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SUPPLEMENT TO PEDIATRICS

Synopsis Book

Best Articles Relevant to Pediatric Allergy and Immunology

Supported by an educational grant from GlaxoSmithKline

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Synopsis Book

Best Articles Relevant to Pediatric Allergy and Immunology

Selected by members of the Section on Allergy and Immunology of the American Academy of Pediatrics from articles appearing in the medical literature between December 1, 1999 and November 30, 2000.

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TIME COURSE OF ALLERGY TO EXTENSIVELY HYDROLYZED COW'S MILK PROTEIN IN INFANTS

de Boissieu D, Dupont C. *J Pediatr.* 2000;136:119–120

Purpose of the Study. The purpose of this investigation was to determine the time course of clinical allergy in a group of infants allergic to cow's milk protein (CMP) and to extensively hydrolyzed formulas (EHF).

Study Population. Twenty-two infants with allergy to cow's milk and EHF were included in this investigation. Clinical symptoms were predominantly digestive in 20 patients and were associated with failure to thrive in 5 patients, irritability in 7, and angioedema in 3. Six patients had eczema.

Methods. Patients received an amino acid-based formula (AABF) for 1 month and then were orally challenged with the EHF previously used. The challenge with the EHF was performed again before the age of 1 year, then repeated every 6 months until 2 years of age if positive. When the challenge indicated that EHF was tolerated or if the patient was >2 years old the challenge was performed with cow's milk, according to the same protocol, once a year. When allergy to non-cow's milk protein was suspected in an infant, skin prick tests were performed, and an elimination diet followed by a single-blind oral challenge was performed for each suspected food.

Results. AABF was used for a mean duration of 11.8 ± 8.7 months (3–30 months) and proved safe in all cases. Nine infants were allergic to CMP, soy, and EHF but no other major food allergens. These patients exhibited only digestive symptoms, and the diagnosis was made before diversification of the diet. The 13 other infants were allergic to at least 4 foods apart from CMP, soy, and EHF and 6 of them exhibited multiple food allergies. Age at diagnosis and age at CMP tolerance were higher in this group, which also includes the 4 infants still intolerant to CMP at age 3 years.

Conclusions. Allergy to EHF seems to encompass 2 different clinical entities. A better prognosis is associated with an earlier diagnosis, predominant digestive symptoms, and the absence of associated allergy to other foods.

Reviewer's Comments. There have been numerous reports of infants with CMA experiencing allergic reactions to extensively hydrolyzed cow's milk protein formulas. AABF has provided a very useful therapy in these infants. This investigation describes clinical features of infants allergic to EHF. The time course of allergy appeared to differ according to the presence or absence of associated allergy to several other foods. Moreover, a better overall prognosis was observed in those infants with isolated allergy to EHF. This information is interesting, but until more data are available, the ultimate decision to use these formulas in infants with documented CMA should be individualized and based on a variety of issues including: presenting symptoms of CMA, clinical course, tolerability of the formula alternatives (eg, soy formula, EHF, AABF), and the costs of administering the formula.

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A MURINE MODEL OF PEANUT ANAPHYLAXIS: T- AND B-CELL RESPONSES TO A MAJOR PEANUT ALLERGEN MIMIC HUMAN RESPONSES

Li X-M, Serebrisky D, Lee S-Y, et al. *J Allergy Clin Immunol.* 2000;106:150–158

Purpose of the Study. To establish a murine model of immunoglobulin E (IgE)-mediated peanut hypersensitivity that closely resembles peanut allergy in humans.

Study Sample. Five-week-old female C3H/HeJ mice maintained on a peanut-free chow.

Methods. C3H/HeJ mice were sensitized to peanut using intragastric administration of freshly ground whole peanut (low-dose and high-dose) with cholera toxin adjuvant. Sensitized mice were challenged via intragastric gavage with crude peanut extract at 3 and 5 weeks, and evidence of anaphylaxis was recorded, including symptoms profile, plasma histamine levels, and mast cell degranulation. Additionally, passive cutaneous anaphylaxis (PCA) testing was conducted using pooled sera from a subset of mice. IgE antibody concentrations and splenocyte proliferative responses were used to evaluate T- and B-cell responses to the major peanut allergens, Ara h 1 and Ara h 2. The Ara h 2 isoforms and allergenic epitopes recognized by IgE antibodies in the sera of mice and patients with peanut allergy were compared.

Results. The orally sensitized mice displayed hypersensitivity reactions with clinical symptoms similar to those seen in humans. PCA testing was performed to confirm an IgE-mediated, and not IgG1-mediated, process. The positive PCA reaction was eliminated by heat inactivation of the immune sera, indicating the role of IgE. Furthermore, mast cell degranulation in ear samples and histamine levels in plasma were greater in peanut-sensitized mice.

Ara h 1 and Ara h 2 are the major peanut allergens. Splenocyte proliferative responses to Ara h 1 and h 2, as well as IgE antibodies specific to Ara h 1 and Ara h 2 in the sera of sensitized mice, indicate that the T- and B-cell responses are similar to those in humans. The peanut-specific IgE increased significantly after sensitization and was higher after low-dose sensitization. Furthermore, murine and human IgE recognize the same 8 Ara h 2 isoforms and have 9 of 11 IgE-binding epitopes in common.

Conclusions. The investigators successfully generated a mouse model of peanut anaphylaxis, using oral sensitization and challenges, mimicking peanut anaphylaxis in humans.

Reviewers' Comments. In recent decades the prevalence of peanut allergy in the United States has increased. Peanuts are highly allergenic and account for the majority fatal and near-fatal allergic reactions. Ingestion of even minute amounts of peanut allergen can be life-threatening, precluding human testing; therefore, the development of an animal model is an integral part of designing appropriate and safe immunomodulatory therapy for peanut allergy. Currently, the only option available for patients with peanut allergy is avoidance. Hence, the model developed in this elegant study is invaluable to advances for the treatment of peanut allergy.

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ANAPHYLAXIS

BIPHASIC ANAPHYLACTIC REACTIONS IN PEDIATRICS

Lee JM, Greenes DS. *Pediatrics.* 2000;106:762–766

Purpose of the Study. The objectives of this investigation were to evaluate the incidence of biphasic reactions in pediatric anaphylaxis, to document risk factors that predict biphasic reactions, and to evaluate the utility of an inpatient observation for pediatric patients whose symptoms of anaphylaxis have resolved.

Study Population. All patients admitted to Boston Children's Hospital with acute anaphylaxis between 1985 and

1999. The patients ranged in age from 1 year to 13 years and triggers for anaphylaxis included foods in 47% of cases, medications in 22%, insect stings in 11%, immunotherapy in 3%, and unknown in 15%.

Methods. This was a retrospective analysis in which data were extracted from medical records regarding past medical history, presenting signs and symptoms, therapy, and hospital course. Patients were defined as having resolved anaphylaxis if all symptoms had disappeared and no therapy was needed for at least 1 hour. Biphasic reactions were defined as worsening symptoms requiring additional therapy after apparent resolution of anaphylaxis. Significant biphasic reactions were defined as requiring additional intervention with oxygen, vasopressors, intubation, subcutaneous epinephrine, or unscheduled bronchodilator therapy. Individuals were defined as benefiting from a 24-hour observation if they had a significant biphasic reaction within 24 hours of admission.

Results. Of 108 anaphylactic events, 2 were fatal and 1 was defined as a protracted anaphylactic episode. Of the remaining 105 patients with resolution of anaphylaxis, 6 had biphasic reactions, of which 3 were significant. In those with biphasic reactions, the median time from the onset of symptoms to the initial delivery of subcutaneous epinephrine was 190 minutes, compared with 48 minutes for those without biphasic reaction. Patients with and without biphasic reactions did not differ significantly in the incidence of initial epinephrine use, initial steroid use, or serious respiratory or cardiovascular symptoms on initial presentation. Two of 105 patients clinically benefited from a 24-hour inpatient observation. Only 1 of the individuals with biphasic anaphylaxis required vasopressors and intubation. Asymptomatic intervals varied from 1.3 hours to 28.4 hours, with the most severe episode requiring intubation having an asymptomatic interval 5.8 hours.

Conclusions. The overall incidence of biphasic reactions was 6%, with an incidence of significant biphasic reactions of 3% among, patients admitted to a children's hospital with anaphylaxis. Delayed delivery of subcutaneous epinephrine was associated with a higher incidence of biphasic anaphylaxis. Approximately 2% of individuals with anaphylaxis benefited from a 24-hour observation period after symptoms had resolved.

Reviewer's Comments. Although retrospective, this is a welcome study in that it characterizes the occurrence of biphasic anaphylaxis in a large group of children. The rate of biphasic reactions was similar to the 5% to 7% rate quoted by one study, but was considerably less than the 20% to 30% biphasic reaction rate reported for adults in other studies. It is also important to note that a delay in the administration of epinephrine, well-characterized as a risk factor for fatal anaphylaxis, also appears to be a major risk factor for the occurrence of a biphasic reaction.

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USE ASSESSMENT OF SELF-ADMINISTERED EPINEPHRINE AMONG FOOD-ALLERGIC CHILDREN AND PEDIATRICIANS

Sicherer SH, Forman JA, Noone SA. *Pediatrics.* 2000;105: 359–362

Purpose of the Study. Food allergy is a common cause of anaphylaxis and early treatment with epinephrine can be life-saving. The authors sought to determine the ability of families with food-allergic children and pediatricians to properly administer self-injectable epinephrine.

Study Population. The families of consecutive, newly referred, food-allergic pediatric patients who had previously been prescribed epinephrine by another caretaker were enrolled. In addition, a sampling of pediatricians was also included in the study.

Methods. Parents or teenage patients answered a questionnaire concerning proper administration of self-injectable epinephrine. Patients/families were also asked to demonstrate the use of the devices with which they were familiar.

Results. One hundred one families of food-allergic children (mean age: 6.4 years) were enrolled. Self-injectable epinephrine had been prescribed a mean of 2.7 years previously, primarily by pediatricians (n = 46) and allergists (n = 49). Patients had been prescribed EpiPen (n = 93), EpiE-Z Pen (n = 11), and Ana-Kit (n = 3). Eighty-six percent of the families responded that they had the device with them "at all times," but only 71% of this group had the medication with them at the time of the visit. Among those with the epinephrine with them, 10% of the devices were expired. Thus, only 55% of the 101 families had unexpired epinephrine on hand at the time of the survey. Among children in school, 77% had the medication available in school, and 81% stated that the school was aware of the indications for administration. Only 32% of the participants were able to correctly demonstrate the use of the device.

Twenty-nine attending pediatricians were enrolled with a mean of 14 years in practice and a mean of 4 epinephrine prescriptions per year. Eighty-six percent of the pediatricians reported familiarity with the EpiPen device, 17% with EpiE-Z Pen, and 7% with the Ana-Kit. Overall, 18% were familiar with and able to demonstrate correct use of at least 1 device (21% correctly demonstrated the EpiPen). Seventeen pediatric residents were enrolled; 65% were familiar with the EpiPen and 36% demonstrated it correctly.

Conclusions. A substantial portion of parents of food-allergic children and food-allergic teenagers were unable to demonstrate correctly the use of their self-injectable epinephrine. In addition, a large number may not have the medication readily available at the time of need. Many pediatricians are also not familiar with these devices and may fail to accurately review their use with patients. Improved patient and physician education are needed to ensure proper administration of this life-saving medication.

Reviewer's Comments. This is 1 of at least 2 studies that demonstrated lack of familiarity with self-injectable epinephrine in many patients, parents, and even primary care physicians. It is essential that at the time the medication is prescribed that there be education of the child, parent, and other caretakers regarding the use of these devices.

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OUTDATED EPIPEN AND EPIPEN JR AUTOINJECTORS: PAST THEIR PRIME?

Simons FER, Gu X, Simmons KJ. *J Allergy Clin Immunol.* 2000;105:1025–1030

Purpose of the Study. To evaluate unused, outdated EpiPen and EpiPen Jr autoinjectors for epinephrine bioavailability and epinephrine content.

Methods. This was a prospective, randomized, crossover study of epinephrine bioavailability after injection from outdated autoinjectors in rabbits. Controls included EpiPen and EpiPen Jr autoinjectors that had not expired and intramuscular injection of 0.9% saline solution. In ad-