

## Letter to the Editor

**Anaphylaxis to diphtheria, tetanus, and pertussis vaccines among children with cow's milk allergy**

To the Editor:

Immediate-type hypersensitivity to cow's milk affects approximately 1% to 2% of young children, can persist, and can be fatal.<sup>1,2</sup> Vaccines against tetanus, diphtheria, and pertussis are routinely given to children in multiple doses throughout childhood. Anaphylactic reactions to these vaccines are rare and are generally attributed to the vaccine toxoids.<sup>3,4</sup> The US national Vaccine Adverse Events Reporting System lists 39 anaphylactic reactions to DTaP, DTP, or Tdap vaccines for patients aged 0 to 17 years from 2007-2010.<sup>5</sup> In this period we observed 8 children in our single center with a history of anaphylactic reactions to booster doses of these vaccines. We noted that these vaccines are labeled as being processed in medium containing casamino acids (derived from cow's milk), raising the concern that residual casein in the vaccines might have triggered these reactions. We are not aware of prior reports linking milk contamination to anaphylaxis from these vaccines. To investigate this possibility, we reviewed the medical history of the affected children and tested 8 lots of the vaccines for residual casein.

The clinical characteristics of the 8 children were obtained by means of chart review (approved by the institutional review board) and are shown in Table I. These patients were selected based on reports of anaphylactic reactions to the vaccines and not because of a history of milk allergy. Each patient had symptoms consistent with anaphylaxis<sup>6</sup> within 1 hour of administration of the vaccine. Six of the patients had prior acute allergic reactions to cow's milk, including severe reactions in 5 patients and reactions to trace exposures in 4 patients. One patient was given a diagnosis of milk allergy based on serologic testing performed to evaluate atopic dermatitis, and another was given a diagnosis based on serologic testing to evaluate proctocolitis. Each of the patients had an increased milk-specific IgE level documented within 2 years of the reaction to the vaccine. Although milk-specific IgE levels do not necessarily correlate with severity, the recorded levels are far above those that typically correlate with reactivity.<sup>7</sup>

The vaccine package inserts for the DTaP and Tdap vaccines, including those for Adacel, Boostrix, Daptacel, Infanrix, Kinrix, Pediarix, and Pentacel, all state that either the tetanus toxin is produced by growing *Clostridium tetani* in a modified Latham medium derived from bovine casein or that the *C tetani* is grown in modified Mueller-Miller casamino acid medium.

Additionally, for the acellular pertussis vaccine components, all of the vaccines use a modified Stainer-Scholte medium, but only the Adacel, Pentacel, and Daptacel vaccines specifically mention this being modified with casamino acids. To determine whether there was casein in the vaccines, we performed assays on 5 different lots of the Tdap vaccine and 3 different lots of the DTaP vaccine. We also performed assays on 3 different lots of the influenza vaccine and 1 lot of the hepatitis B vaccine, which do not report processing in medium containing casamino acids, to act as negative controls.

For the assays, 96-well Immulon 4HBX plates (Fisher Scientific, Pittsburgh, Pa) were coated overnight with 50  $\mu$ L/well of 1  $\mu$ g/mL casein (Sigma-Aldrich, St Louis, Mo) diluted in

0.05 mol/L carbonate-bicarbonate buffer (pH 9.6). After washing (3 times) with phosphate-buffered saline containing 0.05% Tween-20 (PBS-T), the plates were blocked with 0.1 mL of PBS-T-ovalbumin 0.07% (OVA grade V, Sigma-Aldrich) per well for 1 hour. Samples (1:1 and 1:2 dilutions) and standards (0.19-190 ng/mL) were prepared and mixed (1:1) with rabbit anti-casein polyclonal antibody (a gift from Ross Laboratories, Columbus, Ohio) diluted at 1:50,000 in blocking buffer. This inhibition mix was incubated for 2 hours at 37°C. A mixture (1:1) of the same antibody with blocking buffer without competing casein was also prepared for cutoff determination. Fifty microliters per well of the test mixture was then pipetted in quadruplicates into the coated microtiter plates and incubated for 1 hour at 31°C. After washing (3 times) with PBS-T, 50  $\mu$ L/well of horseradish peroxidase-labeled goat anti-rabbit IgG (Sigma-Aldrich) diluted to 0.4  $\mu$ g/mL in blocking buffer was added and incubated for 1 hour at 31°C. Plates were washed (6 times) with PBS-T, and 50  $\mu$ L/well of TMB (KPL, Inc, Gaithersburg, Md) was added and allowed to develop at room temperature for 60 minutes. Absorbance values were read at 650 nm with SoftMax Pro software, and the concentration of casein in analytes was obtained from the linear part of the standard curve by using a 5-parameter model. The presence of casein was confirmed in all samples of the Tdap and DTaP vaccines, whereas no casein was found in the negative controls (Table II).

In summary, we identified 8 patients with severe milk allergy who reacted with anaphylaxis to Tdap or DTaP vaccines, which are processed in a broth derived from casein. We identified casein in 8 lots of the vaccines, raising the concern that residual casein in the vaccines might result in reactions for highly sensitive patients with milk allergy.

Allergic reactions have been noted to trace amounts of ingested milk protein.<sup>8,9</sup> We suspect that smaller injected doses, similar to insect sting-induced anaphylaxis, trigger reactions in sensitive patients because digestion is bypassed. Most children with cow's milk allergy receive these vaccines without incident, but the patients we identified have very severe milk allergy, very high milk-specific IgE levels, and, for 4 of them, past reactions to trace milk contamination. These children tolerated their initial vaccinations but reacted to booster doses. This observation is most likely explained by increasing milk sensitivity of the children as they aged, as reflected in the personal histories of several of the children. The number of patients at our single center and their clinical features of severe milk allergy and immediate severe reactions to the vaccine argue against alternative explanations for the reactions. Unfortunately, we were not able to test the lots of the vaccines associated with the reactions, and there might be variability in milk protein content influencing the risks.

In conclusion, our novel observation raises a concern regarding booster vaccination of children with high levels of milk allergy with Tdap and DTaP. Although the children we identified appear by history and testing to be exquisitely allergic to milk, we cannot accurately define a high-risk group based on this case series. Clearly, many highly sensitive children with milk allergy tolerate the vaccines because these reactions are apparently rare. Further studies will be necessary to make more definitive recommendations regarding which children might be at risk. Manufacturer investigation and possible labeling or elimination of casein from the vaccines might avoid this risk. In the interim, caution is

**TABLE I.** Clinical characteristics of the children who reacted to the tetanus vaccines

Age at time of reaction (y)	Sex	Milk allergy history	Asthma history	Milk-specific IgE level (kIU <sub>A</sub> /L)	Symptoms of reaction after vaccination	Treatments given	Vaccine administered	Time to reaction after vaccine administration
4	Male	Proctocolitis from cow's milk-based formula at 3 mo of age	Yes	82.9	Diffuse hives, respiratory distress	Diphenhydramine, oral steroid	DTaP	10 min
5	Male	Hives, lip angioedema, wheezing at 3 y of age after eating turkey with milk contamination	Yes	>100	Repetitive cough, sneezing, rhinorrhea	Albuterol, diphenhydramine	DTaP	10 min
5	Male	Urticaria, edema of the face, and wheezing after contact with milk-based formula at 2 y of age	Yes	>100	Generalized urticaria, facial swelling, wheezing, retractions, difficulty breathing	Diphenhydramine, epinephrine	DTaP	Immediately
6	Male	Milk was eliminated based on allergy testing as an infant after presenting with atopic dermatitis	Yes	>100	Cough, hives, facial swelling	Levalbuterol, diphenhydramine	DTaP	Within 15 min
11	Male	Urticaria and vomiting at 11 mo of age after eating yogurt; facial swelling and diffuse rash at 8 y of age after eating turkey with milk contamination	Yes	58.9	Generalized urticaria, sneezing, congestion, wheezing	Levalbuterol, diphenhydramine, oral steroid	Tdap	Within 10 min
11	Female	Vomiting after milk-based formula as an infant; angioedema of hands after contact with spilled milk at 1 y of age	Yes	96.1	Throat tightness, wheezing, respiratory distress	Epinephrine	Tdap	Driving home from pediatrician
16	Female	Cough, wheezing, and vomiting after milk at 1 y of age; respiratory distress, vomiting, hypotension, and cardiac arrest after eating pasta sprinkled with cheese at 8 y of age	No	>100	Nasal congestion, watery eyes, hives, wheezing, chest tightness	Diphenhydramine, oral steroid	Tdap	Within 1 h
17	Male	Hives, lip, and tongue swelling; diarrhea; and abdominal pain at 4 y of age	Yes	>100	Wheezing, respiratory distress, flushing of face and neck	Epinephrine	Tdap	Within 20 min

advised when immunizing highly sensitive children with milk allergy with booster doses of these vaccines.

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**TABLE II.** Mean casein concentrations in vaccine samples examined

Vaccine	Brand name	Lot numbers	Casein (ng/mL)
Tdap	Adacel	C3727BA	12.7
Tdap	Adacel	C3518AA	13.6
Tdap	Adacel	C3819AA	8.1
Tdap	Adacel	C3246BA	17.3
Tdap	Adacel	C3448AA	11.8
DTaP	Daptacel	C3192BA	10
DTaP	Infanrix	AC14B099BA	18.3
DTaP	Infanrix	AC14B121BB	12.2
Influenza	Fluarix	AFLUA531BA	0
Influenza	Fluzone	UT3667AA	0
Influenza	Fluvirin	111814P1	0
Hepatitis B (recombinant)	Recombivax	1023Y	0

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