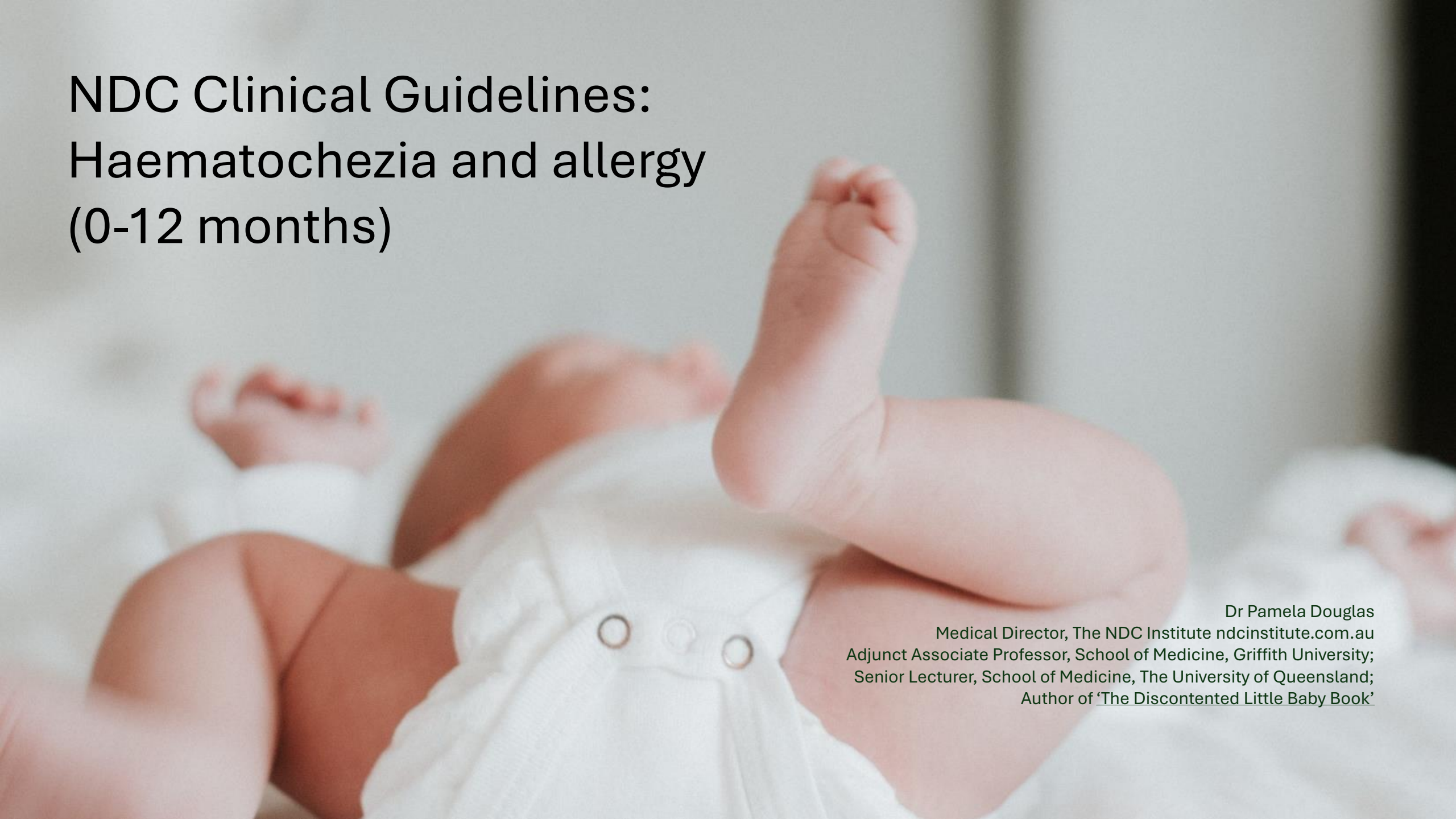


NDC Clinical Guidelines: Haematochezia and allergy (0-12 months)



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Neuroprotective Developmental Care clinical guidelines

Assessment + management of breast milk and commercial milk formula fed infants (0-12 months) with the following conditions:

1. Non-IgE, mixed IgE/non-IgE, and IgE-mediated immune reactions, including

The role of cow's milk protein allergy (CMPA)

Food protein-induced allergic proctocolitis (FPIAP)

Food protein-induced enterocolitis syndrome (FPIES)

Very Early Onset Eosinophilic Oesophagitis (EoE), and

2. Benign non-allergic infantile proctocolitis (BNIP).



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The medical generalist lens

NDC clinical guidelines

- Apply the transdisciplinary generalist's complexity lenses to research studies and their translation into clinical guidelines.
- Identify **omitted variable biases** in primary studies which claim to establish links between immune reactions and unsettled infant behaviour, which then continue to bias systematic or narrative reviews.
- Protect against unintended outcomes (including overdiagnosis and overtreatment) which occur when interpretative lenses are implicit and reductionist, not explicitly identified and named.



The following signs, alone or in a cluster, are NOT supported by evidence as signs of IgE or non-IgE mediated immune reactions in infants:

- Feeding aversion or fussiness during feeds
- Fussy behaviour after a feed
- Colic or excessive infant crying (except in severe case of colitis - blood mixed throughout and discolouring stools pink or red)
- Reflux or frequent vomiting
- Poor weight gain or failure to thrive
- Loose, green, or mucousy stool
- Mild to moderate eczema

Applying a 'cluster of signs' criteria in infant allergy diagnosis drives overdiagnosis and overtreatment.

Cow's milk proteins in breast milk

- > 99% of infants with CMPA tolerate breastmilk from a mother who consumes dairy products. There is almost no circumstance in which a breastfeeding mother should eliminate dairy from her diet.
- Exclusive breastfeeding associated with prevalence CMPA = 0.4-0.8%
c.f. 2% of infants who have received formula or solid foods.
- Beta-lactoglobulin (β -LG) = whey protein found in the milk of cows, goats, sheep but NOT human milk. β -LG
 - Is the cow's milk protein most closely linked to CMPA
 - Levels in breast milk range from 0 $\mu\text{g/L}$ (in 42-52% of samples) to 8 $\mu\text{g/L}$, occasionally up to 800 $\mu\text{g/L}$.
 - Considerable variation in levels among women consuming the same amount of cow's milk, reflecting differences in maternal gut absorption and protein transfer into milk.
 - Measurable concentrations detected up to 7 days after maternal cow's milk intake.

Haematochezia

= blood in stool

These guidelines consider haematochezia caused by

1. Non-allergic benign proctocolitis
2. Food protein induced proctocolitis

Exclude²

Table 1 Differential Diagnosis for Rectal Bleeding in Infants

Anal fissures
Coagulopathy
Food protein induced allergic proctocolitis
Food protein induced enterocolitis syndrome
Food protein induced enteropathy
Hirschsprung enterocolitis
Infectious colitis
Intussusception
Meckel's diverticulum
Necrotizing enterocolitis
Sepsis
Swallowed maternal blood
Vascular malformation
Very early onset inflammatory bowel disease
Volvulus

Also swallowed blood syndrome in first days of life?¹

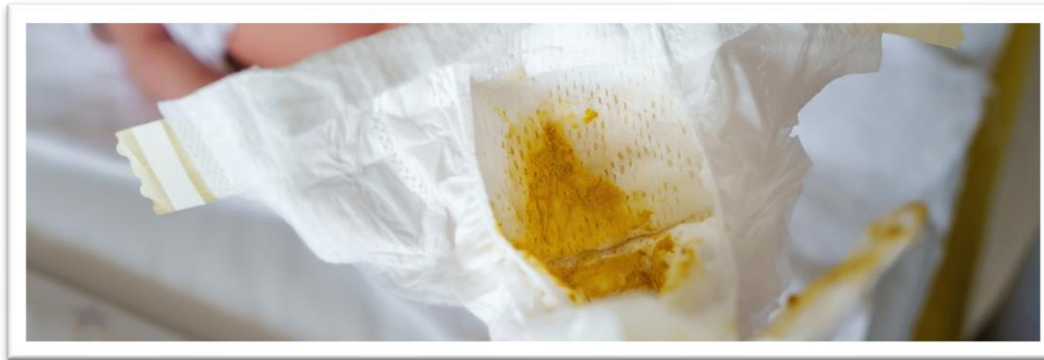
¹Lin et al 2022;

²Mahoney et al 2025 p.3

Prevalence of haematochezia

= blood in stool

Green stools are normal; mucous in stool is normal. Neither are signs of gut dysbiosis, clinically relevant inflammation, lactose overload or other gut abnormalities. ¹⁻³



- Most common in first 8 weeks of life, quite frequent in first 6 months
- Prevalence not clear – but common presentation

¹Gustin et al 2018; ²Huysentruyt et al 2019; ³Vandenplas et al 2024

Haematochezia is not an indication for

Faecal occult blood tests
Faecal calprotectin
Blood tests

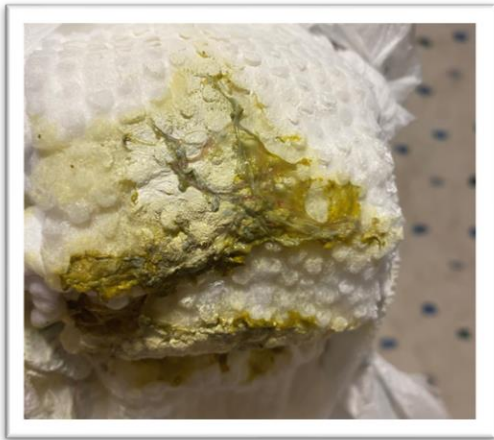


What is non-allergic benign infantile proctocolitis?

Term coined by Gelsomino et al 2021; previously had other names including idiopathic neonatal transient colitis¹

Most common cause of small amounts of blood in stool

(e.g. Lazare et al 2020 n = 19 breastfed infants all tested positive with blood in stool after 3-week elimination of dairy and soy products, which eliminated FPIAP)



Presentation

- Under 6 months of age
- Small drops or streaks of blood in or on stool
- Doesn't continue more than 2 months
- Isn't getting worse

¹Hwang and Hong 2013 ; ²Lazare et al 2020; ³Gelsomino et al 2021

What is non-allergic benign infantile proctocolitis?

Associated on endoscopy and colonoscopy (research studies) with mild and temporary inflammation in distal colonic or rectal mucosa but **NOT** elsewhere in gut.

No signs of immune cells indicating allergy in blood stream.

?Low grade viral infection



Management of non-allergic benign infantile proctocolitis

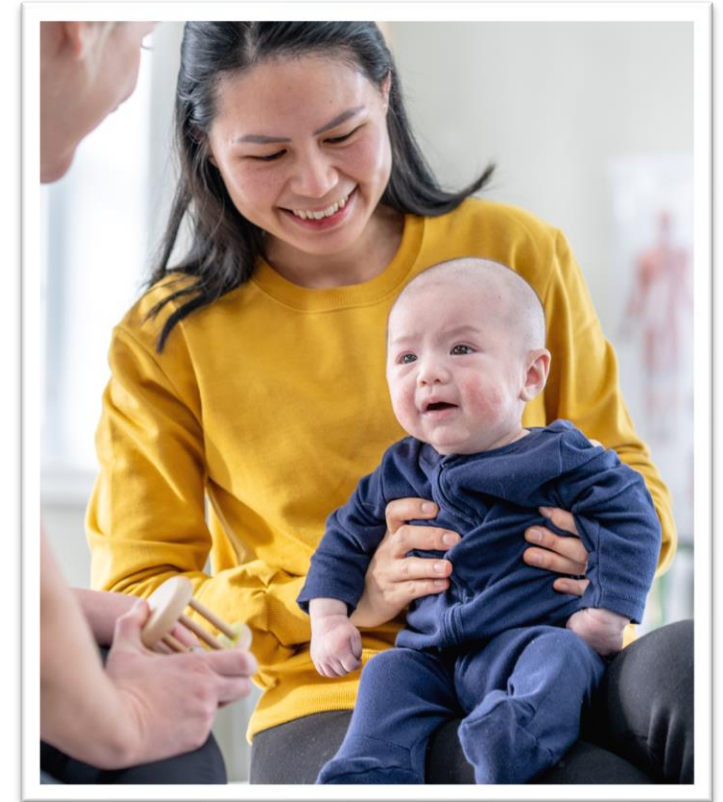
- ***Wait and watch for two months***
- Frequent flexible breastfeeds
- No investigation required
- Not allergic or related to food proteins (either breast milk proteins or from solids)
- Reassure parents no link with IgE-mediated allergy (e.g. to solids) later on
- Deal with any co-presentations separately:
 - Unsettled infant behaviour
 - Benign vomiting (reflux)
 - Eczema
 - Weight gain concerns
- Review if bleeding worsens or persists at two months

Eczema is a common inflammation of infant skin

- If small or moderate patches, no reason to consider allergy
- Consider allergy if very severe and extensive eczema (only)
→ trial elimination diet

Similarly, distal colon or rectal mucosa is commonly inflamed, resulting in bleeding in early infancy

- If small or moderate patches, no reason to consider allergy
- Consider allergy if severe and extensive resulting in substantial or worsening haematochezia
→ trial elimination diet



Arvola et al 2006

- Microvillus layer had virus particle aggregates (not found in faeces) in 8 of 32 in study of healthy infants with haematochezia

Wurm et al 2023

- During recruitment, more than half of healthy infants presenting with rectal bleeding were found to have a gut virus or pathogen on stool analysis (and eliminated from study)
- 14 infants with rectal bleeding (av age 11.1 wks) cf 55 controls (av age 12.7 wks)
- Rectal bleeding infants
 - Less bifidobacterium and other microbiome changes cf non-bleeding infants
 - Aggregates of eosinophils in colonic mucosa
- After 4 weeks cow's milk elimination diet, microbiome of infants with rectal bleeding partially changed to look more like microbiome of non-bleeding, but these changes in microbiome might have occurred regardless of diet
- No explanation for how an ingested protein causes an allergic reaction in distal colon only without other gut or immune cells in blood stream being affected.

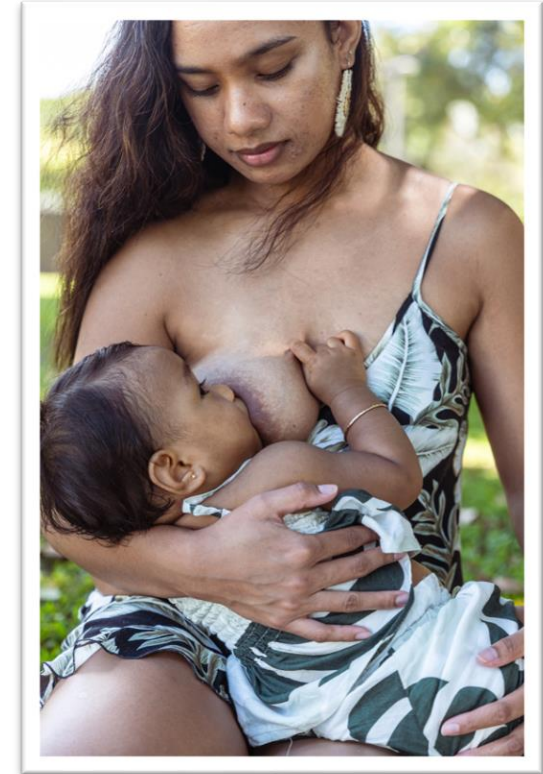
**Non-IgE-mediated immune reaction
in breastfed infants**

Non-IgE-mediated allergies in breastfed infants

1. *Constipation*
2. *Coeliac disease*
3. *Cow's milk-induced iron deficiency anaemia*
4. **Food protein-induced allergic proctocolitis**
5. **Food protein induced enterocolitis syndrome**
6. *Anaphylaxis*

Most infant constipation is not CMA

- Breastfed babies may not pass stool for many days at a time.
- Constipation and a true gastro-oesophageal reflux disease in an older child may be classified as food protein-induced dysmotility disorders.



Food protein induced allergic proctocolitis: background

No reliable prevalence data.

Overdiagnosed + overtreated.

Only 15-40% infants with rectal bleeding are finally diagnosed with FPIAP after diagnostic dietary intervention.

Partial or exclusive breastfeeding protects against true FPIAP.

Usually outgrown by 1-3 years of age.

Not associated with eosinophilic oesophagitis or later inflammatory bowel disease.
Histology shows elevated eosinophils + degranulation in rectosigmoid colon close to lymphoid nodules.

No signs of immune cells indicating allergy in blood stream.

Not associated with vomiting, diarrhea or failure to thrive (but these *are* signs of food protein induced enteropathy syndrome)

Mahoney et al 2025; Arvola et al 2006; Miceli et al 2018; Mennini et al 2020; Gelsomino et al 2021; McWilliam et al 2023; Wurm et al 2023; Silvatore et al 2024; Tran et al 2024; Vandenplas et al 2024

Food protein induced allergic proctocolitis: presentation

- Older than 6 months of age
- Pink or red stool *OR*
- Amount of blood in stool is increasing over time *OR*
- Blood in stool has gone on for two months without resolving.



Arvola et al 2006; Miceli et al 2018; Mennini et al 2020; Gelsomino et al 2021; McWilliam et al 2023; Wurm et al 2023; Silvatore et al 2024; Tran et al 2024; Vandenplas et al 2024

Food protein induced allergic proctocolitis: management

- Oral food challenge is gold standard (home-based)
- Start with cow's milk protein elimination diet for 2-4 weeks
- Resolution of haematochezia indicates FPIAP
 - Usually within a few days but up to within a fortnight
- Confirm diagnosis with oral challenge 2-4 weeks after commencement
- Continue cow's milk protein elimination for 6-12 months if symptoms recur
- Reintroduce cow's milk protein if no resolution of symptoms after 2-4 weeks with dietary elimination

Food protein induced allergic proctocolitis: management

- High cross-reactivity of cow's milk protein with goats and sheep's milk proteins (relevant to formula-fed infants in particular)
- Usually no reason to eliminate soy, egg and wheat as these protein allergies are¹
 - Uncommon
 - Prevalence and relevance remain poorly established
- Once developmentally ready introduce variety of complementary foods
- Safe to introduce multiple foods at once
- Infants with moderate to severe eczema are at highest risk for egg and peanut allergies
- Reintroduction of trigger food once asymptomatic for period of time guided by age and feeding tolerance (directly into diet or by human milk)

Food protein induced allergic proctocolitis: commercial milk formulas

If formula fed infant has persisting haematochezia, advise (in order of preference)³

1. Extensively hydrolysed cow's milk formula or hydrolysed rice formula
2. Amino acid-based formulas
3. Soy formulas (*note: some studies suggest 10-14% of children with CMPA may have co-existent soy allergy*)



Food protein induced allergic proctocolitis: solids

- Ladder approach progressing from extensively heated to less heated forms of milk and egg may be considered
- Not standardised, not supported with reliable evidence of benefit



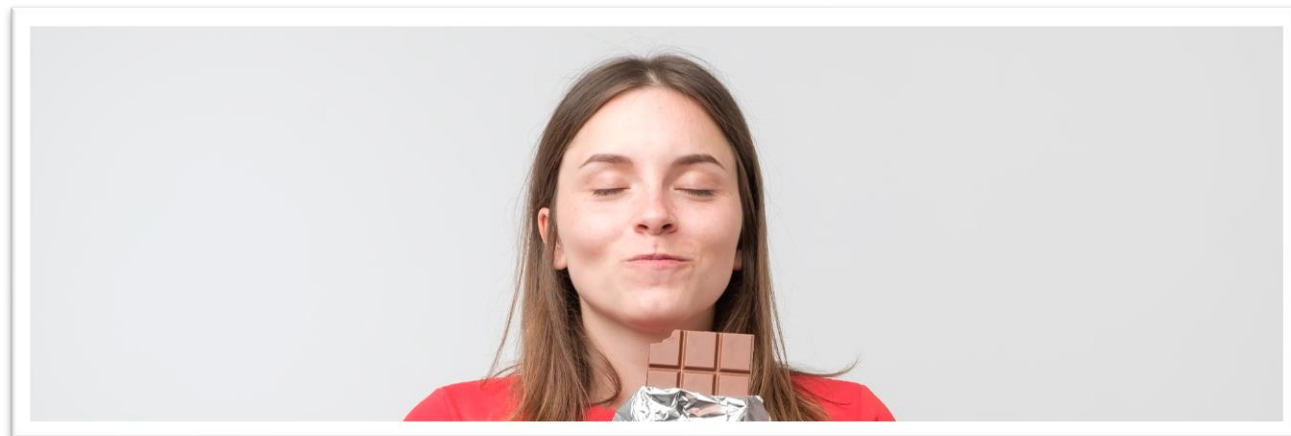
Table 3 Mahoney et al 2025 p.7

Table 3 Considerations for Use of a Milk Ladder vs. Unheated Milk

Potential Considerations	Milk Ladder	Unheated Milk (cow's milk, formula, human milk or yogurt)
Time and Effort	• Baking takes more time • Milk protein content of commercially prepared products is proprietary information so home baked is best • Length of trial may take 2 or more weeks	• Minimal time • Length of trial likely brief or day(s)
Equipment Required	• Oven, measuring equipment and multiple ingredients	• No special equipment required
Severity of Symptoms if Intolerant	• Likely less severe in early ladder steps	• May be more severe
Education Required	• Must be able to follow a recipe • Provider must provide advisement re: time interval between steps on the ladder	• Minimal
Nutritional Composition	• Varies based on recipe chosen but generally more added sugar and refined flour	• Can avoid added sugars
Feeding Skills	• Texture of baked goods may not be accepted in younger infants or those with delayed chewing skills or oral aversion	• Milk can be offered in the form of a beverage (if age-appropriate) • Yogurt can be offered by spoon, in a pouch or as a dip • Cheese can be offered as a finger food, or soft cheeses can be spread on crackers

Food protein induced allergic proctocolitis: risks of overdiagnosis and overtreatment

- Burden of eliminating food stuffs
- Unnecessary family stress
- Failure to identify underlying causes of infant behaviour
- Breastfeeding mother loses dairy benefits (*acknowledging many cultures eat limited dairy but maintain good nutrition*)
 - Calcium
 - Vitamin D
- Mealtime stress which increases risk of trajectories of disrupted relationship with food
- Increased risk of infant cow's milk protein allergy later on



Food protein induced allergic proctocolitis: risks of overdiagnosis and overtreatment

Tran et al 2024 [case series]

5 infants

- Rectal bleeding diagnosed with FPIAP
- Placed on elimination diets of unknown duration (either maternal elimination diet if breastfeeding or by formula change)
- Developed persisting cow's milk allergy down the track

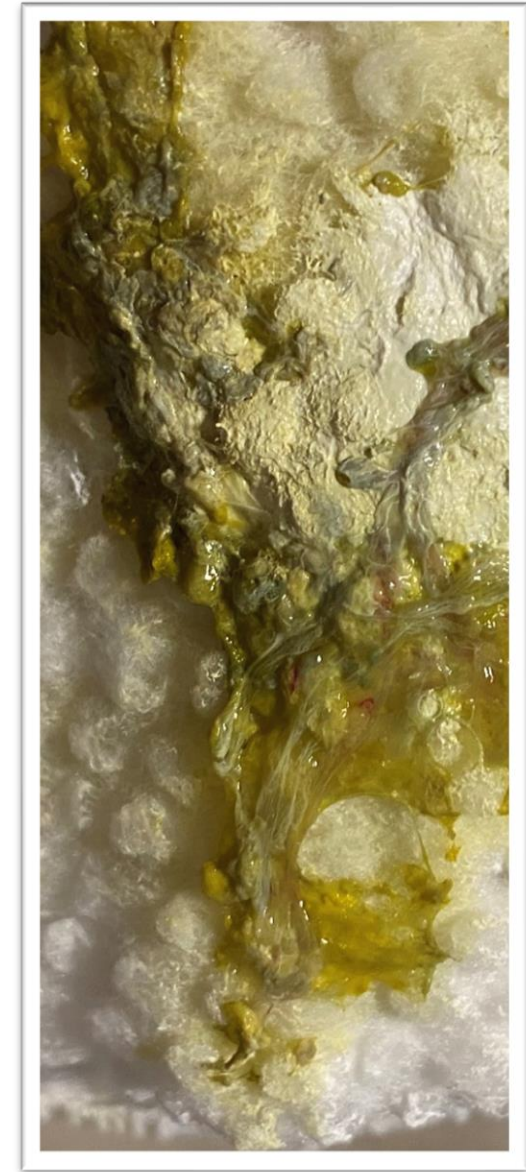
Interpretation:

Either

Infant rectal bleeding is always FPIAP, associated with persisting cow's milk allergy

or

Cow's milk elimination diets, which are not indicated if non-allergic benign infantile proctocolitis, result in persisting cow's milk allergy¹.



¹ McWilliams et al 2023

‘Cluster of signs’ concept lacks evidence base
→ drives overdiagnosis and overtreatment of allergy in infants

The following signs, alone or in a cluster, are not linked with non-IgE mediated allergy infants

- Feeding aversion: fussy during feeds or “in pain with feed”
- Colic (sometimes told that if infant is fussy after 16 weeks more likely to be allergy)
- Reflux
- Frequent vomiting
- Poor weight gain or failure to thrive
- Loose mucousy stool
- Eczema – rarely driven by food



Non-IgE mediated allergy in breastfed infants: busting myths

Don't diagnose non-IgE mediated allergy by 'cluster' of symptoms

- Not evidence-based clinical practice
- 'Clusters' not linked with haematochezia
- Directly causes overdiagnosis, overtreatment, and increased allergy prevalence¹

Don't advice breastfeeding mothers to look for pattern of unsettled infant behaviour in 12-24 hour period after ingestion of dairy/soy/eggs/wheat etc

- Not evidence-based clinical practice
- Exacerbates maternal anxiety
- Directly causes overdiagnosis, overtreatment, and increased allergy prevalence¹

¹ McWilliam et al 2023

Non-IgE mediated allergy in breastfed infants: busting myths

- Little evidence to suggest significant adverse effects associated with untreated FPIAP
- Haemoglobin levels same between human milk fed infants with persistent rectal bleeding whose parents use dietary elimination compared to control groups



Food protein induced enterocolitis (or enteropathy) syndrome

- Prevalence uncertain – varies across regions
- Absence of IgE-mediated skin or respiratory signs and symptoms
- Cow's milk, fish, eggs, and grains most frequently reported triggers worldwide
- Mostly first year of life (but can present later into adulthood)
- Usually resolves by 3-5 years
- Predominantly formula fed infants
- Rare in breastfed babies but can occur e.g. when breastfed baby takes formula or commences solids which contain cow's milk protein
 - Symptoms occur within the first few weeks of introducing cow's milk or soy protein
 - Early-onset neonatal FPIES rare, presents within hours or days post-birth, usually immediately after initiation of formula
 - If triggered by solid food, emerges 4-7 months of age
- No diagnostic test – blood IgE and skin prick tests don't help
- Cell mediated immune reaction (non-IgE-mediated hypersensitivity)
- Management = avoidance of offending foods
- Oral food challenge has a role depending on individual case (high risk procedure conducted in emergency support setting)

Food protein induced enteropathy syndrome

Acute FPIES

- Repetitive vomiting 1-4 hours after feed
- Pallor, sweatiness, clamminess, lethargy
- Diarrhoea
- Dehydration
- Metabolic derangements
- Hypovolemia (shock)

Requires emergency medical care

- Often misdiagnosed as sepsis or viral gastroenteritis
- Intravenous hydration, antiemetics (ondansetron) + occasionally corticosteroids
- Management = long term avoidance of trigger foods + nutritional support

Chronic FPIES

- Intermittent vomiting
- Frequent watery diarrhoea
- Abdominal distention
- Pallor after feeds
- Hypotonia, lethargy
- Dehydration
- Faltering growth
- Protein-losing enteropathy
 - Impaired growth
 - Low serum albumin
 - Oedema

Requires prompt or urgent medical care If over 6 months of age can use soy-based formula

Management = long term avoidance of trigger foods

IgE-mediated immune reaction in breastfed infants

IgE mediated cow's milk allergy in breastfed infants

- Typically occurs with direct ingestion of dairy
- Skin signs (urticaria, severe eczema, erythema)
- Hayfever
- Reactive Airways
- Vomiting two hours after takes in formula or dairy
- Swelling (angioedema)
- Accompanied by positive skin prick test or serum IgE in older infants
- **Mix of non-IgE and IgE mediated CMA possible**

- Cow's milk allergy prevalence is estimated at 0.4%-0.8% in exclusively breastfed infants prior to introduction of any breast milk substitutes or solid foods
- In about 2% of infants otherwise
- Cow's milk proteins don't usually occur at high enough levels in breast milk to trigger allergic reactions in babies regardless of how much dairy mother consumes
- The only absolute medical contraindication to breastfeeding or use of donor breastmilk is classic galactosaemia.

Munblit et al 2020

- 99% of babies and toddlers with true cow's milk allergy tolerate breast milk from a woman who is consuming dairy products without having an allergic reaction.

McWilliam et al 2023

- Concentrations of cow's milk proteins in breast milk vary widely, irrespective of the amounts consumed by the mother and the timing of consumption.
- Beta lactaglobulin (cow's milk protein) detected in about half of samples regardless of cow's milk consumption.
- It is difficult to consume enough dairy for beta lactaglobulin to reach a significant level in breast milk.

Management of IgE mediated immune reaction: breastfed infant

Even in the case of a true cow's milk protein IgE mediated immune reaction, maternal elimination diet should not be a standard recommendation for breastfeeding babies.

Consider in severe cases.

If maternal elimination diet is indicated, Allen et al 2022 propose that goat and sheep milk protein should also be avoided due to cross-reactivity, and that re-introduction would occur if a two-week trial does not result in resolution of symptoms, or two weeks after symptoms have resolved.

Soy can be used in breastfed infants with CMPA.

Management of IgE mediated immune reaction: commercial milk formula fed infant

Change to extensively hydrolysed formula

Allen et al 2022 find that cross-reactivity between cow's milk and soy-based formulas is low, so infants with cow's milk allergy and food protein induced enteropathy syndrome who are over six months of age could use soy-based formula.

Mehta et al 2022 demonstrate that volumes of specialised formula prescriptions have increased two-fold in the past twenty years in the UK, Australia and Norway, in the absence of increased prevalence of milk allergy.

- Propose that most infants prescribed specialised formula do not have milk allergy.
- Identify up to a ten-fold excess prescription rate relative to true rate of milk allergy.
- Observe that unnecessary specialised formula use increases consumption of free sugars (such as glucose or sucrose, which substitute for the lactose found in breast milk and formula), risking dental decay and obesity in later life.

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Overdiagnosis of infant eosinophilic oesophagitis increases risk of adverse infant outcomes

- Very Early Onset Eosinophilic Esophagitis (EoE)
- Mixed IgE-mediated and non-IgE-mediated immune response
- Commonly diagnosed in infants < 12 months old who present with
 - Feeding difficulties
 - Feeding refusal
 - Poor weight gain
 - Vomiting
 - Failure to thrive
 - Irritability
 - Choking or gagging with feeds
- 17% of paediatric EoE diagnoses noted to occur in early life (0-24 months)¹
- Increased risk if also has IgE immune responses (asthma, allergic rhinitis, severe eczema, IgE-mediated food allergy)
- Diagnosis requires
 - Signs of 'oesophageal dysfunction' (attributed to signs listed above)
 - Refractory to acid suppression therapy (including PPIs)
 - Endoscopy: visible inflammation + biopsy → > 15 eosinophils per high power field^{1,2}

Overdiagnosis of infant eosinophilic oesophagitis increases risk of adverse infant outcomes

- The diagnosis of EoE is applied in the way the diagnosis of infant GORD was historically applied:
 - Disease with significant morbidity (inflammation → fibrosis) identified in older children
 - Extrapolated back to explain behaviour of unsettled infants (developmentally different population)
 - In practice, infants often not investigated with endoscopy + biopsy
 - Commenced on dietary restriction for *assumed* diagnoses of EoE, especially if not responding to PPIs.
- Problems
 - Reductionist or medicalised lens applied to interpretation of research
 - **Multiple omitted variable biases in primary sources**
 - Omitted variable biases then persist in systematic and narrative reviews
 - Infant endoscopies < 6-12 months known to rarely show visible inflammation (infant GORD research)
 - No reliable evidence in primary sources to show presenting signs resolve more with dietary restriction than with passage of time
 - PPIs known to be associated with increased risk of EoE; both PPIs and unnecessary elimination diets known to increase risk of allergy in later infancy or childhood.

Overdiagnosis of infant eosinophilic oesophagitis increases risk of adverse outcomes

Current use of diagnosis of Very Early Onset Eosinophilic Esophagitis (V-EoE) mostly relies on Lyles et al 2021

- Retrospective chart review (methodologically weak)
- Histologic and gross endoscopic features in infants 12 months old or less (n=57) c.f. children 14-18 years of age (n=70)
- V-EoE had lower endoscopic scores; Late Onset-EoE had more oesophageal strictures
- No evidence that infant signs resolved more quickly with dietary restrictions than with passage of time
- Key 'risk' factors identified include early infant use of acid-blocking medications, antibiotics, prematurity, caesarean delivery
 - All associated with unsettled infant behaviour
 - Not necessary hypothesise EoE as mediating link (given multiple other omitted variables once considerations of unsettled infant behaviour are integrated with interdisciplinary research literature)

Things to note about consensus guidelines

Consensus guidelines require critical analysis going back to primary sources of research

Consensus guidelines are conservative collective interpretations of evidence (an important safety mechanism in advancement of medicine) but there is often gap between evidence and consensus guidelines for this reason

Consensus guidelines relating to unsettled infant behaviour have particularly large gap between evidence and practice due to health system blind spots + omitted variable biases in care of mothers and infants, including failure to consider breastfeeding problems

Complex primary care health presentations and related research are most effectively analysed using lens of

- Complexity science (compared to dominant reductionist lenses)
- Evolutionary biology
- Holistic, generalist clinical practice.

Related resources

(click on links for deeper dive + analysis of key research studies)

[What the research tells us about food protein immune reactions in infants: prevalence, mechanisms, overdiagnosis](#)

[What the research tells us about food protein immune reactions in infants: diagnostic categories and management](#)

[Infant allergy, unsettled behaviour, and the gut: PLAIN LANGUAGE SUMMARY for health professionals](#)

[Infant haematochezia \(blood in the stool\): PLAIN LANGUAGE SUMMARY for health professionals](#)

[Commercial milk formula use in the first days of life increases allergy risk](#)



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