Cow's Milk Allergy: Mechanisms, Diagnosis, and Treatment

Presented by
David Fleischer, MD
Professor of Pediatrics
Section Head, Allergy & Immunology
Director, Allergy & Immunology Center
University of Colorado School of Medicine
Children's Hospital Colorado

Carina Venter, PhD, RD
Associate Professor of Pediatrics
Section of Allergy & Immunology
University of Colorado Denver School of Medicine
Children's Hospital Colorado

Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS
Faculty Presenters

David Fleischer, MD
Professor of Pediatrics
Section Head, Allergy & Immunology
Director, Allergy & Immunology Center
University of Colorado School of Medicine
Children’s Hospital Colorado
Aurora, Colorado

Carina Venter, PhD, RD
Associate Professor of Pediatrics
Section of Allergy & Immunology
University of Colorado Denver School of Medicine
Children’s Hospital Colorado
Aurora, Colorado
Learning Objectives

- Apply current standard of care for the diagnosis and management of cow’s milk allergy in infants
- Link research targets to diagnosis and treatment of cow’s milk allergy
- Specify nutritional strategies to manage food allergy in infants
MODULE 1: DIAGNOSING AND MANAGING FOOD ALLERGIES IN INFANTS

• Define food allergy
• Diagnosis of food allergies in infants
  – Cow’s milk allergy (CMA), specifically
• Prevalence of food allergies
• Strategies for proper diagnosis
• Distinguish between IgE-mediated and non-IgE-mediated food reactions
Food Allergy Defined

- NIAID consensus definition: Adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food

- Food allergy develops as a lack of oral tolerance, which is a default immune response by the gut-associated lymphoid tissues to ingested antigens that is modified by the gut microbiota

NIAID, National Institute of Allergy and Infectious Diseases.

Types of Adverse Reactions to Food

Adverse Food Reaction

Food Aversion

Immune Mediated (food allergy)
- IgE Mediated
- Non-IgE Mediated
- Mixed IgE and Non-IgE Mediated
- Cell Mediated

Non-Immune Mediated (food intolerance)
- Toxic
- Metabolic
- Pharmacologic
- Idio-syncratic
- Other
IgE

Gastrointestinal Hypersensitivity Disorders
- Pollen-Food Allergy Syndrome
- Immediate GI Hypersensitivity
  - Eosinophilic Esophagitis
  - Eosinophilic Gastritis
  - Eosinophilic Gastroenteritis
- Dietary Protein Enterocolitis
- Dietary Protein Proctitis
- Dietary Protein Enteropathy (Celiac Disease)

Cutaneous Hypersensitivity Disorders
- Acute Urticaria & Angioedema
- Acute Contact Urticaria
- Atopic Dermatitis
- Dermatitis Herpetiformis

Respiratory Hypersensitivity Disorders
- Allergic Rhinitis
- Acute Bronchospasm
- Asthma
- Food-induced Pulmonary Hemosiderosis (Heiner’s Syndrome)

Systemic Hypersensitivity Disorders
- Generalized Anaphylaxis
- Food-associated Exercise-induced Anaphylaxis

Non-IgE

Food Allergy Prevalence in Infants and Toddlers

• Food allergy affects 4–8% of children <5 years in U.S.
  – ~5.9 million children under age 18
  – 38.7% have history of severe reactions
  – 30% have multiple food allergies

• Comparatively, 3–4% of the general population in developed countries

• Prevalence increasing
  – Peanut and tree nut allergies increased considerably over the past decade (more than tripled 1997–2008)

• Our focus—cow’s milk allergy (CMA)
  – Prevalence of 2.5% <1 yr old in US

▶ See appendix. Updated to prevalence slides added November 2020.

https://www.niaid.nih.gov/diseases-conditions/food-allergy
### Major Food Allergy in Infants and Toddlers

<table>
<thead>
<tr>
<th>Most Common Food Allergies</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Cow’s milk allergy (CMA)</td>
</tr>
<tr>
<td>Egg</td>
</tr>
<tr>
<td>Wheat</td>
</tr>
<tr>
<td>Soybean</td>
</tr>
<tr>
<td>Peanut</td>
</tr>
<tr>
<td>Tree nuts</td>
</tr>
<tr>
<td>Shellfish</td>
</tr>
<tr>
<td>Fish</td>
</tr>
</tbody>
</table>

*Most common of food allergies, with prevalence in children ranging between 1.9% and 4.9%.

Diagnostic Approach to the Evaluation of Food Allergy

- Detailed History & Physical
  - IgE-mediated
    - SPT or ImmunoCAP
      - Reconsider
      - Elimination Diet
        - Specific Allergen Elimination Diet
          - Reconsider
          - Food Challenge
            - Reconsider
  - IgE & Non-IgE-mediated
    - Reconsider
    - Elimination Diet
  - Non-IgE-mediated
    - GI Consultation/Endoscopy
      - Reconsider

SPT, skin-prick test.
## IgE-mediated vs non-IgE-mediated Reactions

Important to differentiate clinically between IgE-mediated and non-IgE-mediated characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IgE-mediated</th>
<th>Non-IgE-mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from exposure to reaction</td>
<td>Immediate onset—minutes to 2 hours</td>
<td>Delayed onset; usually ≥2 hours</td>
</tr>
<tr>
<td>Severity</td>
<td>Mild to anaphylaxis</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td></td>
<td>More severe presentations</td>
<td>More severe presentations</td>
</tr>
<tr>
<td>Duration</td>
<td>Usually persist beyond 1 year of age</td>
<td>Often persist beyond 1 year of age</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Clinical history</td>
<td>Clinical history</td>
</tr>
<tr>
<td></td>
<td>Specific serum IgE, skin-prick test</td>
<td>Elimination diet</td>
</tr>
<tr>
<td></td>
<td>Oral challenge</td>
<td>Oral food challenge when indicated</td>
</tr>
</tbody>
</table>
Diagnostic Approach to the Evaluation of IgE-Mediated Food Allergy

- Family and personal history of allergic disease
- List of suspected foods
- Precise description of reactions

**Symptoms**
- **Cutaneous**
  - Flushing, hives, angioedema, eczema
- **Gastrointestinal**
  - Oropharyngeal pruritus and edema, abdominal cramping, nausea, vomiting, diarrhea
- **Pulmonary**
  - Rhinitis, laryngeal edema, wheezing, coughing, & shortness of breath
- **Cardiovascular**
  - Hypotension, tachycardia, arrhythmias
- **Neurological**
  - Loss of consciousness
- **Behavioral**
  - Irritability (preceding or in combination with other symptoms)

**Detailed History & Physical**

**IgE-mediated**

**SPT or ImmunoCAP**

**Elimination Diet**

**Food Challenge**

**Specific Allergen Elimination Diet**

**Food Challenge or Done**

**Done**

Evaluation of Infant

Symptoms common with infant health issues may not be IgE-mediated CMA related

• Irritability (colic)
• Gastroesophageal reflux
  – Vomiting hours after a meal (‘delayed gastric emptying’) may be associated to allergy
• Atopic dermatitis
  – Environmental issues may be due to irritants, microbes, and allergens

Treatment: Patient Education

General Considerations:
- Establish an elimination diet
- Teach how to avoid the offending food
  - Teach label reading
  - Review likely sources of accidental exposure
- Provide reliable sources of information
  - Consultation with a registered dietician
  - Food Allergy Research and Education (foodallergy.org)
- Suggest purchasing an identification bracelet, necklace, card
- Develop an ACTION PLAN for treatment of accidental exposures
- Train how to administer epinephrine by injection
- Encourage ALWAYS having rescue medications available
- Educate extended family and caretakers
Long-Term Management

• Reinforce need to carry medications at all times and review use of medical devices (epinephrine auto-injector, inhaler if asthmatic)
• Food challenge indicated by history and/or lab results?
• Aid in interactions with school and community
• Answer questions
• Suggestions regarding impact on quality of life
• Is referral indicated
  – Allergist
  – Gastroenterologist
  – Dietician
  – Psychosocial clinician
Clinical-Case Presentation of IgE-Mediated Infant: 6 ½ months

- Atopic parents: dad hay fever and mom asthma
- **Mild eczema in early infancy** (well controlled with emollients)
- Exclusively breast fed for 6 months
- Maintaining growth
- Developed **urticaria and angioedema** after first bottle of cow’s milk formula at 6 months (within 10 min)
- Given goat’s milk as an alternative but suffered same reaction

### Diagnostic method

<table>
<thead>
<tr>
<th>Diagnostic method</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>✔</td>
</tr>
<tr>
<td>SPT</td>
<td>✔</td>
</tr>
<tr>
<td>Specific IgE test</td>
<td>✔</td>
</tr>
<tr>
<td>Oral food challenge – office setting</td>
<td>x/?</td>
</tr>
<tr>
<td>Cow’s milk avoidance from maternal diet for around 4 weeks and reintroduction</td>
<td>NA</td>
</tr>
</tbody>
</table>
Mechanism: Type of cow’s milk allergy?

- Cow's milk allergies
  - IgE mediated cow's milk allergies
  - Non-IgE mediated cow's milk allergies
    - Cow's milk protein-induced enterocolitis/enteropathy/proctocolitis
    - Eosinophilic esophagitis induced by cow’s milk
    - Mild to moderate non-IgE mediated cow's milk allergies
## Diagnosis

### Diagnostic method

<table>
<thead>
<tr>
<th>Diagnostic method</th>
<th>✔️</th>
<th>❌</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>SPT</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>Specific IgE test</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>Oral food challenge – office setting</td>
<td>x/?</td>
<td></td>
</tr>
<tr>
<td>Cow’s milk avoidance from maternal diet for around 4 weeks and reintroduction</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

- Specific IgE to milk 40 kuA/L
- Milk skin-prick test 3 mm
- ? Food Challenge
- ? Specific IgE to casein
- ? Component testing
# What Do the Guidelines Recommend Regarding Formula Choice?

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>DRACMA</th>
<th>BSACI Guidelines</th>
<th>NIAID US Guidelines</th>
<th>ESPGHAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>AAF</td>
<td>AAF</td>
<td>No specific recommendation</td>
<td>AAF</td>
</tr>
<tr>
<td>Acute urticaria or angioedema</td>
<td>EHF</td>
<td>EHF</td>
<td>No specific recommendation</td>
<td>EHF</td>
</tr>
<tr>
<td>Atopic eczema/dermatitis</td>
<td>EHF</td>
<td>EHF</td>
<td>No specific recommendation</td>
<td>EHF</td>
</tr>
<tr>
<td>Eosinophilic Esophagitis</td>
<td>AAF</td>
<td>AAF</td>
<td>The NIAID guidelines acknowledge that trials in EoE have shown symptom relief and endoscopic improvement in almost all children on AAF/elemental diet, though no specific recommendation on formula choice is made.</td>
<td>AAF (as specified by current ESPGHAN guidelines on EoE)</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>EHF</td>
<td>EHF</td>
<td>No specific recommendation</td>
<td>EHF</td>
</tr>
<tr>
<td>Cow’s milk protein-induced enteropathy</td>
<td>EHF</td>
<td>EHF unless in which case AAF</td>
<td>No specific recommendation</td>
<td>EHF but AAF if complicated by faltering growth</td>
</tr>
<tr>
<td>FPIES</td>
<td>EHF</td>
<td>AAF</td>
<td>Hypoallergenic formulas are recommended</td>
<td>EHF</td>
</tr>
<tr>
<td>Proctocolitis</td>
<td>EHF</td>
<td>EHF</td>
<td>No specific recommendation</td>
<td>EHF</td>
</tr>
<tr>
<td>Breastfeeding with ongoing symptoms (already on maternal elimination diet) or requiring a top-up formula</td>
<td>No recommendation</td>
<td>AAF</td>
<td>No specific recommendation</td>
<td>With severe symptoms that are complicated by growth faltering, a hypoallergenic formula up to 2 weeks may be warranted. In many countries, AAF is used for diagnostic elimination in extremely sick exclusively breast-fed infants. Although this is not evidence based, it is aimed at stabilizing symptoms.</td>
</tr>
</tbody>
</table>

AAF, amino-acid formula; EHF, Extensively hydrolyzed formula; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology and Nutrition.
MODULE 2: IMMUNOLOGIC RESEARCH

- Science behind infant food allergies
- Immune response and microbiome
- Pathophysiology of CMA
- Source of Intolerance
Immune Response

Microbiome

- Ensures integrity of the gut wall and regulation of the immune system
- Diverse microbiome associated with tolerance development
- The role of diet diversity in this is unclear

Allergy Research Targets

Additional research targets include

• Gut microbiome
  – What does an ideal gut microbiome look like?

• Prebiotics and probiotics
  – Their particular role on the microbiome and tolerance induction

• How to manipulate the microbiome to induce tolerance

Pathophysiology of Cow’s Milk Allergy

• Triggers—Principal cow’s milk allergens
  – Casein fraction of proteins (αs1-, αs2-, β-, and κ-casein)
  – Whey proteins (α-lactalbumin and β-lactoglobulin)
• Complex interplay
  – Epithelial barrier
  – Mucosal and systemic immune response
  – Route of exposure
  – Microbiome and other influences resulting in allergy or tolerance
Breast Milk and What it Provides

Tolerance

• Support the infant’s developing immune system
• Tolerance to potential food allergens?

Graphical abstract

MODULE 3: NUTRITIONAL TREATMENT STRATEGIES

• Current standards of care
• Clinical recommendations for severe food allergies
• Interventional therapies for treatment of food allergy
• Suitable infant formulas
• Mechanisms and triggers of allergy
  • New research targets for allergy treatments
  • Clinical trials underway
Current Standard of Care—IgE-Mediated Cow’s Milk Allergy

• CMA elimination diet

• Monitor growth
  – Weight
  – Length
  – Head circumference
Growth and Food Allergy

Recommended Treatment of CMA

• Breastfed infants
  – May need to consider avoidance of cow’s milk protein from maternal diet
  – May take up to 72 hrs to clear breast milk antigens

• Infants <6 months
  – Formulas extensively hydrolyzed protein or amino acid-based formula

• Infants >6 months
  – Soy formula may be appropriate in IgE-mediated cases
  – Country specific: Not to be used in infants with food allergy <6 months of age

Clinical Recommendations: Suitable Infant Formulas

- Elemental/amino acid
- Extensively hydrolyzed casein
- Extensively hydrolyzed whey
- Soy formula
Hypoallergenic Formulas

• May be used in the absence of breast milk

• AAP/ESPGHAN define **hypoallergenic formula** as immunoreactive protein <1% of total nitrogen containing substance, which translates to the majority of peptides <1.5 kDa

• Tolerated by 90% of patients with CMP allergy

• **Hypoallergenic formula** include both EHF and AAF

AAF, Amino-acid formulas; AAP, American Academy of Pediatrics; CMP, cow’s milk protein; EHF, extensively hydrolyzed formulas; ESPGHAN, European Society for Pediatric Gastroenterology Hepatology and Nutrition.

Amino-Acid & Extensively Hydrolyzed Formulas

**Amino-acid formulas (AAF)**
- Provide protein only in free amino acids and no peptides
- High cost may be limiting factor

**Extensively hydrolyzed formulas (EHF): whey or casein**
- EHF casein first hypoallergenic formulas (>60 year history)
- EHF whey—newer additions to treatment of CMPA; some have lactose added

CMPA, cow's milk protein allergy.

Soy-Protein Formula

- Option for soy-negative (SPT/sIgE) CMPA infants >6 months of age who refuse a hypoallergenic formula
- IgE-mediated infants 2%–14% more likely to tolerate soy formula
- Useful in resource-poor environments
- Some nutritional disadvantages
  - Absorption of minerals and trace elements may be lower because of phytate content
  - Contain appreciable amounts of isoflavone that can lead to high serum concentrations in infants

sIgE, specific IgE.

Which Formula is Right for Your Patient?

- Degree of hydrolysis
- Fat source and content
- Presence or absence of lactose
- Nutritional status of child
- Nutrient profile:
  - Additional iron
  - Varying calcium and vitamin D
  - Contain pro/prebiotics
- Palatability/flavor
- Culture and religion
- Pre/Probiotics
- Cost
### When to use Amino Acid-Based Formula?

<table>
<thead>
<tr>
<th>Publications</th>
<th>Breastfeeding</th>
<th>Severe GI symptoms</th>
<th>Growth Faltering</th>
<th>Multiple Allergies</th>
<th>Atopic Dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hill et al. 1995</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Sicherer et al. 2001</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Kaczmarski et al. 2005</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Isolauri et al. 1995</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>De Boissieu et al. 2002</td>
<td></td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>De Boissieu et al. 1997</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vanderhoof et al. 1997</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lucarelli et al. 2011</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

Allergy Management Strategies

• Introduction of solid food in CMA-baby diet
  – What to do when (re)introducing food in allergic baby
  – Ongoing management includes planned reintroduction of milk protein

• Use of extensively hydrolyzed protein formula + supplement
Management of Cow’s Milk Allergy

- 2012 RCT: Effect of LGG on tolerance acquisition in infants with CMA
- 2017 RCT; n=220
- EHCF+LGG reduces incidence of other allergic manifestations and hastens development of oral tolerance in children with IgE-mediated CMA

Berni-Canani et al. 2012. study shows dietary management with extensively hydrolyzed casein-based formula (eHCF) supplemented with the probiotic Lactobacillus rhamnosus GG (LGG) results in a higher rate of tolerance acquisition in infants with CMA than in those treated with eHCF without supplementation in both IgE (p=0.46) and non-IgE mediated CMA (p=0.006).

Putting both groups (IgE and non-IgE) together: 60% had positive DBPCFC in the non-LGG group and 45% in supplemented group.

DBPCFC, double-blind, placebo-controlled food challenge; EHCF, extensively hydrolyzed casein formula; LGG, Lactobacillus rhamnosus GG.
Interventional Therapies

- Food immunotherapy aims to desensitize patients to the food to which they are allergic
  - May result in a less severe or absence of allergic reaction with accidental ingestion by inducing desensitization

- Desensitization: a reversible state typically induced by short-term exposure to allergen; once administration of allergen is discontinued, the previous level of clinical reactivity returns.

Oral Immunotherapy

- Patients ingest small, but gradually increasing, allergen doses over every 2 weeks for several months until they reach a maintenance dose
  - Doses are given under medical supervision
- Higher risk of systemic reactions compared to epicutaneous immunotherapy
- Risk of eosinophilic esophagitis (EoE)
- FDA-approved with a commercial product (Palforzia) for peanut only

Epicutaneous Immunotherapy

- Single, daily-dose patch
  - Applied to back in children
- First patch applied at study site
- Additional applications at home
- 2-week treatment initiation leading to 24-hour wear time
- No restrictions to daily activities required

EPIT peanut patch is under clinical investigation and has not been approved for marketing within or outside the European Union.
Future Care—Relevant Clinical Trials

**MILES Results:** Support Viaskin Milk 300μg as the Potential First Treatment for CMPA in Children 2-11

**Response Rate (ITT*)**

<table>
<thead>
<tr>
<th>% of Responders (90% CI)</th>
<th>Placebo n = 40</th>
<th>150 μg n = 38</th>
<th>300 μg n = 38</th>
<th>500 μg n = 36</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>32.5%</td>
<td>34.2%</td>
<td><strong>57.9%</strong></td>
<td>38.9%</td>
</tr>
</tbody>
</table>

*Missing data (failure to repeat) considered as non-responders in ITT population
P-values obtained using exact logistic regression
ITT, Intent-to-Treat

**Favorable safety, tolerability and compliance**

- Overall discontinuation rate of 4.5%
  - 1.5% dropout due to AEs
- Most AEs related to application site (mild to moderate)
- No severe anaphylaxis
- No SAEs or epinephrine related to treatment
- Treatment adherence was high
  - Mean patient compliance > 95%

What the Future Holds

- Better understanding of mechanisms and triggers of allergy provide new research targets
- Better understanding of genetic, epigenetic, and environmental risk factors
- Future therapies
  - Milk patch for EoE
  - Milk patch for IgE-mediated food allergy
  - Milk patch for diagnosis
  - Manipulation of the microbiome to develop tolerance
  - Development of milk peptides that can lead to tolerance development

EoE, eosinophilic esophagitis; EPIT, epicutaneous immunotherapy.
Key Takeaways

✓ No approved interventional treatments for CMA, to date
✓ Standard of care is advancing beyond food allergen avoidance and injectable epinephrine for acute allergic reactions
✓ CMA allergy generally has a favorable prognosis
✓ Majority of children will outgrow their food allergy
✓ Food allergy should be managed by individualized avoidance strategy, label reading and involvement of an RDN

Prevalence of Childhood Food Allergy (FA) in the US


Overall Convincing FA Prevalence = 7.6% (7.1%-8.1%)
Overall Physician-diagnosed FA Prevalence = 4.7% (4.3%-5.0%)

<table>
<thead>
<tr>
<th>Food Allergy</th>
<th>Convincing Food Allergy</th>
<th>Physician-diagnosed Food Allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>2.2%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Milk</td>
<td>1.9%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Shellfish</td>
<td>1.3%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Tree nuts</td>
<td>1.2%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Egg</td>
<td>0.9%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Fin Fish</td>
<td>0.6%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Wheat</td>
<td>0.5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Soy</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Sesame</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>
### Food Allergen Prevalence by Age Among Children with FA

<table>
<thead>
<tr>
<th>Age</th>
<th>PEANUT</th>
<th>TREE NUT</th>
<th>MILK</th>
<th>SHELLFISH</th>
<th>EGG</th>
<th>FIN FISH</th>
<th>WHEAT</th>
<th>SOY</th>
<th>SESAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 y</td>
<td>20.2%</td>
<td>9.0%</td>
<td>53.0%</td>
<td>7.1%</td>
<td>13.5%</td>
<td>2.6%</td>
<td>14.9%</td>
<td>15.4%</td>
<td>4.6%</td>
</tr>
<tr>
<td>1 y</td>
<td>24.6%</td>
<td>8.0%</td>
<td>37.8%</td>
<td>5.1%</td>
<td>22.8%</td>
<td>6.4%</td>
<td>6.0%</td>
<td>16.6%</td>
<td>4.9%</td>
</tr>
<tr>
<td>2 y</td>
<td>24.5%</td>
<td>10.9%</td>
<td>43.5%</td>
<td>11.5%</td>
<td>14.1%</td>
<td>6.0%</td>
<td>9.9%</td>
<td>8.6%</td>
<td>2.3%</td>
</tr>
<tr>
<td>3–5 y</td>
<td>25.1%</td>
<td>15.9%</td>
<td>33.6%</td>
<td>13.0%</td>
<td>15.0%</td>
<td>6.2%</td>
<td>6.6%</td>
<td>6.9%</td>
<td>2.7%</td>
</tr>
<tr>
<td>6–10 y</td>
<td>32.8%</td>
<td>17.6%</td>
<td>24.4%</td>
<td>18.4%</td>
<td>10.8%</td>
<td>7.8%</td>
<td>6.4%</td>
<td>6.5%</td>
<td>3.3%</td>
</tr>
<tr>
<td>11–13 y</td>
<td>30.5%</td>
<td>21.3%</td>
<td>14.9%</td>
<td>20.2%</td>
<td>12.8%</td>
<td>7.1%</td>
<td>6.2%</td>
<td>3.6%</td>
<td>1.8%</td>
</tr>
<tr>
<td>≥14 y</td>
<td>29.5%</td>
<td>13.3%</td>
<td>16.0%</td>
<td>21.3%</td>
<td>6.6%</td>
<td>7.9%</td>
<td>5.4%</td>
<td>3.0%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>