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"CAROL DAVILA" din BUCUREȘTI

UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE
"CAROL DAVILA", BUCUREȘTI
ȘCOALA DOCTORALĂ
DOMENIUL MEDICINĂ

Observational clinical study regarding diagnosis and treatment of pediatric patients with atopic dermatitis and food allergies

PhD THESIS SUMMARY

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Fundamental Problem

Personalized Diagnosis and Therapeutic Management of Atopic Dermatitis Associated with

Food Allergies in the Pediatric Population

Atopic dermatitis (AD) or atopic eczema is a chronic, relapsing inflammatory skin pathology characterized by an erythematous rash associated with skin xerosis and pruritus. Most often, AD is associated with other allergic diseases, in a proportion of 20% among children, and approximately 3% in adults. According to the World Health Organization, according to a 2022 report, this inflammatory eczema affects 220 million people worldwide. Since the disease affects the quality of life of both patients and their families, it ranks first in terms of morbidity among non-fatal skin pathologies.

The etiopathogenesis of AD is complex, with genetic, immunological or environmental factors being involved. Pediatric patients with AD also sometimes present other manifestations of the "atopic march". Regarding the genomic study, the exact genes involved could not be identified, but certain chromosomes were highlighted, which seem to have implications in the production of the disease: chromosomes 1, 3, 5, 11, 15 or 17. In approximately 75%, the filaggrin gene, located on chromosome 1, seems to be involved. Among aeroallergens, the most frequent are house dust mites and ragweed. Infections represent one of the most important trigger factors in the production of AD, through the interaction of microbial antigens with the immune system. In another context, recent studies have shown a direct link between AD and the intestinal microbiome; the most frequently involved strains being: Bacteroides, Lactobacillus and Clostridium. The physiological and diverse skin microbiome inhibits the colonization of pathogens, thus having an anti-inflammatory effect and modulating the immune response. The skin of pediatric patients with AD presents a skin dysbiosis with an increased level of S. aureus.

The most recent classification divides AD into the extrinsic form, associated with an increased level of IgE; and the intrinsic form, associated with a normal level of IgE. The extrinsic form is predominant and is associated with food allergies, but also with skin barrier

dysfunctions and mutations of the filaggrin gene. The intrinsic form is usually associated with a metal allergy, being frequent among women. In order to quantify the evolution of the disease, but also the response to treatment, several scores have been proposed: SCORAD (the Scoring Atopic Dermatitis), POEM (patient-oriented eczema measure), BSA (body surface area), V-IGA (the investigator's global assessment), EASI (eczema area and severity index).

In the case of AD, laboratory investigations have a limited role, in most situations having the role of identifying trigger factors. The serum level of total IgE has the role of both classifying AD in intrinsic versus extrinsic form, and of establishing the prognosis of the disease. The most frequently implicated food allergens in AD are: cow's milk protein, peanuts, eggs, fish, soy, and gluten. Patch testing is one of the diagnostic methods of AD trigger factors, but, at present, there is no general consensus in this regard. Also, prick testing has similar valences. According to recent studies, prick testing for food allergens is less specific than for aero-allergens.

The evolution of AD is chronic, with episodes of exacerbation and episodes of remission, so that the management of these pediatric patients requires an individualized, long-term approach. First of all, it is necessary to restore the skin barrier, but also to reduce local inflammation, by combining emollients with topical calcineurin inhibitors and topical corticosteroids. In 2021, a new topical treatment for AD was approved in the United States of America. Ruxolitinib 1.5% cream is recommended in moderate or severe forms of the disease, for short-term and discontinuous treatment, in children over 12 years of age. Systemic therapy of AD is reserved for moderate and severe cases, associated with impaired quality of life of patients, and which are non-responsive to topical treatment and phototherapy. In the case of pediatric patients, the risk-benefit balance is calculated extremely carefully. Tralokinumab, also a monoclonal antibody, approved in 2021, inhibits Th2 pathway cytokines, by neutralizing IL-13 and preventing its binding to receptors. With a similar mechanism of action to tralokinumab, there is also lebrikizumab, which targets and neutralizes IL-13. Phase III studies are already available for adolescents with moderate to severe AD. Cendakimab is also part of the monoclonal antibodies, with action against IL-13, but is still in phase II studies. Janus kinase (JAK) inhibitors are already approved for severe forms of AD. A JAK-1 inhibitor, Upadacitinib, is recommended for children over 12 years of age and weighing over 40 kg.

Baricitinib, a JAK-1 and JAK-2 inhibitor, is in a phase III study, with a view to approval for pediatric patients between 2 and 17 years of age. In a series of clinical trials, topical application of probiotics that inhibit S. aureus colonization has beneficial effects on the restoration of the skin microbiota, and, consequently, on the control of AD. The administration of oral probiotics in pediatric patients with AD brings varying benefits, depending on the strains involved, the study design, but also the population studied.

In the vast majority of cases, the evolution of AD is favorable, with improvement occurring at any age. However, one third of patients develop allergic asthma, and the same percentage allergic rhinitis. A recent study, conducted on a group of approximately 7,000 pediatric patients with mild or moderate forms of AD, showed that the pathology persists until around the age of 10.

Hypotheses and objectives

Currently, there is a limited number of studies in the specialized literature that quantify the association between AD and food allergies. This is the reason why the data related to the association between the two pathologies, their evolution and prognosis, are not fully known. Thus, the purpose of the present work was to identify a possible association between the personalized therapeutic management of food allergies, immediate (Ig E) and delayed (non-IgE) and the evolution of AD.

The main objective is to follow the evolution of AD in patients who associate IgE and non-IgE food allergies, under complex, personalized management.

The secondary objectives were represented by:

• translating the POEM score into Romanian, in children with atopic dermatitis, and correlating it with the SCORAD score;

• following the evolution of AD in pediatric patients who also associate skin dysbiosis, who received personalized therapy, in order to correct the affected microbiota;

• monitoring the evolution of AD in pediatric patients who also associate intestinal dysbiosis, who received personalized therapy, in order to correct the affected microbiota.

Material and Method

The present research represents an observational, retrospective study. It was carried out within the Sf. Constantin Hospital, Braşov, Romania. It involved the use of data from patients who had several presentations in our unit, between September 2025 and February 2026.

In order to achieve the purpose, main and secondary objectives of this work, 4 studies were carried out: study I which aimed to translate the POEM score into Romanian, in children with atopic dermatitis, and its correlation with the SCORAD score; study II which evaluated the evolution of AD in pediatric patients who also associate cutaneous dysbiosis, who received personalized therapy, in order to correct the affected microbiota; study III evaluated the evolution of AD in pediatric patients associated with intestinal dysbiosis, who received personalized therapy, in order to correct the affected microbiota; study IV evaluated the evolution of AD in patients associated with IgE and non-IgE food allergies, under complex, personalized management.

Following the application of the inclusion and exclusion criteria, study I included 90 pediatric patients diagnosed with AD; study II included 41 pediatric patients diagnosed with AD and skin dysbiosis (which also associates food allergies); study III included 21 pediatric patients diagnosed with AD and intestinal dysbiosis (which also associates food allergies); and study IV included 85 pediatric patients diagnosed with AD and food allergies.

For each patient, the following were analyzed: demographic data, clinical parameters (scores), laboratory investigations and therapeutic management. Approval was obtained from the hospital's Ethics Board, as well as informed consent from the parents.

Study I

1. Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin pathology, with an undulating evolution, presenting episodes of exacerbation, with pruritic lesions, and periods of remission. This eczema usually manifests itself in the first year of life (0–6 months) (60% of cases) and affects the quality of life. For this reason, careful monitoring is necessary: itching, sleep, daily

activity. Two essential tools are frequently used to follow up these pediatric patients. First, in order to quantify the impact of the disease on the quality of life of pediatric patients with atopic dermatitis, the Patient-Oriented Eczema Measure (POEM) is a useful option. On the other hand, clinical evaluation should always be performed by the specialist doctor, calculating the SCORAD score.

2. Aim and objectives of the research

The aim of this study was to translate the POEM score into Romanian, among pediatric patients with AD. The primary objective was to correlate the POEM score with the SCORAD score.

The secondary objectives were: to correlate the 2 scores with other associated allergic pathologies; to quantify a possible association between the child's clinical data (cesarean section, in vitro pregnancy, premature birth, nutrition).

3. Material and method

Study I included 90 pediatric patients diagnosed with AD, for whom the POEM and SCORAD scores were completed. The impact of AD on pediatric patients was assessed using the POEM questionnaire. It quantifies the impact on the child's quality of life during the previous week. The group was also divided into 2 other subgroups: under 5 years of age (the caregiver answered for the child) and over 5 years of age (the child answered together with the caregiver). During the same visit, the SCORAD score was completed to quantify and classify the form of AD.

4. Results

The study group included 90 pediatric patients: 42 males (47.77%) and 48 females (52.23%), with a female predominance. Regarding age, we divided the main group into 2 subgroups: ≤5 years (65 patients – 72.23%) and >5 years (25 patients – 27.77%).

Comparison of socio-demographic and clinical characteristics and POEM and SCORAD scores means

For children ≤5 years, the POEM score value was 12.26±0.65. For children >5 years, the POEM score value was 11.89±1.02 ($p=0.793$). There were no statistically significant

differences in the POEM scores means between the 2 age groups; although younger children developed slightly more severe forms. Regarding SCORAD, the data were similar between the 2 groups: 36.93±1.88 (≤5 years) and 36.69±3.14 (>5 years), with p=0.923.

Regarding the distribution by gender, there was also no statistically significant difference: the POEM score was 11.93±0.80 (female) and 12.29±0.76 (male), with p=0.755; on the other hand, the mean SCORAD was 35.65±2.41 (female) and 37.84±2.17 (male), with p=0.501.

Association of DA with other allergic pathologies

The association of atopic dermatitis with other atopic diseases was statistically significant. The most frequent association was food allergy (13.5%), followed by allergic rhinitis (8.88%) and then allergic bronchial asthma (8.1%). Regarding the correlation with the scores, the data showed: the POEM score was 15.62±0.87 for the association with allergic diseases versus 10.70±0.60 for the absence of other atopic diseases, with p<0.01. The SCORAD score showed similar results: mean±SD was 48.28±1.98 for the association with allergic diseases versus 32.17±1.83 for the absence of other atopic diseases, with p<0.01.

Correlation between socio-demographic factors and AD severity

Socio-demographic and clinical factors such as cesarean delivery, in vitro pregnancy, premature birth, nutrition, were investigated to establish a correlation between them and the severity of atopic dermatitis. Although we could not identify a relevant correlation, some differences were present. The POEM score was 12.86±0.63 for children born by cesarean section, versus 9.71±0.94 for children born vaginally, with p=0.14. We found similar results for SCORAD: 39.19±1.79 for children born by cesarean section, versus 29.05±3.15 for those born vaginally, with p=0.07. We also investigated prematurity, as it can influence the severity of the disease: the POEM score was 14.52±0.97 for premature children versus 11.39±0.63 for term children, with p=0.11. For SCORAD, the mean was 41.52±2.86 in premature infants, versus 35.39±1.89 in term infants, with p=0.108. In vitro fertilization does not seem to influence the evolution and severity of the disease, but some differences were found: the POEM score was 15.36±1.23 for in vitro conceived newborns, versus 11.67±0.58 for the others, with p=0.16; regarding SCORAD, the mean was 42.10±4.34 for in vitro conceived newborns, versus 36.09±1.73 for the others, with p=0,023.

Figure 1. Linear regression coefficients for predictors of (A) POEM and (B) SCORAD scores with 95% CI

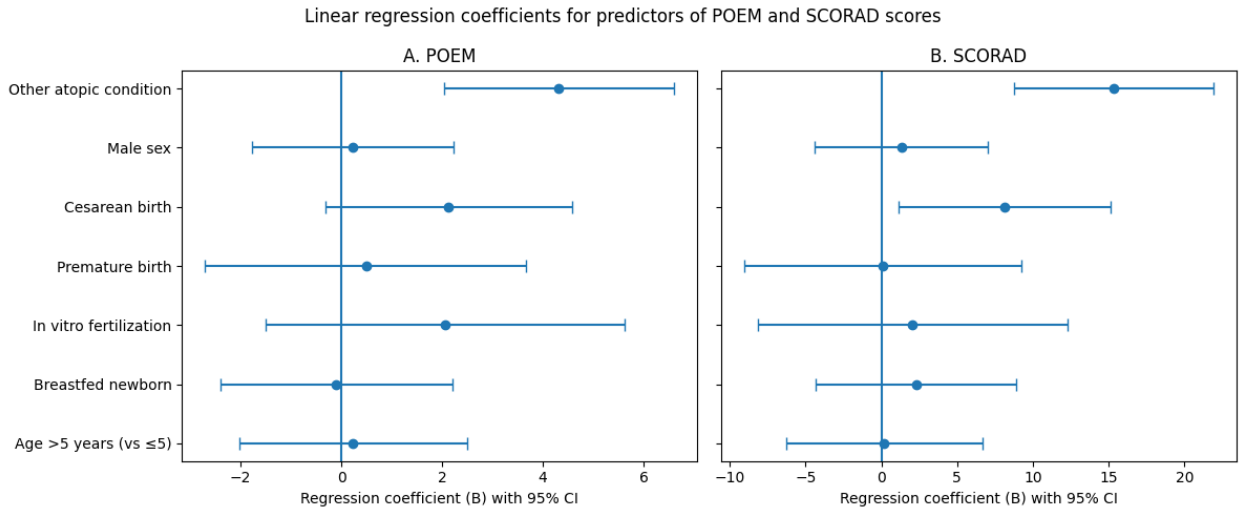
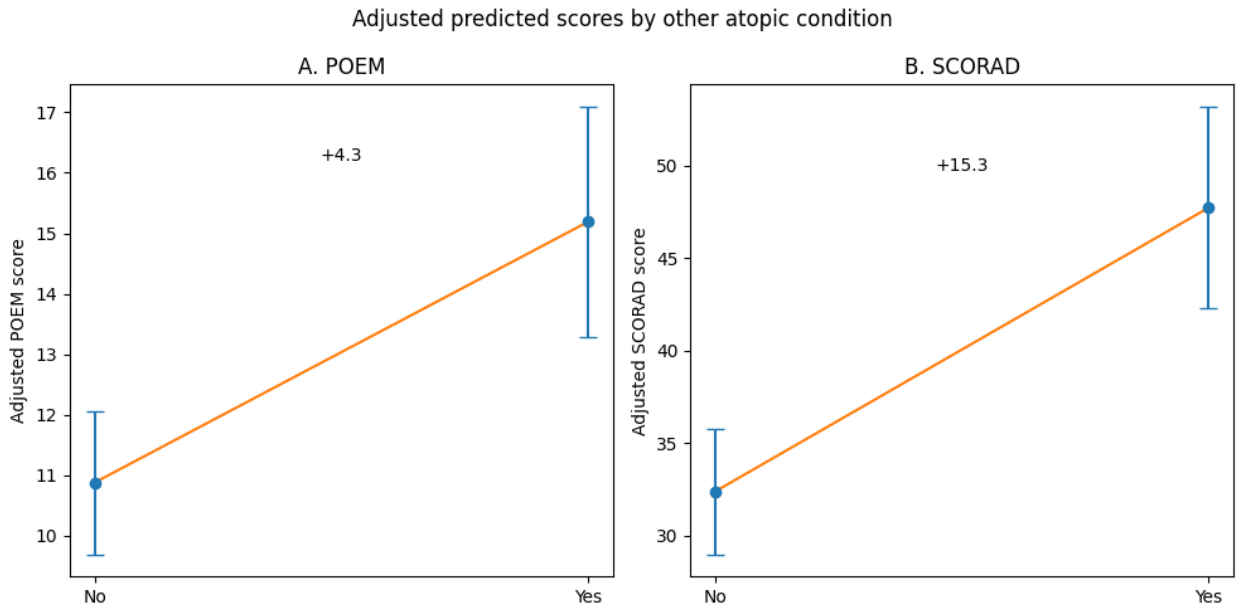


Figure 2. Predicted adjusted scores of (A) POEM and (B) SCORAD according to the variable “other conditions”



5. Discussion

According to the literature, this study is the first published study investigating the correlation between POEM and SCORAD scores in Romanian children with atopic dermatitis. A high percentage of patients in our study were born by cesarean section, as this practice is known to be increasing worldwide. According to some studies, atopic diseases seem to occur more frequently in infants born by cesarean section than in those born vaginally. Regarding breastfeeding, the World Health Organization also recommends breastfeeding infants up to 2 years of age. Studies have shown that breastfeeding may have a protective effect on AD in children; however, other studies have identified insignificant or even negative effects.

The correlation between prematurity and AD is widely investigated, but additional studies are still needed. A meta-analysis in this area was conducted, which included thirteen articles with a total of over 4 million participants, and in most studies (n = 8) prematurity was associated with a lower risk of atopic dermatitis. Another study did not find a significant correlation between pediatric patients born prematurely and those born at term, regarding food allergies or AD.

Regarding the association with other pathologies, other authors demonstrated similar conclusions to our study: premature infants had a higher risk of developing asthma; also, pulmonary hypertension or cardiorespiratory comorbidities are risk factors for asthma.

6. Stage conclusions

This study represents the first study to investigate the correlation between POEM and SCORAD scores in Romanian pediatric patients with AD. SCORAD and POEM scores were strongly correlated. Certain factors, such as prematurity or breastfeeding, do not seem to have influenced the course of the disease in our patient cohort. However, other atopic diseases, such as asthma, have been associated with more severe forms of atopic dermatitis.

Study II

1. Introduction

Atopic dermatitis (AD) is a dermatological condition that often affects young children. AD is manifested by skin barrier dysfunction and inflammation. Skin barrier dysfunction is caused

by alteration of the stratum corneum; this outer layer of the skin is essential for maintaining hydrophobic properties, rheological properties and skin pH. The skin microbiota is represented by all resident microorganisms at the skin level and is made up of bacteria, fungi, viruses and mites; its role is to maintain the integrity of the skin barrier and local immunity.

2. Aim and objectives of the research

The aim of this work was to follow the evolution of AD in pediatric patients who also associate skin dysbiosis, who received personalized therapy, in order to correct the affected microbiota.

The main objective was to analyze the skin microbiota in pediatric patients with AD. Secondary objectives aimed to quantify a possible association between clinical data (cesarean section, in vitro pregnancy, premature birth, nutrition) and skin dysbiosis.

3. Material and method

Study II included 41 pediatric patients diagnosed with AD and skin dysbiosis. For this group of pediatric patients, we also noted the POEM and SCORAD scores before the start of treatment (visit 0). To quantify the efficacy of the therapy, the scores were also calculated at the first visit (after 14 days) and at the second visit (after 30 days).

In order to be able to compare prematurely born children with those born at term, the following data were also recorded: sex, age, premature or full-term birth, other associated atopic diseases, cesarean section birth compared to vaginal birth, in vitro fertilization, newborn breast-fed or formula-fed.

4. Results

Comparison between socio-demographic and clinical characteristics and mean POEM and SCORAD scores

In the study, 41 children with atopic dermatitis were included (24 boys, 58.5%; mean age 39.78 ± 45.64 months). The majority were born by cesarean section (34, 82.9%), of whom 12 (29.3%) were born prematurely and 5 (12.2%) were conceived by in vitro fertilization. Fifteen children (36.6%) were breastfed in the newborn period. Initial POEM and SCORAD scores indicated moderate-severe atopic dermatitis (POEM: 15.41 ± 5.11; SCORAD: 45.89 ± 11.51).

Local versus systemic treatment

Regarding treatment, most received local antibiotic therapy (34, 82.9%) and emollients (36, 87.8%), and corticosteroids were prescribed in 25 cases (61.0%). Regarding topical antibiotics, most children received gentamicin (23, 67.64%), followed by fusidic acid (19, 55.88%) and then mupirocin (11, 32.35%). Due to lesions associated with crusts, these patients were also recommended chlorhexidine solution for disinfection (2, 5.88). All pediatric patients received emollients, to control microinflammation. For the inflammatory phenomenon, topical corticosteroids were prescribed: low-potency dermatocorticosteroids: hydrocortisone (11, 32.35%); medium potency: betamethasone (9, 26.34%) and mometasone (5, 14.7%). Another class of drugs recommended for anti-inflammatory effect were calcineurin inhibitors: tacrolimus (2, 5.88%) and pimecrolimus (4, 11.76%). Eleven children (26.8%) required systemic therapy in addition to local treatment: trimethoprim-sulfamethoxazole (5, 45.45%); cefuroxime (2, 18.18%); vancomycin (1, 9.09%); gentamicin (1, 9.09%); ceftriaxone (1, 9.09%); cefpodoxime (1, 9.09%).

Results of skin dysbiosis analysis

Skin culture was positive for Staphylococcus aureus in 19 patients (46.3%): MSSA (14; 73.68%) or MRSA (5, 26.31%). Other relevant microorganisms that were identified (34.1% of patients): Enterobacter cloacae (1, 7.14%); Klebsiella oxytoca (1, 7.14%); Pantoea agglomerans (1, 7.14%); Staphylococcus hominis (1, 7.14%); Staphylococcus epidermidis (11, 26.82%); Enterococcus faecium (1, 7.14%); Staphylococcus warneri (2, 21.42%); Staphylococcus sciuri (1, 7.14%); Proteus mirabilis (1, 7.14%); Streptococcus viridans (1, 7.14%); Klebsiella pneumoniae (1, 7.14%).

POEM and SCORAD scores evolution over 30 days

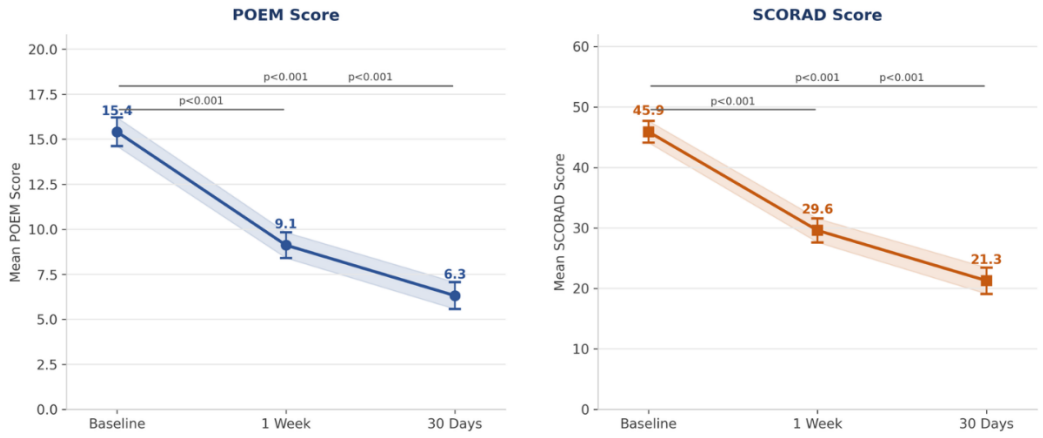
Both POEM and SCORAD scores demonstrated significant and progressive improvement at all three assessment times (Figure 1). Mean POEM scores decreased from 15.41 ± 5.11 at baseline to 9.12 ± 4.57 at 14 days and 6.32 ± 4.77 at 30 days. Mean SCORAD scores decreased similarly, from 45.89 ± 11.51 at baseline to 29.59 ± 12.63 at 14 days and 21.28 ± 13.93 at 30 days. Repeated-measures ANOVA confirmed a statistically significant effect of time on POEM scores (Mauchly's $W = 0.832$, $p = .028$; Greenhouse–Geisser correction: $F(1.71, 68.48) =$

94.07, $p < .001$, partial $\eta^2 = 0.702$, power = 1.000) and on SCORAD scores (Mauchly's W = 0.760, $p = .005$; Greenhouse–Geisser correction: $F(1.61, 64.48) = 116.08$, $p < .001$, partial $\eta^2 = 0.744$, power = 1.000), both indicating very large effect sizes. Post-hoc pairwise comparisons with Bonferroni correction revealed significant differences between all three time points for both outcomes (all $p < .001$), indicating that improvement occurred both within the first 14 days and continued significantly through day 30. Descriptively, S. aureus-positive patients had higher mean POEM and SCORAD scores at both baseline and day 30 compared with S. aureus-negative patients, with both groups demonstrating improvement over the study period.

Predictors of disease severity at 30 days

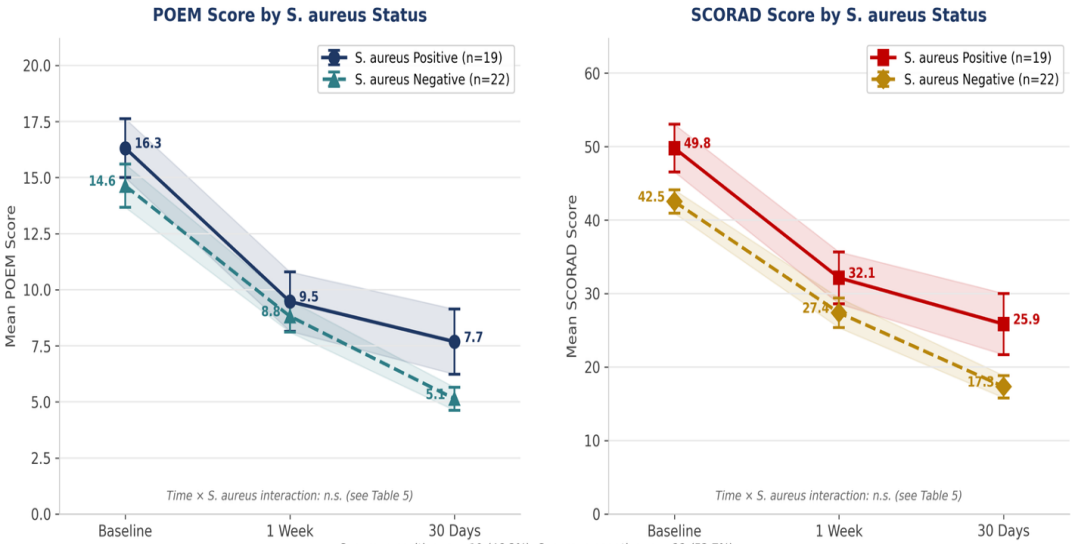
A hierarchical linear regression was performed to identify predictors of POEM and SCORAD scores at 30 days (Table 6). In Model 1, baseline POEM score significantly predicted POEM severity at 30 days ($R^2 = 0.220$, $p = .002$), explaining 22.0% of the variance in outcome scores. Adding perinatal and demographic characteristics to Model 2 (age, sex, preterm birth, breastfeeding, cesarean section, and IVF) did not significantly improve model fit ($\Delta R^2 = 0.054$, $p = .872$), indicating that these variables did not provide significant predictive information beyond baseline POEM severity. For SCORAD, baseline score was a stronger predictor of 30-day outcome ($R^2 = 0.310$, $p < .001$), explaining 31.0% of the variance. Similarly, adding baseline characteristics to Model 2 did not significantly improve prediction ($\Delta R^2 = 0.083$, $p = .612$). For both outcomes, baseline disease severity emerged as the main determinant of 30-day clinical status, and perinatal and demographic factors did not provide significant additional predictive value in this study sample.

Figure 1. Evolution of POEM and SCORAD Scores Over 30 Days (N = 41)



Error bars represent standard error of the mean (SEM). All pairwise comparisons significant at $p < 0.001$ (Bonferroni-corrected repeated measures ANOVA with Greenhouse-Geisser correction, partial $\eta^2 = 0.702$).

Figure 2. POEM and SCORAD Trajectories by Staphylococcus aureus Skin Colonisation Status



S. aureus positive: n = 19 (46.3%); S. aureus negative: n = 22 (53.7%).
Error bars represent standard error of the mean (SEM). Both groups improved across all time points.
Time × S. aureus interaction non-significant for POEM ($p = 0.385$, partial $\eta^2 = 0.024$) and SCORAD ($p = 0.483$, partial $\eta^2 = 0.017$).

5. Discussion

The study analyzed possible correlations between personalized therapeutic management of skin dysbiosis and the evolution of AD.

The skin microbiota is defined as a “microbial fingerprint” and is influenced by endogenous and exogenous factors. Age is one of the most important factors. Recent studies show that the

risk of developing food allergies (AA) and respiratory allergies increases with the development of a dysfunctional skin barrier.

In AD there is a hereditary defect of the epidermal barrier, a filaggrin mutation, which leads to skin dysbiosis and, consequently, to overpopulation with S. aureus. Furthermore, S. aureus triggers the inflammatory cascade through the secretion of cytokines (IL-4, IL-13, IL-22) and has a major role in the severity of the disease and acute episodes.

6. Stage conclusions

AD is a complex autoimmune disease, with varied evolutions. Most commonly, in severe forms of the disease, the lesions become superinfected, and the rash no longer responds to treatment. On the other hand, in the context of a damaged skin barrier, AD is also associated with skin dysbiosis. Over time, the patient may also develop food allergies. Thus, personalized treatment of AD, which also includes the management of skin dysbiosis, may benefit these pediatric patients.

Study III

1. Introduction

Recent studies have also demonstrated a correlation between AD and the use of antibiotics in the first years of life. On the other hand, large families and childhood infections seem to decrease the risk of AD. This theory is known as the “hygiene hypothesis”: reduced exposure to certain viral and bacterial pathogens.

In recent years, a link has been demonstrated between the alteration of the intestinal microbiota in the early stages of life and allergic diseases. A recent study showed that children with AD have an altered intestinal microbiota, with reduced diversity, especially if the disease began at 6 months or 2 years. The mechanism of the gut–skin axis in AD consists of the modified production of bacterial metabolites and short-chain fatty acids.

2. Research aim and objectives

The aim of this study was to follow the evolution of AD in pediatric patients who also associate intestinal dysbiosis and who received personalized therapy, in order to correct the affected microbiota.

The primary objective was to analyze the gut microbiota in pediatric patients with AD. Secondary objectives aimed at quantifying a possible association between clinical data (cesarean section, in vitro pregnancy, preterm birth, nutrition) and intestinal dysbiosis.

3. Material and method

Study III included 21 pediatric patients diagnosed with AD and intestinal dysbiosis. For this group of pediatric patients, we also recorded the POEM and SCORAD scores before the start of treatment (visit 0). To quantify the efficacy of the therapy, the scores were also calculated at the first visit (after 30 days) and at the second visit (after 90 days).

In order to be able to compare prematurely born children with those born at term, the following data were also recorded: sex, age, premature or term birth, other associated atopic diseases, cesarean section birth compared to vaginal birth, in vitro fertilization, newborn breast-fed or formula-fed.

4. Results

Sample Characteristics

Twenty-one children with atopic dermatitis were included in the analysis. The mean age was 4.86 ± 3.75 months, and 47.6% (n = 10) were male. The majority were born by cesarean section (85.7%), and 42.9% were born preterm. One child (4.8%) was conceived by in vitro fertilization, and 42.9% were breastfed. The index for intestinal dysbiosis (high putrefactive flora) was identified in 15 children (71.4%), and the median Flora Index was 5 (IQR 3.5–6). The means of the initial POEM and SCORAD scores were 14.67 ± 5.22 and 41.66 ± 15.28, respectively.

POEM and SCORAD Evolution

Both POEM and SCORAD scores decreased substantially over the three visits. The mean POEM decreased from 14.67 ± 5.22 at baseline to 9.76 ± 4.29 at 7 days and 7.10 ± 3.82 at 90 days. The mean SCORAD followed a similar trajectory, decreasing from 41.66 ± 15.28 at baseline to 26.02 ± 11.63 at 7 days and 17.93 ± 11.68 at 30 days. A repeated-measures ANOVA confirmed a significant within-subject effect of time for both scales. For POEM, $F(2, 40) = 63.04$, $p < .001$, partial $\eta^2 = .759$, observed power = 1.000. For SCORAD, $F(1.39, 27.71) =$

59.56, $p < .001$, partial $\eta^2 = .749$, observed power = 1.000. All pairwise contrasts between time points were statistically significant (Table 4b). The largest mean differences were observed between baseline and 90 days for both scales (POEM: 7.57, 95% CI 5.45–9.69, $p < .001$; SCORAD: 23.73, 95% CI 16.59–30.86, $p < .001$).

Between-group differences by Highly Positive Putrefactive Flora (also in English)

Children with Highly Positive Putrefactive Flora had significantly higher POEM scores than those with negative flora both at baseline (median 15, IQR 8 vs 9, IQR 5; $p = 0.021$) and at 90 days (7, IQR 5 vs 4.5, IQR 4; $p = 0.041$). For SCORAD, between-group differences did not reach statistical significance at baseline (44.45, IQR 24.90 vs 33.13, IQR 14.20; $p = 0.276$), but were significant at 90 days (20.70, IQR 7.05 vs 11.38, IQR 4.98; $p = 0.032$). These bivariate findings indicate that High Putrefaction Flora is associated with a higher severity of AD, especially at a later time point.

5. Discussion

Reduction of SCORAD and EASI scores was associated with oral administration of probiotics (Lactobacilli, Bifidobacteria): the microbiota produces increased levels of SCFA and tryptophan metabolites; thus, the differentiation of regulatory T cells is facilitated and also the secretion of IL-10 and TGF-β. In this way, the Th2-type immune response is inhibited. However, the optimal initiation time, dose and duration of probiotic administration are still under debate.

6. Stage conclusions

Personalized treatment of AD, including by treating intestinal dysbiosis, may benefit these pediatric patients. In our study, we found a significant correlation between the severity of AD and the degree of intestinal dysbiosis. Moreover, the putrefactive flora index is directly proportional to the severity of dermatitis, especially at a late stage.

Study IV

1. Introduction

Patients with AD are at higher risk of food allergy (AA), as they associate a damaged skin barrier; in this way, exposure to food antigens leads to the production of specific

immunoglobulin E, and over time, to sensitization to these specific allergens. On the other hand, recent studies show that skin inflammation leads to intestinal inflammation and intestinal dysbiosis.

2. Research aim and objectives

The aim of this study was to follow the evolution of AD in pediatric patients who also associate food allergies, of the immediate IgE, delayed non-IgE, or mixed type, who benefited from personalized therapeutic management.

The main objective was to analyze an association between food allergies and other related pathologies (growth retardation, gastroesophageal reflux disease, allergic proctocolitis, intestinal parasitosis, anemia, allergic rhinitis, asthma), among pediatric patients with AD. Secondary objectives aimed to quantify a possible association between clinical data (cesarean section, in vitro pregnancy, premature birth, diet) and food allergies.

3. Material and method

Study IV included 85 pediatric patients diagnosed with AD and food allergies. For this group of pediatric patients, the SCORAD score was calculated before the start of therapeutic management (visit 0). In order to quantify the efficacy of therapy, the score was calculated at the second visit (after 90 days). At the same time, associated pathologies were also highlighted.

In order to compare prematurely born children with those born at term, the following data were also recorded: sex, age, premature or term birth, other associated atopic diseases, cesarean section birth compared to vaginal birth, in vitro fertilization, newborn fed naturally or formula.

4. Results

Recoding of variables

For the various food allergens, they were grouped into three clinically significant categories: milk protein, egg, and gluten/wheat; all remaining allergens (nuts, potatoes, bananas, fish, and other foods) were aggregated into a single category “other allergens.” Systemic therapies were classified into three groups: probiotics (all preparations of Lactobacillus, Bifidobacterium, Enterococcus, Streptococcus thermophilus, and Saccharomyces boulardii, including inulin as a prebiotic adjuvant), antihistamines (cetirizine, ketotifen, desloratadine, and levocetirizine in

all formulations), and inhaled/intranasal agents (inhaled corticosteroids, bronchodilators, montelukast, and intranasal antihistamines). Topical therapies were classified as emollients, topical corticosteroids (agents ending in '-son' or '-zona', including methylprednisolone aceponate), and calcineurin inhibitors (tacrolimus and pimecrolimus).

Primary outcome

Response to treatment was quantified as the percent improvement in SCORAD score from baseline (T0) to final assessment (T2). The distribution of percent improvement was examined before analysis; one patient had a negative value (worsening, −15.8%), and the rest of the group demonstrated improvements ranging from 0 to 76.9%. (Figure 1).

Secondary outcomes

The vast majority (76.5%) of pediatric patients with AD had delayed-type allergies. Pediatric patients diagnosed with AD and delayed-type non-IgE food allergies develop more severe forms of eczema. The most common non-IgE food triggers include: cow's milk protein allergy, egg, gluten. The most common IgE food triggers include: cow's milk protein allergy, egg, nut, potato. The most severe forms of AD were developed by patients with mixed food allergies, IgE and non-IgE (16.47%). Among patients with AD and food allergies, 24.7% also had associated intestinal dysbiosis. Intestinal dysbiosis is the strongest predictor for the unfavorable evolution of AD. In the case of pediatric patients with AD and food allergies, by excluding the incriminated foods for 3 months, the skin condition improved significantly: the SCORAD score decreased by 51.6%. Among patients with AD and food allergies, a large proportion also presented other associated pathologies: gastrointestinal pathologies (gastroesophageal reflux disease – 22.35%; allergic proctocolitis – 16.47%; intestinal parasitosis – 15.29%); growth retardation – 9.41%; respiratory pathologies (allergic rhinitis, asthma) – 9.41%; iron deficiency anemia – 5.88%. The younger the age at which therapeutic intervention was performed (personalized treatment of intestinal dysbiosis and exclusion diet for the offending foods), the better the evolution of AD was. (Figure 2).

Figure 1. SCORAD before and after treatment

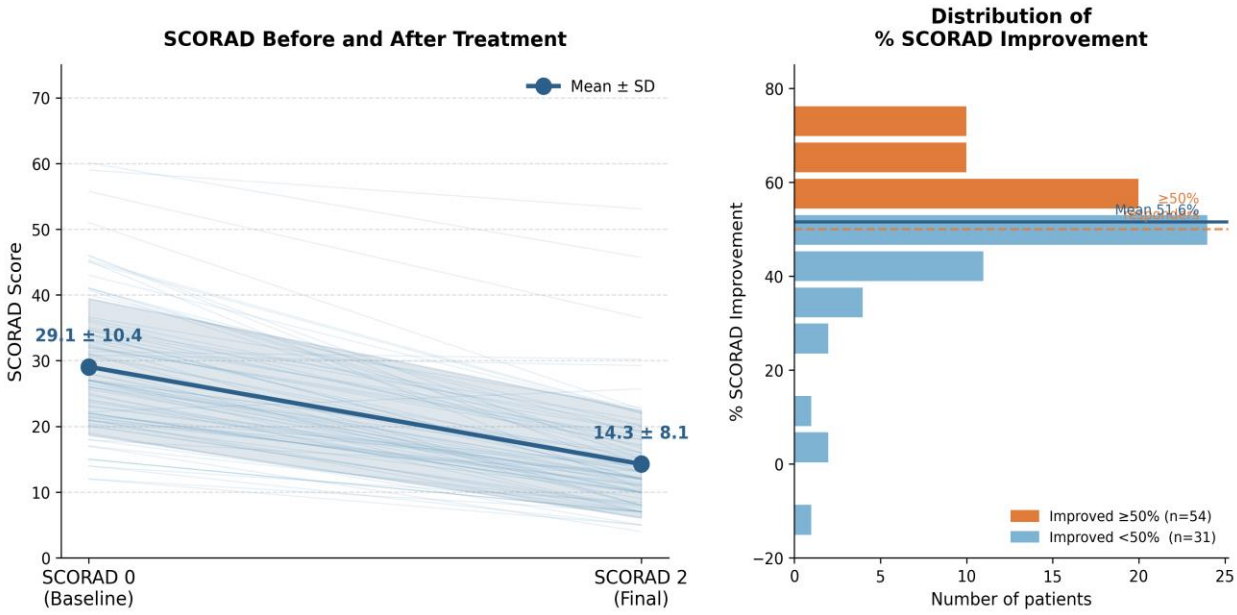
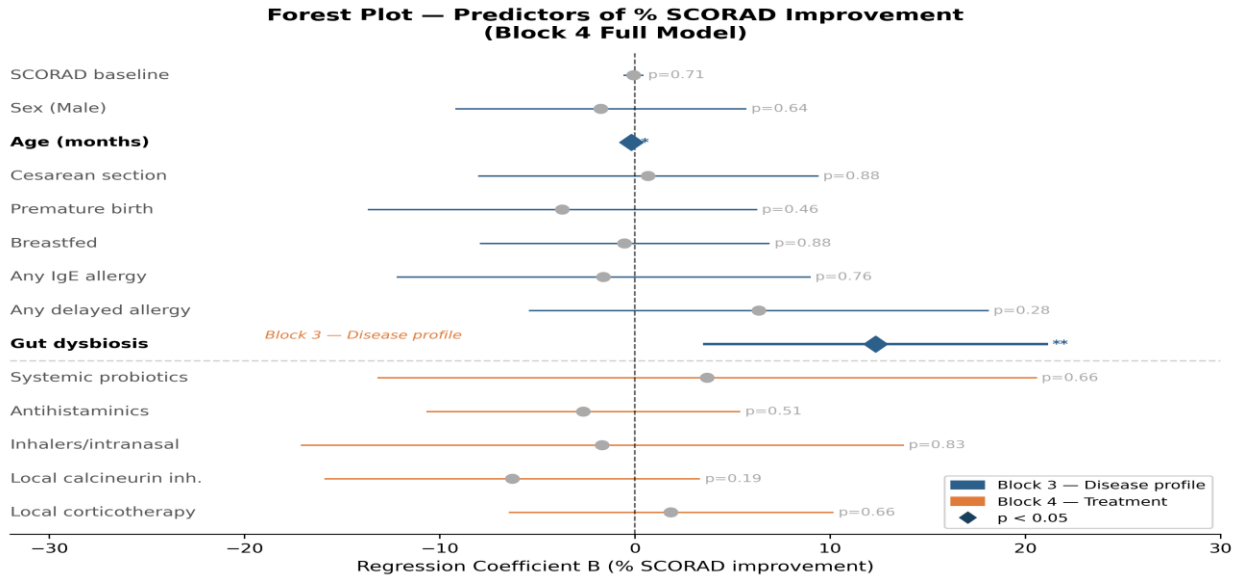


Figure 2. Forest Plot — Block 4 Regression Coefficients



5. Stage conclusions

Pediatric patients diagnosed with AD and delayed non-IgE food allergies develop more severe forms of eczema. Among patients with AD and food allergies, approximately one quarter also

have associated intestinal dysbiosis, which is the strongest predictor for the unfavorable evolution of AD.

General conclusions

In the group of patients studied, there is a statistically significant correlation between the SCORAD score, calculated by the dermatologist, and the subjective POEM questionnaire, completed by the relative/patient. No statistically significant correlation was identified between the severity of AD and the socio-demographic factors investigated (pregnancy obtained through in vitro fertilization, premature age at birth, birth by cesarean section, nutrition), within the group investigated.

Cutaneous dysbiosis within AD showed a positive therapeutic response to local therapy, individualized with antibiotics (gentamicin, mupirocin, fusidic acid), corticosteroids (hydrocortisone, betamethasone, mometasone) and emollients. In patients who associated AD with cutaneous dysbiosis, both POEM and SCORAD scores demonstrated a significant and progressive improvement during the three evaluation visits. Similar results were obtained in the case of intestinal dysbiosis.

The vast majority (76.5%) of pediatric patients with AD presented with delayed-type allergies. At the same time, they also presented with more severe forms of eczema. The most frequently identified non-IgE food triggers were cow's milk protein, egg, gluten.

Personal contributions

The current study is a pioneering study in Romania, on a representative group of pediatric patients with AD, who presented in the outpatient department of St. Constantin Hospital, Braşov.

This observational, retrospective, non-interventional study has a high degree of originality, being the first conducted in Romania that brings important information regarding the personalized management of pediatric patients with AD and food allergies, who have an unfavorable response to standard therapy, and present multiple relapses of the disease.

The idea of the study started precisely from the need to individually treat these pediatric patients with moderate or severe forms of AD, who have not responded to conventional therapy. In addition, in the specialized literature there is currently no standardized protocol regarding the individualized therapy of patients with AD and food allergies, of immediate or delayed type. The present work offers a broad perspective on the management of these children.

The results obtained may represent support for the development of a therapeutic management guide for pediatric patients with AD and food allergies.

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