Cow's Milk Allergy

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Cow's Milk Allergy (CMA)

- Associated with a variety of different medical conditions
- Mechanisms responsible are not all understood
- Include IgE-mediated and non-IgE mediated reactions
- Known collectively as CMA

Mechanisms Responsible for CMA

- IgE-mediated reactions include classical allergy symptoms:
  - Urticaria
  - Wheezing
- Non-IgE-mediated reactions include:
  - Colic
  - Vomiting
  - Diarrhea

Cow's Milk Allergy: Characteristics

- Onset of IgE-mediated reaction
  - Typically immediately following first known ingestion of cow's milk
  - Sensitization may have occurred earlier due to exposure to "hidden sources" of cow's milk (in breast milk; infant formulae; in utero)
  - Diagnosis usually made by parents
- Onset is rare in adults

Cow's Milk Allergy Prevalence

- Prevalence in children:
  - Disagreement because some reports include both IgE-mediated and non-IgE-mediated
  - Others report only ige-mediated
- Mechanism not specified:
  - Bock (1987) 0.6%
  - Jakobsson and Lindberg (1979): 1 - 2%
  - Gerrard (1973) 7.5%
- IgE-mediated:
  - Schwartz (1991) 4%
- Children with atopic dermatitis:
  - Sampson and Albergo (1989) 20%

Suggested Classification Scheme for CMA

[Hill et al, 1986]

Group 1: Immediate Reactors

- Reaction within 45 minutes after milk ingestion
- Symptoms include urticaria, angioedema, exacerbation of eczema, cough, wheeze, vomiting
- Skin test positive (STP) to CMA
- Elevated IgE to CMA by RAST or ELISA

Suggested Classification Scheme for CMA

Group 2: Intermediate Reactors

- Reaction 45 minutes to 20 hours after milk ingestion
- Symptoms include vomiting, diarrhea
- Skin test negative to cow's milk allergens
- Insignificant elevation of IgE to cow's milk in RAST or ELISA

Suggested Classification Scheme for CMA

Group 3: Late Reactors

- Reaction more than 20 hours after milk ingestion
- Symptoms include diarrhea, colic, with or without wheezing, with or without exacerbation of eczema
- Those with eczema skin test positive to cow's milk allergens
- Insignificant elevation of IgE to cow's milk in RAST or ELISA

IgE-mediated Reaction

[Schwartz, 1991]

Typical scenario of first exposure to cow's milk:

- Infant refuses to take more after first taste
- Cries as if in pain
- Swelling of lips, tongue, and mucous membranes of throat in 1-2 minutes
- May be followed by laryngeal edema (throat constriction)

IgE-mediated Reaction
continued

- May be accompanied by wheezing
- Occasionally urticaria spreads over entire body
- In severe cases shock may occur
- Usually spontaneous recovery in 15-60 minutes
- Infant appears exhausted after reaction

Adverse Reactions to CM - Associated Conditions

Gastrointestinal

Infantile colic

Gastrointestinal bleeding

- Occult
- Gross

Enterocolitis

Milk-sensitive enteropathy

Protein-losing enteropathy

Eosinophilic gastroenterology

Oral allergy food syndrome

Genitourinary

Enuresis

Orthostatic proteinuria

Nephrotic syndrome

Cardiovascular

Anaphylactic shock

Exercise-induced anaphylaxis

Adverse Reactions to CM - Associated Conditions: continued

Cutaneous

- Atopic dermatitis
- Contact urticaria
- Generalized urticaria
- Angioedema
- Dermatitis herpetiformis

Neurologic

- Migraine
- Tension-fatigue syndrome
- Sleeplessness
- Hyperactivity
- Attention deficit disorder
- Behaviour disorders

Adverse Reactions to CM - Associated Conditions: continued

Respiratory

- Rhinitis
- Serous otitis media
- Cough/wheeze
- Laryngeal stridor
- Asthma
- Occupational asthma
- Exercise-induced asthma
- Recurrent pulmonary infiltrates
- Pulmonary hemosiderosis

Hematologic

- Anemia
- Thrombocytopenia
- Eosinophilia

Adverse Reactions to CM - Associated Conditions: continued

Metabolic

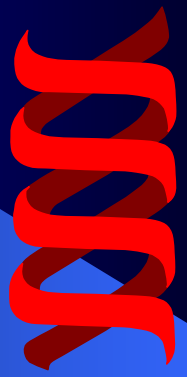
- Hyperproteinemia
- Lactose intolerance
- Galactosemia
- Phenylketonuria

Other

- Sudden infant death syndrome (SIDS)
- Infantile cortical hyperostosis

IgE-mediated CMA: Predisposing Factors in Breast-fed Infants

1. Genetic predisposition
   - family history of CMA
2. Early exposure to cow's milk
   - in utero
   - in newborn nursery
3. Inadvertent exposure to cow's milk allergens
   - in mother's milk



IgE-mediated CMA: Predisposing Factors in Breast-fed Infants continued

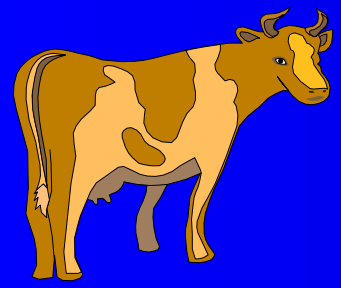
4. Feeding of cow's milk by relatives and caregivers

5. "Early exposure of the at-risk breast-fed infant to tiny amounts of cow's milk allergens is more important than any immunologic property of the antigen"

Feeding Formula to Breast-fed Infants in Newborn Nurseries

- Area of ongoing controversy
- Theoretically would contribute to sensitization of potentially allergic infants to milk
- 68% breast-fed infants with IgE-mediated CMA had received some CMA in newborn nursery
- Recommendation
  - Avoid isolated feedings of infant formulae to breast-fed infants in neonatal period

[Schwartz, 1991]



Cow's Milk Antigens

- More than 25 proteins in cow's milk can induce antibody production in humans
- β-lactoglobulin (in whey), casein, and bovine serum albumin are the most important antigens
- Casein antigens include:
  - α_{s1} ; α_{s2} ; β ; κ
- Clinical reactions have occurred to all the major cow's milk antigens

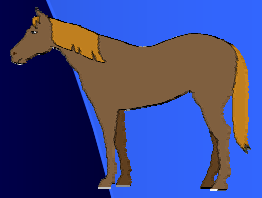
Human Milk Antigens

- Human milk is predominantly whey (80% whey and 20% casein)
  - total casein content varies during lactation (20% in early lactation, 45% in late lactation)
- Human milk lacks α_{s1} and α_{s2} caseins and β-lactoglobulin
- These tend to be most frequent allergens in cow's milk, suggesting tolerance to those encountered from maternal source

Milk Antigens from Other Species

Goat Milk

- Many goat's milk proteins cross-react with cow's milk proteins
- The majority of children allergic to cow's milk are or will become allergic to goat's milk
- Goat's milk is deficient in folate



Mare's Milk

- Fewer proteins are similar to cow's milk proteins
- In research studies, most milk allergic children tolerated mare's milk (25 children +CMA; 1 + Mare milk)

Infant Formulae

- Many infant formulas are casein-predominant and others are whey-predominant
- No definite policy for use of either type in most hospitals
- Cow's milk allergic infant should not be given either type
- IgE antibodies to soy proteins occur commonly in children with IgE antibodies to cow's milk (67%) (Dannaeus et al, 1977)

Infant Formulae

- Hydrolysis and heat treatment may change the nature of the milk proteins
- Some proteins lose allergenicity
- But new antigens may be produced
- Partially hydrolysed whey formula (Good Start®) contains allergens and should not be used in management of established cow's milk allergy

Infant Formulae

- Extensively hydrolysed casein formulae (e.g. Nutramigen®, Alimentum®, Pregestamil® are usually tolerated
- In Europe an extensively hydrolysed whey formula is available (Profylac®)
- However, some infants with skin and respiratory IgE-mediated CMA may have serious reactions to them
- No cow's milk hydrolysate formula should be considered completely safe for all children with IgE-mediated CMA
- Introduction should be conducted with caution

Management of CMA

- Elimination of all milk and all foods containing cow's milk proteins
- People intolerant to bovine serum albumin may not tolerate beef
- Breast milk of mothers following a diet devoid of cow's milk protein is the ideal food
- In the small number of infants intolerant to lactose, breast milk may have to be pre-treated with lactase enzyme. Breast-feeding should not be discontinued.

Management of CMA

- Protein hydrolysate infant formula may be tolerated; however they are expensive and bitter-tasting
- Some hydrolysate formula can induce anaphylaxis because of large molecular weight peptides, especially partially hydrolyzed whey formula (Good Start®)

Hidden Sources of Cow's Milk Antigens

- Casein is used as a food emulsifier
- Whey is used as a food fortifier
- Margarines contain whey and/or casein
- Many processed foods contain milk proteins (e.g. breads, cereals, pastas, soups, toppings, gravy and sauce mixes, sausages, canned meats, etc.)

Hidden Sources of Cow's Milk Antigens

- Foods containing "flavouring" may contain lactalbumin
- "Lactose" may contain α-lactalbumin and β-lactoglobulin
- Leather may be sprayed with casein after it has been tanned
- Casein may be found in a number of non-food items e.g.

artists' paints
cosmetics
photoetching chemicals
insect spray
paper coating
pet food
contraceptive foams
home permanents
industrial glue
leather finishes
particle board

Prognosis

[Gryboski, 1991]

- Most infants will outgrow milk allergy by 3 years of age, but may become intolerant to other foods
- About 25% will develop respiratory allergies
- After 1 year many children will tolerate beef

Prognosis

[Bishop, 1990]

- 28% of milk allergic infants tolerated milk by 2 years of age
  - 56% by 4 years of age
  - 78% by 6 years of age
- Of milk-allergic children studied:
  - 50% were also allergic to egg and soy
  - 30% to peanut

Gastroesophageal Reflux (GER) and Milk Protein Intolerance

- Symptoms:
  - Distressed behaviour
  - Irritability
  - Esophageal reflux
  - vomiting
- Esophagitis diagnosed by histologic evidence
- Food protein intolerance associated with significant number of cases

Gastroesophageal Reflux (GER) and Milk Protein Intolerance

- These are also symptoms of cow's milk allergy (CMA)
- Previous studies indicate that 40% of infants with distressed behaviour and signs of GER also have CMA

Gastroesophageal Reflux (GER) and Milk Protein Intolerance

- Study in 19 infants (Hill et al 2000)
  - Elimination of all sources of cow's milk, use of extensively hydrolysed cow's milk based formula, and antireflux medication failed to resolve symptoms
  - 9 had histological evidence of esophagitis
  - 9 had inflammatory changes in stomach and/or duodenum
  - 1 had no evidence of histologic abnormality

Gastroesophageal Reflux (GER) and Milk Protein Intolerance

- Symptoms remitted in all infants within 2 weeks on amino acid-based formula (Neocate)
- Previous formulae included;
  - milk-based (CMF) - soy-based
  - casein hydrolysate (eHF) -whey hydrolysate (pHF)
- Challenge with previous formulae after 3 months on AAF:
  - 12 relapsed after median 7 days on previous formula
  - 7 tolerated previous formulae (CMF - 3; whey hydrolysate - 2; soy - 1; casein hydrolysate - 1)

Reasons for Not Using Cow's Milk in First Year

1. Low content and bioavailability of iron in milk may result in iron deficiency
2. Iron deficiency in early childhood can lead to changes in behavior that may not be reversed even with iron supplementation sufficient to correct anemia

Reasons for Not Using Cow's Milk in First Year

3. Studies on rats indicate that the number of dopamine D-2 receptors in the brain is reduced by even a temporary period of iron deficiency in infancy
4. Whole cow's milk causes nutritionally significant loss of iron in the stool
5. High calcium, high phosphorous, low vitamin C decreases bioavailability of iron from other dietary sources such as infant cereals

Reasons for Not Using Cow's Milk in First Year (continued)

6. Increased intestinal permeability in immature infant may contribute to the high incidence of cow's milk protein allergy (7-16%)
7. Possibility of cow's milk protein contributing to juvenile diabetes in susceptible infants