

# Formula choices in infants with cow's milk allergy

Sharon Kipfer Ran D. Goldman MD FRCPC

## Abstract

**Question** I frequently encounter infants with symptoms suggestive of allergy after being introduced to standard cow's milk formula. Parents are concerned and ask for recommendations regarding formula alternatives. Which formulas are best for children with cow's milk allergy?

**Answer** Cow's milk allergy is common, and the criterion standard for diagnosis is elimination, provocation (with a double-blind, placebo-controlled food challenge protocol), and re-elimination. The allergy is treated by eliminating cow's milk protein from the diet. Formula alternatives include hydrolyzed cow's milk formula, rice-based formula, soy-based formula, and amino acid-based formula, which are all nutritionally adequate alternatives to cow's milk formula. Symptom severity, patient preference, cost, and efficacy are factors to be considered when choosing an alternative.

Exclusive breastfeeding has been recommended by the World Health Organization to be the sole form of nutrition for infants in the first 6 months of life.<sup>1</sup> However, many women might supplement or replace breastfeeding with infant formula for reasons including difficulties with breastfeeding and concern for maternal and child health.<sup>2</sup> The most commonly used and recommended infant formula has cow's milk as a source of protein. However, infants who are introduced to these formulas develop cow's milk allergy (CMA) more frequently compared to exclusively breastfed infants.<sup>3</sup>

## Cow's milk allergy

Cow's milk allergy is one of the most common food allergies in infants,<sup>4,5</sup> with a 14% to 17% reporting rate by parents, and a much lower reporting rate by health care professionals.<sup>3,6</sup> A review of 229 papers on CMA from 1967 to 2001 reported a CMA incidence of 2% to 3% in the first year of life.<sup>5</sup> This is similar to the 2.7% reported by the World Allergy Organization (WAO) following a review of 5 studies of CMA in northern Europe.<sup>7</sup> The discrepancy between parental reporting and clinically confirmed CMA rates might be because of parental misattribution of common symptoms of infancy (ie, regurgitation, colic, eczema) to CMA.<sup>6</sup>

The main allergens in cow's milk are whey proteins ( $\alpha$ -lactalbumin,  $\beta$ -lactoglobulin, bovine serum albumin, and bovine immunoglobulins) and casein proteins ( $\alpha$ -s1,  $\alpha$ -s2,  $\beta$ -casein,  $\kappa$ -casein).<sup>7</sup> Immunoglobulin E (IgE)-mediated reactions present within 2 hours of exposure and manifest with cutaneous, gastrointestinal, and respiratory symptoms.<sup>6,7</sup> Non-IgE-mediated reactions are less common and present as delayed reactions, typically involving gastrointestinal symptoms.<sup>6</sup> Other symptoms might include food-protein-induced enterocolitis syndrome, bloody stool relating to allergic proctocolitis, or chronic gastrointestinal symptoms such as diarrhea and failure to thrive.<sup>6</sup> Anaphylaxis is rare but does occur in 0.8% to 9% of infants with CMA.<sup>7</sup>

## Diagnosing CMA

Varying presentations, CMA symptoms that overlap with normal symptoms of infancy, and a lack of validated diagnostic tests lead to misdiagnosis of CMA.<sup>6</sup> Knowing the milk or dairy content of all ingested food and beverages, symptom presentation, results of cutaneous skin prick tests and atopy patch tests, and food-specific serum IgE levels can help with diagnosis.<sup>6</sup> The criterion standard for CMA diagnosis is the oral food challenge test, which involves elimination; provocation using double-blind, placebo-controlled food challenge protocol; and re-elimination.<sup>7,8</sup> However, if objective CMA symptoms are present in young children, results of the open-food challenge can be considered sufficient evidence for CMA diagnosis.<sup>7</sup>

## Treating with elimination

Treating using elimination of cow's milk from the diet<sup>4</sup> results in remission in 85% of infants.<sup>5,7</sup> In exclusively breastfed infants, this involves elimination of all milk products from the mother's diet.<sup>4,6,7</sup> In infants younger than 2 years old who are fed any amount of formula, this necessitates a substitute formula.<sup>7</sup> Substitutes include hydrolyzed cow's milk protein, hydrolyzed rice or soy protein, and amino acid-based formula. Factors that must be considered are formula efficacy, adequate nutrient intake, family preferences, and cost.<sup>4,9</sup>

## Hydrolyzed cow's milk formula

Partially hydrolyzed cow's milk formula should not be used to treat CMA, as cross-reactivity has been demonstrated in roughly 50% of infants with CMA.<sup>7,8</sup> However, an extensively hydrolyzed formula that contains no peptides with a molecular weight greater than 5000 Da is hypoallergenic<sup>10</sup>; according to the American Academy of Pediatrics and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), more than 90% of children with CMA will tolerate it.<sup>8,10</sup> In an open randomized controlled trial of 92 infants with known CMA, extensively hydrolyzed formula was well

tolerated and nutritionally adequate for infant growth.<sup>11</sup> Among 170 infants younger than 2 years of age with confirmed CMA, only 2.2% had a reaction to extensively hydrolyzed formula compared to 10% using soy-based formula.<sup>12</sup> Formula type is essential to consider in cases of severe allergy.<sup>4,8,9</sup> Nevertheless, bitter taste,<sup>11,13-15</sup> cost,<sup>9</sup> and risk of anaphylaxis<sup>8</sup> are challenges to using extensively hydrolyzed cow's milk formula.

### Hydrolyzed rice formula

Hydrolyzed rice formulas have been used in Europe for decades but are not universally available.<sup>13</sup> A recent review of 11 clinical trials using hydrolyzed rice formula in infants with CMA reported no cross-reactivity. Seven studies found satisfactory growth patterns in healthy children and catch-up growth in children with CMA.<sup>14</sup> A multicentre study of 100 infants with confirmed CMA used a skin prick test to detect rice-specific IgE level in 4% of infants; there were no associated symptoms.<sup>9</sup> Western blotting results were negative in rice-sensitized children, indicating hydrolysis of rice protein in formula modifies its allergenic properties and prevents an immune response.<sup>9</sup> Limitations of hydrolyzed rice formula include accessibility to formula<sup>13</sup> and bitter taste that might reduce adherence.<sup>14</sup> Partially hydrolyzed rice formulas are equally as efficacious in CMA treatment and taste scores match those of soy formulas.<sup>15</sup>

### Soy-based formula

Using soy-based formula in the treatment of CMA in infants has long been an area of controversy. Soy formulas have been shown to promote appropriate infant growth patterns, but some studies suggest lower weight gain in infants fed soy formula compared to cow's milk formula.<sup>16</sup> A randomized controlled trial of 170 infants with confirmed CMA reported allergic responses in 10% of infants fed soy formula.<sup>12</sup> Adverse reactions to soy were similar in IgE-mediated and non-IgE-mediated CMA, and reactions were more common in infants younger than 6 months of age.<sup>7,12,17</sup> A randomized-order, double-blind test of 50 adult participants (mean age of 34.4 years) comparing 12 different milk alternatives for infants with CMA based on taste, texture, and smell found soy formula to have the highest overall scores, followed by soy and rice hydrolysates.<sup>15</sup> Soy-based formulas are also more affordable than extensively hydrolyzed formulas.<sup>17</sup> Soy-based formula limitations are the unknown effects of phytate and phytoestrogens found in soy<sup>13,16</sup> and cross-reactivity with CMA, especially in younger infants.<sup>4,8,12</sup>

### Amino acid-based formula

Amino acid-based formulas are composed of elemental amino acids. They are hypoallergenic—as defined by the American Academy of Pediatrics—and are indicated in cases where infants are unable to tolerate extensively

hydrolyzed hypoallergenic formulas (eg, cow's milk or soy milk),<sup>4,7,14</sup> or in infants who have anaphylactic reactions to cow's milk protein.<sup>7</sup> Use of amino acid-based formula demonstrated nutritional adequacy in growth patterns of infants with CMA (tolerance of 100%).<sup>4</sup> The main drawbacks are increased cost (6 to 8 times more expensive than extensively hydrolyzed formula)<sup>13</sup> and poor palatability because of the elemental form, resulting in refusal by some infants.<sup>9</sup>

### Selecting formula alternatives

Symptom severity, patient preference, cost, and efficacy should be considered when selecting a formula alternative, as all options are nutritionally adequate alternatives to cow's milk formula.<sup>4,6-9</sup>

Soy formula, although reported to cause reaction in 10% to 14% of infants with CMA,<sup>8,12</sup> is more palatable and more affordable than extensively hydrolyzed formula.<sup>13,15</sup> Guidelines from the ESPGHAN and the WAO recommend against soy formula in infants younger than 6 months of age with CMA because of cross-reactivity,<sup>7,10</sup> but soy formula might be recommended for IgE-mediated CMA after 6 months of age.<sup>4,10,12,16</sup> Hydrolyzed soy formula was also found to be hypoallergenic and should be considered.<sup>7</sup>

Extensively hydrolyzed cow's milk formula is recommended as first-line treatment for CMA in infants by the ESPGHAN and the WAO.<sup>7,10</sup> A prospective, open randomized controlled trial in Spain comparing extensively hydrolyzed formula and hydrolyzed rice formula in 92 infants diagnosed with IgE-mediated CMA reported that growth curves followed normal patterns with both options, and hydrolyzed rice formula was well tolerated by all infants with moderate to severe CMA, while extensively hydrolyzed formula induced an allergic response in 1 child.<sup>11</sup> Rice-based formula is more palatable and more affordable when compared to extensively hydrolyzed formula,<sup>11</sup> and is recommended as first-line treatment in infant CMA when available, even in severe clinical cases.<sup>9,13,14</sup>

In treating children with allergy to cow's milk and soy formula, hydrolyzed rice formula and extensively hydrolyzed formula should be considered. A study of 18 children (median age of 5 years) with CMA who were treated with soy-based formula but subsequently developed reactions after 2 to 18 months of treatment evaluated the efficacy of hydrolyzed rice formula as an option for infants with CMA and soy allergy.<sup>18</sup> Results of a skin prick test showed reactions to rice in 8 children and to rice hydrolysate in 2 children, and serology results found antibodies to rice in 7 children. However, results of double-blind, placebo-controlled food challenge tests with hydrolyzed rice formula were found to be negative in all cases, supporting the notion of rice-based formula as an alternative to amino acid-based formula in treating infants with CMA and soy allergy.<sup>18</sup> In infants with

an allergic reaction or an anaphylactic reaction to extensively hydrolyzed formula, amino acid-based formula is indicated.<sup>4,7,14</sup> If symptoms do not improve with amino acid-based formula, the diagnosis is likely not CMA.<sup>3</sup> Alternative mammalian milk formulas are not indicated in infants with CMA because of cross-reactivity.<sup>3,7</sup>

#### Competing interests

None declared

#### Correspondence

Dr Ran D. Goldman; e-mail [rgoldman@cw.bc.ca](mailto:rgoldman@cw.bc.ca)

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