

# Resolution of recurrent aphthous ulcers after discontinuation of cow's milk protein intake

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**A**phthous ulcers are 1 of the most common oral mucosal conditions, and study results have shown a prevalence of approximately 1.5% among children and youth in the United States.<sup>1</sup> Clinically, recurrent aphthous ulcers (RAUs) manifest as yellowish, shallow, painful, round or oval ulcers with an erythematous halo that are self-limiting and recur periodically.<sup>2</sup> In most people who are affected, these occur infrequently, are smaller than 1 centimeter in diameter and heal

within 1 to 2 weeks without treatment.<sup>2,3</sup> However, a subset of people who are affected have a more severe manifestation, with frequent occurrence of multiple or large ulcerations, which can be painful, particularly when eating and toothbrushing. This type of manifestation results in compromised nutrition and oral hygiene and negatively affects quality of life.<sup>4</sup>

The pathophysiological nature of RAUs is understood poorly, and the trigger for RAU remains unknown in most patients. However, patients often report factors such as local trauma, stress, various foods, and hormonal variation as triggers for flare-ups of RAU.<sup>5</sup> Food is often a suspected trigger, and authors of published studies have investigated the role of dietary triggers in RAU. Results from studies in which the investigators evaluated self-reports of dietary triggers for RAU have shown that patients identify a variety of foods as potential triggers, particularly acidic or spicy foods.<sup>6</sup> However, discontinuation of many of the commonly suspected foods, such as acidic or spicy foods, has not led to a decrease in frequency or complete resolution of RAU.

## ABSTRACT

**Background and Overview.** Authors of published studies have reported elevated levels of circulating antibodies to cow's milk protein (CMP) in patients with recurrent aphthous ulcers (RAUs), and authors of case reports have described resolution of RAU after dairy elimination.

**Case Description.** A 10-year-old girl and an 11-year-old boy, both with 5-year histories of frequent RAU episodes, with multiple ulcerations, underwent dairy elimination trials. Both were free of oral ulcers within 2 weeks of discontinuing CMP and remained so with a CMP-free diet. In addition, the first patient had recurrence of ulcerations after occasional ingestion of CMP-containing foods. She showed elevated blood levels of immunoglobulin E in reaction to CMP and soy. Soy intake did not trigger the ulcerations.

**Conclusions and Practical Implications.** The proportion of patients with RAU in whom CMP acts as a trigger is unknown. However, CMP elimination trials are safe and feasible and, therefore, should be considered, particularly before use of medications with potential side effects.

**Key Words.** Recurrent aphthous ulceration; cow's milk protein; dairy elimination.

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Patients rarely identify cow's milk as a suspected trigger. However, authors of case reports have described resolution of RAU after dairy elimination,<sup>7-9</sup> and the authors of a case control study<sup>10</sup> found elevated levels of circulating antibodies to cow's milk protein (CMP) in patients with RAU.

We describe the cases of 2 patients with RAU diagnosed on the basis of clinical examination results and history; they had rapid resolution of RAU after elimination of cow's milk and cow's milk products from their

 Supplemental material is available online.

diets. Both patients sought care for oral ulcerations, which were consistent with a diagnosis of recurrent aphthous stomatitis on the basis of clinical appearance and history. These cases underscore the importance of updating standard treatment recommendations for RAU to include consideration of dietary CMP elimination trials.

### CASE 1

A 10-year-old girl accompanied by her mother sought care at our oral medicine clinic with a chief symptom of canker sores. Her mother reported that the onset of recurrent oral ulcers had been at least 5 years previously; the ulcers lasted 1 to 2 weeks before healing completely and occurred frequently, such that the patient almost always had oral ulcers. The longest interval the patient was free of ulcers was approximately 1 week. However, the patient reported that on that day she did not feel the presence of any ulceration in her oral cavity. The patient's mother had not noted any skin, eye, or genital lesions but reported that the patient had occasional nosebleeds.

The patient had no known medical problems and had undergone routine blood testing 1 to 2 years previously, the results of which were within normal limits. She was not receiving any medications and took multivitamins occasionally. She had no known drug allergies, but her mother reported that she had received a diagnosis of cow's milk allergy as an infant, although she had restarted regular ingestion of cow's milk products years ago without any identified adverse effects.

At examination, no ulcerations were evident on the oral mucosa. However, on the basis of the history, we made a provisional diagnosis of RAU. We asked the patient's mother to forward her blood test results and recommended eliminating CMP from her diet.

At the next examination in 2.5 months, the patient again was accompanied by her mother who reported that she had eliminated milk and milk products from her daughter's diet shortly after the last visit; within a week, all oral ulcers had cleared. During the 2-month period during which she discontinued cow's milk, she did not notice any oral sores. The patient had some dairy intake a week ago and subsequently developed an oral ulcer. At examination, we noted a round pseudomembrane-covered ulceration with surrounding erythema on the lower right labial mucosa, with an appearance consistent with aphthous ulceration. We advised continued CMP elimination and discussed blood testing for total and food-specific immunoglobulin E (IgE) with the mother. During a telephone call with the patient's mother approximately 6 months after the follow-up appointment, she reported that the patient had not been completely without dairy; however, she had had only occasional intake (mainly at school), and they had noticed a definite correlation between ingestion of cow's milk or milk products and subsequent oral ulcerations.

Shortly afterward, the patient had undergone a blood test measuring total and food-specific IgE levels (standard food panel).

The total IgE level was elevated at 329 kilounits per liter (normal level, < 115 kU/L). Food-specific IgE antibodies to the following foods were included in the standard food panel: milk (cow), egg whites, peanuts, wheat, soybeans, codfish, shrimp, walnuts, corn, sesame seeds, clams, and scallops. The levels for all except milk (cow) and soybeans were within normal limits. IgE levels in reaction to milk were elevated at 0.87 kU/L. This is in the Class 2 range (0.71-3.50 kU/L), which is a moderately elevated level indicating that this food is a probable contributing factor to total allergic load. Specific IgE levels in reaction to soybeans also were elevated at 3.18 kU/L, but the patient had been ingesting soy foods regularly without them triggering oral ulcerations according to the patient and her mother.

### CASE 2

An 11-year-old boy accompanied by his mother sought care for mouth sores. The onset of recurrent oral sores that lasted approximately 2 weeks before they healed was approximately 5 years previously; however, they had become more frequent in the past 2 years. During this time, new ulcers formed before the existing ones had healed, and the patient was rarely completely free of oral ulcers. Ulcers were limited to the mouth. The patient previously had tried chlorhexidine mouthrinse, beta-methasone paste, and homeopathic borax pills as prescribed by his doctors without much relief.

The patient's medical history indicated that he had asthma and a history of eczema. His current medications included albuterol inhalers as needed and daily homeopathic borax pills. He had no known drug or food allergies. At examination, we noted oval ulcerations with erythematous borders at 3 oral sites on nonkeratinized mucosa—on the labial mucosa (Figure), lower anterior alveolar mucosa, and right lateral portion of the tongue. We diagnosed RAU on the basis of the history and clinical appearance of the ulcerations. We recommended that the patient discontinue the homeopathic borax pills and start eliminating CMP from his diet.

The patient returned for a follow-up visit in 8 weeks, again accompanied by his mother, and they reported that he had achieved complete elimination of CMP from his diet. After approximately 2 weeks of CMP discontinuation, he noticed that all existing oral ulcerations had healed and new ulcers had stopped occurring and that he had been free of oral ulcers since then. At oral examination, his mucosa was within normal limits with no ulcerations. We gave his mother the option of

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**ABBREVIATION KEY.** CMP: Cow's milk protein. IgE: Immunoglobulin E. RAU: Recurrent aphthous ulcer.

food-specific IgE testing, but given the dramatic response to dairy elimination, particularly given his long history of frequent occurrence of oral ulcers before this, she decided to continue dairy elimination without any laboratory tests at that time.

## DISCUSSION

Identification of food triggers in RAU can be challenging because there may be a time lag between ingestion of the food and occurrence of a flare-up. If an environmental trigger for RAU can be identified for a given patient, so that avoidance of the trigger results in a decrease in the frequency or complete elimination of recurrences, a clinically significant positive effect on the health of the patient can occur—alleviation of oral discomfort, improvement in oral hygiene and nutrition, and elimination of medications with potential side effects.

Cow's milk is a common food allergen<sup>11</sup> and has been identified as a possible trigger for autoimmune conditions such as rheumatoid arthritis,<sup>12,13</sup> atopic dermatitis,<sup>14</sup> insulin-dependent type 1 diabetes,<sup>15</sup> lupus,<sup>16</sup> and eczema,<sup>17</sup> as well as for common childhood conditions such as asthma.<sup>18</sup> Cow's milk ingestion also may influence the severity of an autoimmune disease, as is seen with the greater severity of atopic dermatitis in children with a diagnosis of cow's milk allergy.<sup>14</sup>

Study investigators have found elevated levels of circulating antibodies to CMP in patients with RAU.<sup>10,19-22</sup> Besu and colleagues<sup>10,19</sup> reported on findings from a case control study that included 50 patients with RAU and 50 control participants (volunteer blood donors). Serum anti-CMP immunoglobulin A, immunoglobulin G, and IgE were significantly higher in patients with RAU than in control patients. Results of further evaluation for antibodies to specific CMPs showed that antibodies to the  $\alpha$ ,  $\beta$ , and  $\kappa$  casein from cow's milk were all elevated, with smaller elevations in the whey proteins.<sup>10,19</sup>

Although the etiopathogenesis of RAU is not well understood, there are compelling case reports, including our report, in which the authors have described resolution of RAU after CMP elimination<sup>7-10</sup> in both adults and children, which suggests that in at least a subgroup of patients, CMP is a causative factor for RAU. To our knowledge, the first of these reports was published in 1984.<sup>7</sup> However, awareness of this association is low among both patients and health care providers. In our survey of dentists and dental hygienists during a continuing education program (Appendix, available online at the end of this article), we found that only 6 of 33 respondents recommended dairy elimination trials to patients with RAU.

The 2 patients we describe in this report had rapid resolution of their long-standing and frequent RAU within 2 weeks of dairy elimination. In 1 case, oral challenges led to recurrence of ulcerations, providing



**Figure.** Case 2. Ovoid ulceration on labial mucosa seen at initial examination.

further evidence of CMP being the causative factor for RAU in this patient. Although they were both children, these patients were able to eliminate CMP from their diet with relative ease, given some involvement from their parents in preparing CMP-free meals and simple instructions from the clinician to the parent and child on how to identify CMP in foods. CMP is present in all dairy products made from cow's milk, such as yogurt, cheese, cream, and butter, which are common ingredients in cooking and baking. Therefore, in addition to liquid cow's milk, these milk products and any foods that contain these products as ingredients also need to be discontinued during a CMP elimination trial. Some packaged foods may list ingredients derived from cow's milk, such as casein, caseinate, or whey. Such packaged foods also should be avoided during a CMP elimination trial.

The accuracy of laboratory or allergy testing in determining triggers for RAU is unknown. In addition, the proportion of patients with RAU in whom CMPs act as a trigger is uncertain. Thus, it is not possible to quantify the contribution of dietary components, including cow's milk, to causation of RAU from a population-based perspective at this time. Therefore, more clinical studies of dietary triggers in RAU are needed. Also, and more broadly, studies to evaluate the accuracy of immunologic testing for identification of such dietary triggers in immunologic conditions, including RAU, are needed.

However, from the perspective of treating an individual patient, dietary elimination to evaluate the response of an immunologic reaction to a particular food is the criterion standard to determine whether that food plays a role in that patient's disease process.<sup>23</sup> For this reason, and because a CMP elimination trial is relatively simple and free of adverse effects, we recommend that CMP elimination should be tried in patients with frequent occurrence of RAU before use of medications, particularly medications with potential side

effects. Our cases, along with those in other reports, underscore the importance of updating standard treatment recommendations for RAU to include CMP elimination trials.

## CONCLUSIONS

The proportion of patients with RAU in whom CMP acts as a trigger is unknown. However, CMP elimination trials are safe and feasible and, therefore, should be considered, particularly before use of medications with potential side effects. ■

## SUPPLEMENTAL DATA

Supplemental data related to this article can be found at: <http://dx.doi.org/10.1016/j.adaj.2017.02.028>.

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