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 16 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

Ong PY, Ohtake T, Brandt C, et al. *N Engl J Med*. 2002; 347:1151–1160

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 immunodot blot analysis (for LL-37) and Western blot analysis (for 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 psoriasis. In comparison, immunostaining for these peptides was significantly decreased in acute and chronic lesions from patients with atopic dermatitis ($P = .006$ and $P = .03$, respectively). RT-PCR showed significantly lower expression of HBD-2 mRNA and LL-37 mRNA in atopic lesions than in psoriatic lesions ($P = .009$ and $P = .02$, 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

Reitamo S, Van Leent EJM, Ho V, et al. *J Allergy Clin Immunol*. 2002;109:539–546

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

index (mEASI). A graded physician's global evaluation regarding clinical response was also included. Adverse events and laboratory assessments were obtained.

Results. A total of 560 patients were enrolled. Study discontinuations were as follows: 21 of 189 in 0.03% tacrolimus group, 13 of 186 in 0.1% tacrolimus group, and 20 of 185 in hydrocortisone group. The mEASI, mean area under the curve (mAUC) as percentage of baseline showed the 0.03% tacrolimus (44.8%) and 0.1% tacrolimus (39.8%) to be more effective than 1% hydrocortisone (64%), and 0.1% tacrolimus to be the most effective treatment. Transient skin-burning was reported more often in the tacrolimus groups. Laboratory parameters showed no treatment differences and no significant changes between groups.

Conclusions. Tacrolimus 0.03% and 0.1% ointments were more effective and showed equivalent safety when compared with 1% hydrocortisone in the treatment of children with moderate-to-severe AD.

Reviewer's Comments. This study demonstrates the usefulness and safety of tacrolimus ointment for children with moderate-to-severe AD. This new class of nonsteroid, immunomodulatory medications provides important therapeutic alternatives to long-term corticosteroid therapies for young children.

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LONG-TERM TREATMENT WITH CETIRIZINE OF INFANTS WITH ATOPIC DERMATITIS: A MULTI-COUNTRY, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL (THE ETAC TRIAL) OVER 18 MONTHS

Diepgen TL and the Early Treatment of the Atopic Child Study Group. *Pediatr Allergy Immunol.* 2002;13:278–286

Purpose of the Study. To analyze the effects of long-term use of cetirizine on the severity, natural history, and treatment of atopic dermatitis (AD).

Study Population. A total of 795 infants, 12 to 24 months old, with active AD for at least 1 month and 1 parent or sibling with a history of AD, allergic rhinitis, or asthma were enrolled from 12 European countries and Canada.

Methods. This was a prospective, randomized, double-blind, parallel-group study comparing cetirizine with placebo in infants with AD and a family history of atopy. Systemic corticosteroids, cromoglycate, and oral antihistamines were discontinued; however, topical therapy for AD was continued. After a washout period, participants then received treatment with 0.25 mg/kg of cetirizine or placebo twice daily for 18 months. Follow-up visits were at 1 and 3 months, then every 13 weeks during the 18-month treatment period. At each visit, atopy status, severity of AD based on the SCORAD index (an objective rating scale used to determine AD severity), concomitant therapy and adverse experiences were recorded. Blood and urine samples were followed throughout the study to evaluate total and specific immunoglobulin E (IgE) and eosinophil counts.

Results. During the treatment period, participants in both groups had a steady decline in the severity of AD based on both the subjective symptom score and SCORAD index. Although this decline was statistically significant ($P < .001$), no difference was observed between study groups. There were no specific recommendations or restrictions for additional therapy for AD during the treatment period, and significantly more participants in the placebo group were treated with additional oral H1 antihistamines when compared with the treatment group (25% vs 19%; $P = .03$). There was no statistically significant difference observed in topical steroid use between groups; however, the duration of moderate-to-strong topical steroids (class II-IV) was longer in the placebo group (25% of the days vs 18%; $P = .067$). This relative corticosteriod-sparing effect was statistically significant for infants with severe disease (SCORAD index ≥25) at baseline (35% of days vs 26%; $P = .014$). The number of participants who developed urticaria was significantly lower in the treatment group than placebo (5.8% vs. 16%, $P < .001$). There were no significant differences in the occurrence of other adverse events between groups.

Conclusions. The use of cetirizine in infants with AD appears to be safe and significantly reduces the use of additional H1 antihistamines and the occurrence of urticaria. Results also suggest that cetirizine has a relative corticosteroid-sparing effect by decreasing the duration of moderate-to-potent topical steroid use.

Reviewers' Comments. Oral antihistamine therapy has become a major component of the treatment of AD based largely on anecdotal experience. This is the first large prospective study evaluating the long-term efficacy and safety of treatment of AD with cetirizine in an atopic population. Cetirizine proved to be safe as patients in the treatment group did not experience significantly more adverse reactions, but, in fact, had a significantly decreased risk of urticaria. One limitation of this study was the lack of restriction of additional antihistamines during the treatment period. Significantly more patients on placebo used H1 antihistamines, and this suggests that antihistamine therapy is an effective, if not essential, component in the treatment of AD. It is likely that more significant differences in topical or systemic steroid use, concomitant medication use, or disease severity may have been observed between groups if this class of drugs was restricted. Patients in the treatment group had fewer days of moderate-to-potent topical steroid use, and this difference was statistically significant in severe disease further supporting the use of antihistamines as an effective component in the management of AD. Because this study was a part of the ETAC trial, the primary endpoint for efficacy was asthma with secondary endpoints for efficacy in the duration and severity of AD. Future studies designed with efficacy for treatment of AD as the primary endpoint with more specific restrictions and limitations on concomitant therapy would also be very useful.

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DRUG ALLERGY

LACK OF PENICILLIN RESENSITIZATION IN PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY AFTER RECEIVING REPEATED PENICILLIN COURSES

Solenksy R, Earl HS, Gruchalla RS. *Arch Intern Med.* 2002;162:822–826

Purpose of the Study. To determine the rate of penicillin (PCN) resensitization in adults with a history of PCN allergy after exposure to multiple courses of PCN.

Study Population. Fifty-three adults with a clinical history consistent with an acute, immunoglobulin E (IgE)-mediated reaction to PCN.

Methods. Adults >18 years of age who had a history consistent with an acute, IgE-mediated reaction to PCN were recruited for the study. Participants underwent PCN

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Stacie M. Jones

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