Publisher
MEDRESEARCH
www.medresearch.in

Pediatric Review - International Journal of Pediatric Research

2025 Volume 12 Number 1 Jan-Mar

E-ISSN:2349-3267
P-ISSN:2349-5499
RNI:MPENG/2017/74037

Review Article
Inhaled Corticosteroids

Role of Inhaled Corticosteroids in Pediatric Asthma and Virus-induced wheeze

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DOI:https://doi.org/10.17511/ijpr.2025.i01.02

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Inhaled corticosteroids (ICS) are one of the important components of childhood asthma pharmacotherapy and a common first-line treatment. Treatment with ICS decreases asthma mortality and morbidity reduces symptoms, improves lung function, improves symptoms in childhood viral-induced wheezing and reduces the number of asthma exacerbations. This study reviews the role of ICS in childhood asthma, including their mechanism of action, clinical efficacy, safety profile, and adherence challenges. The benefits of ICS in controlling symptoms and reducing morbidity outweigh their potential risks when used appropriately in proper dosages. Strategies for optimizing ICS therapy and addressing concerns about long-term use are also discussed.

Keywords: Asthma, Children, Wheeze Nebulization, Pediatric, wheezing, Inhaled corticosteroids, Budesonide, Beclomethasone, Fluticasone, Asthma exacerbation, Asthma maintenance

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How to Cite this Article

Singh R, Role of Inhaled Corticosteroids in Pediatric Asthma and Virus-induced wheeze. Pediatric Rev Int J Pediatr Res. 2025;12(1):5-12.
Available From
https://pediatrics.medresearch.in/index.php/ijpr/article/view/787

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2025-02-01	2025-02-10	2025-02-21	2025-03-01	2025-03-10

Conflict of Interest	Funding	Ethical Approval	Plagiarism X-checker	Note
None	Nil	Yes	12.52	

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 and school attendance [1].

Signs and symptoms of asthma include the following:

- Wheezing
- Coughing
- Shortness of breath
- Chest tightness/pain

The differential diagnosis of asthma in young children is particularly challenging because it must be made mainly on symptoms and clinical context (eg, personal and family history of atopy, and frequency and duration of wheezing) owing to difficulties in obtaining high-quality test results for airflow limitation and bronchodilator responsiveness. In the absence of a clear diagnosis, a probability-based approach is often used. The goal of asthma therapy for children is to achieve asthma control by optimizing lung function, reducing day and night time symptoms, reducing limitations in daytime activities and the need for reliever treatment and reducing asthma exacerbations. However, especially in children, it is important to achieve control with a minimum of side effects of medication. Most of the guidelines advocate the use of ICS for the treatment of persistent asthma [2].

Virus-induced wheeze [3]

Asthma is a heterogeneous disease and has variable manifestations, and severity varies greatly between age groups.[4], [5]. Children in general and those under the age of 5 years in particular are prone to developing symptoms that may be misclassified as asthma when infected with respiratory viruses [6].

Children who wheeze intermittently during a viral infection and are well between episodes are known to have viral-induced wheezing. The efficacy of ICS in the treatment of episodic viral wheeze in preschool children is controversial. The majority of asthma exacerbations in school-aged children are associated with viral infections [7]. Intermittent versus daily ICS treatment in children was reviewed by the Cochrane Airways Group [8].

This review showed that children benefited from intermittent use of high-dose ICS (1,600– 3,200 µg/day BDP or BUD) as evidenced by a reduction in the severity of symptoms. There was also a reduced requirement for oral corticosteroids.

Management of Pediatric Asthma

Pharmacologic treatment is the mainstay of management in most patients with asthma. National and international guidelines advise initiating pharmacologic therapy based on the frequency and severity of symptoms, history of exacerbations requiring systemic glucocorticoids, and results of lung function measurement (asthma severity), and subsequently adjusting therapy up or down, as needed, according to a stepwise approach, to achieve good asthma control [9], [10].

The most commonly used controller medications for children <12 years of age are inhaled glucocorticoids (also called inhaled corticosteroids [ICS]), inhaled glucocorticoids plus inhaled long-acting beta-agonists (LABAs), and oral leukotriene receptor antagonists (LTRAs) in combination with inhaled glucocorticoids.

Inhaled glucocorticoids—Glucocorticoids are the most effective anti-inflammatory agents available for the treatment of asthma. They act by inhibiting most steps in the cascade of the inflammatory response [11].ICS works by reducing airway inflammation, decreasing mucus production, and preventing airway remodelling.

They act by binding to glucocorticoid receptors in the airway epithelial cells, leading to the suppression of pro-inflammatory cytokines such as interleukins and tumour necrosis factor-alpha (TNF-α). This results in reduced airway hyperresponsiveness and improved lung function over time.

Inhaled glucocorticoids are delivered directly to the airways at a dose much lower than needed when given systemically and have minimal side effects.

- **Specific preparations**– The approved inhaled glucocorticoid preparations available for use in children <12 years are listed in table (table 1).
- **Time to improvement**– A reduction in asthma symptoms may occur rapidly, and reduced inflammation is seen within hours. Lung function continues to improve over four weeks and then plateaus.

- It may take as long as three months to reach a plateau in response, and any changes in dose should be made at intervals of three months or more [12].
- **Time to loss of effect after discontinuation**– When inhaled glucocorticoids are discontinued, there may be gradual incr. in symptom & airway responsiveness back to pretreatment value.
- **Dosing**– Initial dosing of inhaled glucocorticoids depends upon severity of asthma symptoms at time treatment is started. Dose-response curve for clinical efficacy of inhaled glucocorticoids is relatively flat, with most benefits obtained at lowest doses used and only small additional benefits attained with higher doses.
- Long-term control therapy is then stepped up or down at one- to six-month intervals, depending upon clinical response and ongoing severity of disease.
- **Delivery**– The mode of delivery for inhaled glucocorticoids greatly influences drug deposition in lungs and frequency of local and systemic side effects. Delivery systems include MDIs (with or without spacers/valved holding chambers), nebulizers, and dry powder inhalers (DPIs).
- **Adverse effects**– The effect of chronic inhaled glucocorticoid use in children on adult height appears small.

Table 1: Inhaled corticosteroid dose regimens for children [10]

	Pediatric Low Dose	Pediatric moderate dose	Pediatric moderate dose
Beclometasone dipropionate			
Standard particle CFC-free inhalers	100 - 200micrograms per day in 2 divided doses	300 - 400 micrograms per day in 2 divided doses	500 - 800 micrograms per day in 2 divided doses.
Extra Fine particle CFC-free inhalers	100 micrograms per day in 2 divided doses	300 - 400 micrograms per day in 2 divided doses	300 - 400 micrograms per day in 2 divided doses
Budesonide			
Dry powder inhalers	100 - 200 micrograms per day as a single dose or in 2 divided doses	300 - 400 micrograms per day as a single dose or in 2 divided doses	500 - 800 micrograms per day in 2 divided doses
Fluticasone propionate			
Metered dose and dry powder inhalers	100 micrograms per day in 2 divided doses	150 - 200 micrograms per day in 2 divided doses	250 - 400 micrograms per day in 2 divided doses
Ciclesonide			
Metered dose inhaler	80 micrograms per day as a single dose	160 micrograms per day as a single dose or in 2 divided doses	240 – 320 micrograms per day in 2 divided doses
Mometasone			
Dry powder inhaler	110 mcg/inhalation One inhalation OD	110 mcg/inhalation 2-3 inhalations OD	110 mcg/inhalation 4 inhalations OD or 2 inhalations BID. 220 mcg/inhalation-2 inhalations OD or 1 inhalation BID.

Table 2: Approach to initial asthma therapy in children less than 4 years [1], [23], [24]

		Step 1	Step 2	Step 3	Step 4
Criteria		All of the following -Daytime symptoms ≤ 2 days/week -No night awakenings (due to asthma) -No interference with activities -0 to exacerbation treated with oral corticosteroids per year and no risk factors for exacerbations	Any of the following -Daytime symptoms 3-6 days/week -1-2 night awakenings per month. -minimal interference with activities ≥2 exacerbations treated with oral corticosteroids per year and no risk factors for exacerbations	Any of the following -Daytime symptoms 3-4 night awakenings per month. -Occasional limitation in normal activities ≥2 exacerbations treated with oral corticosteroids in 6 months.	Any of the following -Symptoms throughout the day. -Night awakenings > once a week. -frequent limitations in normal activities
Reliever Therapy		SABA as needed	SABA as needed	SABA as needed	SABA as needed
Controller Therapy	Preferred	A short course of daily medium-dose ICS beginning at the start of a respiratory tract infection	Daily low dose ICS	Daily medium dose ICS Or daily low dose ICS & LABA	Daily high dose ICS Or daily medium dose ICS & LABA
	alternative	none	Intermittent low dose ICS. Or Daily LTRA	Daily low dose ICS + LTRA	Daily medium dose ICS + LTRA

Table 3: Approach to initial asthma therapy in children 4-11 years of age. [1], [23], [24]).

		Step 1	Step 2	Step 3	Step 4
Criteria		All of the following -Daytime symptoms ≤ 2 days/week -No night awakenings (due to asthma) -No interference with normal activities -SABA use for symptoms ≤ 2 days/week. -no more than one exacerbation treated with oral corticosteroids per year and no risk factors for exacerbations -FEV1>80% of predicted & FEV1/FVC >85% of predicted.	Any of the following -Daytime symptoms 3-6 days/week -up to 4 night awakenings per month. But not more than once/week. -minimal interference with normal activities ≥2 exacerbations treated with oral corticosteroids per year. -SABA used for symptoms 3-6 days/week. -FEV1>80% of predicted & FEV1/FVC >80% of predicted.	Any of the following -Asthma symptoms daily -night awakenings more than once/week. But not every night. -Some limitations in normal activities ≥2 exacerbations treated with oral corticosteroids per year. -SABA use daily. -FEV1 between 60-80% of predicted & FEV1/FVC between 75-80% of predicted.	Any of the following -nightly awakenings -frequent limitations in normal activities. -FEV1 <60 % of predicted & FEV1/FVC < 75% of predicted.
Reliever Therapy	Preferred	SABA as needed	SABA as needed	Low dose ICS –formoterol (fast acting LABA) as needed plus daily as controller therapy.	Medium dose ICS –formoterol (fast-acting LABA) as needed plus daily as controller therapy.
	or			Or	or
	Alternative			SABA as needed with alternative controller medicines	SABA as needed with alternative controller medicines
Controller Therapy	Preferred	Maintenance therapy is not needed	Daily Low Dose ICS	Daily Low Dose of ICS-Formoterol plus on a needed basis	Daily medium Dose ICS-Formoterol plus on a needed basis
	Alternative	Low dose ICS whenever SABA is used	Low dose ICS whenever SABA is used Or Daily LTRA	Daily Low dose ICS-LABA (use slow onset LABA not formoterol) Or Daily medium dose ICS Or Daily Low dose ICS + LTRA	Daily medium dose ICS-LABA (use slow onset LABA not formoterol) Or Daily high dose ICS Or Daily medium dose ICS + LTRA Or Daily medium dose ICS-LABA+ tiotropium or LTRA

Functional effects of inhaled corticosteroids

ICS prevents the late but not the early allergic response. However, prolonged treatment with ICS is found to be effective in reducing the early response to an allergen challenge in a time-dependent and probably dose-dependent way [13]. Moreover, ICS does not protect against bronchoconstriction when given immediately before exercise [14]. Regular treatment with ICS is effective in reducing bronchial responsiveness to direct and indirect stimuli and reduces the prevalence and severity of exercise-induced asthma [14].

Inhaled corticosteroid resistance

Relative resistance is seen in patients who require high doses of inhaled and oral steroids (steroid-dependent asthma). Biopsy studies have demonstrated the typical eosinophilic inflammation of asthma in those patients [15].

Persistent immune activation and airway inflammation, which to varying degrees is resistant to glucocorticoid therapy, appears to define the immunologic abnormality underlying steroid-resistant asthma [16].

Certain cytokines (particularly interleukin-2, interleukin-4, and interleukin-13- 13, which show increased expression in bronchial biopsy samples from patients with steroid-resistant asthma) may induce a reduction in affinity of GRs in inflammatory cells, such as T-lymphocytes, resulting in local resistance to the anti-inflammatory actions of corticosteroids [17].

Moreover, the inhibitory effect of corticosteroids on cytokine release is reduced in peripheral blood mononuclear cells from patients with steroid-resistant and steroid-dependent asthma [18].

Local adverse effects

Relatively few studies sought to evaluate local side effects of ICS as they are generally viewed as minor complications of therapy. Nevertheless, approximately 5–10 % of subjects treated with ICSs report adverse effects in the oral cavity. The local effects can be clinically significant, affect patient quality of life, and hinder compliance with therapy [19], [20]. Local deposition of glucocorticoids is, thus, an important risk factor for oropharyngeal candidiasis [21].

Table 4 - Potential local and systemic side effects of inhaled corticosteroids [22]

Local	Systemic
Pharyngitis	Suppressed HPA-axis function
Dysphonia	Adrenal crisis (with insufficiency
Reflex cough	Suppressed growth velocity
Bronchospasm	Decreased lower-leg length
Oropharyngeal candidiasis	Reduced bone mineral density Osteoporosis Bone fractures
	Skin thinning Skin bruising
	Cataracts Glaucoma

Asthma self-management plan

All children with asthma should receive self-management education and a written personalized asthma plan. However, remember some patients will have specific needs. Less than 50% of people use their medicines as prescribed.

Advise on:

- When and how to take their medicines
- Correct inhaler technique
- Avoidance of known trigger factors
- Recognizing poor control.

For an acute asthma attack in children [23] [24]

Use a SABA (Salbutamol) via a large-volume spacer to relieve acute symptoms.

- For a child, give a puff every 30–60 seconds, up to 10 puffs. Each puff should be given one at a time and inhaled with five tidal breaths. Repeat every 10–20 minutes according to clinical response.
- Prescribe a short course of oral prednisolone

01. < 2 years prednisolone 10mg daily for up to 3 days
01. 2 – 5 years: 20mg daily for up to 3 days is usually sufficient
02. 5 years: 30mg – 40mg daily, up to 3 days is usually sufficient

Decreasing maintenance treatment

Consider decreasing maintenance treatment when a person's asthma has been controlled with their

Current maintenance therapy **for at least** 3 months

Criteria for stepping down

- Doses of medication can be reduced by 25-50% every 3 months for stable patients while maintaining symptom control.
- After treatment is stepped down the patient should have their treatment reviewed within 4-8 weeks.
- Stepping down should be explained to the patient and be part of their personalised asthma action plan.
- Only consider stopping ICS treatment completely for people who are using low-dose ICS alone as maintenance therapy and are symptom-free.

Uncontrolled asthma

Uncontrolled asthma is defined as

- 3 or more days a week with symptoms or
- 3 or more days a week requiring the use of a SABA or
- 1 or more nights a week with awakening due to asthma.

Monitoring asthma control [25]

If there is evidence of poorly controlled asthma the following should be considered and addressed appropriately:

- Review/confirm asthma diagnosis.
- Check the inhaler technique at every review and ask the patient to demonstrate it. Failure to use the inhaler device properly leads to decreased drug delivery and treatment failure.
- Check medication adherence. Is the patient taking the medicines as prescribed? Look at the prescribing history to see if it is consistent with the amount the patient should have taken.

- Always ask about the child's exposure to smoking. Offer smoking cessation advice to patients/parents/caretakers. Advocate a smoke-free home and car. Smoking reduces the effect of inhaled steroids and increased doses may be needed in smokers.
- Link with rhinitis. Asthma and rhinitis co-exist in the majority of patients. Diagnosis of co-morbid rhinitis should be actively pursued in all patients with uncontrolled asthma.
- Adjusting therapy. After consideration of diagnosis, adherence, inhaler technique, smoking status, triggers and concomitant rhinitis, patients with poorly controlled asthma should be advised to step up their It is equally important to consider stepping down treatment in patients who are consistently well-controlled. [26]
- After adjusting maintenance treatment, review the response to treatment changes in 4 to 8

Conclusion

Inhaled corticosteroids (ICS) have proven efficacy in the preventive treatment of persistent asthma in children. This assumes that the appropriate patients are targeted and the dose is titrated against clinical benefit and risk of side effects [27]. The efficacy of ICS in preschool children with episodic viral wheeze remains controversial, while ICS treatment of preschool children with multiple-trigger wheeze appears to be at least somewhat effective.

However, the effect size in preschool children with multiple-trigger wheezing is smaller than the effect size in school-aged children with asthma. The addition of long-acting beta-agonists (LABAs), usually as combination therapy, should only be considered if children fail a trial of inhaled steroids. In children with ongoing problems with exercise-induced symptoms, despite inhaled corticosteroids, the addition of leukotriene antagonists is effective.

The evidence is less clear for the efficacy of inhaled corticosteroids in children with intermittent viral-induced wheezing which is the most common pattern of wheezing in the preschool years. ICS are generally well tolerated in both school-aged and preschool children, and adverse events tend to be minimal in both age groups when the ICS is used in appropriate doses [28]

Abbreviations

SABA	Short-acting beta2 agonist
ICS	Inhaled corticosteroid
LTRA	Leukotriene receptor antagonist
LABA	Long-acting beta agonist
MART	Maintenance and reliever therapy
FEV1	Forced expiratory volume in one seond
FVC	Forced vital capacity
MDI	Metered dose inhaler

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