



## MOC-CME Review

# Mammalian milk allergy: case presentation and review of prevalence, diagnosis, and treatment



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## Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

## Learning Objectives

At the conclusion of this activity, participants should be able to:

- Distinguish different types of mammalian milk allergy
- Detect cross-reactivity in mammalian milk proteins
- Evaluate nuances and difficulties of allergen avoidance in specific mammalian milk allergy

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J.A. Bernstein – PI, Consultant, Speaker for AstraZeneca, CSL Behring, Novartis/Genentech, and Shire, he received research grants and fees; Speaker for Baxalta, he received fees; Consultant for Imedics, he received fees; PI and Consultant for Boehringer Ingelheim and GlaxoSmithKline, he received research grants and fees. M.H. Grayson – Clinical research for Polyphor, Ltd., he received a research grant. G.D. Marshall – Clinical Research for Stallergens and Sanofi, he received research grants; J. Oppenheimer – Consultant for DBV Technologies, GlaxoSmithKline, and Kaleo, he received other financial gains; Clinical research for AstraZeneca, Boehringer Ingelheim, and Novartis, he received research grants. G. Krishnaswamy – Clinical Research for CSL Behring, he received a research grant. M. Ngoc Pham have no relevant financial relationships to disclose. Any unapproved/investigative uses of therapeutic agents/devices discussed are appropriately noted.

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## Clinical Vignette

A 5-year-old boy with a history of mild intermittent asthma and allergic rhinoconjunctivitis was seen for evaluation of anaphylactic reactions.

For the past few years, he has been having multiple anaphylactic reactions that develop soon after food ingestion. The first reaction occurred after he had eaten a slice of plain cheese pizza. He developed urticaria, wheezing, and emesis within 10 minutes, for which he received intramuscular epinephrine and diphenhydramine and was taken to the emergency department. He subsequently ate pizza from the same restaurant without symptoms and continued to eat pizza weekly without issues. A year later, he had a reaction after consuming fresh bread and butter from an Italian deli. Again, he immediately developed urticaria, wheezing, and emesis. He was treated with epinephrine and was observed in the emergency department. His tryptase level in the emergency department was 3.6 ng/mL. He subsequently ate bread from that same Italian deli without problems. Another reaction occurred after he ate store-bought frozen cheese ravioli. Symptoms included urticaria, wheezing, and emesis, which resolved after treatment with epinephrine. Most recently, he had a sample of Pecorino Romano cheese and developed anaphylaxis, requiring treatment with a total of 3 epinephrine doses. Tryptase level in the emergency department was noted to be increased at 26.8 ng/mL. These episodes were not associated with exercise, concurrent illnesses, or medications.

He has an unrestricted diet. He drinks milk daily and frequently eats cheese, yogurt, and ice cream. He has mild intermittent asthma that is well controlled with albuterol as needed. He has not had severe exacerbations requiring oral steroids or hospitalization. He also has allergic rhinoconjunctivitis that is well controlled on fluticasone nasal spray and cetirizine.

He was evaluated by another allergist for his reactions before seeking consultation in our practice. He was told that food allergy was unlikely given his tolerance of diverse foods, including the major allergens. Because his baseline tryptase level was not increased, a mast cell disorder was considered unlikely. As a result, he was given the diagnosis of idiopathic anaphylaxis. After his most recent episode of severe anaphylaxis, he presented to our practice for further evaluation.

Skin prick testing was performed using fresh goat's milk cheese, fresh sheep's milk cheese, yogurt (made from cow's milk), and feta cheese (made from a mixture of sheep's and goat's milk; [Table 1](#)). Serum specific immunoglobulin E (IgE) levels were 1.14 kIU/L for cow's milk, higher than 100.00 kIU/L for goat's milk, and 78.00 kIU/L for sheep's milk. Total serum IgE was 241 kIU/L. Baseline tryptase level was 3 ng/mL.

This case describes a patient with specific goat's and sheep's milk allergies, but tolerance to cow's milk proteins. Based on his history of reactions and significantly increased IgE levels, he was advised to avoid goat's and sheep's milk. He did have a positive skin test reaction to fresh cow's milk yogurt, and because testing with fresh foods can have high sensitivity but low specificity, serum specific IgE testing to cow's milk was performed.<sup>1</sup> His cow's milk serum IgE was significantly lower than the goat's and sheep's milk IgE values, at a level at which there is low likelihood of clinical reactivity (<50% positive predictive value), and he presented with a history of frequent tolerance of cow's milk and other cow's milk-based foods; thus, he was advised to continue including cow's milk in the diet on a regular basis.<sup>2</sup> The family was counseled on the risk of cross-contamination of cow's milk products with goat's and sheep's milk and that not all dairy products are made with cow's milk.

## Introduction

Cow's milk allergy is the most common cause of food allergy in young children and affects approximately 2% to 3% of infants.<sup>3,4</sup> Cow's milk allergy presents as a wide range of clinical syndromes

**Table 1**  
Skin Prick Test Results of Fresh Food Items Used as Preparations

| Food item           | Resulting wheal/flare (mm) |
|---------------------|----------------------------|
| Histamine           | 7/19                       |
| Saline              | 0/0                        |
| Goat's milk cheese  | 5/18                       |
| Sheep's milk cheese | 5/17                       |
| Yogurt (cow milk)   | 5/15                       |
| Feta cheese         | 4/16                       |

**Table 2**

Taxonomy of Mammalian Species That Are Phylogenically Related Sheds More Light on Clinical Cross-reactivity Among Mammalian Milks<sup>8,9</sup>

| Order          | Suborder              | Family              | Subfamily          | Genus    | Common Name |
|----------------|-----------------------|---------------------|--------------------|----------|-------------|
| Primates       | Haplorhini            | Hominidae           | Homininae          | Homo     | human       |
| Artiodactyla   | Ruminathia            | Bovidae             | Bovinae            | Bos      | cow         |
|                |                       |                     |                    | Syncerus | buffalo     |
|                |                       |                     | Caprinae           | Capra    | goat        |
|                |                       |                     |                    | Ovis     | sheep       |
|                |                       |                     |                    | Sus      | pig         |
|                | Suiformes<br>Tylopoda | Suidae<br>Camelidae | Suinae<br>Camelini | Camelus  | camel       |
|                |                       |                     |                    | Lama     | llama       |
|                |                       |                     |                    | Equus    | horse       |
|                |                       |                     |                    |          | donkey      |
|                |                       |                     |                    |          |             |
| Perissodactyla |                       | Equidae             |                    |          |             |

and can be IgE or non-IgE mediated. The diagnosis of IgE mediated allergy to cow's milk is suspected based on a convincing history and evidence of sensitization detected by skin prick testing and/or specific IgE testing. In cases in which the diagnosis is not certain, oral food challenge is beneficial to confirm the allergy. For other types of allergy to cow's milk proteins, few reliable tests are available and the diagnosis mainly relies on clinical history and, in some cases, oral food challenge results. This case highlights that allergy to other mammalian milks in the setting of cow's milk tolerance is possible.

### Mammalian Milk Cross-Reactivity

Cow, goat, and sheep are phylogenically related animals; thus, high homology exists among their milk proteins.<sup>5–7</sup> Sheep and goat are in the same subfamily and thus are more closely related to each other than to cow, which is in the same family but in a different subfamily (Table 2).<sup>8–10</sup> Therefore, patients with cow's milk allergy often have allergic reactions triggered by ingestion of goat's and sheep's milk. In prior studies, approximately 92% of patients with allergy to cow's milk reacted to goat's milk, whereas 4% of patients allergic to cow's milk reacted to mare's milk.<sup>11–13</sup> Bellioni et al<sup>12</sup> reported that children who had positive skin test reactions and specific IgE levels to cow's milk also had positive test reactions to goat's milk. On oral food challenge, 24 of the 26 patients who reacted to cow's milk also had a positive oral food challenge reaction to goat's milk. Similarly, in a study by Rodriguez del Rio et al,<sup>14</sup> of subjects who had successfully undergone cow's milk oral immunotherapy, 26% had a goat's milk allergy when challenged, with 47% of these subjects experiencing anaphylaxis. This high prevalence suggests that the evaluation of goat's milk allergy is important in those with concurrent cow's milk allergy.

Cross-reactivities to other mammalian milks also are possible, but less frequent. In a study of 25 children 19 to 72 months of age who had positive skin test and oral food challenge reactions to

**Table 3**

Comparison of Amino Acid Sequences of Major Proteins From Different Mammalian Species<sup>a</sup>

|             | Sequence homology, % |            |             |
|-------------|----------------------|------------|-------------|
|             | Cow vs goat          | Cow vs ewe | Goat vs ewe |
| BLG         | 96                   | 96         | 99          |
| ALA         | 95                   | 94         | 99          |
| Casein      |                      |            |             |
| $\alpha_s1$ | 87                   | 89         | 97          |
| $\alpha_s2$ | 88                   | 89         | 98          |
| $\beta$     | 90                   | 90         | 99          |
| $\kappa$    | 85                   | 84         | 95          |

Abbreviations: ALA,  $\alpha$ -lactalbumin; BLG,  $\beta$ -lactoglobulin.

<sup>a</sup>Reprinted with permission from Wal JM. Bovine milk allergenicity. *Ann Allergy Asthma Immunol*. 2004;93(suppl 3):S2–S11.<sup>7</sup> License number 3981151067886.

**Table 4**

Sequence Homology for Casein  $\alpha$  S1 and S2 When Comparing Cow's Milk, Goat's Milk, and Sheep's Milk<sup>a</sup>

|                                                              | Casein $\alpha$ S1 | Casein $\alpha$ S2 |
|--------------------------------------------------------------|--------------------|--------------------|
| Congruent Base Pairs between cow's, goat's, and sheep's milk | 186/214 (86.9%)    | 193/223 (86.5%)    |

<sup>a</sup>Adapted from Masoodi TA, Shafi G. Analysis of casein alpha S1 and S2 proteins from different mammalian species. *Bioinformation*. 2010;4:430–435.<sup>16</sup>

cow's milk, 2 had positive skin test reactions to mare's milk.<sup>13</sup> Only 1 child had a positive oral food challenge reaction to mare's milk.<sup>13</sup> Studies of deer's milk and buffalo's milk have shown cross-reactivity with cow's milk, but there is a lower rate of cross-reactivity with donkey's milk, mare's milk, pig's milk, and camel's milk.<sup>15</sup>

Casein and whey proteins are considered the main allergens in cow's milk, with casein being the largest component (80%) of cow's milk.<sup>7</sup> Cow's, goat's, and sheep's milk share greater than 90% sequence homology between their  $\alpha$ -lactalbumin and  $\beta$ -lactoglobulin proteins (Table 3).<sup>7</sup> In regard to casein, cow, sheep, and goat  $\alpha$ -casein share more than 86% of their sequence (Table 4), whereas cow and mare caseins share only approximately 50% to 60% sequence homology.<sup>15,16</sup> Because of this high homology, individuals allergic to cow's milk are generally counseled to avoid goat's and sheep's milk.

### Selective Mammalian Milk Allergy

This case is not typical because the patient tolerated cow's milk but reacted to goat's milk and sheep's milk. Unlike cow's milk allergy, selective mammalian milk allergy and tolerance to cow's milk are uncommon and have been reported only as case reports.<sup>4,17–19</sup> The first case series published in 1995 described 2 young children who had detectable specific IgE levels to goat's and sheep's milk casein but undetectable levels to cow's milk casein.<sup>17</sup> Having goat's and sheep's milk allergies is common, and some studies have shown a higher degree of cross-reactivity between goat's and sheep's milk casein than cow's milk casein.<sup>19</sup>

The largest series of specific mammalian milk allergy included 28 children 15 months to 16 years old.<sup>18</sup> All children had severe allergy after ingestion of goat's and sheep's milk; 16 had anaphylactic reactions. Several of these reactions to goat's and sheep's milk were later found to be hidden allergens. All these children tolerated cow's milk products. Cow's milk caseins were poorly or not at all recognized by the patients' IgE, whereas  $\alpha$ -casein S(1),  $\alpha$ -casein S(2), and  $\beta$ -caseins from goat's and sheep's milk were recognized with high specificity and affinity.

Selective allergies to other mammalian milks have been reported. One case report described a middle-age woman who had mare's milk allergy and had positive test reactions to sheep's and goat's milks, but she tolerated cow's milk.<sup>20</sup> Similarly, Broekaert et al<sup>21</sup> described a 70-year-old man who tolerated cow's milk but had anaphylaxis after ingestion of mozzarella cheese made from buffalo's milk.

As reflected in these cases, selective mammalian milk allergies usually do not manifest in early childhood because the introduction of foods made from goat's, sheep's, or other mammalian milks typically does not occur until later in life.

According to the International Dairy Federation, goat's milk and sheep's milk account for approximately 2% and 1%, respectively, of the total milk production in the world, after cow's milk (83%) and buffalo's milk (13%).<sup>22</sup> It is expected that production and consumption of these other mammalian milks will continue to increase worldwide.<sup>22</sup> Thus, more cases of specific mammalian milk allergy could be seen in the future.<sup>18</sup>

**Table 5**  
Cheeses Made From Different Mammalian Milks<sup>24,28</sup>

|              | Cow's milk | Sheep's milk | Goat's milk | Buffalo's milk |
|--------------|------------|--------------|-------------|----------------|
| Ricotta      | X          | X            | X           | X              |
| Feta         | X          | X            | X           |                |
| Mozzarella   | X          |              |             | X              |
| Gouda        | X          |              |             |                |
| Roquefort    |            | X            |             |                |
| Manchego     |            | X            |             |                |
| Pecorino     |            | X            |             |                |
| Humboldt fog |            |              | X           |                |
| Caprino      |            |              | X           |                |
| Chevre       |            |              | X           |                |

## Current Understanding

There have been a few studies in recent years examining specific mammalian milk allergies that have shed more light on our current understanding.

Despite a sequence homology of greater than 90% between bovine and caprine  $\beta$ -caseins, in patients allergic to goat's milk but tolerant to cow's milk, IgE antibodies recognize caprine  $\beta$ -casein without cross-reacting with bovine  $\beta$ -casein.<sup>6</sup> A study by Bernard et al<sup>6</sup> showed that in these patients, the IgE-binding epitope most recognized was located in caprine domains 49 to 79, which differed from its bovine counterpart by 3 amino acid substitutions. Similarly, Hazebrouck et al<sup>23</sup> found that with a 5-amino acid substitution in caprine  $\beta$ -casein, IgE reactivity was decreased in patients who were allergic to goat's milk but tolerant of cow's milk.

Studies have suggested that perinatal influences might play a role in the development of allergic disorders. A case review describing a set of identical twins—1 with goat's and sheep's milk allergy without cow's milk allergy and 1 without milk allergies—illustrates this potential influence in food allergy. The major difference in early development for these twins was that the infant with the goat's and sheep's milk allergy experienced a more stressful prenatal period with impaired placental blood flow in utero.<sup>24</sup> It is unclear how stress influences the development of food allergies, but this report and other studies suggest that further investigation might be warranted.<sup>24–27</sup>

## Evaluation of Mammalian Milk Allergy

The diagnostic workup of mammalian milk protein allergy includes obtaining a detailed history and skin prick testing and/or detection of milk-specific IgE antibodies. An oral food challenge is the gold standard for food allergy diagnosis. When a diagnosis of sheep's and goat's milk allergy is established, it is important to ascertain whether cow's milk can be tolerated to guide avoidance recommendations. Because most patients with specific goat's or sheep's milk allergies are generally older at diagnosis, a history of tolerance or allergy to cow's milk products typically is available. Cow's milk is the most common milk used in dairy products in the United States and is an important nutritional source for young children; thus, there are significant benefits of including cow's milk in the diet, if possible.

## Management

Avoidance is the mainstay of food allergy management. Eliminating milk from the diet can be difficult and this clinical case highlights the importance of being aware of cross-contamination and hidden ingredients. Goat's milk and sheep's milk are used in the same way as cow's milk and can be processed into dried milk, evaporated milk, cheese, and yogurt.

Cheese products, primarily composed of casein proteins, are the most common source of cross-contamination of mammalian milk,

as opposed to milk and yogurt, because of the common use of mixtures of mammalian milks in cheese (Table 5). In addition to avoiding cheeses made from specific mammalian milks, patients are advised to be aware of food items that might have cheese as a minor or hidden ingredient, such as pasta dishes, pastries, snack platters, salads, and sandwiches.

The Food Allergen Labeling and Consumer Protection Act (FALCPA) requires products to declare the 8 major allergens, including cow's milk, peanuts, and tree nuts. However, there are many food ingredients, such as other mammalian milk products, that are not governed by these laws. Because the FALCPA covers only cow's milk, there is little guidance from labeling for other mammalian milks. Therefore, it would be important to address any concerns to the manufacturer. Dining out with a specific mammalian milk allergy also can be very difficult because restaurants can use many different cheese and milk preparations, making risk of cross-contamination a problem, so informing the chef and restaurant staff of the allergy is an essential precaution.

Although heating decreases the immunogenicity of cow's milk and most children with cow's milk allergy can tolerate extensively heated forms of cow's milk, this is not the case for goat's and sheep's milk.<sup>29</sup> A study examining basophil activation in patients with cow's milk allergy with and without goat's and/or sheep's milk allergies found that stimulation of donor basophils passively sensitized with blood from subjects with goat's and sheep's milk allergy with heated sheep's milk resulted in a significantly larger percentage of activated basophils compared with stimulation with heated cow's milk ( $P = .039$ ).<sup>29</sup> Western blot analysis examining IgE binding showed that heating time increased immunogenicity of goat's and sheep's milk.<sup>29</sup> Although there is no evidence for or against baked goat's or sheep's milk tolerance in specific mammalian allergy, avoidance of goat's and sheep's milk in all forms is advised given these limited data suggesting increased immunogenicity with heating.

In addition to being known ingredients in food, mammalian milks can appear as hidden ingredients in soaps, skin care products, and cosmetics that are not overseen by the FALCPA; thus, caution is warranted. As with any other food allergy, accidental exposures and allergic reactions are possible, so preparedness is a crucial aspect of management. Epinephrine auto-injectors and written emergency actions plans should be provided because severe reactions are possible and death in the case of sheep's milk allergy has been reported.<sup>18,30</sup>

## Conclusion

This case emphasizes the importance of obtaining an accurate history and awareness that dairy products can include mammalian milks other than cow's milk. This knowledge will help guide diagnostic testing and ultimately more precise recommendations for avoidance. Because of high homology, cow's milk allergy often co-exists with goat's and sheep's milk allergies. However, specific allergies to goat's or sheep's milk in the setting of cow's milk tolerance are possible, as in the present patient. Specific mammalian milk allergies are especially important to pinpoint and delineate because cow's milk is an essential part of the Western diet, particularly in growing children. Although the natural history of specific mammalian allergy is unknown, regular follow-up is important to ensure that allergen avoidance is continued and preparedness with emergency medications and action plans in case of allergic reaction is reinforced.

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