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Predicting outcome of repeat milk, egg, or peanut oral food challenges

To the Editor:

Food allergy affects about 12 million people in the United States, including 3 million children.¹ Frequently, oral food challenges (OFCs) are necessary to obtain a definitive diagnosis or to expand a restricted diet. Clinical guidelines exist to determine who should have initial OFCs,²⁻⁵ but few data exist regarding the factors that may predict the outcome of repeat OFCs in patients who previously failed an OFC.

Records were reviewed of patients with food allergy who underwent clinically indicated OFCs to milk, egg, and/or peanut between August 1991 and April 2009. Patients were identified who reacted during their initial OFC and underwent a subsequent OFC to the same food. The decisions on whether and when to offer a repeat OFC was based on the interval since the previous challenge and clinical indicators including repeat food-specific IgE measurements and exposure and symptom history since the initial challenge. Data were collected on the severity of OFC reactions, the dose that caused the reaction, patient age at the time of OFCs, time interval between initial and repeat OFCs, and food-

specific IgE measurements at the time of the OFCs. Reaction severity was classified as mild, moderate, or severe based on the type and number of systems involved (oral, skin, gastrointestinal, respiratory, or cardiovascular) in the reaction.⁶ The ingestion amount was expressed as the percentage of the potential 6-g challenge consumed causing symptoms during a failed OFC. Serum samples were analyzed before challenge for milk, egg, or peanut-specific IgE antibody by using the Phadia CAP system FEIA (Phadia, Uppsala, Sweden). Statistical analyses were performed with StataSE 8.0 (StataCorp, College Station, Tex). Analyses of relationships between categorical predictor variables and outcome of the repeat OFC were conducted by using the χ^2 test, and relationships between continuous predictor variables and OFC outcome were examined by using the Mann-Whitney *U* test.

We identified 101 patients who failed initial OFCs to milk, egg, and/or peanut and went on to have a repeat OFC. Of the 101 subjects, 11 subjects had OFCs on separate occasions to 2 different foods for a total of 112 matched initial and repeat OFCs. Sixty-six (58.9%) repeat OFCs were unsuccessful (Table I). More patients with severe initial OFC reactions failed subsequent OFCs (70.4% vs 29.6%), although this finding was not statistically significant because of the modest sample size. However, when reaction severity was examined by food, severity of the initial OFC reaction was significant only for milk, for which 12 of the 13 patients who had a severe initial OFC reaction failed the repeat OFC ($P = .002$). The challenge dose that caused a reaction during initial OFCs was not predictive of repeat OFC results, with mean initial OFC doses of 39.7% for those who failed their repeat OFC compared with 41.5% in those who passed. The mean age at the initial OFC of patients who failed or passed repeat OFCs was also similar (4.8 vs 5.1 years), as was the interval between the initial and repeat OFCs (2.9 years, range, 0.7-10.1; vs 2.8 years, range, 0.5-8.6). There was no difference between median food-specific IgE measurements at the time of the initial OFC for passed and failed repeat OFCs. However, at the time of repeat OFC, the median milk IgE level for those who passed the repeat OFC was 0.6 kU/L compared with 2.0 kU/L for those who failed ($P = .0008$). For egg and peanut, median IgE measurements at the time of repeat OFC for passed versus failed challenges were 0.7 versus 1.0 kU/L and 0.4 versus 1.1 kU/L, respectively.

Thirty subjects went on to have a third OFC with a total of 34 third OFCs (16 to milk, 12 to egg, and 6 to peanut). The pass rate was similar to that in the second OFCs at 41.2% with a total of 14 passing (7 to milk, 5 to egg, and 2 to peanut). The severity of the reaction for the first or second OFC was not related to the outcome of the third OFC for any foods. The intervals between the first and third OFCs and the second and third OFCs were significant predictors of third OFC outcome for milk ($P = .01$ and $.03$, respectively) with a longer interval between OFCs related to passing the third milk OFC.

In summary, 41% of patients who failed their initial milk, egg, or peanut OFC went on to pass a repeat OFC to the same food. The severity of the reaction at the initial OFC may be a predictor of the outcome of the repeat OFC, but it was significant only for milk. Although severity did not appear to be a predictor of repeat OFC outcome for egg or peanut, this should be evaluated in a future study with a larger population. The interval between OFCs was predictive only for milk and then only between the second and third OFCs. Food-specific IgE measurements at the initial OFC did not predict the outcome of the repeat OFC. However, patients who passed their repeat milk OFC did have a significantly lower

TABLE I. Predictors of outcome of repeated OFC

Initial OFC N = 112	Failed repeated OFC N = 66	Passed repeated OFC N = 46
Mild reaction n = 39	64.1% (n = 25)	35.9% (n = 14)
Mod reaction n = 46	47.8% (n = 22)	52.2% (n = 24)
Severe reaction n = 27	70.4% (n = 19)	29.6% (n = 8)
Challenge dose (%)	39.7	41.5
Mean age (y)	4.8	5.1
Interval (y)	2.9	2.8
IgE (kU/L)	2.2	1.8

Initial OFC (milk) N = 46	Failed repeated OFC (milk) N = 31	Passed repeated OFC (milk) N = 15
Mild reaction n = 20	75% (n = 15)	25% (n = 5)
Mod reaction n = 13	30.8% (n = 4)	69.2% (n = 9)
Severe reaction n = 13	92.3% (n = 12)*	7.7% (n = 1)*
Challenge dose (%)	31.6	32.7
Mean age (y)	4.7	4.2
Interval (y)	2.9	2.3
IgE (kU/L)	2.7	1.7

Initial OFC (egg) N = 38	Failed repeated OFC (egg) N = 20	Passed repeated OFC (egg) N = 18
Mild reaction n = 6	50% (n = 3)	50% (n = 3)
Mod reaction n = 22	54.5% (n = 12)	45.5% (n = 10)
Severe reaction n = 10	50% (n = 5)	50% (n = 5)
Challenge dose (%)	53.3	35.4
Mean age (y)	2.6	5.9
Interval (y)	2.6	2.9
IgE (kU/L)	1.3	1.5

Initial OFC (peanut) N = 28	Failed repeated OFC (peanut) N = 15	Passed repeated OFC (peanut) N = 13
Mild reaction n = 13	53.8% (n = 7)	46.2% (n = 6)
Mod reaction n = 11	54.5% (n = 6)	45.5% (n = 5)
Severe reaction n = 4	50% (n = 2)	50% (n = 2)
Challenge dose (%)	38.8	63.6
Mean age (y)	5.4	5.1
Interval (y)	3.2	3.0
IgE (kU/L)	2.4	2.2

Mod, Moderate.

*P = .002.

milk-specific IgE level at the time of the repeat OFC than those who failed their repeat milk OFC. Because this was a retrospective chart review of a clinical population rather than a designed research protocol, uncontrolled factors such as seasonality, patient maturity, and family/patient decisions of whether and when to repeat OFC likely had some impact. However, with the possible exception of those who have severe symptoms to their initial milk OFC, the circumstances of the initial failed OFC are

poorly correlated with the outcomes of repeat OFCs. This suggests patients who have not had known reactions in the interim should be considered candidates for a repeat OFC, regardless of the circumstances of the initial OFC.

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Altered epigenetic regulation and increasing severity of bronchial hyperresponsiveness in atopic asthmatic children

To the Editor:

Environmental influences are believed to shape clinical outcomes in part through epigenetic mechanisms that alter susceptibility to or maintenance of chronic diseases, such as asthma and allergies.¹ Better understanding of the roles of epigenetics in these processes is key to understanding the pathogenesis of chronic inflammatory conditions, as well as to developing prophylactic strategies to reduce their incidence or modulate their intensity. Mechanisms controlling gene expression include methylation of DNA and modifications (eg, acetylation, methylation, and phosphorylation) of histone tails, actively modifying what is known as the "histone code."² Recent evidence suggests that the *in vivo* balance of histone deacetylase (HDAC) and histone acetyltransferase (HAT) activities provides an important mechanism that governs gene expression potential.^{2,3} One limitation of studies to date that seek to assess the effect of (de)acetylation in human subjects is that many focus solely on HDAC or HAT activity when the net ratio of the 2 is thought to be the most relevant outcome.

We recently reported that experimental alteration of the endogenous HDAC/HAT balance in healthy children changes recall T_H1/T_H2 cytokine responses by CD4⁺CD45RO⁺ (antigen-experienced/memory) cells.⁴ Others, using whole cell lysates,