

Practical considerations of nebulized corticosteroid in children with acute asthmatic exacerbation: A consensus

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Abstract

Background: Acute asthmatic exacerbation in children causes economic burdens both directly and indirectly. The GINA guideline does mention the use of inhaled or oral corticosteroids in the treatment of asthmatic exacerbation, it provides little practical guidance on the use of nebulized corticosteroid.

Objective: To review and recommend the practical considerations in the use of nebulized corticosteroid in children with acute asthmatic exacerbation.

Methods: This consensus was developed by a group of expert pediatricians in respiratory and allergy fields in Thailand. The recommendations were made based on a review of published studies and clinical opinions. The eligible studies were confined to those published in English, and randomized controlled trials and meta-analyses involving nebulized corticosteroids in asthmatic exacerbation in children aged between 1-18 years.

Results: There were 13 randomized controlled-trial studies published from 1998 to 2017. Nine of the 13 studies compared nebulized with systemic corticosteroid conducted in moderate to severe exacerbation, while the remaining four compared nebulized corticosteroid with placebo conducted in mild to severe exacerbation. The admission rate was significantly lower in severe exacerbation (one study) and pooled four mild to severe exacerbation studies comparing with placebo (p 0.022). Other clinical parameters were significantly improved with nebulized corticosteroid such as clinical scores, systemic corticosteroid/bronchodilator use, or shorter ER stays. Only one study used fluticasone, while the other 12 studies conducted by budesonide (92.31%).

Conclusion: Nebulized corticosteroid may offer an effective therapeutic option for the management of acute exacerbation of asthma in all severities. Nebulized budesonide is the preferred corticosteroid.

Key words: budesonide, admission, bronchodilator, randomized-controlled trial, meta-analysis

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Introduction

The prevalence of asthma in Thai children was 7.8-15% and 8.7-13.9% in 6- and 13-year-old children, respectively.^{1,2} A study conducted on 6-12 year-old Thai students with asthma showed that 46.7% of them were controlled, 43.4% were partially controlled and 10% were uncontrolled.³ Acute asthmatic exacerbation is still a problem in Thailand. A survey conducted in 400 Thai patients with asthma; 9.5% had aged between 12 and 17 years showed that 36% had exacerbations in the

previous year, 17% had been hospitalized and 35% had an unscheduled emergency visit to a healthcare facility.⁴ A study on the annual cost of treatment children with asthma in Chiang Mai and Lumphun showed that the average total cost per person was 258 USD, of which 216 USD was direct and 41 USD was indirect.⁵ Similar finding from a study in Ramathibodi Hospital showed that the annual direct costs for asthmatic children aged less than 20-year-old in Thailand was estimated to be 278 USD, of which those patients with at least one exacerbation and without any exacerbation costing 463.6 USD and 241.6 USD respectively.⁶

The 2018 update of the Global Strategy for Asthma Management and Prevention recommends systemic or high-dose inhaled corticosteroid for asthma exacerbation.⁷ Inhaled corticosteroid can be delivered via a pressurized metered-dose inhaler [pMDI], with or without a spacer, a dry powder inhaler [DPI], or a nebulizer. Any types of inhaled corticosteroid should be administered within one hour of presentation to the hospital. Although pMDI with a spacer is commonly used to deliver corticosteroid in children with asthma, nebulized corticosteroid offers an effective option for patients who may be unwilling or unable to use a pMDI.⁸ This is especially relevant in children with an acute asthmatic exacerbation who may be challenged to perform the precision technique with an inhaler.

While the GINA guideline does mention the use of inhaled or oral corticosteroids in the treatment of asthmatic exacerbation, it provides little practical guidance on the use of nebulized corticosteroid. This consensus aims to review and recommend the practical considerations in the use of nebulized corticosteroid in children with acute asthmatic exacerbation.

Methods

This consensus was developed by a group of expert pediatricians in respiratory and allergy fields in Thailand. A series of meetings was held in Bangkok to discuss the role of nebulized corticosteroid in acute asthmatic exacerbation in children. The recommendations were made based on a review of published studies and clinical opinions. The eligible studies were confined to those published in English, and randomized controlled trials and meta-analyses involving nebulized corticosteroids in asthmatic exacerbation in children aged between 1-18 years.

Recommendations

An overview of the treatment algorithm is captured in **figure 1**. It is adapted from the Thai asthma guideline.⁹

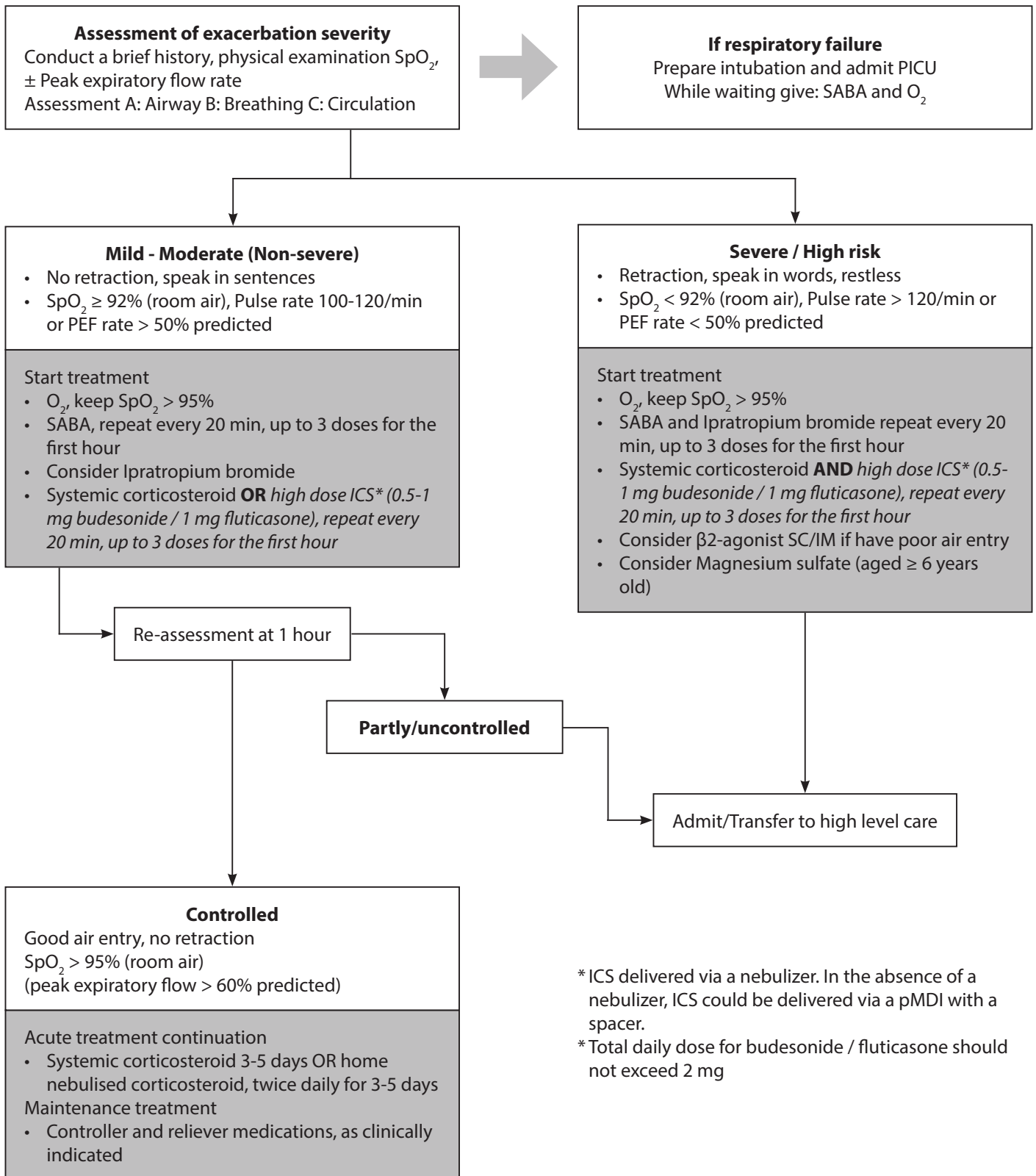
Severity of Asthmatic Exacerbations

- Nebulized high-dose corticosteroid is recommended in the treatment of all severities [mild, moderate and severe] of asthmatic exacerbation in children at least 1 year old [**Figure 1**] by the below evidence.
- The severity of asthmatic exacerbation should first be established based on the existence of retraction, degree of difficulty in speaking, SpO₂, pulse rate and peak expiratory flow rate, as stipulated in the Thai Asthma guideline.⁹

There were 13 randomized controlled-trial studies published from 1998 to 2017.¹⁰⁻²² Of those, two studies conducted in hospital setting, while the other 10 studies conducted at the emergency room [ER] and one study conducted at an asthma clinic. Nine of the 13 studies compared nebulized with systemic corticosteroid [**Table 1**],¹⁰⁻¹⁸ while the remaining four compared nebulized corticosteroid with placebo [**Table 2**].¹⁹⁻²²

Studies on moderate to severe asthma exacerbation. Of the nine systemic corticosteroid-controlled studies compared with nebulized budesonide,¹⁰⁻¹⁸ five studies evaluated the admission rate as the main outcome. There were 200 patients with moderate asthma attack in all studies with age ranged between 1-18 years. All the studies used nebulized budesonide mostly 3 times daily with total dose between 800 microgram and 3 mg. Nebulized budesonide had better clinical outcomes over systemic corticosteroid without suppression of pituitary adrenal axis.¹⁷ Combination of admission rate by the three studies, the admission rate was slightly lower but not different between nebulized budesonide [149/660 patients; 22.58%] versus systemic corticosteroid [171/649 patients or 26.35%; p 0.123].^{10,11,14} In one study from Saudi Arabia 30.9% of the patients in the study had severe asthma exacerbation.¹⁵ Treatment with nebulized budesonide vs placebo was compared. The results showed a significant improvement in group with nebulized budesonide in several parameters including clinical scores,^{11,13,18} peak flow,^{12,15} fewer use of bronchodilator,¹⁷ the reduction in intravenous corticosteroid use,¹¹ and shorter length of emergency room stays.¹⁵ The admission rate in severe case with baseline clinical score of over or equal to 13 was significantly lower in nebulized budesonide group than placebo group [p 0.03].¹⁵ There were two studies comparing groups receiving nebulized budesonide versus systemic corticosteroids which showed a better asthma score and a lower use of bronchodilator in the nebulized budesonide group.^{16,17}

Studies on mild to severe asthma exacerbation. In the four placebo-controlled studies, which was done in the hospital setting, there were 384 patients with mild to severe asthmatic exacerbation with age ranging from 2 to 15 years.¹⁹⁻²² Three studies used nebulized budesonide with daily dose range between 2-11 mg, while another study used 1.5 mg of fluticasone. Two studies from Mexico and China found positive results using nebulized corticosteroids over placebo in clinical score, admission rate, systemic corticosteroid need, and complete remission rate. Even though clinical outcomes in Milani and Sekerel studies were not statistical significant,^{19,20} analysis as a meta-analysis by Chen et al, showed statistical significance.²² The admission rate,^{19,22} and systemic corticosteroid need were both statistically different between the nebulized budesonide and placebo arms.^{20,22} The admission rate was significantly higher in placebo [11/69; 15.9%] than nebulized budesonide group [3/76; 3.9%, p 0.022]. Systemic corticosteroid need, an indicator of treatment failure, was also significantly higher in placebo group [32/88; 36.4%] than nebulized budesonide group [12/92; 13.0%, p < 0.001].



Adapted from Thai Pediatric Asthma Guideline 2015-2016

Figure 1. Management of pediatric asthma exacerbation in hospital

Table 1. Studies comparing nebulized corticosteroids with systemic corticosteroids in children with asthma exacerbation at hospital setting.

Factors/study	Sung 1998, Canada [10]	Devidayal 1999, India [11]	Nuhoglu 2005, Turkey [12]	Upham 2011, USA [13]	Razi 2012, Australia [14]	Alangari 2014, Saudi Arabia [15]	Akhtaruzzaman 2014, Bangladesh [16]	Yanagida 2015, Japan [17]	Sharma 2017, India [18]
Design	RCT, double blinded	RCT, double blinded	RCT, double blinded	RCT, double blinded	RCT	RCT, double blinded	RCT, double blinded	RCT	RCT
Numbers of patients	42	80	26	169	100	906	66	40	80
Setting	Moderate-severe	Moderate-severe	Moderate; PIS 3-6	Moderate to severe	PIS 7-13	Moderate to severe	Moderate to severe	Moderate	Moderate
Site	ER	ER	ER	ER	ER	ER	Hospital	Hospital	ER
Age	6 months-18 years (median 3.5-4.4 years)	2-12 years	5-15 years	2-18 years; mean 6.2-6.3 years	6 months-6 years	2-12 years	5-15 years	< 5 years	1-18 years (average 5.59-6.22 years)
Treatment	Oral prednisolone 1 mg/kg Nebulized salbutamol q 30 minutes x 3 doses, then q 1 hr x 4 hours 4 ml of nebulized budesonide	Oxygen Nebulized salbutamol Nebulized budesonide 800 microgram Oral prednisolone	3 doses of nebulized salbutamol Single dose of IM methylprednisolone 1 mg nebulized budesonide	Albuterol, ipratropium bromide, systemic corticosteroid 2 doses of albuterol with budesonide then one ipratropium bromide	3 doses of budesonide 1 mg/2 ml with salbutamol 0.15 mg/kg/dose (maximum 5 mg) at 0, 20, 40 min 1 dose of IM methylprednisolone 1 mg/kg, ipratropium bromide, salbutamol at 80, 120, 180 minutes	3 doses of 500 microgram of budesonide Salbutamol Oral prednisolone 2 mg/kg	Oral prednisolone 1 mg/kg Nebulized salbutamol plus ipratropium bromide q 20 minutes x 3 doses than q 1 hour x 2 doses 2 mg of nebulized budesonide (4 ml) after first dose of bronchodilator	3 times of Procaterol 0.3 ml Budesonide suspension 0.5 mg/2 ml	Oxygen 5-6 LPM Inhaled salbutamol q 1 h x 3 hours then q 6 hours Budesonide 800 microgram x 3 doses then 800 microgram q 12 hours x 3-5 days
Dose of nebulized corticosteroid	2 mg budesonide x 1	800 microgram budesonide (800 microgram x 1)	1 mg of budesonide	2 mg budesonide	3 mg budesonide (1 mg x 3)	1.5 mg budesonide (0.5 mg x 3)	2 mg budesonide x 1	1.5 mg of budesonide (0.5 mg x 3)	2.4 mg budesonide initially (800 microgram x 3)
Control	Oral prednisolone 1 mg/kg Nebulized salbutamol q 30 minutes x 3 doses, then q 1 hr x 4 hours 4 ml of nebulized normal saline	Oxygen Nebulized salbutamol Nebulized placebo Oral prednisolone	3 doses of nebulized salbutamol Single dose of IM methylprednisolone 1 mg nebulized normal saline	Albuterol, ipratropium bromide, systemic corticosteroid 2 doses of albuterol with normal saline then one ipratropium bromide	Normal saline 2 ml, salbutamol 3 doses at same interval 1 dose of IM methylprednisolone 1 mg/kg, ipratropium bromide, salbutamol at 80, 120, 180 minutes	3 doses of normal saline Salbutamol Oral prednisolone 2 mg/kg	Oral prednisolone 1 mg/kg Nebulized salbutamol plus ipratropium bromide q 20 minutes x 3 doses than q 1 hour x 2 doses 4 ml of normal saline after first dose of bronchodilator	3 times of Procaterol 0.3 ml Cromoglycate 2 ml iv methylprednisolone 1 mg/kg/d	Oxygen 5-6 LPM Inhaled salbutamol q 1 h x 3 hours then q 6 hours Oral prednisolone 2 mg/kg/d

Note. RCT: randomized controlled trial, ER: emergency room, PIS: pulmonary index score, outcomes showed numbers in treatment group vs control group respectively.

Table 2. Studies comparing nebulized corticosteroids with placebo in children with asthma exacerbation at hospital setting.

Factors/study	Milani 2004, Brazil* [19]	Sekerel 2005, Turkey [20]	Estrada 2005, Mexico** [21]	Chen 2013, China [20]
Design	RCT, double blinded	RCT, double blinded	RCT, double blinded	RCT, double blinded
Numbers of patients	49	67	150	118
Setting	Moderate	Mild to moderate	Moderate	Moderate to severe
Site	Clinic	ER	ER	ER
Age	2-7 years	6-15 years	Mean 9.8-10 years	Mean 7.9-8.2 years
Treatment	3 ml of salbutamol 4 ml of budesonide (2 mg)	3 doses of nebulized budesonide (1 mg/dose) at ER Nebulized budesonide twice/day x 4 days at home	3 doses of salbutamol 30 microgram/kg plus fluticasone 500 microgram/dose q 15 minutes	4 ml of mixture of salbutamol, ipratropium and 0.05% budesonide 2 ml q 20 minutes x 3 doses
Dose of nebulized corticosteroid	2 mg budesonide	3 mg at ER, total of 11 mg of budesonide	1.5 mg of fluticasone	3 mg of budesonide
Control	3 ml of salbutamol 4 ml of normal saline	Same regimen but use normal saline	3 doses of salbutamol 30 microgram/kg q 15 minutes	4 ml of mixture of salbutamol, ipratropium and normal saline 2 ml q 20 minutes x 3 doses
Outcomes	Admission 0/17 vs 1/15 (p 0.469)	Systemic corticosteroid need 2/33 vs 7/34 (p 0.07)	Treatment group had better clinical score at 2 hours (p < 0.05)	Admission 3/59 vs 10/54 (p 0.037)
	Clinical score at 1-2 hours 6.2 (2.2) vs 5.64 (2.4)			Systemic corticosteroid need 10/59 vs 25/54 (p 0.011)
				Complete remission at 2 hours 50/59 vs 25/54 (p 0.004)

Note. RCT: randomized controlled trial, * another group received inhaled placebo with oral prednisolone 1 mg/kg, ** another group received 3 doses of salbutamol plus 2 doses of fluticasone 500 microgram/dose, outcomes showed numbers in treatment group vs control group respectively.

Table 3. Pharmacological properties of budesonide and fluticasone

ICS	Budesonide	Fluticasone
Mean Absorption Time	1 hour	7 hours
Tmax	15.5 mins	50.8 mins
Half life	2.8 hours and low systemic potency	14.4 hours and high systemic potency
Water solubility (µg/ml)	16	<0.1
Dissolution time	6 mins	> 8 hours
Residence time in airway/lung tissue	Similar or longer	Shorter
Volume distribution	Low (183 L)	High (318 L)
Pneumonia risk	Low	High

Table adapted from reference no. 34, 37

Note. ICS: Inhale Corticosteroid

including savings from shortened the hospital stay – of nebulized corticosteroid may be lower than oral prednisolone. The study showed that hospital length of stay was shorter by 36 hours and the cost of treatment with budesonide was lower by 130 USD compared with placebo.¹⁴

Post-Nebulization Monitoring

- The clinical status of the patient should be evaluated at the end of each nebulized corticosteroid dose to determine whether any subsequent doses are needed.
- If three nebulized doses are required, the need for more intensive treatment and monitoring in the hospital is recommended.

- If the clinical status of the patient is improved at the end of the first hour of initiating nebulization, the patient should continue home nebulized corticosteroid for 3-5 days¹⁸ if available or start systemic corticosteroid at home for 3-5 days.
- If the clinical status of the patient is not improved at the end of the first hour of initiating nebulization, the patient should be hospitalized, and be initiated or maintained on systemic corticosteroid as part of the inpatient treatment.

For those with clinical responses with nebulized corticosteroid, defined by improvement of clinical score such as asthma index or pulmonary index score, short-term corticosteroids

are needed. If available, home nebulized budesonide is justified with a dose of 1 mg twice a day for 3-5 days. An alternative treatment is oral prednisolone 0.5-1 mg/kg/day for 3-5 days. Note that those with clinical responses may have a risk of ER revisit and hospitalization rate of 4.18% [16/383] and 0.78% [3/383], respectively.¹⁵

Choice of Corticosteroid

- Nebulized budesonide is the preferred corticosteroid.
- Nebulized fluticasone is an alternative if budesonide is not available.

First, pharmacological properties of budesonide are better than fluticasone [Table 4]. Budesonide has faster absorption time [1 hr vs 7 hr], more water solubility [16 vs 0.1 microgram/ml], and longer deposit in airways or lung tissues than fluticasone.³¹ Second, budesonide has lower pneumonia risk which is relatively constant across all doses, while fluticasone increases risks of pneumonia as a dose-dependent fashion.³² Finally, budesonide has lower systemic side effects than fluticasone.³¹ These findings may indicate that nebulized budesonide has faster clinical improvement and fewer side effects than nebulized fluticasone.

Home Nebulization

- Home nebulization may be considered only for a short period as a continuation of the acute treatment in a healthcare facility after demonstrable improvement in the clinical status of the patient who first presented with acute asthmatic exacerbation
- Home nebulized corticosteroid should be administered twice a day as maintenance for 3-5 days after clinical improvement following acute treatment of acute asthmatic exacerbation
- The use and care of a nebulizer should be based on the recommendations from the American Association for Respiratory Care.

There is no randomized controlled trial comparing nebulized corticosteroids and inhaled corticosteroids to treat home asthma exacerbations in children. Currently, there are some evidence of inhaled corticosteroids at home for treat and prevent asthma exacerbations as follows:

A meta-analysis study compared an increasing and stable dose of inhaled corticosteroids to treat asthma exacerbations at home in patients with mild to moderate asthma.³³ The study included three studies with 422 children and five studies with 1,247 adults. The primary outcome of this study was treatment failure identified by a need of rescue systemic corticosteroids. A sub-group analysis in children showed that increasing dose of inhaled corticosteroids at home was not better than stable dose of inhaled corticosteroids [odds ratio of 0.93; 95% confidence interval of 0.61, 1.41] for the primary outcome.

Another study in children compared a quintupled dose of fluticasone [220 microgram/inhalation; twice a day] for seven days versus low-dose fluticasone [44 microgram/inhalation; twice a day]. This study was a randomized, double-blind study

conducted in 17 sites in the US with 254 mild to moderate children with history of one exacerbation in the past years. The average age of all patients was 8.0 [SD 1.9] years.³⁴ The study found that severe asthma exacerbations/year were comparable between both groups [0.48 vs 0.37 in quintupled dose and low-dose; p value 0.30]. Other outcomes were also not statistically different between both groups such as the time to the first exacerbation or the rate of treatment failure. A study conducted in Turkey using a 4-, 8-, and 8-day of inhaled corticosteroid plus azithromycin at home to treat asthma exacerbation also found good response rate at 84%, 83%, and 94% of the three regimens.³⁵ The inhaled corticosteroids in this study were budesonide and fluticasone.

The role of inhaled corticosteroid at home in children with mild to moderate asthma to treat asthma exacerbations are still controversial. The home regimen, types, or duration of inhaled corticosteroid use are still limited. For nebulized corticosteroid, there is no clinical data to show efficacy on treatment and prevention of asthma exacerbation at home. One study from Turkey evaluated nebulized budesonide versus placebo at home after the ER visit.²⁰ The 1 mg of budesonide or placebo was given twice a day for four days. The FEV1 improvement in both groups for both short term [at ER] and long term [day sixth] were not statistical different. The home nebulized budesonide group had a trend of fewer patients who required systemic corticosteroid than placebo group [2/33 vs 7/34; p value 0.073]. No major side effects of nebulized budesonide were reported in a 72-hour study.¹⁹ Two out of 17 patients [11.76%] had coughing, while one out of 15 patients [6.67%] in placebo group did. Nebulized corticosteroid treatment at home needs more attention on care, use, and side effects.

Conclusions

Nebulized corticosteroid may offer an effective therapeutic option for the management of acute exacerbation of asthma in all severities. It may be used within the first hour of presentation of acute treatment. Nebulized budesonide is the preferred corticosteroid. Home nebulization if available may be used for a short period as a continuation of the acute treatment in a healthcare facility only after demonstrable improvement in the clinical status of the patient who first presented with acute asthmatic exacerbation.

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