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RESEARCH ARTICLE

Analysis of FeNO levels in 496 asthma patients

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Nitric oxide (NO) plays an important role in the lungs and airways as an endogenous relaxation factor, neurotransmitter, and inflammatory mediator. However, the significance of the fractional exhaled nitric oxide (FeNO) level in asthma patients is yet to be clarified. In this study, the data of 500 outpatients from the Department of Respiratory Diseases of Guizhou Provincial People's Hospital between August 2023 and December 2023 were retrospectively analyzed, and among them, adult asthma patients with no hypermetabolic disease, no acute stress, no history of long-term hormone use, and the ability to cooperate in FeNO testing were included. These patients were divided into the allergy-positive group and allergy-negative group, and the results revealed that the measured FeNO level was not significant correlated with age, sex, or pulmonary function parameters (forced expiratory volume in one second percentage (FEV1%), forced vital capacity (FVC), and FEV1/FVC) ($P>0.05$) but was significantly positively correlated with the peripheral blood percentage of eosinophils (EOS%) ($P<0.01$). In addition, the effects of sex and common comorbidities on the measured FeNO level were not statistically significant ($P>0.05$), and the measured FeNO level of the smoking population was significantly lower than that of the nonsmoking population ($P<0.05$). Moreover, the measured FeNO levels were different for patients with different allergies. Among 217 patients positive for allergic reactions to inhaled allergens, dust mites were the allergens for 66 patients, and the measured FeNO level was (67.36±49.88) parts per billion (ppb); pollens were the allergens for 53 patients, and the measured FeNO level was (44.18±19.63) ppb; and cooking oil fumes (COFs) were the allergens for 41 patients, and the measured FeNO level was (38.92 ± 15.75) ppb. In 57 patients with allergic reactions to multiple allergens, the measured FeNO level was (99.22 ± 98.3) ppb. The FeNO level in patients with dust mite allergies was significantly greater than those in patients with COF and pollen allergies ($P <0.05$). Finally, we concluded that the FeNO level in asthma patients was not affected by age or sex, was significantly correlated with EOS%, and was affected by smoking history. FeNO levels differed among asthma patients with different allergies.

Keywords: asthma; fractional exhaled nitric oxide; dust mites; pollen; cooking oil fumes

Abbreviations: NO, Nitric oxide; FeNO, fractional exhaled nitric oxide; PEF, peak expiratory flow; FVC, forced vital capacity; FEV1,forced expiratory volume in one second ;GINA, the Global Initiative for Asthma ; COFs, cooking oil fumes; sIgE, Allergen-specific IgE.

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Introduction

Nitric oxide (NO) in human exhaled breath is produced by airway epithelial cells. The oxidative deamination of arginine generates endogenous NO through the activity of NO synthase. NO plays an important role in the lungs and airways as an endogenous relaxation factor, neurotransmitter, and inflammatory mediator [1]. In the early 1990s, for the first time, Gustafsson et al. reported the detection of NO in human exhaled breath. The fractional exhaled nitric oxide (FeNO) test is a noninvasive technique for detecting airway inflammation that was developed in recent years; in addition to its noninvasiveness, the FeNO test is simple to perform and has shown good

reproducibility, safety [2][3], and high specificity and sensitivity for detecting allergic airway inflammation [4].

To date, a variety of methods for the detection of FeNO have been developed in China and abroad, such as laser detection, electrochemical detection, spectrophotometric detection, fluorescence detection, and ion mobility spectrometry; however, the chemiluminescence method, in which the principle of luminescence and heat production by the reaction between NO and O3 is utilized to measure FeNO levels, is the "gold-standard" method for FeNO detection [5] and can be performed online or offline. Compared with other NO detection technologies, the chemiluminescence method has strong sensitivity, fast return of results, high reliability, and good accuracy. Internationally, the American Thoracic Society (ATS) and European Respiratory Society (ERS) reached a consensus on the procedures to use for respiratory tract NO detection and the standard parameters of FeNO detection, stipulating the international unified use of 50 mL/second as the standard detection flow rate [6] and parts per billion (ppb) (1 ppb =1×10-9 mol/L) as the standard FeNO concentration unit [7].

The relationship between FeNO and asthma has been a popular topic in recent years. Although mucosal biopsy under bronchoscopy and bronchoalveolar lavage (BAL) are the "gold standards" for determining the inflammatory phenotype of asthma patients, owing to the high risk, difficulty in repeating, and relatively high degree of trauma associated with these procedures, they are not easy to implement widely. Currently, more clinical researchers are determining asthma inflammatory phenotypes by indirectly evaluating eosinophil counts in blood or sputum, pulmonary function test (PFT) results, and inflammatory indicators such as IgE and C-reactive protein (CRP) [8]. In a systematic review and meta-analysis published in 2017, Karrasch et al. [9] included a total of 26 studies with 4518 patients to investigate the accuracy of FeNO testing in the diagnosis of asthma, and the results revealed that, as a detection method, the specificity of FeNO was greater than the sensitivity. In addition, several foreign studies [10][11][12] have found that increased FeNO is often accompanied by decreased peak expiratory flow (PEF), forced vital capacity (FVC), and forced expiratory volume in one second (FEV1). When a patient's FeNO level is above 50 ppb and the patient has relevant clinical symptoms, he/she can be diagnosed with asthma.

Large-scale research trials have been conducted in Europe, the United States and other countries, and the reference values or critical values for the FeNO normal range proposed in different studies vary. Many foreign studies have shown that the measured FeNO level may be affected by many factors, including age, sex, race, height, weight, dietary habits, pulmonary function, and disease status. However, for these factors, conclusions in different studies vary widely, and there is no uniform understanding. At present, FeNO testing has been widely promoted and used in China, but there are different opinions on the relationships between FeNO levels and various indicators [13, 14, 15]. Therefore, it is very important to establish a clear FeNO normal range and critical values and investigate the influences of various factors on FeNO.

In this study, a regression analysis of the medical record data of adult outpatients at Guizhou Provincial People's Hospital from August 2023 to December 2023 was performed to address these problems and thus further help the development of individualized treatment plans for patients.

Patients and Methods

Inclusion and exclusion criteria

Five hundred newly diagnosed asthma patients at the Respiratory Medicine Outpatient Clinic of Guizhou Provincial People's Hospital between August 2023 and December 2023 were enrolled in this study.

The included asthma patients met the following diagnostic criteria of the Global Initiative for Asthma (GINA) guidelines: (1) main manifestations were repeated wheezing episodes, chest tightness, cough, dyspnoea and other symptoms, and during the asthma attack, scattered or diffuse rales could be detected in both lungs, mainly in the expiratory phase; (2) symptoms could remit spontaneously or be relieved after the use of antispasmodic and antiasthmatic drugs, and symptoms could be exacerbated by triggers, such as exposure to allergens, infections, exercise, and environmental changes; (3) results of a bronchodilator test were positive, i.e. showed an increase in pulmonary function FEV1 of more than 12% after inhalation of salbutamol aerosol and an absolute increase in FEV1 of more than 200 mL; (4) and patients were able to cooperate in pulmonary function and FeNO tests.

The exclusion criteria were as follows: incomplete information; hypermetabolic diseases, such as pregnancy and hyperthyroidism; long-term oral hormone use; and acute stress. Patients were divided into an allergy-positive patient group and an allergy-negative patient group according to the number of inhaled allergens to which they

had a positive allergic reaction (1 and ≥2) and allergy to each specific allergen.

Data acquisition

The basic patient information acquired included sex, age, admission time, disease course, smoking history, drug allergy history, and previous medical history (diabetes, hypertension, heart disease, respiratory disease, allergic diseases, and others).

Information on cough, chest tightness, difficulty breathing, and other discomforts related to exposure to pollen, dust mites, and cooking oil fumes (COFs) was collected from the patients' medical history.

Evaluation methods

(1) Routine blood tests: A Beckman Coulter automatic haematology analyser was used. Patients were told to avoid strenuous exercise, such as running, cycling, and climbing, before blood collection, and they were asked to rest for approximately 15 minutes before venous blood collection.

(2) Range of total IgE (IU/mL): 0-100.

(3) Allergen-specific IgE (sIgE): The enzyme-linked immunosorbent assay (ELISA) capture method was used. There were 4 types of allergens: house dust mites (HDMs), cat and dog dander, birch, and juniper. The grading criteria for the sIgE level of each allergen (IU/mL) are shown in Table 1.

Table 1. Classification criteria for allergens.

Positive level	IU/mL	sIgE concentration
1	0.35-0.7	Low (weak positive)
2	0.7-3.5	Medium (moderate positive)
3	3.5-17.5	High (strongly positive)
4	17.5-50	Very high (strongly positive)
5	50-100	Extremely high (strongly positive)
6	>100	Ultrahigh (strongly positive)

(4) Pulmonary function: The temperature, humidity, pressure, test gas and volume were calibrated before measurement. Basic PFTs were performed according to operational requirements: while in a standing or sitting position, the patient tightly wrapped their lips around the disposable mouthpiece to avoid air leakage at the corners of the mouth. The patient used a nose clip. The patient was instructed to breathe calmly for a few cycles, inhale deeply to the total lung volume, and exhale forcefully, with the exhalation process lasting approximately 6 seconds. This procedure was repeated 3 times. The FEV1 and FVC were recorded and analysed by the PFT system, and the average values were used in the analyses. Double inhalation and coughing were avoided during the entire process.

(5) Bronchodilation test: Patients with obstructive ventilation dysfunction (OVD) as indicated by the PFT were instructed to breathe calmly a few times, exhale deeply once, inhale deeply and slowly once, and then inhale 400 μg of salbutamol aerosol and hold their breath for approximately 10 seconds. After 15-30 minutes, the PFT was performed again. Bronchodilation test positivity was determined as follows: after the inhalation of bronchodilators, the increase in FEV1 was >12%, and the absolute increase was >200 mL.

(6) Bronchial challenge test: The bronchial challenge test was performed according to the patient's PFT results and medical history. The patient breathed calmly a few times, exhaled deeply, and inhaled slowly and deeply. The patient was then administered the drug spray (0.9% saline) according to the protocol. This was followed by a 2-minute wait period for a response. The PFT was performed again to obtain observation data after drug treatment. If the decrease in FEV1 was less than 20%, drug spray administration continued according to the protocol, and the PFT was repeated. If the decrease in FEV1 was more than 20%, the bronchial challenge test was positive, the test was ended, and the bronchodilator spray was administered.

(7) FeNO test: A Swedish NIOX-IINO exhaled NO measurement system (airway inflammation detector) was used. Detection methods: The test was performed in strict accordance with clinical regulations [16]. The patient was asked to sit up, the nose of the patient was clamped with a nose clip, and the patient breathed calmly for 3-4 breaths. After the patient's breathing stabilized, the patient was asked to exhale to the residual air level. The patient inhaled deeply through the mouthpiece (this gas was passed through a special filter to remove the exogenous NO) to the maximum lung capacity; then, they slowly exhaled at a constant airflow of approximately 50 mL/second; according to the automated display on the computer screen, the exhaled air reached a relatively stable platform. The test was repeated three times so that an effective FeNO level that was within the limit (the allowable deviation of the measured FeNO level was less than 10% or the difference between two measurements was less than 5%) could be obtained, and the average effective FeNO level was recorded as the final value. The measured FeNO levels were recorded in units of ppb (ppb=109).

Table 2. General information of the 500 patients.

	Negative for allergic reactions to specific allergens	Positive for allergic reactions to specific allergens
Age (years)	47.76±16.91	47.84±16.87
Male (n)	125	89
Female (n)	153	128
Smoking history (n)	118	84
Leukocytes ($\times 10^9$/L)	7.562±1.181	7.707±1.251
Percentage of eosinophils (EOS%)	3.425±1.535	4.483±1.716
Total IgE	10.13±11.27	10.08±10.02
FEV1 (L)	2.65±0.23	2.61±0.30
FVC (L)	3.73±0.29	3.71±0.30
FEV1/FVC (%)	71±8.1	71±8.6
Bronchodilation/bronchial challenge test positivity (n)	57	60
Hypertension (n)	25	21
Diabetes (n)	19	24
Coronary heart disease (n)	21	15
FeNO (ppb)	27.76±11.89	64.69±62.76
FeNO>25ppb, n (%)*	169 (60%)	175 (80%)

*There were 169 allergy-negative patients with an FeNO>25 ppb, accounting for 60% of all allergy-negative patients, and there were 175 allergy-positive patients with an FeNO>25 ppb, accounting for 80% of all allergy-positive patients.

Application of FeNO in the diagnosis of asthma

For patients with chronic cough and/or wheezing and/or difficulty breathing for more than 6 weeks, the following diagnoses and evaluations can be considered. ① FeNO<25 ppb suggests that there is no eosinophilic inflammation and the response to hormone therapy is poor; and possible diagnoses are as follows: noneosinophilic asthma (neutrophilic inflammation), asthmatic bronchitis, gastroesophageal reflux disease, sinusitis, chronic obstructive pulmonary disease, vocal cord dysfunction, bronchiectasis, cystic fibrosis, and primary ciliary movement disorder. ② For patients with FeNO values of 25-50 ppb, comprehensive consideration should be given, clinical evaluation should be performed, and a second diagnosis should be made in a short period of time. ③ FeNO>50 ppb suggests eosinophilic airway inflammation, which is likely to respond well to hormone therapy [16].

Statistical Analysis

A data sheet of patient medical record data was created, and all the data were statistically analysed and processed via SPSS 26.0 software. The measurement data were expressed as the mean ± standard deviation. Differences between two groups were analysed via an independent-sample t test, and correlation analysis was performed via Pearson correlation analysis.

Results

Description of the general information of asthma patients

A total of 496 asthma patients who met the inclusion criteria were included in this study, including 279 allergy-negative patients and 217 allergy-positive patients. The age range of the allergy-negative patients was 14-86 years, and the mean age was 47.76 ± 16.91 years; the age range of the allergy-positive patients was 14-90 years, and the mean age was 47.84±16.87 years. Among male patients, 89 were allergy-positive patients, and 125 were allergy-negative patients. Among female patients, 128 were allergy-positive patients, and 153 were allergy-negative patients. Eighty-four allergy-positive patients and 118 allergy-negative patients had a history of smoking. There were 169 allergy-negative patients with an FeNO>25 ppb, accounting for 60% of all allergy-negative patients, and there were 175 allergy-positive patients with an FeNO>25 ppb, accounting for 80% of all allergy-positive patients, as shown in Table 2.

Correlation analysis of each factor and FeNO

The correlation analysis was conducted on each indicator, and the results are shown in Tables 3 and 4. The measured FeNO level showed no significant correlation with age, peripheral blood parameters (leukocyte count and total IgE), or pulmonary function indicators (FEV1%, FVC, and FEV1/FVC) (P>0.05). The measured FeNO level was

significantly positively correlated with the percentage eosinophils in peripheral blood (EOS%) (P<0.01). Neither sex nor common comorbidities had a significant effect on the measured FeNO level (P>0.05). Smoking had a statistically significant effect on the measured FeNO level; i.e., in the smoking population, the measured FeNO level was lower than that in the nonsmoking population (P<0.05).

Table 3. Correlation analysis of FeNO.

	Indicators	*R*	*P*
Peripheral blood parameters	Age	0.007	0.871
	Leukocyte count	0.009	0.028
	EOS%	0.548	0.001
	Total IgE	-0.017	0.705
Pulmonary function indicators	FEV1%	0.001	0.967
	FVC	-0.0004	0.992
	FEV1/FVC	-0.012	0.776

The measured FeNO level was not significantly correlated with age, peripheral blood parameters (leukocyte count and total IgE), or pulmonary function indicators (FEV1%, FVC, and FEV1/FVC) (P>0.05); however, the measured FeNO level was significantly positively correlated with EOS% (P<0.01). FEV1, forced expiratory volume in one second; FVC, forced vital capacity; FeNO, fractional exhaled nitric oxide; EOS%, percentage of eosinophils.

Table 4. Effects of different factors influencing FeNO.

	Yes (male)	FeNO	No (female)	FeNO	*P*
Sex	215	45.09±44.34	281	43.02±47.64	<0.05
Smoking history	202	42.03±36.69	294	45.32±51.76	0.035
diabetes	42	54.15±57.3	452	42.79±44.77	0.027
Hypertension	46	41.54±22.93	450	44.16±47.96	0.042
Coronary heart disease	67	47.95±44.7	429	43.29±46.45	0.036

Neither sex or common comorbidities had a significant effect on the measured FeNO level (P>0.05). Smoking had a statistically significant effect on the FeNO level; i.e., the measured FeNO level in the smoking population was lower than that in the nonsmoking population (P<0.001).

Table 5 Measured FeNO level for each inhaled allergen.

Allergens	Number of patients with an allergy	FeNO (ppb)	*P*
Dust mites	66	67.36±49.88	0.023
Pollen	53	44.18±19.63	0.036
COFs*	41	38.92±15.75	0.016
Multiple	57	99.22±98.3	0.024

*COFs, cooking oil fumes.

Relationship between each allergen and the measured FeNO level

According to each indicator, the allergy-positive patients were divided into groups according to the allergen to which they had a positive allergic reaction: dust mites, pollen, COFs, and multiple allergens (Table 5). The measured FeNO levels were different (P<0.05) for different allergens. Among the allergy-positive patients, dust mites were the allergens for 66 patients, and the measured FeNO level was (67.36±49.88) ppb; pollens were the allergens for 53 patients, and the measured FeNO level was (44.18±19.63) ppb; and COFs were the allergens for 41 patients, and the measured FeNO level was (38.92 ± 15.75) ppb. In patients with allergic reactions to multiple allergens, the measured FeNO level was (99.22 ± 98.3) ppb (P<0.001).

Discussion

The treatment process of asthma patients includes not only prevention but also diagnosis. As a heterogeneous disease [16], a variety of biomarkers are needed to assist in the diagnosis and treatment of asthma. FeNO is an important noninvasive marker that effectively reflects the airway inflammation status of asthma patients, and it has become increasingly used in asthma diagnosis [14][17]. In 1991, Gustafsson et al. [18] reported that FeNO originated from respiratory epithelial cells. Subsequently, Alving et al. [19] and other researchers reported that FeNO could be used to detect various respiratory diseases. In 1997, the ERS formulated technical standards for the detection of FeNO for the first time in the world [20]. In 2003, for the first time, the US Food and Drug Administration (FDA) approved the use of FeNO detection equipment for the clinical evaluation of airway inflammatory diseases such as asthma [21]. Since then, many countries have successively developed FeNO detection technologies. In 2005, the ATS and ERS jointly announced the technical standard guidelines for FeNO detection [22]. In 2008, the Asthma group of the Chinese Thoracic Society of the Chinese Medical Association included the FeNO detection technology in the Guidelines for Bronchial Asthma Prevention and Management [23] and introduced third-generation NIOX mobile measurement equipment. In 2009, the ATS/ERS jointly recommended FeNO detection as a means of asthma management [24]. Long-term clinical research and practice have led to unanimous approval of the clinical application of FeNO detection. The clinical value of FeNO as a bioindicator for the assessment of airway inflammation has been demonstrated by virtue of the noninvasiveness, simplicity, accuracy, reliability, and reproducibility of its testing.

Allergens are the most important external cause of asthma. Allergic reactions are involved in the immune-inflammatory mechanism of asthma, thus mediating the process of histamine synthesis and the release of multiple inflammatory mediators to mediate smooth muscle contraction, increased mucus secretion, increased vascular permeability, and infiltration of inflammatory cells, which in turn trigger the clinical symptoms of asthma [16][25]. The FeNO in asthma patients is mainly from airway epithelial cells on the bronchial wall, T cells, and macrophages. Owing to the stimulation of inflammatory mediators (interferon-gamma (IFN-y), tumour necrosis factor-Q (TNF-Q), interleukin (IL)-lB, IL-4, etc.), the concentration of inducible nitric oxide synthase (iNOS) increases, the NO content increases, and the FeNO level increases [26]. Both allergens and FeNO are involved in the excitation process of the inflammatory response.

In this study, the outpatient medical record data of 496 adult asthma patients at Guizhou Provincial People's Hospital between August 2023 and December 2023 were analysed. Analysis of patient general information revealed that FeNO was not affected by age, sex, or common comorbidities. Since this was a retrospective study, the real-time detailed conditions of the patients could not be evaluated, and patient follow-up was relatively difficult because the patients were outpatients.

Smoking can decrease FeNO, as also shown by Louie et al. in 2013 in patients with overlap syndrome, and the reasons are as follows: smoking produces a relatively high concentration of NO, which in turn inhibits the secretion of NOS in the cells, thereby reducing the formation of endogenous NO; the stress response in smoking patients can consume NO and reduce FeNO levels; and smoking leads to the shedding of necrotic respiratory epithelial cells, promotes the production of noneosinophils, and indirectly reduces NOS levels [27][28][29].

In terms of pulmonary function, FEV1%, FVC, and FEV1/FVC are all clinical indicators that reflect the degree of airway limitation and airway resistance, but controversy exists regarding the correlation between pulmonary function and airway inflammation. This study showed that there was no significant correlation between FeNO and pulmonary function (FEV1%, FVC, and FEV1/FVC), which is consistent with the results of the studies by Strunk RC et al. [30-33]. The pulmonary function of patients is usually affected by age, smoking, disease progression and other factors. However, the 496 patients in this study had a large age range and different disease histories, which may have affected the results of this study. In this study, FeNO, bronchodilation, and bronchial challenge tests were performed; 117 patients had positive bronchodilation or bronchial challenge test results; and the specificity of the tests was high. Future studies could include larger patient samples.

Some scholars believe that the eosinophilic cationic protein (ECP), major basic protein (MBP), leukotrienes (hTs), and platelet-active factor (PAF) produced by eosinophils play important roles in the pathogenesis of asthma [34]. The peripheral blood eosinophil count reflects systemic eosinophilic inflammation, but it may have low sensitivity for diagnosing airway eosinophilic inflammation, and its correlation with the FeNO level is still under study [38]. In this study, the peripheral blood EOS% was 4.483 ± 1.716%, there was a significantly positive correlation between the FeNO concentration and the EOS% ($P<0.0001$, $r=0.548$), and this result was similar to that reported by Malinovschi A et al. in 2013, who studied the correlation between the peripheral blood eosinophil count and the FeNO level in 12,408 people aged 6-80 years. EOS% is affected by the eosinophil count, which indirectly affects the FeNO level. However, Malinovschi A et al. reported that the correlation coefficient (r) was low and proposed that FeNO and the peripheral blood eosinophil count may reflect two different inflammatory mechanisms [35]. Large-sample studies are still needed to corroborate the correlations of FeNO level and EOS%.

In this study, dust mites were the allergens for 66 patients, and the measured FeNO level was (67.36±49.88) ppb; pollens were the allergens for 53 patients, and the measured FeNO level was (44.18±19.63) ppb; COFs were the allergens for 41 patients, and the measured FeNO level was (38.92 ± 15.75) ppb, and in patients with allergic reactions to multiple allergens, the measured FeNO level was (99.22 ± 98.3) ppb. Statistical analysis revealed that there was a significant difference ($P<0.0001$), which is consistent with previous reports (Simpson et al., 1999, Janson et al., 2005, and Sordillo et al., 2011) [36][37][38]. This study has several limitations. First, this study had a retrospective design, and the patients were outpatients. Second, for most patients included in this study, sIgE evaluations for allergens other than inhaled allergens and skin prick tests for HDMs were not performed, and the completeness of the test data was unsatisfactory, creating human errors. To further explore correlation analyses between sIgE and FeNO, the sample size should be increased, and effective grouping should be performed according to established guidelines [36].

Conclusions

The measured FeNO level was not affected by sex, age, common comorbidities, peripheral blood parameters (leukocyte count and total IgE), or pulmonary function indicators (FEV1%, FVC, and FEV1/FVC) but was significantly positively correlated with EOS%. The measured FeNO level in smoking patients was lower than that in nonsmokers, and the measured FeNO level in asthma patients with dust mites as the allergen was greater than that of patients with pollen and COFs as allergens. In addition, the measured FeNO level of asthma patients with allergic reactions to multiple allergens was greater than that of patients with allergic reactions to a single allergen.

Ethics Approval

Ethical approval was granted from the ethics committee of Guizhou Provincial People's Hospital.

Patient Consent for Publication

Before enrollment, all patients were informed fully and written informed consent was obtained from the patients for the publication of clinical information.

Availability of Data and Material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicting Interest

The authors declare that they have no conflict of interests.

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