High-risk infants fed with standard cow's milk formula as a supplement or replacement of breast milk may be exposed to a higher likelihood of developing atopic dermatitis

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Cost-Effectiveness of Partially Hydrolyzed Whey Protein Formula in the Primary Prevention of Atopic Dermatitis in High-Risk Urban Infants in Southeast Asia

by M. Botteman and P. Detzel

Key insights

Proteins found in standard cow's milk formula have been associated with an increased risk of atopic dermatitis, especially in infants with a familial predisposition towards atopy. Compared to standard cow's milk formula, partially or extensively hydrolyzed formulas are alternative protein sources that may reduce the risk of atopic dermatitis and other allergic disorders when used in high-risk infants. This study compared the long-term (i.e. 6 years) economic impact of using a partially hydrolyzed whey-based formula instead of a standard cow's milk formula in the first 17 weeks of life in nonexclusively breastfed infants who are at high risk of developing atopic dermatitis in Malaysia, Singapore, and the Philippines. The analysis was based on the 6-year results of the German Infant Nutritional Intervention (GINI) study, a large randomized clinical trial comparing the risk of atopic dermatitis in following feeding with standard cow's milk formula versus partially hydrolyzed whey-based formula.

Current knowledge

The development of childhood atopic dermatitis is associated with substantial costs, which vary depending on the country and disease severity. The main drivers of total costs are medical treatments, physician visits, and other indirect costs such as parental time lost to attend a child with atopic dermatitis. These costs are likely to be underestimated as they do not include the out-of-pocket expenses incurred by the patients' families, since these are poorly documented.

Practical implications

The use of partially hydrolyzed whey-based formula as a replacement for cow's milk formula in at-risk healthy infants reduces the clinical, economic, and quality of life burden due to

Cost-effectiveness of partially hydrolyzed whey formula (PHF-W) versus standard cow's milk formula (CMF) in infants at risk of developing atopic dermatitis.

atopic dermatitis. The 6-year net savings due to the risk reduction of atopic dermatitis per at-risk infant associated with the use of partially hydrolyzed whey-based formula were USD 237 in the Philippines, USD 372 in Malaysia, and USD 739 in Singapore. The higher initial cost of the formula itself was outweighed by the substantial decrease in costs due to the risk reduction of atopic dermatitis.

Recommended reading

von Berg A, Filipiak-Pittroff B, Kramer U, et al: Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. *J Allergy Clin Immunol* 2013;131:1565–1573.

Cost-Effectiveness of Partially Hydrolyzed Whey Protein Formula in the Primary Prevention of Atopic Dermatitis in High-Risk Urban Infants in Southeast Asia

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Key Messages

- The objective of the present study was to compare the estimates of the economic impact of reducing the incidence of atopic dermatitis (AD) by feeding a partially hydrolyzed whey-based formula instead of a standard cow's milk formula to high-risk nonexclusively breastfed urban infants for the first 17 weeks of life in the Philippines, Malaysia, and Singapore.
- Mathematical models integrating literature, current costs, and expert clinician opinion were used. Modeled outcomes included AD risk reduction, time spent after AD diagnosis, AD symptom-free days, quality-adjusted life years, and costs (direct and indirect).
- Feeding high-risk urban infants partially hydrolyzed formulas instead of standard infant formula resulted in an estimated significant risk reduction of developing AD, a 0.69-year reduction in the time spent after AD diagnosis, and 16- to 38-day reductions of flares, depending on the country.
- The per-child AD-related 6-year cost-saving estimates when feeding high-risk infants with partially hydrolyzed whey-based formula versus cow's milk formula were USD 739 in Singapore, USD 372 in Malaysia, and USD 237 in the Philippines.

Key Words

Cost-effectiveness analysis · Prevention of atopic dermatitis · Partially hydrolyzed whey formula · Southeast Asia

Abstract

Background: Atopic dermatitis (AD) is one of the most common skin conditions among infants. Proteins found in cow's milk formula (CMF) have been found to be attributable to heightened AD risk, particularly in infants with familial AD heredity. Previous studies have suggested that intervention with partially hydrolyzed formula in nonexclusively breastfed infants can have a protective effect against AD development. **Objective:** The aim of the present study was to compare the estimates of the economic impact of reducing the AD incidence by feeding a partially hydrolyzed whey-based formula (PHF-W) instead of a standard CMF to high-risk nonexclusively breastfed urban infants for the first 17 weeks of life in the Philippines, Malaysia, and Singapore. **Methods:** In each country, a mathematical model simulated AD incidence and burden from birth to 6 years of age of using PHF-W versus CMF in the target population using data from the German Infant Nutritional Intervention study. The models integrated literature, current cost and market data, and expert clinician opinion. Modeled outcomes included AD risk reduction, time spent after AD diagnosis, AD symptom-free

days, quality-adjusted life years (QALYs), and costs (direct and indirect). Outcomes were discounted at 3% per year. Costs were expressed in USD. **Results:** Feeding high-risk infants PHF-W instead of CMF resulted in an estimated absolute 14% (95% CI 1–24) AD risk reduction, a 0.69-year (95% CI 0.25–1.13) reduction in the time spent after AD diagnosis per child, reductions of 16–38 AD days, and gains in 0.02–0.04 QALYs, depending on the country. The per-child AD-related 6-year cost-saving estimates of feeding high-risk infants with PHF-W versus CMF were USD 739 in Singapore, USD 372 in Malaysia, and USD 237 in the Philippines.

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Introduction

Atopic dermatitis (AD) is a common inflammatory skin disorder affecting infants and young children [1, 2]. In Singapore, approximately 10–20% of children aged 6–7 years have atopic eczema [3–5]; secular trends suggest that this prevalence may be increasing [6]. AD is characterized by a chronic component which can lead to lifelong skin symptoms [7]. As such, AD imposes a substantial economic and quality of life (QOL) burden on patients, families, and societies [8–11]. Estimates of the annual direct cost of AD in Asia are limited but have ranged from USD 199 in Thailand [12] to USD 1,253 in South Korea [13].

A child's risk of developing AD is affected by a combination of immunologic, environmental, and genetic factors [3, 14, 15]. In particular, if one parent has allergies, a child's risk doubles; if both parents have allergies, the risk increases four-fold [15]. In Singapore, at least one first-degree family member with atopy was noted in 70% of children with AD [3]. Additionally, studies from various countries report that approximately one third of children with AD had a diagnosis of allergy or intolerance to cow's milk and, conversely, up to 50% of infants with allergy or intolerance to cow's milk had AD [16, 17]. Although the World Health Organization (WHO) recommends exclusive breastfeeding through the first 6 months of life [18, 19], this recommendation is not always followed. In such instances, high-risk infants fed with standard cow's milk formula (CMF) as a supplement or replacement for breast milk may be exposed to a higher likelihood of developing AD.

Partially or extensively hydrolyzed formulas are two alternative protein sources that have been shown to reduce the risk of AD and other allergies compared to CMF in these high-risk infants [20–24]. In particular, the German Infant Nutritional Intervention (GINI), the largest comparative trial of infant formula in high-risk infants, found that nonexclusively breastfed infants with atopic heredity randomized to a partially hydrolyzed whey-based formula (PHF-W) versus CMF for the first 4 months of life experienced a lower cumulative incidence of AD 6 years following birth (27.4 vs. 39.1%; adjusted RR = 0.64; 95% CI 0.48–0.86) [23]. On the basis of such data, several national and international allergy organizations have suggested hydrolyzed formulas as an allergy risk reduction strategy for these high-risk infants [18, 25, 26].

As demonstrated in previous studies, the potentially higher costs of PHF-W relative to CMF during the 17-week interventional period should be partially offset by direct and indirect cost savings and QOL improvements associated with AD incidence reduction in this high-risk population [27–31].

The present study aggregated the modeling results of three national health-economic studies (the Philippines [31], Singapore [32], and Malaysia [33]). Using health-economic modeling techniques that combine data from the GINI study [23], expert opinions, and local cost data, these studies estimated the clinical and economic impact of PHF-W intervention for the first 17 weeks of life compared to CMF among high-risk urban infants in three Southeast Asian countries. A more detailed description of the methodology can be found in the publication on the Philippines [31].

Model Structure

Overview

Mathematical modeling (i.e. Markov cohort techniques, which are an extension of life table analysis) [34] was used to compare costs and outcomes associated with AD development over time among high-risk urban infants with first-degree atopic heredity partially or completely fed with PHF-W versus CMF in early infancy (from birth to week 17). Cohorts were followed from birth to 6 years of age. The target population, risk reduction, formula feeding and duration, and age-specific AD incidence were selected on the basis of the GINI study [23, 35].

The analysis adopted a societal perspective and included direct and indirect costs associated with formula and AD treatment. The

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Table 1. Epidemiologic inputs and clinical assumptions

	Malaysia		Philippines		Singapore	
	<1 year of age	>1 year of age	<1 year of age	>1 year of age	<1 year of age	>1 year of age
Distribution of cases, %						
Mild AD	43.3	50.0	60.0	85.0	57.5	80.0
Moderate AD	36.7	28.3	25.0	10.0	37.5	16.5
Severe AD	20.0	21.7	15.0	5.0	5.0	3.5
Mild AD management, %						
Switch formula	3.3	0.0	5.0	0.0	0.0	0.0
Combined	26.7	0.0	25.0	0.0	5.0	0.0
Medical	70.0	100.0	70.0	100.0	95.0	100.0
Moderate AD management, %						
Switch formula	3.3	0.0	0.0	0.0	0.0	0.0
Combined	35.0	0.0	80.0	0.0	20.0	0.0
Medical	61.7	100.0	20.0	100.0	80.0	100.0
Severe AD management, %						
Switch formula	1.7	0.0	0.0	0.0	0.0	0.0
Combined	45.0	0.0	90.0	0.0	20.0	0.0
Medical	53.3	100.0	10.0	100.0	80.0	100.0
Response rates, %						
All severities: formula switch	7.0	n.a.	5.0	n.a.	n.a.	n.a.
Mild AD, first-line PT	85.0	83.0	98.0	98.0	84.7	83.0
Moderate AD, first-line PT	67.0	67.0	65.0	75.0	66.7	63.3
Severe AD, first-line PT	53.0	52.0	30.0	50.0	55.0	48.3
Response rates, %						
To second-line PT (all AD severity)	68.0	68.0	90.0	90.0	73.0	73.0
To third-line PT (all AD severity)	83.0	83.0	95.0	95.0	80.0	80.0
To fourth-line PT (all AD severity)	n.a.	n.a.	13.0	13.0	n.a.	n.a.
To combination treatment (all AD severity)	77.0	n.a.	93.0	n.a.	70.0	n.a.
12-week probability of flare-ups, %						
Mild AD	40.0	40.0	30.0	10.0	11.7	11.0
Moderate AD	50.5	53.0	50.0	30.0	36.7	35.0
Severe AD	58.0	60.0	70.0	50.0	60.0	63.3

PT = Pharmacotherapy; n.a. = not applicable.

primary outcomes for each treatment arm included the proportion of patients developing AD, the number of days without AD symptoms, the time spent after AD diagnosis, quality-adjusted life years (QALYs), and overall costs.

Similar to previously published models [27–31], three treatment approaches were possible after initial AD development, as confirmed by pediatricians with AD treatment experience in these three countries. Depending on the country of analysis, AD patients could go through a series of dietary modifications (i.e. up to two formula types) and up to three different pharmacological treatments. Three country-specific mathematical models were developed to reflect the specificities of each country in AD management.

Model Parameters

Epidemiologic inputs and clinical assumptions are provided in table 1. Probability of AD and flares were stratified by severity (i.e. mild, moderate, and severe) and age (i.e. 0–1 year; >1–6 years). Based on the data from GINI, it was estimated that the 1-, 3-, and 6-year proportions of children initially fed with CMF who developed AD were 16.8, 33.5, and 39.1%, respectively. The corresponding figures for children initially fed PHF-W were 9.1, 19.4, and 25.0%, respectively.

Daily formula intake was age adjusted for nutrient needs from birth to 12 months by means of a previously reported method [31] that accounted for partial breastfeeding. Formula acquisition costs were based on market share in the three countries and end-consumer formula prices. The analysis took into account the addi-

Fig. 1. Annualized direct medical and other costs of AD by severity and country.

tional incremental costs that would be incurred as a result of feeding with alternative infant formula (such as PHF-W, soy-based formula, and extensively hydrolyzed formula).

Three groups of experts (3–4 per country) provided information on the type and amount of resources used with each treatment modality based on severity of AD, including the number of inpatient and outpatient visits (general practitioners or specialists) required for the management of AD by severity and therapy. For example, in Singapore, upon AD development, 50% of children saw a general practitioner and 36% saw a specialist. The number of general practitioner visits per child after initial AD development and for each flare was 0.20 for mild cases, 1.00 for moderate cases, and 0.70 for severe cases. The corresponding number of specialist visits was 0.38, 1.45, and 3.17 per child for mild, moderate, and severe cases, respectively.

Inpatient stays were assumed to occur once upon initial AD development in 2–24% of cases, depending on severity at presentation, age, and country. Specific IgE and skin prick tests were assumed to be performed in all children upon initial AD development.

Costs of inpatient/outpatient visits and diagnostic tests were based on average fees charged in the hospitals or laboratories of the three countries where information was available.

Emollients and/or moisturizer creams were assumed to be used by nearly all AD patients. Medicine acquisition costs were obtained from an online drug information tool commonly used in these countries. Reduced productivity (i.e. indirect costs) included lost work days to care for children with AD following the initial physician visit.

Based on previously published data, young children who did not have AD were assumed to experience a utility of 1.000, while those in controlled AD state after an episode had a utility of 0.980; thus, it is recognized that mild, subclinical episodes could permanently reduce QOL [36, 37]. The utilities associated with mild, moderate, and severe AD episodes were 0.863, 0.690, and 0.450, respectively.

Fig. 2. Components of direct costs for AD in different countries.

Outcome Measures and Analyses

Using the data on AD incidence, flares, and episode duration, it was possible to estimate the per-child 6-year AD risk and the expected number of days with AD symptoms. Several incremental cost-effectiveness ratios (ICERs) were computed to estimate the relative economic value of PHF-W versus CMF, including the incremental cost per AD case avoided, incremental cost per AD-free day gained, and incremental cost per QALY gained.

In addition to the base case analysis, various sensitivity analyses were carried out to evaluate the robustness of the results. First, deterministic univariate sensitivity analyses were conducted on individual model parameters while keeping the base case values for other parameters in the model unchanged. Scenario analyses were conducted to test the impact of changing key model assumptions either alone or in combination. These included omitting any flares from the analysis and restricting the analysis to 1 year (as opposed to the 6-year time frame). Finally, multivariate, probabilistic sensitivity analyses were used.

All results were reported after applying a discount rate of 3% to all costs and effects beyond year 1. All costs reported in the study represent 2013 values, expressed in USD.

Results

Cost of the Treatment of AD

Figure 1 provides an overview of the annualized direct medical and other (indirect and nonmedical) costs by country and severity level. The overall costs for the treatment of a severe AD case (USD 2,538) are highest in Singapore, roughly twice that in the Philippines and Malaysia. These differences do not reflect the per capita wealth differences of these countries due to the focus on high-

Table 2. Results

	PHF-W arm (95% CI)	CMF arm (95% CI)	Difference (95% CI)
<i>Clinical effects</i>			
Proportion of children developing AD, %	25 (13–47)	39 (23–59)	–14 (–24 to –1)
Years of life after AD diagnosis	1.00 (0.57–1.69)	1.69 (1.03–2.43)	–0.69 (–1.13 to –0.25)
<i>Days with AD symptoms</i>			
Malaysia	55 (32–111)	93 (58–169)	–38 (–2 to –94)
Philippines	28 (19–33)	50 (33–59)	–22 (–14 to –26)
Singapore	23 (11–37)	39 (21–54)	–16 (–25 to –5)
<i>Discounted QALYs</i>			
Malaysia	5.52 (5.44–5.55)	5.48 (5.37–5.53)	0.04 (0.02–0.08)
Philippines	5.46 (5.40–5.49)	5.43 (5.33–5.48)	0.03 (0.01–0.07)
Singapore	5.54 (5.29–5.81)	5.52 (5.26–5.80)	0.02 (0.01–0.08)
<i>Cost effects</i>			
Total costs in Malaysia, USD	556 (290–960)	909 (537–1,354)	–352 (–596 to –100)
Total costs in the Philippines, USD	369 (182–492)	606 (373–741)	–237 (–323 to –94)
Total costs in Singapore, USD	1,316 (681–2,302)	2,055 (1,183–3,124)	–739 (–1,341 to –142)

risk urban infants. Whereas the costs in Singapore reflect the average costs per infant in that country, the treatment costs in the two other countries are representative only of the infants in the most affluent households.

The components of direct medical costs are generally consistent across countries, with pharmacological and physician's visits accounting for the majority of costs (fig. 2). The relative homogeneity of the direct medical cost splits across countries is likely the consequence of consistent national treatment guidelines across the region but also linked to the recurrent nature of the disease and the rather symptomatic nature of AD treatment. Furthermore, traditional treatments were not taken into account. A study in South Korea showed that these costs were higher than direct medical costs [13].

The cost-effectiveness of reducing AD risk is driven by treatment costs but also by the efficacy and incremental costs of the nutritional intervention; partially hydrolyzed formulas are more expensive than intact protein formulas (i.e. CMF). The effectiveness of the intervention in terms of risk reduction (clinical effects) reflects the outcomes of the GINI study, whereas cost-effectiveness also takes specific treatment costs into account.

CMF was associated with a higher AD incidence (+14%) compared to PHF-W (CMF vs. PHF-W: 39 vs. 25%; 95% CI for the difference 1–24; table 2), while PHF-W was associated with less AD days (ranging from –16 to –38 days, depending on country) and fewer years (–0.69 years) in a post-AD diagnosis state (CMF vs. PHF-W:

Fig. 3. Costs per at-risk infant per country per formula type.

1.69 vs. 1.00 years; 95% CI for the difference 0.25–1.13). Discounted QALYs were higher with PHF-W than with CMF, for a net difference varying from 0.02 to 0.04 QALYs, depending on country (table 2).

Primary drivers of total costs were associated with pharmacological treatments followed by indirect costs and physician visits. The resulting 6-year net savings due to risk reduction of AD per high-risk infant with PHF-W were USD –237 (95% CI –323 to –96) in the Philippines, USD –372 (95% CI –547 to –190) in Malay-

sia, and USD −739 (95% CI −1,341 to −142) in Singapore (table 2).

The comparison of PHF-W versus CMF using ICER values showed PHF-W to be a net cost saving strategy in all three countries and also resulted in reduction of AD cases and gains in AD-free days and QALYs. The higher formula costs for PHF-W in these countries were offset by reductions in AD-related costs.

Thus, PHF-W was the ‘dominant’ strategy (i.e. more effective and less expensive) relative to CMF in all three countries (fig. 3). Probabilistic statistical analysis also indicated that PHF-W was dominant in almost all 5,000 model runs in all three countries.

In univariate sensitivity analysis, the relative risk of cumulative AD incidence for PHF-W and CMF, and the probability of AD with CMF, had the largest influence on the difference in cost between PHF-W and CMF. Other variables with potentially minor effects on net cost savings were the costs of PHF-W, CMF, and emollients.

PHF-W as a replacement for CMF in healthy infants at risk was not only cost effective but cost saving compared to standard formula.

Discussion

In the review of these three different cost-effectiveness studies, early nutritional intervention with PHF-W as a replacement for CMF in healthy infants at risk was not only cost effective but cost saving compared to standard formula. It improves the QOL of infants by reducing the risk of developing AD and also leads to significant savings from a societal perspective.

Based on the present model, the development of AD in childhood is associated with significant costs, which vary across countries and by severity.

These costs are likely underestimated as they do not fully account for many of the out-of-pocket expenses and indirect costs incurred by families with children with AD, as these are poorly documented or measured and the expert panels could only provide limited information on some of these expenses. Another difficulty of using health-economic models developed in high-income countries is based on the assumption that all members of the society have equal access to universal health-care services. Health-care access is highly heterogeneous across South-east Asia and dependent on household disposable income.

Conclusion

The present analysis compared the results of three cost-effectiveness studies using modeling techniques to assess the long-term cost-effectiveness of preventing AD via early nutritional intervention with PHF-W versus CMF in healthy infants with atopic heredity who are not exclusively breastfed. The analysis was conducted from a societal perspective, focusing on the urban population. The results suggest that across the region, the use of PHF-W in the defined patient population may be a dominant strategy relative to the use of CMF as it reduces the clinical and QOL burden of AD while decreasing overall costs, even after the inclusion of formula costs. While the analysis was conducted on the basis of limited evidence, various sensitivity and scenario analyses show that these conclusions may be robust. Nevertheless, additional research regarding the epidemiology, severity, treatment patterns, and resource use associated with the prevention and treatment of AD in these three countries are warranted.

Disclosure Statement

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