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For infants whose clinical history and physical exam suggest a specific food allergy, a well-designed oral food challenge is the most reliable test.

## Q/What's the best approach to diagnosing food allergies in infants?

### EVIDENCE-BASED ANSWER

**A** | A WELL-DESIGNED ORAL FOOD CHALLENGE (OFC) is the most reliable diagnostic test for infants whose clinical history and physical examination suggest a specific food allergy (strength of recommendation [SOR]: **C**, consensus guidelines).

Serum-specific immunoglobulin E (IgE), atopy patch testing (APT), and skin prick testing (SPT) are all alternatives to

OFC, but the likelihood ratios are not robust and the tests vary widely in sensitivity and specificity to different allergens. For diagnosing egg and milk allergies, larger wheal sizes with SPT are more predictive of a positive OFC (SOR: **C**, extrapolated from cohort studies evaluating mixed populations of infants, children, and teenagers).

### Evidence summary

The American Academy of Allergy, Asthma and Immunology (AAAAI) states that a double-blind, placebo-controlled OFC is the best test for diagnosing infants clinically suspected of having food allergies (that is, who develop gastrointestinal symptoms after eating a specific food). However, performing an OFC in an infant is often difficult and potentially dangerous, especially if a severe allergy is suspected; testing also may eliminate nutritious foods, such as milk and eggs, from the infant's diet.<sup>1</sup> For these reasons, physicians have sought simpler alternatives to the OFC.

### Comparisons of serum and skin testing with OFCs produce variable, weak results

Two large cohort studies compared OFCs with serum and skin testing in infants, children, and teenagers. Overall, serum and skin testing didn't produce robust results and the results varied with the antigen (TABLE).

In 1 study, researchers compared specific serum IgE levels with OFC results for 4 foods—milk, eggs, wheat, and soy—in 501 consecutive pediatric patients referred to an allergy ward based on clinical or parental suspicion

of food allergy. Children ranged in age from 1 month to 16 years (median age 13 months); results for infants were not provided separately. Eighty-eight percent of the children were atopic. Investigators measured serum IgE (using the Pharmacia CAP-system fluorescence enzyme immunoassay) before administering the OFCs.

Of 992 OFCs performed, 445 (45%) were positive (defined as producing urticaria, angioedema, wheezing, vomiting, diarrhea, abdominal pain, shock, or exacerbation of eczema). Most OFCs (73%) were double-blind placebo-controlled, but investigators performed open OFCs in infants and in children with a history of immediate allergic reactions. Investigators retrospectively analyzed serum-specific IgE levels for the 4 food antigens and compared them with the results of the OFCs. Positive likelihood ratios (LR+) for IgE testing ranged from 1.3 to 2.0 for the 4 antigens; negative likelihood ratios (LR-) ranged from 0.31 to 0.59.<sup>2</sup>

The second cohort study compared APT and SPT with OFCs for the same 4 food antigens (milk, eggs, wheat, soy) in 437 children. The study population comprised consecutive referrals to a pediatric immunology depart-

TABLE

## How allergy tests in infants and children compare with an oral food challenge

Test*	Sensitivity (%)	Specificity (%)	LR+	LR-
<b>Milk</b>				
IgE <sup>2</sup>	83	53	1.8	0.32
SPT <sup>3</sup>	85	70	2.8	0.21
APT <sup>3</sup>	31	95	6.2	0.73
<b>Egg</b>				
IgE <sup>2</sup>	97	51	2.0	0.59
SPT <sup>3</sup>	93	54	2.0	0.13
APT <sup>3</sup>	41	87	3.2	0.68
<b>Wheat</b>				
IgE <sup>2</sup>	79	38	1.3	0.55
SPT <sup>3</sup>	75	64	2.1	0.39
APT <sup>3</sup>	27	89	2.5	0.82
<b>Soy</b>				
IgE <sup>2</sup>	69	50	1.4	0.31
SPT <sup>3</sup>	29	85	1.9	0.84
APT <sup>3</sup>	23	86	1.6	0.90

APT, atopy patch test; IgE, serum immunoglobulin E; LR+, positive likelihood ratio; LR-, negative likelihood ratio; SPT, skin prick test.

\*Positive tests were defined as follows:

IgE=serum level >0.35 kU/L (detection limit of assay).

SPT=wheal  $\geq$ 3 mm.

APT=erythema with skin surface change.

ment based on either parental suspicion of a food allergy or a positive IgE test. The children ranged in age from 3 months to 14 years (median age 13 months); results for infants weren't provided separately. Ninety percent of the children were atopic. Investigators performed APTs and SPTs for the 4 food antigens on all children and OFCs only for foods that were clinically suspect (total OFCs=873).

As in the previous study, investigators performed open OFCs (23%) in infants and children with a history of immediate reaction. A positive APT was defined by erythema with infiltration or papules, and a positive SPT by a wheal  $\geq$ 3 mm. For the SPT, the LR+ ranged from 1.9 to 2.8 for the 4 antigens, and the LR- ranged from 0.13 (for egg) to 0.84. For the APT, the LR+ ranged from 1.6 to 6.2 (for milk), whereas the LR- was of little value, ranging from 0.68 to 0.90.<sup>3</sup>

### For milk and eggs, the larger the wheal, the more sensitive the skin test

The size of the wheal may increase the sensitivity of the SPT in some situations. A cohort study similar to the ones described previously compared SPT with OFCs in children with possible food allergies and found that a large SPT wheal was highly correlated with OFC-confirmed allergy to milk and eggs.<sup>4</sup>

Investigators recruited 385 children—3 months to 14 years of age (median age 22 months), results for infants not provided separately—from consecutive referrals to a pediatric immunology department. Most children (87%) were atopic. Investigators performed SPTs, followed by OFCs for milk, egg, wheat, and soy allergens. Overall, 312 (43%) of the OFCs were positive. Wheals measuring  $\geq$ 13 mm for eggs and  $\geq$ 12.5 mm for milk correlated well with OFC results (95% positive pre-

> Serum and skin testing offer alternatives to an oral food challenge, but have weak likelihood ratios and wide variations in sensitivity and specificity to different allergens.

## CLINICAL INQUIRIES

dictive value). Wheal sizes for wheat and soy were poorly predictive, however.<sup>4</sup>

### No validation yet for new techniques to improve accuracy and safety

New techniques to improve the accuracy and safety of allergy testing have yet to be validated clinically. One cohort study of 58 children that used fresh fruit or vegetable preparations for SPT instead of commonly used commercial extracts found added sensitivity.<sup>5</sup> Another cohort study of 142 children allowed suspect foods to contact only the labial mucosa in order to reduce the risk of systemic reactions

(1 case of anaphylaxis occurred nevertheless).<sup>6</sup>

### Recommendations

The AAAAI guidelines state that history and physical examination help determine that food is causing symptoms and that an OFC is diagnostic of food allergy (but risks and benefits must be considered, including the possibility of severe adverse reaction).<sup>1</sup> The guidelines note that other available tests, including food-specific IgE and skin tests, are not specific enough for screening but may be used when a particular food allergy is clinically suspected. **JFP**

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