

## CASE REPORT

# Food-specific IgG Antibody–guided Elimination Diets Followed by Resolution of Asthma Symptoms and Reduction in Pharmacological Interventions in Two Patients: A Case Report

两位患者食品特异性 IgG 抗体导向的排斥饮食后解决哮喘症状且减少药物干预：一份病例报告

Dietas de exclusión de alimentos específicos guiados por anticuerpos IgG seguidas de resolución de síntomas de asma y reducción de intervenciones farmacológicas en dos pacientes: Informe de un caso

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## ABSTRACT

Asthma is one of the most common causes of office visits in the primary care and emergency care settings. Individuals are often able to maintain symptomatic control with long-term pharmacological therapy. Exacerbations of asthma commonly occur due to exposure to triggers such as viruses, pollutants, and allergens. While it is widely accepted that exposure to immunoglobulin E food allergens can exacerbate asthma symptoms, there is little evidence examining delayed immunoglobulin G-mediated reactions to food. Here we present two clinical cases of individuals who experienced a reduction in asthma symptoms, decreased dependence on pharmacological therapies, and increased quality of life by eliminating foods that demonstrated reactivity to immunoglobulin G levels identified through serum testing.

## 摘要

哮喘是初级医疗机构和急诊医疗机构的最常见就诊疾病之一。使用长期药物治疗的患者通常能够维持症状的控制。哮喘通常会在接触病毒、污染物和过敏原等触发因素后加重。虽然人们普遍认为接触免疫球蛋白 E 食物类过敏原可加重哮喘症状，但极少有证据对免疫球蛋白 G 介导的迟发型食物过敏反应进行分析。本文介绍了两例临床病例，他们通过杜绝食用对免疫球蛋白 G 水平表现出反应性的食物（由血清测试鉴定），实现了哮喘症状的减轻，降低了对药物治疗的依赖，并提高了生活质量。

## SINOPSIS

El asma es una de las causas más frecuentes de visita a la consulta del médico de atención primaria y a urgencias. A menudo los pacientes pueden controlar sus síntomas

con tratamiento farmacológico de larga duración. Las exacerbaciones del asma ocurren por lo general debido a exposición a desencadenantes como virus, contaminantes y alérgenos. Si bien se acepta por lo general que la exposición a alérgenos alimentarios que causan la producción de inmunoglobulina E puede exacerbar los síntomas de asma, hay poca evidencia al examinar las reacciones retardadas a alimentos mediadas por inmunoglobulina G. Presentamos aquí dos casos clínicos de individuos que experimentaron una reducción de los síntomas de asma, disminución en su dependencia a tratamientos farmacológicos y una mejora en su calidad de vida eliminando alimentos que demostraron reactividad a los niveles de inmunoglobulina G identificados mediante análisis de suero.

## INTRODUCTION

Asthma, a common chronic inflammatory disease of the airways is characterized by a reduction in airway size due to smooth muscle constriction, edema of the airways, and mucus hypersecretion.<sup>1</sup> These changes lead to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. This inflammation can potentiate the preexisting airway hyperresponsiveness to stimuli such as pollutants, allergens, and viruses.<sup>2</sup>

Atopy is a major hereditary risk factor for the development of asthma. Atopic individuals have heightened immune responses to foreign antigens that tend towards an antigen-specific immunoglobulin E (IgE) allergic response.<sup>3</sup> IgE food allergens trig-

ger an immediate inflammatory reaction characterized by angioedema, urticaria, asthma, and/or anaphylaxis. The presence of IgE antibodies in the serum directed toward foods is not diagnostic of allergy until confirmation through challenge testing.<sup>4</sup> Asthmatics with food allergies are more likely to experience severe exacerbations of asthma.<sup>5</sup> Patients and clinicians are aware that delayed-acting food allergens may exist outside of IgE antibody reactions. However, accurate and clinically effective laboratory testing for non-IgE food allergens remains elusive and is not widely used. Laboratory testing for immunoglobulin G (IgG) and subfraction IgG<sub>4</sub> food antibodies is becoming increasingly available to the public. However, research on IgG and food allergens

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remains controversial and inconclusive.<sup>6-9</sup>

In this case report, we utilized an enzyme-linked immunosorbent assay (ELISA) for IgG antibody assessment (US BioTek Laboratories, Shoreline, Washington) on 2 patients with asthma. This serum test measures total IgG<sub>1</sub>-IgG<sub>4</sub> against 96 foods and reports them on a semi-quantitative scale ranging from 0 (“no reactivity”) to IV (“extremely high-reactivity”). Many physicians interpret ELISA IgG results differently and use varying treatment protocols for duration and extent of food elimination. For the patients described here, we recommended a trial period of complete avoidance of potential food allergens while monitoring for any symptomatic changes. Based on clinical experiences in utilizing the IgG antibody assessments for the treatment of asthma, we determined the classes of food to eliminate. The patients understood that the results of the ELISA test were not meant to indicate anaphylactic allergens but were meant to provide treatment considerations. In the cases presented, any changes made to medications were relayed to the prescribing physicians through the patients who maintained regular follow-up exams.

arteries was noted. However pulmonary hypertension was ruled out after further cardiac and pulmonary evaluation. Her asthma medications, fluticasone-salmeterol and albuterol, were prescribed by her primary care physician.

At the first visit, she reported her asthma severity as 9/10 due to its progressive impact on her quality of life. She had audible wheezing; however she did not appear in acute distress. She reported recent episodes of low pulse oximetry at 86% to 87% at home while her pulse oximetry in the office was 95% (Table 1). At this visit, an ELISA test was ordered. Pending the results, she was instructed to remove wheat, dairy, and eggs from her diet due to the physician’s experience that many asthmatics’ ELISA results indicated high reactivity to these foods.

### OUTCOMES (PATIENT A)

At the 21-day follow-up, the patient reported compliance with our dietary recommendations and improvements in breathing and quality of life severity score (Figure). For the first time in years, she was able to hike 1.5 miles without the use of her rescue inhaler

**Table 1** Medication and Symptom Chart for Patients A and B<sup>a</sup>

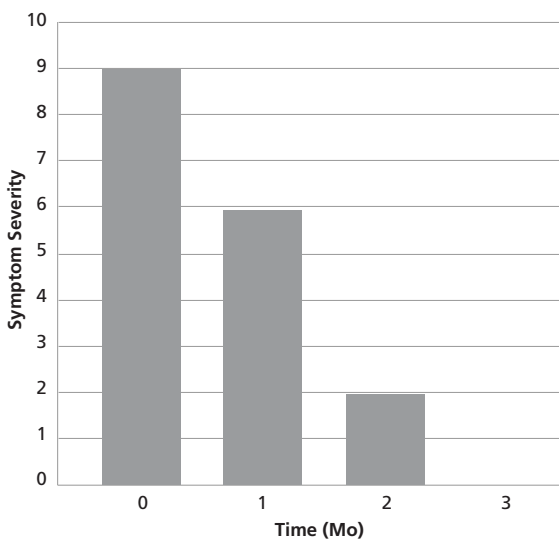
A. Medication	Intake	21 d	49 d	91 d
Fluticasone-salmeterol 250/50	Twice daily	Twice daily	Once daily	None
Albuterol	Twice daily	Once	None	Used twice while in cold weather
B.	Intake	21 d	49 d	91 d
<b>Asthma Attack Frequency</b>	2-3 attacks per wk	1 attack since last visit	None since last visit	None since last visit
<b>Energy</b>	6/10	8/10	Not reported	Not reported
<b>Pulse Oxygen</b>	86% to 95%	88% to 94%	95%	96%
<b>Physical Exam</b>	Audible wheezing	Lungs clear	Lungs clear	Lungs clear

<sup>a</sup> Frequency of asthma medication dosing, asthma symptoms, and characteristics of physical exam and history at the time of intake and subsequent visits.

### PRESENTING CONCERNS AND INTERVENTION (PATIENT A)

The patient was a 61-year-old, 160-cm, 76.2-kg white female who was diagnosed with asthma at the age of 16 years. Known allergens included penicillin, sulfa drugs, and aspirin. She reported a worsening of asthma symptoms over the 18 months prior to her initial visit. In particular, she was experiencing increased dyspnea with exertion and decreased quality of life.

In the 2 years prior to seeing us, overnight oximetry studies indicated low oxygen saturation of 81%, with total time below 88% at 86 minutes. We were unaware of whether she received a formal diagnosis of sleep apnea. A 6-minute walk assessment conducted by her pulmonologist revealed 92% oxygen saturation at rest on room air, which decreased to 88% while walking 500 meters and stabilized to 95% 2 minutes post-walking with a Borg scale of 3/10. Due to her fluctuating pulse oximetry on light exertion, supplemental oxygen was recommended by her pulmonologist. On chest radiographs a prominence of her pulmonary



**Figure** Asthma symptom severity for Patient A. Patient self-reported severity of asthma symptoms at intake (month 0) and at subsequent visits. Scale is from 0 to 10 with 10 being the most severe.

and had lost 4.5 kg of weight. Her asthma attack frequency decreased to one episode since the last visit. She attributed the one attack to accidentally consuming dairy. She was instructed to eliminate class III and IV-specific IgG offending foods based on her ELISA test results (Table 2). These foods included wheat, dairy, and eggs, which we had initially suggested to eliminate from her diet.

**Table 2** Enzyme-linked Immunosorbent Assay (ELISA) Results for IgG Food Allergens for Patient A<sup>a</sup>

<b>Class III-specific IgG</b>	Casein, cottage cheese, hazelnut, milk, yogurt
<b>Class IV-specific IgG</b>	Almond, chicken egg white, chicken egg yolk, coffee bean, cranberry, duck egg whole, rye, sesame seed, spelt, wheat gliadin, wheat gluten, whey, whole wheat

<sup>a</sup> The ELISA report measured all 4 subclasses of IgG against 96 foods. The results are reported on a semi-quantitative scale ranging between 0 (no reactivity) to IV (extremely high reactivity). The class III and IV reactive foods for Patient A are shown.

At the 49-day follow-up, she reported strict adherence to our dietary protocol. She experienced a cessation of asthma attacks as well as early morning and nighttime coughing since the last visit (Table 3). She had contracted an upper respiratory infection, which in the past would have triggered an asthma exacerbation. However, for the first time in years, she could clear her sputum easily and did not need increased pharmacological interventions. She reported no need for her albuterol inhaler since the last visit (Table 1). Her asthma symptom severity continued to decrease (Figure) and she lost an additional 2.2 kg. We recommended that she continue following the elimination diet and advised her to decrease her fluticasone-salmeterol dosage by half over a period of 10 days. If she was feeling well, she was recommended to discontinue her medication.

At the next visit 6 weeks later, she reported only one asthma attack since the previous visit and her energy level continued to increase (Table 2). She used her albuterol inhaler preventively twice prior to going outside while vacationing in a very cold climate.

**PRESENTING CONCERNS AND INTERVENTION (PATIENT B)**

The patient was a 12-year-old, 157-cm, 45-kg white male who initially presented to the clinic for asthma.

Known allergens included grass and pollen diagnosed with skin prick testing. His primary care physician prescribed montelukast sodium, fluticasone-salmeterol, albuterol and cetirizine hydrochloride to manage his asthma and allergies. At the initial visit, an ELISA test was ordered and results indicated high IgG reactivity to eggs as well as mild to severe reactivity to milk, cheese, wheat, yeast, citrus, casein, and corn (Table 2). He and his parents were instructed to remove these foods from his diet.

**OUTCOMES (PATIENT B)**

At the 10-week visit, the patient reported a decreased need for albuterol, fewer episodes of nocturnal dyspnea, and less abdominal pain (Table 3). At the 19-week visit, he developed an upper respiratory tract infection and began dosing his medications as recommended by his primary care physician to prevent an acute exacerbation of his asthma (Table 3). The patient felt frustrated with the dietary protocol and began occasional ingestion of reactive foods. A daily natural antihistamine (vitamin C 150 mg, quercetin 200 mg, stinging nettles leaf 200 mg, bromelain 50 mg, and n-acetyl-L-cysteine 24 mg) was added to his protocol, and he was encouraged to continue following the allergy elimination diet.

At the 23-week visit, in order to improve compliance, his parents reported implementing 1 “cheat day” a week, during which he could consume restricted foods. On those days, he would typically consume pizza and noticed wheezing before bed. At the 26-week visit, the patient presented with well-controlled asthma symptoms. He had discontinued his cetirizine. He also discontinued the natural antihistamine for a few days but soon noticed his allergy symptoms returning. These symptoms subsided when he resumed the natural antihistamine. He only needed his albuterol treatment twice per week (Table 3). The family had discontinued the other prescription medications and would use them on an “as needed” basis.

At the 30-week visit, the patient presented with nightly symptoms of wheezing. He was very congested and reported a cough due to increased mucous in his throat. In the past month, he reported wheezing for about 15 days and used his albuterol inhaler 15 times. He began taking cetirizine 2 to 3 weeks prior to the appointment. The patient reported the he had been eating wheat daily,

**Table 3** Medication Dosing for Patient B<sup>a</sup>

Medications	Initial	10 wk	19 wk	23 wk	26 wk	30 wk	35 wk	48 wk
Montelukast sodium	At bedtime	At bedtime	At bedtime	Occasionally, as needed	Discontinued	Daily	Discontinued	None
Fluticasone-salmeterol	Not reported	Not reported	Twice a day	Occasionally, as needed	Discontinued	Daily	Discontinued	Occasionally
Albuterol	Every night	“Less breathing treatments”	Daily	Twice per wk	2 times in the past 2 mo	15 times in the past mo	None 2 wk prior Once 4 wk prior	At least every night
Cetirizine hydrochloride	Daily	Every night	Daily	Discontinued	Discontinued	Daily	Frequent use	None

<sup>a</sup> The frequency of asthma medication use at the time of intake and subsequent visits.

dairy 3 to 4 days a week, and soy and eggs occasionally. His asthma appeared to be uncontrolled, and we stressed the importance of taking his prescribed medications and following the dietary recommendations for the management of his asthma.

At 32 weeks, we had a phone check-in during which the mother reported compliance with the dietary recommendations and good control of his asthma where he only needed the albuterol once in the past week and was taking the medications as recommended. At 35 weeks, his asthma had improved. At 40 weeks, he reported that he had two attacks since the last visit and one occurred immediately after he ate eggs. He was again encouraged to continue avoiding eggs.

At the 45-week visit, the patient presented to clinic with a flare of his asthma symptoms. He reported that he felt as if he had pneumonia and wheezing was audible. He required albuterol nebulizer treatments every night since the last visit. In discussion, the patient admitted to consuming significant amounts of gluten, dairy, eggs, and citrus at almost every meal during the past month. At this visit, we reinforced the importance of following the recommendations to manage the asthma symptoms. The parents agreed to take him to his primary care physician's office immediately to have a chest x-ray and follow the physician's recommendations. At this point, we explained to the parents that the patient exhibited low compliance to the diet and that strict pharmacological management of his asthma was required.

At the 48-week follow-up, we learned that his physician had diagnosed an asthma exacerbation due to acute bronchitis. His primary care physician put him on a 5-day course of steroids and had him continue his previously prescribed pharmacological regimen. The parents wanted to continue their efforts at implementing the dietary changes. We advised the parents to maintain strict pharmacological control of the asthma since the patient felt unable to comply with our dietary recommendations.

## DISCUSSION

Both of these patients demonstrated a substantial relief in symptoms of asthma and a decreased need for pharmacological control associated with initiating an IgG antibody-guided elimination diet. Patient A's reliance on albuterol decreased as her asthma attack frequency decreased to none. Her symptom severity scores decreased at each visit, and she was able to engage in physical activities such as hiking without getting breathless for the first time in years. Patient B evidenced a cyclic pattern of exacerbation and remission of his asthma symptoms, which appeared to be correlated with his varying compliance to the dietary protocol and prescribed medications.

Experimental models in the 1980s demonstrated the capacity for immunoglobulin G<sub>4</sub> (IgG<sub>4</sub>) to stimulate histamine release by leukocytes.<sup>10,11</sup> In a study from 1998, an experimental model proved the ability of IgG<sub>4</sub> to bind to basophils and stimulate histamine

release.<sup>12</sup> The experimental design was limited to artificial conditions and chimeric models. Attempts at replicating these properties of IgG and IgG<sub>4</sub> have had conflicting results. Some studies show the rise in IgG levels may be physiological and reflective of recent exposure to foods.<sup>13,14</sup> Others have found IgG levels to correlate with IgE levels suggesting that they share similar production pathways.<sup>15-17</sup> However, IgG levels have also been found to be elevated in individuals who have been avoiding known food allergens.<sup>17,18</sup> In one study, IgG and IgG<sub>4</sub> antibody levels to foods were higher in atopic children compared to age-matched controls,<sup>15</sup> while another study speculated that IgG levels during prenatal development may actually be predictive of the development of atopy later in life.<sup>19</sup> It has been speculated that IgG<sub>4</sub> plays a protective role in blocking IgE reactivity and promoting tolerance to allergens after oral immunotherapy treatment.<sup>20,21</sup> Children with eczema diagnosed with food allergens via challenge testing had high levels of circulating IgG<sub>4</sub> antibodies if they were able to demonstrate tolerance by age 4 and a half. In contrast, children who were unable to tolerate adding the foods back into their diet had significantly lower levels of IgG<sub>4</sub>.<sup>22</sup>

The therapeutic value of eliminating IgG-reactive foods has been demonstrated for symptomatic reduction in irritable bowel syndrome<sup>23,24</sup> and migraine.<sup>25</sup> This same phenomenon has also been noted for other inflammatory bowel diseases as well.<sup>26</sup> In bronchial provocation tests, asthmatics with elevated IgG<sub>4</sub> antibodies to allergenic substances experienced delayed reductions in pulmonary function post-exposure. However, individuals with IgE antibodies to allergenic substances had immediate changes in pulmonary function, while individuals with both IgG<sub>4</sub> and IgE antibodies exhibited a dual response.<sup>27</sup>

Factors other than the elimination diets may have contributed to these patients' improvement. Patient A was overweight at her initial visit with a BMI of 29.8. By her third visit, she has lost around 6.8 kg. It is possible that her reduction in weight improved her pulmonary function and decreased her symptoms of asthma. This phenomenon has been previously evidenced in obese asthmatics.<sup>28</sup> Although neither of our patients had been diagnosed with gastroesophageal reflux disease (GERD), asthmatics can experience an aggravation of asthma symptom severity if there is underlying GERD.<sup>29,30</sup> Both patients found relief of asthma symptoms after modifying their diet in ways that could reduce GERD symptoms. Thus it is possible that improvement of undiagnosed GERD may have contributed to improvement.<sup>31</sup>

Compliance to the elimination diet can often be problematic, especially for pediatric patients as evidenced by patient B. In spite of recognizing his symptomatic relief while following the elimination diet, he still preferred to consume high-reactivity foods. Long-term consequences of persistent asthma can cause permanent and irreversible airway remodeling.<sup>32</sup> Pediatricians and family physicians who provide chil-

**Table 4** Enzyme-linked Immunosorbent Assay (ELISA) Results for IgG Food Allergens for Patient B

<b>Class II-specific IgG</b>	Baker's yeast, barley, casein, corn, garlic, goat milk, grape, kidney bean, mushroom, soy bean
<b>Class III-specific IgG</b>	Cheddar cheese, chicken egg white, chicken egg yolk, coconut, cottage cheese, Duck egg whole, grapefruit, lemon, milk, mozzarella cheese, orange, pinto bean, rye, spelt, string bean, wheat gliadin, wheat gluten, whey, whole wheat, yogurt

<sup>a</sup> The ELISA report measured all 4 subclasses of IgG against 96 foods. The results are reported on a semi-quantitative scale ranging between 0 (no reactivity) to IV (extremely high reactivity). The class II and III reactive foods for Patient B are shown.

dren therapeutic dietary modifications for asthma management may face the challenge of a noncompliant patient and parents whose primary goal is to wean their children off of medications. These situations can be dangerous. It is important to encourage in-office discussions with the child and parents about whether the dietary modifications are realistic. It is also important to stress to parents that strict compliance to pharmacological therapy is important when the child is unable to comply with dietary recommendations in order to avoid asthma exacerbations.

Based on the presented cases, in patients with poorly controlled asthma, physicians may consider routinely testing and screening patients for the presence of IgG food antibodies. Physicians should inform their patients that this testing is not diagnostic of food allergens,<sup>6-9</sup> but elimination diets based on IgG food antibodies may help alleviate their symptoms. Unfortunately, there are no guidelines on what class of reactivity and how long food allergens should be eliminated. In our experience, we recommend complete avoidance of class II or III and higher food groups (Table 4) for at least 2 months in order to detect symptomatic improvement. Eventual challenge testing through reintroduction of foods one at a time is recommended to determine which food groups seem to act as triggers and which can be added back into the diet. Future studies should include controlled trials on IgG antibody directed food elimination diets on asthmatics, testing IgG levels post-elimination diet, comparing IgG testing with IgG<sub>4</sub> testing and studies on the reliability and validity of IgG testing between different assays, methods, and commercial laboratories.

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