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ORIGINAL RESEARCH



## Expert panel on practice patterns in the management of cow's milk protein allergy and associated economic burden of disease on health service in Turkey

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### ABSTRACT

**Aims:** To evaluate practice patterns in the management of cow's milk protein allergy (CMPA) and associated economic burden of disease on health service in Turkey.

**Materials and methods:** This study was based on experts' views on the practice patterns in management of CMPA manifesting with either proctocolitis or eczema symptoms and, thereby, aimed to estimate economic burden of CMPA. Practice patterns were determined via patient flow charts developed by experts using the modified Delphi method for CMPA presented with proctocolitis and eczema. Per patient total 2-year direct medical costs were calculated, including cost items of physician visits, laboratory tests, and treatment.

**Results:** According to the consensus opinion of experts, 2-year total direct medical cost from a payer perspective and societal perspective was calculated to be \$US2,116.05 and \$US2,435.84, respectively, in an infant with CMPA presenting with proctocolitis symptoms, and \$US4,001.65 and \$US4,828.90, respectively, in an infant with CMPA presenting with eczema symptoms. Clinical nutrition was the primary cost driver that accounted for 89–92% of 2-year total direct medical costs, while the highest total direct medical cost estimated from a payer perspective and societal perspective was noted for the management of an exclusively formula-fed infant presenting either with proctocolitis (\$US3,743.85 and \$US4,025.63, respectively) or eczema (\$US6,854.10 and \$US7,917.30, respectively). The first line use of amino acid based formula (AAF) was associated with total direct cost increment \$US1,848.08 and \$US3,444.52 in the case of proctocolitis and eczema, respectively.

**Limitations:** Certain limitations to this study should be considered. First, being focused only on direct costs, the lack of data on indirect costs or intangible costs of illness seems to be a major limitation of the present study, which likely results in a downward bias in the estimates of the economic cost of CMPA. Second, given the limited number of studies concerning epidemiology and practice patterns in CMPA in Turkey, use of expert clinical opinion of the panel members rather than real-life data on practice patterns that were used to identify direct medical costs might raise a concern with the validity and reliability of the data. Also, while this was a three-step study with six experts included in the first stage (developing local guidelines for diagnosis, treatment, and follow-up of infants with CMPA in Turkey) and 410 pediatricians included in the second stage (a cross-sectional questionnaire-survey to determine pediatricians' awareness and practice of CMPA in infants and children), only four members were included in the present Delphi panel, which allows a limited discussion. Third, lack of sensitivity analyses and exclusion of indirect costs and costs related to alterations in quality of life, behavior of infants, and general well-being of infants and their parents from the cost-analysis seems to be another limitation that may have caused under-estimation of relative cost-effectiveness of the formulae. Fourth, calculation of costs per local guidelines rather than real-life practice patterns is another limitation that, otherwise, would extend the knowledge achieved in the current study. Notwithstanding these limitations, the present expert panel provided practice patterns in the management of CMPA and an estimate of the associated costs, depending on the symptom profile at initial admission for the first time in Turkey.

**Conclusions:** In conclusion, in providing the first health economic data on CMPA in Turkey, the findings revealed that CMPA imposes a substantial burden on the Turkish healthcare system from both a payer perspective and societal perspective, and indicated clinical nutrition as a primary cost driver. Management of infants presenting with eczema, exclusively formula-fed infants, and first line use of AAF were associated with higher estimates for 2-year direct medical costs.

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### KEYWORDS

Cow's milk protein allergy; practice patterns; proctocolitis; eczema; cost-analysis; expert panel; Turkey

## Introduction

Cow's milk protein allergy (CMPA) is a clinically abnormal immune reaction to cow's milk protein (CMP)<sup>1</sup>. CMPA presents with food protein-induced proctocolitis, food protein-induced enterocolitis, enteropathy and eosinophilic disorders, atopy with or without atopic eczema, and allergic rhinitis and/or asthma, depending on the type of (i.e. immediate, delayed, or mixed) immune reaction<sup>2,3</sup>.

Diagnosis is based on detailed history taking and medical examination, followed by an elimination diet, and is confirmed by a standardized oral challenge test or double blind placebo controlled food challenge (DBPCFC) after documentation of significant improvement on the diagnostic elimination, which leads to a definitive diagnosis as well as symptomatic treatment plan<sup>2,4,5</sup>. An appropriate diagnostic approach is crucial to minimize the risk for both over- and under-diagnosis, and to enable the introduction of an appropriate diet and, thus, maintenance of normal growth and development<sup>5,6</sup>.

Awareness of CMPA, alongside appropriate diagnosis and management, is important, given that CMPA poses a considerable burden on patients and their families, and a substantial economic burden on the health service<sup>7,8</sup>.

Although evidence-based guidelines and consensus reports on the diagnosis and management of CMPA are available<sup>1,3,5,7,9–11</sup>, there is a need for region-specific recommendations considering local experiences and challenges for the prevention, diagnosis, and treatment of CMPA in Turkey<sup>4</sup>.

Accordingly, a three-step intervention study was designed, aiming to (a) develop local guidelines for diagnosis, treatment, and follow-up of infants with CMPA in Turkey, (b) determine pediatricians' awareness and practice of CMPA in infants and children, and (c) determine expert panel-based practice patterns and related costs in management of CMPA in Turkey. Data on the first two steps are presented elsewhere<sup>4</sup>. This expert panel study was designed to identify daily practice patterns for the management of CMPA presenting either with proctocolitis or eczema symptoms and, thereby, to estimate the 2-year direct medical cost for the management of infants with CMPA from a payer perspective and societal perspective for the first time in Turkey.

## Methods

### Design

This expert panel study was aimed at identifying practice patterns in daily clinical practice and estimating 2-year total healthcare costs associated with the management of CMPA from public and societal perspectives in Turkey. Practice patterns in the diagnosis, treatment, and follow-up of CMPA in Turkey were determined based on consensus opinion of the expert panel selected from pediatric gastroenterology and pediatric allergy/immunology specialists with experience on CMPA management. Patient flow charts were developed by experts using a modified Delphi method<sup>12</sup> for two separate clinical presentations of a 2-month old pediatric patient with CMPA including proctocolitis and eczema, with respect to

diagnosis, treatment, and follow-up of patients consistent with the current management algorithms applied in their daily clinical practice. Cost-analysis was performed with respect to the price of formula [average price, lowest price, and first-line amino acid based formula (AAF) prescription] and type of clinical nutrition (exclusively breast-fed, non-exclusively breast-fed, exclusively formula-fed) separately in cases presenting with proctocolitis or eczema.

### Expert panel

A total of four experts from tertiary centers located in Ankara and Istanbul provinces were selected based on their clinical practice and scientific background. All experts were informed about the study via e-mail by the sponsor and then participated in the three consecutive meetings conducted between March 2015 and December 2015 for (a) developing local guidelines for diagnosis, treatment, and follow-up of infants with CMPA in Turkey, (b) reviewing findings from a cross-sectional questionnaire-survey conducted among 410 pediatricians in Turkey on pediatricians' awareness and practice of CMPA in infants and children, and (c) determining a practice patterns algorithm for the management of CMPA, based on data collected from guideline development and physician survey stages of the study.

Accordingly, the present study included an analysis of economic burden of CMPA in Turkey, based on third expert panel meeting results on practice patterns algorithms for the management of an infant with CMPA presenting with proctocolitis or eczema.

### Cost analysis

Per patient total 2-year direct medical costs were calculated based on cost items including physician visits (primary care, secondary care, tertiary care), laboratory tests (routine hemogram, blood biochemistry, serum, and stool immunology), and treatment (with respect to formula and clinical nutrition type), both from a payer perspective (only direct medical costs using prices of the imbursement authority "Social Security Institution (SSI)" in Turkey) and a societal perspective (only direct medical costs using resale prices). For drugs, retail prices from the updated price list and updated institution discount list of SSI for May 2016 were taken into account in calculation of the unit costs. Costs related to nutritional and other non-pharmacological treatments and tests were calculated considering the Health Implementation Notification by SSI, while nutritional treatment costs were calculated as weighted for weekly energy requirement and infant distribution percentage. Physician/dietician visit costs were calculated using unit prices, also based on the same SSI notification. The time horizon of analysis was 2 years. Monetary results were converted by using the 2.97 \$US/TL May 2016 exchange rate.

Total direct medical costs were also calculated based on recommended clinical nutrition scenarios without being weighted for ongoing treatment percentage, while direct non-medical costs of different origin (e.g. transfers of patient

and caregivers for examinations and/or hospitalization, home care, etc.) and indirect costs were not included in the cost analysis.

### Statistical analysis

Descriptive statistics were used to summarize results on practice patterns for the CMPA management. Expenses related to diagnosis, treatment, and follow-up of CMPA were the main cost-analysis related parameters of the study. The cost model was based on the following equation:

$$\text{Cost} = \sum (\text{Frequency; \%}) \times (\text{Unit price; TL}) \times (\text{patient ratio; \%}).$$

## Results

### Physician visits cost item

According to expert panel consensus on practice pattern algorithms and unit costs, the 2-year cost of physician visits item was calculated to be \$US165.58 in an infant presenting with proctocolitis, and to be \$US157.44 in an infant presenting with proctocolitis, both from payer and societal perspectives (Table 1).

### Laboratory tests cost item

According to expert panel consensus on practice pattern algorithms and unit costs, the 2-year cost of laboratory tests

item was calculated to be \$US17.24 (from a payer perspective) and \$US32.32 (from a societal perspective) in an infant presenting with proctocolitis, while it was \$US103.43 and \$US105.59, respectively, in an infant presenting with eczema (Table 2).

### Direct medical costs with respect to formula prices

Unit cost of formulae (cost per kcal) calculated based on average formula prices, as weighted for weekly energy requirement and infant distribution percentage, were \$US0.010/kcal and \$US0.011/kcal for extensively hydrolyzed formula (eHF), while they were \$US0.016/kcal and \$US0.021/kcal for aminoacid based formula (AAF) from payer and societal perspectives, respectively (Table 3).

In an infant with CMPA presenting with proctocolitis, 2-year total direct medical costs from payer and societal perspectives were \$US2,116.05 (treatment items costed \$US1,933.23) and \$US2,435.84 (treatment item costed \$US2,237.94), respectively, based on average formula prices, whereas they were \$US3,302.72 (treatment items costed \$US3,119.90) and \$US4,283.92 (treatment item costed \$US4,086.02), respectively, based on first line use of AAF. As compared with average formula prices, first line use of AAF was associated with incremental total direct medical costs of \$US1,186.67 and \$US1,848.08 from payer and societal perspectives, respectively (Table 4).

In an infant with CMPA presenting with eczema, 2-year total direct medical costs from payer and societal

**Table 1.** Cost of physician visits recommended by expert panel in the management of an infant with CMPA presenting with proctocolitis or eczema.

| Physician visits                                      | Visit count <sup>a</sup> |                  | Unit cost (USD) | 2-year cost (USD) <sup>a</sup> |        |                    |        |
|-------------------------------------------------------|--------------------------|------------------|-----------------|--------------------------------|--------|--------------------|--------|
|                                                       | Proctocolitis            | Eczema           |                 | Payer perspective              |        | Social perspective |        |
|                                                       |                          |                  |                 | Proctocolitis                  | Eczema | Proctocolitis      | Eczema |
| Primary care (Family physician, general practitioner) | 1.0                      | 1.0              | 6.73            | 6.73                           | 6.73   | 6.73               | 6.73   |
| Secondary care (General pediatrician)                 | 1.0                      | 2.0              | 8.02            | 8.02                           | 16.04  | 8.02               | 16.04  |
| Tertiary care (Pediatric gastroenterologist)          | 10.7 <sup>b</sup>        | 0.0              | 13.46           | 144.07                         | 0.00   | 144.07             | 0.00   |
| Tertiary care (Pediatric allergists)                  | 0.5                      | 8.0 <sup>b</sup> | 13.46           | 6.73                           | 107.72 | 6.73               | 107.72 |
| Dietitian                                             | 0.0                      | 2.0              | 6.73            | 0.00                           | 13.47  | 0.00               | 13.47  |
| Total physician visit cost (USD)                      |                          |                  |                 | 165.58                         | 157.44 | 165.58             | 157.44 |

<sup>a</sup>Weighted for the percentage of infants subjected for tolerance test and additional follow-up.

<sup>b</sup>Tolerance test and additional follow-up for those failed to develop tolerance in 12 months.

**Table 2.** Cost of laboratory tests recommended by expert panel in the management of an infant with CMPA presenting with proctocolitis or eczema.

| Laboratory tests                  | Procedure count <sup>a</sup> |        | Unit cost (USD) | 2-year cost (USD) <sup>a</sup> |        |                    |        |
|-----------------------------------|------------------------------|--------|-----------------|--------------------------------|--------|--------------------|--------|
|                                   | Proctocolitis                | Eczema |                 | Payer perspective              |        | Social perspective |        |
|                                   |                              |        |                 | Proctocolitis                  | Eczema | Proctocolitis      | Eczema |
| Serum alkaline phosphatase        | 1.0                          | 2.0    | 0.37            | 0.00                           | 0.00   | 0.37               | 0.74   |
| Serum phosphorus                  | 0.5                          | 3.0    | 20.20           | 0.00                           | 0.00   | 0.34               | 0.67   |
| Serum calcium                     | 1.0                          | 2.0    | 0.34            | 0.00                           | 0.00   | 0.37               | 0.74   |
| Skin tests                        | 1.0                          | 2.0    | 0.37            | 10.10                          | 60.61  | 10.10              | 60.61  |
| Serum specific IgE                | 0.5                          | 3.0    | 14.28           | 7.14                           | 42.83  | 7.14               | 42.83  |
| Complete blood count              | 2.0                          | NA     | 1.01            | 0.00                           | NA     | 2.02               | NA     |
| Stool culture                     | 1.0                          | NA     | 1.01            | 0.00                           | NA     | 1.01               | NA     |
| Stool pH                          | 2.0                          | NA     | 0.44            | 0.00                           | NA     | 0.88               | NA     |
| Stool microscopy                  | 3.0                          | NA     | 1.72            | 0.00                           | NA     | 5.15               | NA     |
| Fecal occult blood test           | 3.0                          | NA     | 1.18            | 0.00                           | NA     | 3.54               | NA     |
| Fecal reducing substances test    | 2.0                          | NA     | 0.34            | 0.00                           | NA     | 0.67               | NA     |
| Fecal fat test                    | 1.0                          | NA     | 0.74            | 0.00                           | NA     | 0.74               | NA     |
| Total laboratory tests cost (USD) |                              |        |                 | 17.24                          | 103.43 | 32.32              | 105.59 |

IgE, immunoglobulin E; NA, not applicable.

<sup>a</sup>Weighted for the percentage of infants subjected to the procedure.

**Table 3.** Unit cost (per kcal) of formulae used for calculation of clinical nutrition cost item.

| Total kcal per package               |       | Payer perspective |                       | Societal perspective |                       |
|--------------------------------------|-------|-------------------|-----------------------|----------------------|-----------------------|
|                                      |       | Price (\$US)      | Cost per kcal (\$US)* | Price (\$US)         | Cost per kcal (\$US)* |
| Extensively hydrolyzed formula (eHF) |       |                   |                       |                      |                       |
| Similac Alimentum                    | 2,100 | 23.62             | 0.011                 | 26.54                | 0.013                 |
| Bebelac Pepti Junior                 | 2,259 | 19.84             | 0.009                 | 22.29                | 0.010                 |
| Lowest price                         |       |                   | 0.009                 |                      | 0.010                 |
| Average price                        |       |                   | 0.010                 |                      | 0.011                 |
| Aminoacid based formula (AAF)        |       |                   |                       |                      |                       |
| Aptamil pregomin AS                  | 2,000 | 35.11             | 0.018                 | 50.16                | 0.025                 |
| Neocate                              | 1,932 | 29.4              | 0.015                 | 33.37                | 0.017                 |
| Lowest price                         |       |                   | 0.015                 |                      | 0.017                 |
| Average price                        |       |                   | 0.016                 |                      | 0.021                 |

\*Cost per kcal values are rounded to three decimals.

**Table 4.** The 2-year total direct medical costs related to management of an infant with CMPA presenting with proctocolitis with respect to formula prices

|                               | Cost-payer perspective (\$US) |                     |          | Cost-societal perspective (\$US) |                     |          |
|-------------------------------|-------------------------------|---------------------|----------|----------------------------------|---------------------|----------|
|                               | Year-1                        | Year-2 <sup>a</sup> | Total    | Year-1                           | Year-2 <sup>a</sup> | Total    |
| Physician visits              | 161.54                        | 4.04                | 165.58   | 161.54                           | 4.04                | 165.58   |
| Laboratory tests              | 17.24                         | 0.00                | 17.24    | 32.32                            | 0.00                | 32.32    |
| <b>Treatments</b>             |                               |                     |          |                                  |                     |          |
| Average formula prices        | 1,348.04                      | 585.19              | 1,933.23 | 1,572.45                         | 665.49              | 2,237.94 |
| Lowest formula prices         | 1,184.11                      | 514.97              | 1,699.07 | 1,382.72                         | 581.29              | 1,964.01 |
| First line use of AAF         | 2,183.63                      | 936.27              | 3,119.90 | 2,873.77                         | 1,212.26            | 4,086.02 |
| <b>Total</b>                  |                               |                     |          |                                  |                     |          |
| Average formula prices        | 1,526.82                      | 589.23              | 2,116.05 | 1,766.31                         | 669.53              | 2,435.84 |
| Lowest formula prices         | 1,362.89                      | 519.01              | 1,881.89 | 1,576.58                         | 585.33              | 2,161.91 |
| First line use of AAF         | 2,362.41                      | 940.31              | 3,302.72 | 3,067.63                         | 1,216.30            | 4,283.92 |
| Incremental cost <sup>b</sup> | 835.59                        | 351.08              | 1,186.67 | 1,301.32                         | 546.77              | 1,848.08 |

Costs are weighted for the percentage of infants who are exclusively breast-fed or breast-fed and formula combination, or exclusively formula fed.

<sup>a</sup>After the 12 month control visit, symptoms were considered to persist in 15% of infants.

<sup>b</sup>Incremental cost: difference between first line use of AAF and average formula prices.

perspectives were \$US4,001.65 (treatment items costed \$US3,698.20) and \$US4,828.90 (treatment item costed \$US4,291.51), respectively, based on average formula prices, whereas they were \$US6,213.41 (treatment items costed \$US5,909.96) and \$US8,273.42 (treatment item costed \$US7,736.03), respectively, based on first line use of AAF. As compared with average formula prices, first line use of AAF was associated with incremental total direct medical costs of \$US2,211.76 and \$US3,444.52 from payer and societal perspectives, respectively (Table 5).

### Direct medical costs with respect to clinical nutrition recommendations

In an infant with CMPA presenting with proctocolitis, 2-year total direct medical costs from payer and societal perspectives were \$US501.68 (treatment item costed \$US318.87) and \$US707.82 (treatment item costed \$US509.92), respectively, in an exclusively breast-fed infant, \$US1,963.33 (treatment item costed \$US1,780.52) and \$US2,289.31 (treatment item costed \$US2,091.41), respectively, in a non-exclusively breast-fed infant, and \$US3,743.85 (treatment item costed \$US3,561.04) and \$US4,025.63 (treatment item costed \$US3,827.73), respectively, in an exclusively formula-fed infant (Table 6).

In an infant with CMPA presenting with eczema, 2-year total direct medical costs from payer and societal perspectives were \$US588.82 (treatment item costed \$US284.77) and \$US1,009.26 (treatment item costed \$US471.87), respectively,

in an exclusively breast-fed infant, \$US3,355.54 (treatment item costed \$US3,052.09) and \$US4,139.07 (treatment item costed \$US3,601.68), respectively, in a non-exclusively breast-fed infant, and \$US6,854.10 (treatment item costed \$US6,550.65) and \$US7,917.31 (treatment item costed \$US7,379.92), respectively, in an exclusively formula-fed infant. The contribution of non-nutritional treatments including mometasone furoate, moisturizing cream, and baby cleansing products to total direct cost was \$US42.58 and \$US274.36 from payers and societal perspectives, respectively (Table 7).

### Discussion

Being the first health economic study on CMPA in Turkey, our findings revealed the considerable economic burden of CMPA in an infant presenting with proctocolitis (\$US2,116.05 from a payer perspective and \$US2,435.84 from a societal perspective) or eczema (\$US4,001.65 from a payer perspective and \$4,828.90 from a societal perspective), based on average formula prices in Turkey. Management of CMPA in an infant presenting with eczema as compared with proctocolitis was associated with higher 2-year total direct medical costs in terms of average formula prices and nutritional treatment recommendations.

Our findings revealed a high economic burden of CMPA on health economics in Turkey. This seems to be in agreement with data from past studies which indicated an

**Table 5.** The 2-year total direct medical costs related to management of an infant with CMPA presenting with eczema with respect to formula prices.

|                               | Cost-payer perspective (\$US) |                     |          | Cost-societal perspective (\$US) |                     |          |
|-------------------------------|-------------------------------|---------------------|----------|----------------------------------|---------------------|----------|
|                               | Year-1                        | Year-2 <sup>a</sup> | Total    | Year-1                           | Year-2 <sup>a</sup> | Total    |
| Physician visits              | 117.04                        | 40.40               | 157.44   | 117.04                           | 40.40               | 157.44   |
| Laboratory tests              | 36.94                         | 66.49               | 103.43   | 37.71                            | 67.88               | 105.59   |
| Treatments                    |                               |                     |          |                                  |                     |          |
| Average formula prices        | 1,348.04                      | 2,350.16            | 3,698.20 | 1,572.45                         | 2,719.06            | 4,291.51 |
| Lowest formula prices         | 1,186.59                      | 2,084.26            | 3,270.85 | 1,391.00                         | 2,420.23            | 3,811.23 |
| First line use of AAF         | 2,183.63                      | 3,726.33            | 5,909.96 | 2,873.77                         | 4,862.27            | 7,736.03 |
| Others <sup>b</sup>           | 23.65                         | 18.92               | 42.58    | 152.42                           | 121.94              | 274.36   |
| Total                         |                               |                     |          |                                  |                     |          |
| Average formula prices        | 1,525.67                      | 2,475.97            | 4,001.65 | 1,879.62                         | 2,949.28            | 4,828.90 |
| Lowest formula prices         | 1,364.22                      | 2,210.07            | 3,574.30 | 1,698.17                         | 2,650.45            | 4,348.62 |
| First line use of AAF         | 2,361.26                      | 3,852.14            | 6,213.41 | 3,180.94                         | 5,092.49            | 8,273.42 |
| Incremental cost <sup>c</sup> | 835.59                        | 1,376.17            | 2,211.76 | 1,301.32                         | 2,143.21            | 3,444.52 |

Costs are weighted for the percentage of infants who are exclusively breast-fed, non-exclusively breast-fed, or exclusively formula fed.

<sup>a</sup>After the 12 month control visit, symptoms were considered to persist in 80% of infants.

<sup>b</sup>Other treatments included mometasone furoate, moisturizing cream, and baby cleansing products.

<sup>c</sup>Incremental cost: difference between first line use of AAF and average formula prices.

**Table 6.** The 2-year total direct medical costs related to management of an infant with CMPA presenting with proctocolitis with respect to expert panel clinical nutrition recommendations.

|                            | Cost-payer perspective (\$US) |                     |          | Cost-societal perspective (\$US) |                     |          |
|----------------------------|-------------------------------|---------------------|----------|----------------------------------|---------------------|----------|
|                            | Year-1                        | Year-2 <sup>a</sup> | Total    | Year-1                           | Year-2 <sup>a</sup> | Total    |
| Physician visits           | 161.54                        | 4.04                | 165.58   | 161.54                           | 4.04                | 165.58   |
| Laboratory tests           | 17.24                         | 0.00                | 17.24    | 32.32                            | 0.00                | 32.32    |
| Treatments                 |                               |                     |          |                                  |                     |          |
| Exclusively breast-fed     | 0.00                          | 318.87              | 318.87   | 66.03                            | 443.89              | 509.92   |
| Non-exclusively breast-fed | 1,416.87                      | 363.65              | 1,780.52 | 1,664.79                         | 426.62              | 2,091.41 |
| Exclusively formula-fed    | 2,833.74                      | 727.30              | 3,561.04 | 3,003.66                         | 824.07              | 3,827.73 |
| Total                      |                               |                     |          |                                  |                     |          |
| Exclusively breast-fed     | 178.77                        | 322.91              | 501.68   | 259.89                           | 447.93              | 707.82   |
| Non-exclusively breast-fed | 1,595.64                      | 367.69              | 1,963.33 | 1,858.65                         | 430.66              | 2,289.31 |
| Exclusively formula-fed    | 3,012.52                      | 731.34              | 3,743.85 | 3,197.52                         | 828.11              | 4,025.63 |

Calculated based on recommended clinical nutrition without being weighted for ongoing treatment percentage.

<sup>a</sup>After the 12 month control visit, symptoms were considered to persist in 15% of infants.

**Table 7.** The 2-year total direct medical costs related to management of an infant with CMPA presenting with eczema with respect to expert panel clinical nutrition recommendations.

|                            | Cost-payer perspective (\$US) |                     |          | Cost-societal perspective (\$US) |                     |          |
|----------------------------|-------------------------------|---------------------|----------|----------------------------------|---------------------|----------|
|                            | Year-1                        | Year-2 <sup>a</sup> | Total    | Year-1                           | Year-2 <sup>a</sup> | Total    |
| Physician visits           | 117.04                        | 40.40               | 157.44   | 117.04                           | 40.40               | 157.44   |
| Laboratory tests           | 36.94                         | 66.49               | 103.43   | 37.71                            | 67.88               | 105.59   |
| Treatments                 |                               |                     |          |                                  |                     |          |
| Exclusively breast-fed     | 0.00                          | 284.77              | 284.77   | 66.03                            | 405.84              | 471.87   |
| Non-exclusively breast-fed | 1,264.37                      | 1,787.72            | 3,052.09 | 1,494.60                         | 2,107.08            | 3,601.68 |
| Exclusively formula-fed    | 2,528.74                      | 4,021.91            | 6,550.65 | 2,857.15                         | 4,522.76            | 7,379.92 |
| Others <sup>b</sup>        | 23.65                         | 18.92               | 42.58    | 152.42                           | 121.94              | 274.36   |
| Total                      |                               |                     |          |                                  |                     |          |
| Exclusively breast-fed     | 177.63                        | 410.58              | 588.22   | 373.20                           | 636.06              | 1,009.26 |
| Non-exclusively breast-fed | 1,442.00                      | 1,913.53            | 3,355.54 | 1,801.77                         | 2,337.30            | 4,139.07 |
| Exclusively formula-fed    | 2,706.37                      | 4,147.72            | 6,854.10 | 3,164.32                         | 4,752.98            | 7,917.31 |

Calculated based on recommended clinical nutrition without being weighted for ongoing treatment percentage.

<sup>a</sup>After the 12 month control visit, symptoms were considered to persist in 80% of infants.

<sup>b</sup>Other treatments included mometasone furoate, moisturizing cream, and baby cleansing products.

association of CMPA with an estimated 12-monthly health-care cost of €11.28 million in The Netherlands<sup>13</sup>, 6-monthly cost of AU\$6.5 million in Australia<sup>14</sup>, 12-monthly cost of €202.0 (private sector) and €89.0 (public sector) in South Africa<sup>15</sup>, 12-monthly cost of £1,853 and £3,161 per patient in the eHF and AAF groups, respectively, in the UK<sup>16</sup>, and 12-monthly cost of £1,381 per patient and annual cost of

£25.6 million in the Health Improvement Network (THIN) Database<sup>17</sup>.

Clinical nutrition preparations were the primary cost driver in our study that accounted for 89.0–92.0% of total 2-year direct medical costs, based on average formula prices. Likewise, clinical nutrition preparations were reported to account for 91% of the total 12-monthly cost in

The Netherlands<sup>13</sup>, 62% of the total 6-monthly cost in the Australian database<sup>14</sup>, and 37% and 54% of total 12-monthly cost of managing patients with CMPA in the eHF and AAF groups, respectively in the UK<sup>16</sup>.

Managing an exclusively formula-fed infant presenting either with proctocolitis (\$US3,743.85 from a payer perspective and \$US4,025.63 from a societal perspective) or eczema (\$US6,854.10 and \$US7,917.31, respectively) was associated with the highest estimates of direct medical costs in our analysis.

Besides, when compared to average formula prices, use of AAF as a first-line treatment was associated with cost increments of \$US1,186.67 (56.0%) from a paper perspective and \$US1,848.08 (76.0%) from a societal perspective in proctocolitis, and cost increments of \$US2,211.76 (55.0%) from a payer perspective and \$US3,444.52 (71.0%) from a societal perspective in eczema groups. This seems consistent with past studies from Brazil, Spain, Italy, the UK, and the US, which indicated initial dietary management with an eHF instead of an AAF to afford more cost-effective use of healthcare resources in the management of CMPA<sup>16,18–21</sup>.

The total incremental 12-monthly health service cost of starting treatment with an AAF instead of an eHF was estimated to be £1,308 in the UK<sup>16</sup>, while authors considered starting treatment with an eHF as the cost-effective strategy, given the similar clinical outcomes between two groups<sup>16</sup>. Additionally, the cost-effectiveness of an eHF relative to an AAF was reported to be very sensitive to the time to symptom resolution and the acquisition cost of the formulae, while it was less sensitive to the number of GP visits, outpatient visits, and hospital admissions<sup>16</sup>. Similarly, expected costs of managing CMPA in The Netherlands were reported to be most sensitive to the acquisition costs of eHF and AAF, whereas they were insensitive to changes in the number of physician visits<sup>13</sup>.

However, sensitivity analysis in the Australian CMPA database revealed a similar 6-monthly cost (AU\$7.1 million) of prescribing first-line eHF or AAF, along with a reduced likelihood of follow-up visits to pediatric immunologists/allergists and pediatric gastroenterologists among infants prescribed with first-line AAF than eHF due to the lower probability of a need for switching diet in the former group<sup>14</sup>.

Cost-analysis for the physician visits item in the present study was based on expert consensus estimated visit numbers required up to (three visits for proctocolitis, two visits for eczema) and after consulting with a pediatric gastroenterologist or pediatric allergists/immunologists (11 visits for proctocolitis, six visits for eczema). This seems notable, given that analysis of the THIN database revealed a higher number of follow-up visits with a mean 14.0 general pediatrician visits (once in every 3 weeks) for CMA after the diagnosis and identified physician visits as the major cost driver (44%) followed by clinical nutrition (38%)<sup>17</sup>.

Notably, 60% of all infants were initially treated with soy, 18% with an eHF, and 3% with an AAF in the THIN CMPA database<sup>17</sup>, while the acquisition costs of the clinical nutrition preparations as well as soy intolerance were indicated to have an impact on expected costs in a study from South Africa, in which the primary cost driver in the

management of CMPA was also reported to be physician visits<sup>15</sup>.

Hence, identification of clinical nutrition as the primary cost driver in our study might also be associated with the fact that soy is not considered amongst the recommended options for clinical nutrition for infants aged <6-months with CMPA in Turkey<sup>4</sup>.

The second-step of our study (presented elsewhere) was based on a questionnaire-survey conducted among 410 pediatricians in Turkey, and revealed that practice patterns in the management of exclusively breast-fed infants with CMPA were in accordance with the European Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines<sup>5</sup>. Overall, 95.4% of physicians considered CMPA to be able to develop in an exclusively breast-fed infant, and 79.4% identified continuation of breast feeding via elimination of CMP containing products from the maternal diet to be the treatment of choice in this group. AAF was the most commonly selected formula by pediatricians for infants presenting with anaphylaxis (58.8%), enterocolitis (40.7%), or multiple food allergies (52.0%), and in at-risk infants with no chance of exclusive breastfeeding (40.2%). However, inappropriate practice patterns were noted among physicians considering the first-line treatment among non-exclusively breast-fed infants with use of AAF (45.8%) rather than eHF (23.2%). This seems notable, given the recommendation of eHF in this group<sup>5,7,22,23</sup>, due to its lower cost and higher efficacy in inducing tolerance than AAF<sup>16,24</sup>. Notably, pediatric gastroenterologists had more appropriate practice patterns in CMPA with respect to evidence-based therapeutic formula selection when compared to pediatric allergists/immunologists who had a higher tendency to prescribe AAF as a first-line treatment, possibly due to the higher likelihood of encountering cases with anaphylaxis than proctocolitis in their clinical practice.

It should also be noted that first line AAF was prescribed only in 20% of all newly-diagnosed infants with CMA aged <6 months, while the other 80% started treatment with an eHF in the THIN database<sup>16</sup>. Also, acquisition of eHF was reported to be the primary cost driver accounting for 72% of the total cost (ranged from €8.68–€14.21 million), while acquisition of AAF accounted for 19% of the total cost (ranged from €9.50–€19.84 million) in The Netherlands<sup>13</sup>.

Conversely, AAF regimens comprise ~80% of the current formula market in Turkey, based largely on their safety, particularly in cases presenting with eczema, despite the fact that they should be reserved for those infants with eHF intolerance or failure or severe symptoms<sup>16</sup>. Given the cost increments associated with first-line use of AAF, the tendency for over-prescribing AAF among Turkish physicians seems to contribute to a high economic burden of disease on health economics, as well as higher direct medical costs associated with managing an infant presenting with eczema rather than proctocolitis symptoms. This emphasizes that practice patterns in use of formula-based therapy of infants with CPMA in clinical practice in Turkey should be improved in terms of compatibility with therapeutic indications specified for each formula.

Our findings are in agreement with data from other countries in terms of identification of clinical nutrition preparations as the key cost driver<sup>13,14,16</sup>, as well as cost-effectiveness of using eHF rather than AAF as a first-line treatment<sup>16,18–21</sup>. Nonetheless, it should be noted that, given the considerable heterogeneity in experiences from different countries regarding practice patterns in the management of CMPA including responsible clinicians, referral patterns, diagnostic and therapeutic strategies, comparison of findings between countries has been considered to be difficult<sup>17</sup>.

Certain limitations to this study should be considered. First, being focused only on direct costs, lack of data on indirect costs (loss of productivity due to the illness), or intangible costs of illness (costs of suffering for the patient and his/her family) seems to be the major limitation of the present study, which likely results in a downward bias in our estimates of the economic cost of CMPA. Second, given the limited number of studies concerning epidemiology and practice patterns in CMPA in Turkey, use of expert clinical opinion of the panel members rather than real-life data to obtain practice patterns that were used to identify direct medical costs might raise a concern with the validity and reliability of the data. Also, while this was a three-step study with six experts included in the first stage (developing local guidelines for diagnosis, treatment, and follow-up of infants with CMPA in Turkey) and 410 pediatricians included in the second stage (a cross-sectional questionnaire-survey to determine pediatricians' awareness and practice of CMPA in infants and children), only four members were included in the present Delphi panel, which allows a limited discussion. Third, lack of sensitivity analyses and exclusion of indirect costs and costs related to alterations in quality-of-life, behavior of infants, and general well-being of infants and their parents from the cost-analysis seems to be another limitation which may have caused under-estimation of the relative cost-effectiveness of the formulae. Fourth, calculation of costs per local guidelines rather than real-life practice patterns is another limitation which otherwise would extend the knowledge achieved in the current study. Notwithstanding these limitations, the present expert panel provided practice patterns in the management of CMPA and an estimate of the associated costs, depending on the symptom profile at initial admission, for the first time in Turkey.

## Conclusions

In conclusion, providing the first health economic data on CMPA in Turkey via expert consensus on practice patterns in management of CMPA, our findings revealed that CMPA imposes a substantial burden on the Turkish healthcare system from both a payer perspective and a societal perspective. Clinical nutrition was the primary cost driver; while remarkably higher costs were noted in the case of managing an exclusively formula-fed infant, as well as managing an infant presenting with eczema rather than proctocolitis symptoms. Along with a tendency for prescribing AAF rather than eHF as a first-line treatment in infants with CMPA

among pediatricians, use of AAF as a first-line treatment was associated with a remarkable increase in the total cost.

## Transparency

### Declaration of funding

This study was supported by Abbott Nutrition Turkey. Abbott Nutrition Turkey did not have any role in the study design, data collection, analysis, and interpretation of data, or in the writing of the article and the decision to submit it for publication.

### Declaration of financial/other relationships

OS is an Abbott employee. BES declares that he has no conflict of interest.

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## References

1. Boyce JA, Assa'ad A, Burks AW, et al. NIAID-sponsored expert panel guidelines for the diagnosis and management of food allergy in the United States: Summary of the NIAID-sponsored expert panel report. *J Allergy Clin Immunol* 2010;126:1105-18
2. Dupont C. Diagnosis of cow's milk allergy in children: determining the gold standard? *Expert Rev Clin Immunol* 2014;10:257-67
3. Fiocchi A, Brozek J, Schünemann H, et al. World Allergy Organization (WAO) diagnosis and rationale for action against cow's milk allergy (DRACMA) guidelines. *World Allergy Organ J* 2010;3:57-161
4. Kansu A, Yüce A, Dalgıç B, et al. Consensus statement on diagnosis, treatment and follow-up of cow's milk protein allergy among infants and children in Turkey. *Turk J Pediatr* 2016;58:1-11
5. Koletzko S, Niggemann B, Arato A, et al.; European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. *J Pediatr Gastroenterol Nutr* 2012;55:221-9
6. Eggesbo M, Botten G, Halvorsen R, et al. The prevalence of CMA/CMPI in young children: the validity of parentally perceived reactions in a population-based study. *Allergy* 2001;56:393-402
7. Vandenplas Y, Abuabat A, Al-Hammadi S, et al. Middle East consensus statement on the prevention, diagnosis, and management of cow's milk protein allergy. *Pediatr Gastroenterol Hepatol Nutr* 2014;17:61-73
8. Mazigh S, Yahiaoui S, Ben Rabeh R, et al. Diagnosis and management of cow's protein milk allergy in infant. *Tunis Med* 2015;93:205-11
9. Greer FR, Sicherer SH, Burks AW, American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008;121:183-91

10. Kemp AS, Hill DJ, Allen KJ, et al. Guidelines for the use of infant formulae to treat cow's milk protein allergy: an Australian consensus panel opinion. *Med J Aust* 2008;188:109-12
11. Allen KJ, Davidson GP, Day AS, et al. Management of cow's milk protein allergy in infants and young children: an expert panel perspective. *J Paediatr Child Health* 2009; 45:481-6
12. Okoli C, Pawlowski SD. The Delphi method as a research tool: an example, design considerations and applications. *Inf Manage* 2004;42:15-29
13. Sladkevicius E, Guest JF. Budget impact of managing cow milk allergy in the Netherlands. *J Med Econ* 2010;13:273-83
14. Guest JF, Nagy E. Modelling the resource implications and budget impact of managing cow milk allergy in Australia. *Curr Med Res Opin* 2009;25:339-49
15. Sladkevicius E, Guest JF. Modelling the health economic impact of managing cow milk allergy in South Africa. *J Med Econ* 2010;13:257-72
16. Taylor RR, Sladkevicius E, Panca M, et al. Cost-effectiveness of using an extensively hydrolysed formula compared to an amino acid formula as first-line treatment for cow milk allergy in the UK. *Pediatr Allergy Immunol* 2012;23:240
17. Sladkevicius E, Nagy E, Lack G, et al. Resource implications and budget impact of managing cow milk allergy in the UK. *J Med Econ* 2010;13:119-28
18. Guest JF, Panca M, Ovcinnikova O, et al. Relative cost-effectiveness of an extensively hydrolyzed casein formula containing the probiotic *Lactobacillus rhamnosus* GG in managing infants with cow's milk allergy in Italy. *Clinicoecon Outcomes Res* 2015;7:325-36
19. Guest JF, Weidlich D, Mascuñan Díaz JI, et al. Relative cost-effectiveness of using an extensively hydrolysed casein formula containing the probiotic *Lactobacillus rhamnosus* GG in managing infants with cow's milk allergy in Spain. *Clinicoecon Outcomes Res* 2015;7:583-91
20. Ovcinnikova O, Panca M, Guest JF. Cost-effectiveness of using an extensively hydrolyzed casein formula plus the probiotic *Lactobacillus rhamnosus* GG compared to an extensively hydrolyzed formula alone or an amino acid formula as first-line dietary-management for cow's milk allergy in the US. *Clinicoecon Outcomes Res* 2015;7:145-52
21. Guest JF, Yang AC, Oba J, et al. Relative cost-effectiveness of using an extensively hydrolyzed casein formula in managing infants with cow's milk allergy in Brazil. *Clinicoecon Outcomes Res* 2016;8:629-39
22. Vandenplas Y, De Greef E, Devreker T. Treatment of cow's milk protein allergy. *Pediatr Gastroenterol Hepatol Nutr* 2014;17:1-5
23. Isolauri E, Sutas Y, Mäkinen-Kiljunen S, et al. Efficacy and safety of hydrolyzed cow milk and amino acid-derived formulae in infants with cow milk allergy. *J Pediatr* 1995;127:550-7
24. Berni Canani R, Nocerino R, Terrin G, et al. Formula selection for management of children with cow's milk allergy influences the rate of acquisition of tolerance: a prospective multicenter study. *J Pediatr* 2013;163:771-7