A Multicenter Registry Study Examining the Efficacy of Specific Immunotherapy Guided by Component-Resolved Diagnosis for Dust Mite Allergens in Chinese Pediatric Patients With Rhinitis and/or Asthma（Explorer Study）

Research Proposal

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Research Department	Pulmonology Department
Project Source	Investigator-Initiated Research

1. Research Background

Allergic Rhinitis (AR) is an IgE-mediated inflammation of the nasal mucosa and one of the most common allergic diseases in children. Its global prevalence continues to rise, particularly in industrialized nations and rapidly urbanizing areas, affecting approximately 10%-40% of the population worldwide (reaching up to 50% in some regions). AR significantly impairs the quality of life in affected children and frequently coexists with other conditions such as asthma, establishing it as one of the most prevalent chronic diseases [1]. Asthma is the most common chronic inflammatory airway disease globally, affecting about 10-15% of children worldwide [2] and ranking as the second leading cause of death among chronic respiratory diseases. Allergic Asthma (AA) is the most predominant subtype in children (accounting for 80% of childhood asthma cases), characterized by airway inflammation and structural remodeling. This leads to airway hyperresponsiveness and reversible airflow limitation, manifesting as dyspnea, wheezing, and coughing, often accompanied by conditions like AR, and severely impacting quality of life [3]. Although the implementation of asthma management and prevention strategies has somewhat reduced prevalence and mortality rates, the absolute number of asthma cases is still rising due to population growth [4].

House Dust Mites (HDM) are among the most significant indoor allergens worldwide, closely linked to allergic diseases such as AR, AA, and atopic dermatitis. The primary HDM species are Dermatophagoides pteronyssinus and Dermatophagoides farinae, which are widely distributed in human living environments. HDM are complex mixtures composed of various proteins, referred to as "components." As of 2025, the WHO/IUIS has officially named 39 HDM allergen components (Der p/f numbering system). Among these, Der p 1, Der p 2, Der f 1, Der f 2, and Der p 23 are considered major components, serving as core sensitizing allergens. Most HDM-allergic children (>50%) are sensitive to these major components, which are strongly correlated with clinical symptoms (e.g., asthma, rhinitis) and are primary targets for specific immunotherapy [5, 6]. Intermediate components exhibit sensitization rates of 25–50% and may become predominant sensitizers in specific populations or regions. They can potentially exacerbate allergic symptoms, and some are associated with cross-reactivity, but they are not core

therapeutic targets. Minor components have sensitization rates <25%; they are often cross-reactive proteins that do not directly cause HDM allergy symptoms or only sensitize individuals in specific populations. Furthermore, the sensitization characteristics of HDM components vary significantly across different geographical regions within China [7]. Component-Resolved Diagnostics (CRD) is a more precise allergy diagnostic method. It uses natural or recombinant single-component allergens to identify the specific molecules causing the allergy. By detecting specific IgE (sIgE) antibodies against individual allergen components, CRD helps distinguish between genuine sensitization and cross-reactivity, such as differentiating co-sensitization (where specific components from two or more different allergen sources are recognized by distinct sIgE antibodies) from cross-sensitization (where structurally similar allergen components from multiple sources are recognized by the same sIgE antibodies), thereby improving diagnostic accuracy [5].

Allergen Immunotherapy (AIT), also known as desensitization therapy, is a causative treatment for allergic diseases. It works by gradually exposing the patient to the allergen, inducing immune tolerance, and thereby reducing or eliminating allergic symptoms. AIT is indicated for patients with clearly identified and unavoidable allergens (e.g., dust mites, pollen), those with poor symptom control on pharmacotherapy or requiring long-term medication, and those unwilling to use long-term medication. AIT is currently the only treatment modality with the potential to alter the natural course of allergic diseases, although it requires careful patient selection and long-term adherence [8]. Prior to initiating AIT, the causative allergen must be clearly identified through skin prick tests or sIgE detection. When indications are met, AIT can significantly enhance quality of life and reduce long-term complications [9].

Preliminary studies by our group have revealed that most children are sensitized to multiple HDM components simultaneously, including not only major components but also intermediate and minor ones. Current guidelines do not provide clear recommendations on whether specific immunotherapy should be administered to children sensitized exclusively to intermediate and minor components. Furthermore, there is a lack of national data on the efficacy and long-term follow-up outcomes of specific immunotherapy in children with HDM allergy.

This study aims to systematically collect and analyze real-world data from HDM-positive children undergoing AIT nationwide. We will evaluate the differential

efficacy and long-term benefits of AIT among children with different sensitization profiles (major, intermediate, and minor components). The ultimate goal is to provide evidence-based support and decision-making guidance for the development of precise and personalized clinical protocols for HDM AIT.

2. Research Objectives

To observe the differences in efficacy of AIT among children with different sensitization profiles through CRD for house dust mites in children with AR with or without concomitant AA. The study will focus on evaluating the clinical benefits of AIT specifically for children sensitized to intermediate and minor components, thereby providing an evidence-based foundation for establishing precise AIT strategies guided by CRD.

3. Research Methods

3.1 This study is a multicenter observational registry study, with a planned enrollment of 1,000 cases. Our institution serves as the lead research unit, with multiple clinical centers across the country participating. All children meeting the inclusion and exclusion criteria will receive AIT for a full 3 years. Each research center will recruit eligible subjects according to the inclusion and exclusion criteria and obtain signed informed consent forms (applicable to prospective studies). Relevant clinical information will be collected according to the prospective research plan. This registry study does not involve any intervention; it only collects relevant clinical information. All diagnosis and treatment decisions are made by the clinicians. Clinicians may provide appropriate treatment based on the specific conditions of the children.

3.2 Sample Size Estimation

The planned enrollment is 1,000 cases, with 50-100 cases per center. Descriptive and exploratory analyses will be performed on the data; no statistical hypotheses have been formulated. In general, quantitative variables will be summarized using the following descriptive statistics: number of cases, mean, standard deviation, median, Q1, Q3, minimum, and maximum. Qualitative variables will be summarized by the

number and percentage of children in each category. This study will calculate changes in VAS scores and medication scores before and after treatment, as well as the incidence of adverse reactions, rates of new sensitization, rates of new-onset asthma, and treatment adherence. Differences among subgroups with different component sensitization profiles will be compared, and related influencing factors will be analyzed.

4. Study Subjects

This study plans to enroll children aged 5 to 18 years who undergo subcutaneous specific immunotherapy with dual-mite (HDM) preparations, have allergen testing indicating HDM allergy, and are recruited from multiple clinical research centers nationwide during the period from October 2025 to October 2028.

4.1 Inclusion Criteria (All of the following must be met)

(1) Age: 5 years $\leq$ age < 18 years.

(2) 1) Allergic rhinitis induced by Dermatophagoides pteronyssinus and/or Dermatophagoides farinae; OR 2) Serum specific IgE $\geq$ 0.70 kU/L (for Dermatophagoides pteronyssinus and/or Dermatophagoides farinae).

(3) Children meeting criterion (2) must undergo allergen component testing.

(4) If accompanied by bronchial asthma, asthma must be diagnosed according to the guidelines for the diagnosis and prevention of bronchial asthma in children (2025 Edition), and asthma symptoms must be confirmed to be well-controlled.

(5) Receiving subcutaneous AIT with dual-mite (HDM) preparations.

4.2 Exclusion Criteria (Meeting any one of the following criteria leads to exclusion)

(1) In the investigator's judgment, the subject and/or parents/legal guardians are unable to understand and comply with the study requirements, including children and their parents/legal guardians with cognitive impairments, mental illnesses, or difficulty adhering to long-term treatment or recognizing adverse reactions.

(2) Children with severe or uncontrolled asthma (FEV1 < 70% predicted value) or with irreversible airflow obstruction.

(3) Children using beta-blockers or angiotensin-converting enzyme inhibitors (ACEIs).

(4) Children with severe autoimmune diseases or immunodeficiencies, including AIDS, inflammatory bowel disease, etc., or those using immunosuppressants.

(5) Children with severe cardiovascular diseases or malignancies.

(6) Children with incomplete clinical data.

4.3 Withdrawal Criteria

Subjects may voluntarily withdraw from this study at any time for any reason. Children will also be withdrawn from the study if any of the following occur:

(1) The subject and/or parents/legal guardians fail to follow the project team's guidance, indicating poor compliance.

(2) The study physician determines that continuing the study would pose unnecessary harm.

(3) The study is terminated by the Ethics Committee or a regulatory authority.

5. Study Procedures

5.1 Screening Phase

(1) Children and their parents/guardians are informed about the study and agree to participate, signing the informed consent form.

(2) Children are assigned a study number, and all information is de-identified.

(3) Collection of medical history, including personal basic information, medical history, primary symptoms, and clinical diagnosis.

(4) Verification that the child meets the inclusion and exclusion criteria.

(5) Assessments

① Subject Characteristics Assessment

a. Demographic data;

b. Allergy history;

c. Comorbidity status;

② Baseline Biological Indicators

Detection using immunoblotting and component microfluidic chip assays: Intra-assay coefficient of variation (CV) for the same reagent lot and chip lot <10%; inter-assay CV for the same reagent and chip lot tested at different time points <15%;

③ Exclusion of Confounding Factors

a. Pre-treatment influences: Excluding children currently receiving or having received anti-IgE immunotherapy within the past six months;

④ Sample Suitability Validation

Serum must avoid hemolysis interference (hemoglobin ≤ 0.5 g/dL). Retain serum samples (stored at -80°C).

(6) Eligible subjects are enrolled according to the inclusion/exclusion criteria. Serum specific IgE is detected by Zhejiang DIA-UP using the immunoblotting method. A 2ml blood sample is collected in a yellow-top tube, centrifuged at 3000 rpm for 8 minutes, and the upper serum layer is aliquoted into labeled EP tubes. Serological testing is performed using the allergen component-resolved diagnostics multiplex assay (microfluidic chip method) from Hyrisky Bio (Xiamen).

5.2 Visit Phase

(1) Enrolled children receive AIT using a dual-mite allergen preparation (NHD, Dermatophagoides farinae/Dermatophagoides pteronyssinus: 50%/50%). This registry study does not involve any intervention; it only collects relevant clinical information. The collection of clinical information does not involve any identifiable private information of the children (i.e., information is de-identified). All treatment decisions are made by the clinicians. Clinicians provide the optimal treatment plan for each child based on the current AIT treatment standards and relevant guidelines of their respective hospitals. No pre-set grouping is designated for this registry study.

(2) Dynamic Visit Schedule

Visit	Time Window	Testing Content	Clinical Assessment
V1	Baseline (Month 0)	FeNO/nNO, Eosinophil percentage and count, sIgE, Components (sIgE/sIgG4), SPT, Lung function	VAS, Medication score, ACT/CACT, Quality of life assessment, Adverse reactions
V2	Month 3	FeNO/nNO, Lung function	VAS, Medication score, ACT/CACT, Quality of life assessment, Adverse reactions
V3	Month 6	FeNO/nNO, Lung function	VAS, Medication score, ACT/CACT, Quality of life assessment, Adverse reactions

V4	Month 12	FeNO/nNO, Eosinophil percentage and count, sIgE, Components (sIgE/sIgG4), SPT, Lung function	VAS, Medication score, ACT/CACT, Quality of life assessment, Adverse reactions
V5	Month 24	FeNO/nNO, Eosinophil percentage and count, sIgE, Components (sIgE/sIgG4), Lung function	VAS, Medication score, ACT/CACT, Quality of life assessment, Adverse reactions
V6	Month 36	FeNO/nNO, Eosinophil percentage and count, sIgE, Components (sIgE/sIgG4), SPT, Lung function	VAS, Medication score, ACT/CACT, Quality of life assessment, Adverse reactions

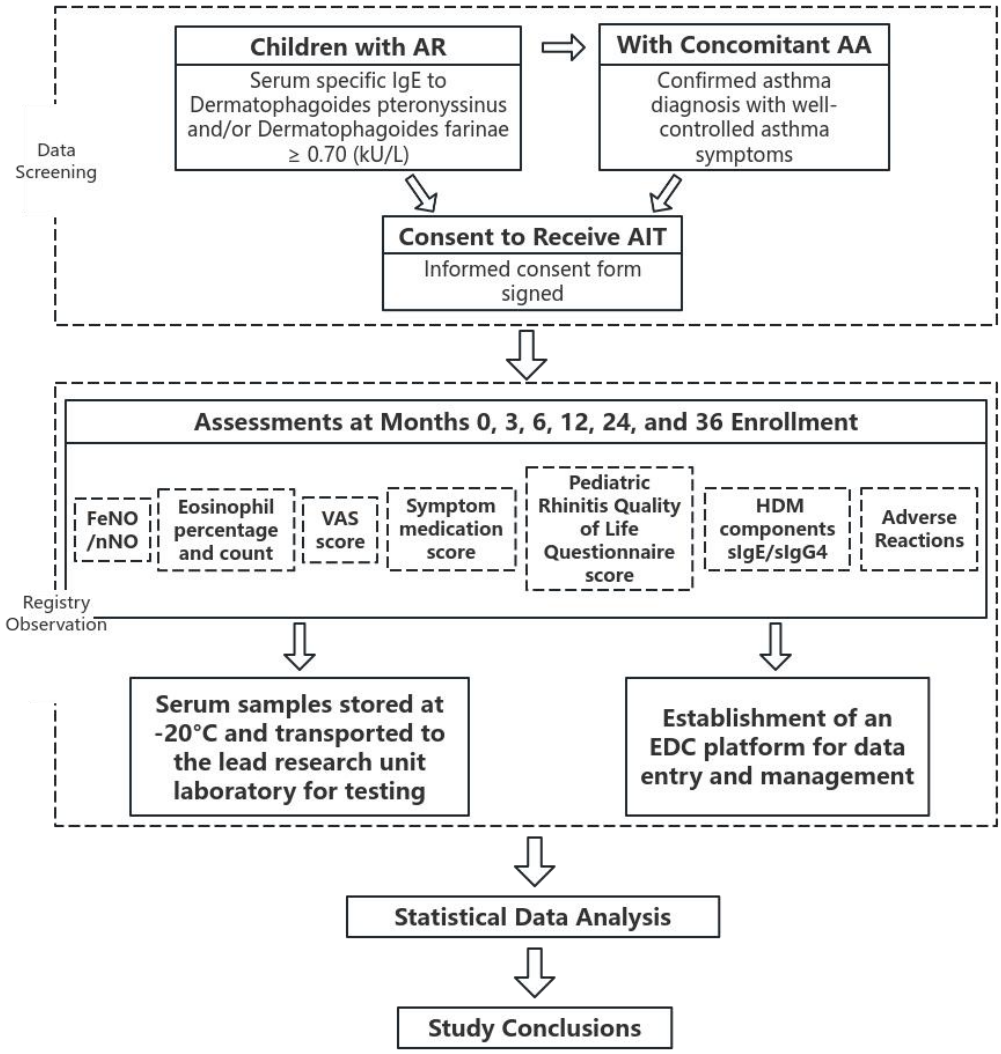
All children are required to undergo VAS and Allergic Rhinitis Quality of Life assessments. Children with rhinitis accompanied by asthma additionally require ACT/CACT assessments. Lung function test results, if completed, are collected according to the clinician's decision.
Abbreviations: FeNO/nNO:Fractional Exhaled Nitric Oxide / Nasal Nitric Oxide; SPT: Skin Prick Test; Components: Include major components (Der p 1, Der p 2, Der p 23, Der f 1, Der f 2), intermediate components (Der p 5, Der p 7, Der p 21), and minor components (Der p 10); VAS: Visual Analog Scale; Medication score: Symptom Medication Score; Quality of life assessment: Allergic Rhinitis Quality of Life; ACT/CACT: Asthma Control Test / Childhood Asthma Control Test; sIgE: Specific Immunoglobulin E; sIgG4: Specific Immunoglobulin G4;

5.3 Data Compilation and Analysis

Data from all participating centers will be compiled and statistically analyzed. Efficacy will be evaluated by grouping children according to different HDM component sensitization patterns. The following parameters will be assessed: changes from baseline in VAS scores and medication scores after 1, 2, and 3 years of AIT in children with different sensitization patterns; incidence and severity of adverse

reactions; rates of new sensitization and new-onset asthma; and treatment adherence rates. Valuable conclusions will be derived.

5.4 Flowchart



6. Evaluation Indicators

6.1 Efficacy Assessment

Assessment Time (Months)	Primary Indicators	Secondary Indicators
0	VAS, Medication	ACT/CACT, Quality of life assessment, sIgE,

	score		Components (sIgE/sIgG4), FeNO/nNO, Eosinophil percentage and count, Adverse reactions, SPT, Lung function
3, 6	VAS, score	Medication	ACT/CACT, Quality of life assessment, FeNO/nNO, Adverse reactions, Lung function
12, 24, 36	VAS, score	Medication	ACT/CACT, Quality of life assessment, sIgE, sIgG4, Components (sIgE/sIgG4), FeNO/nNO, Eosinophil percentage and count, SPT, Adverse reactions, SPT, Lung function

All children are required to undergo assessment of primary indicators. Children with rhinitis accompanied by asthma additionally require ACT/CACT assessment. Secondary indicators are collected based on the clinician's decision for children who complete the relevant examinations. Lung function test results are collected for children with rhinitis accompanied by asthma.
Abbreviations: VAS: Visual Analog Scale; Medication score: Symptom Medication Score; ACT/CACT: Asthma Control Test / Childhood Asthma Control Test; Quality of life assessment: Allergic Rhinitis Quality of Life Assessment; Components: Include major components (Der p 1, Der p 2, Der p 23, Der f 1, Der f 2), intermediate components (Der p 5, Der p 7, Der p 21), and minor components (Der p 10); SPT: Skin Prick Test; FeNO/nNO: Fractional Exhaled Nitric Oxide / Nasal Nitric Oxide; sIgE: Specific Immunoglobulin E; sIgG4: Specific Immunoglobulin G4;

6.2 Safety Assessment

(1) Local Adverse Reactions: Redness, induration, pruritus, pain at the injection site; Others: Local lymph node enlargement, gastrointestinal discomfort (nausea, abdominal pain).

(2) Systemic Adverse Reactions (Graded by Severity)

Grade	Symptoms	Management
Mild	Urticaria, rhinitis, mild asthma (FEV_1 > 70% predicted)	Oral antihistamines, nebulization, observation
Moderate	Widespread urticaria, throat tightness, moderate asthma (FEV_1 60-70% predicted)	Intramuscular epinephrine (0.3-0.5 mg), corticosteroids

Severe	Anaphylactic shock, asphyxia (FEV_1 < 60% predicted), hypotension	Immediate intramuscular epinephrine (0.5 mg), transfer to emergency care

7. Risk Prevention and Management

7.1 Data Privacy Risk: The study process involves collecting a large amount of personal information, posing a risk of information leakage. Strict data protection measures must be implemented to ensure the security and privacy of this information. First, data will be de-identified to reduce the risk of personal privacy disclosure. Second, data access permissions will be restricted to minimize the possibility of information leakage.

7.2 Result Interpretation Risk: The results of scientific research require careful interpretation to avoid over-interpretation or misleading conclusions, while also paying attention to personal privacy protection. All personnel involved in the study will receive professional training to ensure they can correctly execute the experimental procedures.

7.3 Adverse Reaction Risk of AIT: The children enrolled in this study will all use immunotherapy preparations that are widely used in current clinical practice. The researchers will primarily provide clinical guidance to the children, instructing them on desensitization treatment and medication use, so the potential clinical risks are relatively low. Furthermore, if any discomfort, change in condition, or unexpected situation occurs during the study period, the researchers will promptly make a judgment and provide appropriate medical advice or treatment to ensure the child's safety.

Adverse Reaction Prevention Measures:

① Prophylactic Medication: Consider administering antihistamines or corticosteroids in advance;

② Post-injection Observation: Observe for 30 minutes after injection;

③ Emergency Medication: Children with a history of systemic reactions should carry an epinephrine auto-injector;

④ Symptom Recording: Record symptoms to assist the physician in adjusting the treatment plan.

Adverse Reaction Management Procedure:

① Immediate Management: Assess the severity of the adverse reaction. For local itching and redness/swelling, apply ice compresses. For children with mild systemic reactions, provide observation and antihistamines, etc. For children with moderate systemic reactions, administer intramuscular epinephrine and corticosteroids. For children with severe systemic reactions, administer intramuscular epinephrine, provide oxygen, and place in a supine position. For more severe reactions or cases that do not improve, transfer the child to emergency care.

② Reporting: Complete an adverse event form and report to the hospital's drug safety department.

③ Treatment Plan Adjustment: For children with mild to moderate reactions, consider fractionated dosing. For children with severe reactions, suspend AIT and re-evaluate the indications.

8. Adverse Event Recording and Reporting

During the study period, researchers should closely monitor the occurrence of adverse events (AEs). In the event of an adverse event (including significant adverse events), the researcher should analyze the cause, make a judgment, and follow up, observe, and record the time of onset, symptoms, severity, duration, management measures, and outcome of the AE, as well as assess its correlation with the study. All relevant medical documents should be recorded in the source documents, including laboratory test result reports.

In the event of a serious adverse event (SAE), immediate measures must be taken to protect the subject. The researcher must promptly complete the "Serious Adverse Event Report Form" and report it to the Ethics Committee within 24 hours. Subjects who experience a serious adverse event should be followed up and documented until the condition resolves or until death.

9. Data Management

Completion of Case Report Forms (CRFs): Case Report Forms will be completed by the clinical investigators.

Data Entry and Modification: Data entry and management will be the responsibility of Yujia Xiao and Shuxian Li. Data entry and management will be performed using an EDC platform. To ensure data accuracy, two data administrators will independently perform double data entry and verification.

Database Lock: After confirming that the established database is error-free, the principal investigator and statistical analysts will lock the database.

10. Statistical Analysis Methods

This study will conduct descriptive and exploratory analyses of the data without formulating any statistical hypotheses. All statistical analyses will be performed using SPSS 23.0 software. Count data will be presented as percentages (%). Comparisons between two groups will be analyzed using the Chi-square test or Fisher's exact test, as appropriate. Measurement data not following a normal distribution will be expressed as median (interquartile range). Comparisons between two independent samples will be conducted using the Wilcoxon rank-sum test. Generalized estimating equations (GEE) will be employed to evaluate the efficacy of different treatment regimens. A P-value < 0.05 will be considered statistically significant.

The following outcomes will be calculated: changes in VAS scores and medication scores from baseline, changes in sIgG4/sIgE ratios, rates of new sensitization, incidence of adverse reactions, and treatment adherence. Differences among subgroups stratified by component sensitization profiles will be compared, and associated influencing factors will be analyzed.

11. Dissemination of Research Findings

The findings of this research will be disseminated in the form of comprehensive summary reports and peer-reviewed publications (papers).

12. Ethical Considerations

12.1 Risks and Benefits

This study is a multicenter observational registry study. As an observational (non-interventional) study, it involves only the collection of relevant clinical information, with all diagnostic and therapeutic decisions resting solely with the attending clinicians. Clinicians will provide appropriate treatment based on each child's specific condition. The potential risk to subjects is confined exclusively to matters of privacy protection.

Participation in this study may help clarify the specific component sensitization profile of the child's house dust mite allergy, which could potentially inform decisions regarding immunotherapy, although this is not guaranteed. Furthermore, the information generated by this study will contribute valuable insights into diseases associated with house dust mite allergy, such as allergic rhinitis and asthma, potentially benefiting future patients suffering from similar conditions.

12.2 Protection of Subject Privacy

Access to subjects' personal medical records will be restricted solely to the researchers involved in this study. All researchers will sign confidentiality agreements or investigator statements that explicitly include provisions for maintaining confidentiality. The Ethics Committee and relevant regulatory authorities have the right to access clinical trial records. Data processing will employ anonymization techniques, omitting any information that could identify individual subjects. Publication of research results will not disclose subjects' personal information. Subjects' medical records will be securely stored in the archives of the Children's Hospital, Zhejiang University School of Medicine, under strict security and confidentiality protocols.

12.3 Informed Consent and Signing of the Informed Consent Form

Prior to the initiation of the clinical study, the investigator must provide the subject and their legal guardian with comprehensive information regarding the clinical study, including its nature, purpose, potential benefits, and risks, ensuring full comprehension by both parties.

For subjects under 8 years of age who possess sufficient understanding and the capacity to express their views, the child's willingness to participate must be sought, in addition to obtaining signed informed consent from their legal guardian.

For subjects aged 8 years and older, signed informed consent is required from both the legal guardian and the subject themselves.

The clinical study may only commence after the informed consent form has been duly signed.

Detailed contact information, including address and telephone number, will be obtained from each patient. Conversely, the physician will provide their own contact information to the patient, ensuring that the patient can reach the researcher at any time if needed.

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