BANGLADESH J CHILD HEALTH 2023; VOL 47 (2) : 59-64

Review Article

Approach to a Child with Cow's Milk Allergy

MD. RUKUNUZZAMAN[1], KHAN LAMIA NAHID[2], RUBAIYAT ALAM[3], FAHMIDA BEGUM[4], MD ATIAR RAHMAN[5], MD. WAHIDUZZAMAN MAZUMDER[6], NADIRA MUSABBIR[7]

Abstract:

Cow's milk allergy is a common problem in childhood that needs frequent visits to a pediatrician. The objective of this review is to provide the general pediatrician with an overview of cow's milk allergy in children discussing the etiology, patient evaluation, and management. This review provides an approach to a child with cow's milk allergy based on the best available evidence from electronic literature searches. Cow's milk allergy may be IgE-mediated, non-IgE-mediated, and mixed. IgE-mediated reactions occur immediately after ingestion of milk. Skin manifestations like erythema, hives, pruritus, angioedema, and flaring of eczematous lesions are common manifestations of IgE-mediated food allergy. Non-IgE-mediated cow's milk allergies are proctocolitis, enterocolitis, enteropathy, and contact dermatitis. Cow's milk-induced allergic proctocolitis is the common cause of rectal bleeding from 1 day to 6 months of age. The key to the diagnosis of food allergy depends on obtaining a good history and physical examination. Quantitative measurements of serum cow's milk specific IgE and skin prick test are useful tests. Strict avoidance of the offending food is the mainstay of management.

Keywords: *Child, Cow's milk allergy*

DOI: https://doi.org/10.3329/bjch.v47i2.77666

Introduction

Cow's milk allergy (CMA) also called cow's milk protein allergy (CMPA), is the most common food allergy in young children. CMA does not include other adverse reactions to milk, such as lactose intolerance (which is nonimmune mediated). CMA is found in more than 2 percent of children under four years of age.[1] CMA is even more prevalent in infants.[2] Much of reported CMA is non-IgE mediated.[3] About one-half of CMA is non-IgE-mediated allergic conditions, such as dietary protein-induced proctitis/colitis, enteropathy, and enterocolitis.[4] Up to 50 percent of children with CMA also have a concomitant allergy to other foods.[5] The resolution of CMA is variable, depending upon the type of allergy (IgE-mediated or non-IgE mediated).[6] Non-IgE-mediated CMA tends to resolve more quickly. The common cow's milk protein-induced proctocolitis typically resolves by one year of age.[7] Food protein-induced enterocolitis syndrome (FPIES) usually resolves by the age of two to three years.[5] IgE-mediated food allergy undergoes resolution slowly. Introduction of extensively heated cow's milk may speed resolution of IgE-mediated CMA.[8] IgE-mediated CMA do not resolute before 2 years and forty percent resolute by 10 years.[9]

Cow's milk protein allergen

Cow's milk contains 3 g of protein/100 ml and includes at least 25 different proteins- all of which may act as antigens.[10] Cow's milk contains two types of protein-

1. Professor, Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
2. Associate Professor, Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
3. Assistant Professor, Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
4. Associate Professor, Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
5. Assistant Professor, Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
6. Associate Professor, Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
7. Assistant Professor, Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

Correspondence: Professor. Md. Rukunuzzaman, Professor, Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. E-mail: dr.rukon@gmail.com, Mobile: 01709975042

casein and whey. Casein comprises 80 percent of the total cow's milk protein. It includes- alphaS1, alphaS2, beta and kappa. Whey comprises 20 percent of total protein. It includes- alpha-lactalbumin (ALA), beta-lactoglobulin (BLG), bovine lactoferrin, bovine serum albumin (BSA), and bovine immunoglobulins proteins.[6]

Most patients with CMA are sensitized to several milk proteins simultaneously, including casein, BLG, ALA, BSA, bovine lactoferrin, and bovine immunoglobulins.[7]

Casein, BLG, and ALA are the major milk allergens, and co-sensitization to these three allergens is common. Sensitization to milk proteins present in very low concentrations, such as bovine lactoferrin, BSA, and bovine immunoglobulins, is also seen in up to half of patients with CMA.[8]

Cooking diminishes the allergenicity of whey proteins, particularly BLG, by denaturation of heat-labile proteins that result in loss of conformational epitopes. This may explain why extensively heated milk (eg, milk in baked goods) is better tolerated by many patients. Similarly, yogurt cultures, which ferment and acidify milk, diminish the amount of intact whey protein in milk and may result in better tolerance of yogurt-based dairy products.[11]

Pathogenesis

- IgE mediated- Acute allergic responses to milk are due to IgE directed against various allergens in milk. All milk proteins are potential allergens, and polysensitization to several proteins occurs in most patients.[12]
- Non- IgE mediated- CMA also occurs as the non-IgE-mediated mechanism. After ingestion of cow's milk, cow's milk allergen-specific T lymphocytes secrete cytokines that lead to CMA.[13]
- Mixed- Cow's milk allergy also occurs due to mixed IgE and non-IgE mediated processes.

Different antigen and host-related factors have been described as being capable of influencing the induction of either food allergy or tolerance: [14, 15]

1. Antigen dose: low doses of antigen induce tolerance and high doses produce allergy.
2. Form of antigen: particles have a stronger sensitizing effect than soluble allergens. Food processing also exerts an influence; in this regard, pasteurized milk proteins show increased binding to Peyer's patches, giving rise to an enhanced Th2 response.
3. Timing of exposure: greater tolerance is achieved by introducing appropriate amounts at early ages.
4. Exposure route: extraintestinal food antigen exposure routes are more intensely sensitizing.
5. Age: sensitization to food antigens is more frequent in children.
6. Genetic factors: genetic susceptibility plays a role in food allergy development.
7. Microbiota: the microbial environment of the intestine stimulates the immune system and favors tolerance.
8. Exposures that affect the intestinal environment: maternal breastfeeding (favors tolerance), antacid drug treatment (favors sensitization), Cox-2 inhibitor use (favors loss of tolerance in experimental studies).[11]

Classification of cow's milk allergy:

The classification of cow's milk allergy is similar to other food allergies. Cow's milk allergies can be classified as IgE-mediated, non- IgE mediated, and mixed adverse immune response.[16]

	Mechanism	Disorder
1.	Ig E mediated	• Gastrointestinal- - Oral allergy syndrome - Gastrointestinal anaphylaxis • Cutaneous- Urticaria, angioedema • Respiratory- Acute rhinoconjunctivitis, bronchospasm • Generalized- Anaphylactic shock
2.	Non- IgE mediated (Cell mediated)	• Gastrointestinal- Food protein-induced proctocolitis, food protein-induced enterocolitis, food protein-induced enteropathy • Cutaneous- Contact dermatitis • Respiratory- Food-induced pulmonary hemosiderosis
3.	Mixed (Ig E mediated and non-IgE mediated)	• Gastrointestinal- Eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenterocolitis • Cutaneous- Atopic dermatitis, contact dermatitis • Respiratory- Asthma.

IgE Mediated Cow's Milk Allergy:
All IgE-mediated food allergies (cow's milk, egg, soya, nut, fish) may have similar features.

Pathogenesis: Inflammatory mediators are released when food antigens bind with IgE antibodies on mast cells and basophils. These inflammatory mediators result in allergic reactions.[17]

Clinical features: These reactions are sudden on onset, and typically begin within minutes to hours from the time of ingestion. Signs and symptoms that occur in this acute reaction can be classified as cutaneous, ocular, gastrointestinal, respiratory, and cardiovascular, in isolation or combination.[18]

- Skin symptoms are the most common manifestation of IgE-mediated food allergy. These acute food allergy reactions include erythema, hives, pruritus, angioedema, and flaring of the eczematous lesion.[5]
- Ocular symptoms include pruritus, tearing, periorbital edema, and conjunctival erythema.[6]
- Gastrointestinal symptoms include nausea, vomiting, abdominal pain and diarrhea. Upper gastrointestinal symptoms usually begin within minutes of ingestion. Diarrhea may have delayed onset, beginning 2-6 hours after ingestion of the allergen.[7]
- Respiratory tract symptoms include nasal congestion, rhinorrhea, hoarseness, stridor, tachypnea, wheezing and cough, edema of the larynx, and dyspnea.[8]
- Cardiovascular symptoms include increased venular permeability, widened pulse pressure, increased heart rate and cardiac output, flushing, dizziness, and fainting. These effects lead to decreased organ perfusion followed by anaphylactic shock.[9]

Investigations
The key to the diagnosis of food allergy depends on obtaining a good history and physical examination. The following investigation may be needed.

1. Complete blood count may show eosinophilia.
2. Skin prick test with cow's milk allergen- Skin testing is performed via the intraepidermal route using the prick technique with whole milk or the milk protein fractions. A positive reading is represented by a papule (wheal) measuring 3 mm or more in size. The sensitivity of skin testing with milk is highly variable (50-100%).[19]
3. Quantitative measurements of cow's milk specific IgE- serum cow's milk specific IgE will be increased. Serum-specific IgE allows quantitative assessment of sensitization to an allergen. In this case, a determination can be made for whole milk and/or milk fractions. In clinical practice, a value of 0.35 kUA/l is used as a positivity cut-off point. Determinations can be made in the application to cow's milk, -lactoalbumin (Bos d4), -lactoglobulin (Bos d5), bovine seroalbumin (Bos d6), casein (Bos d8), and goat's milk.[20]
4. Elimination diets-elimination diet involves removing cow's milk protein from a baby's diet for a short period of time, and then monitoring the effect on the baby. Foods containing cow's milk protein are completely removed from the diet of breastfeeding mums. For formula-fed babies, the baby is switched onto a special hypoallergenic formula. A trial of up to 4 weeks is usually given.[21]
5. Food challenge- is usually not needed and is sometimes dangerous.

Treatment
1. Food avoidance: strict avoidance of the offending food is the mainstay of management. Patients must be educated on avoiding known allergens and recognition of reactions, some of which may be life-threatening. Cow's milk proteins have been found to be present in breast milk. That is why, in exclusively breast-fed children, a milk and dairy product exclusion diet in the nursing mother has been suggested.[22]
2. Severe anaphylactic reaction may need antihistamine, steroids and epinephrine.

Non-IgE-mediated reactions- The non-IgE-mediated reactions usually have a delayed onset beyond two hours of ingestion. Non-IgE-mediated reactions include food protein-induced allergic proctocolitis, enterocolitis syndrome, enteropathy and Heiner syndrome.

Food protein-induced allergic proctocolitis (FPIAP)
FPIAP is a common cause of rectal bleeding in breast-fed or formula-fed infants. Cow's milk is the most common trigger. Soy, and egg may also trigger FPIAP. Allergy tests (skin tests or blood tests for Immunoglobulin E [IgE] antibodies) are negative for infants with FPIAP and therefore not useful.[23]

Diagnosis is based on: [7, 8, 23]

- Excluding diagnosis of other causes of blood in bowel movements or blood-stained diarrhea, such as gastroenteritis, infections, anal fissures, or bowel malformations/anomalies.
- If FPIAP is considered likely, then symptoms should resolve once the offending food/s are eliminated from the breastfeeding mother's and/ or infant's diet.
- After symptoms have resolved, the cow's milk may be re-introduced to confirm the diagnosis.

Pathogenesis of FPIAP: Food allergen-specific T lymphocytes secrete cytokines that lead to delayed chronic inflammation.[24]

Clinical manifestation of FPIAP: [23]

- Focused history and physical examination are sufficient to establish a diagnosis of FPAIP.
- History of intake of cow's milk by the patient or the breastfeeding mother. >50% child of FPIAP are exclusively breastfed.
- Present between 1 day and 6 months of age.
- Generally presenting symptoms are a combination of rectal bleeding and streaks of mucus in stool in an otherwise healthy infant.
- Infants may be fussy or have an increased frequency of bowel movements.
- Blood loss is typically modest but occasionally may cause anemia.
- Warning signs like unwell appearance or fever, poor weight gain, failure to thrive, frank diarrhea forceful vomiting or abdominal distension should be evaluated that suggest a diagnosis other than FPAIP.

Investigation of FPIAP[5, 6, 24]

- CBC- usually normal, occasional eosinophilia
- Stool routine and culture- pus cells in stool but no bacterial growth on culture
- Quantitative measurements of food-specific IgE antibodies-usually normal
- Skin prick test with common food allergen is negative
- Elimination diets: cow's milk is removed from the child's diet and the breastfeeding mother's diet. Then the child is monitored for improvement of symptoms. If the symptoms fail to improve within 2- 8 weeks then the foods removed from the diet are unlikely to be the causative agent.
- Food challenges: Under careful medical supervision a small quantity of the suspected food is given to the child in progressively increasing portion sizes every 10-15 minutes until the cumulative total of food given equals approximately one standard serving of food. The patient is then observed. Rectal bleeding starts in 6-72 hours after the food challenge.
- Colonoscopy is reserved for patients with atypical symptoms. Colonoscopic findings are confined to the distal colon and include mild colitis, patchy erythema, and edematous mucosa with loss of vascularity.
- Histopathological findings include focal colitis, lymphonodular hyperplasia and eosinophilic infiltration.

Treatment[23, 24]

- Elimination diets: suspected foods are removed from the child's diet.
- Continue breastfeeding after the elimination of cow's milk from the maternal diet.
- Reintroduce cow's milk after 9-12 months.

Prognosis: Resolved by 9-12 months[24]

Food protein-induced enterocolitis syndrome

Food protein-induced enterocolitis syndrome (FPIES) is a disease that primarily occurs in infants. Cow's milk is the most common offending allergens. Other allergenic foods are soya, eggs, pea, fish.[1, 2]

Clinical features of FPIES

It can present in one of two ways- acute and chronic.[25]

- Acute manifestations include severe vomiting and diarrhea within two to four hours after ingestion of the offending allergen, causing profound dehydration, bloody stool, lethargy and shock.
- Chronic exposure to the offending allergen may present with regurgitation, diarrhea, failure to thrive and hypoalbuminemia

Investigation of FPIES[26]

- CBC- no eosinophilia
- Stool routine and culture- pus cells in stool but no bacterial growth on culture

- Quantitative measurements of food-specific IgE antibodies-usually normal
- Skin prick test with common food allergen is negative
- Colonoscopy is reserved for patients with atypical symptoms. Grossly erythematous and edematous colonic mucosa with loss of vascularity is found.
- Histopathology reveals prominent colitis and eosinophilic infiltration.

Treatment of FPIES[27]

- Elimination diets: suspected foods are removed from the child's diet.
- Continue breastfeeding after the elimination of cow's milk food from the maternal diet.

Prognosis of FPIES- Resolved by 2 years[25]

Food protein-induced enteropathy- Food protein-induced enteropathy (FPE) presents with protracted diarrhea in the first nine months of life, within weeks after the introduction of the trigger food. The majority of affected infants have failure to thrive, and some present with malabsorption. It may be difficult to distinguish FPE from postenteritis syndrome, especially because FPE can develop after infectious gastroenteritis leading to secondary lactose intolerance.[28]

Heiner syndrome- Heiner syndrome (food-induced pulmonary hemosiderosis) is a pulmonary disease that is caused by food hypersensitivity, primarily to cow's milk. This disorder mainly affects infants. Symptoms include cough, recurrent fever, wheezing, nasal congestion, recurrent otitis media, hemoptysis, failure to thrive, dyspnea, colic, anorexia, vomiting, diarrhea, and hematochezia. Patients have precipitating antibodies IgG to cow's milk proteins and may also have milk-specific IgE. Radiologic evidence of pulmonary infiltrates was a universal finding.[29]

Mixed IgE- and non-IgE-mediated reactions- The mixed reactions may have either humoral and/or cell-mediated mechanisms and may present with acute and/or chronic symptoms.[29]

Atopic dermatitis (eczema) - Food allergy plays a pathogenic role in a subset of patients, primarily infants and children, with atopic dermatitis. Milk is the second most common allergy reported in infants and young children with moderate-to-severe atopic dermatitis (egg allergy is the most common).[30]

Allergic eosinophilic gastrointestinal disorders- Milk is also among the major allergens identified in allergic eosinophilic esophagitis, a disorder characterized by eosinophilic inflammation of the esophagus. Patients with this disorder have symptoms suggestive of gastroesophageal reflux (GER) but are unresponsive to conventional reflux therapies.[31]

Conclusion

Cow's milk allergy is the most common food allergy in children. Cow's milk allergy may be IgE-mediated, non-IgE-mediated, and mixed. Non-IgE-mediated allergy is commoner than IgE-mediated reactions. Cow's milk-induced allergic proctocolitis is the most common non-IgE-mediated reaction. History and physical examination are the key to the diagnosis of food allergy. Quantitative measurements of serum cow's milk specific IgE and skin prick test are useful and readily available tests in Bangladesh. Avoidance of cow's milk is the ultimate treatment.

References

1. Nwaru BI, Hickstein L, Panesar SS, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. Allergy 2014; 69: 992-1007.
2. Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics 2011; 128:e9-17.
3. McGowan EC, Keet CA. Prevalence of self-reported food allergy in the National Health and Nutrition Examination Survey (NHANES) 2007-2010. J Allergy Clin Immunol 2013; 132:1216-1219.
4. Schoemaker AA, Sprikkelman AB, Grimshaw KE, et al. Incidence and natural history of challenge-proven cow's milk allergy in European children—Euro Prevall birth cohort. Allergy 2015; 70:963-972
5. Høst A. Frequency of cow's milk allergy in childhood. Ann Allergy Asthma Immunol 2002; 89:33-37
6. Høst A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. Clinical course in relation to clinical and immunological type of hypersensitivity reaction. Allergy 1990; 45:587-596
7. Hill DJ, Firer MA, Ball G, Hosking CS. Natural history of cows' milk allergy in children: immunological outcome over 2 years. Clin Exp Allergy 1993; 23:124-131
8. Lambert R, Grimshaw KEC, Ellis B, et al. Evidence that eating baked egg or milk influences egg or milk allergy resolution: a systematic review. Clin Exp Allergy 2017; 47:829-837
9. Santos A, Dias A, Pinheiro JA. Predictive factors for the persistence of cow's milk allergy. Pediatr Allergy Immunol 2010; 21:1127-1134
10. Wal JM. Bovine milk allergenicity. Ann Allergy Asthma Immunol. 2004; 93(5 Suppl 3):S2.
11. Kim JS, Nowak-Wêgrzyn A, Sicherer SH, et al. Dietary baked milk accelerates the resolution of cow's milk allergy in children. J Allergy Clin Immunol 2011; 128:125-131

12. Strobel S. Immunity induced after a feed of antigen during early life: oral tolerance v. sensitization. Proc Nutr Soc. 2001; 60:437–442.

13. Caffarelli C, Baldi F, Bendandi B, Calzone L, Marani M. Pasquinelli P on behalf of EWGPAG. Cow's milk protein allergy in children: a practical guide. Ital J Pediatr. 2010; 36:5.

14. Chehade m, Mayer L. Oral tolerance and its relation to food hypersensitivities. J Allergy Clin Immunol. 2005; 115: 3-12.

15. Roth-Walter F, Berin MC, Arnaboldi P, et al. Pasteurization of milk proteins promotes allergic sensitization by enhancing uptake through Peyer's patches. Allergy. 2008; 63:882-890

16. Ngamphaiboon J, Chatchatee P, Thongkaew T. Cow's milk allergy in Thai children. Asian Pac J Allergy Immunol 2008; 26:199-204

17. A. Martorell-Aragonésa, L. Echeverría-Zudaireb, E. Alonso-Lebreroc, J. Boné-Calvod, M.F. Martín-Munoz ˜ e, S. Nevot-Falcóf, et al. Position document: IgE-mediated cow's milk allergy. Allergol Immunopathol (Madr). 2015; 43(5):507-526.

18. Martorell A, Plaza AM, Boné J, Nevot S, García Ara MC, Echeverria L, et al. Cow's milk protein allergy. A multicenter study: clinical and epidemiological aspects. Allergol Immunopathol. 2006; 34:46-53.

19. Sampson H. A comparative study of commercial food antigen extracts for the diagnosis of food hypersensitivity. J Allergy Clin Immunol. 1988; 82:718-26.

20. Sampson H, Ho DG. Relationship between food –specific IgE concentrations and the risk of positive food challenges in children and adolescents. J Allergy Clin Immunol. 1997; 100:444—51.

21. Isolauri E, Sütas Y, Salo MK, Isosomppi R, Kaila M. Elimination diet in cow's milk allergy: risk for impaired growth in young children. J Pediatr. 1998; 132(6):1004-9.

22. Huang F, Kim JS. IgE-mediated cow's milk allergy in children. Curr Allergy Asthma Rep. 2012; 12:630—40.

23. Caubet JC, Szajewska H, Shamir R, Nowak-Wegrzyn A. Non-IgE-mediated gastrointestinal food allergies in children. Pediatr Allergy Immunol 2017; 28: 6-17.

24. Venter C, Brown T, Meyer R., Walsh J, Shah N, Nowak-Wegrzyn A, et al. Better recognition, diagnosis and management of non-IgE-mediated cow's milk allergy in infancy. *Clin Transl Allergy* 2017; 7: 26

25. Nowak-Wêgrzyn A, Jarocka-Cyrta E, Moschione Castro A. Food Protein-Induced Enterocolitis Syndrome. J Investig Allergol Clin Immunol. 2017; 27(1):1-18.

26. Caubet JC, Ford LS, Sickles L, Järvinen KM, Sicherer SH, Sampson HA, Nowak-Wêgrzyn A. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. J Allergy Clin Immunol. 2014; 134(2):382-9.

27. Nowak-Wegrzyn A, Berin MC, Mehr S. Food Protein-Induced Enterocolitis Syndrome. J Allergy Clin Immunol Pract. 2020; 8(1):24-35.

28. Kakiuchi, T.; Furukawa, R. Diagnosis of Food Protein-Induced Enteropathy Based on Gastrointestinal Mucosal Pathology before and after Elimination Diet Therapy: A Case Report. Pediatr. Rep. 2022; 14: 380-385.

29. Ojuawo AB, Ojuawo OB, Aladesanmi AO, Adio MO, Abdulkadir MB, Mokuolu OA. Heiner Syndrome: An uncommon cause of failure to thrive. Malawi Med J. 2019; 31(3):227-229.

30. Thomsen SF. Atopic dermatitis: natural history, diagnosis, and treatment. ISRN Allergy 2014; 35:4250. doi:10.1155/2014/354250. PMC 4004110. PMID 25006501.

31. Dellon ES, Hirano I. Epidemiology and Natural History of Eosinophilic Esophagitis. Gastroenterology 2018; 154(2):319-332.