Research Article

Clinical Efficacy of Spleen Aminopeptide Combined with Budesonide and Levosalbutamol Hydrochloride, and Its Effects on Inflammatory Markers and Immune Function in Pediatric Bronchial Asthma

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Abstract

Background: Bronchial asthma (BA) is a heterogeneous disease characterized primarily by chronic airway inflammation and airway hyperresponsiveness (AHR).

Objectives: This was a retrospective study aimed at exploring the clinical efficacy of spleen aminopeptide (SA) combined with budesonide (BUD) and levosalbutamol hydrochloride (LEV) as a therapy for pediatric BA, and to observe its effects on inflammatory markers and immune function.

Methods: From June 2022 to June 2023, eighty individuals diagnosed with BA were divided into two groups: A control group and an observation group, based on different therapeutic methods. The control group received inhalation therapy with nebulized BUD and LEV, while the observation group received the same inhalation therapy as the control group, along with SA oral lyophilized powder (SAOLP) treatment. A comparative analysis was conducted between the two groups, evaluating clinical efficacy, changes in inflammatory markers and immunological parameters, and adverse drug reactions (ADRs).

Results: Upon treatment completion, the observation group exhibited an overall response rate (ORR) of 95.00%, whereas the control group showed an ORR of 80.00% (P < 0.05). Additionally, the observation group had a significantly shorter length of hospital stay (LoHS) and a more rapid improvement in symptoms compared to the control group (both P < 0.05). Following treatment, both groups demonstrated significant decreases in interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α) levels (all P < 0.05). However, these reductions were more pronounced in the observation group than in the control group (all P < 0.05). Similarly, after treatment, both groups showed significant increases in T cell subsets CD3$^+$ and CD4$^+$, the CD4$^+$/CD8$^+$ ratio, and levels of immunoglobulin M (IgM), immunoglobulin A (IgA), and immunoglobulin G (IgG) (all P < 0.05), with these changes being more evident in the observation group than in the control group (all P < 0.05). Both groups experienced adverse reactions during the treatment, with an overall adverse reaction rate (OADRR) of 7.50% in the observation group and 10.00% in the control group ($\chi^2 = 0.157$, P = 0.692).

Conclusions: The combined therapy using SA, BUD, and LEV can significantly improve immune function and reduce inflammatory markers, thereby achieving satisfactory efficacy in treating pediatric BA with a clinically safe profile.

Keywords: Children, Bronchial Asthma, Spleen Aminopeptide, Inflammatory Markers, Immune Function

1. Background

Bronchial asthma (BA) is a heterogeneous disease characterized primarily by chronic airway inflammation and airway hyperresponsiveness (AHR). Pathologically, inflammatory cells infiltrate the airway mucosa and release inflammatory mediators, leading to airway mucus hypersecretion and smooth muscle spasms (1). Clinically, BA typically manifests as recurrent chest tightness, wheezing, shortness of breath, and coughing, with symptoms often occurring or worsening at night or in the early morning (2). Statistics (3, 4) indicate that BA has a global incidence ranging from 0.3% to 17.0%. In China, BA is a common chronic respiratory disease in pediatric patients, with an

incidence as high as 4.63% (5), which has been increasing year by year due to worsening air pollution. Data shows that approximately 300 million people worldwide suffer from BA, with one-third of them being children (6). The prevalence of asthma in urban children in China was 0.96% in 1990, 1.66% in 2000, and 2.38% in 2010 (7).

As a condition that is difficult to cure, BA hinders the healthy growth of pediatric patients due to recurrent symptoms and frequent relapses triggered by environmental stimuli, seriously affecting the physical and mental health of affected children. Given the significant impact of BA, researchers have shown a keen interest in the diagnosis and treatment of the disease. However, there is no universally accepted standard treatment for managing BA in pediatric patients. Ideally, treatment regimens for children with BA should aim to control symptoms and help patients resume normal activities, including learning.

Currently, step-up/down targeted therapy is the mainstay of BA treatment (7). The primary drugs used are bronchodilators and glucocorticoids, which aim to achieve and maintain effective symptom control, restore patients to their normal level of activity, maintain lung function, and prevent acute exacerbations and BA-related deaths. Evidence has shown that the onset and prognosis of BA are associated with the immune system and lung function, and the long-term use of glucocorticoids in BA treatment can impair immune function. Spleen aminopeptide (SA) is a clinically common immunomodulatory agent known for its immunosuppressive, immune function-enhancing, and anti-inflammatory properties. Previous studies have demonstrated that SA can effectively improve the overall treatment efficacy in children with BA and enhance their immune function. However, there have been no reports on the treatment of pediatric BA with the combination of SAs, budesonide (BUD), and salbutamol (8).

2. Objectives

The purpose of this research was to evaluate the clinical efficacy of a combined therapy consisting of SA, BUD, and levosalbutamol hydrochloride (LEV) in the treatment of pediatric BA and to assess its impact on immune function and inflammatory markers. The following sections provide a detailed report of the study.

3. Methods

3.1. General Information

This was a retrospective study. Sample Size Estimation: The study was divided into a combination group and a control group with a 1:1 ratio. The primary efficacy index, FEV1%pred, was calculated using the formula for estimating the mean sample size of two groups. The calculation was based on $\alpha = 0.05$ and a power of 90%, considering the dropout rate. It was determined that the minimum sample size for each group was 35 cases. A total of 40 patients were collected for each group, resulting in 80 patients included in the study. The calculation formula used is as follows: $n = 2 \times (Z\alpha + Z\beta)^2 \times \sigma^2/\delta^2$.

Between June 2022 and June 2023, eighty children diagnosed with BA were selected from our medical facility and assigned to either the observation group or the control group according to the treatment method (n = 40 per group). The study received approval from the Institutional Ethics Committee of our hospital (No.: 2021-10; October 27, 2021), and prior to the research, written informed consent was obtained from the guardians of all participants.

Inclusion Criteria: (1) meeting the diagnostic criteria for BA (9); (2). aged 6 - 12 years; (3) good tolerance to the drugs used in this study and high treatment compliance; (4) informed consent provided and signed by the guardian. Exclusion Criteria: (1) concomitant severe liver or kidney dysfunction; (2) hypersensitivity; (3) interfering immune diseases or chronic inflammatory diseases; (4) recent use of oral immunosuppressants, steroids, or any other drugs that might affect the study results.

Treatment Protocol: Both groups received symptomatic treatment, including standard anti-infective therapy, oxygen therapy, spasmolysants, bronchodilators, and medication for fluid and electrolyte balance. In addition, the control group underwent inhalation therapy with nebulized BUD and LEV, three times a day for 15 minutes each session. The observation group received the same treatment as the control group, plus SA oral lyophilized powder (SAOLP) at a dosage of 2 mg daily, dissolved in 10 mL of cold water and taken orally once daily. Both groups were treated for 2 consecutive weeks, with dedicated

guidance and supervision during medication application.

3.2. Efficacy Evaluation

Efficacy was evaluated for both groups on the last day of the 2-week treatment span using the following criteria: (1) complete response (CR), defined as the disappearance of all clinical symptoms, such as cough and wheezing, with noticeable improvement compared to the pre-treatment condition; (2) partial response (PR), defined as the disappearance of almost all clinical symptoms, fewer relapses during and after the treatment period, and some improvement compared to the pre-treatment condition; (3) no response (NR), defined as no remission of clinical symptoms, no improvement compared to the pre-treatment condition, or even worsening of symptoms after treatment.

The study defined the overall response rate (ORR) as the proportion of patients who achieved either a partial or complete response to the therapy. Additionally, the study evaluated and compared the length of hospital stay (LoHS) and the time taken for symptom improvement between the two groups.

3.3. Inflammatory Markers and Immunological Parameters

(1) inflammatory Markers, each patient provided a 5 mL fasting venous blood sample, which was centrifuged at a radius of 5 cm and 4000 rpm for ten minutes to collect and store the serum at -80°C. The levels of interleukin-2 (IL-2), interleukin-6 (IL-6), and interleukin-4 (IL-4) were measured using flow cytometry (9), while the levels of C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α) were determined using turbidimetric immunoassay; (2) immunological parameters, fasting blood (3 mL) was collected from each patient, centrifuged at 4000 rpm with a centrifugal radius of 5 cm for 10 minutes, to harvest plasma from the upper layer. Flow cytometry was used to analyze the peripheral blood T cell subsets, specifically CD4$^+$, CD3$^+$, and the CD4$^+$/CD8$^+$ ratio. Additionally, immunoglobulin G (IgG) levels were measured using turbidimetric immunoassay, while immunoglobulin M (IgM) (10) and immunoglobulin A (IgA) levels were also assessed.

Two researchers independently assessed the risk of bias in the included studies and cross-checked the results.

3.4. Statistical Analysis

Data analysis was conducted using SPSS 22.0 software. Mean and standard deviation (±) were used to express measurement data, and differences between the two groups were analyzed using the *t*-test. Within-group pre- and post-treatment data were represented by means, and differences before and after treatment within each group were analyzed using the paired *t*-test. Counts and percentages were compared using the chi-square test. Differences were considered statistically significant when P < 0.05.

4. Results

The observation group, consisting of 22 boys and 18 girls aged between 6 - 12 years, with a mean age of (8.63 ± 1.84) years, was compared to the control group, which included 24 boys and 16 girls, with a mean age of (8.48 ± 2.08) years and an age range of 6 - 12 years. The two groups were deemed comparable based on their general characteristics, as no significant differences were detected (all P > 0.05). Please refer to Table 1 for more details.

Following therapy, the observation group demonstrated an ORR of 95.00%, while the control group showed an ORR of 80.00%. A statistically significant difference was observed between the two groups (χ² = 4.114, P = 0.043), as shown in Table 2.

Length of Hospital Stay and Time to Symptom Improvement: Both LoHS and time to symptom improvement were significantly shorter in the observation group compared to the control group (all P < 0.05). See Table 3 for details.

Initially, there were no significant differences in IL-8, IL-6, IL-2, IL-4, TNF-α levels, and CRP between the two groups before treatment (all P > 0.05). However, following treatment, both groups exhibited significant reductions in IL-6, IL-2, IL-8, IL-4, TNF-α levels, and CRP (all P < 0.05). The reduction was notably more pronounced in the observation group compared to the control group (all P < 0.05). For more information, please refer to Table 4.

Similarly, there were no substantial differences in CD3$^+$, CD4$^+$, CD4$^+$/CD8$^+$, IgM, IgG, and IgA levels between the two groups before treatment (all P > 0.05). After

Table 1. General Information

Variables	Observation (n = 40)	Control (n = 40)	t/χ²	P-Value
Age (y)	8.63 ± 1.84	8.48 ± 2.08	0.342	0.733 [a]
Sex (n)			0.205	0.651 [b]
Male	22 (55.00)	24 (60.00)		
Female	18 (45.00)	16 (40.00)		
Disease course (day)	3.13 ± 1.67	2.9 5 ± 1.58	0.481	0.632 [a]
Disease severity [n (%)]			0.282	0.868 [b]
Mild	11 (27.50)	9 (22.50)		
Moderate	21 (52.50)	22 (55.00)		
Severe	8 (20.00)	9 (22.50)		

[a] independent-sample *t*-test.

[b] Chi-square test.

Table 2. Clinical Efficacy [a]

Groups	n	CR	PR	NR	ORR (%)
Observation	40	34 (85.00)	4 (10.00)	2 (5.00)	38 (95.00)
Control	40	29 (72.50)	3 (7.50)	8 (20.00)	32 (80.00)
χ²-value					4.114
P-value					0.043 [b]

Abbreviation: CR, complete response; PR, partial response; NR, no response; ORR, overall response rate.

[a] Values are expressed as No (%) unless otherwise indicated.

[b] Chi-square test.

Table 3. Clinical Efficacy [a]

Groups	n	LoHS	Time to Complete Remission of Cough	Time to Complete Remission of Suffocative Asthma	Time to Complete Remission of Wheezing
Observation	40	6.20 ± 1.56	3.78 ± 0.83	2.28 ± 0.45	4.13 ± 0.97
Control	40	7.33 ± 1.31	4.35 ± 1.00	2.58 ± 0.75	4.65 ± 1.10
***t*-value**		3.500	2.794	2.172	2.270
P-value [b]		0.001	0.007	0.033	0.026

[a] Values are expressed as mean ±SD unless otherwise indicated.

[b] Independent-sample *t*-test.

treatment, both groups showed significant increases in CD3⁺, CD4⁺, CD4⁺/CD8⁺, IgM, IgG, and IgA levels compared to their pre-treatment levels (all P < 0.05). These increases were more pronounced in the observation group than in the control group (all P < 0.05). For more information, please refer to Table 5.

Throughout the treatment period, adverse drug reactions (ADRs) were observed in both groups. In the observation group, there was one case of dizziness and two cases of nausea, resulting in an overall adverse reaction rate (OADRR) of 7.50%. In the control group,

there were two cases of nausea and two cases of dizziness, leading to an OADRR of 10.00%. Notably, there was no significant difference in OADRR between the two groups ($\chi^2 = 0.157$, P = 0.692).

5. Discussion

As a common chronic condition in childhood, BA is a heterogeneous disease primarily characterized by AHR and chronic inflammation, and it is associated with numerous factors ([11]). Reportedly, infection, allergen exposure, and vigorous exercise can trigger an acute

Table 4. Pre- and Post-Treatment Levels of Inflammatory Markers [a]

Outcome Measure (Time Point)	Observation	Control	t	P-Value [b]
IL-2 (μg/L)				
Pre-treatment	10.71 ± 5.51	10.87 ± 3.80	0.146	0.884
Post-treatment	4.51 ± 2.29	7.24 ± 3.26	4.324	< 0.001
IL-4 (pg/mL)				
Pre-treatment	2.53 ± 0.50	2.42 ± 0.39	1.033	0.305
Post-treatment [c]	1.09 ± 0.35	1.36 ± 0.73	2.116	0.038
IL-6 (ng/L)				
Pre-treatment	112.62 ± 7.65	112.18 ± 6.09	0.285	0.777
Post-treatment [c]	53.83 ± 5.99	57.49 ± 5.62	2.822	0.006
IL-8 (ng/L)				
Pre-treatment	10.42 ± 3.83	10.84 ± 3.16	0.544	0.588
Post-treatment [c]	5.50 ± 2.45	6.80 ± 2.75	2.224	0.029
CRP (mg/L)				
Pre-treatment	37.05 ± 3.72	35.85 ± 3.56	1.475	0.144
Post-treatment [c]	13.33 ± 2.48	18.74 ± 3.16	8.514	< 0.001
TNF-α (ng/L)				
Pre-treatment	1.76 ± 0.18	1.73 ± 0.16	0.572	0.569
Post-treatment [c]	1.10 ± 0.10	1.28 ± 0.07	9.051	< 0.001

Abbreviations: IL-2, interleukin-2; IL-4, interleukin-4; IL-6, interleukin-6; IL-8, interleukin-8; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α.

[a] Values are expressed as mean ±SD unless otherwise indicated.

[b] Independent-sample *t*-test.

[c] $P < 0.05$ paired *t*-test.

onset of asthma ([12]). In China, the incidence of pediatric BA is on the rise, yet the overall management remains suboptimal. Generally, pediatric patients with BA are treated with anti-inflammatory agents, expectorants, and bronchodilators. Without effective management, symptoms can persist into adulthood, making BA a lifelong illness. Moreover, patients and their families bear significant physical, mental, and financial burdens due to long-term treatment and high drug doses ([13]). While inhalation therapy using nebulized medicines is a proven approach for ensuring efficacy and prompt symptom control, the choice of nebulized medicines should consider their adaptability and safety profiles ([14]).

This study demonstrated that, after treatment, the levels of T lymphocyte subsets (CD3+, CD4+, CD4+/CD8+) and immunoglobulins (IgM, IgG, IgA) were significantly higher in both groups of children compared to pre-treatment levels, with the observation group showing significantly higher levels than the control group ($P < 0.05$). The levels of inflammatory factors (IL-2, IL-4, IL-6, IL-8, CRP, and TNF-α) were significantly reduced compared to pre-treatment levels, and the reduction was more pronounced in the observation group than in the control group ($P < 0.05$). These findings are consistent with multiple other studies.

This suggests that SA s can effectively regulate the immune levels in children with BA, enhance their immune function, and inhibit inflammatory factors. The underlying mechanism is that SAs contain immune regulatory factors that act on regulatory T cells, promote helper T cell-mediated cellular immunity, inhibit helper T cell-mediated humoral immunity, regulate the Th1/Th2 balance, and modulate the release of inflammatory factors. This dual action helps in regulating immunity and suppressing inflammatory responses.

Spleen aminopeptide belongs to a complex of peptides and nucleotides and is considered a new type of immune enhancer ([15]). It contains various essential amino acids, trace elements, and immune regulatory factors vital for the human body. Spleen aminopeptides

Table 5. Pre- and Post-Treatment Levels of Immunological Parameters [a]

Outcome Measure (Time Point)	Observation	Control	t	P-Value [b]
CD3$^+$ (%)				
Before-treatment	42.64 ± 6.44	42.86 ± 6.19	0.154	0.878
After-treatment	48.56 ± 6.36	43.30 ± 6.14	3.768	< 0.001
CD4$^+$ (%)				
Before-treatment	27.31 ± 4.12	27.52 ± 3.83	0.239	0.812
After-treatment [c]	38.27 ± 4.67	34.05 ± 4.83	3.971	< 0.001
CD4$^+$/CD8$^+$ (%)				
Before-treatment	1.28 ± 0.10	1.28 ± 0.07	0.206	0.837
After-treatment [c]	1.76 ± 0.18	1.55 ± 0.16	5.276	< 0.001
IgM (g/L)				
Before-treatment	1.40 ± 0.65	1.39 ± 0.71	0.121	0.904
After-treatment [c]	2.77 ± 0.64	2.42 ± 0.52	2.741	0.008
IgG (g/L)				
Before-treatment	1.36 ± 0.27	1.33 ± 0.31	0.474	0.637
After-treatment [c]	2.85 ± 0.76	2.32 ± 0.48	3.753	< 0.001
IgA (g/L)				
Before-treatment	1.35 ± 0.27	1.32 ± 0.31	0.464	0.644
After-treatment [c]	2.83 ± 0.76	2.24 ± 0.42	4.254	< 0.001

Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin M.

[a] Values are expressed as mean ±SD unless otherwise indicated.

[b] Independent-sample *t*-test.

[c] P < 0.05 paired *t*-test.

can promote lymphocyte activation, receptor regulation, and immune information transmission, improving immune suppression, enhancing the synergistic and proliferative effects of immune cells, increasing the activity of the monocyte-macrophage system, reducing local inflammatory reactions, and alleviating respiratory infections. Research has shown that SAs can improve the immune function of patients with BA ([16], [17]), activate and regulate T cell subsets, enhance the cytotoxic effects of T lymphocytes, stimulate cytokine secretion by immune cells, reduce IgE-mediated type I hypersensitivity reactions, and alleviate AHR. Furthermore, SAs promote immune information transmission, lymphocyte activation, and receptor regulation, enhance immune cell proliferation and synergistic effects, improve immune suppression caused by adrenal corticosteroids, boost monocyte-macrophage system activity, reduce respiratory infections and local inflammatory responses, and strengthen the overall immune function of somatic cells.

The results of this study showed that the total effective rate of treatment in the observation group was significantly higher than that in the control group after treatment (P < 0.05). However, there was no significant difference in the total incidence of ADRs between the two groups of children (χ^2 = 0.157, P = 0.692). These findings suggest that the combination of SAs with BUD and salbutamol can significantly reduce the inflammatory response in children, improve immune function, and provide good clinical efficacy with a high safety profile in the treatment of pediatric BA.

Budesonide, a non-halogenated adrenal glucocorticoid, can inhibit the production and release of inflammatory cytokines ([18]), combat allergies and infections, improve capillary permeability, inhibit and reduce IgE activity ([19], [20]), rapidly alleviate asthma symptoms in children, and improve lung function. Salbutamol, a β2 receptor agonist ([21]), can relax bronchial smooth muscle, enhance mucosal ciliary movement, and promote the discharge of airway secretions. Research has shown that salbutamol can

inhibit the release of inflammatory factors (22, 23), reduce airway inflammation, exert anti-inflammatory effects, and improve clinical symptoms in children with BA.

5.1. Limitations

However, this study has some limitations, such as a small sample size and a short follow-up period. To further evaluate the clinical efficacy of this treatment, future studies should expand the sample size and extend the follow-up period. Currently, there is relatively little research on the treatment of BA using the combination of SAs, BUD, and salbutamol hydrochloride in clinical practice. There are no reports on major adverse reactions or the combined use of these three treatments, highlighting the need for further research in the future.

5.2. Conclusions

This study demonstrates that the combination of SAs, BUD, and LEV can significantly improve the immune function of children with BA, reduce the levels of inflammatory factors, and achieve excellent clinical outcomes. The combined therapy is more effective than the use of a single drug and does not increase the incidence of ADRs.

Footnotes

Authors' Contribution: D. Z. and S. H., designed this study and prepared this manuscript; N. R., collected and analyzed clinical data; X. Y. and B. Z., participated in acquisition, analysis, or interpretation of data and draft the manuscript. All authors read and approved the final manuscript.

Conflict of Interests Statement: The authors declare no conflicts of interest.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

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References

1. Rehman A, Amin F, Sadeeqa S. Prevalence of asthma and its management: A review. *J Pak Med Assoc*. 2018;**68**(12):1823-7. [PubMed ID: 30504949].

2. Shine S, Muhamud S, Demelash A. Prevalence and associated factors of bronchial asthma among adult patients in Debre Berhan Referral Hospital, Ethiopia 2018: a cross-sectional study. *BMC Res Notes*. 2019;**12**(1):608. [PubMed ID: 31547859]. [PubMed Central ID: PMC6757354]. https://doi.org/10.1186/s13104-019-4670-9.

3. Castillo Vizuete JA, Sastre J, Del Cuvillo Bernal A, Picado C, Martinez Moragon E, Ignacio Garcia JM, et al. Asthma, rhinitis, and nasal polyp multimorbidities. *Arch Bronconeumol (Engl Ed)*. 2019;**55**(3):146-55. [PubMed ID: 30449614]. https://doi.org/10.1016/j.arbres.2018.09.001.

4. Kianmehr M, Rezaee A, Mahmoudi M, Ghorani V, Boskabady MH. T helper cells subtypes and their cytokine gene expression affected by carvacrol in sensitized mice administered during sensitization period. *J Cell Biochem*. 2019;**120**(4):5343-54. [PubMed ID: 30387169]. https://doi.org/10.1002/jcb.27812.

5. Boulet LP, Reddel HK, Bateman E, Pedersen S, FitzGerald JM, O'Byrne PM. The Global Initiative for Asthma (GINA): 25 years later. *Eur Respir J*. 2019;**54**(2). [PubMed ID: 31273040]. https://doi.org/10.1183/13993003.00598-2019.

6. Huang K, Yang T, Xu J, Yang L, Zhao J, Zhang X, et al. Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. *Lancet*. 2019;**394**(10196):407-18. [PubMed ID: 31230828]. https://doi.org/10.1016/S0140-6736(19)31147-X.

7. Ruan JW, Zhou JR, Yuan XL, Zeng JH, Wu YL, Yuan SR. Meta-analysis of the efficacy of spleen in the treatment of children with bronchial asthma. *J Gannan Med College*. 2023;**43**(2):166-75. https://doi.org/10.3969/j.issn.1001-5779.2023.02.010.

8. Subspecialty Group of Respiratory Diseases SOPCMA, Editorial Board CJOP. [Guideline for the diagnosis and optimal management of asthma in children(2016)]. *Zhonghua Er Ke Za Zhi*. 2016;**54**(3):167-81. Chinese. [PubMed ID: 26957061]. https://doi.org/10.3760/cma.j.issn.0578-1310.2016.03.003.

9. Maryamchik E, Gallagher KME, Preffer FI, Kadauke S, Maus MV. New directions in chimeric antigen receptor T cell [CAR-T] therapy and related flow cytometry. *Cytometry B Clin Cytom*. 2020;**98**(4):299-327. [PubMed ID: 32352629]. https://doi.org/10.1002/cyto.b.21880.

10. Zeng D, Li W, Zhou J, Wen X, Chen S, Xie X, et al. Analysis of the immunoglobin E molecular sensitization profile in children with allergic asthma and predictive factors for the efficacy of allergy immunotherapy. *Ann Transl Med*. 2020;**8**(21):1459. [PubMed ID: 33313204]. [PubMed Central ID: PMC7723661]. https://doi.org/10.21037/atm-20-7314.

11. Ma T, Wang H, Wang X. Effectiveness and Response Predictors of Omalizumab in Treating Patients with Seasonal Allergic Rhinitis: A Real-World Study. *J Asthma Allergy*. 2021;**14**:59-66. [PubMed ID: 33519214]. [PubMed Central ID: PMC7837594]. https://doi.org/10.2147/JAA.S288952.

12. DePriest K, Butz A, Curriero FC, Perrin N, Gross D. Associations among neighborhood greenspace, neighborhood violence, and children's asthma control in an urban city. *Ann Allergy Asthma Immunol*.

2019;**123**(6):608-10. [PubMed ID: 31610235]. [PubMed Central ID: PMC6915955]. https://doi.org/10.1016/j.anai.2019.10.003.

13. Licari A, Manti S, Chiappini E, Ciprandi G, Marseglia GL. Severe asthma in children: Current goals and unmet needs. *Pediatr Allergy Immunol.* 2020;**31 Suppl 24**:40-2. [PubMed ID: 32017220]. https://doi.org/10.1111/pai.13168.

14. Gao S, Yu L, Zhang J, Li X, Zhou J, Zeng P, et al. Expression and clinical significance of VCAM-1, IL-6, and IL-17A in patients with allergic rhinitis. *Ann Palliat Med.* 2021;**10**(4):4516-22. [PubMed ID: 33966399]. https://doi.org/10.21037/apm-21-546.

15. Yue Y, Liang Q, Shi L, Bai WJ, Fu J. Effect of comprehensive nursing intervention on the efficacy of spleen aminopeptide combined with aerosol inhalation in the treatment of pediatric pneumonia. *Pak J Med Sci.* 2023;**39**(4):1086-90. [PubMed ID: 37492332]. [PubMed Central ID: PMC10364302]. https://doi.org/10.12669/pjms.39.4.7195.

16. Kawa Y, Nagano T, Yoshizaki A, Dokuni R, Katsurada M, Terashita T, et al. Role of S1P/S1PR3 axis in release of CCL20 from human bronchial epithelial cells. *PLoS One.* 2018;**13**(9). e0203211. [PubMed ID: 30192865]. [PubMed Central ID: PMC6128515]. https://doi.org/10.1371/journal.pone.0203211.

17. Prosekova EV, Sitdikova TS, Dolgopolov MS, Turyanskaya AI, Sabynych VA, Zabelina NR. Parameters of innate and adaptive immune response in children with virus-induced and allergen-induced bronchial asthma phenotypes. *Bulletin Siberian Med.* 2017;**16**(2):170-9.

18. Eremija J, Carr TF. Immunotherapy for Asthma. *Semin Respir Crit Care Med.* 2022;**43**(5):709-19. [PubMed ID: 35714626].

https://doi.org/10.1055/s-0042-1749454.

19. Wang J, Ma X, Shang K, Wu S, Ma Y, Ma Z, et al. Safety and efficacy of spleen aminopeptide oral lyophilized powder for improving quality of life and immune response in patients with advanced breast cancer: a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Anticancer Drugs.* 2021;**32**(10):1067-75. [PubMed ID: 34261911]. [PubMed Central ID: PMC8517102]. https://doi.org/10.1097/CAD.0000000000001109.

20. Wu Y, Dong X, Wu R, Zheng X, Jin Y, Yang H. Efficacy and safety of spleen aminopeptide oral lyophilized powder in ameliorating liver injury in infants and children with human cytomegalovirus infection: a single-center study in China. *Transl Pediatr.* 2021;**10**(1):136-45. [PubMed ID: 33633945]. [PubMed Central ID: PMC7882289]. https://doi.org/10.21037/tp-20-173.

21. Houdouin V, Dubus JC. What is the impact of outdoor pollution on children's asthma? *Arch Pediatr.* 2019;**26**(8):487-91. [PubMed ID: 31685409]. https://doi.org/10.1016/j.arcped.2019.10.007.

22. Cao X, Zhong P, Li G, Zhu J, Zheng Y. Application of probiotics in adjuvant treatment of infant allergic rhinitis: A randomized controlled study. *Medicine (Baltimore).* 2020;**99**(18). e20095. [PubMed ID: 32358397]. [PubMed Central ID: PMC7440258]. https://doi.org/10.1097/MD.0000000000020095.

23. Gu ZW, Wang YX, Cao ZW. Neutralization of interleukin-17 suppresses allergic rhinitis symptoms by downregulating Th2 and Th17 responses and upregulating the Treg response. *Oncotarget.* 2017;**8**(14):22361-9. [PubMed ID: 28423590]. [PubMed Central ID: PMC5410229]. https://doi.org/10.18632/oncotarget.15652.