

Beef Allergy in Children

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Beef allergy was poorly known before the '90s. Since then, a number of papers appeared elucidating the nature, epidemiology, and symptoms of beef allergy in children allergic to cow's milk and children suffering from atopic dermatitis. It is now clear that beef allergy is not an infrequent occurrence, with an incidence between 3.28% and 6.52% among children with atopic dermatitis, its incidence may be as much as 0.3% in the general population. A diagnosis of beef allergy must be supported by skin prick tests, RASTs, and challenges. The specificity and sensitivity according to type of test and the type of extract, however, remains to be evaluated. Despite the fact that other allergens can be sensitizing, the major beef allergen is bovine serum albumin (BSA). Beef-sensitive children are also sensitized to ovine serum albumin, as well as to other serum albumins; therefore, the use of alternative meats in beef-allergic children must be carefully evaluated on an individual basis. Because industrial heat processing is more efficient than domestic cooking in reducing reactivity in beef-sensitive children, freeze-drying and homogenization may support the introduction of processed beef into the diet of beef-allergic children. *Nutrition* 2000;16:454–457. ©Elsevier Science Inc. 2000

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BEEF ALLERGY IS NOT AS INFREQUENT AS SOMETIMES THOUGHT

It is often mentioned that meat allergy rarely occurs during childhood, although an adverse immune reaction and bovine allergens have been linked in children with atopic dermatitis.^{1,2} In a 1985 study, Sampson and McCaskill found that 18 of 113 (15.9%) atopic children tested positive to a skin-prick test (SPT) to beef, although only two (1.8%) could be confirmed in a double-blind, placebo-controlled food challenge (DBPCFC).³ In a 1986 study of 15 children with atopic dermatitis who were also allergic to cow's milk, two (13.3%) tested positive at oral challenge with beef.⁴ In a recent study, we were able to diagnose beef allergy in a larger population of children but with a higher portion of beef.⁵ Among 184 atopic children, 20 (10.86%) were reactive to beef, 12 (6.52%) of whom had a clinical response during open challenge with 180 g of beef prepared to reproduce home conditions. A study by Werfel et al.⁶ in 1997 diagnosed beef allergy among 11 (3.28%) of 335 atopic children, but the challenge dose of beef was unstated and from an infant food preparation, with no indication of processing methods. Eight of these children reacted positively to beef challenge, whereas three developed symptoms during a later open challenge, although they had tested negative at diagnostic challenge. This is also the only study dealing with cross-reactivity between beef and cow's milk allergens (Table I). Although the majority of cases of beef-allergic children respond positively to milk proteins at SPT, the issue of cow's milk allergy (CMA) among beef-allergic children has never been addressed from their perspective. With a 6.52% frequency among atopic, SPT-positive children,⁴ beef allergy cannot be said to be a rare condition, at least in our population. Because atopic dermatitis may affect as many as 5% of the general pediatric population,⁷ the incidence of beef

TABLE I.

SETTING, SENSITIVITY, AND PREVALENCE OF BEEF ALLERGY IN THE LITERATURE

Reference	Setting	SPT+ to beef	Beef challenge+
Sampson ¹	AD	15.9%	1.8%
Sampson ²	CMA	—	13.3%
Fiocchi et al. ⁵	AD, food SPT+	10.86%	6.52%
Werfel et al. ⁶	AD	26.56%	3.28%
	CMA	84%	20%
Fiocchi et al. ⁸	Reporting beef allergy	100%	58.83%

+, positive; AD, atopic dermatitis; CMA, cow's milk allergy; SPT, skin-prick test.

allergy may be as much as 0.3% in the general population. Whether meat allergy is currently on the rise as are other allergies in industrialized nations remains for epidemiologists to settle. What is certain, however, is that a non-negligible number of patients may require the allocation of medical resources for an extensive diagnostic work-up and long-term follow-up care (Table I).

DIAGNOSING BEEF ALLERGY

Allergists hear more reports of "meat allergy" than they are able to confirm from an increasing number of pediatric patients. This secular trend is unfolding when the prevalence of a relatively rare condition is unknown in the general adult population, let alone for patients with polyvalent sensitizations. To compound the problem, the performance characteristics of cutaneous diagnostic tests with meat allergen extracts have never been estimated.

If self-reports of an immediate reaction after a beef-burger meal are confirmed in 1 of 300 infants by appropriate challenge, ques-

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TABLE II.

BEEF-SPECIFIC IMMUNOGLOBULIN E DETECTED BY IMMUNOBLOTTING		
Protein	Positive responses	
	Class	Number
Actin (<i>n</i> = 12)	III	8
	II	2
	I	2
BSA (<i>n</i> = 12)	V	4
	IV	2
	III	4
	II	2
Myoglobin (<i>n</i> = .5)	II	3
	I	2
Myosin (<i>n</i> = 0)	Any	0
Tropomyosin (<i>n</i> = 0)	Any	0

BSA, bovine serum albumin.

tions about the reliability and the accuracy of the test procedure must be raised. Direct challenges mobilize non-negligible patient and hospital resources, although they are still the reference standard in any allergy work-up. The place of skin testing in the allergy work-up depends on the validation of the allergen extracts, both fresh and commercial, and on the choice of testing strategy. Does the precise nature of the allergen in the test kit matter? Should a first, negative test with one kind of allergen be followed by a second test with the other kind? When should a direct food challenge be mounted? Given the fact that the prevalence of specific food allergies is unknown, is a challenge warranted on the strength of a suspicion index alone, as the general prevalence of the condition is unknown? Can a course of action, for example, allergen avoidance, be recommended on the outcome of one kind of skin test if its result agrees with the report? The allergist must generate from the results of skin tests and preliminary answers from these questions an informed decision, but there are limited data about the mechanism of the allergenicity of beef.

THE MAJOR BEEF ALLERGEN IS BOVINE SERUM ALBUMIN

Cattle-to-people contact through beef has occurred so long in the West that tolerance to bovine proteins is widespread. The precise mechanism and which individual bovine protein is to blame remain unknown, although serum albumins are known allergy triggers^{9,10} and bovine serum albumin (BSA) in particular has been implicated in CMA. All beef-allergic children react to BSA at SPT, but only some of them do so during blinded challenge.⁵ Specifically, circulating immunoglobulin E to BSA and actin can be demonstrated at immunoblot in all of these children (Table II).¹² Actin is involved in all immunoblotting responses, even when the same children do not respond to actin at SPT. Whether the polymer (F-actin) or the monomeric (G-actin) form is present may account for the variability of a response modulated by the conformational variation of actin. Thus, allergenicity needs to be established in the individual by direct challenge. Other bovine proteins, such as myosin, tropomyosin, and myoglobin, fail to react with the sera of beef-allergic children.¹³ Thus, taken together, these data indicate that BSA is the preferential allergen in beef-allergic children.

TABLE III.

RELATIONSHIP BETWEEN SEQUENCE IDENTITY OF DIFFERENT SERUM ALBUMINS AND POSITIVE RESPONSES OBTAINED BY SPT AND IMMUNOBLOTTING			
Animal species	%Identity with BSA	%Positive SPT	%Positive blotting
Beef	100	100	100
Mutton	92.26	100	66.6
Pork	78.84	50	50
Horse	74.14	50	0
Rabbit	72.20	33.3	0
Turkey	Not found	33.3	0
Chicken	44.98	0	0

BSA, bovine serum albumin; SPT, skin-prick test.

BEEF-SENSITIVE CHILDREN ARE SENSITIVE TO BSA, OVINE SERUM ALBUMIN, AND TO OTHER SERUM ALBUMINS

The presence of a specific immunoglobulin E in mammalian or avian meat poses a serious nutritional problem for children with food allergy and in particular for polyallergic children. Lamb and turkey can be proposed as beef substitutes,¹⁴ but little is known about the cross-reactivity between beef and these protein sources. Pork can trigger an adverse reaction in 1.8% to 18%^{3,15} of atopic patients, and Sampson et al. identified 21 children with SPTs positive for chicken of a population of 132 (15.9%).⁴ Adverse reactions to ovine proteins have been reported by 50% of beef-allergic children who had eaten mutton.⁵ Moreover, a population of beef-allergic children reacted more to ovine serum albumin (OSA) than to BSA at DBPCFC; BSA and OSA share 552 of 607 amino-acid sequences^{11,16,17} and thus may be biochemically close enough for cross-reactivity. There is a clear relationship between the percentage of sequence identity of different serum albumins with BSA and the number of positive responses at SPT and immunoblotting in the sera of beef-allergic children (Table III).¹¹ These and other data indicate a wide cross-sensitization between the meat of different and of related animal species. The use of alternative meats in beef-allergic children, therefore, must be carefully evaluated for the individual patient, and no meat or milk can be considered "hypoallergenic."

ENZYMATIC DIGESTION CAN AFFECT BOVINE AND OVINE MEAT ALLERGENICITY

Many children testing positive at SPT for meat are in fact clinically tolerant to various meats because enzymatic digestion may modify the structural characteristics of food allergens. We investigated whether a different pattern of gastrointestinal serum albumin proteolysis could justify a different allergic potential of BSA^{18,19} and found that after 5 min of digestion in the stomach, the reduction in SPT wheal-and-flare response to both BSA and OSA was statistically significant when compared with the response to undigested protein. Two and four hours after peptic digestion, no children showed SPT-induced wheals classifiable for positive response to OSA, and two were positive to BSA. Electrophoresis shows that mutton is somewhat less activated than beef after 5 min. These data indicate that peptic attack is able to influence the allergenicity of serum albumins. It is also possible that native BSA polypeptide fragments are more active than the whole molecule, which may be the reason beef-allergic children seldom show oral symptoms but, more frequently, gastrointestinal symptoms or systemic reactions.

TABLE IV.

CLINICAL CHARACTERISTICS, WHEEL AREA IN SQUARE MILLIMETERS, AND DBPCFC OF 10 MEAT-ALLERGIC CHILDREN										
	Child									
	1	2	3	4	5	6	7	8	9	10
Age (y)	2.25	1.58	4.33	3.00	1.25	1.33	2.50	3.66	2.83	4.41
Sex	M	F	M	F	M	M	M	F	M	F
SPT (mm ²)										
Beef	12.5	12.5	28.2	3.1	7.0	3.1	28.2	7.0	12.5	12.5
Raw meat	19.6	12.5	12.5	7.0	7.0	7.0	12.5	19.6	12.5	19.6
Cooked beef	12.5	3.1	7.0	3.1	12.5	3.1	12.5	7.0	7	7.0
HB	—	—	—	—	—	—	—	—	—	—
FDB	—	—	7.0	—	—	—	—	—	—	—
BSA	12.5	12.5	38.5	12.5	12.5	7.0	12.5	12.5	38.5	12.5
Heated BSA	28.2	—	28.2	3.1	7.0	—	28.2	—	12.5	3.1
DBPCFC										
Beef										
HB	—	—	—	—	—	—	—	—	—	—
FDB	—	—	—	—	—	—	—	—	—	—
BSA	L	—	L	—	—	—	R,A	—	U	U
Heated BSA	L	—	—	—	—	—	R,C	—	L	U

A, asthma; BSA, bovine serum albumin; C, cough; DBPCFC, double-blind, placebo-controlled food challenge; F, female; FDB, freeze-dried beef; HB, homogenized beef; L, lip edema; M, male; R, rhinitis; SPT, skin-prick test; U, urticaria.

INDUSTRIAL PROCESSING, BUT NOT HOME COOKING, MAY REDUCE THE ALLERGENICITY OF BEEF

There are few data on the effect of digestion or cooking on the allergenicity of beef proteins. Some studies have found that cooking alters the reactivity of beef²⁰ and fish.²¹ To assess the influence of industrial heat processing on skin and clinical reactivity to beef, another study investigated the effects of heating in the home and in the processing plant on both cutaneous and systemic allergic reactivity to BSA by direct challenge performed in this institution.²² A series of 10 children reporting immediate reactions to the ingestion of beef were confirmed to be allergic by using a double-blinded challenge, controlled with turkey meat as a placebo. To reproduce home conditions, the meat was steam-cooked for 5 min at 100°C to make increasing doses of 12, 24, 48, and 96 g of minced beef or turkey. The doses were doubled every 30 min for 4 h and were discontinued at the first onset of symptoms or with a negative response after the eighth dose. A commercial extract of beef (BCE), solubilized in glycerol 50% at 1 mg/mL concentration (supplied by Bayer-Italy), was compared with cooked, homogenized (HB; supplied by Heinz-Plada, Milan, Italy), and freeze-dried (FDB; Heinz-Plada) beef extracts. A DBPCFC with 150 g of HB and 60 g of FDB (found in 180 g of raw beef) was administered on separate days. The placebo foods used in the meat challenge were 150 g of homogenized turkey and 60 g of freeze-dried turkey preparation. In the BSA challenge, either lactose (as a placebo) or BSA masked in pear juice (additive-free except for ascorbic acid) was administered after a negative SPT for pear juice. Children who had tested positive to raw BSA challenge were recalled 3 to 7 d later, and a DBPCFC with heat-treated BSA was administered under the same experimental protocol. The total BSA dose administered masked in 100 g of beef was determined by sodium dodecyl sulfate–polyacrylamide gel electrophoresis and laser densitometry. Raw beef, cooked beef, and unheated BSA elicited positive SPTs in all patients (Table III). Wheal diameters of BCE and BSA and of BCE and heat-treated BSA significantly correlated. A higher degree of correlation between the BCE and both raw and cooked beef was found. These data indicate that the BCE mediated a higher degree of sensitivity to raw or cooked beef

and confirm that BSA is a major allergen in BCE. Cooking alters the allergic reactivity of the skin to raw bovine meat and can be said to similarly modify reactivity to BSA. Reactivity to cooked beef and to BSA, however, differ significantly, thus suggesting that heat inactivation of BSA may not be a factor in the different allergenic properties elicited by cooked and raw beef. Five of 10 patients responded positively to challenge to uncooked BSA: two with urticaria, one with coughing and allergic rhinitis, and two with a lip oedema. DBPCFCs with heat-treated BSA were positive in four of these patients (Table IV). Most important, HB and FDB preparations lose their ability to elicit a positive SPT challenge. Although all children were reactive to cooked beef and some of them to heated BSA in challenges, there was no hypersensitivity reaction to either HB or FDB. Our interpretation is that industrial heat processing is more efficient than domestic cooking in reducing reactivity in beef-sensitive children. Home processing does not spread heat uniformly, however, and cooking methods may affect the complex protein matrix of meat in different ways. However, technologic treatment also has been shown to influence the digestibility of beef.²³

USE OF RAW BEEF IN SPTS

Although fresh produce,²⁴ fish, crustacean, mollusk, peanut, and egg²⁵ have all been used for diagnostic purposes in allergy studies, their diagnostic accuracy has seldom been evaluated. The specificity and sensitivity according to type of extract, however, is often neglected in the published data where fresh beef was used as a test allergen.⁸ When patients with a hypersensitivity to BCE were confirmed to be allergic to fresh meat and the diameter of wheals was consistently larger, the published data seem to support the usefulness of the raw, native allergen at SPT in meat allergy work-up.

CONCLUSIONS

The removal of beef and milk from the diet of beef-allergic toddlers may pose nutritional problems, because many beef-

allergic children are also allergic to milk and most are polyallergic patients for whom access to other protein sources must be carefully monitored.²⁶ Milk, dairy products, and meat represent an important source of proteins in the Western world (individual consumption of beef reaches 30 kg per annum in the United States¹³) and CMA is frequent, even though meat allergy may be not so infrequent. However, there is no scientific basis for the elimination of beef from the diet of the majority of CMA children. Lamb and turkey have been proposed as beef and milk substitutes, even though little is known about the prevalence of reactions due to cross-reactivity in the atopic population. In planning a regimen that restricts beef, however, freeze-drying and homogenization may support the introduction of processed beef into the diet.

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