1. Kongres Udruženja pedijatara Crne Gore

Angioedema, Atopic dermatitis and FPIAP assotiated with cow's-milk protein allergy

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Prevalence of CMPA

- Cow's-milk protein (CMP) is the leading cause of food allergy in infants and young children younger than 3 years.
- CMPA does seem to peak in the first year of life.
- Recent data confirm a lower prevalence of CMPA in about 1% of formula-fed infants.
- The incidence of CMPA in exclusively breastfed infants is almost always reported to be low in the range of 0.4%–0.5%
- The probability of an IgE-mediated allergic reaction in an infant breastfed by a woman consuming the relevant food can be estimated as ≤1:1000 for CM, egg, peanut and wheat
- But figures as high as 2.1% are reported as well, suggesting an over diagnosis of CMPA in breastfed infants
- It remains unanswered whether these differences reflect a different genetic background, a difference in selection of patients or both.

Schoemaker AA, Sprikkelman AB, Grimshaw KE, et al. Incidence and natural history of challenge-proven cow's milk allergy in European children – EuroPrevall birth cohort. Allergy 2015;70:963–72.

Høst A, Husby S, Osterballe O. A prospective study of cow's milk allergy in exclusively breast-fed infants. Incidence, pathogenetic role of early inadvertent exposure to cow's milk formula, and characterization of bovine milk protein in human milk. Acta Paediatr Scand. 1988;77:663–70.

Saarinen KM, Juntunen-Backman K, Järvenpää AL, et al. Breastfeeding and the development of cows' milk protein allergy. Adv Exp Med Biol 2000;478:121–30.

Risk factors

- History of allergic disease in first degree family members, has been recognized as a risk factor for allergic disease.
- Having a sibling with allergic disease doubles the risk for food allergy in the child compared with having no family history of allergy, even in the absence of a parental history of allergy.
- Absence of family history does not exclude the possibility of CMPA
- Confounding variables are among others pollution and the administration of medication such as antibiotics (over-use) and proton pump inhibitors early in life.
- Living in an industrial versus a rural, farming environment has been known for many years to be a risk factor for allergic disease.
- This may be related to a difference in GI microbiome development.

Hensley Alford S, Zoratti E, Peterson EL, et al. Parental history of atopic disease: disease pattern and risk of pediatric atopy in off spring. J Allergy Clin Immunol 2004;114:1046–50.

Turner PJ, Feeney M, Meyer R, Perkin MR, Fox AT. Implementing primary prevention of food allergy in infants: new BSACI guidance published. Clin Exp Allergy 2018;48:912–5.

Vallès Y, Pilar Francino M. Air pollution, early life microbiome, and development. Curr Environ Health Rep 2018;5:512–21.

Jackson CM, Mahmood MM, Järvinen KM. Farming lifestyle and human milk: modulation of the infant microbiome and protection against allergy. Acta Paediatr 2022;111:54–8.

Clinical presentation of CMPA

- The diagnosis of CMPA should only be suspected on the basis of a complete history and physical examination.
- CMPA can induce a diverse range of symptoms of variable intensity in infants. It is helpful to differentiate between the “immediate” (early) reactions and “delayed” (late) reactions.
- Immediate reactions occur from minutes up to 2 hours after allergen ingestion and are more likely to be IgE mediated
- Delayed reactions (non-IgE mediated) manifest up to 48 hours or even 1 week following ingestion.
- Combinations of immediate and delayed reactions (mixed ones) to the same allergen may occur in the same patient.
- The severity of IgE-mediated allergy may be difficult to categorize as external factors often determine the severity of reaction with anaphylaxis being the most severe presentation.

Venter C, Brown T, Shah N, Walsh J, Fox AT. Diagnosis and management of non-IgE-mediated cow’s milk allergy in infancy – a UK primary care practical guide. Clin Transl Allergy 2013;3:23. doi:10.1186/2045-7022-3-23.

Venter C, Brown T, Meyer R, et al. Better recognition, diagnosis and management of non-IgE-mediated cow’s milk allergy in infancy: iMAP—an international interpretation of the MAP (Milk Allergy in Primary Care) guideline. Clin Transl Allergy 2017;7:26. doi:10.1186/ s13601-017-0162-y

Clinical presentation of CMPA

- Clinical manifestations are predominantly cutaneous (70%–75%), and less frequently gastrointestinal (GI) (13%–34%) and respiratory (1%–8%)
- Up to 1 infant in 4 presents with a combination of symptoms involving more than 1 organ or system.
- The existence of a family history of allergy, the involvement of several organ systems (digestive, cutaneous, respiratory) and lack of improvement to usual therapeutic measures increases the likelihood of non-IgE mediated CMPA in these cases
- Sensitization to cow's-milk allergens through breast-feeding manifests primarily as exacerbation of atopic eczema and/or as allergic proctocolitis.

Signs and symptoms associated with cow's milk allergy*

	IgE†	Non-IgE†
General	Anaphylaxis	Colic, irritability Failure to thrive Iron deficiency anaemia
Gastro-intestinal‡	Regurgitation, vomiting Diarrhoea	Food refusal Dysphagia Regurgitation, vomiting‡ Diarrhoea‡ Constipation Anal fissures Perianal rash Blood loss
Respiratory‡	Rhinitis and/or conjunctivitis Asthma Mild dysphonia	Rhinitis Wheezing Chronic cough
Skin	Eczema (atopic dermatitis) Acute urticaria‡ Angio-oedema Oral allergy syndrome	Eczema (atopic dermatitis)

IgE = immunoglobulin E. * None of the symptoms is specific. † Patients may also present with mixed IgE and non-IgE symptoms. ‡ Unrelated to infection.

Koletzko S, Niggemann B, Arato A, et al. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. J Pediatr Gastroenterol Nutr 2012;55:221–9.

de Boissieu D, Matarazzo P, Rocchiccioli F, et al. Multiple food allergy: a possible diagnosis in breastfed infants. Acta Paediatr 1997;86: 1042–6.

Vandenplas, Y., Broekaert, I., Domellöf, M., et al. An ESPGHAN Position Paper on the Diagnosis, Management, and Prevention of Cow's Milk Allergy . J Pediatr Gastroenterol Nutr 2024;78:386–413

Clinical presentation of CMPA Gastrointestinal

Clinical symptoms and signs in the digestive tract may be due to inflammation, dysmotility, or a combination of both.

- The spectrum of non-IgE-mediated CMA is broad encompassing symptoms that range in severity from mild rectal bleeding in milk protein induced proctocolitis to severe vomiting and a sepsis-like presentation that can be seen in food protein-induced enterocolitis syndrome (FPIES)
- **FPIAP** occurs mostly in breastfed infants, and is in most cases a benign, easily recognized condition that may not need treatment in some breastfed infants, depending on the severity and frequency of blood in the stools.
- Symptoms of acute **FPIES** usually appear within 24 hours after food ingestion.
- Chronic **FPIES** is almost exclusively reported in infants younger than 4 months of age fed with CM or soy infant formula.
- The diagnosis of FPIES is based on a clinical history of typical characteristic signs and improvement of symptoms after withdrawal of the suspected trigger food.
- CMA is considered a possible factor in the pathogenesis of **EoE.**
- In patients not responding to conventional therapies for **GOR(D)**, CMA can be considered, and patients trialled on a time limited elimination diet for 2–4 weeks which should be followed by an OFC.

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Case presentation

- A 7-month-old male infant presented with swelling and redness of the lips and cheeks few minutes after ingestion of cow's milk. He has had atopic dermatitis since he was 3 months old with changes localized to the facial region.
- Family history: First cousin of the infant has a proven CMPA.
- On examination with pale skin and present eczematous changes on the cheeks and on a small area on the lateral sides of both upper legs.
- CBC - Le= 9,39 x10 /L Er= 4,29x10 /L Hgb = 100g/L HCT = 26,2% PLT= 459x10 /L
- Serum iron= 2.1 umol/l
- Total IgE =181 IU/ml
- Specific IgE grade 3 directed to milk (10.6 kU/ml), β-lactoglobulin (11.6 kU/ml), casein (3.53 kU/ml), α-lactalbumin (6.23 Ku/ml) and
- Specific IgE grade 2 diretcted to white (3.32 kU/ml) and yolk egg (0.722 kU/ml)

Case presentation

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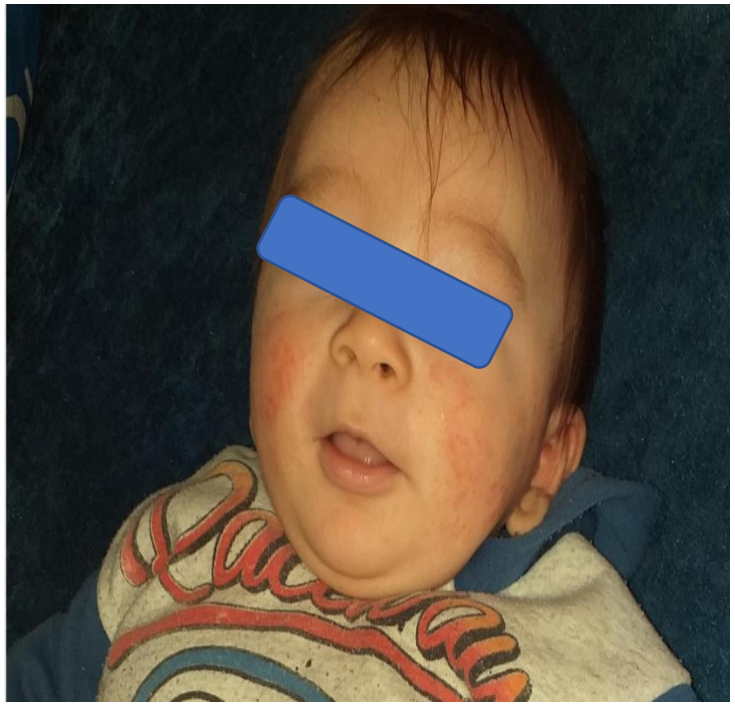
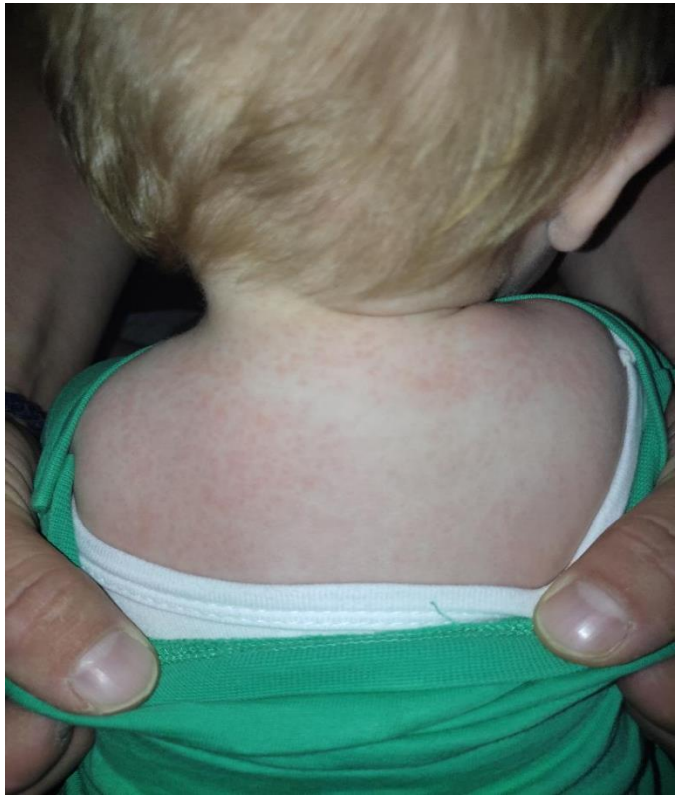
- The infant was fed with eHF, breastmilk (mother avoided all types of milk and milk products from her diet) and all infant's complementary feedings were free of CMP.
- Iron replacement therapy was introduced.
- Few days after the first examination with the appearance of liquid stools for three days and in few of them bloody mucus was observed.
- After one month of the elimination diet, the mother introduced a dairy product into her diet, but after 24 hours the infant developed a rash on his back and chest.
- On the last control without eczematous changes on the skin and with normal stools.
- Control CBC - Le= 11,91x10 /L Er= 4,69 x10 /L Hgb = 119g/L HCT = 29,69% PLT= 330x10 /L
- Serum Iron= 7.5 umol/l



Before elimination diet



Reintroduction CMP after 1 month of elimination diet

After 3 months of elimination diet

Diagnostic workup

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An ESPGHAN Position Paper on the Diagnosis, Management, and Prevention of Cow's Milk Allergy

Cow's milk allergy (CMA) is frequently misdiagnosed (especially overdiagnosed) and inadequately treated in infants and young children

This study provides updates and recommendations based on the European Society of Paediatric Gastroenteology, Hepatology, and Nutrition (ESPGHAN) guidelines for CMA

Best practice for confirming CMA diagnosis upon suspicion

Breastfed baby

Continue breastfeeding; mother should be on a CM-free diet and calcium for 2–4 weeks

Symptoms improve or disappear

- **No**
  - **Good compliance** — Not CMA
  - **Doubtful compliance** — Refer patient to dietitian or nutritionist for reevaluation
- **Yes** → Reintroduction/challenge CM
  - No symptoms → Not CMA
  - Symptoms → CMA

Formula-fed baby — Mild to moderate symptoms

May require extensively hydrolysed formula (eHF) or hydrolysed rice formula (HRF) for 2–4 weeks

Symptoms improve or disappear

- **eHF/HRF** → Yes → Reintroduction/challenge CM
  - No symptoms → Not CMA
  - Symptoms → CMA
- **eHF** → No → May not be CMA → Consider switching to other regimens to confirm
- **HRF** → No → Not CMA

Formula-fed baby — Severe symptoms/anaphylaxis

Amino acid (based) formula (AAF) for 2–4 weeks

Symptoms improve or disappear

- **No** → Not CMA
- **Yes** → CMA

Long-term management

- Eliminate all CM sources (refer to dietitian/nutritionist)
- Consider breast milk or eHF/HRF/AAF (depending on tolerance) for 6 months or until 9 to 12 months of age
- Monitor tolerance development

To confirm the diagnosis of CMA and avoid overdiagnosis, an oral food challenge test is recommended after a short diagnostic elimination diet

An ESPGHAN Position Paper on the Diagnosis, Management, and Prevention of Cow's Milk Allergy
Vandenplas et al. (2023)

JPGN

Diagnostic workup

- In IgE-mediated allergy, the response to the diagnostic elimination diet is to be expected within 1–2 weeks.
- In non-IgE mediated allergy, the response to the diagnostic elimination diet is to be expected within 2–4 weeks.
- Testing for specific IgE against CMP or an SPT with natural cow's-milk or whole-protein formula should be performed.
- CMPA can be assumed with a high likelihood if testing for specific IgE is positive.
- A positive test for specific IgE at the time of diagnosis predicts a longer period of intolerance as compared with those children who have negative tests.
- An OFC is mandatory in the work-up of infants with CMPA, except for those presenting with life-threatening symptoms such as anaphylaxis and with high levels of sIgE.
- In this situation, the oral challenge test can be omitted.
- The child should be given a strict CMP-free diet for a period of at least 6 months or up to the moment when the infant reaches 12 months, before an oral food challenge is performed.
- DBPCFC is recommended for unclear cases and research purposes.

Koletzko, S., Niggemann, B., Arato, A. et al. (2012). Diagnostic Approach and Management of Cow's-Milk Protein Allergy in Infants and Children: ESPGHAN GI Committee Oractical Guidelines. J. Pediatr Gastroenterol Nutr55(2), 221-229.

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Diagnostic workup

- A specialist should assess the patient before an oral challenge is performed in a hospital with adequate emergency facilities.
- In IgE-mediated CMPA, sIgE levels should be measured before the challenge and guide timing of the OFC.
- The starting dose during an oral milk challenge should be lower than a dose that can induce a reaction.
- If severe immediate reactions are expected, the OFC should start with a drop on the lips followed by a stepwise increasing dosing of small volumes at 30-minute intervals to end up with 100 mL.
- Patients should be observed for at least 2 hours following the maximum dose. If no reaction occurs during the OFC, CM should be continued at home every day with at least 200 mL/ day for at least 2 weeks.
- An OFC should preferably be carried out in a hospital setting when: there is a history of immediate allergic reactions; the reaction is unpredictable; and in case of severe atopic eczema with the difficulty in accurately assessing a reaction.

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Patients With Atopic Eczema

- The condition of the skin should be documented and graded according to severity (eg, by SCORing Atopic Dermatitis [SCORAD]) before and after the challenge and then again 24 and 48 hours later.
- If the results cannot be clearly interpreted, then a placebo-controlled challenge should be performed as further confirmation, even in infancy.

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Patients With Diarrhea

- If CMPA manifests clinically with diarrhea, the stool frequency and consistency should be documented (eg, in infants with a stool form scale).
- If significant diarrhea recurs during the challenge then the diagnosis of CMPA is confirmed and a therapeutic formula can be recommended.
- If there are no recurrent symptoms, then the child should continue to receive its previous formula.

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Reevaluation

- The duration of the first therapeutic elimination diet should last for 6 months or up to the moment when the infant reaches 12 months, whatever is attained first.
- After 6 months of elimination diet, or when the child is 1 year old, an OFC should be performed.
- If OFC is positive, then the elimination diet is usually continued for between 6 and 12 months.
- If the challenge is negative, then cow's milk is fully reintroduced into the child's diet.

The prognosis for CMPA in infancy and young childhood is good. Approximately 50% of affected children develop tolerance by the age of 1 year,>75% by the age of 3 years, and>90% are tolerant at 6 years of age.

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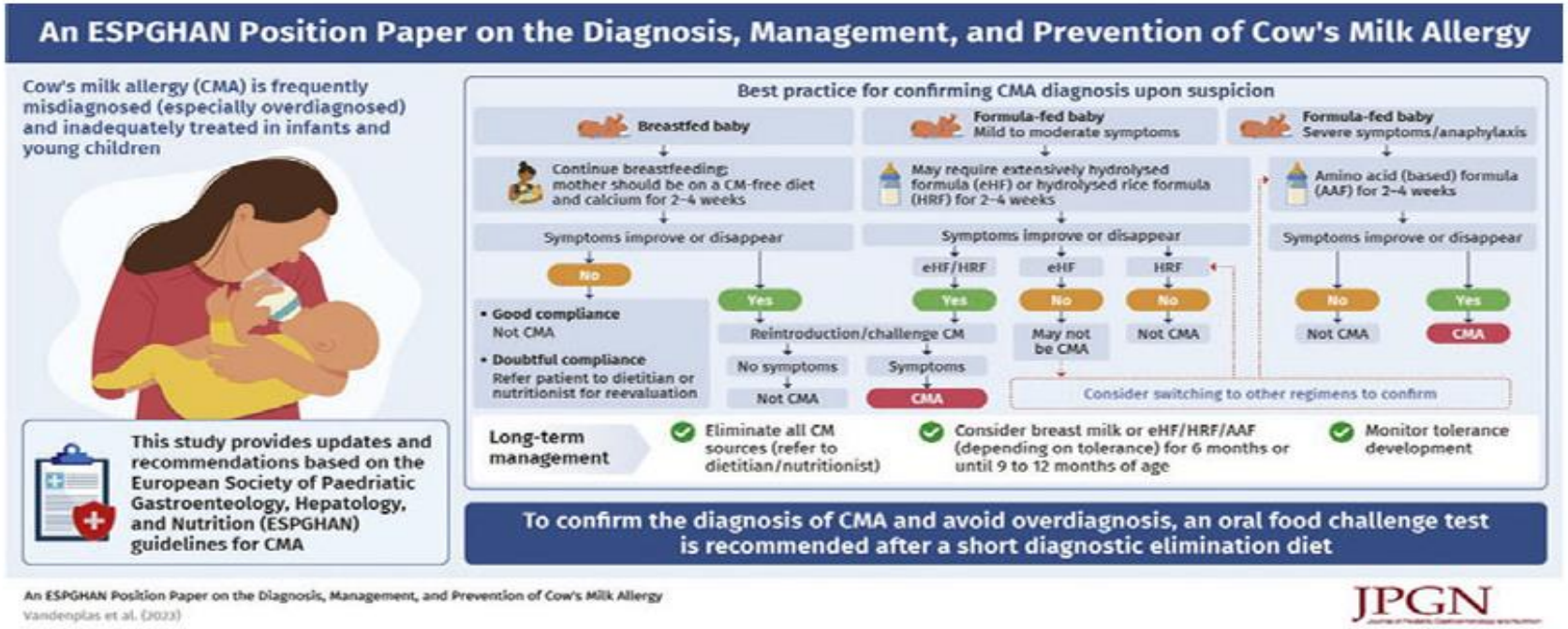

Thank you for your attention