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Cow's milk protein allergy**

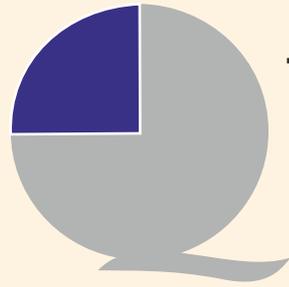


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Review:

Practical approach to management of Cow's milk protein allergy

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Practical approach to management of Cows milk protein allergy

Introduction

Since ancient period Cow's Milk (CM) is one of the first complementary foods introduced into an infant's diet. It also is commonly consumed throughout childhood as part of a balanced diet. Cow's milk protein (CMP) may initiate multiple adverse reactions, affecting skin, gastrointestinal (GI) tract or respiratory system.⁽¹⁾ Cow's milk protein allergy (CMPA) is frequent in pediatric population and as comorbidity of atopic dermatitis. The prevalence in general population is approximately 2 to 3%. CMP-induced adverse reactions are classified on immunological basis; IgE mediated, non-IgE mediated or both types occurring simultaneously.⁽²⁾ CMP-induced allergy spectrum range from immediate-onset IgE-mediated to delayed-onset GI symptoms or chronic eczema. The diagnostic modalities have strengths and limitations as well. The mainstay of treatment is avoidance of CMP. The dietetic input can circumvent any nutritional compromise. This review is intended to highlight the broad spectrum of manifestations of CMP allergy and to offer an approach to the diagnosis and treatment thereof.^{(1), (2)}

History

Evidence of cow's milk in diet dates back to approximately 9000 years ago. But prior to 370 B. C. Hippocrates reported adverse reactions for the first time; as skin and gastrointestinal symptoms after CM consumption. A causal relationship between these symptoms and milk consumption was proposed by Galen. At the beginning of the 20th century reports published in German literature were mainly diarrhea, growth retardation as well as anaphylactic shock after milk consumption.⁽³⁾ The frequency of similar cases has increased recently.

Prevalence of cow's milk allergy

Besides mother's milk, cow's milk proteins are typically the first foreign proteins consumed in large quantities by an infant. Typically CMA is the first phenomenon of atopic symptomatology and "allergic march". Variations of its prevalence may be attributable to different diagnostic methods or age of study population. Overall frequencies of self-reported CMA are much higher than medically confirmed diagnoses, in children and adults as well. A meta-analysis of relevant original studies since 1990 was done by Rona et al. The prevalence is 1.2- 17% in self-reported CMA; 0- 3% in double-blind placebo controlled food challenge or open challenge; and 2- 9% in studies based on skin prick testing (SPT) and IgE assessment.⁽⁴⁾ The prevalence of CMA is increasing with a decrease in breast feeding and increase in feeding with cow's milk-based formulas.⁽⁵⁾

Overall frequencies of self-reported CMA are much higher than medically confirmed diagnoses, in children and adults as well.

At present, 0.6 - 2.5% of preschoolers, 0.3% of older children and teens and less than 0.5% of adults suffer from CMA.⁽⁶⁾

It is interesting to learn that, the majority of CM allergic infants outgrow their CMA; 45–50% at 1 year, 60–75% at 2 years, and 85 - 90% at 3 years of age.^(7,8) While another study reported CMA resolution in 19% of the children by 4 years of age, in 42% by 8 years of age, in 64% by 12 years of age and in 79% by 16 years of age.⁽⁸⁾ The mechanisms underlying the development of clinical tolerance are not fully understood. Some of the several factors are:⁽⁹⁾

- a. Decline of IgE antibodies due to avoidance,
- b. Development of blocking IgG antibodies due to regular intake of CM and/or
- c. Presence of IgE antibodies against mainly conformational epitopes and not against sequential epitopes.

The risk is persistent if reactions to < 10 ml of milk during an oral food challenge and large wheal size reactions in skin prick test are there.⁽¹⁰⁾ Low levels of milk-specific IgE and small wheals during SPTs indicate resolution.⁽¹¹⁾ A recent observational study measured the severity of atopic dermatitis (AD) for the natural course of milk allergy in infants younger than 15 months. A web-based calculator for prognosis was based on milk-specific IgE levels, SPT wheal sizes and severity of AD.⁽¹²⁾ Genetic predisposition for allergy (i.e., atopy), early ingestion of small amounts of CM and factors related to the intestinal microbiome determine risk for developing CMA.

Clinical presentation

CMPA in infants affect GIT and other organ systems with diverse range of symptoms of variable intensity. Usual age of presentation is at weaning with CM or rarely during lactation.⁽¹³⁾ Hypersensitive infants have pulmonary hemosiderosis and chronic symptoms such as recurrent fevers, weight loss and failure to thrive.⁽¹³⁾ Suspected IgE-mediated milk allergy can be confirmed by testing for specific IgE to milk (skin prick test or blood tests) whereas suspected non-IgE-mediated disease do not need these tests.

Food-protein-induced enterocolitis syndrome (FPIES) in infants, is usually due to CMPA. It presents with recurrent vomiting, lethargy, pallor, diarrhea with blood and/or mucus, and dehydration with metabolic acidosis in the acute setting, and hypoalbuminemia and failure to thrive in a chronic form. The diagnosed on basis of clinical presentation and cow's milk protein (CMP) avoidance/challenge may be missed or delayed.⁽¹⁴⁾ Children with active milk-FPIES have low levels of cslgG, cslgG4, and cslgA. Their deficient T-cell mediated TGF- β responses to casein, render TGF- β as a promising biomarker. It would help to identify children who are likely to experience FPIES reactions to this allergen.⁽¹⁵⁾

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Cow's milk can accentuate wheezing in asthmatic children. Both skin prick test (SPT) and slgE testing have suboptimal reliability.⁽¹⁶⁾ Urticaria, angioedema, pruritus, rashes and flushing occur in IgE-

mediated skin reactions. Since atopic dermatitis is usually T cell-mediated; T cell activation may be enhanced by IgE-facilitated allergen presentation.⁽¹⁷⁾ Respiratory symptoms of CMA are rhinoconjunctivitis, wheezing, coughing, asthma exacerbation and laryngeal edema.

About 60% of CMA owe to immediate and IgE-associated mechanisms with one or more organs involvement. After peanuts and tree nuts, CM is the third most common food component that causes

10–19% of all food-induced anaphylactic cases.⁽¹³⁾ Typical IgE-associated symptoms appear immediately or within 1–2 h. It affects skin, respiratory system, gastrointestinal tract and/or appear as systemic anaphylactic reactions in severe cases.⁽⁶⁾ Anaphylaxis present as cardiovascular collapse, syncope or incontinence as the most severe characteristics.⁽⁶⁾ Acute gastrointestinal symptoms include oral itching, abdominal pain, nausea, vomiting and diarrhea. Furthermore, food-dependent exercise-induced anaphylaxis is reported in infants who outgrew their allergy or after an oral immunotherapy.⁽¹⁸⁾

In nutshell baby with CMPA can present with:

- Oral pruritis, vomiting, diarrhoea and colic
- Mucus or bloody stools
- Vomiting, diarrhoea, dyspepsia and gastroesophageal reflux
- Malabsorption, protein losing enteropathy

The non-IgE-mediated mechanisms of CMA are difficult to diagnose.⁽¹⁹⁾ Symptoms have delayed onset, around 2 h to several days after CM consumption. Patients show negative results in skin prick tests due to lack of circulating CM protein-specific IgE.⁽¹³⁾ The estimated prevalence is around 0.5% in infants but is more common in adults.⁽²⁰⁾ The predominant clinical symptoms (usually GI) include enterocolitis, proctitis, proctocolitis, enteropathy, irritable bowel syndrome, eosinophilic esophagitis and constipation.⁽¹³⁾ Its role in gastroesophageal reflux (GER) and infantile colic and constipation is not confirmed and needs further investigation.⁽¹³⁾ Delayed respiratory symptoms include pulmonary hemosiderosis, chronic cough, tachypnea, wheezing and rales. Sometimes atopic dermatitis appears as a chronic symptom after CM ingestion.

Immune mechanisms in CMA

A defect in the development or breakdown of oral tolerance i.e. immunological hyporesponsiveness to ingested innocuous antigen present as CMA. Immunomodulatory factors in human milk influence the development and maturation of the mucosal immune system of the infants. Mucosal tissue homeostasis is the result of the perinatal establishment of mucosal induced immune tolerance.⁽²¹⁾

Secretory IgA (SIgA) inhibits inappropriate immune activation by microorganisms and antigens by reinforcing the epithelial barrier of intestinal and respiratory tracts. Although B cells are present in gut tissue during early development, plasma cells producing dimeric IgA are only generated after birth to provide SIgA to the lumen. Maternal SIgA is provided by breast milk during the early postnatal period.⁽²¹⁾

Breast milk is a rich source of SIgA with lesser amounts of IgG and IgM. Mother's intestinal B-cells migrate to mammary gland ("enteromammary link") and release IgA in human milk.⁽²²⁾ Thus antibody specificity of breast milk reflects the antigenic stimulation encountered by maternal gut.⁽²³⁾ Total and food-specific IgA levels in breast milk and development of allergic disease in older children have no consistent association.⁽²⁴⁾ Lower levels of total and CM-specific IgA have been demonstrated in colostrum and breast milk of mothers with offspring developing CMA.⁽²⁵⁾ Its etiology is unknown but unrelated to maternal atopy.

Several mechanisms leading to the initial sensitization to CM proteins are hypothesized. One is sensitization before birth: small amounts of food proteins consumed by pregnant women can reach

the foetus via the placenta. IgE may be already produced by foetuses in early pregnancy and can be detected in cord blood.⁽²⁶⁾

The other possibility is sensitization following intake of CM early after birth. Early contact with CM proteins leads to sensitization or clinical tolerance; is still a controversy. Interestingly, if babies should be exclusively breast fed; sensitization to human milk also has been reported.⁽²⁷⁾

With ongoing debate on the precise format, several immunological mechanisms are held responsible for non-IgE-mediated reactions to CM proteins. Neither the measurement of CM allergen-specific IgG nor IgA are useful for diagnosis of non-IgE-associated CMA.⁽²⁸⁾ Atopy patch test measures CM allergen-specific T cell responses, which may be useful to assess T cell-mediated reactions. Symptoms may be caused by cow's milk-specific T cell responses. Antibody-mediated mechanisms may involve Type II or Type III hypersensitivity mechanisms such as ADCC (antibody-dependent cell-mediated cytotoxicity) or complement activation.⁽²⁹⁾ Th1/Th2 imbalances are assumed to have an impact too.

It is quite possible that allergy is mediated through both IgE- and non-IgE-mediated reactions. Humoral and/or cell-mediated mechanisms together lead to acute and chronic clinical manifestations which appear as atopic dermatitis and eosinophilic gastroenteropathies (esophagitis and gastroenteritis).⁽¹³⁾ Positive skin prick tests and/or serum specific IgE for CM are positive only in IgE mediated CMPA. Atopic patch testing may be useful in diagnosing occasional non IgE-mediated patients. The prognosis is good with avoidance of cow's milk and dairy products.

Symptoms diminish by the time patients grow up to 3 years old. The mediation by stimulation of Th2 cells lead to high production of interleukin (IL)-4, IL5 and IL-13. Regulatory T cells (Tregs) play an important role in suppression of Th2 function, and thus inhibiting allergic reaction. IL-10 is a major regulatory cytokine of inflammatory responses and has a key role in induction and maintenance of energetic states. IL-10 also actively suppress the T-cell response to allergens entering by the mucosal route in healthy subjects. The IL-10 level in the DBPCFC-negative group who had undergone previous oral challenge with positive results is high. This point out its role in outgrowing food allergy and a useful tool in the diagnosis of food tolerance in previously food-allergic patients.⁽²⁾

Immunoglobulin G (IgG) antibodies to food allergens are produced in both atopic and non-atopic children. Allergic symptoms and atopic sensitization accompany high levels of IgG4, an IgG subclass antibody. IgG4 antibodies production share regulatory mechanism with IgE, e.g. IL-4 from Th2 cells induces both IgE and IgG4 switching in B-cells. But their control by IL-10 is distinct; as IL-10 inhibits IgE production but up-regulates the secretion of IgG4, e.g. Tregs stimulate B cell to increase IgG4 and to suppress IgE.⁽²⁾

In egg allergy cases, natural development of tolerance was coupled with an increase in ovalbumin-specific IgG4 level and a decrease in ovabumin-specific IgE level. Atopic children and adults without CMPA; who maintained tolerance to cow's milk, had elevated levels of specific IgG4. Additional confirmation is from a study to identify immunological differences between infants with clinical signs of eczema and sensitization to food allergens before and after a 6-wk treatment period and at 4 years of age.⁽²⁾

Allergens in cow's milk

One litre of cow's milk contains around 30–35 g of 25 different proteins, but only some of them are known allergens. Acidification of raw skim milk to pH 4.6 at 20 °C obtains two fractions of the total milk proteins: 80% coagulum containing casein proteins and 20% lactoserum (whey proteins).⁽³⁰⁾ The

casein fraction (Bos d 8, *Bos domesticus*) is made of different percentages of four proteins: α S1-casein (Bos d 9, 32%), α S2-casein (Bos d 10, 10%), β -casein (Bos d 11, 28%) and κ -casein (Bos d 12, 10%). α S1-casein is the most important allergen of the casein fraction.⁽³¹⁾

Most important allergens of whey fraction are α -lactalbumin (Bos d 4), β -lactoglobulin (Bos d 5) which account for 5% and 10% respectively of the total milk proteins. (30) Others minor allergens with few reports are immunoglobulins (Bos d 7), bovine serum albumin (BSA, Bos d 6) and traces of lactoferrin (Bos d lactoferrin).(32)

Human IgE response to CM proteins is characterized by a great variability. The major problem of CMA is inability to identify single allergen or particular structure with key role in allergenicity of milk. Approximately 75% of CMA patients are sensitized to several proteins with variable IgE response in specificity and intensity. Most abundant proteins of CM, namely caseins, β -lactoglobulin and α -lactalbumin are most frequently recognized allergens.^{(9),(33)} Extensive IgE binding studies in large populations of clinically well-defined CM allergic patients and an assessment of the allergenic activity of the individual allergen components can define clinically most relevant allergens.⁽⁹⁾ Small study groups selected on basis of on different criteria have displayed variable prevalence of IgE reactivity to certain CM proteins.^{(9),(33)}

Diagnosis of cow's milk allergy

After a thorough clinical history, diagnosis of CMA can be reached. Food-specific IgE and risk of clinical symptoms correlate.⁽³⁴⁾ Skin prick test is a fast method to detect sensitization. But a positive test is not specific; it neither confirm food as a cause nor unambiguously demonstrate an IgE-mediated allergy. It can only be confirmed by detection of allergen-specific IgE (e.g. false positive reaction in urticaria factitia patient).

The diagnostic test CAP-FEIA System or UniCAP can detect specific IgE antibodies in serum. (Phadia, Uppsala, Sweden). Atopy patch tests are used as diagnostic tools for non-IgE mediated CMA reactions but its reagents, methods of application and interpretation are not standardized. The double-blind placebo-controlled oral food challenge (DBPCFC), can diagnose food (milk) allergies. This gold standard test can be performed only after the suspected food is eliminated from the diet.⁽³⁵⁾ Skin prick tests, patch tests and serum specific IgE are only indicative of CMPA.

Double-blind placebo-controlled food challenge (DBPCFC)

As per standardized protocol of European Academy of Allergy and Clinical Immunology (2004), patients consumes progressively increasing quantities of CM.⁽³⁶⁾ Appearance of adverse reaction indicate positive test and the challenge is stopped. Symptoms (elevated cow's milk-specific IgE levels, young age and atopic dermatitis)⁽³⁷⁾ appear earlier and more organ systems are affected. It is necessary to challenge the patient until clear objective symptoms occur without doing harm to the tested person by reaching the maximum response. DBPCFC can be used in these positive cases to exclude bias. It is a standardized test, which obtain a clear diagnosis and caution the patient about diets.⁽³⁸⁾ Unfortunately it is not suitable to estimate the risk of a reaction after CM consumption since augmentation factors cannot be excluded. Still it is useful to determine the minimum eliciting dose for an acute allergic reaction.⁽³⁹⁾ Despite the clear diagnosis this test has several disadvantages: it is very time consuming, costly, can only be performed under medical guidance and bears the risk of inducing severe anaphylactic reactions.⁽³⁸⁾ The test is negative if a considerable amount has been consumed without reactions and confirmed by an open food challenge (not double blind or placebo controlled).

Skin prick test (SPT)

A SPT is a fast and inexpensive test to detect sensitization in IgE-mediated disorders. Commercial CM extract or fresh milk or single allergen components and a saline-glycerine control are pricked with a lancet into the epidermis of a patient. If the patient has IgE antibodies against the food allergen, a wheal greater than the saline control will appear. The negative predictive value using fresh milk is excellent (>95%). Unfortunately the specificity of this test is poor and unable to prove tested food component as trigger.⁽⁴⁰⁾ Positive predictive values (PPV) could not be set up in spite of several studies due to conflicting results. 95% PPV of a clinical reaction in children 2 years of age or younger is indicated by wheal diameter of 6 to 12.5 mm and 8 to 15 mm in children older than 2 years.^(3,41-43)

In SPT, Calvani et al. found highest negative predictive value with fresh milk whereas greatest positive predictive value with commercial extract of casein.⁽⁴³⁾ Protein composition of crude and commercially available allergen extracts is markedly different and yield different test results with SPT.⁽⁴⁴⁾ Additional forms of diagnostic tests may overcome these differences and contamination of skin test solutions. E.g. *in vivo* tests using purified allergen components as single solutions or mixes.⁽⁴⁵⁾

Atopy patch test (APT)

Atopic dermatitis, delayed reactions after CM consumption or gastrointestinal symptoms lacking specific IgE are indications of APTs.⁽⁴⁶⁾ It is diagnostic of eosinophilic esophagitis in all age groups and gastrointestinal symptoms after CM consumption in preterm infants. (47) It can predict oral tolerance in children with gastrointestinal symptoms suffering from non-IgE-mediated CMA.(28) An allergens applied at patients back are sealed by patch for up to 48 h and skin reactions are documented after its removal and after another 24–48 h. Unfortunately reagents, application methods or guidelines for interpretation have not been standardized so far. So parallel use of multiple tests for the diagnosis of CMA is still recommend after analyzing the diagnostic value of APT.(3)

Assessment of cow's milk allergen-specific IgE

Sera obtained from venous blood samples are exposed to solid matrix-bound allergens (skimmed CM) and then detected by a secondarily labelled antibody specific for the Fc portion of human IgE. Therefore the sensitivity of IgE determination is very high. Occasional irrelevant positive results, can be interpreted with help of clinical history. These IgE antibody assays are offered by Phadia (ImmunoCAP System), Siemens Healthcare Diagnostics (Immulite), Hycor Biomedical (HYTEC-288) and few other companies. Sampson are pioneers in providing predictive values for IgE. The values range anywhere between 1.5 to 46 kUA/L for different age group.⁽⁴⁸⁾ The differences are mainly due to various study populations regarding selection criteria or age of participants or different criteria for determining a failed or passed challenge.⁽⁴⁹⁾

Improvement of diagnosis

Purified natural and recombinant cow's milk allergens

The majority of diagnostic tests are based on natural allergen extracts. Their drawbacks like lacking sufficient quality (absence of important allergens), presence of contamination and undefined non-allergenic components lead to inaccurate diagnosis of CMA.⁽⁵⁰⁾ Recently a lot of effort done on identification and characterization of relevant milk allergens.

Pure and well characterized allergens allow mapping of IgE, IgG and T cell epitopes using sera from CM allergic patients. The investigation of mechanisms underlying allergies and development of diagnostic

tools is possible with knowledge of allergen structure, characteristics and position of the epitopes. This will lead to production of endotoxin-free recombinant allergens in high quantities.⁽⁵¹⁾ Recombinant allergens have a defined quality and concentration and are composed of single isoforms. Natural allergen preparations expressed in *E. coli* are mixture of different isoforms with various biological activities. Lack of carbohydrates in natural forms does not allow its recognition by carbohydrate-specific IgE antibodies often leading to clinically irrelevant results.

CM extract purification procedures does not yield CM allergens α S1-casein and α S2-casein. Their pure form obtained separately by recombinant technology not only improve diagnosis, but also facilitate an important progress from extract-based to component-resolved diagnosis (CRD). Additional use of recombinant purified proteins allows identification of cross-reactive allergens and explains allergic symptoms after consumption of various foods.⁽⁵²⁾

Sometimes eukaryotic expression systems is used to acquire correctly folded proteins. Since all proteins expressed in *E. coli* do not have correct folding or comparable characteristics of their natural counterparts.

The milk proteins α -lactalbumin, β -lactoglobulin, α S1-casein, α S2-casein, β -casein and κ -casein have been expressed in *E. coli* and their purity, fold and IgE reactivity is established. Future use single recombinant allergens or a mix of several recombinant cow's milk allergens will contain the allergen repertoire and all relevant IgE epitopes. It will rule out disturbing materials responsible for tree and grass pollen allergy.⁽⁵³⁾

Component-resolved diagnosis (CRD) and microarray technology

Current serological test systems in clinical practice like ELISA, RAST or CAP-FEIA are not suitable for component-resolved diagnosis. These single allergy tests require a big amount of patients' sera, and are work- and time-intensive and expensive. Progress in the fields of molecular biology, biochemistry and biotechnology led to the development of protein microarray chips or other multiplex technologies.⁽⁵²⁾ Currently commercially available protein microarrays allows detection of IgE reactivity to 103 allergenic molecules (ImmunoCAP ISAC-CRD 103, Phadia, Uppsala, Sweden) in routine use or to even more allergens in research settings.

The routine application of microarray technology requires only minute amounts of patients' sera. It is of particular importance in case of diagnosis of milk allergy in infants and children. A single assay can determine reactivity profiles of allergic individuals to large numbers of disease-causing allergens.

Basophil mediator release/basophil activation tests

IgE antibodies are not only capable of binding allergens but also induce mediator release. It can be checked with different available methods to avoid provocation tests.⁽⁵⁴⁾ In basophil histamine and leukotriene C₄ release assays, basophils from sensitized patients, IgE-depleted stripped basophils from healthy donors, basophil cell lines or animal cell lines transfected with human IgE high affinity receptors are incubated with patients' sera containing IgE antibodies. Basophils incubated with different concentrations of allergens crosslink Fc ϵ RI-bound IgE and induce mediator release.⁽⁵⁵⁾ Released mediators are measured by radioimmunoassay or enzyme-linked immunosorbent assay.

Another test method analyse basophil activation markers CD203c or CD63. It includes measurement of allergen-induced basophil activation by flow cytometry. The basophil tests determine clinical course of CMA and decision of food challenge.⁽⁵⁶⁾

IgG/IgA antibodies

Measurement of cow's milk-specific IgE antibodies has become a standardized test method. In case of non-IgE-mediated hypersensitive reactions, *in vitro* cellular or antibody-based test systems are still controversial. Observations in early 1980s on IgG₄ induced mediator release from basophils; has endorsed idea of testing IgG when IgE is lacking.⁽⁵⁷⁾

Therapy and prevention

Risk of CMPA in mother's milk fed infants is low. On confirmation, CMPA designate elimination diet (of CM) for the mother. Elimination diet by a double-blind placebo controlled food challenge is the gold standard for diagnosis. Elimination of the offending "allergen from the infants' diet is the main treatment principle. Formula fed infants who test positive to food challenge, should receive an extensively hydrolysed formula and cow's milk-free diet". The next is an amino acid based formula for those who do not improve or have severe CMPA with life-threatening symptoms.⁽⁵⁸⁾

Avoidance of cow's milk and dietary treatment

A detailed clinical history and cow's milk-specific *in vitro* tests identify the allergy-eliciting food components. The current treatment of CMA is the elimination of CM from the daily nutrition.⁽⁵⁹⁾ Some patients suffering from CMA may tolerate small amounts of extensively heated or baked milk. It is a prognostic indicator, so its inclusion in daily diet has a positive influence on the development of tolerance. An appropriate diet should take into account improvement of symptoms, nutritional deficiencies, increase in cost and time. Parents are advised to administer milk formulas until at least 2 years of age, especially to CM allergic infants. Almost 95% of them tolerate extensively hydrolyzed formulas (eHF), which is the most suitable alternative, cheaper and offer similar clinical outcomes as amino acid formulas.⁽⁶⁰⁾ But to those with persistent symptoms an amino acid formula needs to be prescribed. A well-balanced diet with a proper calorie/protein ratio, amino acid composition and calcium source should be administered. Milk reintroduction under medical guidance should be done once the child outgrow CMA.⁽³⁾

The non-invasive milk APT test can diagnose CMA in preterm infants. This early finding helps to decide which type of formula (standard CM formula, extensively hydrolyzed CM formula, and amino acid based formula) is administered.⁽⁴⁷⁾

High amino acid sequence homologies between the allergens from cow, sheep and goat make them unsuitable substitute for CMA infants.⁽¹³⁾ Milk of other mammal's (mare, camel and donkey) form an appropriate alternative as their protein composition differ from cow's milk and are therefore better accepted.⁽⁶¹⁾ A few reports of clinical reactivity and sensitivity to human milk, could not be assigned any clinical relevance.⁽²⁷⁾

All CM derived products (cheese, yoghurt, butter and cream) should be excluded from diet of CMA patients.⁽³²⁾

Bovine serum albumin is present in milk, beef, and cow's dander. CMA patients suffer beef allergy as well as allergic and respiratory symptoms after contact with cows.⁽⁶²⁾ Some parents opt for vegetable alternatives due to various opinion or convictions.

Management

- Key dietary management is removal of allergenic protein from the diet 3-4 years, though most of the affected infants overcome CMPA by 2 years. Even a breastfeeding mother should quit all dairy products if milk allergy is suspected in the infant and shift to calcium supplements.^{(63),(64)}

Table 1: Comparison of non-IgE mediated cow's milk allergy and lactose intolerance

	Non-IgE-mediated milk allergy	Lactose intolerance
Symptoms	Gastrointestinal, skin, or respiratory	Bowel only, for example, pain, flatulence, diarrhoea
Mechanism	Immune reaction to milk protein	Non-immune. Reduced ability to digest lactose
Tests	Exclusion diet (NO MILK PROTEIN) (symptom improvement) and then reintroduction (symptom recurrence). May take 4–6 weeks for symptoms to improve	Exclusion diet (LOW LACTOSE) (symptom improvement) and then reintroduction (symptom recurrence). Usually improve within 48 hours of exclusion
Dietary advice (including formulas)	A diet free from cow's milk protein. Exclude all cow's milk and products. Consider tolerance acquisition and introduction of, for example, extensively baked products after 6 months	Low lactose diet - exclude cow's milk and foods containing cow's milk, although some with low lactose may be tolerated by some individuals
		If secondary, should resolve by 6 weeks

- In a formula-fed infant, choice of formula is determined by the severity of the symptoms.⁽⁶³⁾ Most infants respond to extensively hydrolysed formulas, where the milk protein is broken down.
- Amino acid formulas should be reserved for severe symptoms and those not responding to an extensively hydrolysed formula.^{(63), (64)} It can also be used first line if top-up feeds are required in an infant who is exclusively breast fed and shows symptoms suggestive of cow's milk allergy.⁽⁶⁴⁾
- At least 6 months of milk protein free diet should pass before considering tolerance. Extensively baked milk products will be tolerated before less well cooked milk.⁽⁶⁴⁾
- Isoflavones in soya may exert a weak oestrogenic effect so it is not recommended below 6 months of age. The risk of cross-reactivity is up to 14% in individuals with IgE-mediated cow's milk allergy and up to 60% with non-IgE-mediated cow's milk allergy,⁽⁶⁵⁾
- Rice milk (rice protein-based eHF) can be an alternative to a CMP-based eHF. It is not recommended in those aged <4.5 years due to the arsenic content.⁽⁶⁵⁾
- Cross-reaction between mammalian milks render goat's milk and products unsuitable for CMA infants.⁽⁶⁵⁾

Medical treatment

Guidelines for the dietary management of CMPA infants recommend substitution of cow's milk with extensively hydrolyzed casein or whey protein formulas (eHF).^{(66),(67),(68)} As per American Academy of Pediatrics (AAP) eHF is a preferred therapeutic option with Soy Infant Formula (SIF) as a second choice.⁽⁶⁷⁾ However, eHFs are substantially more expensive than standard or soy infant formulae and generally have a bitter taste, which often hampers its acceptability.⁽⁶⁷⁾ Some infants may still be intolerant or allergic to these eHFs.^{(66), (68)} In those cases, amino acid formulae (AAF) are an effective

dietary treatment but even they are substantially more expensive and have also a bitter taste.^{(66),(67),(68)}

Soy protein-based formulas have been available for almost 100 years. Since the first use of soy formula as a milk substitute for an infant unable to tolerate a cow milk protein-based formula, the formulation has changed to the current soy protein isolate. Despite very limited indications for its use, soy protein-based formulas in the United States may account for nearly 25% of the formula market.⁽⁶⁷⁾ Soy infant formula (SIF) is cautioned, as it can induce symptoms in upto 15% of CMA infants.⁽⁶⁷⁾ Though tolerance of soy is better in immunoglobulin E (IgE) compared with non-IgE-mediated CMPA. ESPGHAN and an Australian expert panel suggest avoiding SIF before the age of 6 months.⁽⁶⁶⁾

In accordance with current guidelines, this extensively hydrolyzed rice protein infant formula (eRHF) was tolerated by more than 90 % of children with proven CMPA with a 95% confidence interval. This eRHF is an adequate and safe alternative to cow milk-based eHF.⁽⁶⁹⁾

The diagnosis of CMPA first require high index of suspicion. It is confirmed by medical history, and improvement of symptoms on elimination of CMP from the infant's diet. The elimination of CMP would be unjustified, and sometimes harmful without such meticulous analysis. Till the child reach 9-12 months of age, elimination diet should be strictly followed. Maternal CM avoidance was associated with lower levels of mucosal specific IgA levels and development of CMA in infants.⁽⁷⁰⁾ Early exposure to CMP as a supplement to breast-feeding might promote tolerance. If breast feeding is not possible due to child or mother's issues; extensively hydrolysed formula (eHF) of CMP is the first choice. The alternative is an amino acid-based formula if eHF is not tolerated.

For infants >6 months soya protein-based infant formulae may be a suitable alternative, only after establishing tolerance to soya protein by clinical challenge. Soy is a reasonable feeding alternative in patients with IgE-mediated CMA.⁽²⁰⁾ Resolution of CMPA is expected by 2nd or 3rd year of age but is determined by the child and type of CMPA. IgE-mediated CMPA is a more persistent form. At 9-12 months age, an oral food challenge in hospital ward can assess development of tolerance. It will decide whether continued reintroduction of CMP at home is tolerable. Some children will tolerate only a limited daily amount of CMP. The current therapeutic options of repeated exposure accelerate the acquisition of tolerance.⁽⁷¹⁾

Reintroduction of cow's milk in milk-allergic children

CMPA is one of the most common food allergies in childhood. But its prognosis is generally good and cow's milk (CM) is usually reintroduced in diet. The heterogeneous natural history of CMPA is closely related to the immunological and clinical phenotype.

Non-IgE-mediated CMPA has better prognosis as a high percentage of them development of tolerance at an earlier age. IgE-mediated disease with severe symptoms may persist for longer or ever. Majority of children will outgrow their allergy, but individual timing of tolerance acquisition is largely unknown. Reevaluation of milk-allergy every 6-12 months, and reintroduction of CM after a negative Oral Food Challenge (OFC) is proposed in most of the current guidelines on diagnosis and management of CMPA. However, OFC procedure is time consuming, expensive and not without risk. So some useful prognostic information in the course of CMPA can be obtained through clinical variables, measurements of sIgE levels, and SPT wheal sizes to crude (whole) CM protein and individual milk protein components. Clear-cut clinical or laboratory criteria to predict which children and at what age are more likely to pass a repeat (reintroduction) OFC are not available. Factors that accurately predict the outcome of reintroduction OFC and the timing of tolerance development would be extremely useful in daily clinical practice.

In the past, challenge of CM reintroduction was attempted when children with CMPA were more likely to have developed tolerance. Recent new approach for milk and egg allergy is specific oral tolerance induction (SOTI); a promising method for the treatment of food allergies. Several studies have demonstrated acquisition of tolerance to heated milk and egg protein by allergic patients. Yet 'when and how' of CM reintroduction continue to be a challenge.(72)

Drug treatment

Oral antihistamine for mild cutaneous or digestive reactions and an epinephrine auto-injector for systemic or respiratory reactions may be needed in CMA.(1), (40)

Other non-specific treatments is monoclonal anti-IgE antibodies to reduce free IgE antibodies in the blood of allergic patients. This leads to a reduction of basophil activation and an increased threshold dose. (73)

Probiotics

European Society of Pediatric Gastroenterology and Nutrition (ESPGHAN) and the American Academy of Pediatrics have set a criteria for probiotics. If they are proven safe and tolerated well, can be added to formulas used for CMA. A properly designed DBPCFC is used to test the formula. Under double-blind, placebo-controlled conditions, with 95% confidence if at least 90% of infants and children have no reaction to the formula; it can be considered hypoallergenic. LGG has been used safely over 25 years even in preterm infants. Addition of LGG to eHCF achieve a hypoallergenic formula that satisfying both ESPGHAN and American Academy of Pediatrics guidelines.(74)

Hidden food allergens in marketed probiotic compounds are unsafe for CMA subjects and pose an emerging problem. More accurate screening tests can detect residual food proteins in end products to prove its safety for food allergic patients. Allergic subjects should opt for only well characterized products with better information on their labels about CMP content.(75)

Immunotherapy (IT) and future strategies for specific immunotherapy

Immunotherapeutic treatment is well established for respiratory allergies, since long duration.(50) Subcutaneous immunotherapy for peanut allergy has to be withdrawn after severe reactions. With no marketed and approved therapy, other possibilities could be different immunomodulatory treatments such as oral or sublingual immunotherapy or safer injections using well defined recombinant allergens with reduced allergenicity. (76)Studies that compare long-term consequences and effectiveness of different immunotherapies in contrast their risk-benefit are need.

Oral immunotherapy (OIT)

The mechanisms of immunotherapy are decrease in milk-specific IgE and basophil mediator release; increase in blocking antibodies (IgG₄) and eventual induction of regulatory T-cells.(59) In general increasing doses of CM are given in a special sequence: initial dose escalation during a controlled setting, then a regular consumption of tolerated doses during a build-up phase which is followed from a maintenance dose at home .(77) High doses of antigen induce non-responsiveness resulting from anergy or deletion of antigen-specific T lymphocytes, whereas administration of continuous low doses induces regulatory T cells.(77)

Due to lack of controlled studies testing standardized protocols and outcome measurements, oral immunotherapy is not recommended for routine practice. But it has shown some promising improvements in life quality of patients with severe and persistent CMA.

It effectively treated severe systemic reactions and induced tolerance in 36% of 30 CM allergic children.⁽⁷⁸⁾ In 54%, it was possible to induce a higher threshold level of accepted CM (5–150 ml). Skripak et al. demonstrated beneficial induction of milk-specific IgG levels, predominantly IgG₄ with OIT. Despite increased threshold levels in treated group, the milk-specific IgE levels did not change significantly in either treatment or control group.⁽⁷⁹⁾ The adverse reactions are common and completely unpredictable.⁽³⁾ Standardized protocols with optimal dose, degree of *protection*, ideal duration, safety, efficacy for different ages and severity of adverse reactions need to be designed.⁽⁷⁷⁾

Sublingual immunotherapy (SLIT)

In rush period, milk is kept under tongue in increasing dose and continued for weeks to months during maintenance. Keeping milk under tongue for 2 min, increased the threshold dose after 6 months in a small cohort of patients ($n = 8$).⁽⁸⁰⁾

Compared to SLIT, OIT more efficiently desensitizes CM probably due to higher treatment dose in range of several grams. However more systemic side effects were encountered during OIT.⁽⁸¹⁾ Upcoming studies with optimal dose for SLIT may improve efficacy.

Epicutaneous patch (EPIT)

A small study treated CM allergic children with epicutaneous patches of skimmed milk powder applied for 48 h each week for 3 months. Induction of higher milk tolerance level was accompanied by frequent side effects as pruritus and eczema. The immunological mechanisms underlying this treatment are unknown.⁽⁸²⁾

Cow's milk allergy prevention

European and American guidelines recommend exclusive breast feeding for 4 - 6 months and a delayed introduction of solid food components in infants with atopic risk.⁽⁸³⁾ There is room for designing different preventive strategies in future.

- An early introduction of possible food allergens has been beneficial in newer trials and reduced frequency of CMA.
- Hydrolyzed formulas containing tolerogenic peptides may induce tolerance detected as lack of allergen-specific humoral and cellular immune responses.
- CM based formulas supplemented with prebiotics has beneficial effect on reduction of atopic dermatitis in infants.⁽⁸⁴⁾

The lack of awareness of guidelines on CMPA and the training identified as necessary on this topic has bearing on the recognition and management of this food allergy. Training programs for physicians would benefit and improve diagnosis and management.

Conclusions

Standardized testing materials such as purified natural allergens and recombinant proteins have improved CMA diagnosis. Advance from extract-based to defined and well characterized allergens has paved way for component-resolved and personalized diagnosis. So far avoidance of CM is the treatment and oral immunotherapy is performed only in specialized settings. The future goals is developing new forms of effective immunotherapy with reduced risk of severe side effects.

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Dear Doctor,

Cow's milk protein allergy (CMPA) is found in about 2 to 6% of children, with the highest prevalence in the first year of age. Large number of children are referred for suspected CMPA based on parent perception, symptoms such as cutaneous eruption, insomnia, persistent nasal obstruction, seborrheic dermatitis or positive results to unorthodox investigations. Moreover, parents often put their children on unnecessary diet without an adequate medical and dietary supervision. These inappropriate dietary restrictions may lead to nutritional imbalances, especially in early. Therefore, an correct diagnosis of CMPA is essential in order to prevent not only the risk of rickets, decreased bone mineralization, anaemia, poor growth and hypoalbuminemia, but also that of immediate clinical reactions or severe chronic gastroenteropathy leading to malabsorption.

It is indeed a pleasure to present to you this QMR issue by Prof. Dr. Bhaskar Moni Chatterjee, renowned paediatrician. In this issue, he is enlightening us on 'Practical Approach to Management of Cows Milk Protein Allergy'.

I sign off by once again reminding you to continue sending in your comments and suggestion regarding the QMR. Do write to me at balaji.more@raptakos.com with your write ups, notes or tidbits on various topics of interest that can make for informative and interesting reading.

With best regards,

Dr. Balaji More

Vice President - Medical



Feedback form: January - March 2019
Practical approach to management of Cows milk protein allergy

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