and a prospective survey of fatal and severe reactions from March 1998–February 2000 were performed.

Methods. Details of death certificates from the offices of national statistics were reviewed for fatal allergic food reactions via codes from the International Classification of Diseases, Ninth Revision (ICD-9), and inquiries were sent to pediatricians asking them to report on patients under 16 who died or were admitted to the hospital for an allergic reaction to food.

Results. Eight children died in a population of 13 million children, yielding an incidence of 0.006 deaths per 100,000 children. Milk caused 4 of the deaths, peanut, 2; egg white, 1; and mixed food, 1. Two children died despite receiving early epinephrine before admission, and 1 child with a mixed food reaction died from an epinephrine overdose. Over the 2-year prospective period, there were 6 near-fatal reactions, none caused by peanut, and 49 severe ones, 10 caused by peanut, yielding incidences of 0.02 and 0.19 per 100,000 children per year, respectively. All fatal cases and 5 of 6 near-fatal cases had a clear history of asthma. Those suffering the most severe reactions tended to have had severe previous reactions, but it was notable that in 2 of 3 fatal reactions and 5 of 6 near-fatal reactions, the previous event had not required urgent hospital treatment.

Conclusions. The finding of so few deaths in such a large population should reassure parents and doctors that the risk of death is small. The child with food allergy and asthma may be at particular risk. Although a previous mild reaction may not be as reassuring as had been thought, the absence of asthma may be. Early administration of epinephrine may not prevent death, and concomitant treatment for the asthmatic component of an allergic reaction may be very important.

Reviewers' Comments. Although the risk of death from food allergies may be small, parents and physicians should not be lulled into a false sense of security regarding the potential severity of adverse reactions to foods. Concomitant asthma places patients with food allergy at particular risk of a severe reaction. Although some foods more commonly cause severe reactions, it is important to note that any food theoretically can cause a severe life-threatening reaction, and the fact that milk caused more food-related deaths than peanut in this study emphasizes this point. The authors also mention that early epinephrine use may not prevent death, but it is still the general consensus that early and proper use of epinephrine in severe food reactions is associated with a better prognosis.

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MATERNO-FETAL PASSAGE OF NUTRITIVE AND INHALANT ALLERGENS ACROSS PLACENTAS OF TERM AND PRETERM DELIVERIES PERFUSED IN VITRO


Purpose of the Study. The pre- and postnatal environment appears to be of crucial importance for the manifestation of allergic diseases that often begin in infancy. This study sought to determine if food and inhalant allergens are transported across placenta.

Study Population. Placentas from 44 normal term pregnancies and from 4 preterm pregnancies (26, 28, 32, and 34 weeks of gestation) were investigated.

Methods. Placentas were obtained immediately after delivery to recover functionally active maternal and fetal circulation. A fetal artery and a fetal vein were cannulated and perfused with pure medium, whereas the intervillous space of placenta was flushed with allergen containing medium (materno-placental circulation). Samples were collected throughout the perfusion experiment from fetal venous outflow and tested for the presence of β-lactoglobulin (BLG), ovalbumin (OVA) and the inhalant birch pollen allergen Bet v 1.

Results. Transplacental transfer of BLG, OVA, and Bet v 1 was detected in both term and premature placentas. The allergens were readily detectable in fetal effluent at the beginning of the perfusion experiment and allergen levels reached plateau after about 2 hours. The steady state transfer rate of BLG and OVA in term placentas was 0.012% ± 0.001 and 0.013% ± 0.001 of total dose. The observed transfer rate of Bet v 1 after 2 hours of perfusion was 0.155% ± 0.034 of total dose. Transplacentally transferred concentration of BLG and OVA in preterm placentas increased continuously throughout perfusion time.

Conclusions. Allergen-specific cord blood reactivity may be attributed to low levels of allergens crossing the human placenta and providing the fetus with the necessary stimulus for T cell priming.

Reviewers' Comments. An accumulating body of evidence supports the transplacental transfer of food and environmental allergens. Specific immunoglobulin (IgE) antibodies are present in the cord blood and furthermore, peripheral blood mononuclear cells from fetuses as early as 20 weeks of gestation proliferate on stimulation with specific allergens indicating previous exposure. Transplacental transfer of food allergens such as peanut may be partially responsible for early sensitization and development of food allergy.

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ANAPHYLAXIS

EPINEP JR VERSUS EPINEP IN YOUNG CHILDREN WEIGHING 15 TO 30 KG AT RISK FOR ANAPHYLAXIS


Purpose of the Study. Epinephrine autoinjectors are widely prescribed for out-of-hospital treatment of children at risk for anaphylaxis. Prescribing physicians face the dilemma of choosing either the 0.15-mg Epipen Jr or the 0.30-mg EpiPen when neither dose is deemed optimal. These investigators studied the rate and extent of epinephrine absorption after administration of either EpiPen Jr or EpiPen in children weighing 15 to 30 kg.

Study Population. Ten children were recruited from pediatric allergy practices with the following entry criteria: age, 4 to 8 years; weight, 15 to 30 kg; history of severe acute allergic reaction(s); and current EpiPen Jr or EpiPen carriage. Eight patients had peanut anaphylaxis, while 1 each had anaphylaxis to egg and fish.

Methods. Study patients were randomly assigned in double-blind manner to self-administer either EpiPen Jr or EpiPen in the lateral thigh after formal review of proper administration technique. Plasma epinephrine concentrations, blood glucose, blood pressure, heart rate, and ad-
verse effects were monitored before and for 180 minutes after the injection.

**Results.** The 5 children who used EpiPen Jr had a mean age of 5.4 years, mean weight of 18.0 kg, and achieved a maximum plasma epinephrine concentration of 2037 pg/mL at 15 minutes. Those who used EpiPen had a mean age of 6.6 years, mean weight of 25.4 kg, and had maximum plasma epinephrine concentrations of 2289 pg/mL at 15 minutes. Mean systolic blood pressure 30 minutes after injection was significantly higher with the EpiPen than with EpiPen Jr. Transient pallor was noted in all 10 subjects after injection. Tremor and anxiety were noted in some subjects receiving EpiPen Jr and in all subjects receiving EpiPen. Some of the EpiPen recipients also experienced headache and nausea.

**Conclusions.** Although EpiPen raised systolic blood pressure significantly more than did EpiPen Jr, the higher-dose device was associated with distinctly more side effects. The small study sample size, coupled with the fact that the children receiving EpiPen Jr were significantly smaller, likely explains the failure to identify a significant difference in peak plasma epinephrine concentrations after the 2 different doses. In the absence of more dosing options in children in the 15- to 30-kg weight range, the prescribing physician must rely on certain clinical details. The EpiPen should be considered when: weight is close to 30 kg; the patient has asthma (a known poor prognostic factor in anaphylaxis); history of severe acute allergic event; and suboptimal access to emergency care. The adverse effects of epinephrine are largely unavoidable, given the narrow therapeutic index of the drug. This fact is not justification for delay in administering epinephrine, because such delay is also associated with poorer prognosis. Additional EpiPen fixed doses need to be made available for children in the 15- to 30-kg range.

**Reviewer’s Comments.** The major problem we face is parental/other responsible party fear of administering the EpiPen or EpiPen Jr device, despite extensive education regarding all aspects of the clinical problem, including the treachery that comes with the “wait to see if things get worse” approach. Although it would be good if we could fine-tune EpiPen dosing better in the weight group discussed in this article, this core compliance problem will remain. Proper contingency treatment with an EpiPen of whatever dosing strength will continue to require lots of encouragement and reinforcement for parents especially.

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**ATOPIC DERMATITIS**

**ENDOGENOUS ANTIMICROBIAL PEPTIDES AND SKIN INFECTIONS IN ATOPIC DERMATITIS**


**Purpose of the Study.** The immune system of human skin contains several antimicrobial peptides, particularly cathelicidins (LL-37) and β-defensins. Although these peptides are negligible in normal skin, they accumulate in skin affected by inflammatory diseases such as psoriasis. The purpose of this study was to compare the levels of expression of LL-37 and human β-defensin 2 (HBD-2) in inflamed skin from patients with atopic dermatitis and from those with psoriasis.

**Study Population.** Patients with atopic dermatitis or psoriasis were compared with normal controls with no skin disease.

**Methods.** The expression of LL-37 and HBD-2 protein in skin biopsy specimens was determined by immunohistochemical analysis. The amount of antimicrobial peptides in extracts of skin samples was also analyzed by immunoblot and Western blot analysis for LL-37 and HBD-2. Reverse transcriptase-polymerase chain reaction (RT-PCR) assays were used to confirm the relative expression of HBD-2 and LL-37 messenger RNA (mRNA) in the skin-biopsy specimens. These peptides were also tested for antimicrobial activity against *Staphylococcus aureus* with the use of a colony-forming assay.

**Results.** Immunohistochemical analysis confirmed the presence of abundant LL-37 and HBD-2 in the superficial epidermis of all patients with atopic dermatitis. In comparison, immunostaining for these peptides was significantly decreased in acute and chronic lesions from patients with atopic dermatitis (*P* = 0.006 and *P* = 0.03, respectively). RT-PCR showed significantly lower expression of HBD-2 mRNA and LL-37 mRNA in atopic lesions than in psoriatic lesions (*P* = 0.009 and *P* = 0.02, respectively). The combination of LL-37 and HBD-2 showed synergistic antimicrobial activity by effectively killing *S aureus*.

**Conclusions.** A deficiency in the expression of antimicrobial peptides may account for the susceptibility of patients with atopic dermatitis to skin infection with *S aureus*.

**Reviewer’s Comments.** It has long been recognized that patients with atopic dermatitis have an enormous predilection for cutaneous infections with *S aureus*, as well as viral pathogens. Although this could be attributable in part to damage to the skin through excessive scratching, it has also been presumed that specific immunologic mechanisms must also play a role. This study elegantly unravels at least part of the immunologic basis for this common clinical problem.

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**EFFICACY AND SAFETY OF TACROLIMUS OINTMENT COMPARED WITH THAT OF HYDROCORTISONE ACETATE OINTMENT IN CHILDREN WITH ATOPIC DERMATITIS**


**Purpose of the Study.** To compare 0.03% and 0.1% tacrolimus ointment with 1% hydrocortisone acetate ointment in children 2 to 15 years of age with moderate-to-severe atopic dermatitis (AD).

**Study Population.** Children ages 2 to 15 years with a diagnosis of AD were recruited from 27 centers in 6 European countries and Canada. Patients were required to have a severity grading of moderate to severe (using established criteria) and at least 5%, but not >60%, total body surface area (BSA) involvement.

**Methods.** This was a phase III, multicenter, randomized, double-blind, parallel-group trial. Patients were randomized (1:1:1) to receive 0.03% or 0.1% tacrolimus or 1% hydrocortisone acetate. Treatment included application of a thin layer of ointment twice daily to active skin lesions until clearing of lesions for 7 days. Other therapies were prohibited with the exception of inhaled or intranasal corticosteroids (maximum dose: 1 mg/day) and nonmedicated emollients or bath oils. Assessments were at baseline, days 3 and 7 and weeks 2 and 3 of treatment and 2 weeks after completing treatment (week 5). Assessments included investigator rating of skin disease and BSA involvement and patient symptoms assessment symptoms. These were used to calculate the modified eczema area and severity
EPIPEN JR VERSUS EPIPEN IN YOUNG CHILDREN WEIGHING 15 TO 30 kg AT RISK FOR ANAPHYLAXIS

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