Cow's Milk Protein Allergy and Feeding Intolerances in Infancy

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Disclosure

- I have no relevant financial relationships with the manufacturers(s) of any commercial products(s) and/or provider of commercial services discussed in this CME activity
- I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

Most common infant feeding intolerances

- Colic
- Irritability
- Reflux (GER)
- Bloody stools
- Constipation
- Loose stools
- Emesis (bloody, bilious, mucus)
- Gas
- Abdominal distension (severity, discoloration, bowel loops present, firmness assessment)
- Dyspnea and/or Tachypnea
- Cardiac concerns – tachycardia, mottling/pallor, hypotension, etc.

Corkins, M. R., & Balint, J. (2015). *A.S.P.E.N. Pediatric Nutrition Support Core Curriculum*. American Society for Parenteral and Enteral Nutrition.

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Cow's milk protein allergy
Cow's milk protein intolerance
Lactose intolerance
Lactose sensitivity
Virus
Gastroparesis
GERD
Intestinal dysbiosis
Necrotizing Enterocolitis
Cardiac concern (compromised mesenteric perfusion)

assessment)

Cow's Milk Protein Allergy

- Allergy definition: immune-mediated (IgE or non-IgE) response to cow's milk protein
- Prevalence is 2.5% of infants
  - 4.9% of the World under Age 3, approx. 5-7% formula-fed babies and 0.5-1% in breastfed babies
- Resolution: 50% by 1 y/o, nearly 100% by 3 y/o
- Symptoms
  - Symptoms develop quick. Usually after 1 week of exposure, usually within 1st month of life.
  - 2 symptoms in 2 organ systems (cutaneous, GI, and/or respiratory)
  - Pruritus, erythema, hives, atopic eczema, angioedema in lips, tongue, and palate, nausea, colicky abdominal pain, V/D, reflux, blood in stool or mucus, abdominal pain, food refusal/aversion, constipation, anal redness, pallor, fatigue, growth faltering, respiratory symptoms (itching, sneezing, rhinorrhea, congestion, cough, wheezing, SOB)
- Treatment
  - Partially hydrolyzed formula (90%) → Extensively hydrolyzed formula / Amino acid formula (10%)
    - Goat's milk and soy milk products are not recommended
  - If breastfeeding, remove all dairy* from maternal diet

*Mom needs education!

1. Differentiating milk allergy (IgE and non-IgE mediated) from lactose intolerance: understanding the underlying mechanisms and presentations Joanne Walsh, Rosan Meyer, Neil Shah, James Quekett, Adam T Fox British Journal of General Practice 2016; 66 (649): e609-e611. **DOI:** 10.3399/bjgp16X686521
2. Corkins, M. R., & Balint, J. (2015). *A.S.P.E.N. Pediatric Nutrition Support Core Curriculum*. American Society for Parenteral and Enteral Nutrition.
3. Jarvinen-Seppo, K. M. (2021, March 29). *Milk allergy: Clinical features and diagnosis*. UpToDate. Retrieved July 24, 2022, from https://www.uptodate.com/contents/milk-allergy-clinical-features-and-diagnosis#H2

Non-IgE Allergies

Eosinophilic Esophagitis (EoE)

- "Disorder of the esophagus characterized by upper GI symptoms in association with esophageal mucosal eosinophilia"
- **Presentation**: children under 5 with food refusal, regurgitation, emesis, abdominal pain, dysphagia
- **Treatment**: systemic and topical corticosteroids. Nutrition therapy (amino acid based formula) is an adjunct to steroids.

Food Protein-Induced Enterocolitis (FPIES)

- Non-IgE mediated allergic disorder affecting a large proportion of the entire GI tract
- **Presentation**: <12m with delayed V/D 2-3 hours after ingestion, no cutaneous or respiratory symptoms. Usually presents within 1-4 weeks following introduction of allergen.
  - 30% develop atopic diseases
- Offending food is cow's milk protein, soy, or rice… or grains, poultry, fruit, or vegetable. Very rare that it is breastmilk.
- Skin prick test or serologic in vitro are negative, an oral food challenge can confirm dx
  - 2017 International Consensus Guideline on dx and management of FPIES
- **Treatment**: remove the antigen, 80% tolerate hydrolyzed formula and 20% require amino acids formula

1. Corkins, M. R., Balint, J., & Seebeck, N. D. (2015). *The A.S.P.E.N. Pediatric Nutrition Support Core Curriculum* (2nd ed.). American Society for Parenteral and Enteral Nutrition.
2. Nowak-Wegrzyn, A. (2022, July). *Food protein-induced enterocolitis syndrome (FPIES)*. UpToDate. Retrieved July 9, 2022, from https://www.uptodate.com/contents/food-protein-induced-enterocolitis-syndrome-fpies?search=feeding+intolerance&topicRef=5897&source=see_link#H115042881
3. Bonis, Peter A (2022, July). *Clinical Manifestations and diagnosis of eosinophilic esophagitis (EoE)*. UpToDate. Retrieved July 9, 2022, from https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-eosinophilic-esophagitis-eoe?search=EoE&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

Non-IgE Allergies

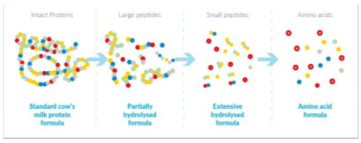
Food protein-induced allergic proctocolitis of infancy

- Allergic "protein intolerance" characterized by inflammation of the distal colon, not IgE mediated
- **Symptoms**: Rectal bleeding in an otherwise healthy young infant, significant irritability and diarrhea
- **Presentation**: Begins first few weeks of life, resolved by late infancy, allergen is cows milk or soy
- **Treatment**: Eliminate the allergen from mother's diet, 95% resolve with extensively hydrolyzed formula, 5% require amino acid formula

Liacouras, Chris (2022, July). *Food protein-induced proctocolitis of infancy*. UpToDate. Retrieved July 9, 2022, from https://www.uptodate.com/contents/food-protein-induced-allergic-proctocolitis-of-infancy?search=feeding%20intolerance&source=search_result&selectedTitle=4~61&usage_type=default&display_rank=4

What is a hydrolyzed formula?

- Proteins are broken down, so the body reacts less when exposed
- Contain reduced or no lactose
- Casein and whey ratios vary between products
- Soy is inappropriate.



Corkins, M. R., Balint, J., & Seebeck, N. D. (2015). *The A.S.P.E.N. Pediatric Nutrition Support Core Curriculum* (2nd ed.). American Society for Parenteral and Enteral Nutrition.

Photo: https://babyformulaexpert.com/baby-formula-protein-type/

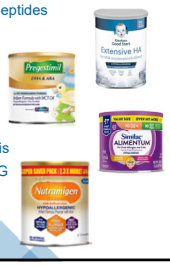
Casein & Whey

- Unmodified cow's milk: 18% whey, 82% casein
- Human milk: 60-70% whey, 30-40% casein
  - Secretory IgA and Lactoferrin are two whey proteins in human milk
- Infant formulas aim for 60:40 whey: casein but vary for desired outcomes
- Whey – faster gastric emptying time, easily digestible
- Casein – less soluble, slower digestion

Corkins, M. R., Balint, J., & Seebeck, N. D. (2015). *The A.S.P.E.N. Pediatric Nutrition Support Core Curriculum* (2nd ed.). American Society for Parenteral and Enteral Nutrition.

Extensively Hydrolyzed Protein Formula

- Protein: Mix of free amino acids and small peptides
- Fat: LCT/MCT mix
- Carbohydrate: Corn (lactose-free!)
  - Except Alimentum that is "sugar"
- Osmolality: higher than standard



- Gerber Extensive HA: whey protein + B lactis
- Nutramigen: hydrolyzed casein + AAs + LGG
- Alimentum: hydrolyzed casein + AAs
- Pregestimil: hydrolyzed casein only

Amino Acid Formula

- Protein: amino acids
- Carbohydrate: Corn syrup (lactose free)
- Fat: MCT/LCT mix

Colic

- Definition: full-force crying, 3+ hours/day on 3+ days/week, x3+ weeks
- Etiology: multifactorial
- Resolution: 3-4 months of age
- Treatment:
  - First line: caregiver breaks, burping, soothing techniques
  - Second line: Extensively hydrolyzed formula

Turner, T. L., & Palamountain, S. (n.d.). *Infantile colic: Management and outcome*. UpToDate. Retrieved July 23, 2022, from https://www.uptodate.com/contents/infantile-colic-management-and-outcome?topicRef=1205&source=see_link

Gordon M, Biagioli E, Sornenti M, et al. Dietary modifications for infantile colic. Cochrane Database Syst Rev 2018; 10:CD011029.

Lactose Intolerance

Caution in patients at increased risk for weak bones.

Types

- Developmental lactase deficiency: temporary lactase deficiency due to underdevelopment
- Congenital lactase deficiency: rare, genetic difference
- Primary lactose intolerance: 70% of the global adult population
  - Infant diet can tolerate lactose. Lactase expression decreases as age. No expression at 5 y.o.
- Secondary lactose intolerance: occurs due to small bowel damage causing secondary or transient lactase deficiency
  - Microvilli flattening due to celiac, SIBO, Crohn's, or GI virus (norovirus)

- Symptoms: abdominal pain, bloating, gas, colicky, irritable, diarrhea within 30-120 minutes after ingestion
- Treatment: Reduced lactose or lactose-free formula

1. Gordon M, Biagioli E, Sorrenti M, Lingua C, Moja L, Banks SSC, Ceratto S, Savino F. Dietary modifications for infantile colic. Cochrane Database of Systematic Reviews 2018, Issue 10. Art. No.: CD011029. DOI: 10.1002/14651858.CD011029.pub2.
2. Di Costanzo, M., Biasucci, G., Maddalena, Y., Di Scala, C., De Caro, C., Caligiuro, A., & Canani, R. B. (2021). Lactose intolerance in pediatric patients and common misunderstandings about cow's milk allergy. *Pediatric Annals*, 50(4). https://doi.org/10.3928/19382359-20210312-01
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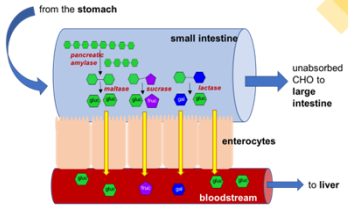
GI Changes associated with a virus

- Secondary lactose intolerance
- Lactose is located on the brush border enzymes
- Microvilli blunting due to virus



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Low / Reduced Lactose Formulas

Protein: intact milk protein isolate **Carbohydrate**: corn and sucrose, lactose-free **Fat**: LCT 5 HMOs prebiotic	**Protein**: hydrolyzed nonfat milk + whey concentrate **Carbohydrate**: corn, reduced lactose **Fat**: LCT	**Protein**: whey protein hydrolysate **Carbohydrate**: corn and sucrose, lactose free **Fat**: LCT 2'FL HMO prebiotic

Impactful on…

- ✓ Microbiota
- ✓ Plasma metabolic profiles
  - Cell signaling, inflammation regulation, and immune system functioning
- ✓ Zn and Ca absorption

1. Uy, N., Graf, L., Lemley, K. V., & Kaskel, F. (2014). Effects of gluten-free, dairy-free diet on childhood nephrotic syndrome and gut microbiota. *Pediatric Research*, 77(1–2), 252–255. https://doi.org/10.1038/pr.2014.159
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Gastroparesis

- Definition: delayed gastric emptying
- Symptoms: constipation, reflux
- Treatment Options
  - Time for migrating motor complex (MMC) to develop, mature, and strengthen
  - Feeding time stress assessment
  - Increase G-tube infusion time: improve gastric emptying, and aid in maturation of duodenal motor pattern
  - Decrease volume and increase feeding frequency
  - Evaluation food composition (CHO vs protein vs fat, additives)
    - Consider solid food intake (acidic foods and soluble fibers have slower transit time)
    - Carbs empty first. Fats empty last.
  - Decrease calorie concentration
  - Warm milk
  - Medication treatment

Meyer, R., Foong, R.-X. M., Thapar, N., Kritas, S., & Shah, N. (2015, October 15). *Systematic review of the impact of feed protein type and degree of hydrolysis on gastric emptying in children - BMC gastroenterology*. BioMed Central. Retrieved August 10, 2022, from https://bmcgastroenterol.biomedcentral.com/articles/10.1186/s12876-015-0369-0

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GER / GERD

- Definition: "the passage of gastric contents into the esophagus with or without regurgitation and/or vomiting"
  - GER**D** "when reflux leads to troublesome symptoms and/or complications, such as esophagitis or stricturing."
  - *Refractory GERD* is when symptoms do not respond to treatment after 8 weeks
- Prevalence: difficult to estimate
- Symptoms: excessive crying, back arching, regurgitation, and irritability
- No gold standard diagnostic tool for infants and children
  - pH-MII testing: strong recommendation to use to correlate persistent troublesome symptoms with acid and non-acid gastroesophageal events
- Treatment
  - None if thriving, despite symptom presence

Rosen R, Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, Gupta S, Langendam M, Staiano A, Thapar N, Tipnis N, Tabbers M. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2018 Mar;66(3):516-554. doi: 10.1097/MPG.0000000000001889. PMID: 29470322; PMCID: PMC5958910.

Table 2

Outline of the proposed side effects associated with proton pump inhibitors use, and the evidence supporting the association

Potential side effects	Level of evidence showing an association with PPI use
Acute Interstitial Nephritis	Level III
Bacterial overgrowth in the stomach, small and large intestine	Murine models
Bacterial enteric infections Causative agents: *Clostridium difficile* *Salmonella* species *Campylobacter* species	Level I
Pneumonia (Community-acquired)	Level I
Necrotizing enterocolitis	Level III[1]
Blood stream infections, including candidemia	Level III[1]
Allergic sensitization in adults and in children with *in utero exposure*	Level III Study and Murine Models
Parietal and Enterochromaffin-like cell hyperplasia	Level II
Fundic gland polyps	Level III
Vitamin B12 deficiency	Level III
Fractures (osteoporotic and non-osteoporotic)	Level III
Hypomagnesemia	Level IV and one level III study
Reduced Antiplatelet effect of Clopidogrel	Level II
Adverse Cardiovascular outcomes due to Clopidogrel interactions	Level III[2]

Open in a separate window

[1]Only single reports showing an association with acid inhibition induced by H2RA treatment;
[2]RCTs (level II) not shown an increase risk of adverse outcomes.

Safe M, Chan WH, Leach ST, Sutton L, Lui K, Krishnan U. Widespread use of gastric acid inhibitors in infants: Are they needed? Are they safe? World J Gastrointest Pharmacol Ther. 2016 Nov 6;7(4):531-539. doi: 10.4292/wjgpt.v7.i4.531. PMID: 27867886; PMCID: PMC5095572.

Summary of the 2018 NASPGHAN-ESPGHAN Pediatric Gastroesophageal Reflux Clinical Practice Guideline

Focus on Infants

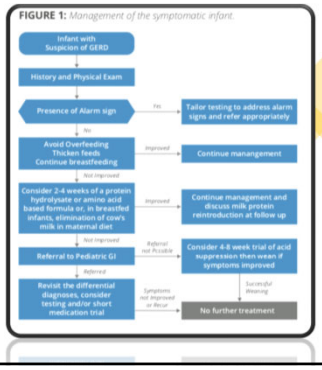
BACKGROUND

In 2009, the joint committee of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) published a medical position paper on gastroesophageal reflux (GER)* and GER disease (GERD)*

OVERVIEW OF RECOMMENDATIONS

The summation of the guidelines approach to infants with frequent regurgitation or vomiting suspected of GERD is shown in the algorithm below (Figure 1).

FIGURE 1: Management of the symptomatic infant.



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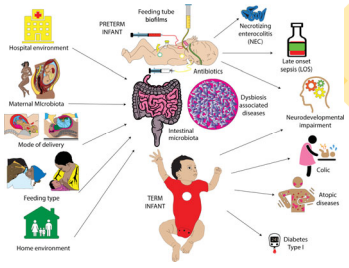
Summary: https://naspghan.org/files/documents/pdfs/position-papers/PedGERD%20Summary%20FINAL.pdf

Added Rice Formulas

- Designed to thicken when it hits the acidic pH of the stomach
  - Does not work if receiving pH altering drug
  - AR has max concentration of 24kcal/oz

Intestinal Dysbiosis

- Definition: imbalance of bacteria in the microbiome associated with less healthy outcomes
- Symptoms: fussiness/colic, gas, atopic diseases
- Treatment: probiotics – evidence still emerging
  - BF babies: high Actinobacteria
  - Formula babies: higher γ-proteobacteria



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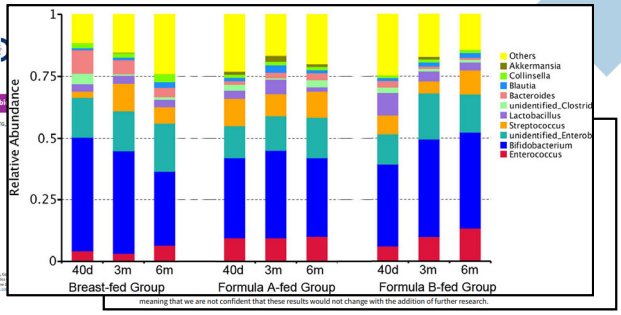
O'Sullivan A, Farver M, Smilowitz JT. The Influence of Early Infant-Feeding Practices on the Intestinal Microbiome and Body Composition in Infants. Nutr Metab Insights. 2015 Dec 16;8(Suppl 1):1-9. doi: 10.4137/NMI.S29530. Erratum in: Nutr Metab Insights. 2016 Oct 27;8(Suppl 1):87. PMID: 26715853; PMCID: PMC4686345.



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Prebiotics & Probiotics

- Prebiotic definition: "a substrate that is selectively utilized by host microorganisms conferring a health benefit"
  - Human Milk Oligosaccharides (HMOs) – non-digestible sugar chain (3-22 units)
    - Function: antibacterial effects, etc
    - Most common is 2-FL
- Probiotic definition: "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host"
- Which probiotic to choose?
  - None are FDA approved or regulated.
  - Product purity, potency, and safety concerns.
  - Note storage recommendations.
  - Emphasize a trial period.
- Some infant formulas contain beneficial bacteria

ISAPP

1. Koletzko, B., Cheah, F.-C., Domellöf, M., Poindexter, B., Vain, N., & Goudoever, J. B. van (Eds.). (2021). *Nutritional care of preterm infants scientific basis and practical guidelines* (2nd ed.). Karger.
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3. Corkins, M. R., & Balint, J. (2015). *A.S.P.E.N. Pediatric Nutrition Support Core Curriculum*. American Society for Parenteral and Enteral Nutrition.

Summary

- Many intolerances
- Many formulas
- Emphasize formula trial period
- Identify symptoms first, choose formula carefully
- If you don't have to go more specialized, don't. Maybe simply a brand change will resolve issue.
- Amino acid formula will usually fix the problem, but….
  - not always necessary
  - gives the wrong message to the family
  - may delay gut maturation
  - $$$ and difficult to find

Addressing Common Feeding Intolerances

- **Colic** → counsel on first line treatment → trial probiotic with L reuteri → extensively hydrolyzed formula
- **Irritability** → no formula change unless impacting quality of life → Whey protein formula or reduced lactose formula
- **Reflux (GER)** → Follow algorithm. Slide 19.
- **Bloody stools** → Cow's milk protein allergy, trial extensively hydrolyzed protein formula first.
- **Constipation** → no formula change, consider impact of non-formula intake, discuss non-dietary interventions
- **Loose stools** → no formula change, unless water loss stools and losing weight → reduced lactose formula or change to formula with prebiotic HMOs
- **Emesis** (bloody, bilious, mucus) → consider escalation of care for more thorough assessment → consider an extensively hydrolyzed formula (cow's milk protein allergy)
- **Gas** → no formula change unless impairing growth or quality of life → term infant formula with HMOs/reduced lactose/probiotic
- **Abdominal distension** → consider need for care escalation → partially hydrolyzed formula
- **Dyspnea and/or Tachypnea** → escalate to inpatient/specialist
- **Cardiac concerns** – tachycardia, mottling/pallor, hypotension, etc. → escalate to inpatient/specialist

Questions?

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