



**ΔΗΜΟΚΡΙΤΕΙΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΡΑΚΗΣ**  
**ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ**

**ΕΡΓΑΣΤΗΡΙΟ ΥΓΙΕΙΝΗΣ ΚΑΙ ΠΡΟΣΤΑΣΙΑΣ ΠΕΡΙΒΑΛΛΟΝΤΟΣ**

ΜΕΤΑΠΤΥΧΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΣΠΟΥΔΩΝ  
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ΜΕΤΑΠΤΥΧΙΑΚΗ ΔΙΠΛΩΜΑΤΙΚΗ ΔΙΑΤΡΙΒΗ

**“Dietary and Microbiome Influences in the Pathogenesis and Management  
of Atopic Eczema”**

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**«Η επίδραση της δίαιτας και το μικροβιώματος στην παθογένεια και αντιμετώπιση της ατοπικής δερματίτιδας»**

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**“Dietary and Microbiome Influences in the Pathogenesis and Management  
of Atopic Eczema”**

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*This work is dedicated to my husband and my two sons, whose love, patience, and unwavering support give me the strength to continue learning and striving to contribute meaningfully to the advancement of medical science.*

## Περίληψη

Η Ατοπική Δερματίτιδα (ΑΔ) αποτελεί μία από τις πιο συχνές χρόνιες φλεγμονώδεις δερματοπάθειες, που επηρεάζει ιδιαίτερα παιδιά αλλά και ενήλικες, επηρεάζοντας σημαντικά την ποιότητα ζωής των ασθενών. Τα τελευταία χρόνια, η ερευνητική εστίαση έχει στραφεί στην κατανόηση των πολύπλοκων αλληλεπιδράσεων μεταξύ του ανοσοποιητικού συστήματος, του δερματικού φραγμού, της μικροβιακής χλωρίδας και της διατροφής. Η ΑΔ δεν θεωρείται πλέον απλώς δερματική νόσος, αλλά ένα σύστημα ανοσολογικής και μεταβολικής απορρύθμισης.

Η παρούσα θεωρητική εργασία διερευνά εκτενώς τον ρόλο της διατροφής και του μικροβιώματος στην παθογένεια, έκφραση και θεραπεία της ΑΔ. Αναλύονται οι μηχανισμοί μέσω των οποίων η ανισορροπία του εντερικού μικροβιώματος μπορεί να οδηγήσει σε φλεγμονή μέσω του άξονα εντέρου-δέρματος. Εξετάζονται διατροφικοί παράγοντες όπως τα ωμέγα-3 λιπαρά οξέα, τα αντιοξειδωτικά, οι πρεβιοτικές και προβιοτικές ουσίες, αλλά και ο ρόλος των τροφικών αλλεργιών και του αποκλεισμού συγκεκριμένων τροφών από τη διατροφή .

Ιδιαίτερη έμφαση δίνεται επίσης στον ρόλο της πρόωμης έκθεσης σε αλλεργιογόνα και της ανοσοεκπαίδευσης μέσω της διατροφής, στη σημασία της βιταμίνης D, καθώς και στη χρήση νέων θεραπευτικών στρατηγικών που στοχεύουν στο μικροβίωμα. Στόχος της παρούσας διατριβής είναι να προτείνει ένα ολοκληρωμένο πλαίσιο πρόληψης και διαχείρισης της ΑΔ, μέσω μιας πολυδιάστατης προσέγγισης που εστιάζει τόσο στις κλασικές όσο και στις συμπληρωματικές θεραπευτικές μεθόδους.

Λέξεις κλειδιά: ατοπική δερματίτιδα, ατοπικό έκζεμα, μικροβίωμα, άξονας εντέρου-δέρματος, τροφική αλλεργία

## Abstract

Atopic eczema (AE), also referred to as atopic dermatitis, is a prevalent chronic relapsing inflammatory skin condition that substantially impairs quality of life and often presents in early childhood. Recent scientific progress has shifted the understanding of AE from a localized skin disorder to a systemic disease involving immunological dysregulation, genetic susceptibility, and significant interactions between nutrition and the human microbiome.

This theoretical dissertation explores in depth the tripartite relationship between diet, gut and skin microbiota, and immune function in AE. A strong focus is placed on the gut–skin axis as a key mediator in the pathogenesis and progression of atopic inflammation. Mechanistic and clinical data are reviewed to understand how diet and microbial diversity shape immune tolerance, influence cytokine environments, and modulate barrier function.

The dissertation further analyses the role of early-life nutrition, the impact of processed and Western-style diets, and the therapeutic potential of anti-inflammatory dietary patterns such as the Mediterranean diet. It also discusses emerging microbiome-modulating therapies, including probiotics, prebiotics, synbiotics, postbiotics, and fecal microbiota transplantation, and how these interventions may offer personalized treatment options.

Additionally, the role of food allergies is discussed not only as triggers of eczema but also in terms of their immunological roots and diagnostic challenges. The potential of dietary interventions in both prevention and management of AE is emphasized, underscoring the need for evidence-based, patient-tailored strategies.

By integrating dermatological, immunological, nutritional, and microbiome sciences, this work contributes to a holistic framework for understanding AE and presents novel insights for future precision medicine approaches aimed at improving patient outcomes through individualized care.

Keywords: atopic dermatitis, atopic eczema, microbiome, skin-gut axis, , food allergy

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## Introduction

Atopic eczema (AE), or atopic dermatitis, is a common chronic relapsing inflammatory skin disease that impacts both children and adults. It is one of the most common skin diseases worldwide, occurring in as many as 20% of children and approximately 10% of adults, especially in developed countries (Nuttan, 2015; Odhiambo et al., 2009). AE is not just a disease of the skin, but is a systemic condition that has numerous immunological, environmental, and microbiological bases (3). Its rising prevalence over the past few decades is the result of a complex interplay of genetic susceptibility, immune dysregulation, skin barrier dysfunction, environmental triggers, and changes in the microbiome (Silverberg et al., 2013; Elias and Steinhoff, 2008; Cork et al., 2009).

Symptomatic presentation is with pruritus, xerosis and eczematous lesions with age-related distribution. It's commonly the first sign of the so-called "atopic march," the process in which eczema develops to food allergies, allergic rhinitis and asthma (Spergel, 2010). AE has a major negative impact on quality of life, including on sleep, school/work, and psychosocial functioning (Chamlin and Chren, 2010).

Structural and biochemical differences such as decreased filaggrin expression, ceramide depletion and increased transepidermal water loss. (TEWL) contribute to epidermal barrier defect in AE and play a very important role in the pathogenesis of AE (Palmer et al., 2006; Fallon et al., 2009). Loss-of-function mutations in the FLG gene, which encodes filaggrin, have been identified as major predisposing factors in early-onset and severe disease, especially when associated with food allergy and asthma (Brown and McLean, 2012; Leung et al., 2004). These abnormalities result in increased skin permeability to allergens and microbial products, which sensitise it to inflammatory stimuli.

Meanwhile, AE is characterized by strong immune dysregulation with a T-helper 2 (Th2) cytokine preponderance, especially in acute lesions. Cytokines like IL-4, IL-13, and IL-5 mediate IgE synthesis, eosinophil maturation, and barrier repair defects (Guttman-Yassky et al., 2011). In chronic eczema, other Th1, Th17, and Th22 responses contribute to epidermal thickening, inflammation, and lichenification (Brunner et al., 2017; Salem et al., 2018). Such immune polarization is now recognized to be influenced by early life exposures, such as mode of delivery, antibiotic consumption and nutritional behaviour.

One of the most revolutionary concepts in recent years is the gut-skin axis, a reciprocal dialogue between the gut and the skin that is achieved by connections in the microbial, immune, and neuroendocrine systems (Salem et al., 2018; Lee et al., 2018). Gut dysbiosis, defined as an imbalance in the diversity and role of gut microbiota, has been associated with the pathogenesis of AE. Interestingly, babies who develop AE have lower gut microbial abundance, and the *Bifidobacterium* and *Faecalibacterium prausnitzii* have decreased whereas the pro-inflammatory species such as *Escherichia coli* and *Clostridium* spp are

increased. (Abrahamsson et al., 2012; Kim et al., 2019). These alterations disturb immune tolerance, alter the gut epithelial barrier and lead to systemic inflammation, which can further promote skin manifestations.

Diet is a critical modifier of the gut microbiota and systemic immune modulation. The Western diet, high in refined sugars, saturated fats and low in fiber, promotes elevated levels of pro-inflammatory cytokines, oxidative stress and modification in gut microbial profile (Sausenthaler et al.,2007; Sicherer and Sampson,2014). Conversely, polyphenol-, fiber- and omega-3 fatty acid-rich Mediterranean-type diets support beneficial microbial taxa, increase levels of short-chain fatty acids (SCFA) and are inversely related to the prevalence of allergic and inflammatory conditions, including AE (Lack,2012; Du Toit et al.,2015).

Metabolites of microbes also play an important role, with short chain fatty acids (SCFAs), including butyrate and propionate, conferring anti-inflammatory and barrier-related effects. They induce T-dependent regulatory T-cell (Treg) differentiation, improve gut integrity, and inhibit Th2 responses, which are the basis for the gut–skin axis (Kalliomaki et al.,2001, Navarro-Lopez et al.,2018)). Vitamin D, zinc and selenium are also modulators of barrier function and immune homeostasis, and deficiencies in these micronutrients have also been found to be associated with AE severity (Udompataikul et al.,2001; Okuda et al.,2021; Tan-Lim and Esteban-Ipac, 2018).

To this complexity, food allergies, especially in children with early onset or moderate-severe eczema, must also be considered. The dual-allergen exposure hypothesis suggests, that allergic sensitization through the impaired barrier function of the skin might develop via the antigens present beneath the food remnants, while oral exposure to antigens may result in immune tolerance (Gruber et al.,2010). Hence, infants with eczema will have increased likelihood to develop of IgE-mediated allergies, mainly cow's milk, egg, peanut, and wheat (Fiocchi et al.,2015). Yet, blind elimination diets without an established diagnosis may result in nutrient deficiencies, emphasizing the importance of evidence-based nutritional management.

The enteric microbiota also modulates the effectiveness of treatment. The field of microbiomes-based therapies, for example probiotics, prebiotics, synbiotics and even fecal microbiota transplantation (FMT), is still in its naissance. A few RCTs have demonstrated that feeding the strains *Lactobacillus rhamnosus* GG and *Bifidobacterium breve*, among others, could prevent the appearance of or decrease the severity of AE by high-risk infants (Monteiro et al.,2013; Chassaing et al.,2015; Muraro et al., 2014). Personalized medicine that combines metagenomics, metaproteomics, and metabolomics is expected to build a new platform for stratifying AE patients and providing individual treatment (Dzidic et al.,2017).

This thesis examines the complex relationship between atopic eczema, diet and microbiome. It intends to summarise recent evidence about the cultural, immunogenetic and microbiological features of AE, underline the role of dietary and environmental factors, and discuss therapeutic strategies directed at the microbiota.

By means of an interdisciplinary literature search, which encompasses the fields of dermatology, immunology, gastroenterology, and nutritional science, the following aims of the present paper are pursued:

- Investigate the clinical features, epidemiology, and immunology of AE
- To assess the contribution of different dietary components to skin inflammation and allergic sensitization
- Examine the gut–skin axis as both a theoretical and treatment paradigm
- To investigate the mechanisms and clinical significance of food allergy in AE
- Examine the state of the art and emerging treatments in the areas of nutrition and microbiome modulation
- Suggest integrative approaches for prevention and for long-term disease management.

By integration across these domains, this dissertation seeks to address a holistic, and clinically translational, understanding of AE, and to inform the design of future interventions that go beyond symptomatic management to the fundamental causes of inflammation and immune dysfunction.

## Chapter 1: Clinical Description of Atopic Eczema

### 1.1 Introduction

Atopic eczema (AE), also known as atopic dermatitis (AD), is a chronic, recurring inflammatory skin disease that significantly affects patients' quality of life and imposes a considerable global healthcare burden. AE is a multifactorial condition arising from the interplay of genetic predisposition, immune dysregulation, epidermal barrier dysfunction, environmental factors, and microbiome alterations. No single factor is sufficient to cause AE independently, but rather the disease results from a convergence of these interrelated mechanisms. Clinically, AE is characterized by xerosis, pruritus, and eczematous lesions and is often the earliest manifestation of the atopic triad, which also includes asthma and allergic rhinitis (Nutten, 2015; Leung and Guttman-Yassky, 2014).

### 1.2 Epidemiology

AE is one of the most common chronic dermatologic conditions, especially in childhood. It affects approximately 15–20% of children and 5–10% of adults in developed nations (Bieber, 2008). In most cases, AE begins early in life, with 60% of patients developing symptoms before their first birthday and 90% by the age of five (Ili et al., 2004). However, late-onset and adult AE are increasingly recognized, especially in industrialized countries where prevalence has tripled in recent decades (Barbarot et al., 2018).

Prevalence varies with geography and ethnicity, pointing to environmental and socioeconomic influences. For instance, AE is more prevalent in urban than rural areas, likely due to differences in hygiene, pollution, and lifestyle (Williams et al., 2008). Rates are especially high in Northern and Western Europe, North America, and parts of Asia (Odhiambo et al., 2009).

### 1.3 Etiopathogenesis

The pathogenesis of AE involves several interdependent factors:

#### 1.3.1 Genetic Predisposition

AE has a strong genetic basis, with familial clustering frequently observed. Monozygotic twins show a concordance rate of up to 85%, compared to approximately 20% in dizygotic twins (Schultz Larsen and Hanifin, 1992). The most studied genetic contributor is the *filaggrin* (*FLG*) gene, which encodes a protein essential for epidermal barrier structure. Loss-of-function mutations in *FLG* are present in 20–50% of patients with moderate to severe AE and are associated with early-onset, severe disease, and comorbid conditions such as asthma and food allergy (Palmer et al., 2006; Irvine et al., 2011). Other implicated genes include those regulating immune responses (e.g., IL-4, IL-13, IL-31), skin barrier proteins

(e.g., SPINK5, CLDN1), and innate immunity (e.g., TLR2, TSLP) (Bieber, 2008; Kong and Segre, 2012).

### **1.3.2 Impaired Skin Barrier**

A hallmark of AE is a dysfunctional skin barrier that facilitates transepidermal water loss and allows easier penetration of allergens and pathogens. The stratum corneum is disrupted by abnormalities in keratinocyte differentiation, lipid composition, and pH regulation. FLG deficiency, reduced ceramides, and elevated skin pH all contribute to xerosis and increased microbial colonization (Elias and Steinhoff, 2008; Proksch et al., 2006).

### **1.3.3 Immune Dysregulation**

AE is driven by a predominantly Th2-skewed immune response, especially in the acute phase. This leads to increased levels of IL-4, IL-5, and IL-13, which promote IgE production, eosinophilia, and inflammation (Brandt and Sivaprasad, 2011; Gittler et al., 2012; Brunner and Guttman-Yassky, 2017). In chronic lesions, Th1, Th17, and Th22 responses also become prominent, resulting in lichenification and epidermal thickening. IL-31 has been identified as a key mediator of itch, while IL-22 contributes to impaired barrier function (Dillon et al., 2004; Eyerich and Novak, 2013).

### **1.3.4 The Microbiome and Skin Infection**

AE skin is frequently colonized by *Staphylococcus aureus* (*S. aureus*), found in up to 90% of affected skin and 30–50% of non-affected skin (Kong et al., 2012). *S. aureus* produces exotoxins that act as superantigens, amplifying Th2 inflammation and disrupting barrier function (Travers et al., 2010). AE is also associated with reduced cutaneous microbiome diversity, including lower levels of *Cutibacterium* and *Streptococcus* species. Restoring microbial balance is a potential therapeutic strategy (Totte et al., 2016, Sanford and Gallo, 2013).

### **1.3.5 Environmental Triggers**

Environmental factors play a crucial role in both the onset and exacerbation of AE. Common triggers include:

- House dust mites, pet dander, pollen, and mould
- Soaps, detergents, and wool fabrics
- Cold weather and humidity fluctuations
- Air pollutants such as tobacco smoke and nitrogen dioxide (Kim et al., 2019)

Infants raised in urban environments or exposed to pollutants may develop Th2-skewed immune profiles (Renz and Skevaki, 2021). Additionally, higher rates of cesarean delivery and reduced breastfeeding may impair microbial diversity and promote atopic tendencies (Azad et al., 2014).

### **1.3.6 Role of Epigenetics**

Emerging evidence suggests that epigenetic modifications, such as DNA methylation and histone acetylation, influence immune responses in AE. Prenatal exposures—including maternal diet and smoking—may alter gene expression in the fetus and predispose to allergic inflammation later in life (Dissanayake et al., 2020).

### **1.3.7 Neuroimmune Interaction and Itch Pathway**

Pruritus in AE is sustained by neuroimmune pathways involving IL-31, substance P, nerve growth factor, and protease-activated receptors. These mediators increase nerve fiber density and sensitivity, perpetuating the itch-scratch cycle (Stander et al., 2007; Cevikbas and Steinhoff, 2018). Chronic scratching leads to epidermal injury, further promoting inflammation and lichenification.

## **1.4 Other Clinical Features**

### **1.4.1 Clinical Features and Distribution**

AE typically follows an age-specific distribution pattern:

- **Infantile stage (0–2 years):** Erythematous, weeping lesions on cheeks, scalp, and extensor surfaces; diaper area often spared
- **Childhood phase (2–12 years):** Flexural involvement of elbows, knees, wrists, and ankles
- **Adolescents and adults:** Localized or diffuse disease affecting hands, face, eyelids, and neck; chronic hand eczema is common in adults, particularly due to occupational exposure (Thyssen et al., 2010) also see Table 1 (Blume-Peytavi and Metz 2020).

Table 1.: The clinical manifestations of AE according to age

| <b>Age</b>                 | Newborns and infants (0–2 years old)   | Children (2–10 years old)   | Teenagers and adults (>10 years old)  |
|----------------------------|--|---|---|
| <b>Anatomical sites</b>    | Scalp, convex areas of the face (cheeks, forehead, and earlobes), and extensor surfaces of the extremities | Perioral area, nape of the neck, folds of the areas that flex, and extremities (hands and feet) | Perioral area, neck, folds of the areas that flex, extensor surfaces of arms and thighs, and extremities (hands and feet) |
| <b>Skin manifestations</b> | Acute lesions: erythema, edema, vesicles, erosions, and crusts   | Subacute lesions: crusts and lichenification  | Chronic lesions: hyperkeratosis, lichenification, and cutaneous fissures  |

( Adapted from Weidinger and Novak (2016), Silverberg et al. (2013).

#### 1.4.2 Complications

AE can lead to several complications:

- Secondary infections (*S. aureus*, herpes simplex [eczema herpeticum], molluscum contagiosum, coxsackievirus) (Beck et al.,2009)
- Ocular involvement (e.g., blepharitis, conjunctivitis, keratoconjunctivitis)
- Failure to thrive in children with severe disease, likely due to systemic inflammation and sleep disruption (Oh et al., 2014)

Pruritus remains the most distressing symptom, often resulting in excoriations, sleep disturbance, and reduced quality of life (Yosipovitch and Papoiu, 2008, Kim et al., 2016).

#### 1.4.3 Atopic Stigmata

Clinical signs that support the diagnosis include:

- Dennie–Morgan infraorbital folds

- Keratosis pilaris
- Hyperlinear palms
- Pityriasis alba
- Periorbital darkening
- Lichenification and prurigo nodularis (Williams, 2005)

## 1.5 Diagnosis

### 1.5.1 Hanifin and Rajka Criteria

This set includes four major and 23 minor criteria. A diagnosis typically requires at least three major and three minor features (Hanifin and Rajka, 1980).

#### Major criteria

- Pruritus
- Early age of onset
- Typical morphology and distribution; flexural lichenification and linearity in adults; facial and extensor involvement during infancy and childhood
- Chronic or chronically relapsing dermatitis
- Personal or family history of atopy (asthma, allergic rhinoconjunctivitis, atopic dermatitis)

#### Minor criteria

- Xerosis
- Hand/foot non specific dermatitis
- Pityriasis alba
- Nipple eczema
- White dermografism
- Subcapsular catarac
- Increased serum Ig E level
- Immediate (i.e. type 1) skin response
- Susceptibility to cutaneous infections (especially Staphylococcus aureus and Herpes simplex)

### 1.5.2 UK Working Party Criteria

Designed for epidemiologic research and clinical screening, this tool is practical and widely used, particularly in paediatrics.

**Core requirement:** Itchy skin condition plus three or more of:

- Flexural involvement
- History of asthma or hay fever
- History of dry skin

- Onset before age two
- Visible flexural dermatitis (Williams et al., 1994)

### **1.5.3 Diagnostic Tools**

Though AE is primarily a clinical diagnosis, some tests can support evaluation:

- Elevated serum total IgE (nonspecific)
- Eosinophilia (in severe disease)
- Allergen-specific IgE or skin prick testing
- Patch testing for suspected contact dermatitis

### **1.5.4 Diagnostic Challenges**

AE must be distinguished from:

- Seborrheic dermatitis (especially in infants)
- Psoriasis
- Scabies
- Allergic contact dermatitis
- Tinea infections
- Cutaneous T-cell lymphoma (in adults with late-onset, therapy-resistant disease)

Histopathology in unclear cases may reveal spongiosis, parakeratosis, acanthosis, and perivascular lymphocytic infiltration (O'Toole, 1997).

## **1.6 Impact on Quality of Life**

AE significantly impairs quality of life by affecting self-esteem, sleep, and daily activities. It is linked to emotional distress, including anxiety and depression, especially in adolescents and adults (Drucker et al., 2017; Lewis – Jones, 2006).

Tools such as the Dermatology Life Quality Index (DLQI) and the Children's DLQI (CDLQI) are commonly used to assess this impact (Basra et al., 2007). Nocturnal itch contributes to behavioral and cognitive issues in children (Chamlin et al., 2005).

### **1.7 Comorbidities and Systemic Association**

AE is strongly linked to other atopic conditions, including:

- Asthma
- Allergic rhinitis
- Food allergy

This progression is described as the “atopic march” (Saeki and Tamaki, 2007). In adults, AE is increasingly associated with metabolic syndrome, cardiovascular diseases, and autoimmune conditions, likely due to systemic inflammation (Silverberg and Greenland, 2015; Thyssen et al., 2020; Flohr and Mann, 2014).

The gut–skin axis, discussed in Chapter 3, also implicates the microbiome in systemic immune modulation.

## **Chapter 2: Dietary aspects: Effects on Atopic Eczema**

### **2.1 Introduction**

Atopic eczema (AE; atopic dermatitis) is a common, chronic relapsing inflammatory skin disease, in which a genetic, immunologic, as well as environmental basis for the disease is implicated with diet as a key factor. Growing evidence suggests that dietary patterns and nutrients may be associated with the onset, severity and management of disease, and there is now interest in both pro- and anti-inflammatory dietary components. Furthermore, nutrition has an intimate relationship with the composition of gut microbiota that in turn can influence the systemic and skin immune response.

This section investigates the impact of factors of the diet on the pathogenesis and course of AE and reviews the use of evidence-based dietary interventions in both children and adults with eczema.

### **2.2 Early-Life Nutrition and Immune Programming**

The prenatal and early postnatal periods are critical windows during which nutrition shapes immune system development and tolerance induction. Maternal diet during pregnancy has been shown to influence the risk of AE in offspring. For instance, maternal intake of oily fish, vegetables, and fermented foods has been inversely associated with eczema development, likely through effects on fetal immune maturation and microbial priming (Venter et al., 2020; Chatzi et al., 2008).

Breastfeeding remains a controversial topic in AE prevention. While some studies suggest exclusive breastfeeding for at least 4–6 months may reduce the risk of AE, others show modest or no benefit. The variability in findings may be attributed to differences in maternal atopic status, breast milk composition, and microbiota transfer (Lodge et al., 2015; Kull et al., 2010).

### **2.3 Western Diet and Inflammogenic Potential**

Current dietary habits in developed countries are frequently marked by high consumption of saturated fats, refined sugars, and processed foods, as well as low fiber intake—a diet often referred to as the “Western diet.” A number of epidemiological studies have linked this pattern of diet to greater prevalence and severity of atopic eczema [Sausenthaler et al., 2007; Kim et al., 2020; Barros et al., 2015].

Foods that have a high glycemic index (GI) tend to increase insulin and insulin-like growth factor 1 (IGF-1) signaling, result in increased production of pro-inflammatory cytokines, and may exacerbate skin inflammation [Berthon and Wood, 2015]. Furthermore, high omega-6 fatty acids from processed seed oils stimulates inflammation by the arachidonic acid pathway, also affecting the physiopathology of eczema [Jang et al., 2015].

Table 1: Pro-Inflammatory Components of the Western Diet and Their Impact on AE [Kim et al., 2019, Deleu et al., 2021]

| <b>Dietary Component</b> | <b>Mechanism in AE Pathogenesis</b>                   | <b>Evidence Summary</b>     |
|--------------------------|---|-----------------------------|
| High sugar intake        | Increases insulin/IGF-1 → Th2 activation              | Observational + mechanistic |
| Refined carbohydrates    | Promotes oxidative stress and inflammation            | Cohort studies              |
| Saturated/trans fats     | Alters lipid metabolism, increases Th1/Th17 responses | Animal + human data         |
| Omega-6 fatty acids      | Excessive prostaglandin E2 → barrier dysfunction      | Biochemical studies         |
| Processed meats          | Contains nitrites and advanced glycation end products | Case-control studies        |

## 2.4 Anti-inflammatory and Protective Diets

Conversely, diets high in fruits, vegetables, whole grains,  $\Omega$ -3 fatty acids and antioxidant content within a Mediterranean-style dietary pattern have been associated with lowered levels of systemic inflammation and possibly protection from allergic diseases (Castro-Rodriguez and Garcia-Marcos, 2008; Willet et al., 1995, Arrieta et al., 2014). Some cohort studies have reported that the risk of eczema in children was decreased when the mother's diet contained high quantities of vegetables, fish, and vitamin E during pregnancy [Okada et al., 2010].

Antioxidants, for example vitamins A, C, and E, and polyphenols which have anti-oxidative effect [Wu and Meydani, 2004]; protect against oxidative stress and modulate inflammation, which might lead to better skin integrity and decrease in flare frequency.

Table 2: Protective Nutrients and Their Functions in Eczema [Navarro-Lopez et al., 2018]

| <b>Nutrient/Food Group</b> | <b>Mechanism of Action</b>                       | <b>Source Examples</b>        |
|----------------------------|--|-------------------------------|
| Omega-3 fatty acids        | Inhibits leukotrienes, modulates Th1/Th2 balance | Oily fish, flaxseed, walnuts  |
| Vitamin A (beta-carotene)  | Antioxidant, supports skin integrity             | Carrots, sweet potatoes       |
| Polyphenols                | Suppresses inflammatory signaling                | Berries, green tea, olive oil |
| Vitamin D                  | Enhances T-reg cells, promotes barrier repair    | Fatty fish, sun exposure      |
| Fiber (prebiotic)          | SCFA production, promotes gut barrier integrity  | Whole grains, legumes         |

## **2.5 Role of Individual Nutrients**

### **2.5.1 Vitamin D**

Vitamin D is an immunoregulator hormone, which improves the innate immunity and T-cell function. Several observational studies have consistently demonstrated lower serum 25(OH)D levels in AE patients, especially in patients with more severe AE (Peroni et al., 2011; Kanda et al., 2020; Sidbury et al., 2008). Clinical trials have shown that vitamin D supplementation (especially in deficient subjects) might reduce the severity of eczema, pruritus and improve quality of life [Holick, 2007; Allen and Koplin, 2012].

### **2.5.2 Omega-3 Fatty Acids**

Omega-3 polyunsaturated fatty acids (PUFAs) including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have anti-inflammatory properties through the suppression of leukotriene B4 and the stimulation of resolvins. Supplementation has been found to be beneficial with respect to eczema severity, in particular when delivered in-utero or during lactation [Dunstan et al., 2003; Maslova et al., 2013; Calder, 2010].

### **2.5.3 Zinc, Selenium, and Other Micronutrient**

Micronutrients such as zinc, selenium and iron are associated with skin barrier maintenance and immune function. Zinc Deficiency is linked to poor wound healing and increased skin susceptibility to infection and inflammation [Kim et al., 2010; Ogawa et al., 2018].

## **2.6 Gut Microbiota and Pre/Probiotics**

The gastrointestinal microbiota is critical for immune maturation and oral tolerance. Dysbiosis of the gut microflora has been associated with the etiology of allergic diseases like AE [Zheng et al., 2016].

### **2.6.1 Probiotics**

As per World Health Organization, probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Several randomised controlled trials have studied the effect of probiotics in AE. Strains such as *Lactobacillus rhamnosus* GG, *Lactobacillus fermentum*, and *Bifidobacterium breve* have been found to improve the Severity Scoring Atopic Dermatitis SCORAD (Scoring Atopic Dermatitis) index and symptoms control in infants and children [Weston et al., 2005; Wickens et al., 2008; Huang et al., 2017; Kalliomaki et al., 2001]. There is evidence from meta-analyses that the administration of probiotics during pregnancy and the early life may prevent the onset of eczema in high-risk infants [Panduru et al., 2015].

### **2.6.2. Prebiotics and Synbiotics**

Prebiotics are non-digestible food components (usually fibers) that selectively stimulate the growth and/or activity of beneficial gut bacteria, thus improving host health. Prebiotics like fructooligosaccharides or galactooligosaccharides serve as fermentable substrate for beneficial bacteria and potentially enhance microbial diversity and immune tolerance [Thomas and Greer, 2010]. The combination of pre- and probiotics, known as synbiotics, is being studied for combined effect and some positive results have been seen [Wang and Wang, 2015].

## **2.7 The Role of Food Additives and Processed Foods**

There is growing concern that food additives, preservatives, emulsifiers, and synthetic dyes may aggravate eczema in susceptible individuals. Some additives, such as tartrazine (E102) and benzoates, have been reported to trigger flares in children with atopic tendencies (Kumar and Gruchalla, 2005). Additionally, emulsifiers in processed foods disrupt gut barrier function and promote dysbiosis, indirectly fueling systemic inflammation (Chassaing et al., 2015).

## **2.8 Food Allergies and Exclusion Diets**

Food allergens—especially cow's milk, egg, wheat, soy, and peanut—frequently trigger pediatric eczema, particularly those with early-onset, moderate-to-severe disease. Nonetheless, not all eczema is food induced and elimination diets can lead to growth impairment, feeding issues and nutritional deficiencies [Sicherer and Sampson, 2014].

Diagnosis needs to include specific IgE testing, skin prick testing or oral food challenges. Once diagnosed, exclusion diets can reduce the severity of disease and use of pharmacologic therapy [Breuer et al.,; Nowak-Wegrzyn and Fiocchi, 2009; Muraro et al, 2014].

It is important to reintroduction any food under supervision, in order to avoid the risk of food sensitisation and to ensure a balanced and various feeding [Venter and Groetch, 2014].

## **2.9 Histamine and Pseudo-Allergic Reaction**

Some foods may induce non-IgE-mediated reactions mediated by a release of histamine. These include:

- Tomatoes
- Chocolate
- Aged cheeses
- Seafood
- Strawberries

Although the evidence is scant, some patients state that a low-histamine diet is beneficial to them [Kovacova-Hanusikova et al., 2015]. However, their use remains empirical and patient-specific.

## **2.10 Functional Foods and Dietary Supplements**

Emerging data support the use of functional foods and supplements for symptom control in AE:

- Probiotics: Specific strains (e.g., *Lactobacillus rhamnosus* GG, *Bifidobacterium lactis*) may reduce AE severity, especially in children and during pregnancy/lactation (Kalliomaki et al., 2001; Navarro-Lopez et al., 2018).
- Prebiotics (e.g., fructooligosaccharides): Promote the growth of beneficial bacteria and improve stool SCFA profiles (Monteiro et al, 2013) .
- Synbiotics: Combine both, with some evidence of additive benefits (Fiocchi et al., 2015).

A 2018 Cochrane review found moderate-quality evidence for probiotics in reducing SCORAD in children, but heterogeneity in strains and duration remains a limitation (Tan-Lim and Esteban-Ipac, 2018).

### **2.11. Psychological and Behavioral Effects**

Diet may indirectly affect eczema through its effect on sleep, stress and mental health. High refined carbohydrate diets and low tryptophan may also impair serotonin synthesis and impact on mood and pruritus perception [Trimmer and Lundy, 2014]. Furthermore, children with AE often have picky eating behaviors, and their parents may experience significant anxiety over food choices (Kim et al., 2020).

### **2.12 Cultural and Socioeconomic Considerations**

Dietary interventions in AE must be contextualized within cultural norms, food availability, and socioeconomic status. Ultra-processed food consumption is higher in low-income populations, where barriers to accessing fresh, anti-inflammatory foods persist (Kim et al., 2020). Education, affordability, and food literacy are essential for the implementation of long-term dietary changes.

### **2.13 Recommendations/Future work**

There is no “one-size-fits-all” eczema diet, but some science-backed dietary approaches include:

- Ensuring adequate intake of vitamin D, omega-3s, and antioxidants
- Promoting high-fiber, plant-rich diets for microbiota support
- Avoiding ultra-processed, high-GI foods
- Conducting targeted food elimination only after diagnostic confirmation

Subsequent literature would need to investigate the role of personalized nutrition, microbiota profiling, and to focus on longitudinal intervention studies to identify best intervention diets.

## **Chapter 3: The Gut–Skin Axis and Microbiome in Atopic Dermatitis**

### **3.1 Introduction**

The gut–skin axis is an emerging concept and has gained significant interest as communication pathway between gut health, microbiota and skin immune responses. In atopic eczema, dysbiosis of gut microbial ecology has been suggested to be involved in the pathogenesis, via mechanisms of barrier disruption, immune activation and systemic inflammation [Salem et al., 2018 ; Lee et al, 2018; Gueniche et al., 2010].

Trillions of bacteria, archaea, viruses, and fungi modulate immune tolerance, nutrient uptake, and barrier function as part of the gut microbiome. A healthy and balanced gut microbiota is crucial for the maintenance of homeostasis and diminished diversity, and overgrowth of pathogenic strains are correlated with chronic inflammation such as that seen in AE [Milani et al., 2017].

### **3.2 Skin microbiome in Atopic eczema**

The cutaneous microbiome comprises a rich, dynamic ecosystem of bacteria, fungi, viruses and mites colonizing the epidermis and its adnexa, and is an essential contributor to cutaneous homeostasis and immunological defense. For example members of the commensal microbiome including *Staphylococcus epidermidis*, *Cutibacterium acnes* and *Corynebacterium* species all promote skin barrier function, modulate immune responses and restrict colonization by pathogens, largely through mechanisms that, in part, include generation of antimicrobial peptides and competitive exclusion (Byrd et al., 2018; Sanford and Gallo, 2013). Dysbiosis, also characterized as diminished diversity of microbiome and overgrowth of *Staphylococcus aureus* is strongly associated with atopic eczema development and deterioration (Kong et al., 2012; Callewaert et al., 2020). *S. aureus* also contributes to disease exacerbation by generating superantigens and cytotoxins while also disrupting the cutaneous barrier and increasing Th2-polarized inflammation (Nakamura et al., 2013). Indeed, new evidence now points to the potential to re-establish microbial homeostasis, e.g. via topical inoculation of commensal strains such as *Roseomonas mucosa* and *Staphylococcus hominis* or modulating the gut–skin axis as novel therapeutic approaches for atopic dermatitis (Myles et al., 2018; Nakatsuji et al., 2018). Accordingly, the skin microbiome is not just a disease activity indicator, but a potential future therapeutic target.

### **3.3 Gut Microbiome Development and Immune Education**

Gut colonization with microbiota starts at birth and is determined by the type of delivery, feeding habits, antibiotics, and environmental exposure. Vaginal childbirth and breastfeeding are a known source of beneficial bacteria (ex, *Bifidobacterium* and *Lactobacillus*) that drive Th1/Th2 balance [Dzidic et al., 2017; Arrieta et al., 2015; Feehley et al., 2019].

Microbial exposures during infancy is important to train the immune system to differentiate between pathogens and commensals through the process of oral tolerance. Insufficient microbial diversity during early life could lead to a Th2-skewed immune reaction. The expression of Th2-skewed immunity against soluble protein Ags present in the normal environment is recognized as the primary cause of allergic inflammation in atopics [Abrahamsson et al., 2012; Kim et al., 2019].

### 3.4 Gut Dysbiosis in Atopic Dermatitis

The changes of gut microbiota in infants and children with AE have been reported in several studies as follows:

- Decreased microbial diversity
- Reduced levels of Bifidobacterium and Faecalibacterium
- Increased abundance of Clostridium, Escherichia, and Enterococcus [Penders et al., 2007; Ismail et al., 2012; Nylund et al., 2014]

These changes result in compromised barrier function, increased permeability of mucosa and frequent systemic exposure to microbial and diet antigens which exacerbate systemic inflammation and skin immune response [Tanaka and Nakayama,2017].

**Table 1: Common Gut Microbiota Alterations in AE [Lee et al.,2016; Kim and Kim, 2019]**

| Taxa                         | AE-Associated Changes | Role in Health                               |
|------------------------------|-----------------------|--|
| Bifidobacterium              | ↓ Decreased           | Promotes Treg cells, supports barrier        |
| Faecalibacterium prausnitzii | ↓ Decreased           | SCFA production, anti-inflammatory cytokines |

|                  |             |   |
|------------------|-------------|---|
| Clostridium spp. | ↑ Increased | Produces toxins, triggers inflammation  |
| Escherichia coli | ↑ Increased | Endotoxin production, disrupts immunity |

### 3.5 Mechanisms Linking Gut and Skin

#### 3.5.1. Short-Chain Fatty Acids (SCFAs)

These metabolites are derived from the gut microbiota and have been found to exhibit anti-inflammatory properties among other biological activities.

Short chain fatty acids (SCFA), including butyrate, propionate, and acetate, generate by the fermentation of fibers by colon microflora. These metabolites serve several functions:

- Improve the level of integrity of the intestinal barrier
- Induction of Treg differentiation
- Suppress the release of pro-inflammatory cytokine [Tan et al., 2014; Matsumoto et al., 2012; Furusawa et al., 2013]

Butyrate in particular, have been shown to be able to diminish Th2-mediated inflammation, enhance the expression of filaggrin and stabilize mast cells — and may play a protective role in AE [Torii et al., 2015].

#### 3.5.2 Systemic inflammatory mediators

Dysbiosis could induce the translocation of pathogen-associated molecular patterns (PAMP)-like molecules such as lipopolysaccharides LPS and peptidoglycans into circulatory system. These stimulate toll-like receptors (TLRs), which produce TNF- $\alpha$ , IL-6, and IL-1 $\beta$ , which can act at remote sites such as the skin, promoting cutaneous inflammation [Leung, 1999; Mu et al., 2017; Gao et al., 2009].

### 3.5.3 Neuroimmune Pathways

The gut–brain–skin axis underscores a neuroendocrine component where the gut microbiota affect cortisol, serotonin, and neuropeptide signalling. Prolonged stress decelerates microbial composition balance and heightens eczematous symptoms via the feedforward inflammatory cycle [Arck et al., 2006; Bowe and Logan, 2011].

### 3.6 Role of Diet in Modulating the Microbiome

Diet composition most strongly determines microbial composition. High fiber, plant-based diets are conducive to the enrichment of SCFA-producing bacteria, whereas low fiber, high fat diets are conducive to pathogenic species [David et al., 2014; De Filippis et al., 2016].

**Table 2: Dietary Patterns and Microbiome Effects [Deleu et al., 2021; Moszak et al., 2020; Albenberg LG et al., 2014; Agus et al.,2016]**

| Dietary Pattern    | Microbial Impact                    | Clinical Implication in AE |
|--------------------|-------------------------------------|----------------------------|
| Western diet       | ↑ Proteobacteria, ↓ Bifidobacterium | Increases inflammation     |
| Mediterranean diet | ↑ Bacteroides, ↑ SCFA production    | Reduces AE severity        |
| High-fiber diet    | ↑ Microbial diversity, ↑ butyrate   | Supports immune tolerance  |
| High-fat diet      | ↓ Diversity, ↑ endotoxemia          | Worsens barrier integrity  |

### 3.7 Microbiota-Modifying Interventions in AE

#### 3.7.1 Probiotics, Prebiotics and Synbiotics

As already discussed in Chapter 2, probiotics are live micro-organisms that provide a health benefit when consumed in adequate amounts. Prospective studies have evaluated the effect on AE, with all observing decreases in objective SCORAD and improvements in subjective assessments of pruritus, sleep, and number of flares [Kim et al., 2020, Navarro- Lopez et al., 2018, Huang et al., 2017; Kalliomaki et al., 2001].

Beneficial strains include:

- Lactobacillus rhamnosus GG
- Lactobacillus fermentum
- Bifidobacterium breve

Mechanisms include epithelial repair, cytokine modulation, and competitive inhibition of pathogens [West et al., 2017].

Prebiotics are non-digestible fibers that are selectively beneficial for bacterial growth. Examples of such substrates are inulin, fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS). These promote the production of SCFA and of mucosal immunity [Thomas and Greer, 2010].

Synbiotics (probiotics and prebiotics) have synergistic beneficial effects in AE patients and especially high risk children, who have potential to benefit in AE severity reduction and incidence [Foolad, Armstrong and Kimball, 2013].

### **3.7.2 Fecal Microbiota Transplantation (FMT)**

Fecal microbiota transplantation (FMT) has been extensively described in the literature.

FMT is the infusion of the stool from a healthy donor in order to re-establish microbiome diversity. Primarily utilized in *Clostridioides difficile* infection, FMT has been evaluated by early experimental work as a potential treatment for inflammatory skin disorders, such as AE [Bajaj et al., 2017; Chen et al., 2021].

Common problems are standardization, donor screening and long-term safety. Phase III clinical trials are underway to determine its role in dermatology [Park et al., 2017].

## **3.8 Microbiome-Drug Interactions and Therapeutic Modulation**

Emerging studies have indicated that gut microbiota can influence drug treatment efficacy, such as that following administration of corticosteroids and biologics. Medication bioavailability and immune reactivity differ based on the ability of microbial enzymes to activate or break down drugs [Zimmermann et al., 2019; Vich Vila et al., 2018].

Insights into the host–microbiota–drug interaction may potentially direct personalised treatment in the future.

### **3.9 Conclusion and Future Work**

The gut–skin axis is a new therapeutic horizon in the treatment of AE. Meanwhile, microbiome-targeted treatments – such as ‘precision’ probiotics, dietary prebiotics and even postbiotics (beneficial microbial metabolites) – provide exciting adjuncts to standard care.

Prospective and mechanistic investigation is needed to:

- Detect microorganisms associated with different diseases
- Classify patients according to microbiome subtypes
- Several studies propose targeted interventions.

Developing multi-omics pipelines (metagenomics, metabolomics, transcriptomics) will further increase knowledge on the role of the microbial ecosystem in AE and atopic diseases at large.

## **Chapter 4: Food Allergies and Immune Mechanisms in Atopic Eczema**

### **4.1 Introduction**

Atopic eczema (AE) and food allergies (FA) frequently occur together, particularly in infancy when the immune system is immature. Although food allergies are not present in all patients with AE, food-induced eczema flares are well-documented in a subgroup, most notably in those with early onset, moderate to severe or persistent disease [Lack, 2008; Sicherer and Sampson, 2014; Du Toit et al., 2016]. This chapter looks at the immunological basis of food elements in AE, the epidemiology of food allergy in eczema, and the interaction between dietary antigens and the cutaneous and mucosal immune responses.

### **4.2 Prevalence of Food Allergy in AE**

The prevalence of food allergies in children with AE is higher than that in children without the skin condition. From cohort studies, up to 40% of infants with moderate-severe eczema are reported to have immunologically confirmed food allergy [Martin et al., 2015; Hill and Hoskin, 2004]. The worst culprits tend to be:

- \* Cow's milk
- \* Hen's egg
- \* Peanuts
- \* Wheat
- \* Soy

The so-called “atopic march” – i.e., the progression from atopic eczema to food allergy, asthma, and allergic rhinitis — points to common immunopathogenic mechanisms and possibly causal relationships [Belgrave et al, 2014].

### **4.3 Barrier Dysfunction and Sensitization of the Skin**

Impaired skin barrier is key in AE pathogenesis and is also believed to be the site of entry for epicutaneous sensitization to food allergens. The filaggrin (FLG) gene which is essential for skin barrier function is commonly mutated in severe eczema patients and greatly associated with peanut allergy [Brown and McLean, 2009; Flohr et al., 2010].

Dysfunction of the epidermis is found to be responsible for the increased transepidermal water loss (TEWL) and food-derived antigens penetrate the skin, where they activate the

antigen presenting cells, especially Langerhans cells [Kelleher et al., 2015]. These cells present the antigens to lymph nodes, priming naive T cells towards Th2 polarization, thus initiating an allergic response [Novak, 2012].

#### 4.4. Dual-Allergen Exposure Hypothesis

The dual-allergen exposure hypothesis (DAEH) , proposes that early allergen exposure of the skin at sites of barrier defects will lead to sensitization, while early allergen exposure of the oral mucosa through the gastrointestinal tract will lead to tolerance [Lack, 2012].

This hypothesis is further favored by the results of the LEAP study, which found that early introduction of peanuts in high-risk infants significantly reduced the prevalence of peanut allergy by the age of five [Du Toit et al., 2015].

Table 1: Routes of Allergen Exposure and Immunological Outcomes [Lack, 2012Turcanu et al., 2017]

| Route of Exposure | Immune Outcome      | Key Features                                |
|-------------------|---------------------|---|
| Skin (via eczema) | Sensitization (Th2) | IL-4, IL-5, IgE, mast cells                 |
| Oral (gut mucosa) | Tolerance (Tregs)   | IL-10, TGF- $\beta$ , oral antigen exposure |

#### 4.5 IgE- and Non-IgE-Associated Reactions

Food allergies in AE can be:

\* IgE-mediated: Immediate hypersensitivity reactions (e.g., urticaria, anaphylaxis, flares within 2 hours).

\* Non-IgE-mediated: Delayed reactions (e.g., eczematous flares after 24–48 hours), often difficult to detect by standard allergy tests.

Mixed responses are also noted, and differentiating them clinically is important. The oral food challenge (OFC) is still the gold standard for diagnosis, although the skin prick test

(SPT) and serum specific IgE are widely used as screening tests [Sampson 2005; Nowak-Wegrzyn et al., 2009; Muraro et al., 2014].

#### **4.6 T-cell Mediated Immunity and Cytokine Environment**

In AE, Th2 cytokines, such as IL-4, IL-5, and IL-13 are increased, with subsequent induction of IgE production, eosinophil recruitment, and inhibition of barrier-repair genes [Guttman-Yassky and Krueger, 2017; Tordesillas and Berin, 2018].

In food allergy:

- \* IL-4 stimulates B-cell class switching to IgE.
- \* Eosinophilic inflammation is mediated by IL-5.
- \* Epithelial permeability is increased by IL-13.

Furthermore, IL-31 is an increasingly appreciated pruritogen, especially in AE in the context of atopic comorbidities [Raap et al., 2008]. By contrast, Treg cells and their cytokines (IL-10 and TGF- $\beta$ ) are essential for oral tolerance, their normal activity being important for preventing allergies [Smolinska and Jutel, 2020; Palomares et al., 2017].

#### **4.7 Gut Mucosal Immunity and Microbiome**

The intestinal epithelium, which is covered by tight junctions and goblet cells producing mucus, acts as a barrier against dietary antigens. Dendritic cells in the gut-associated lymphoid tissue (GALT) sample luminal antigens and, in the absence of inflammation, induce tolerogenic pathways [Macpherson, Geuking and McCoy, 2005].

Impaired gut homeostasis as the result of dysbiosis, antibiotic use, caesarean section infants and low microbial diversity could favor the development of pro-allergic pathways. Several reports showed reductions of Bifidobacterium and Lactobacillus as well as increments of Clostridia species in children with both AE and FA [West et al., 2015; Thompson – Chagoyan, Vieco and Maldonad, 2011].

#### **4.8 Clinical Impact of Food Allergy Testing in AE**

Routine food allergy testing is not indicated in all patients with AE. Testing should be guided by:

- \* History of reactions to particular foods
- \* Early-onset, severe eczema
- \* Eczema not responding to appropriate topical treatment

Tests include:

- \* SPT
- \* Serum-specific IgE
- \* Atopy patch testing (APT) – selective use only
- \* Oral food challenge (OFC) – gold standard but resource-heavy

False-positives are frequent, especially for IgE testing, because of asymptomatic sensitization (Eigenmann and Caubet, 2012)

Table 2: Diagnostic Tools for Food Allergy in AE. [Fiocchi et al., 2011; Sampson et al., 2014]

| Test               | Type          | Pros                              | Limitations                               |
|--------------------|---------------|-----------------------------------|---|
| Skin prick test    | IgE-mediated  | Rapid, accessible                 | High false-positive rate                  |
| Serum-specific IgE | IgE-mediated  | Useful for tracking sensitization | May not correlate with symptoms           |
| OFC                | Clinical      | Diagnostic gold standard          | Time-consuming, risk of reaction          |
| Atopy patch test   | Cell-mediated | Used in delayed reactions         | Limited availability, low standardization |

#### 4.9 Pros and Cons of Elimination Diets

Hypoallergenic diets could improve a subset of AE patients who prove to have food allergies. Inadequate or over-restrictive diets though, particularly implemented in infants and small children are able to pose the following threat:

- \* Nutritional deficiencies (iron, calcium, vitamin D)
- \* Growth retardation
- \* Feeding difficulties
- \* Social restrictions

Therefore, possible dietary approaches should be conducted under strict medical surveillance performed by specialist allergists and dietitians [Venter and Meyer, 2010; Meyer et al., 2018].

#### **4.10 Early Allergenic Foods Introduction**

Recent recommendations support early (about 4–6 months) introduction of common allergens in infants with eczema, based on evidence from trials such as:

- \* LEAP (Learning Early About Peanut Allergy) [Du Toit et al., 2015]
- \* EAT (Enquiring About Tolerance) [Perkin et al., 2016]

This change disagrees with previous advice to avoid allergens and is especially applicable to infants who are atopic.

#### **4.11 Future Directions**

This is a subject that is still being studied:

- \* Modulation of food tolerance by probiotics
- \* Immune biomarkers for allergy prediction
- \* Relationships among the microbiota, diet and immunity
- \* Immunotherapy (oral or epicutaneous) for food desensitization

Precision medicine incorporating genetic, epigenetic, and microbe data could be used to define risk and interventions.

#### **4.12 Conclusion**

Food allergies and AE have profound epidermal and mucosal immunologic connections. Dietary antigens contribute to eczema for some, identification and management of these factors can lead to enhancement of eczema outcomes. But untargeted testing or intervention may be harmful, illustrating the importance of selective assessment, early intervention if needed, and interdisciplinary care.

## **Chapter 5: Therapeutic Implications: Diet, Microbiome, and Beyond**

### **5.1 Introduction**

Atopic eczema (AE) is a long-term, relapsing condition which requires long-term management. Although topical corticosteroids and calcineurin inhibitors are the preferred agents, emerging evidence points towards the role of inclusion of nutrition and microbiome-targeted therapies as adjuvants or preventive tools. The current chapter discusses therapeutic considerations based on dietary approaches, probiotics, prebiotics, synbiotics, and emerging microbiome-targeting strategies.

### **5.2 Available Recommendations and Pharmacologic Treatment**

Standard treatment includes:

- \* Emollients and moisturizers to repair the skin barrier
- \* Topical corticosteroids (TCS) and calcineurin inhibitors (TCIs) for inflammation
- \* Oral systemic immunosuppressants, for example, cyclosporine and methotrexate in severe cases
- \* Biologic agents such as dupilumab (monoclonal antibody against IL-4R $\alpha$ ), indicated for moderate-to-severe AE [Sidbury et al., 2014; Drucker et al., 2017; Simpson et al., 2016]

Despite its effectiveness, side effects, cost, and long-term immunosuppression led to growing interest in integrative interventions [Paller, Kabashima and Bieber, 2017].

### **5.3 Nutritional Approaches in AE**

#### **5.3.1 Evidence on Anti-inflammatory Diets**

Omega-3 fatty acid, antioxidant, fibre, and polyphenol-rich diets are inversely related to inflammatory markers and eczema severity [Sausenthaler et al., 2007; Kim et al., 2020]. The Mediterranean diet is one of the healthiest diets in the world, characterized by a high intake of fruits, vegetables, legumes, nuts, olive oil and fish. The Mediterranean diet is associated with:

- \* Low burden of childhood eczema
- \* Better SCORAD (Score Atopic Dermatitis) scores
- \* Reduced levels of sensitization [Castro-Rodriguez and Garcia-Marcos, 2008; Chatzi et al., 2008; Willet et al., 1995]

### 5.3.2 Dietary Elimination

For those with established food allergy, exclusion diets might result in symptom relief. However, these should only follow proper diagnostic workup, and prolonged restrictions must be supervised to avoid nutritional deficiencies [Sicherer, 2011; Venter and Groetch, 2014].

Table 1: Overview of Dietary Interventions for AE [Meyer et al., 2012; Zuberbier et al., 2004]

| Strategy                        | Evidence Summary                         | Risks                             |
|---------------------------------|--|-----------------------------------|
| Mediterranean diet              | Reduces inflammation and flares          | Low risk                          |
| Elimination diet (confirmed FA) | Improves eczema control                  | Nutritional deficiency            |
| Low-histamine diet              | Anecdotal benefit in sensitive patients  | Limited evidence                  |
| Anti-inflammatory supplements   | Variable benefit (e.g., vitamin D, zinc) | Possible overdose if unsupervised |

### 5.4 Vitamin D Supplementation

A number of RCTs and meta-analyses provide evidence for the use of vitamin D supplement in AE, especially in patients with serum levels <20 ng/mL. It improves:

\* SCORAD scores

\* Transepidermal water loss

\* Bacterial colonization with *S. aureus* [Peroni et al., 2011; Sidbury et al., 2008; Kanda, Hoashi and Saeki, 2020]

Doses ranging from 400 to 1600 IU/day have been shown effective, with a good safety profile.

## 5.5 Probiotics, Prebiotics and Synbiotics

### 5.5.1 Probiotics

Probiotics have the potential to enhance the health of the skin by altering the gut microbiota composition, maintaining the integrity of mucosal barrier and regulating immune system through the secretion of SCFAs, phenolic compounds and certain neurotransmitters (Zhang et al., 2022) Data from various trials show that the bacteria *Lactobacillus rhamnosus* GG, *Bifidobacterium lactis* and *Lactobacillus fermentum* significantly reduce eczema severity, particularly when given during pregnancy and infancy [Weston et al., 2005; Kalliomaki et al., 2001; Wickens et al., 2008; Huang et al., 2017].

Mechanisms include:

- \* Support of regulatory T cells
- \* Reduction of Th2 skewing
- \* Improvement of the intestinal barrier function

### 5.5.2 Prebiotics and Synbiotics

Prebiotics such as fructooligosaccharides (FOS) and inulin enhance beneficial bacteria, whereas synbiotics (mixed prebiotic-probiotic formulations) demonstrate synergistic effects in small trials [Kim et al., 2020, Navarro-Lopez et al., 2018; Panduru et al., 2015].

Table 2: Evidence Summary for Microbial Therapies [Navarro-Lopez et al., 2018; Kim et al., 2019]

| Intervention    | Population                   | Benefit Observed        | Evidence Level |
|-----------------|------------------------------|-------------------------|----------------|
| L. rhamnosus GG | Pregnant mothers and infants | Reduced incidence of AE | High           |

|              |                                |                                  |          |
|--------------|--------------------------------|----------------------------------|----------|
| B. lactis    | Infants with family history    | Decreased SCORAD                 | Moderate |
| FOS + Inulin | Children with mild-moderate AE | Reduced symptoms, enhanced Tregs | Moderate |

## 5.6 Microbiome Reinstatement Approaches

Novel interventions are emerging with the goal of re-establishing microbial balance, particularly the ones focusing on dysbiotic patients. These include:

- \* Topical microbiome-targeted treatments, such as *S. hominis* to counteract *S. aureus* [Nakatsuji et al., 2017]
- \* Postbiotics; i.e., beneficial microbial metabolites (e.g., SCFAs)
- \* Fecal microbiota transplantation (FMT), as yet experimental in AE [Smits et al., 2013; Park et al., 2017; Bajaj et al., 2017]

Studies have so far shown early promise, but large clinical trials are still needed to determine long-term safety and efficacy. Novel treatments will be discussed further in Chapter 6.

## 5.7 Personalised Nutrition and Precision Medicine

The way forward for AE management are personalised strategies and approaches that combine:

- \* Nutritional profiling
- \* Microbiome sequencing
- \* Genetic markers (such as FLG mutations)
- \* Epigenetics and metabolomics signatures [Zeevi et al., 2015; Zmora, Suez and Elinav, 2019]

These approaches might make it possible to predict the response to diets or probiotics and prevent pointless interventions, thus increase cost-effectiveness.

### **5.8 Practical Recommendations:**

- \* Promote anti-inflammatory, whole-food diets that include plenty of plants and healthy fats.
- \* Food allergies should be tested before embarking on elimination.
- \* Treat vitamin D deficiency.
- \* Probiotics can be considered in high-risk children.
- \* Avoid unsupported extreme diets.

Multidisciplinary intervention among dermatologists, allergists, dietitians, and primary care improves adherence to therapy and results in a comprehensive outcome.

### **5.9 Conclusion**

Although traditional therapies continue to be the cornerstone of AE therapy, adjunctive approaches addressing diet and the microbiome are based on promising evidence. From probiotics and vitamin D to Mediterranean diets and microbial therapies, the growing toolbox represents a move toward integrative dermatology.

Ongoing research should prioritize randomized controlled trials, mechanistic insights, and real-world data to guide best practice and maximize therapeutic benefit.

## **Chapter 6: Integrated Perspectives and Future Directions in Atopic Eczema, Diet, and the Microbiome**

### **6.1 Introduction**

Atopic eczema (AE) serves as a classical model of a complex disease in which genetics, immune dysregulation, microbiome, environment, and lifestyle converge. Huge advances have been made in the past 20 years in our understanding of the pathophysiological complexity of AE — but the evidence is increasingly directed towards a more holistic approach to its treatment. The present chapter summarizes major findings of previous chapters and explores future trends in the field of prevention, therapy, and personalized medicine.

### **6.2 Systems Biology in Atopic Eczema**

Atopic eczema is considered as more than a skin disease, but a system's immune dysregulation caused by early-life exposures, gut and skin microbiota changes, and environmental exposures. The epidermal barrier, the intestinal epithelium integrity, and the mucosal immunity work together to define the susceptibility, the course of the disease, and the response to treatments [Weidinger and Novak, 2016; Guttman – Yassky and Krueger, 2017; Elias and Steinhoff, 2008].

This systems perspective helps to account for why topical corticosteroids are efficacious but do not target the underlying drivers of chronic inflammation, and why upon discontinuation, flare-up is frequent. Therapies need to go beyond symptomatic management towards microbiologic, nutritional, and immunologic aspects.

### **6.3 Integration of Nutrition and Microbiome Science**

From the preceding chapters, several key therapeutic and preventive implications arise:

- \* Diets rich in polyphenols, fiber, and omega-3 fatty acids modulate inflammation and enhance microbial diversity [Kim et al, 2019; De Filippis et al., 2016; Barros et al., 2015].
- \* The gut–skin axis offers a mechanistic link between dietary intake and skin homeostasis.
- \* Early-life dietary exposures influence oral tolerance, microbial priming, and risk of AE [Lack, 2012; Venter and Groetch, 2014; Abrahamsson et al., 2012].

It is increasingly accepted that dietary interventions are not only complementary, but in some subgroups, fundamental to the management of chronic diseases in the long term.

Table 1: Multi-Domain Influences in Atopic Eczema [Elias, et al., 2008; Deleu et al., 2021; Nutten, 2015]

| Domain           | Key Influence                              | Therapeutic Example                    |
|------------------|--|--|
| Genetic          | FLG mutations, cytokine gene polymorphisms | Biologics targeting IL-4R, IL-13       |
| Barrier function | TEWL, ceramide loss                        | Emollients, barrier repair creams      |
| Immune system    | Th2/Th17 imbalance, Treg deficiency        | Dupilumab, probiotics, vitamin D       |
| Microbiome       | Dysbiosis, SCFA deficiency                 | Prebiotics, synbiotics, FMT (research) |
| Nutrition        | Pro/anti-inflammatory nutrients            | Mediterranean diet, allergen exposure  |

## 6.4 Novel Adjuvant Therapies on the Horizon

### 6.4.1 Live Biotherapeutics

Next-generation probiotic therapeutics, including genetically engineered strains and live biotherapeutic products (LBPs), are under investigation to restore cutaneous and intestinal microbial balance. These may include:

- \* Modified strains such as *Lactobacillus* species which express anti-inflammatory peptides.
- \* Topical *Roseomonas mucosa* reported to be effective in AE in children [Myles et al., 2018; Nakatsuji et al., 2018].

**6.4.2 Postbiotics** – the non-viable bacterial structures or metabolic products – provide anti-inflammatory and barrier-supporting effects without the issues of viability that can accompany live probiotics. The most promising to date being SCFA supplementation (butyrate and propionate) [Tan et al., 2014].

### **6.4.3 Synthetic Antimicrobial Peptides (AMPs)**

Antimicrobial peptides (AMPs) are innate immune molecules with both antimicrobial and immunomodulatory properties. In atopic dermatitis (AD), reduced levels of AMPs such as LL-37 and  $\beta$ -defensins contribute to increased *Staphylococcus aureus* colonization and inflammation. Synthetic AMPs like omiganan have been shown to restore microbial balance, reduce *S. aureus*, and activate immune pathways such as NF- $\kappa$ B and interferon- $\gamma$ , offering a promising novel therapeutic option (Nakamura et al., 2013; Nakatsuji et al., 2018).

### **6.4.4 Microbiota Transplantation**

Microbiota transplantation aims to re-establish a healthy microbial ecosystem either on the skin or in the gut. Transplanting coagulase-negative staphylococci (CoNS), such as *S. epidermidis* or *S. hominis*, may inhibit *S. aureus* and reduce skin inflammation (Callewaert et al., 2020; Byrd et al., 2018). Fecal microbiota transplantation (FMT) is an emerging systemic strategy that can rebalance gut microbiota, increase short-chain fatty acid levels, and modulate immune responses by shifting the Th2-dominant profile commonly seen in AD (Renz et al., 2018; Zheng et al., 2020).

All the above treatments may be very useful in stratification of patients for personalised treatment, prediction of response to:

- \* Probiotics vs. biologics.
- \* Vitamin D vs. omega-3 supplementation.
- \* Remission with diet vs. dependence on pharmacology [O'Toole, Marchesi and Hill, 2017; Suez et al., 2018; Zeevi et al., 2015].

## **6.5 Prevention in High-Risk Populations**

Currently, substantial evidence is available on the preventive potential of early allergen introduction, maternal diet modulation, and intervention with probiotics in pregnancy and infancy for the prevention of AE:

- \* LEAP trial: Introduction of peanut lowered the risk of allergy by 81% [Du Toit et al., 2015].

\* ProPACT and Panda trials: Probiotic use during pregnancy and breastfeeding have reduced AE occurrence approximately 20–30% [Kalliomaki et al., 2001; Wickens et al., 2018].

Prevention will have to shift from allergen avoidance to immune education and microbial nurturing, starting before birth.

## **6.6 Health Equity and Public Health Relevance**

The prevalence of AE is rising around the world and at higher rates among urban, low socioeconomic, and minority groups. Quality of diet, access to medical care, and environmental exposures all affect the outcome. Comprehensive, equity-focused strategy must include:

- \* Nutritional education.
- \* Diet, particularly microbiota-supporting ones.
- \* Culturally appropriate care pathways.

## **6.7 Conclusion**

The future of atopic eczema management lies in integration: combining biomedical therapies with nutrition science, microbiome research, and personalised care frameworks. The diet–microbiome–immune triad offers a rich terrain for preventive innovation, therapeutic advancement, and long-term remission.

Investment in translational research, longitudinal cohort studies, and implementation science will be crucial to fully realise the promise of a precision, holistic approach to AE.

## Conclusion

Atopic dermatitis was once considered to be solely a cutaneous inflammatory disease, but is now acknowledged as a systemic disease characterised by complex relationship between epidermal barrier impairment, immune dysfunction, genetic predisposition, environmental and notably, gut and skin microbiota.

In the thesis, we have investigated in depth the triad of diet, microbiome and immune pathways in AE. Diet patterns are now known to have inflammatory and anti-inflammatory effects on AE risk and severity. The Westernized diet — high in processed foods, saturated fats and sugar — can create systemic inflammation and microbial imbalance. In contrast, nutrient-rich diets such as the Mediterranean diet support microbial diversity, reduce Th2/Th17-driven inflammation, and enhance skin and gut barrier integrity.

The gut–skin axis represents a mechanistic link between these factors. Early life alteration of the gut microbiome, via caesarean section, formula feeding, antibiotic exposure or low fibre intake, primes individuals for Th2-deviated immune responses and defective oral tolerance. Growing evidence of the importance of short-chain fatty acids, probiotic interventions, and postbiotic and microbiome transplantation mechanisms continues to support the clinical relevance of the microbiota.

Food allergies continue to be a significant, albeit complex, factor in the development of eczema especially among infants and children with early onset or severe disease. Selective dietary elimination in children with IgE sensitisation can be helpful, but exclusion simply on the basis of sensitisation may be unsafe. In contrast, early exposure to allergens and microbial priming may lead to long-term tolerance development and a lesser allergic disease load.

From a clinical perspective, there is increasing evidence that integrative therapies — such as diet, vitamin D supplementation, and judicious use of probiotics — can be used as an adjunct with traditional pharmacologic therapy. While biologics like dupilumab have transformed care for moderate-to-severe AE, they do not address the underlying drivers of dysbiosis and nutritional imbalance, highlighting the need for multimodal care pathways.

Looking forward, the future of AE management lies in precision medicine. Multi-omics tools capable of profiling genomic, microbiomic, metabolomic, and immunologic parameters will allow for more accurate disease phenotyping, risk stratification, and tailored interventions. Public health policies must additionally be directed to the adoption of dietary guidance and the promotion of microbiome-friendly surroundings, even in underserved areas.

In conclusion, a holistic understanding of AE — one that includes nutrition, microbiota, immune function, and environment — is essential for both prevention and sustainable disease control. The integration of dermatology with nutritional science and microbial ecology represents a paradigm shift with the potential to transform outcomes for millions living with atopic eczema.

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