Economic Burden of Atopic Dermatitis in High-Risk Infants Receiving Cow's Milk or Partially Hydrolyzed 100% Whey-Based Formula

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Objective To estimate the health and economic impact of feeding partially hydrolyzed formula–whey (PHF-W) instead of standard cow's milk formula (CMF) for the first 4 months of life among US infants at high risk for developing atopic dermatitis (AD).

Study design A Markov model was developed integrating published data, a survey of US pediatricians, costing sources and market data, and expert opinion. Key modeled outcomes included reduction in AD risk, time spent post AD diagnosis, days without AD flare, and AD-related costs. Costs and clinical consequences were discounted at 3% annually.

Results An estimated absolute 14-percentage point reduction in AD risk was calculated with the use of PHF-W compared with CMF (95% CI for difference, 3%-22%). Relative to CMF, PHF-W decreased the time spent post-AD diagnosis by 8.3 months (95% CI, 2.78-13.31) per child and increased days without AD flare by 39 days (95% CI, 13-63) per child. The AD-related, 6-year total cost estimate was $495 less (95% CI, −$813 to −$157) per child with PHF-W ($724 per child; 95% CI, $385-$1269) compared with CMF ($1219 per child; 95% CI, $741-$1824).

Conclusion Utilization of PHF-W in place of CMF as the initial infant formula administered to high-risk US infants not exclusively breastfed during the first 4 months of life may reduce the incidence and economic burden of AD. Broad implementation of this strategy could result in a minimum savings of $355 million per year to society. *(J Pediatr 2015;166:1145-51)*.

Atopic dermatitis (AD) is an increasingly prevalent chronic skin disease which typically presents during infancy.[1] In the US, AD affects 11%-17% of children.[2,3] More than 50% of children with AD will develop asthma and allergies in the first few years of life.[4] Pediatric AD is associated with a considerable resource use, economic, and quality of life burdens.[1,5-7]

Results from the German Infant Nutritional Intervention (GINI) study demonstrated that infants with atopic heredity fed a standard intact protein cow's milk formula (CMF) during the first 4 months of life had a higher incidence of AD up to age 10 years compared with those fed a partially hydrolyzed 100% whey-based formula (partially hydrolyzed formula–whey [PHF-W]) or an extensively hydrolyzed casein formula (extensively hydrolyzed formula–casein [EHF-C]) during the first 4 months of life.[8] These findings, from the largest independent study on this topic to date, have been observed or confirmed in several subsequent studies, including meta-analyses.[9-12] As a result, the use of hydrolyzed formulas is considered a viable AD risk-reduction strategy in high-risk formula-fed infants by US and European organizations.[13-15]

In the US, PHF-W is marketed for routine use in healthy infants from birth, and the cost is about the same as for intact CMFs. In contrast, EHF-C is typically reserved for infants with special nutritional needs and not typically used in healthy infants from birth. EHF-C costs more than routine intact CMFs and may require a physician's prescription under the Special Supplemental Nutrition Program for Women, Infants, and Children.

The use of PHF-W in high-risk infants has been found to be cost-effective and/or cost-saving compared with CMF in several developed countries, including

AD	Atopic dermatitis
ADCS	Atopic dermatitis-controlled state
CMF	Cow's milk formula
EHF-C	Extensively hydrolyzed formula–casein
GINI	German Infant Nutritional Intervention
PHF-W	Partially hydrolyzed formula–whey
PSA	Probabilistic sensitivity analysis
uSA	Univariate deterministic sensitivity analysis

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Germany,[16] Australia,[17] and France.[18] Similar information is lacking for the US, however. In the present study, we used established health economic mathematical modeling techniques[19,20] to estimate the economic impact of feeding US infants at high-risk for developing AD with PHF-W instead of CMF for the first 4 months of life.

Methods

Our analysis was conducted using Markov cohort modeling techniques,[21,22] adopting a US societal perspective to include direct medical (eg, physician visits), direct nonmedical (eg, transportation costs for physician visits), and indirect (eg, productive time lost attending a sick child) costs associated with formula feeding and AD treatment regardless of the party ultimately bearing these costs. Consistent with the GINI study,[23] a 6-year time horizon was adopted to capture the longer-term impact of this early, short-term nutritional intervention. Likewise, the target population (high-risk infants, defined as having at least 1 biologic parent or sibling with an allergic disease history), age at formula initiation, formula feeding duration, and AD incidence were based on the GINI study.[24]

Model Structure

Our model follows for up to age 6 years a simulated cohort of newborns who initiated a 4-month feeding course of PHF-W or CMF (**Figure 1**; available at www.jpeds.com). All formula use was assumed to continue until age 12 months using age- and nutrition requirement–appropriate volumes. Over time, it was assumed that a percentage of children developed AD, based on the GINI study, and as a result were treated by: (1) a change in infant formula only; (2) the addition of pharmacotherapy only with no change in formula; or (3) a change in infant formula and addition of pharmacotherapy. These approaches were selected in accordance with previous models (eg, that of Iskedjian et al),[18] a US survey of 101 pediatricians on the management patterns of AD in infants and toddlers (children aged ≤36 months),[25] and the opinion of 4 clinicians with expertise in treating pediatric AD. Infants who may have responded to a given formula change were assumed to continue on it until age 12 months or their next AD flare. Children who responded to pharmacotherapy were assumed to finish their treatment course and remained on their assigned formula until age 12 months. Thus, from year 1 through year 6, the pharmacotherapy-only treatment approach was used exclusively.

In this model, treatment response rates were assumed to be assessed every 2 weeks and determined the speed at which AD symptoms resolved and children were transitioned to an AD-controlled state (ADCS). Children in the ADCS were at risk for acute dermatitis flares, which were treated with generally treatment algorithms as the initial AD event. Mortality risk unrelated to AD was included as well, to account for lost PHF-W investment in cases of premature death (for simplicity, not shown in **Figure 1**).[26]

Model Inputs

Several model inputs were obtained from a 2011 survey of 101 US pediatricians on the management patterns of AD in infants and toddlers (children aged ≤36 months).[25] The design and key results of that survey are available elsewhere.[25] In brief, a convenience sample of US practicing pediatricians, the majority from the 25 most populous states, was identified. Survey questions assessed physician characteristics, referral patterns, laboratory test use, emollient use, treatment approach (based on age, severity, and symptom location, ie, face or trunk and extremities), recurrence, and hospitalization. Additional questions were aimed at quantifying AD treatment-associated costs. Questions regarding dietary management were defined as formula changes and were limited to infants (age <12 months) not exclusively breastfed. A pharmacologic approach was defined as prescribing or suggesting active medications.

The age-stratified biweekly AD probabilities for CMF (**Table I**; available at www.jpeds.com) were obtained using the linear interpolation of the 1-, 3-, and 6-year cumulative incidence data from the GINI study.[23] The corresponding probabilities for PHF-W were derived on the basis of the cumulative relative risk from the same study, by multiplying the adjusted relative risk by the 6-year cumulative incidence.[23] The case severity distribution (**Table I**) was derived from the US pediatrician survey. The distribution of treatment modalities and their corresponding response rates by age and initial severity of AD presentation, as well as flare risk by age and severity, were obtained from the US pediatrician survey (**Table I**).

Daily formula volume intake was estimated using unpublished data (unpublished data, Nestlé Nutrition, July 3, 2013) from the Feeding Infants and Toddlers Study.[27,28] All infant formula acquisition prices and relative market shares were estimated using Nielsen data (unpublished data, Nestlé Nutrition, June 5, 2013). The cost of the initially assigned formulas were estimated as $16.13/356 g for PHF-W and $16.13/353 g for CMF. Up to 2 treatment formula changes were allowed in the event that AD developed and treatment included a switch from initially assigned formula to a treatment formula. The latter included EHF-C, an amino acid-based formula, a soy-based formula, and, for patients assigned CMF, PHF-W, and vice-versa, in proportions reported in the US pediatrician survey. Treatment formula costs were based on the acquisition prices of each type of formula and their relative usage frequency, as reported in the US pediatrician survey. Only the additional costs incurred as a result of feeding with an alternative infant formula above and beyond the cost of CMF were considered, because infants would be fed with formula until age 12 months when not exclusively breastfed.

Pharmacotherapy regimen utilization was determined using data from the US pediatrician survey, supplemented with clinical expert opinion (**Table II**; available at www.jpeds.com) and corresponding costs were obtained from drug price references,[29] including online retailers (eg, http://www.google.com/shopping) for over-the-counter products.