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ORIGINAL RESEARCH

# Efficacy of OM-85 in Children with Recurrent Respiratory Tract Infections: Relationship with Allergic and Immunological Features

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**ABSTRACT**

OM-85 is an immunomodulatory agent used for the prevention of recurrent respiratory tract infections (RTIs) in children; however, the influence of allergic and immunological characteristics on treatment response remains unclear. This study evaluated changes in infection frequency before and after OM-85 treatment and examined whether treatment response was associated with allergic status or immunological characteristics. This single-center, retrospective cohort study included 114 children treated with OM-85 for recurrent RTIs. Annual upper (URTI) and lower (LRTI) respiratory tract infection episodes before and after treatment were compared. Treatment responses were analyzed according to atopic status, inhalant allergen sensitization, and immunoglobulin status (normal, transient hypogammaglobulinemia, and partial IgA deficiency). Independent predictors of post-treatment infection burden were assessed using multivariable linear (ANCOVA) and negative binomial regression analyses. The median age was 56.5 months; 46.5% of patients were atopic, 28.1% had partial IgA deficiency, and 8.8% had transient hypogammaglobulinemia. Following OM-85 treatment, median annual URTI episodes decreased from 8 to 5 (40.6%; $p<0.001$; $r=0.78$), and LRTI episodes from 1 to 0 (63.2%; $p<0.001$; r=0.54). The proportion of children with frequent URTIs (≥6/year) declined from 84.2% to 33.3%, and those with at least one LRTI episode from 60.5% to 32.5%. The reduction was significant in both atopic and non-atopic patients and in subgroups with normal or low immunoglobulin levels. In multivariable analysis, the only independent predictor of post-treatment burden was baseline infection burden. OM-85 treatment was associated with a reduction in both upper and lower respiratory tract infection frequency independently of allergic status and serum immunoglobulin level, with baseline infection burden being the factor most strongly associated with post-treatment infection burden. The greatest clinical benefit is expected in children with frequent infections, and this group may constitute a priority target population for this preventive strategy.

**Keywords: OM-85. Recurrent Respiratory Tract Infection. Atopy. Immunoglobulin.**

**Tekrarlayan Solunum Yolu Enfeksiyonu Olan Çocuklarda OM-85 Etkinliğinin Alerjik ve İmmünolojik Özelliklerle İlişkisi**

**ÖZET**

OM-85, çocuklarda tekrarlayan solunum yolu enfeksiyonlarının önlenmesinde kullanılan bir immünomodülatördür; ancak alerjik ve immünolojik özelliklerin tedavi yanıtı üzerindeki etkisi halen tam olarak açıklığa kavuşmamıştır. Bu çalışmada OM-85 tedavisi başlanan çocuklarda tedavi öncesi ve sonrası enfeksiyon sıklığını ve bunun alerjik durum ile immünolojik özelliklerle ilişkisini değerlendirmeyi amaçladık. Bu tek merkezli, retrospektif kohort çalışmasına tekrarlayan solunum yolu enfeksiyonu (SYE) nedeniyle OM-85 başlanan 114 çocuk alındı. Tedavi öncesi ve sonrası yıllık üst (ÜSYE) ve alt (ASYE) solunum yolu enfeksiyon atakları karşılaştırıldı. Atopik/non-atopik, inhalan duyarlı/duyarsız ve immünglobulin düzeyi durumu (normal, transient hipogamaglobulinemi, parsiyel IgA eksikliği) incelendi. Tedavi sonrası enfeksiyon yükünün bağımsız belirleyicileri çok değişkenli doğrusal (ANCOVA) ve negatif binomiyal regresyonla değerlendirildi. Ortanca yaş 56,5 aydı; olguların %46,5'i atopik, %28,1'i parsiyel IgA eksikliği ve %8,8'i transient hipogamaglobulinemi grubundaydı. OM-85 sonrası yıllık ÜSYE atağı ortanca 8'den 5'e (%40,6; p<0,001; r=0,78), ASYE 1'den 0'a (%63,2; p<0,001; r=0,54) geriledi. Sık ÜSYE (≥6/yıl) oranı %84,2'den %33,3'e, herhangi bir ASYE atağı oranı %60,5'ten %32,5'e düştü. Azalma; hem atopik hem non-atopik hastalarda ve normal ya da düşük immünglobulin düzeyine sahip alt gruplarda anlamlıydı. Çok değişkenli analizde tedavi sonrası enfeksiyon yükünün tek bağımsız belirleyicisi bazal enfeksiyon yüküydü. OM-85 tedavisi, alerjik durum ve serum immünglobulin düzeyinden bağımsız olarak hem üst hem alt solunum yolu enfeksiyon sıklığında azalma ile ilişkiliydi; tedavi sonrası enfeksiyon yüküyle en güçlü ilişkili faktör bazal enfeksiyon yüküydü. En fazla klinik yarar sık enfeksiyon geçiren çocuklarda beklenmekte olup bu grup, söz konusu koruyucu strateji için öncelikli hedef popülasyonu oluşturabilir.

**Anahtar Kelimeler: OM-85. Tekrarlayan Solunum Yolu Enfeksiyonu. Atopi. İmmünglobulin.**

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Recurrent respiratory tract infections (RTIs) are among the most common infectious conditions in early childhood and are associated with substantial morbidity, increased healthcare utilization, and a significant economic burden[1,2]. In addition, these infection outbreaks lead to frequent antibiotic use, hospitalizations, and significant school absenteeism in children[2,3]. Recurrent RTIs are estimated to occur in approximately 6–25% of children under six years of age.[4-6]. In addition, viral respiratory tract infections experienced in early childhood are considered a significant trigger for the development of wheezing and asthma[7]. These findings demonstrate that RTIs are not merely a clinical picture limited to recurrent infections, but also a significant risk marker for long-term respiratory morbidity.

Commonly accepted criteria for recurrent respiratory tract infections are six or more respiratory tract infections per year, at least one upper respiratory tract infection (URTI) per month during the September–April period, or more than three lower respiratory tract infections (LRTIs) per year[4]. Although most children with recurrent RTIs do not have a serious underlying immunodeficiency, a significant proportion may have mild humoral deficiencies. The most common humoral disorders of childhood, transient hypogammaglobulinemia, selective or partial IgA deficiency, and IgG subclass deficiency, typically manifest as recurrent bacterial upper and lower respiratory tract infections[8]. A large series from Türkiye reported that the most frequent reasons for presentation in children with transient and unclassifiable hypogammaglobulinemia were upper and lower respiratory tract infections and asthma[9]. Therefore, immunological evaluation of children with recurrent RTIs is important for identifying underlying humoral defects that can guide treatment[10].

The relationship between atopy and early-life microbial exposure has been debated for many years within the framework of the hygiene hypothesis. It has been suggested that early microbial exposure may be protective not only against infections but also against allergic diseases, and that bacterial lysates may influence the onset and persistence of wheezing[11,12]. The association between respiratory microbiome dysbiosis and asthma pathogenesis, the protective effect of farm environment and early exposure to diverse microbes, and the potential of oral/sublingual bacterial lysate administration to reduce lung inflammation have been reported[13]. One approach to reducing this burden is the use of non-specific bacterial immunomodulators. OM-85 is a lyophilized oral bacterial lysate obtained from 21 strains of eight common respiratory pathogens. Experimental and clinical studies show that OM-85 stimulates innate immunity via Toll-like receptors, activates mucosal dendritic cells, regulates Th1/Th2 balance, and produces both antiviral and immunomodulatory effects through 'trained immunity'[11]. De Benedetto and Sevieri schematized the five-stage immune response process of OM-85, from ingestion to antibody production in the respiratory mucosa, highlighting that oral lysate initiates immune cell activation in gastrointestinal Peyer's patches, followed by migration of mucosal immune cells to the respiratory tract, where secretory IgA production increases[14].

In children initiated with OM-85 due to recurrent infections, the distribution of atopic/allergic status and immunological characteristics, and how the effect of OM-85 on infection burden varies according to these characteristics, have not been sufficiently defined. This study aimed to determine the frequency of infections and clinical and laboratory characteristics before and after treatment in children initiated on OM-85, and to evaluate their relationships with allergic/atopic status and immunological characteristics.

## Materials and Methods

This single-center, retrospective cohort study included 114 children who were initiated on OM-85 for recurrent respiratory tract infections between 2024 and 2025 at the Pediatric Immunology and Allergy Clinic of University of Health Sciences, Bursa Faculty of Medicine, Bursa City Hospital. The electronic medical records of all eligible patients were retrospectively reviewed.

Recurrent respiratory tract infection was defined by de Martino et al. criteria as: ≥6 URTIs per year, or ≥1 URTI per month during the September–April period, or ≥3 LRTIs per year[4]. Patients with known primary immunodeficiency, cystic fibrosis, chronic lung disease, congenital heart disease, or chromosomal/congenital anomalies, as well as those whose records were unavailable, were excluded from the study. Demographic characteristics and treatment regimen were obtained from medical records and parental reports. Infection burden was evaluated using the annual number of URTI and LRTI (recurrent bronchiolitis/bronchitis and pneumonia) episodes before and after OM-85 treatment, as well as antibiotic use for respiratory tract infections, history of infection-related hospitalization, and recurrent tonsillitis.

Allergies were defined as atopic (inhalant allergen sensitivity, food allergy, and physician-diagnosed allergic diseases (atopic dermatitis, allergic rhinitis, asthma)) and non-atopic groups according to skin prick test results and specific IgE panel results (≥0.35 IU/mL positivity threshold). Cases were grouped into atopic-non-atopic and inhalant sensitive-insensitive categories in the analysis.

Laboratory evaluations included complete blood count, serum total IgE, immunoglobulin levels (IgG,

IgA, and IgM), and lymphocyte subset analysis. Based on age-specific reference ranges for serum immunoglobulin levels, patients were classified into three groups: normal immunoglobulin levels, transient hypogammaglobulinemia, and partial IgA deficiency. Partial IgA deficiency was defined as serum IgA levels below 2 SD for age; transient hypogammaglobulinemia was defined as conditions in which serum IgG and/or IgA levels were temporarily low for age and expected to normalize during follow-up.[9] In addition, environmental and perinatal history variables (daycare attendance, smoking exposure, mode of delivery, prematurity, duration of breastfeeding) were recorded.

OM-85 was administered according to the recommended standard regimen: 3.5 mg orally once daily for children <12 years and 7 mg once daily for those ≥12 years, during the first 10 consecutive days of each month for three consecutive months, with 20-day treatment-free intervals between courses[15].

*Statistical Analysis*

Statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 23.0; IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed with the Shapiro-Wilk test. Non-normally distributed continuous variables were summarized as median (interquartile range, IQR), and categorical variables as counts and percentages. Pre- and post-treatment comparisons were performed using the Wilcoxon signed-rank test, and changes in proportions using the McNemar test; effect sizes were calculated as $r = Z/\sqrt{N}$. Two independent groups were compared using the Mann-Whitney U test, categorical variables using the chi-square or Fisher's exact test, and more than two groups using the Kruskal-Wallis test. Correlations were evaluated with the Spearman correlation coefficient. To identify independent predictors of post-treatment infection burden, multivariable linear regression (ANCOVA) was performed including the baseline infection count and potential confounders, and the findings were confirmed with negative binomial regression appropriate for count data. Perinatal and environmental variables (mode of delivery, prematurity, consanguinity, breastfeeding duration, daycare attendance, and smoking exposure) were recorded for descriptive purposes only and were not entered as predictors into the multivariable models to avoid overfitting. A two-sided $p<0.05$ was considered statistically significant.

## Results

A total of 114 children were included in the study, comprising 64 (56.1%) boys and 50 (43.9%) girls. The median age was 56.5 months (IQR, 41.0–75.5 months). Overall, atopy was identified in 53 patients (46.5%), inhalant allergen sensitization in 43 (37.7%), and food allergy in 22 (19.3%). Among the diagnosed allergic diseases, allergic rhinitis was the most common (22.8%, n = 26), followed by atopic dermatitis (10.5%, n = 12) and asthma (9.6%, n = 11). According to immunological classification, 72 patients (63.2%) had normal immunoglobulin levels, 32 (28.1%) had partial IgA deficiency, and 10 (8.8%) had transient hypogammaglobulinemia. The most common accompanying clinical features were adenoid hypertrophy (54/101, 53.5%), recurrent tonsillitis (36/93, 38.7%), antibiotic use during respiratory tract infections (77/92, 83.7%), and infection requiring hospitalization (35/96, 36.5%). Before treatment, the median annual number of URTI episodes was 8.0 (IQR, 6–10), whereas the median annual number of LRTI episodes was 1.0 (IQR, 0–3). The median number of school days missed due to infections was 3.0 (IQR, 0–7). Regarding environmental and perinatal characteristics, household tobacco smoke exposure was reported in 43.1% of patients, daycare/school attendance in 61.4%, cesarean delivery in 72.5%, a history of prematurity in 12.1%, and parental consanguinity in 9.8%. Demographic characteristics and laboratory findings are presented in Table I.

*The effect of OM-85 treatment on infection frequency.* Compared with baseline, the frequency of both upper and lower respiratory tract infections decreased significantly following OM-85 treatment. The median annual number of URTI episodes decreased from 8 to 5 (mean reduction, 40.6%; Wilcoxon test, $p < 0.001$; $r = 0.78$), while the median annual number of LRTI episodes decreased from 1 to 0 (mean reduction, 63.2%; $p < 0.001$; $r = 0.54$). The proportion of patients with frequent URTIs (≥6 episodes/year; $n = 96$) declined from 84.2% (96/114) to 33.3% (38/114), whereas the proportion of patients with at least one LRTI episode ($n = 69$) decreased from 60.5% (69/114) to 32.5% (37/114) ($p < 0.001$ for both) (Table II, Figure 1).

*Treatment efficacy according to allergic status.* The beneficial effect of OM-85 was consistent regardless of allergic status. Significant reductions in both URTI and LRTI episodes were observed in all subgroups, including atopic and non-atopic patients as well as those with and without inhalant allergen sensitization (all within-group $p < 0.001$). The magnitude of the reduction in URTI episodes did not differ significantly between subgroups ($p=0.178$). Although the reduction in LRTI episodes was greater among patients with inhalant allergen sensitization ($p = 0.043$), this difference appeared to be largely attributable to the higher baseline LRTI burden in this subgroup (Table III).

**Table I.** Demographic and clinical characteristics of the study population

| Variable | Value n (%) |
|---|---|
| **Demographic characteristics n (%) / Median (IQR)** | |
| Female | 50 (43.9) |
| Male | 64 (56.1) |
| Age, months n (%) / Median (IQR) | 56.5 (41.0–75.5) |
| **Atopic and allergic characteristics** | |
| Atopy | 53 (46.5) |
| Inhalant allergen sensitization | 43 (37.7) |
| Food allergy | 22 (19.3) |
| Atopic dermatitis | 12 (10.5) |
| Allergic rhinitis | 26 (22.8) |
| Asthma | 11 (9.6) |
| **Immunoglobulin status based on age-adjusted reference ranges** | |
| Normal immunoglobulin levels | 72 (63.2) |
| Partial IgA deficiency | 32 (28.1) |
| Transient hypogammaglobulinemia | 10 (8.8) |
| **Associated clinical characteristics** | n (%) |
| Adenoid hypertrophy | 54 (53.5) |
| Recurrent tonsillitis | 36 (38.7) |
| Antibiotic use for respiratory tract infections | 77 (83.7) |
| Infection requiring hospitalization | 35 (36.5) |
| Anemia | 14 (12.3) |
| **Baseline infection burden, median (IQR)** | |
| Annual number of URTI episodes | 8.0 (6.0–10.0) |
| Annual number of LRTI episodes | 1.0 (0.0–3.0) |
| School days missed per year | 3.0 (0.0–7.0) |
| **Environmental and perinatal characteristics** | |
| Household tobacco smoke exposure | 44 (43.1) |
| Parental consanguinity | 10 (9.8) |
| Daycare/school attendance | 70 (61.4) |
| Cesarean delivery | 66 (72.5) |
| History of prematurity | 11 (12.1) |
| **Laboratory findings, median (IQR)** | |
| White blood cell count, cells/mm³ | 8720 (7300–10890) |
| Lymphocyte count, cells/mm³ | 3940 (3070–5230) |
| IgG, g/L | 9.2 (7.6–10.9) |
| IgM, g/L | 0.9 (0.7–1.2) |
| IgA, g/L | 0.7 (0.3–1.1) |
| IgE, IU/mL | 55.6 (15.9–114.2) |

IQR: interquartile range. For categorical variables, percentages were calculated on the basis of valid n.

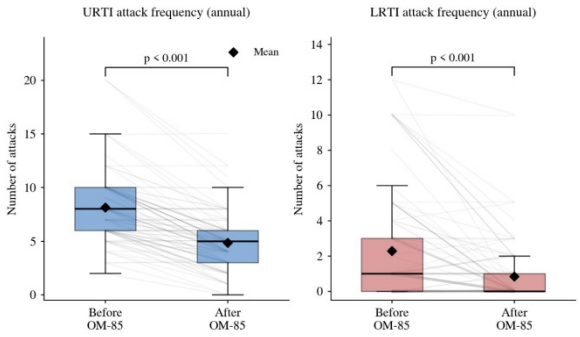



***Figure 1:***
*Annual URTI and LRTI attack counts before and after OM-85 treatment (N = 114). Boxes show the median (horizontal line) and interquartile range, whiskers extend to 1.5×IQR, and diamonds indicate the mean; grey lines connect individual patients. Annual URTI attacks decreased from a median of 8 (IQR 6–10) to 5 (IQR 3–6) and LRTI attacks from 1 (IQR 0–3) to 0 (IQR 0–1). p values are from the Wilcoxon signed-rank test. URTI: upper respiratory tract infection; LRTI: lower respiratory tract infection; IQR: interquartile range.*

**Table II.** Comparison of infection burden before and after OM-85 treatment

| Variable | Before OM-85 treatment | After OM-85 treatment | p |
|---|---|---|---|
| **Annual number of URTI episodes, median (IQR)** | 8.0 (6–10) | 5.0 (3–6) | <0.001 |
| **Annual number of LRTI episodes, median (IQR)** | 1.0 (0–3) | 0.0 (0–1) | <0.001 |
| **Frequent URTI (≥6/year), n (%)** | 96 (84.2) | 38 (33.3) | <0.001 |
| **Any LRTI episode, n (%)** | 69 (60.5) | 37 (32.5) | <0.001 |

Data are presented as median (IQR). Continuous variables were compared using the Wilcoxon signed-rank test, and paired categorical variables were compared using McNemar's test. URTI, upper respiratory tract infection; LRTI, lower respiratory tract infection; IQR, interquartile range.

*Efficacy according to immunoglobulin level.* The reduction in infection frequency after OM-85 was significant in all groups: normal immunoglobulin level, transient hypogammaglobulinemia, and partial IgA deficiency (all within-group $p<0.05$). While the reduction in URTI did not differ between groups ($p=0.888$), the reduction in LRTI was significantly more pronounced in the transient hypogammaglobulinemia and partial IgA deficiency groups compared to the normal group ($p=0.036$) (Table IV). However, this finding should be interpreted with caution because of the small number of patients with transient hypogammaglobulinemia ($n$ = 10) and the higher baseline LRTI burden in this subgroup. Indeed, in the negative binomial regression analysis adjusted for

baseline infection burden, neither immunoglobulin subgroup differed significantly from the normal immunoglobulin group (transient hypogammaglobulinemia: IRR = 0.47, $p$ = 0.226; partial IgA deficiency: IRR = 0.59, $p$ = 0.165, for LRTIs). These findings suggest that the observed between-group difference was largely attributable to differences in baseline infection burden rather than immunoglobulin status. The treatment effects across all subgroups are summarized in Figure 2.

**Table III.** Comparison of the effect of OM-85 according to allergic status

| Subgroup | Infection type | Before OM-85 treatment | After OM-85 treatment | Within-group $p$ value | Between-group $p$ value (Δ) |
|---|---|---|---|---|---|
| Atopic (n=53) | URTI | 8.0 | 5.0 | <0.001 | 0.178 |
| Non-atopic (n=61) | | 8.0 | 5.0 | <0.001 | |
| Atopic (n=53) | LRTI | 1.0 | 0.0 | <0.001 | 0.061 |
| Non-atopic (n=61) | | 1.0 | 0.0 | <0.001 | |
| Inhalant-sensitized (n=43) | URTI | 8.0 | 5.0 | <0.001 | 0.250 |
| Non-sensitized (n=71) | | 8.0 | 5.0 | <0.001 | |
| Inhalant-sensitized (n=43) | LRTI | 1.0 | 0.0 | <0.001 | 0.043 |
| Non-sensitized (n=71) | | 1.0 | 0.0 | <0.001 | |

Values are the median annual number of attacks. Within-group p: Wilcoxon signed-rank test; Δ p: comparison of the magnitude of reduction using the Mann-Whitney U test.

**Table IV.** Comparison of the effect of OM-85 according to immunoglobulin levels

| Group | Infection type | Before OM-85 treatment | After OM-85 treatment | Within-group $p$ value | Between-group KW p |
|---|---|---|---|---|---|
| Normal (n=72) | URTI | 8 (6–10) | 5 (3–6) | <0.001 | 0.888 |
| Transient hypogammaglobulinemia (n=10) | | 8 (6–10) | 5 (3–6) | 0.008 | |
| Partial IgA deficiency (n=32) | | 8 (6–10) | 4 (3–5) | <0.001 | |
| Normal (n=72) | LRTI | 1 (0–3) | 0 (0–1) | <0.001 | 0.036† |
| Transient hypogammaglobulinemia (n=10) | | 3 (1–4) | 0 (0–1) | 0.016 | |
| Partial IgA deficiency (n=32) | | 1 (0–3) | 0 (0–1) | <0.001 | |

Data are presented as the median annual number of infection episodes (IQR). Within-group $p$ values were calculated using the Wilcoxon signed-rank test. KW $p$ values represent comparisons of the magnitude of reduction (before minus after treatment) among immunoglobulin groups using the Kruskal–Wallis test. Because of the small sample size of the transient hypogammaglobulinemia group, these findings should be considered exploratory. Statistically significant between-group differences are indicated by † ($p < 0.05$)

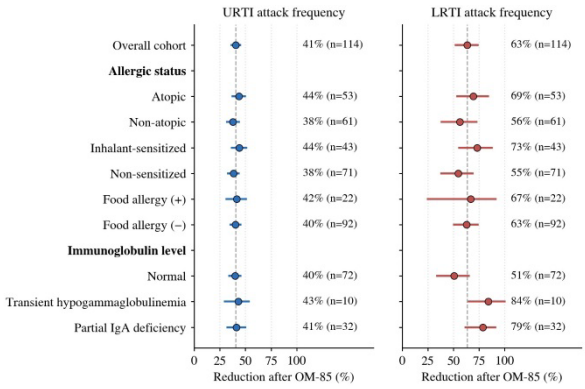



***Figure 2:***

*Efficacy of OM-85 across subgroups. Dots represent the percentage reduction in annual infection frequency after OM-85 treatment (pre- vs. post-treatment), and horizontal bars indicate bootstrap 95% confidence intervals. The dashed vertical line shows the reduction observed in the overall cohort. The reduction was statistically significant in every subgroup (within-group p<0.05, Wilcoxon signed-rank test). URTI: upper respiratory tract infection; LRTI: lower respiratory tract infection; CI: confidence interval.*

*Comparison of atopic and non-atopic patients.* When atopic and non-atopic patients were compared, inhalant allergen sensitization and food allergy were, as expected, significantly more prevalent in the atopic group. However, no statistically significant differences were observed between the groups with respect to infection burden, immunoglobulin levels, or other clinical characteristics (Table V).To identify independent predictors of post-treatment infection burden, multivariable analyses were performed using both analysis of covariance (ANCOVA) and negative binomial regression models. In both analyses, baseline infection burden was the only independent predictor of the number of infections after OM-85 treatment (URTIs: $B$ = 0.58, $p < 0.001$; LRTIs: $B$ = 0.32, $p <$ 0.001). In the ANCOVA models, baseline infection burden was the only independent predictor for both URTIs and LRTIs, and no allergic, immunological, or other clinical variable was independently associated with treatment response. This pattern was confirmed in the negative binomial model for URTIs (all allergic IRRs close to 1; p > 0.60). In the LRTI negative binomial model, however, inhalant allergen sensitization (IRR = 0.10, 95% CI 0.01–0.99; p = 0.049) and male sex (IRR = 0.45, 95% CI 0.23–0.89; p = 0.022) reached nominal significance; given the very wide confidence intervals, the strong collinearity among allergic variables, the small number of LRTI events, and their non-significance in the ANCOVA model, these associations should be regarded as unstable and exploratory (Table VI).

**Table V.** Baseline characteristics according to atopic status

| Variable | Atopic (n=53) | Non-atopic (n=61) | p |
|---|---|---|---|
| Age, months | 61 (43–74) | 52 (38–76) | 0.213 |
| URTI, pre-treatment | 8 (6–10) | 8 (6–10) | 0.773 |
| URTI, post-treatment | 5 (3–6) | 5 (3–6) | 0.608 |
| Days of school absence | 5 (0–10) | 2 (0–5) | 0.079 |
| Leukocytes, /mm³, Median (IQR) | 7965 (6605–10480) | 9250 (7890–11140) | 0.033 |
| IgG, g/L, Median (IQR) | 9.3 (8–11) | 9.0 (7–11) | 0.372 |
| IgE, IU/mL, Median (IQR) | 57.3 (12–118) | 54.0 (19–106) | 0.909 |
| Inhalant sensitization | 42/53 (79%) | 0/61 (0%) | <0.001 |
| Food allergy | 22/53 (42%) | 0/61 (0%) | <0.001 |
| Recurrent tonsillitis | 13/45 (29%) | 23/48 (48%) | 0.095 |
| Daycare / school | 37/53 (70%) | 33/61 (54%) | 0.127 |

Median (IQR) or n/valid n (%); Mann-Whitney U and chi-square/Fisher's exact test.

**Table VI.** Multivariable regression analyses of post-treatment infection burden: ANCOVA and negative binomial models

| Variable | Linear regression (ANCOVA) | | Negative binomial regression | |
|---|---|---|---|---|
| | β (95% CI) | p | IRR (95% CI) | p |
| **Post-treatment URTI episodes ($R^2$ = 0.55; n = 101)** | | | | |
| Baseline URTI episodes | 0.58 (0.46 – 0.69) | <0.001 | 1.12 (1.05 – 1.20) | <0.001 |
| Atopy | 0.55 (−1.34 – 2.43) | 0.567 | 1.15 (0.38 – 3.45) | 0.807 |
| Inhalant sensitization | −1.06 (−2.76 – 0.64) | 0.220 | 0.78 (0.29 – 2.11) | 0.624 |
| Food allergy | −0.74 (−2.27 – 0.79) | 0.338 | 0.85 (0.35 – 2.09) | 0.729 |
| Age | −0.01 (−0.02 – 0.01) | 0.363 | 1.00 (0.99 – 1.01) | 0.796 |
| Male | −0.11 (−0.90 – 0.67) | 0.771 | 0.96 (0.62 – 1.51) | 0.876 |
| Adenoid hypertrophy | 0.18 (−0.62 – 0.98) | 0.662 | 1.04 (0.66 – 1.65) | 0.864 |
| Daycare/school attendance | 0.43 (−0.55 – 1.40) | 0.388 | 1.01 (0.57 – 1.77) | 0.979 |
| **Post-treatment LRTI episodes ($R^2$ = 0.39; n = 101)** | | | | |
| Baseline LRTI episodes | 0.32 (0.23 – 0.41) | <0.001 | 1.31 (1.20 – 1.44) | <0.001 |
| Atopy | 0.61 (−0.84 – 2.06) | 0.406 | 5.59 (0.53 – 59.05) | 0.152 |
| Inhalant sensitization | −1.00 (−2.30 – 0.30) | 0.129 | 0.10 (0.01 – 0.99) | 0.049 |
| Food allergy | −0.59 (−1.78 – 0.59) | 0.323 | 0.18 (0.02 – 1.49) | 0.111 |
| Age | 0.00 (−0.01 – 0.01) | 0.688 | 1.00 (0.99 – 1.02) | 0.712 |
| Male | −0.45 (−1.05 – 0.15) | 0.139 | 0.45 (0.23 – 0.89) | 0.022 |
| Adenoid hypertrophy | −0.17 (−0.78 – 0.44) | 0.572 | 0.79 (0.41 – 1.54) | 0.493 |
| Daycare/school attendance | 0.27 (−0.49 – 1.02) | 0.482 | 0.79 (0.34 – 1.83) | 0.586 |

β, regression coefficient; IRR, incidence rate ratio; CI, confidence interval; *p*, p value. Both models were adjusted for baseline (pre-treatment) infection burden. Because of the high degree of collinearity among atopy, inhalant allergen sensitization, and food allergy, the regression coefficients for allergy-related variables—particularly in the LRTI model—were associated with wide confidence intervals and should therefore be interpreted with caution.

## Discussion and Conclusion

The most common causes of recurrent respiratory tract infections in children are increased pathogen exposure, allergic sensitization, pathologies of the immune system, and environmental factors such as early enrollment in daycare, indoor smoking exposure, and a history of school-age siblings[4]. Immunomodulators such as OM-85 should be considered as an approach that complements the management of modifiable risk factors, such as reducing smoking exposure, daycare selection, and vaccination.

In this study, a 40.6% reduction in the annual number of URTI episodes and a 63.2% reduction in the annual number of LRTI episodes were observed after OM-85 treatment. Furthermore, the percentage of cases with frequent URTIs (≥6/year) decreased from 84.2% to 33.3%, and the percentage of cases with any LRTI episode decreased from 60.5% to 32.5%. Our findings are consistent with several meta-analyses of OM-85 in children; in the Cochrane review by Del-Rio-Navarro et al. the OM-85 subgroup showed a 35.9% reduction in acute respiratory tract infections compared with placebo[16-18]. These findings suggest that OM-85 treatment may offer a clinically significant benefit in children by substantially reducing the burden of both upper and lower respiratory tract infections.

In the phase IV OMPeR ("OM-85 in Pediatric Recurrent respiratory tract infections") randomized controlled trial conducted in Italy with 288 children, OM-85 also significantly reduced the rate of children experiencing at least one infection compared to placebo (65% vs. 33%)[15]. The same study highlighted that the clinical benefit of OM-85 was particularly pronounced in children with a higher baseline infection burden[15]. Cardinale et al. emphasized that OM-85 provides more significant benefit in children with a high incidence of infection and has the potential for long-term prophylaxis[5]. In our study, in multivariable analysis, only the baseline infection burden before treatment was found to be the independent determinant of the decrease in the number of infections after treatment.

This effect of OM-85 is explained by the fact that bacterial lysates stimulate innate immunity via Toll-like receptors (especially TLR-2, TLR-4, and TLR-9), increasing dendritic cell maturation and mucosal secretory IgA response, regulating the Th1/Th2 balance towards Th1, and creating 'trained immunity'[11]. De Boer et al.'s meta-analysis also reported that this immunomodulatory effect is based on Th1 activation and Th2 suppression[19]. Ballarini et al. and Dang et al. have shown in experimental studies that OM-85 enhances airway epithelial and immune cell responses against respiratory viruses such as

rhinovirus, RSV, and influenza; and that it triggers the production of IFN-β, IL-8, CCL2, CCL20, IFN-α, and IL-12 in dendritic cells via NF-κB and MAPK pathways[11, 20]. These findings suggest that OM-85 may provide additional benefit, particularly in the lower respiratory tract/wheezing phenotype. The 63.2% reduction in the number of LRTI attacks in our study is noteworthy and consistent with the literature on the effect of OM-85 on the wheezing phenotype. Razi et al., in a randomized controlled trial conducted in 75 preschool children with wheezing in Türkiye, showed that OM-85 reduced wheezing attacks by 37.9% and that this effect was mainly due to a reduction in the number of respiratory tract infections[21].

One of the principal findings of the present study was that the beneficial effect of OM-85 was independent of allergic status. Significant reductions in respiratory tract infections were observed across all subgroups, including atopic and non-atopic children as well as those with and without inhalant allergen sensitization. Furthermore, after adjustment for baseline infection burden, allergic status was not independently associated with post-treatment infection frequency, whereas baseline infection burden remained the only independent predictor of treatment response. These findings are consistent with those of the OMPeR study, which similarly demonstrated that neither atopy nor a history of recurrent wheezing influenced the clinical efficacy of OM-85[15]. The reduction in LRTI episodes in children with inhalant allergen sensitization appears more pronounced in univariate analysis ($p = 0.043$), possibly because this group had a higher frequency of infections prior to treatment. The fact that patients who initially experienced more infections naturally showed a greater decrease in the number of infections over time (regression effect on the mean) may partially explain this finding. However, in multivariable analyses where potential confounding variables such as age and other atopic characteristics were considered together, the statistical power of this relationship decreased and remained only borderline significant. This suggests that the effect of inhalant allergen sensitivity on infection reduction may not be independent and may be influenced by other clinical characteristics. In the negative binomial model this association reached only borderline significance (IRR = 0.10; $p = 0.049$), and male sex was likewise nominally associated with a lower post-treatment LRTI burden (IRR = 0.45; $p = 0.022$); given the wide confidence intervals, collinearity, and small number of LRTI events, both should be regarded as exploratory rather than independent effects. The fact that baseline infection count was the strongest predictor of post-treatment burden in both analyses indicates that the greatest benefit from OM-85 can be expected in children with frequent infections. This is consistent with both Schaad's meta-analysis and the OMPeR study, where the effect was found to be greater in the high-risk/frequent infection subgroup[15,16]. These findings suggest that children with a higher baseline infection burden may derive greater clinical benefit from OM-85 and could therefore represent an important target population for this preventive strategy.

In our cohort, 28.1% of children had partial IgA deficiency and 8.8% had transient hypogammaglobulinemia. Both conditions are among the most common humoral immunodeficiencies in childhood and are associated with an increased susceptibility to recurrent bacterial respiratory tract infections. Despite this, the beneficial effect of OM-85 was observed across all immunoglobulin subgroups. After adjustment for baseline infection burden, immunoglobulin status was not independently associated with treatment response, suggesting that the clinical efficacy of OM-85 is not confined to children with normal humoral immunity[22]. In the subgroup analysis according to immunoglobulin status, OM-85 treatment was associated with significant reductions in both URTI and LRTI episodes across all three immunoglobulin subgroups. Furthermore, the magnitude of the reduction did not differ significantly among the groups, indicating that immunoglobulin status was not independently associated with treatment response[22,23]. Although the reduction in LRTI episodes appeared to be greater in children with mild humoral immunodeficiency, including transient hypogammaglobulinemia and partial IgA deficiency, than in those with normal immunoglobulin levels, this finding should be interpreted with caution. The greater absolute reduction was largely attributable to the higher baseline LRTI burden in these subgroups, and the between-group difference was no longer significant after adjustment for baseline infection burden. The transient hypogammaglobulinemia subgroup was small (n = 10) and had a substantially higher baseline LRTI burden (median, 3 [IQR, 1–4]) than both the partial IgA deficiency and normal immunoglobulin groups (median, 1 [IQR, 0–3]). Accordingly, after adjustment for baseline infection burden using negative binomial regression, neither mild humoral immunodeficiency subgroup differed significantly from the normal immunoglobulin group (transient hypogammaglobulinemia: IRR = 0.47, $p = 0.226$; partial IgA deficiency: IRR = 0.59, $p = 0.165$). These findings suggest that the greater apparent reduction in LRTI episodes was primarily driven by the higher baseline infection burden rather than by immunoglobulin status itself.

The immunoglobulin subgroup analyses further support our previous observation that allergic status does not independently influence the response to OM-85. In multivariable analyses, baseline infection burden remained the only independent predictor of

treatment response, whereas neither allergic characteristics nor mild humoral immunodeficiency were independently associated with clinical efficacy. These findings suggest that the baseline burden of respiratory tract infections, rather than atopic status or mild humoral immunodeficiency, is the principal determinant of the clinical response to OM-85. Considering the findings of Aytekin et al. showing a relationship between IgA deficiency and atopy, evaluating serum immunoglobulin levels in children with recurrent RTIs is of importance[10,24]. However, further studies are needed to confirm whether the detected mild humoral immunodeficiency is a treatment exclusion criterion or whether it identifies a subgroup of patients who might benefit more from OM-85 treatment.

In our study, cigarette exposure was 43.1% and daycare attendance was 61.4%, which is consistent with the frequency of environmental risk factors of Cardinale et al.[5]. De Benedetto et al. reported that the benefit of OM-85 is more evident in children particularly susceptible to recurrent RTIs, such as those living in high-exposure settings (e.g., orphanages or areas with high air pollution)[14].

The reduction in respiratory tract infections observed after OM-85 would also be expected to translate into a lower need for antibiotic therapy. Consistent with this, a recent meta-analysis demonstrated that OM-85 significantly reduced both the likelihood of antibiotic use (OR = 0.38) and the number of antibiotic courses required.[25] In our cohort, however, post-treatment antibiotic use was not systematically recorded, so this reduction, although anticipated given the observed decline in infection frequency, could not be quantified. Previous systematic reviews have also reported reductions in antibiotic courses and shorter infection durations.[18,26] Given the high baseline rate of antibiotic use in our cohort (83.7%), OM-85's potential to lower antibiotic consumption by reducing infections adds further value to antimicrobial stewardship in the era of increasing antimicrobial resistance.

The retrospective cohort, single-center design of this study and the absence of a control group should be considered when interpreting the results. However, the influence of potential confounding factors was minimized through multivariable analyses. Long-term clinical outcomes and findings related to immunological subgroups need to be confirmed by prospective studies with larger sample sizes.

This study demonstrated a significant reduction in the frequency of both upper and lower respiratory tract infections in children treated with OM-85 for recurrent respiratory tract infections. This benefit was consistently observed in atopic/non-atopic patients and across all immunoglobulin subgroups; baseline infection burden was the principal independent predictor of treatment response in the primary multivariable (ANCOVA) analyses. In contrast, atopic status, inhalant allergen sensitivity, food allergy, and immunoglobulin levels were not independently associated with treatment response. Our findings suggest that atopy or mild humoral immunodeficiency is not a barrier to OM-85 treatment and that baseline infection burden should be considered a key criterion in identifying patients who may benefit most from treatment. These results need to be confirmed by prospective, placebo-controlled studies stratified by allergic status and immunological profile.

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