
Letters

OCCUPATIONAL ASTHMA CAUSED BY *NEUROSPORA SITOPHILA* SENSITIZATION IN A COFFEE DISPENSER SERVICE OPERATOR

The contribution of exposure to sensitizing agents in the workplace should be considered in the case of adult-onset asthma because occupational asthma may account for up to 15% of cases.¹ We describe a young man with recent-onset asthma who received the diagnosis of occupational asthma caused by an unusual mold exposure after thorough workup of his asthma. This is the first described case, to our knowledge, of occupational asthma induced by mold, *Neurospora sitophila*, in a worker exposed to coffee. Our observations suggest that unusual sensitizers in selected cases of occupational asthma should be investigated.

A 29-year-old, previously healthy man, working as a service operator of coffee dispensers, was referred to our allergy outpatient clinic for several episodes of shortness of breath, wheezing, and chest tightness occurring in the last 4 months. The patient reported that respiratory symptoms occurred only when he worked on coffee dispensers located in the less busy places that he visited twice a month, where he noticed a pink to orange powder covering coffee residuals and spraying into the air during cleaning procedures. No symptoms occurred while he worked at coffee dispensers that he visited every day or every other day. Symptoms were well controlled by albuterol inhalation.

The results of skin prick tests with a standard panel of inhalant allergens, including several mold extracts and coffee (Alk-Abellø, Copenhagen, Denmark), were positive only for a mix of fungi extracts (*Mucor mucedo*, *Pullularia pullulans*, *Rhizopus nigricans*, and *N sitophila*). The results of skin prick tests with *M mucedo* and *P pullulans* extracts were negative.

Spirometry results were normal, whereas moderate methacholine airway hyperresponsiveness was present (provocation dose that caused a decrease in forced expiratory volume in 1 second of 20% = 223 µg). Mycologic analysis of coffee residuals, provided by the patient, revealed contamination by *N sitophila* (Fig 1). Specific IgE results (CAP-Phadia, Uppsala, Sweden) for *M mucedo*, *P pullulans*, and *Rhizopus nigricans* were negative, whereas specific IgE for *N sitophila* (Hycor HY*Tech; Hycor Biomedical Inc, Garden Grove, California) was mildly elevated (0.63 kUA/L; reference range, <0.35 kUA/L). Peak expiratory flow (PEF) monitoring showed markedly decreased values on 2 occasions while the patient had asthmatic symptoms a few minutes after being exposed to contaminated coffee residuals.

The patient was advised to wear a mask while working and to remove coffee residuals more frequently to prevent mold colonization. Two months later, the patient reported that he had not had any asthma attacks while regularly using a respiratory mask and attending coffee dispensers more often.

N sitophila (previously named *Monilia sitophila*) is an ascomycete that forms fast-growing pink colonies and numerous spores. *Chrysonilia sitophila*, the anamorph (asexual state) of *N sitophila*, is one of the most frequent fungi colonizing cork,² and it may induce occupational asthma in the wood-processing industry.^{3,4} Warm tem-



Figure 1. Macroscopic aspect of *Neurospora sitophila* contamination found on coffee residuals.

peratures and humidity commonly found in coffee residuals of coffee dispensers may be the ideal environment for mold growth.

The Global Initiative for Asthma document⁵ stresses the need for a systematic inquiry about occupational history and exposure to establish whether a relationship between symptoms and the workplace exists (that is, improvement of symptoms while off duty and worsening of symptoms when back to work). Furthermore, diagnosis of occupational asthma should be confirmed by specific bronchial provocation tests and/or PEF monitoring. This case underlines the great value of looking at unusual sensitizing agents when the occupational history is particularly suggestive. When the relationship with the sensitizing agent has been established, avoidance measures may be all the patient needs to cure the asthma.

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A CASE OF BRONCHOSPASM AND URTICARIA CAUSED BY SHISO INGESTION

Shiso (*Perilla frutescens*), an annual herb of the mint family is traditionally used in Chinese medicine and is known to suppress IgE-mediated responses.^{1,2} Although 2 cases of anaphylaxis caused by Shiso seeds have been reported,³ there have been no documented cases of allergic reactions induced by the Shiso leaf.

We report a case of bronchospasm and localized urticaria caused by Shiso leaf ingestion. A 21-year-old man presented with chest tightness and periorbital urticaria immediately after Shiso leaf ingestion. The patient had a history of allergic rhinitis and oral allergy syndromes to apple and kiwi. On admission, the patient had atopic symptoms and showed strong positive responses to common allergens on a skin prick test (wheat size; alder, 18 × 7 mm; birch, 15 × 7 mm; beech, 14 × 5 mm; ragweed, 4 × 3 mm; Bermuda grass, 4 × 3 mm; and kiwi, 2 × 2 mm). He also demonstrated positive reactions to food allergens, including kiwi (0.71 kUA/L) and apple (2.08 kUA/L), on an Immuno CAP system. The skin prick test that was performed using Shiso leaf extract (10 mg/mL) resulted in a strong positive response (4 × 4 mm), whereas none of the 9 nonatopic healthy control patients had a reaction. An open food challenge test with 4.5, 9, and 18 g of Shiso leaf extract (the weight of 1 Shiso leaf is approximately 1.5 g), which is smaller than the amount in a typical meal, was performed on the patient. These tests resulted in an immediate onset of allergic symptoms, including perioral itching, swelling, shortness of breath, and decreases in lung function (15.5% decrease in forced expiratory volume in 1 second in 18 g of Shiso leaf ingestion).

We performed an open food challenge test with 250, 500, and 1,000 mg of seeds. The seeds had no effect on the patient. Serum specific IgE antibody to Shiso leaf extract (10 mg/mL) was measured using an enzyme-linked immunosorbent assay. No specific IgE binding was noted in the patient's sera or the samples obtained from the 9 nonatopic healthy control patients (Fig 1A). Finally, we performed a histamine releasability test using the patient's basophils. We found a significant increase in histamine-releasing capacity (77.85%) induced after incubation with 10 mg/mL of Shiso leaf extract, which was determined as the optimal concentration in the preliminary experiment as well as calcium ionophore (3 μM) and anti-IgE antibody (10 μg/mL), whereas minimal histamine release in response to Shiso extract was noted in 2 control patients (Fig 1B).

Although Shiso is widely used in drugs and foods, no allergies to the extract have been reported.^{1,2,4} We describe the first case of a systemic allergic response with bronchospasm and localized urticaria after ingestion of the Shiso leaf. Frequent allergic reactions after the ingestion of vegetables and fruits in patients

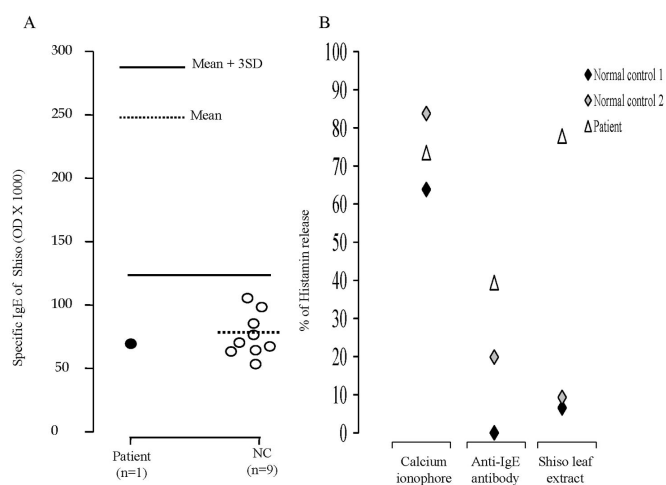


Figure 1. A, Serum specific IgE levels determined using enzyme-linked immunosorbent assay in the patient and in 2 healthy control patients. B, Histamine release test of perilla leaf using the sera of the patient and 2 healthy control patients.

sensitized to tree pollens may be derived from cross-allergenicity between these foods and tree pollens.^{5,6} However, we could not detect any serum specific IgE antibodies to the Shiso leaf extract. Therefore, the possibility of cross-allergenicity with tree pollens and other food allergens to which the patient was sensitized seems low.

In conclusion, we report a case of bronchospasm and localized urticaria caused by Shiso leaf in a patient with allergic rhinitis to tree pollens. This reaction was not mediated by IgE antibodies but rather by direct histamine-releasing effects.

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COMMON VARIABLE IMMUNODEFICIENCY WITH REGULATORY T-CELL DEFICIENCY TREATED WITH RAPAMYCIN

Common variable immunodeficiency (CVID) is a heterogeneous disorder characterized by hypogammaglobulinemia, recurrent infec-

tions, and aberrant T-cell function. A total of 20% to 25% of patients with CVID also have autoimmune manifestations, most often immune thrombocytopenia purpura (ITP), autoimmune hemolytic anemia, and granulomatous disease.¹ Despite significant advances in our understanding of CVID, the disease is frequently refractory to treatment.

We describe a patient with CVID, chronic ITP, and granulomatous disease. The patient first presented to her primary care physician at the age of 2 years with easy bruising and bleeding. Her history was significant only for recurrent episodes of watery diar-

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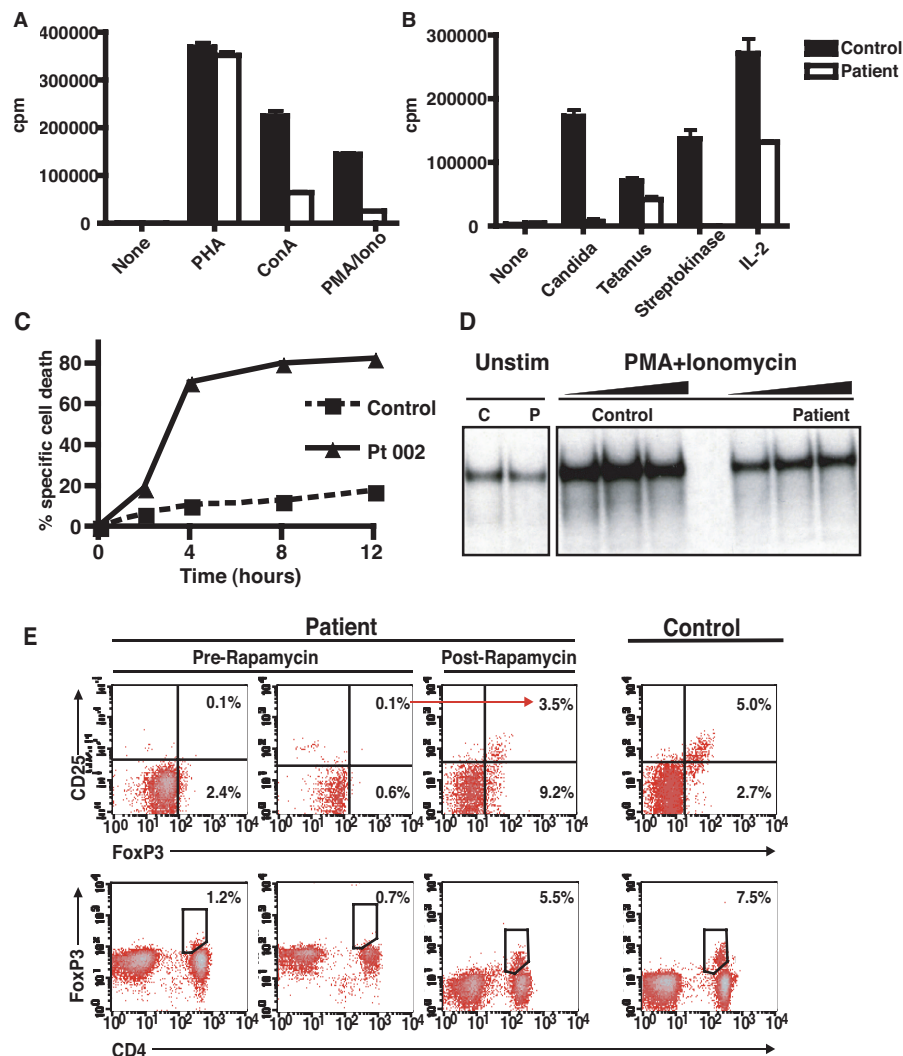


Figure 1. Patient T-cell function and regulatory T-cell profile. A and B, Peripheral blood mononuclear cells (PBMCs) from the patient and healthy controls were stimulated with the indicated treatment for 4 days (nonspecific mitogens; A) or 7 days (specific antigens; B); proliferation was evaluated by the addition of tritiated thymidine for the last 24 hours. C, T cells were obtained by culturing control and patient PBMCs with phytohemagglutinin antigen and interleukin 2 for 7 to 10 days. Specific cell death after treatment of these cells with 50 ng/mL of phorbol myristate acetate (PMA) plus 1 μ M ionomycin was determined by flow cytometry after staining with PE-Annexin V and 7-amino-actinomycin D. D, Cultured patient and control T cells were left unstimulated or stimulated with varying doses of PMA plus ionomycin for 2 hours; cells were then lysed and analyzed for NF- κ B DNA-binding activity by electrophoretic mobility-shift assay as described.⁸ The density of the band is proportional to the amount of DNA-binding activity. E, PBMCs from the patient and a healthy control were analyzed for regulatory T-cell prevalence as determined by the frequency of CD4⁺CD25⁺FoxP3⁺ T cells.

rhea and eczema, and the results of her physical examination were unremarkable. Laboratory studies revealed a platelet count of 4,000/ μ L, a positive Coombs antibody, and a positive antinuclear antibody. She was prescribed corticosteroids, which improved her platelet counts modestly. After recurrent bouts of ITP, further investigation revealed hypogammaglobulinemia and T-cell lymphopenia. Her antibody levels were 164 mg/dL of IgG, 10 mg/dL of IgA, and 21 mg/dL of IgM. Sequencing of the gene encoding Wiskott-Aldrich syndrome protein did not reveal any mutations, and CVID was diagnosed. Despite her hypogammaglobulinemia, the patient's B-cell counts were normal, indicating that her T-cell lymphopenia was unlikely to be attributable to corticosteroid therapy. At the age of 9 years, the patient presented to the emergency department in status epilepticus because of a lesion in the left parietal lobe. Chest computed tomography revealed several lung nodules. The intracranial mass was resected and biopsy specimens of the lung nodules were obtained; histopathologic analysis determined that the former was composed of loosely organized inflammatory tissue, whereas the latter contained many noncaseating granulomas. Lymphocytes were the predominant cell type.

Proliferation of the patient's T cells in response to a panel of specific antigens and nonspecific mitogens was greatly reduced, with the exception of phytohemagglutinin (Fig 1A, B). Proliferation of the patient's T cells to phytohemagglutinin antigen was normal, and proliferation to interleukin 2 was reduced by only 30% to 50%, indicating that the patient's proliferation defect is not explained by the relative paucity of T cells in the crude peripheral blood mononuclear cell preparations from the patient. The reduced proliferation to phorbol myristate acetate (PMA)/ionomycin suggested a relatively distal T-cell-intrinsic defect. We also found that the patient's T cells underwent activation-induced cell death (AICD) at a much higher rate than control cells; only 10% to 20% of the T cells remained viable after 12 hours of activation with PMA/ionomycin (Fig 1C). Furthermore, the T cells exhibited reduced NF- κ B activity shortly after activation with PMA/ionomycin (Fig 1D). Because NF- κ B activation is a critical step in T-cell proliferation and the avoidance of AICD,² this defect provides a possible explanation for the increased AICD and reduced proliferation.

Although the patient's lymphopenia might be explained by increased T-cell apoptosis, it did not provide an obvious explanation for the patient's autoimmunity. One possibility is that the patient's regulatory T-cell function may be impaired to an even greater extent than her conventional T-cell function. Regulatory T cells (Tregs) are critical for the suppression of inappropriate T-cell responses, and individuals lacking Tregs exhibit widespread autoimmunity. Several previous reports have noted Treg deficiencies in a subset of patients with CVID.³ We sought to characterize the patient's Treg compartment. Flow cytometric analysis revealed low numbers of CD4⁺ T cells but comparatively even fewer CD4⁺CD25⁺FoxP3⁺ Tregs (Fig 1E) and few CD4⁺CD25⁺CD127⁻ cells (data not shown). This pattern was observed consistently on several different occasions.

By the age of 13 years, the patient had been treated with corticosteroids for several years, and because of their adverse effects a steroid-sparing therapy was devised. Because several studies had shown that rapamycin increases Treg cell counts and suppressive function,^{4,5} we added rapamycin (1 mg/d) to the patient's regimen. Six months after beginning rapamycin therapy, the patient's Treg counts had nearly recovered to normal levels (Fig 1E). The patient had many more CD25low, FoxP3⁺ T cells after rapamycin treatment than did control samples; previous reports have indicated that this population may also represent Tregs.⁶ Her platelet count also in-

creased to 136,000/ μ L, and she reported reduced diarrhea. Her IgM level also returned to a normal value, whereas her IgA levels remained low.

Rapamycin is used as an immunosuppressive agent in organ transplant recipients and acts to suppress the AKT-mTOR signaling axis and consequently inhibit effector T-cell activity. To our knowledge, this is the first reported use of rapamycin for the treatment of CVID. Given the positive effects on the patient's Treg number and clinical status, we propose that rapamycin may serve as a useful therapy for individuals with CVID, particularly those with regulatory T-cell deficiency.

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ASPIRIN DESENSITIZATION IN A PATIENT WITH ASPIRIN SENSITIVITY AND CHRONIC IDIOPATHIC URTICARIA

Aspirin desensitization has proved to be beneficial in patients with aspirin-exacerbated respiratory disease, chronic rhinosinusitis, and aspirin-induced urticaria who require aspirin treatment for acute coronary syndrome.^{1,2} Desensitization in patients with a history of chronic idiopathic urticaria (CIU) with accompanying aspirin sen-

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sitivity has not been shown.³ We describe a patient who was successfully desensitized to aspirin despite a history of CIU.

The patient is a 49-year-old man with a history of diabetes mellitus, childhood asthma, hypertension, gastroesophageal reflux disease, myocardial infarction, and intermittent hives. He first noticed the hives when he was 16 years old. He developed generalized pruritic lesions that lasted 24 hours and spontaneously disappeared. At the age of 33 years, he was prescribed an adult dose of a nonsteroidal anti-inflammatory drug (NSAID) for a leg injury. A few days later, he noticed hives that began on his legs and spread upward 10 to 15 minutes after taking the NSAID. He took diphenhydramine, and the hives resolved. A few months later, the patient was having mild arthritic pain and took an adult dose of aspirin. Ten minutes later he began to develop hives. The hives again were relieved by oral diphenhydramine treatment. Since that time, despite avoiding NSAIDs and aspirin, the patient reports having outbreaks of hives 5 to 6 times per year with no apparent triggers. He had no respiratory complaints, swelling of eyes or lips, or gastrointestinal problems associated with the hives.

The patient was referred to us for aspirin desensitization because of his history of myocardial infarction. Physical examination findings were normal. There were no hives or evidence of dermatographism. Spirometry showed normal lung function, and autologous serum skin test results were negative. The patient was diagnosed as having CIU and aspirin sensitivity. He was advised of the risks of desensitization and agreed to the procedure.

Aspirin desensitization treatment began with 40 mg given at 10 AM. The patient had some mild itching of his ears, but this spontaneously abated. At 11:30 AM, he was given aspirin, 81 mg. He was observed for 2 hours and had no reaction. Later that afternoon, 3.5 hours after the aspirin administration, the patient had a severe flare-up of generalized urticaria. He took diphenhydramine, 25 mg, and the hives subsided. The next day, he was given aspirin, 81 mg, at 8:30 AM. He had no reaction after 2 hours and was given aspirin, 162 mg, at 10:30 AM. At 12:30 PM, the patient began to have a mild flare of hives, with a few lesions seen on his neck. He was given cetirizine, 10 mg, and the hives resolved in 30 minutes. The next day he was given aspirin, 162 mg, at 8:30 AM. At 11:15 AM he was given aspirin, 325 mg, and remained asymptomatic. The patient was advised to continue with the aspirin, 325 mg/d, and cetirizine, 10 mg nightly. Since the patient's desensitization, his dose of aspirin was reduced from 325 to 81 mg/d after 2 months by his cardiologist, and he is taking cetirizine only as needed. In the 5 months after his desensitization, he had 2 mild urticarial outbreaks that readily resolved with cetirizine treatment.

Aspirin desensitization has been proved to be a safe and effective office procedure,⁴ but its use in patients with aspirin-induced urticaria remains controversial. Grzelewska-Rzymowska et al⁵ and Asad et al⁶ demonstrated that patients with urticaria or angioedema reactions solely related to aspirin could be desensitized in a few days. Wong et al² studied 11 patients, most of whom had acute coronary syndrome and a history of aspirin-induced urticaria and angioedema. They underwent a rapid desensitization protocol, which was successful in 9 patients. This illustrates the possibility that desensitization is possible in single drug-induced urticaria/angioedema.

Simon³ studied aspirin desensitization in patients with a history of chronic urticaria. He desensitized 25 patients to aspirin, 650 mg. However, within 1 day of desensitization, the hives flared. This outbreak was severe, and prednisone was administered to adequately control it. Further aspirin desensitization attempts after the initial

trial only triggered more exacerbations of the hives. Our patient experienced acute urticaria with desensitization but was controlled with oral antihistamines.

The present case demonstrates that aspirin desensitization may be possible in patients with a history of aspirin sensitivity and CIU. We should emphasize that this patient may represent the milder end of the spectrum in that he was responsive to a histamine₁ antihistamine and the autologous serum skin test result was negative. Further studies with more patients are needed to better characterize the possibility of aspirin desensitization in this difficult-to-treat population.

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EMPOWER YOUR PATIENTS: SAVE LIVES

Epinephrine is the initial drug of choice in anaphylactic reactions. Some patients, such as those allergic to foods, latex, or Hymenoptera venom, are at such a high risk for systemic reactions (SRs) that they should always carry an epinephrine autoinjector. Proper treatment depends on the availability of epinephrine, knowledge of indications, and accurate use of the device when needed.¹ Several studies^{2–4} have shown that many patients do not always carry their epinephrine device, are deficient in their knowledge of indications for use (84% of parents), and cannot use the device correctly (63%). One survey¹ of patients' parents showed that training, previous use of epinephrine, and empowerment improved comfort with parental administration of epinephrine autoinjectors. In the severe anaphylactic reactions that have occurred, a delay in administration, inaccurate use, and lack of availability of epinephrine have been cited as contributing to the severity of the reaction.⁵ Physicians are already encouraged in practice parameters to educate patients on the importance of always having an epinephrine autoinjector available.^{1,5} Education by the physician or team is typically achieved using a training device,^{1,3,6,7} but patients may still fear the needle and medication from the autoinjector itself. A survey by Kim et al¹ showed that parental comfort was not affected by their child's previous

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anaphylactic reaction but was correlated with previous epinephrine administration.

One brief correspondence in the *Annals*⁸ described one physician's experience with demonstrating the use of a live epinephrine autoinjector on an asymptomatic, nonreacting patient. Although we believe that the use of medication, especially epinephrine, when not clinically indicated is completely inappropriate and unsafe, we recognize from previous literature that epinephrine autoinjector trainer education alone often falls short of addressing patients' fears of live epinephrine use.

In the SR emergency cart at the Department of Allergy and Immunology, Wilford Hall Medical Center, we now stock epinephrine autoinjectors (EpiPen and EpiPen Jr) in addition to predrawn syringes of epinephrine. The physician of the day (POD) who responds to an SR now has the discretionary option of using the EpiPen. In addition, if the patient is identified to be at high risk for future reactions (food, latex, or venom), hemodynamically stable, and willing, the POD may elect to guide the patient through self-administration under direct physician supervision. We briefly describe a case highlighting the importance and impact of this intervention.

In response to an SR alarm, the POD went promptly to the clinic treatment area, where a mother was found consoling her 2-year-old daughter with a history of peanut allergy. The child had completed peanut skin testing and within 5 minutes had a positive wheal and flare, with generalized urticaria and facial swelling. A focused history described a child with peanut ingestion who developed diffuse urticaria on 3 separate occasions since the age of 11 months. The mother had never administered EpiPen, but the child had received it during a previous emergency department visit. Previously, her primary allergist had demonstrated use of the EpiPen with the trainer at their initial appointment. In less than 60 seconds, the POD elected to use the EpiPen Jr option and asked the mother if she was willing to administer the EpiPen Jr to the child herself with supervision and assistance.

The mother was nervous but willing. We helped position the child on the mother's lap. The POD quickly reviewed the correct use of the EpiPen Jr and then handed the mother the device. Under the POD's supervision, the mother used the autoinjector correctly and was praised for a perfect injection. Within 5 minutes, the child's urticaria began to resolve, her eye swelling resolved, and her affect improved dramatically.

Shortly afterward, we again reviewed use of the EpiPen Jr with the mother. She admitted to having felt intimidated by the device. She related that while she had been instructed by her primary allergist on the indications for use of EpiPen Jr and had been allowed to use the trainer, she was still uncertain whether she could use the device if the time came. After this day's experience, she said she felt very comfortable with its use and extremely confident that if her child unintentionally ingested peanuts in the future she would be ready to administer the EpiPen Jr.

A MEDLINE literature review finds no previous study of in-clinic administration of epinephrine autoinjectors on patients, parental or provider perceptions of comfort, and likelihood of future administration. What better opportunity for training high-risk patients for future SRs is there than the SR that occurs in your office? This case exemplifies the importance of empowering our patients through real-time physician education.

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SUCCESSFUL ADMINISTRATION OF CYTARABINE IN A 16-MONTH-OLD GIRL WITH ACUTE MYELOGENOUS LEUKEMIA AND CYTARABINE SYNDROME

We describe a 16-month-old girl with acute myelogenous leukemia who developed cytarabine syndrome during intravenous cytarabine treatment. She subsequently successfully completed a 5-day course of high-dose cytarabine after 2 days of premedication with methylprednisolone, diphenhydramine, and ranitidine.

Cytarabine syndrome was initially described by Castleberry et al¹ in 1981 as observed in 6 children undergoing treatment with cytarabine alone. The symptoms included fever, malaise, joint or bone pain, maculopapular rash, conjunctivitis, and chest pain. Treatment with corticosteroids 1 day before administration of cytarabine prevented the recurrence of symptoms. Ek et al² reported that pretreatment with corticosteroids decreased the incidence of fever in pediatric patients receiving high-dose cytarabine. The package insert for injectable cytarabine states, "Corticosteroids have been shown to be beneficial in treating or preventing [cytarabine] syndrome. If the symptoms of the syndrome are deemed treatable, corticosteroids should be contemplated as well as continuation of therapy with cytarabine."³ However, in these 3 references and in a review of the English-language literature, specific dosing and timing of the premedication protocol are not given. We report a successful protocol of premedication to prevent the occurrence of cytarabine syndrome.

A 16-month-old, white girl diagnosed as having acute myelogenous leukemia received the first induction of high-dose intrathecal and intravenous cytarabine, etoposide, and daunorubicin without incident. One month later, after the second dose of the second induction with intrathecal and intravenous cytarabine, she developed intermittent fever. Vancomycin and meropenem were prescribed empirically for suspected infection. A day later, the fever persisted and she developed hypotension. Gentamicin was added. She developed a raised erythematous rash during the gentamicin infusion,

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which was attributed to an allergic reaction to the gentamicin. Use of gentamicin was stopped and the rash resolved; however, she continued to have a fever. Ciprofloxacin and metronidazole were added. Approximately 12 hours after the fourth dose of the second induction with cytarabine, she developed hypotension with poor peripheral perfusion. She did not have other skin manifestations. She was resuscitated with 30 mL/kg of isotonic sodium chloride solution and packed red blood cells and was transferred to the pediatric intensive care unit. Ciprofloxacin, vancomycin, and meropenem therapy was continued and amphotericin was added. A complete blood cell count revealed a white blood cell count of $5.5 \times 10^3/\mu\text{L}$ with an absolute neutrophil count of $4.9 \times 10^3/\mu\text{L}$. Blood and urine cultures were negative. Computed tomography of the whole body was normal except for a small left lower lobe lung nodule. Within 24 hours, she became afebrile and normotensive. The administration of the second induction, including cytarabine, was withheld, and the treatment protocol was changed to 5 days of mitoxantrone and etoposide, which she tolerated. Two weeks later she was premedicated with hydrocortisone, 2 mg intravenously, and the cytarabine protocol was resumed with intravenous cytarabine only. Twelve hours after the second dose of the repeated second induction of cytarabine, she developed high temperatures, tachycardia, and vomiting. Use of cytarabine was stopped. She was treated with the same dose of hydrocortisone, twice daily for 4 days, after which the fever abated. She did not develop rash, hypotension, or poor perfusion. She continued to receive etoposide and daunorubicin.

Severe life-threatening anaphylactic reactions to cytarabine have been reported.⁴⁻⁶ However, at least 1 study⁷ showed the presence of circulating immune complexes in a patient with fever, rash, hypotension, and thrombocytopenia after treatment with cytarabine, supporting an immune-related delayed hypersensitivity reaction. In addition, according to Ek et al,⁸ cytarabine induces release of tumor necrosis factor α and other proinflammatory cytokines, which may directly contribute to the symptoms of the cytarabine syndrome. Therefore, desensitization was deemed inappropriate. Instead, a premedication protocol was devised. Intravenous methylprednisolone, 1 mg/kg every 6 hours, diphenhydramine, 1 mg/kg every 6 hours, and ranitidine, 1 mg/kg every 12 hours, were given for 2 days before the administration of high-dose cytarabine infused for 3 hours. This regimen was continued throughout the 5-day treatment course and for 1 day after completion. The cytarabine was tolerated without reaction. Although the reaction was not thought to be due to an IgE-mediated mechanism, both histamine₁- and histamine₂-receptor blockers were included in the protocol because of reports of life-threatening hypersensitivity reactions.⁴⁻⁶ In summary, a premedication and concurrent treatment protocol was successful in allowing the administration of cytarabine in a patient with cytarabine syndrome.

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DETEMIR INSULIN-INDUCED ANAPHYLAXIS

A 79-year-old man with diabetes mellitus of at least 10 years of evolution was referred to our outpatient clinic because of suspected insulin allergy. He had a clinical history of stroke, circulatory insufficiency, and prostate hypertrophy. Some days ago his endocrine specialist changed his previous protamine-aspart insulin treatment to detemir to achieve best metabolic control. After 2 or 3 days of treatment, he presented with sudden dyspnea, dysphagia, itching, and edema in the injection site less than 1 hour after the insulin administration. He required emergency assistance with oxygen, parenteral corticosteroid, and antihistamines. Although he did not report previous use of detemir insulin at first, administration during a former hospital stay was recorded. After consulting with his endocrine specialist, he again started taking protamine-aspart insulin, with good tolerance but poor metabolic control.

A skin prick test with full strength substances and a 1/10 dilution intradermal test were performed with several types of insulin and protamine. Skin prick test concentrations were 100 U/mL for insulins and 10 mg/mL for protamine.¹ Five nondiabetic individuals were tested to find the optimal concentration for a protamine skin test. A skin prick test with latex (ALK-Abelló, Madrid, Spain) was also performed. All results were read at 20 minutes. Histamine and saline were used as positive and negative controls, respectively.

After skin testing, subcutaneous tolerance with some types of insulin was tested under glycemic control to achieve a dose of 10 U. Results of the skin test to insulins are given in Table 1. Only glargine and glulisine insulin yielded negative intradermal test results. The results of a skin prick test with latex were negative. The results of a skin prick test with detemir insulin were positive at 100 U/mL. An intradermal test was not performed. Five healthy controls had negative detemir insulin skin prick test results. Tolerance was performed without incidence with glulisine and glargine insulin.

The patient was diagnosed as having selective allergy to detemir insulin, showing good tolerance to glargine and glulisine insulins. Desensitization was considered² but finally rejected because of the patient's age, associated morbidity, and existence of safe alternatives. After talking with his endocrine specialist, he decided to change treatment to glargine and glulisine insulin, with partial improvement in metabolic control.

Insulin allergy is a rare condition (less than 1% of patients with human insulin preparations).¹ It usually appears in a diabetic patient after a variable period of treatment. Symptoms range from local mild

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Table 1. Skin Test Results

Agent tested	Wheal/flare diameter, mm	
	SPT	ID test
Protamine	Negative	5/15
Rapid (Actrapid; Novo Nordisk, Bagsværd, Denmark)	Negative	6/17
Aspart (Novorapid; Novo Nordisk)	Negative	8/20
Lispro (Humalog; Lilly, Indianapolis, Indiana)	Negative	8/21
Glargine (Lantus; sanofi-aventis, Bridgewater, New Jersey)	Negative	Negative
NPH (Humulina NPH; Lilly)	Negative	11/29
Detemir (Levemir; Novo Nordisk)	14/40	Not performed
Glulisine (Apidra; sanofi-aventis)	Negative	Negative

Abbreviations: ID, intradermal; SPT, skin prick test.

reactions to anaphylaxis, and insulin resistance and poor glycemic control are usually present.³

Cross-reactivity between human insulin and different insulin analogues has been described but its clinical significance on skin tests is difficult to evaluate because even 40% of asymptomatic diabetic patients show positive skin test results or specific IgE to insulin.¹ In some patients, these sensitizations could play a role in insulin resistance via IgE or IgG antibodies.³ Our patient had been using protamine-aspart insulin without problems; however, a positive intradermal test result to these substances was found. Sensitization to additives such as zinc, cresol, and glycerol was ruled out because the patient showed good tolerance to glargine and glulisine insulin, which contains these substances.

Insulin analogues are created by the substitution of 1 or more amino acids in the human insulin chain to increase duration of action or to achieve a best bioavailability. Some studies report that sensitization could be more likely with insulin analogues than with human insulin itself.⁴

Detemir is a recently marketed long action insulin analog. It is created by the elimination of the threonine amino acid at the B30

position and the addition of a myristic acid residue at B29. The first case of detemir insulin reaction was described by Darmon et al in 2005.⁵ They described a man who presented with delayed local reaction to detemir insulin and good tolerance to other analogues. After that, other cases have been reported, with local immediate or delayed reactions but no systemic reactions.^{4,6}

A small number of cases of anaphylaxis to insulin have been reported, some of them with fatal outcome.⁷ Options for treatment include oral antidiabetics (when possible), substitution to a different insulin analog, use of perfusion pumps or specific desensitization,¹ and use of monoclonal antibodies (omalizumab).⁸ To our knowledge, this is the first report of selective anaphylaxis to a newly introduced detemir insulin with good tolerance to other insulin analogues.

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Erratum

In the article “Onset of effect of budesonide and formoterol administered via one pressurized metered-dose inhaler in patients with asthma previously treated with inhaled corticosteroids” by Kaiser et al (*Ann Allergy Asthma Immunol*. 2008;101:295–303), the data for patient-perceived onset of effect (OE) are presented for the overall population of patients 12 years or older in the abstract and for a subset of patients 18 years or older in the body of the manuscript. The “Methods” section of the abstract should read, “Postdose time to 15% or greater improvement in

forced expiratory volume in 1 second and patient-perceived OE (assessed in a subset of patients 18 years and older [study 1, n=553; study 2, n=405]) were evaluated.” The “Results” section of the abstract should read, “More patients receiving budesonide/formoterol vs budesonide and placebo reported feeling their study medication begin to work right away ($P \leq .017$; end of week 1 and end of treatment). Similar results ($P \leq .04$) were observed for patient satisfaction with how quickly they felt their medication begin to work.”