[6] therefore, the skin on the nose and around the mouth should be cleaned shortly after inhalation. Home nebulization for ICS maintenance treatment can be implemented under three potential scenarios: 1) ICS maintenance treatment for 1–3 months to prevent an acute exacerbation;[6] 2) intermittent high-dose treatment (1–2 mg once daily for a week) at the onset of a respiratory infection; and 3) management of an acute exacerbation.[7,63] This guidance should be followed especially when access to healthcare facilities is limited, and to reduce the risk of viral infections and severity of asthma exacerbations during the COVID-19 pandemic. Patients with mild or moderate asthma exacerbations can be effectively managed with home nebulization, instead of receiving treatment at a healthcare facility. Notably, high-dose (0.5–1 mg/dose) nebulized ICS can be added to a systemic corticosteroid in the first hour of treatment to ensure a rapid onset of action.[7] Home nebulization also facilitates the administration of multiple asthma medications, including budesonide and bronchodilators, in one dose, especially during asthma exacerbations. However, it is essential that all patients, including those perceived to be without future risk of exacerbations, are monitored carefully. Although both jet nebulizers and ultrasonic nebulizers produce the desired particle size in an aerosol

drug output, require only tidal breathing, and allow dose modification,[64] jet nebulizers are sturdier and less expensive and nebulize suspensions more effectively than ultrasonic nebulizers, which may cause drug degradation in suspension formulations.[64] However, all nebulizers have inherent limitations, including the length of treatment time and ambient contamination by escaped aerosols.[64]

Asthma education

The education of children's families, caregivers, and healthcare workers is an essential component of asthma management in children. Indeed, a combination of health programs at school and home improved asthma control in children aged 2–6 years from low-income families in the US.[65] However, results of a global survey of national Member Societies of the World Allergy Organization from 31 countries highlighted disparities in the availability of adequate educational material among responding countries, with many reporting a lack of suitable material locally.[66] These findings emphasize the need to develop clear, age appropriate information that can be easily translated and delivered in a culturally and educationally effective format.[66] Additionally, it has been determined that education of patients and caregivers should focus on the identification and avoidance of triggers, increase in understanding of prescribed treatments and the need to adhere to maintenance medications, and the need for appropriate choice and use of delivery devices.[67]

Conclusion

Nebulized inhalation therapy provides multiple advantages that overcome common challenges in the delivery of inhaled medications for asthma, making it an effective treatment strategy for asthma management in pediatric patients who cannot use pMDIs with spacers effectively. While home nebulization should be widely recommended for pediatric patients in specific clinical scenarios, all patients should be monitored carefully including those perceived to be without future risk of exacerbations. Based on the literature review and expert opinion, nebulized budesonide is an effective and well-tolerated treatment option in children aged ≤ 5 years with asthma and should therefore be considered as initial therapy in this patient population. We hope that this algorithm is integrated into routine clinical practice for pediatric asthma management in Thailand and across other countries.

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Conflict of interest

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Author contributions

All authors have read and approved the final manuscript and take full responsibility for the accuracy of its content.

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