Acta Biomed 2025; Vol. 96, N. 5: 17064 DOI: 10.23750/abm.v96i5.17064

Original article

IgE-mediated cow's milk allergy and sensitization in children with moderate to severe atopic dermatitis in Egypt

Heba Gadelrab[1], Ashraf Galal[1], Maged Eissa[1], Marwa Eldeeb[2], Walaa Shoman[1]

[1]Department of Pediatrics, Faculty of Medicine, Alexandria University, Alexandria, Egypt; [2]Department of Dermatology, Venerology, and Andrology, Faculty of Medicine, Alexandria University, Alexandria, Egypt

Abstract. *Background and aim:* Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin condition frequently associated with food allergies, particularly cow's milk allergy (CMA). Understanding the prevalence of IgE-mediated CMA and its relationship with AD is critical for early diagnosis and management. This study aimed to determine the frequency of IgE-mediated cow's milk allergy and sensitization among children with moderate to severe atopic dermatitis attending the Allergy Clinic at Alexandria University Children's Hospital. *Methods:* A prospective cohort study was conducted on 83 children with moderate or severe AD. Detailed clinical histories, SCORAD scoring, and skin prick tests (SPT) using commercial milk extract were performed. IgE-mediated CMA was diagnosed based on positive SPT and immediate clinical reactions after milk ingestion. *Results:* Cow's milk sensitization was detected in 30.1% of patients, while confirmed IgE-mediated CMA was found in 19.3%. All allergic children had infantile-onset AD, with a statistically significant association between early-onset eczema and milk allergy (P:<0.001). No significant correlations were found between CMA and type of early feeding or age of solid food introduction. A majority of allergic children (75%) were exclusively breastfed. *Conclusions:* IgE-mediated cow's milk allergy is prevalent among children with moderate to severe AD in Egypt and is significantly associated with early-onset eczema. These findings highlight the need for targeted allergy screening in infants presenting with AD. (www.actabiomedica.it)

Key words: cow's milk allergy, IgE-mediated sensitization, atopic dermatitis, early-onset eczema, Egypt

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by relapsing pruritic eczematous lesions, predominantly affecting children. Its global prevalence ranges between 15% and 20%, influenced by geographic, genetic, and socioeconomic factors (1, 2). AD is often the initial manifestation in the "atopic march," a term describing the sequential development of atopic diseases such as food allergy, allergic rhinitis, and asthma. Food allergy (FA), particularly in early childhood, is a recognized comorbidity of AD. IgE-mediated food allergy is of special clinical concern due to its rapid-onset symptoms and potential severity, ranging from urticaria and gastrointestinal upset to anaphylaxis (3- 5). Among food allergens, cow's milk is the most commonly implicated in infants and young children (4). IgE-mediated cow's milk allergy (CMA) represents a significant subset of FA, requiring accurate identification for proper management (5, 6). The interplay between AD and IgE-mediated food allergies is multifaceted. Disruption in skin barrier integrity, common in AD, facilitates transcutaneous sensitization to food antigens. This process can lead to the production of food-specific IgE antibodies and the development of systemic allergic responses (7, 8). In turn, food allergies can aggravate eczema severity, especially in younger children with early-onset AD (9-15).

The prevalence of CMA among children with AD varies across populations, with reported sensitization

rates ranging from 20% to 40% (16-18). This variation reflects differences in genetic susceptibility, environmental exposures, dietary practices, and diagnostic approaches. While this relationship has been explored in several countries, including South Africa, Switzerland, and Greece, there is a paucity of data from Middle Eastern and North African regions. Understanding the prevalence and clinical associations of IgE-mediated CMA in children with AD in Egypt is crucial for improving diagnostic and therapeutic strategies. This study aimed to determine the frequency of cow's milk sensitization and confirmed IgE-mediated allergy in Egyptian children with moderate to severe AD. Additionally, the study investigated the relationship between milk allergy and early-life factors, including age at eczema onset, infant feeding practices, and solid food introduction.

Patients and Methods

Setting, study population and research design

This prospective cohort study was conducted over a 12-month period from July 2023 to June 2024 at the Allergy Clinic of Alexandria University Children's Hospital (AUCH), a major tertiary care referral center in Egypt. Eighty-three children and adolescents, aged between 6 months and 15 years, who were diagnosed with moderate to severe atopic dermatitis (AD) and referred for allergy evaluation, were enrolled in the study. Eligible criteria for study inclusion were: (a) children aged 6 months to 15 years; (b) clinical diagnosis of moderate to severe AD based on the objective SCORAD index, and (c) attendance at the AUCH Allergy Clinic during the study period. Exclusion criteria included: (a) mild AD; (b) previously confirmed diagnosis of cow's milk allergy; (c) presence of chronic systemic illnesses or immunodeficiencies, and (c) use of systemic antihistamines or corticosteroids within one week prior to skin testing.

Clinical assessment and data collection

Each child underwent a standardized clinical evaluation, which included: (a) a detailed history: age of eczema onset, feeding practices in the first 4 months (exclusive breastfeeding, formula, or mixed feeding), age at introduction of solid foods, immediate allergic reactions to cow's milk, and family history of atopic diseases (eczema, asthma, or allergic rhinitis); (b) physical examination and dermatological assessment, and (c) severity of AD assessed using the objective SCORAD index, categorized as: Mild: <15; Moderate: 15–40 or Severe: >40 (19,20).

Skin Prick Testing (SPT)

SPT was performed using commercial cow's milk extract (Omega Laboratories, Montréal, Canada), following the European Academy of Allergy and Clinical Immunology guidelines (21). Testing was conducted on the volar forearm, and a wheal diameter ≥3 mm greater than the negative control was considered positive.

Definitions of clinical outcomes

- Milk Sensitization: was defined as a positive SPT to cow's milk extract without a history of clinical symptoms following milk ingestion (22).
- IgE-mediated Cow's Milk Allergy (CMA): was defined as a positive SPT result accompanied by a consistent clinical history of immediate allergic symptoms following ingestion of cow's milk (22).

Statistical analysis

All data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on distribution, Categorical variables were presented as frequencies and percentages. Group comparisons were conducted using the Chi-square test or Fisher's exact test for categorical variables, and Mann-Whitney U or Kruskal-Wallis tests for continuous variables. A p-value ≤ 0.05 was considered statistically significant.

Ethics

The present study has been extracted from a thesis in Pediatrics presented by doctor HG. The Faculty of Medicine for Postgraduate Studies of the Faculty of Medicine, Alexandria University has approved its partial publication. The study was approved by the Ethics Committee of the Faculty of Medicine, Alexandria University, (date of release was 16/6/2022, serial number 0201689). All data were anonymized, and patient confidentiality was strictly maintained. in accordance with principles of the Declaration of Helsinki and its later amendments in 2020 (www.wma.net).

Results

Demographic data

A total of 83 children diagnosed with moderate to severe atopic dermatitis (AD) were enrolled in the study. Of these, 50 (60.2%) were males and 33 (39.8%) were females, resulting in a male-to-female ratio of approximately 1.5:1. The mean age at the time of enrollment was 6.06 ± 3.29 years (range: 0.58–15 years), with a median age of 6 years (interquartile range [IQR]: 3.42–8 years). Most of the participants (80.7%) resided in urban areas, while 19.3% lived in rural settings. Based on the age of onset of eczema, 78.3% of patients had infantile-onset AD (<2 years), 18.1% had preschool-onset (2–<6 years), and 3.6% had school-age onset (6–<12 years). The mean age of eczema onset was 1.19 ± 1.66 years, with a median of 0.5 years (IQR: 0.25–1 year). Regarding feeding practices, 56 children (67.5%) were exclusively breastfed during the first four months of life, while 10 (12.0%) were formula-fed, and 17 (20.5%) received both breast milk and formula. The introduction of solid foods occurred after 6 months in 55 patients (66.3%) and before 6 months in 28 patients (33.7%). A positive family history of atopic dermatitis was reported in 38 children (45.7%), with 16 (19.3%) having an affected parent and 22 (26.5%) having an affected sibling**.** A positive family history of atopic dermatitis was reported in 38 children (45.7%), with 16 (19.3%) having an affected parent and 22 (26.5%) having an affected sibling**.**

Milk sensitization and cow's milk allergy

Out of the 83 children with moderate to severe atopic dermatitis, 25 patients (30.1%) were sensitized to cow's milk based on positive skin prick test (SPT) results. Among these, 16 children (19.3%) met the diagnostic criteria for IgE-mediated cow's milk allergy, exhibiting both positive SPT results and a consistent clinical history of immediate allergic symptoms following milk ingestion. These findings indicate a notably high burden of cow's milk sensitization and confirmed allergy in children with moderate to severe AD, reinforcing the clinical relevance of assessing food allergies in this population. While some children with positive SPTs did not meet the clinical threshold for allergy (i.e., sensitized but not allergic), nearly two-thirds of sensitized individuals progressed to clinical allergy, which underscores the importance of distinguishing between mere sensitization and true IgE-mediated allergy in AD patients. Approximately 30.1% of patients showed milk sensitization, while 19.3% had clinically confirmed IgE-mediated cow's milk allergy. A notably higher percentage of patients were not sensitized (69.9%) or not allergic (80.7%), indicating that while cow's milk is a common allergen, the majority of children with AD in this cohort did not present with milk allergy (Figure 1).

The chart highlights the distinction between sensitization and true clinical allergy, emphasizing the importance of combining skin testing with clinical history in diagnosis. Figure 2 illustrates that the majority of children with atopic dermatitis (69.9%) were neither sensitized nor allergic to cow's milk, while a notable proportion (30.1%) showed either sensitization or confirmed IgE-mediated allergy. This highlights the clinical importance of screening for cow's milk allergy in children with moderate to severe AD.

The association between cow's milk sensitization or allergy and selected clinical parameters in children and adolescents with atopic dermatitis (AD) (n = 83) is presented in Table 1. The study population was categorized into three groups: those without sensitization or allergy (n = 58), those with IgE-mediated cow's milk allergy (n = 16), and those who were sensitized without clinical allergy (n = 9). The table compares the age of eczema onset, type of feeding during the first

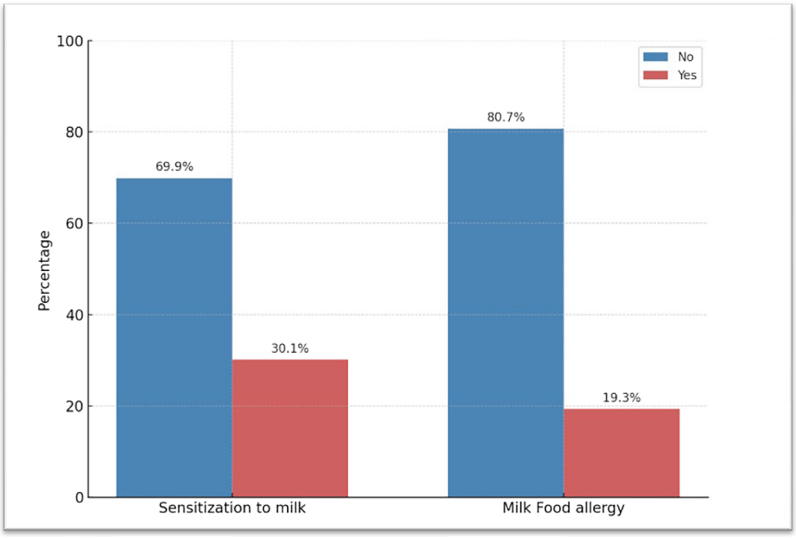

Figure 1. Distribution of the studied cases according to milk food allergy and sensitization to milk (n = 83).

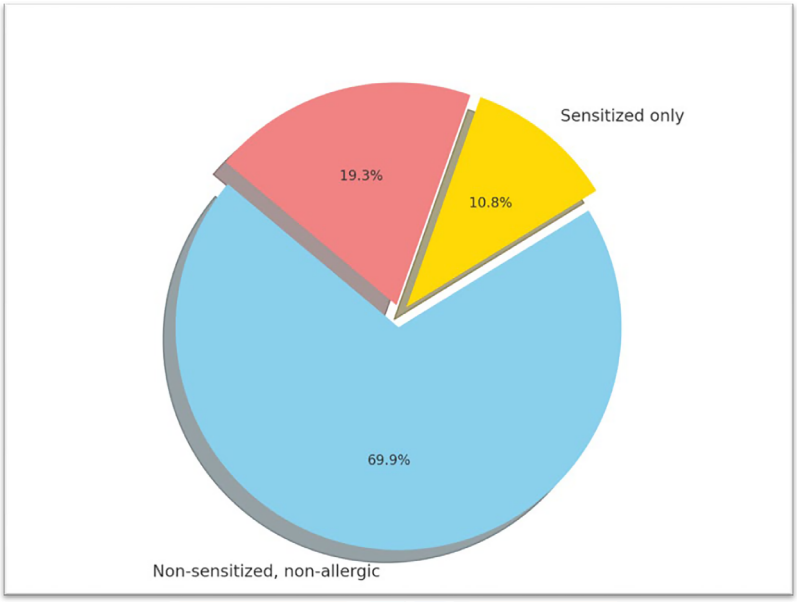

Figure 2. Proportion of children and adolescents with atopic dermatitis according to milk sensitization and IgE-mediated cow's milk allergy (n = 83).

four months of life, and the timing of solid food introduction among the three groups, with corresponding statistical tests and significance levels.

A statistically significant association was found between the age of eczema onset and cow's milk sensitization and allergy (P: < 0.001). Children with IgE-mediated cow's milk allergy had a significantly earlier onset of eczema (mean: 0.13 ± 0.09 years) compared to non-allergic and non-sensitized groups. This supports the concept that early-onset atopic dermatitis

Table 1. Association between cow's milk sensitization/allergy and clinical parameters in children and adolescents with atopic dermatitis (n = 83)

Parameter	Non-sensitized / Non-allergic (n = 58)	IgE-mediated Allergy (n = 16)	Sensitized Only (n = 9)	Statistical Test	P-value
Age of onset of eczema (years)				Kruskal-Wallis (H) = 29.991	< 0.001*
Min – Max	0.08 – 8.00	0.08 – 0.33	0.08 – 4.00		
Mean ± SD	1.53 ± 1.82	0.13 ± 0.09	0.92 ± 1.19		
Median (IQR)	0.75 (0.50–2.00)	0.08 0.08–0.13)	0.50 (0.50–0.75)		
Feeding in the first 4 months				Fisher's Exact Test = 4.745	0.276
Breastfeeding (N and %)	39 (67.2%)	12 (75.0%)	5 (55.6%)		
Formula (N and %)	5 (8.6%)	3 18.8%)	2 (22.2%)		
Mixed (N and %)	14 (24.1%)	1 (6.3%)	2 (22.2%)		
Age of solid food introduction				Chi-square (χ^2) = 2.065	0.356
Before 6 months (N and %)	22 (37.9%)	3 (18.8%)	3 (33.3%)		
After 6 months (N and %)	36 (62.1%)	13 (81.3%)	6 (66.7%)		

Abbreviations: SD = Standard Deviation; IQR = Interquartile Range; H = Kruskal-Wallis test; FET = Fisher's Exact Test; χ^2 = Chi-Square Test. *Statistically significant at P: < 0.05.

is a risk factor for developing food allergies, possibly due to immune priming via impaired skin barriers. No statistically significant associations were found between type of feeding in the first 4 months or the age of first solid food introduction and milk allergy or sensitization (P: 0.276 and 0.356, respectively). These findings suggest that early feeding practices in this cohort did not significantly influence the development of milk allergy. The distribution of early feeding patterns—breastfeeding, formula feeding, and mixed feeding—among children with atopic dermatitis, stratified by their cow's milk sensitization and allergy status is illustrated in Figure 3. The three groups compared include children who were non-sensitized/non-allergic, those with IgE-mediated cow's milk allergy, and those who were sensitized only. This helps highlight potential differences in early nutritional exposures that may be associated with allergic outcomes in this population.

While exclusive breastfeeding was the most common feeding method across all groups, its highest prevalence was observed in the IgE-mediated allergy group (75%), followed by the non-sensitized group (67.2%), and lowest in the sensitized-only group (55.6%). Interestingly, formula feeding and mixed feeding were slightly more frequent in sensitized-only children compared to those with confirmed allergy. However, these differences were not statistically significant (P: 0.276), suggesting that early feeding type alone may not be a strong independent predictor of milk sensitization or allergy in children with atopic dermatitis. The chart helps to contextualize the variation in early-life dietary exposures but reinforces that other factor, such as age of eczema onset or genetic predisposition, may play a more prominent role in the development of IgE-mediated cow's milk allergy.

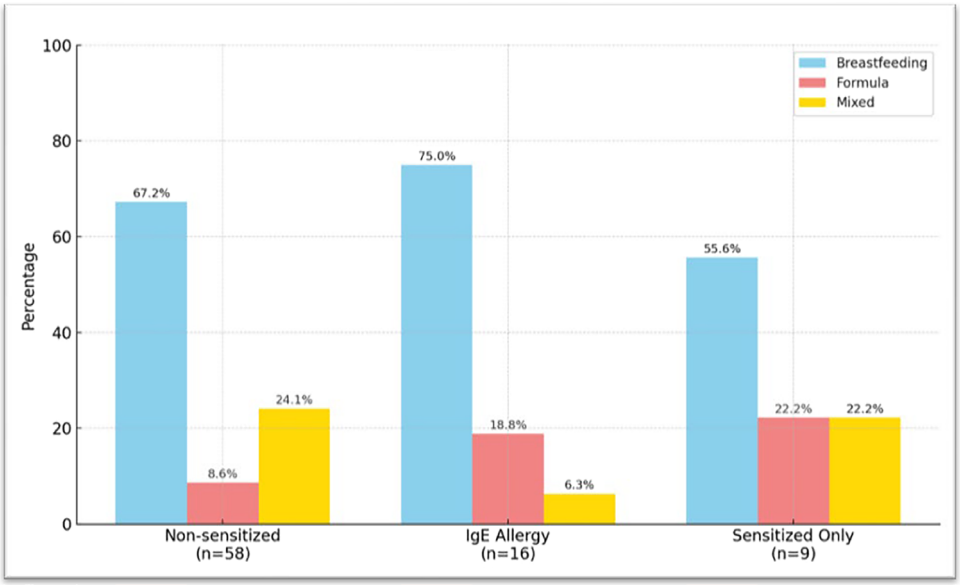

Figure 3. Early feeding patterns in children with atopic dermatitis by cow's milk sensitization and allergy status.

Discussion

This study explored the prevalence of IgE-mediated cow's milk allergy and sensitization in children with moderate to severe atopic dermatitis (AD), and analyzed associations with demographic and early-life nutritional factors. The findings align with many global studies while offering region-specific insight from Egypt. Our study found that 30.1% of children were sensitized to cow's milk, and 19.3% had confirmed IgE-mediated cow's milk allergy. These findings are comparable to reports from Greece, where Mavroudi et al , (13) found a 35% milk sensitization rate in children with AD, and South Africa, where Gray et al (11) reported food sensitization rates of 27%, with milk being one of the top allergens, Similarly, a Swiss study by Eigenmann et al (18)) noted milk sensitization in 31% of AD patients. These similarities suggest that cow's milk remains a prominent food allergen across populations. However, lower prevalence rates have been reported in other settings, likely due to regional differences in dietary exposure, allergy testing protocols, and genetic backgrounds. A notable finding in our cohort was the strong association between early-onset eczema and milk allergy, with all children diagnosed with IgE-mediated CMA having developed AD during infancy. This supports the "atopic march" model and the concept of epicutaneous sensitization. Studies from Taiwan (19) and South Africa (11) also observed that early-onset eczema significantly increases the risk of food allergy, particularly to milk and egg. The likely mechanism involves disruption of the skin barrier, allowing allergen entry and sensitization via antigen-presenting cells, particularly in the absence of prior oral exposure to those proteins (7, 20-22). Regarding feeding type in the first four months, our study found no statistically significant association with the development of cow's milk allergy or sensitization (P: 0.276). This finding is consistent with a study by Mailhol et al (23), who found that breastfeeding had no protective or risk-enhancing effect on food allergy development in children with AD. However, contrasting data from Kim et in Korea indicated that breastfeeding was associated with increased food sensitization, although not with clinical allergy. The discrepancy between these studies may relate to differences in maternal allergen exposure, gut microbiota modulation, and genetic predispositions that alter immune tolerance pathways. The age of first solid food introduction was also not significantly associated with milk allergy

or sensitization in our cohort (P: 0.356). This aligns with more recent findings suggesting that delayed introduction of allergenic foods is not protective, and may in fact increase the risk of allergy by missing a window of immunological tolerance. Guidelines now recommend age-appropriate, early introduction of potential allergens during infancy (25, 26). A shift away from older "avoidance" strategies is supported by large studies such as LEAP and EAT, although such trials were not specific to AD cohorts (26, 27). Our data also revealed that 80.7% of affected children lived in urban areas, consistent with studies showing a higher prevalence of allergic diseases in urban vs. rural settings. Xu et al, (28) reported similar urban-rural disparities in China, and Ahn et al (29) highlighted that air pollution and decreased microbial exposure in urban areas impair immune regulation and exacerbate allergic diseases. This "hygiene hypothesis" supports the idea that reduced microbial stimulation in early life may shift the immune system toward a Th2-dominant allergic profile. From an immunological perspective, the relationship between AD and food allergy, including CMA, can be explained by multiple mechanisms. These include skin barrier dysfunction, particularly with filaggrin mutations, which facilitates allergen entry (8, 30); heightened Th2 cytokine responses (IL-4, IL-13), promoting class switching to IgE (20)and lack of oral tolerance due to delayed or disrupted exposure to dietary proteins. These mechanisms are well-established and further substantiated by animal and human models (7, 21, 31). In summary, our study reinforces that cow's milk sensitization and allergy are prevalent among children with moderate to severe AD in Egypt, particularly those with early-onset eczema. Although feeding practices and timing of food introduction did not show statistically significant associations in this cohort, they remain clinically important variables that may influence allergy outcomes depending on broader environmental and genetic contexts.

Ethic Approval: The study was approved by the Ethics Committee of the Faculty of Medicine, Alexandria University, (date of release was16/6/2022, serial number 0201689).

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: HG conceptualized and designed the study, contributed to data interpretation, and drafted the initial manuscript. AG and ME were involved in clinical assessment and data collection. ME contributed to dermatological evaluation and supported data analysis. WS performed the statistical analysis and contributed to interpretation of results. All authors reviewed and approved the final manuscript and are accountable for the accuracy and integrity of the work.

References

1. Silverberg J, Thyssen J, Paller A, et al. Allergy. 2017; 72(12):2026-30. doi:10.1111/all.13284
2. Suaini NH, Tan CP, Loo EX, et al. Pediatr Allergy Immunol. 2021;32(1):23-33. doi:10.1111/pai.13364
3. Sicherer SH, Sampson HA. J Allergy Clin Immunol. 2014;133(2):291-307.e5. doi:10.1016/j.jaci.2013.11.001
4. Skripak JM, Matsui EC, Mudd K, et al. J Allergy Clin Immunol. 2007;120(5):1172-7. doi:10.1016/j.jaci.2007.08.023
5. Kazatsky AM, Wood RA. Curr Allergy Asthma Rep. 2016;16(3):22. doi:10.1007/s11882-016-0603-3
6. Fiocchi A, Brozek J, Schünemann H, et al. World Allergy Organ J. 2010;3(4):57-161. doi:10.1097/WOX.0b013e3181defeb9
7. Bieber T. Ann Dermatol. 2010;22(2):125-37. doi:10.5021/ad.2010.22.2.125
8. Kuo I-H, Yoshida T, De Benedetto A, et al. J Allergy Clin Immunol. 2013;131(2):266-78. doi:10.1016/j.jaci.2012.12.1565
9. Lack G. J Allergy Clin Immunol. 2008;121(6):1331-6. doi:10.1016/j.jaci.2008.04.032
10. Okada H, Kuhn C, Feillet H, et al. Clin Exp Immunol. 2010;160(1):1-9. doi:10.1111/j.1365-2249.2010.04139.x
11. Gray CL, Levin ME, Zar HJ, et al. Pediatr Allergy Immunol. 2014;25(6):572-9. doi:10.1111/pai.12279
12. Werfel T, Ballmer-Weber B, Eigenmann P, et al. Allergy. 2007;62(7):723-8. doi:10.1111/j.1398-9995.2007.01309.x
13. Mavroudi A, Karagiannidou A, Xinias I, et al. Allergol Immunopathol (Madr). 2017;45(1):77-81. doi:10.1016/j.aller.2016.06.005
14. Kunz B, Oranje A, Labreze L, et al. Dermatology. 1997;195(1):10-9. doi:10.1159/000245854
15. Oranje A, Glazenburg E, Wolkerstorfer A, et al. Br J Dermatol. 2007;157(4):645-8. doi:10.1111/j.1365-2133.2007.08112.x
16. Heinzerling L, Mari A, Bergmann K-C, et al. Clin Transl Allergy. 2013;3:3. doi:10.1186/2045-7022-3-3
17. Panel N-SE. J Allergy Clin Immunol. 2010;126(6 Suppl): S1-S58. doi:10.1016/j.jaci.2010.10.007
18. Eigenmann PA, Calza AM. Pediatr Allergy Immunol. 2000;11(2):95-100. doi:10.1034/j.1399-3038.2000.00095.x

19. Chiu C-Y, Yang C-H, Su K-W, et al. J Microbiol Immunol Infect. 2020;53(6):1008-13. doi:10.1016/j.jmii.2019.07.005
20. Tham EH, Rajakulendran M, Lee BW, et al. Pediatr Allergy Immunol. 2020;31(1):7-18. doi:10.1111/pai.13141
21. Tham EH, Leung DY. Allergy Asthma Immunol Res. 2019;11(1):4-15. doi:10.4168/aair.2019.11.1.4
22. Brough HA, Liu AH, Sicherer S, et al. J Allergy Clin Immunol. 2015;135(1):164-70. doi:10.1016/j.jaci.2014.10.007
23. Mailhol C, Giordano-Labadie F, Lauwers-Cances V, et al. Eur J Dermatol. 2014;24(1):63-9. doi:10.1684/ejd.2013.2220
24. Kim DC, Seo AD, Yang SI, et al. Allergy Asthma Respir Dis. 2016;4(3):188-94. doi:10.4168/aard.2016.4.3.188
25. Greer FR, Sicherer SH, Burks A, et al. Pediatrics. 2019;143(4):e20190281. doi:10.1542/peds.2019-0281
26. Du Toit G, Roberts G, Sayre PH, et al. N Engl J Med. 2015;372(9):803-13. doi:10.1056/NEJMoa1414850. New England Journal of Medicine
27. Perkin MR, Logan K, Marrs T, et al. J Allergy Clin Immunol. 2016;137(5):1477-86.e8. doi:10.1016/j.jaci.2015.12.1924
28. Xu F, Yan SX, Li F, et al. PLoS One. 2012;7(5):e36174. doi:10.1371/journal.pone.0036174. Frontiers+1MedNexus+1
29. Ahn K. J Allergy Clin Immunol. 2014;134(5):993-9. doi:10.1016/j.jaci.2014.09.023. PubMed
30. Venkataraman D, Soto-Ramírez N, Kurukulaaratchy RJ, et al. J Allergy Clin Immunol. 2014;134(4):876-82.e4. doi:10.1016/j.jaci.2014.07.033. PubMed
31. Paul WE, Zhu J. Nat Rev Immunol. 2010;10(4):225-35. doi:10.1038/nri2735.

Correspondence:
Received: 15 March 2025
Accepted: 16 April 2025
Heba Gadelrab, MD
Pediatric Department, Faculty of Medicine,
Alexandria University, Alexandria, Egypt
E-mail: h_shaher@alexmed.edu.eg
ORCID: 0009-0001-1102-4855