Egypt J Pediatr Allergy Immunol 2018;16(2):27-30.

Review article

Is there a role for inhaled corticosteroids in early life wheeze?

Elham Hossny
Professor of Pediatrics, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Content

- Definition and causes of wheeze
- ICS in preschool wheeze
- Prediction of response to ICS
- Factors affecting the response to ICS
- Adverse effects of ICS

Definition and causes of wheeze

Approximately one in three children experience at least one episode of wheezing prior to their third birthday, and the cumulative prevalence of wheeze is almost 50% at the age of 6 yrs.[1,2] Viral induced wheeze is by far the most common cause of recurrent early life wheeze, but other causes should also be considered.

Table (1): Causes of recurrent wheeze in early life

Prevalence	Disease
Common	Viral bronchiolitis Asthma
Less Common	Aspiration Gastroesophageal reflux Foreign body Swallowing dysfunction Bronchopulmonary dysplasia Cystic fibrosis
Uncommon	Congenital heart disease Immunodeficiency Immotile cilia syndrome Congenital structural anomalies Tracheobronchomalacia Vascular ring Lobar emphysema Cystic abnormalities Tracheoesophageal fistula

Modified from El-Gamal and El-Sayed [3]

Upper respiratory tract infections account for more than 80% of wheezing episodes in young children. Most children wheeze only when they have upper respiratory tract infections, are usually non-atopic, and outgrow symptoms by 6 years of age. Yet, since preschool-age children have 6 to 10 upper respiratory tract infections each year, recurrent virus-induced wheezing is associated with considerable distress and use of health care services.[4]

ICS in preschool wheeze

Preschool children with wheeze have deficits in lung function at 6 years of age that persisted until early and middle adulthood. Daily inhaled corticosteroids seem to be the most effective therapy for recurrent wheezing in trials of children with interim symptoms or atopy. Intermittent high-dose inhaled corticosteroids seem effective in moderate-to-severe viral-induced wheezing without interim symptoms.[5]

In a meta-analysis, an improvement in asthma symptoms' score and parental perceived QOL of children favored the ICS use. However, there was no statistical difference in hospitalization rates. Intermittent use of ICS was not associated with any significant increase in adverse events including growth suppression in preschool or school-aged children.[6]

On the other hand, intermittent inhaled corticosteroids in infants with episodic wheezing did not prove efficacy in a clinical trial. There was no effect on the progression from episodic to persistent wheezing as well as no short-term effect on respiratory symptoms.[7] Similarly, long-term effects of ICS for respiratory syncytial virus bronchiolitis were considered doubtful in a randomized placebo-controlled trial. At age 6, the mean FEV1 percentage, bronchial hyper-responsiveness, physician-diagnosed asthma, and parent reported hay fever and eczema were comparable between both groups.[8]

Predicting the response to treatment in wheezy children

Asthma phenotypes could theoretically be used to predict treatment response.[9] Characteristics of the asthma-predictive phenotype in early childhood include male sex, history of wheezing with lower respiratory tract infections, history of parental asthma, history of atopic dermatitis, eosinophilia, early sensitization to food or aeroallergens, and lower lung function in early life.[10]

A study on long-term responses to inhaled anti-inflammatory medications based on childhood

asthma phenotypes identified 5 reproducible patient clusters that could be differentiated on the basis of 3 groups of features: atopic burden, degree of airway obstruction, and history of exacerbation. One cluster demonstrated a positive response to both budesonide and nedocromil compared with placebo, whereas the other cluster demonstrated minimal responses to both budesonide and nedocromil compared with placebo.[11]

Phenotyping asthma by multivariate analyses and more recently by unsupervised analysis of children cohorts revealed three wheeze phenotypes in preschool age: the mild episodic viral wheeze phenotype; the multi-trigger atopic wheeze; and the less often encountered severe non-atopic wheeze. Early onset of allergy in asthma (more prevalent in boys) was associated with poor prognosis unlike the severe non-atopic wheeze phenotype which had a female predominance. The prognosis of the severe non-atopic wheeze depends on time of onset (early or late) of allergic expression.[12] Remission was most frequently observed in mild early viral wheeze while persistence was observed in atopic multiple-trigger wheeze and those with non-atopic uncontrolled wheeze developed severe uncontrolled wheeze in most cases.[13]

Factors affecting response to ICS

There is high inter individual variation in response to ICS as judged by the improvement in lung function, increase in the number of symptom-free days, and reductions in exacerbations and hospitalizations. Using pharmacogenomic approaches, several promising candidate genes associated with response to ICSs have been identified.[14]

Obesity might hinder response to ICS. In one trial, overweight/obese children in the Childhood Asthma Management Program (CAMP) showed a decreased response to inhaled budesonide on emergency department visits or hospitalizations for asthma.[15] In utero smoke (IUS) exposure reduces age-related improvements in airway responsiveness among children with asthma. It appears to blunt the beneficial effects of ICS use on airways responsiveness.[16]

There are factors that affect the delivery of ICS in infants and young children[17]

- Anatomy and physiology: the pharynx and supraglottic area are less rigid, epiglottis is narrow, floppy, and closer to the palate, and the larynx is higher and very close to the base of the tongue.
- Lung deposition: infants are unable to hold their breath, and therefore a greater proportion of the inhaled medication is likely to be exhaled.
- Behavior and adherence: the fit of the face mask, squirming and crying during aerosol administration, and general acceptance of treatment.
- Face-mask seal and design: even a 1-cm gap between the mask and the face reduced the dose delivered to the respiratory tract by 50% [18]
- Crying: it affects not only the breathing patterns of infants but also the adequacy of the seal between the mask and face.
- Inhaled particle size: small particles increased lung deposition and reduced oropharyngeal deposition.

Adherence to ICS Therapy

Poor adherence may persist in children despite a high level of concordance between medical team and parents, even in the absence of socio-economic barriers. In an ancillary study, adherence was assessed by using self-reported and objective data in 5- to 12-year-old children with mild or moderate asthma. A significant decrease occurred in the yearly mean adherence based on objective data (from 69% in year 1 to 52% in year 4). A significant, although smaller, decrease also occurred in mean adherence based on self-report.[19]

Adverse effects of ICS

Adverse effects resulting from the use of ICS are often underestimated in daily clinical practice. Although ICS treatment is generally considered safe in children, the potential adverse effects related to its regular use have been and continue to be a matter of concern. ICS are reported to cause some local and systemic adverse effects (Table 2). This seems to be dose-dependent being most common in individuals receiving high dose ICS with or without oral corticosteroids (OCS).[20]

Effect on growth

Use of ICS for >12 months in children with asthma has a limited impact on annual growth velocity. Among ICS users in one study, there was a slight reduction of about one cm in final adult height which when interpreted in the context of average adult height in England represented a 0.7% reduction compared to non-ICS users.[21] An evidence-based analysis revealed that there is ICS dose-dependent reduction in growth velocity in prepubescent school-aged children with mild to moderate persistent asthma. The choice of ICS molecule (mometasone, ciclesonide or fluticasone)

was not found to affect the level of growth velocity.[22]

Table (2): Potential local and systemic side effects of inhaled corticosteroids [20]

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
	Suppressed HPA-axis function
	Bone fractures
	Osteoporosis
	Skin thinning
	Skin bruising
	Cataracts
	Glaucoma

HPA-axis: hypothalamic pituitary adrenal axis

Effect on adrenal functions

Patients at risk of adrenal suppression (AS) and would benefit from screening include: [23]

- Patients who have symptoms of AS regardless of ICS dose
- Patients who are on higher doses of ICS (≥400 mcg of fluticasone or equivalent)
- Concomitant use of oral steroids
- Concomitant use of ritonavir or ketoconazole
- Recurrent respiratory infections with slow recovery
- Any planned surgical procedure
- Poor growth or unexplained hypoglycemia
- Gastroenteritis, chronic nausea and vomiting, dehydration
- Any other serious medical/surgical illness
- Heat stress, any condition where AI might result in acute adrenal crisis

Effect on bone mineral accretion

Long-term therapy with ICS therapy is safer than frequent bursts of oral corticosteroids on bone mineral status. Nutritional supplementation (e.g. calcium and vitamin D) should blunt the effects of CS on bone mineral density. The potential adverse effects of ICS need to be weighed against the benefit of these drugs to control persistent asthma. ICS therapy should always aim to reach the lowest effective dose that gives asthma control.[24]

Key Notes

- The intermittent use of ICS in infants with episodic wheezing is still controversial and needs further investigations to validate
- Asthma phenotypes could theoretically be used to predict ICS treatment response
- Other potential predictors of the response to ICS include several genes, the body mass index, air pollution, and inutero smoke exposure
- Some anatomic features of the airways in infants may hinder the effect of ICS as well as other factors including crying, face mask fitting, and adherence to therapy
- Use of ICS for >12 months in children with asthma has a limited impact on annual growth velocity.
- Long-term therapy with ICS therapy is safer than frequent bursts of oral corticosteroids on bone mineral status
- ICS therapy should always aim to reach the lowest effective dose
- The potential adverse effects of ICS need to be weighed against the benefit of these drugs to control persistent asthma.

REFERENCES

1. **Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ.** Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995;332:133-8.
2. **Bisgaard H, Szefler S.** Prevalence of asthma-like symptoms in young children. Pediatr Pulmonol 2007;42:723-8.
3. **El-Gamal Y, El-Sayed S.** Wheezing in infancy. World Allergy Organ J 2011;4(5):85-90.
4. **Ducharme FM, Lemire C, Noya FJ, Davis GM, Alos N, Leblond H, Savdie C, Collet JP, Khomenko L, Rivard G, Platt RW.** Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. N Engl J Med 2009;360(4):339-53.
5. **Ducharme FM, Tse SM, Chauhan B.** Diagnosis, management, and prognosis of preschool wheeze. Lancet 2014;383:1593-604.
6. **Chong J, Haran C, Chauhan BF, Asher I.** Intermittent inhaled corticosteroid therapy versus placebo for persistent asthma in children and adults. Cochrane Database Syst Rev 2015;7:CD011032.
7. **Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F.** Intermittent inhaled corticosteroids in infants with episodic wheezing. N Engl J Med 2006;354:1998-2005

8. **Zomer-Kooijker K van der Ent CK, Ermers MJ, Rovers MM, Bont LJ;** RSV Corticosteroid Study Group. Lack of long-term effects of high-dose inhaled beclomethasone for respiratory syncytial virus bronchiolitis: a randomized placebo-controlled trial. Pediatr Infect Dis J 2014;33:19-23.
9. **Hossny E, Potter PC.** WAO Allergic Diseases Resource Center. Treatment of asthma in children 5 years and under based on different global guidelines. Last updated: July 2015. Available from: http://www.worldallergy.org/education-and-programs/education/allergic-disease-resource-center/professionals/treatment-of-asthma-in-children-5-years-and-under. Cited: July 11, 2018.
10. **Durrani S, Guilbert TW.** Early treatment in preschool children: an evidence-based approach. Curr Opin Allergy Clin Immunol 2015;15(2):175-83.
11. **Howrylak JA, Fuhlbrigge AL, Strunk RC, Zeiger RS, Weiss ST, Raby BA;** Childhood Asthma Management Program Research Group. Classification of childhood asthma phenotypes and long-term clinical responses to inhaled anti-inflammatory medications. J Allergy Clin Immunol 2014;133(5):1289-300.
12. **Just J, Saint Pierre P, Amat F, Gouvis-Echraghi R, Lambert-Guillemot N, Guiddir T, Annesi Maesano I.** What lessons can be learned about asthma phenotypes in children from cohort studies? Pediatr Allergy Immunol 2015;26(4):300-5.
13. **Just J, Saint-Pierre P, Gouvis-Echraghi R, Boutin B, Panayotopoulos V, Chebahi N, Ousidhoum-Zidi A, Khau CA.** Wheeze phenotypes in young children have different courses during the preschool period. Ann Allergy Asthma Immunol 2013;111(4):256-61.
14. **Park HW, Dahlin A, Tse S, Duan QL, Schuemann B, Martinez FD, Peters SP, Szefler SJ, Lima JJ, Kubo M, Tamari M, Tantisira KG.** Genetic predictors associated with improvement of asthma symptoms in response to inhaled corticosteroids. J Allergy Clin Immunol 2014;133:664-9.
15. **Forno E, Lescher R, Strunk R, Weiss S, Fuhlbrigge A, Celedón JC;** Childhood Asthma Management Program Research Group. Decreased response to inhaled steroids in overweight and obese asthmatic children. J Allergy Clin Immunol 2011;127(3):741-9.
16. **Cohen RT, Raby BA, Van Steen K, Fuhlbrigge AL, Celedón JC, Rosner BA, Strunk RC, Zeiger RS, Weiss ST;** Childhood Asthma Management Program Research Group. In utero smoke exposure and impaired response to inhaled corticosteroids in children with asthma. J Allergy Clin Immunol 2010;126(3):491-7.
17. **Amirav I, Newhouse MT, Minocchieri S, Castro-Rodriguez JA, Schüepp KG.** Factors that affect the efficacy of inhaled corticosteroids for infants and young children. J Allergy Clin Immunol 2010;125:1206-11.
18. **Everard M, Clark AR, Milner AD.** Drug delivery from jet nebulisers. Arch Dis Child 1992;67:586-91.
19. **Krishnan JA, Bender BG, Wamboldt FS, Szefler SJ, Adkinson NF Jr, Zeiger RS, Wise RA, Bilderback AL, Rand CS;** Adherence Ancillary Study Group. Adherence to inhaled corticosteroids: an ancillary study of the Childhood Asthma Management Program clinical trial. J Allergy Clin Immunol 2012;129(1):112-8.
20. **Hossny E, Rosario N, Lee BW, Singh M, El-Ghoneimy D, Soh JY, Le Souef P.** The use of inhaled corticosteroids in pediatric asthma: update. World Allergy Organ J. 2016;9:26.
21. **Loke YK, Blanco P, Thavarajah M, Wilson AM.** Impact of inhaled corticosteroids on growth in children with asthma: systematic review and meta-analysis. PLoS One 2015;10(7):e0133428.
22. **Pruteanu AI, Chauhan BF, Zhang L, Prietsch SO, Ducharme FM.** Inhaled corticosteroids in children with persistent asthma: dose-response effects on growth. Evid Based Child Health 2014;9(4):931-1046.
23. **Sannarangappa V, Jalleh R.** Inhaled corticosteroids and secondary adrenal insufficiency. Open Respir Med J 2014;8:93-100.
24. **Fuhlbrigge AL, Kelly HW.** Inhaled corticosteroids in children: effects on bone mineral density and growth. Lancet Respir Med 2014;2(6):487-96.