

Table 1: Clinical presentations and differential diagnosis of CMPA conditions (Adapted from Allen et al, 2009)²

Condition	Timing of symptoms in relation to ingestion	Clinical features	Distinguishing features	Occurrence in exclusively breast fed infants	Differential diagnosis	Age of clinical resolution	Useful investigations
Acute allergic reaction (nonanaphylactic)	Immediate, up to 60 min	Perioral/orbital angioedema/ erythema. Generalised urticaria Vomiting, diarrhoea	No recurrence if avoidance complete. Incidence approximately 2% in infants.	Possible	Idiopathic urticaria, insect bite	80% by 3 years	Skin prick test, IgE antibodies, oral food challenge
Anaphylaxis	Immediate, up to 60 min	Respiratory +/- cardiovascular involvement often associated with above features	As above. IM adrenaline treatment of choice. Rare manifestation of CMPA.	Extremely rare	Sepsis, acute cardiovascular or respiratory compromise, seizures	As above	Skin prick test, IgE antibodies
Food protein-induced enterocolitis syndrome	Typically 2–4 hours	Profuse vomiting +/- diarrhoea, sudden onset of pallor and floppiness. 20% present as hypovolaemic shock (with associated metabolic acidosis and methaemoglobinaemia)	Responds to fluid resuscitation, adrenaline not required. Unknown incidence but thought to be approximately 0.3%.	No	Sepsis, gastroenteritis, malrotation, intussusception, metabolic disorder	Most by 3 years of age	History diagnostic, no laboratory markers available
Eczema	Min/hours/days	Pruritic rash	Often generalised, onset at introduction of cows' milk. Incidence due to CMPA unknown.	Yes	Seborrhoeic dermatitis, acrodermatitis enteropathica	Variable, tendency to improve with age	Skin prick test, IgE antibodies, elimination – re-challenge sequence
Eosinophilic oesophagitis	Days	Vomiting, feed refusal, failure to thrive, oesophageal dysmotility	Histological diagnosis, 24 hours pH monitoring usually normal, unresponsive to proton pump inhibitors. Incidence approximately 0.04% in infants.	None reported	GORD, mucosal candidiasis (white plaques)	Unknown	Endoscopy
Cows' milk protein-induced GORD	hours/days	Frequent regurgitation, poor feeding, feed aversion	Partially responsive to proton pump inhibitors when underlying mechanism related to CMPA. Up to 40% of infants with GORD have CMPA.	Yes	Idiopathic GORD, eosinophilic oesophagitis, malrotation	12–18 months	Clinical diagnosis. Requires endoscopy if haematemesis or significant failure to thrive
Enteropathy	hours/days	Vomiting, diarrhoea, severe irritability, failure to thrive, iron deficiency anaemia, protein losing enteropathy	Receiving cow's milk in diet. Unknown incidence due to CMPA.	Yes	Lactose intolerance, coeliac disease giardiasis, immune deficiencies, autoimmune enteropathy	Unknown	Small bowel biopsy for histology, duodenal disaccharidases and microscopy of duodenal aspirate for giardia
Proctocolitis	hours/days	Low-grade rectal bleeding in a well infant	Normal perianal inspection, thriving. CMPA is the most common cause.	Yes	Constipation with anal fissure, infantile inflammatory bowel disease, chronic granulomatous disease, juvenile polyp	12 months	Rectal biopsy only if atypical features or non-responsive to treatment
Colic	hours/days	Paroxysms of unexplained, inconsolable crying	Responds to dietary elimination, early onset soon after the introduction of cows' milk protein. May be caused by CMPA in some cases.	Yes	Idiopathic colic, developmental disorders, urinary tract infection	4–6 months	Cow's milk elimination and re-challenge
Constipation	hours/days	Passage of infrequent and/or hard stools	Responds to dietary elimination, early onset soon after the introduction of cow's milk protein. Unknown incidence due to CMPA.	Yes	Hirschsprung's disease, slow transit constipation	12–18 months	Cow's milk elimination and re-challenge in conjunction with laxative treatment. Rectal biopsy in infants with early-onset severe constipation