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Effect of Budesonide Inhalation on Asthmatic Child: A Randomized Controlled Trial

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Asthma is a diverse inflammatory airway illness characterized by intermittent respiratory manifestations, and inhaled steroids (ICS) constitute the foundation of all asthma management regimens. The aim of this study was to examine the therapeutic efficacy of inhaled Budesonide (BUD) regimens for recurrent wheeze treatment in pre-schoolers.
Methods: This retrospective randomized controlled research involved 70 pediatric subjects aged from 6-12 years old, both sexes having four wheezing episodes or more in the last year; and satisfying at least one main condition or two minor of them. Case selection was rigorously regulated by experts who specialize in children's respiratory disorders diagnosis and treatment, notably asthma. The included children had mild-to-moderate asthma.
Results: After treatment, FEV1, FVC and FEV1: FVC were significantly elevated in group A than group B (P value <0.001). Urgent care visits and hospitalizations because of asthma were significantly lower in group A than group B (P value = 0.003 and 0.008 respectively).

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Conclusions: We have shown that the BUD Inhalation is an effective and safe management for long term asthma treatment. Compared to placebo, BUD was related with a higher decrease in asthma manifestations and a rise in the number episode free days.

Keywords: Budesonide; inhalation; asthmatic child; corticosteroids; spirometry.

1. INTRODUCTION

Asthma is a diverse inflammatory airway illness characterised by intermittent respiratory manifestations, such as wheeze and cough, and varying expiratory airflow restriction across all asthma severity levels [1]. In the last 60 years, the worldwide incidence of asthma has grown; it is believed that over 300 million people live with asthma, involving 11.6% of children aged 6–7 years [2].

Patients continue to have periodic asthma worsening despite the availability of effective maintenance therapies, such as inhaled corticosteroids (ICS), and the rate of asthma exacerbations in both paediatric and adult cases still elevated. Regardless of asthma severity, all cases are at risk for avoidable and possibly deadly exacerbations [3,4].

Short-acting beta2-agonists (SABA), like albuterol (salbutamol), are often utilized by asthma cases of all severity levels as rescue therapy to relieve symptoms. SABA cause smooth muscle relaxation in the airways and give quick manifestation alleviation but have little effect on the underlying airway inflammation. Cases could consequently keep developing asthma deterioration and remain susceptible to exacerbations regardless of their maintenance medication [5,6].

ICS are the basis of all asthma treatment recommendations. They minimize asthma manifestations in children, increase the quality of life (QoL) for asthmatic children and their families, decline school/work absences for cases and their parents, decrease airway inflammation, and enhance lung function, bronchial reactivity, and exercise-induced asthma [7,8].

In these nations, the hospitalization and especially readmission rates for children with acute asthma have declined among older children. Thus, the use of ICS has had a significant influence on the QoL and "mastery" of asthma in asthmatic children [9].

The Childhood Asthma Management Program was developed to assess if continued, long-term therapy (up to four to six years) with ICS (budesonide (BUD)) generates a safe improvement in lung development than treatment for manifestations alone (as required administration of albuterol and prednisone, if necessary) [10,11].

BUD, also treat the inflammation, and during times of deteriorating manifestations, there is indication of a "window of opportunity" in which prompt ICS administration may avoid the signs from escalating into an exacerbation [12].

The local adverse effects of ICS on skin, the mucous membranes of the respiratory tract, and the oropharyngeal region are well-known, although they have received far less emphasis than the systemic adverse ones. Local adverse impacts include perioral dermatitis, oral candidiasis, hoarseness, dysphonia, cough during inhalation, and thirst [13]. We objected to examine the therapeutic efficacy of inhaled BUD regimens for recurrent wheezing treatment in pre-schoolers.

2. METERIALS AND METHODS

This retrospective randomized controlled research involved 70 pediatric subjects aged from 6-12 years old, both sexes having four wheezing episodes or more in the last year; and satisfying at least one main condition or two minor criteria. Important factors involve parental asthma, atopic dermatitis identified by a physician, and allergic sensitivity to at least one aeroallergen. Lesser requirements involve wheeze not associated with colds, peripheral blood eosinophils 4% and milk, egg, or peanut sensitivity. Doctors who specialize in children's respiratory disorders diagnosis and treatment, particularly asthma, closely screened cases.

The case had mild-to-moderate asthma, as indicated by the manifestations or an inhaled bronchodilator usage at least twice per week or daily asthma medication. The responsiveness of the children's airways to methacholine, as evidenced by the concentration of the medication that induced a 20% drop in FEV 1, was at or below 12.5 mg per millilitre. They had no other

severe medical issues. The parents or guardians of the children completed an informed consent form certified by the ethical committee.

Exclusion criteria included wheeze due to organic lesions and mechanical causes; with more than six systemic glucocorticoids; received other asthma control medicines; and their guardians were unaware of the child's medical history or refused to contribute to the research.

2.1 Randomization

Cases were randomly divided equally into two groups by sealed opaque envelopes and a computer-generated sequence. Group A: received BUD (Pulmicort, AstraZeneca, Westborough, Mass.) (200 µg twice daily, delivered by two 100-µg actuations of a breathactuated metered-dose inhaler [Turbuhaler, AstraZeneca]), and group B (control group): received a matching placebo.

To optimise treatment adherence, the total daily dosages of BUD (400 g) and nedocromil (16 mg) were provided as two equal daily doses [14], Albuterol (Ventolin, Glaxo Wellcome, Research Triangle Park, N.C.), two 90-g actuations of a pressurised metered-dose inhaler were administered as required to treat asthma manifestations or avoid exercise-induced bronchospasm. A short course of oral prednisone was suggested for asthma exacerbations. If disease management remained inadequate, replacement or addition of drugs was permitted. To attribute remission, it was permitted to taper the research drug to a dosage of zero (by stepwise decreases from 100% to 50% to 0%), in accordance with predefined methods. The resumption of the full dosage of the research medicine was guided by algorithms [15].

2.2 Asthma management was classified as optimum when four of the following criteria were met

(a) The child has a regular existence, which includes typical physical exercise, (b) 1 application of rescue terbutaline per week, (c) 110 percent PEF diurnal fluctuation on 2.5 days / week, (d) Manifestations of asthma once every week, (e) PEF and/or FEV, 2 100% of predicted normal, (I) <10% decrease in FEV after a standardized exercise test (if completed). When optimum control was achieved, the BUD dosage was reduced.

Asthma management was deemed unsatisfactory when the standards for acceptable control were not met.

2.3 In that case the BUD dosage was raised, or further therapy was administered

If any of the below conditions are met: (a) a decline in morning PEF of more than 20 percent; (b) use of more than five inhalations of rescue terbutaline; and (c) a worsening of symptoms by more than one step (specifically, from 0 to 2 or 1 to 3).

2.4 Outcome Measures

Primary outcomes where spirometry was done twice annually, with readings acquired both before to and after bronchodilator treatment.

Secondary outcomes were the number of systemic corticosteroid courses (intravenous or oral), wheeze episodes, and urgent care visits for wheeze during the 52-week therapy period and side effects of the drug.

Therapy failure meant that wheezing was not under continuous control, an episode was severe enough to necessitate tracheal intubation, or substantial adverse responses to the treatment medicines happened during the follow-up period.

2.5 Statistical Analysis

SPSS v26 was used to do statistical analysis (IBM Inc., Armonk, NY, USA). Comparing the two groups using an unpaired Student's t- test, quantitative data were provided as mean and standard deviation (SD). When applicable, qualitative variables were given as frequency and percentage (%) and analysed using the Chi-square test or Fisher's exact test. A two-tailed P value less than or equal to 0.05 was deemed statistically significant.

3. RESULTS

In this research, 97 subjects were evaluated for eligibility, 18 patients did not match the inclusion criteria, and 9 patients declined to take part in the research. The remaining 70 patients were randomly allocated into 2 groups (35 patients in each). All assigned cases were followed up (Fig. 1).

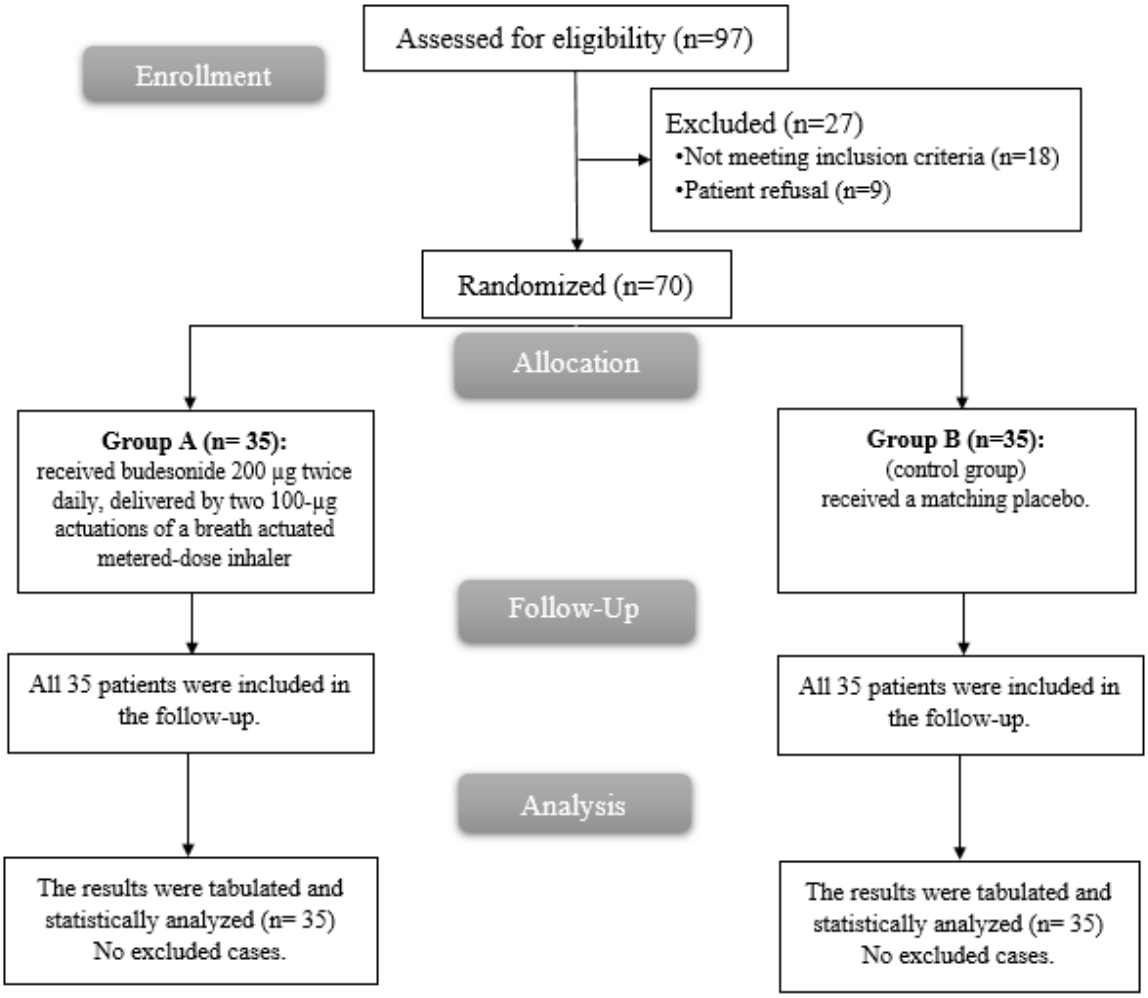

Fig. 1. Consort flowcahat of the enrolled patients

Baseline characteristics (age, sex, weight, height, weight and BMI), age of onset of asthma, duration of asthma, time since diagnosis of asthma, severity of asthma, treatments in 6 months before enrolment, hospitalizations for asthma in year before enrolment and Cases who utilised systemic glucocorticoids in the previous year did not vary substantially among both groups (Table 1).

Risk factors (parent smoker, eczema, parental asthma, rhinitis, any aeroallergen sensitivity and food sensitivity) and laboratory markers were insignificantly different among both groups (Table 2).

Clinical symptoms (night wheezing, day wheezing, day cough and night cough) were insignificantly different between the studied groups (Fig. 2).

Baseline spirometric measures (FEV1, FVC and FEV1: FVC) were insignificantly different between both groups. After treatment, spirometric measures (FEV1, FVC and FEV1: FVC) were significantly elevated in group A than group B (P value <0.001) (Table 3).

Daily diary-card measures (morning peak flow and night awakenings) were insignificantly different between both groups. Regarding the morbidity during follow up, urgent care visits and hospitalizations because of asthma were significantly reduced in group A than group B (P value= 0.003 and 0.008 respectively) whereas fractures were insignificantly different among both groups (Table 4).

Table 1. Baseline characteristics of the studied patients

		Group A (n=35)	Group B (n=35)	P value
Age (years)		9.5 ± 1.84	8.8 ± 1.98	0.154
Sex	Male	31 (88.57%)	28 (80%)	0.324
	Female	4 (11.43%)	7 (20%)	
Weight (Kg)		41.09 ± 9.47	42.2 ± 9.94	0.633
Height (m)		1.45 ± 0.08	1.42 ± 0.07	0.081
BMI (Kg/m2)		19.58 ± 4.63	21.05 ± 5.37	0.224
Age of onset of asthma (years)		4.34 ± 1.03	4.6 ± 1.09	0.313
Duration of asthma		1.38 ± 0.58	1.36 ± 0.61	0.904
Time since diagnosis of asthma (years)		6.74 ± 1.38	7.26 ± 1.42	0.129
Severity of asthma	Mild	18 (51.43%)	16 (45.71%)	0.632
	Moderate	17 (48.57%)	19 (54.29%)	
Treatments in 6 months before enrolment	Cromolyn or nedocromil	17 (48.57%)	11 (31.43%)	0.312
	Inhaled corticosteroid	11 (31.43%)	13 (37.14%)	
	Oral corticosteroid	7 (20%)	11 (31.43%)	
Hospitalizations for asthma in year before enrollment		10 (28.57%)	9 (25.71%)	0.788
Patients who used systemic glucocorticoids over the past year		24 (68.57%)	20 (57.14%)	0.332

BMI: body mass index, Data are presented as mean ± SD or frequency (%)

Table 2. Risk factors and laboratory markers in the studied patients

		Group A (n=35)	Group B (n=35)	P value
Parent smoker		19 (54.29%)	23 (65.71%)	0.329
Eczema		13 (37.14%)	11 (31.43%)	0.614
Parental asthma		22 (62.86%)	15 (42.86%)	0.097
Rhinitis		25 (71.43%)	20 (57.14%)	0.318
Any aeroallergen sensitivity		12 (34.29%)	10 (28.57%)	0.606
Food sensitivity		10 (28.57%)	14 (40%)	0.313
Laboratory markers	High CRP	22 (62.86%)	24 (68.57%)	0.714
	High eosinophil	32 (91.43%)	29 (82.86%)	0.284

CRP: C- reactive protein, Data are presented as mean ± SD or frequency (%)

Table 3. Spirometric measures in the studied patients

		Group A (n=35)	Group B (n=35)	P value
Baseline	**FEV1 (%)**	77.77 ± 4.24	77.83 ± 5.06	0.959
	FVC	72.8 ± 4.19	72.77 ± 4.7	0.979
	FEV1: FVC	1.07 ± 0.08	1.04 ± 0.11	0.152
After treatment	**FEV1 (%)**	90.26±3.45	84.29±3.31	**<0.001***
	FVC	87.77±4.53	80.23±3.11	**<0.001***
	FEV1: FVC	1.06±0.06	1.02±0.06	**<0.001***

*FEV1: forced expiratory volume in one second. FVC: forced vital capacity, Data are presented as mean ± SD or frequency (%), *: statistically significant as P value<0.05*

Table 4. Changes in daily diary-card measures and morbidity during follow up of the studied patients

		Group A (n=35)	Group B (n=35)	P value
Daily diary-card measures	**Morning peak flow**	20 (57.14%)	20 (57.14%)	1.0
	Night awakenings	8 (22.86%)	14 (40%)	0.211
Morbidity	**Urgent care visits due to asthma**	7 (20%)	19 (54.29%)	**0.003***
	Hospitalizations due to asthma	5 (14.29%)	15 (42.86%)	**0.008***
	Fractures	14 (40%)	7 (20%)	0.067

*Data are presented as mean ± SD or frequency (%), *: statistically significant as P value<0.05*

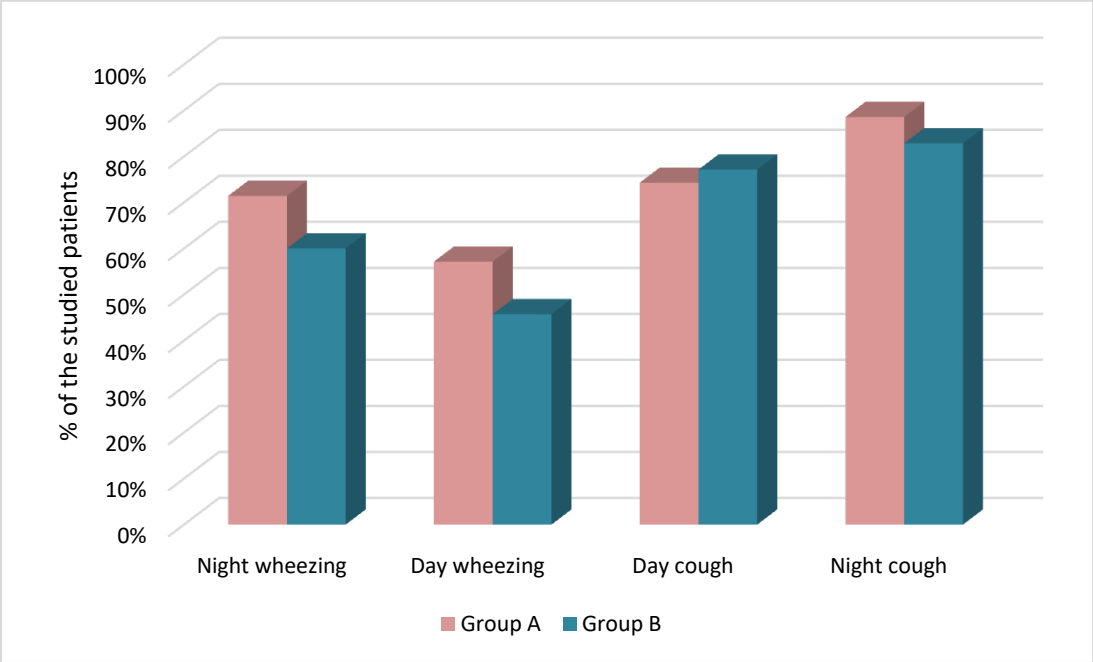

Fig. 2. Symptoms between the studied patients

4. DISCUSSION

Asthma is a condition characterised by persistent airway inflammation, reversible airway obstruction, and enhanced airway reactivity [16]. Current investigations have shown an association between asthma and poor lung development in infancy and a steady loss in pulmonary function in maturity [17,18]. Clinical practice recommendations prescribe anti-inflammatory medications for the long-term management of chronic asthma; ICS or nedocromil therapy is advised for children [19].

Only children with mild to moderate asthma were included in this research. The natural history of an asthma exacerbation may vary depending on the underlying ailment severity and the cause for the exacerbation; bigger research encompassing a range of children with asthma might provide additional information on this topic.

4.1 Result of Pulmonary Function

Our results revealed that BUD increased lung function, as defined by the percentage of the projected value for FEV1 following bronchodilator administration, was unanticipated.

FEV 1 was selected as the major outcome measure as it is universally considered as the greatest clinically meaningful and anticipatory indicator of lung function. It is strongly repeatable, correlates well with disease progression, health care usage, and asthma severity, and properly depicts the natural course of pediatric asthma [20,21]. The value after bronchodilator treatment was selected as the end measure as it reduces the airway constriction impacts and has less time-to-time variation in cases than the value before bronchodilator usage. The BUD usage was related with an increase in the predicted FEV 1 before bronchodilator administration [22].

Before bronchodilator treatment, the ratio of FEV 1 to FVC declined over time in both groups. The reduction was mitigated by BUD. Also, our findings revealed that The BUD group had the lowest incidence of hospitalization, urgent care visits, and further medication need and oral prednisone.

In line with our results Szefler et al. [23] found that an advantage of BUD regarding lung function, as determined by the FEV1 following bronchodilator usage, was apparent at one year, but not at four years; a decrease in linear growth velocity was seen at one year in children who treated with BUD.

It was unexpected that the time between the beginning of asthma manifestations and the initiation of ICS medication was associated with

treatment-induced elevations in FEV and FMEF. This impact of postponed therapy seems to be unaffected by the child's prior therapy. Children with sub-optimally managed asthma potentially develop permanent airway blockage during run-in and control therapy. In addition, it seems that inhaled medications are administered early after the onset of manifestations. This proposal is consistent with the results.

The twofold dosage of ICS provided for just three days was a compromise among usual practice and safety issues [24]. In New Zealand, doubling the dosage of ICS until the child's condition returns to normal is the usual [25]. During this research, however, the children may have received placebo medication for an exacerbation.

Allen et al. [26] revealed that a substantial, albeit minor impairment was reported for oral steroids, but inhaled beclomethasone dipropionate was not related with growth impairment, but with achieving normal final height. Our study had several limitations as single centre research with relatively small sample size.

5. CONCLUSION

We have shown that the BUD Inhalation is an effective and safe management for long term asthma treatment. Compared to placebo, BUD was linked with a higher decrease in asthma manifestations and a rise in the number of episode free days. Further studies are needed with different ages and with different doses and regimen of BUD.

CONSENT

As per international standard or university standard, parental(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Reddel HK, Bacharier LB, Bateman ED, Brightling CE, Brusselle GG, Buhl R, et al. Global Initiative for Asthma Strategy 2021: Executive summary and rationale for key changes. Eur Respir J. 2022;59:45-63.
2. Mattiuzzi C, Lippi G. Worldwide asthma epidemiology: Insights from the global health data exchange database. Int Forum Allergy Rhinol. 2020;10:75-80.
3. Larsson K, Kankaanranta H, Janson C, Lehtimäki L, Ställberg B, Løkke A, et al. Bringing asthma care into the twenty-first century. NPJ Prim Care Respir Med. 2020; 30:25-9.
4. Kaplan A, Mitchell PD, Cave AJ, Gagnon R, Foran V, Ellis AK. Effective asthma management: Is it time to let the AIR out of SABA? J Clin Med. 2020;9:12-9.
5. Nwaru BI, Ekström M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting β(2)-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. Eur Respir J. 2020;55:75-9.
6. Janson C, Menzies-Gow A, Nan C, Nuevo J, Papi A, Quint JK, et al. SABINA: an overview of short-acting β(2)-agonist use in asthma in european countries. Adv Ther. 2020;37:1124-35.
7. Htun ZM, Aldawudi I, Katwal PC, Jirjees S, Khan S. Inhaled corticosteroids as an associated risk factor for asthmatic pneumonia: A literature review. Cureus. 2020;12:87-97.
8. Tosca MA, Di Cicco ME, Leone M, Scavone M, Licari A. Controversies in the treatment of mild asthma. What novelties and practical implications? Pediatr Allergy Immunol. 2022;33:11-4.
9. Usmani OS, Lavorini F, Marshall J, Dunlop WCN, Heron L, Farrington E, et al. Critical inhaler errors in asthma and COPD: A systematic review of impact on health outcomes. Respir Res. 2018;19:10-9.
10. Gupta A, Bhat G, Pianosi P. What is new in the management of childhood asthma? Indian J Pediatr. 2018;85:773-81.
11. Tesse R, Borrelli G, Mongelli G, Mastrorilli V, Cardinale F. Treating pediatric asthma according guidelines. Front Pediatr. 2018;6:234-9.
12. Viswanatha GL, Shylaja H, Nandakumar K, Venkataranganna MV, Prasad NBL. Efficacy and safety of inhalation budesonide in the treatment of pediatric asthma in the emergency department: a systematic review and meta-analysis. Pharmacol Rep. 2020;72:783-98.

13. Nair PA, Bhut A, Patel T. Dermatosis due to steroid exposure: A startle in occupational hazard. Indian Dermatol Online J. 2020;11:651-2.
14. Janjua S, Schmidt S, Ferrer M, Cates CJ. Inhaled steroids with and without regular formoterol for asthma: Serious adverse events. Cochrane Database Syst Rev. 2019;9:69-75.
15. Perez-Garcia J, Herrera-Luis E, Lorenzo-Diaz F, González M, Sardón O, Villar J, et al. Precision medicine in childhood asthma: Omic studies of treatment response. Int J Mol Sci. 2020;21: 105-9.
16. Corlateanu A, Stratan I, Covantev S, Botnaru V, Corlateanu O, Siafakas N. Asthma and stroke: a narrative review. Asthma Res Pract. 2021;7:3-7.
17. Ma H, Li Y, Tang L, Peng X, Jiang L, Wan J, et al. Impact of childhood wheezing on lung function in adulthood: A meta-analysis. Plos One. 2018;13:192-9.
18. Miura S, Iwamoto H, Omori K, Yamaguchi K, Sakamoto S, Horimasu Y, et al. Accelerated decline in lung function in adults with a history of remitted childhood asthma. Eur Respir J. 2022;59:125-9.
19. Cloutier MM, Dixon AE, Krishnan JA, Lemanske RF, Jr, Pace W, Schatz M. Managing asthma in adolescents and adults: 2020 asthma guideline update from the national asthma education and prevention program. JAMA. 2020;324: 2301-17.
20. Huang C, Izmailova ES, Jackson N, Ellis R, Bhatia G, Ruddy M, et al. Remote FEV1 monitoring in asthma patients: A pilot study. Clin Transl Sci. 2021;14:529-35.
21. R PH, Gopalakrishna Mithra CA, Ratageri VH. Pulmonary function tests in childhood asthma: Which indices are better for assessment of severity? Indian J Pediatr. 2022:25-8.
22. Liu J, Wang Y, Tang Y, Liu G, Chen Q. Effects of budesonide combined with salbutamol on pulmonary function and peripheral blood eosinophiles and IgE in patients with acute attack of bronchial asthma. Pak J Med Sci. 2022;38:1495-500.
23. Szefler S, Weiss S, Tonascia J, Adkinson NF, Bender B, Cherniack R, et al. Long-term effects of budesonide or nedocromil in children with asthma. N Engl J Med. 2000;343:1054-63.
24. Hossny E, Rosario N, Lee BW, Singh M, El-Ghoneimy D, Soh JY, et al. The use of inhaled corticosteroids in pediatric asthma: update. World Allergy Organ J. 2016;9:26-33.
25. Garrett J, Williams S, Wong C, Holdaway D. Treatment of acute asthmatic exacerbations with an increased dose of inhaled steroid. Arch Dis Child. 1998;79:12-7.
26. Allen DB, Mullen M, Mullen B. A meta-analysis of the effect of oral and inhaled corticosteroids on growth. J Allergy Clin Immunol. 1994;93:967-76.

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