

Epinephrine Concentrations in EpiPens After the Expiration Date

Cantrell FL, Cantrell P, Wen A, Gerona R. *Ann Intern Med*. 2017;166(12):918–919

PURPOSE OF THE STUDY. To determine if EpiPens are still potent up to 50 months after the labeled expiration date.

STUDY POPULATION. Unused, expired EpiPens were collected from patients and practitioners at a community clinic.

METHODS. Patients and practitioners provided unused, expired EpiPens over a 2-week period. All units were examined for color changes and expiration date. The concentration of epinephrine in two aliquots from each unit was quantified by liquid chromatography and tandem mass spectrometry. Epinephrine-d6 was used as an internal standard.

RESULTS. Thirty-one expired EpiPen and 9 EpiPen Jr autoinjectors were analyzed. All medications were between 1 to 50 months past the labeled expiration date. None were discolored. Sixty-one percent (19 out of 31) of the EpiPen and 56% (5 out of 9) EpiPen Jr devices contained at least 90% of the stated amount of epinephrine. All the devices had at least 80% epinephrine remaining at the time of testing.

CONCLUSIONS. EpiPen and EpiPen Jr autoinjectors retain a majority (at least 80%) of the labeled quantity of epinephrine up to 50 months after the written expiration date.

REVIEWER COMMENTS. Although there appeared to be a trend for the concentration of epinephrine to slightly decrease over time in the devices tested, the authors of this study demonstrate that most of the drug is still present after several years. The limitations of this study include the small number of devices and the unknown number of lots analyzed, and the authors did not assess how the units were stored or handled before and after they were expired. Considering the recent controversy regarding the skyrocketing prices of prescribed self-injectable epinephrine devices, more attention among prescribers and patients has been directed toward the use of expired epinephrine, particularly when it is cost prohibitive or no other alternative is readily available in an emergency situation. Future studies should be focused on outcomes in cases in which expired epinephrine and the minimum dose content that would be needed to deliver a therapeutic effect are used. In the meantime, the authors suggest that, in the event of a severe allergic reaction, it would be more prudent to use an expired EpiPen rather than no EpiPen at all.

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Saritha Kartan, MD
Joyce E. Yu, MD
New York, NY

DRUG ALLERGY

The High Impact of Penicillin Allergy Registration in Hospitalized Patients

van Dijk SM, Gardarsdottir H, Wassenburg M, et al. *J Allergy Clin Immunol Pract*. 2016;4(5):926–931

PURPOSE OF THE STUDY. To assess the impact of a diagnosis of penicillin allergy in hospitalized patients.

STUDY POPULATION. The study included all patients (children and adults) admitted at the University Medical Center in Utrecht, the Netherlands, over a 1-year period who underwent a standardized pharmacotherapeutic interview. There were 997 patients with documentation of penicillin allergy (Pen-A) and 2939 patients without documentation of penicillin allergy (non-Pen-A).

METHODS. This was a prospective, matched cohort study. Patients were registered as having penicillin allergy if the history demonstrated either an evaluation by a specialist or general practitioner and/or symptoms of cutaneous, respiratory, or cardiovascular disturbance or fever. The primary outcome measure was the prevalence of Pen-A registration. Secondary outcomes included the risk of receiving a reserve antibiotic, the risk of death during hospitalization, the duration of hospitalization, and the risk of readmission within 4 and 12 weeks after discharge.

RESULTS. Of hospitalized patients, 5.6% had a Pen-A registration. Compared with non-Pen-A control patients, Pen-A subjects had a significantly higher rate of receiving a broad-spectrum antibiotic (relative risk, 1.38; 95% confidence interval, 1.22–1.56), of receiving 2 or more antibiotics (21.7% vs 16.9%), and of readmission within 12 weeks after discharge (relative risk, 1.28; 95% confidence interval, 1.10–1.49). There was no significant difference between the two groups in terms of duration of hospitalization, mortality during hospitalization, and risk of readmission within 4 weeks of discharge. Of interest, 14.5% of all Pen-A patients treated with antibiotics were exposed to penicillin during the hospitalization.

CONCLUSIONS. Pen-A registration in the hospital setting has a high impact on antibiotic treatment strategies, including the prescription of broad-spectrum antibiotics and multiple antibiotics as well as an increased risk of readmission within 12 weeks after discharge.

REVIEWER COMMENTS. The prevalence of penicillin allergy diagnosis in this hospitalized cohort was 5.6%, which is significantly lower than the reported prevalence of 11% to 15% in other studies conducted in the United States. This difference is likely due to the rigorous standardized interview used in this study. All too often, a report of penicillin allergy by the patient is recorded without attempts to verify the diagnosis or perform diagnostic skin testing. Given the negative impact of such a diagnosis on medical outcomes, it is incumbent upon the general practitioner and

specialist alike to pursue a detailed history of the adverse event and to obtain diagnostic testing when indicated. This approach is now one of the recommended interventions issued by the American Academy of Allergy, Asthma, and Immunology as part of the “Choosing Wisely” campaign.

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Anne-Marie Irani, MD
Richmond, VA

Assessing the Diagnostic Properties of a Graded Oral Provocation Challenge for the Diagnosis of Immediate and Nonimmediate Reactions to Amoxicillin in Children

Mill C, Primeau MN, Medoff E, et al. *JAMA Pediatr*. 2016;170(6):e160033

PURPOSE OF THE STUDY. To assess the accuracy and the negative predictive value of the provocation challenge in a cohort of children referred to a single center with suspected amoxicillin allergy.

STUDY POPULATION. Children with suspected amoxicillin allergy who were referred to the Montreal Children's Hospital in Quebec, Canada, between March 1, 2012, and April 1, 2015, were recruited. Exclusion criteria were any reactions compatible with either Stevens-Johnson syndrome or toxic epidermal necrolysis.

METHODS. Children with a prior history of rash while receiving amoxicillin were administered oral drug challenges (10% of the therapeutic dose, then 90% of the dose 20 minutes later [ie, 50 mg/kg per dose to a maximum of 1.5g]). All children were observed for at least 1 hour after receiving their last dose. Only those with positive challenge results underwent skin testing (prick and intradermal) and were offered a subsequent graded provocation challenge to cefixime (3rd-generation cephalosporin). Univariate and multivariate logistic regressions were compared with determining factors associated with immediate (<1 hour) and nonimmediate reactions (>1 hour) to the provocation challenge.

RESULTS. Of 818 children assessed (median age of 1.7 years [interquartile range 1.0–3.9 years]; 441 [53.9%] male), 771 (94.1%) tolerated amoxicillin without any reaction, 17 (2.1%) developed immediate reactions (all were hives only; 5 reacted to initial 10%), and 31 (3.8%) developed nonimmediate reactions (maculopapular rashes and serum sickness–like reactions). For the 17 children who developed immediate reactions, skin tests were performed 2–3 months later with penicillin and the penicilloyl (major) determinant; the skin test was positive in only 1 patient (5.9%). All 17 tolerated cefixime. The graded amoxicillin challenge had a negative predictive value of 89.1% (95% CI, 77.1%–95.5%). A history of a reaction occurring within 5 minutes of exposure was associated with immediate reactions to amoxicillin. A rash that

lasted longer than 7 days and parental history of drug allergy were associated with nonimmediate reactions to amoxicillin.

CONCLUSIONS. Graded provocation challenges provide an accurate and safe confirmatory test for skin-related reactions to amoxicillin. Further studies are required to assess factors associated with outcomes.

REVIEWER COMMENTS. Over half of the children enrolled in the study had their reaction to amoxicillin with their first exposure; such reactions are less likely to be immune mediated. Moreover, none had a history of anaphylaxis. Thus, these results may be applied to pediatric cases presenting with cutaneous, nonanaphylactic reactions.

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Jennifer S Kim, MD
Chicago, IL

FOOD ALLERGY

Impact of Peanut Consumption in the LEAP Study: Feasibility, Growth, and Nutrition

Feeney M, Du Toit G, Roberts G, et al. *J Allergy Clin Immunol*. 2016;138(4):1108–1118

PURPOSE OF THE STUDY. To evaluate the feasibility of peanut (PN) introduction in infancy and its effects on growth and nutrition.

STUDY POPULATION. This study was a planned secondary analysis from the LEAP trial (*N Engl J Med*. 2015;372:803–813), in which 4- to 11-month-old infants who tolerated PN were advised to eat 6 g of peanut protein per week to age 5 years. The control population included infants who did not tolerate PN during the LEAP trial.

METHODS. PN consumption was monitored by using a validated questionnaire. Anthropomorphic measurements were taken and 3-day food diaries completed for each study visit. Average daily caloric intake and that of macro- and micronutrients were calculated.

RESULTS. The median age at screening was 7.8 months. Median peanut consumption exceeded 6 g throughout the study. Peanut introduction in infancy did not shorten the duration of breastfeeding. There was no difference between groups in weight, height, BMI, tricep skinfold thickness, or other anthropomorphic measurements. Total caloric intake was the same between groups. The percent of energy from carbohydrates was higher in the avoidance group at all time points, whereas the percent of energy from fat was higher in the PN consumption group, especially in the upper quartiles of consumption. The percent of energy from protein was comparable between groups. Similarly, there were no differences in the intake of sodium, calcium, iron, zinc, or vitamin D.

CONCLUSIONS. Early dietary introduction of peanut in high-risk infants who tolerate it has no effect on the duration of breastfeeding, growth, or nutrition.

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Anne-Marie Irani

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Anne-Marie Irani

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