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LETTER TO THE EDITOR Open Access

Multidisciplinary Delphi Consensus on management of children with moderate-severe atopic dermatitis

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Abstract

Atopic dermatitis is a compelling challenge in daily practice. Type 2 inflammation is the most common endotype in children and adolescents with AD. As a result, anti-inflammatory drugs, mainly corticosteroids (CS) and immunomodulatory agents, represent the first-line treatment to dampen type 2 inflammation. However, biologics, particularly dupilumab, dramatically changed the natural history of AD patients. A steering committee composed by expert pediatricians and dermatologists promoted a multidisciplinary Delphi Consensus to improve the knowledge about this topic. Experts in this field participated in the Consensus of three groups of statements concerning definition, diagnosis, and management. There was agreement for all proposed statements. The outcomes of the present multidisciplinary Delphi Consensus propose shared, evidence-based recommendations that may be fruitful in clinical practice.

Keywords Atopic dermatitis, Type 2 inflammation, Itch, Skin lesions, Dupilumab, Phenotype

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Introduction

The prevalence of atopic dermatitis (AD), a chronic cutaneous inflammatory disease, accounts for up to 20% of children and adolescents [1, 2]. Patients with AD usually experience intense pruritus and recurrent eczema [3]. Namely, symptom severity, clinical features, and course are heterogeneous, so the diagnosis is challenging. Hanifin and Rajka proposed diagnostic criteria based on clinical characteristics [4]. The SCORAD index, eczema area and eczema area and severity index (EASI) are the most frequently utilized scoring system for assessing to assess AD severity in both clinical studies and clinical practice [5–7].

Atopic dermatitis often starts in the first 6 months of life, before weaning, but the trajectory may be motley, including early transient, relapsing-remitting, chronic persistent, or recurrent [8]. Atopic dermatitis is frequently associated with asthma and food allergy [9].

Atopic dermatitis pathogenesis is complex and involves several factors, including genetic predisposition, epidermal barrier dysfunction, skin dysbiosis, and immune-mediated type 2 inflammation [10].

In managing AD patients, the primary target is to relieve itching and ensure disease control [11]. Indeed, AD considerably impairs the quality of life and sleep of patients and their caregivers. Consequently, improvement in sleep quality and health-related quality of life represent additional therapeutic objectives. Also, AD imposes a significant burden on families and entails substantial costs [12].

Several treatments are available, and guidelines provide documented recommendations [13]. In particular, as type 2 immunity is involved in many patients, type 2-targeted biologics have recently been introduced and, based on their mechanisms of action, have dramatically modified the clinical course. In this context, Dupilumab, a monoclonal antibody that blocks the interleukin (IL)-4 and IL-13 pathway, is a cornerstone in pediatric AD management, as recently reviewed [14].

Although some recent international guidelines have been published, the topic remains extremely relevant and is the subject of numerous clinical and experimental studies [15–17]. Furthermore, the most recent Italian document was updated over four years ago [18]. Similarly, the most recent update on Dupilumab published by the European Academy of Allergy and Clinical Immunology (EAACI) is now five years old [19]. In addition, it is clinically relevant to contextualize the psychosocial and economic burden of pediatric atopic dermatitis as recently underscored [20].

For the above considered reasons, a steering committee composed by expert pediatricians and dermatologists promoted a multidisciplinary Delphi Consensus on the management of children and adolescents with moderate-to-severe atopic dermatitis. As a recent review analyzed the most recent guidelines and dupilumab data [14], this document displays and discusses the outcomes of this multidisciplinary Delphi Consensus. Therefore, the present multidisciplinary Delphi Consensus aimed to define a series of shared statements concerning atopic dermatitis, with particular regard on moderate-severe phenotype.

Delphi methods

The present Consensus was conducted using a modified Delphi methodology, as recently described [21]. The first round consisted of the constitution of a steering committee composed of experts with academic profiles and a consolidated background in scientific publications, as documented by high-ranking experts. The steering committee's duties included revising the literature on pediatric atopic dermatitis management and drafting a series of statements on AD management in children. In addition, this steering committee conducted a thorough review of dupilumab use in this context. After completing this first round, including achieving full agreement on the defined statements, the steering committee identified a multidisciplinary panel of Italian experts in pediatric AD management, including pediatricians, dermatologists, and allergologists, who are recognized as opinion leaders in their fields based on authoritative publications.

These experts met face-to-face to discuss and vote on the statements (second round).

The list of statements was administered to participants via a real-time web platform that ensured anonymity.

Each panelist scored each statement on the five-point Likert scale: 1, strong disagreement; 2, fair disagreement; 3, no opinion; 4, fair agreement; 5, strong agreement.

The responses were categorized as negative (score 1–2), neutral (score 3), or positive (score 4–5). For each statement, the average score and the percentage of voters who responded positively were considered, and the consensus cut-off was set at 80% agreement. After the second round, the board evaluated the responses to identify areas of agreement and prepared the publication.

Statements

The list of statements is reported in detail in Table 1. The statements consisted of three parts. The first part concerned the definition of the disease and its impact on clinical aspects, including parental life. This part included five statements. The second part addressed the diagnosis and staging of patients with atopic dermatitis and included seven statements. The third part presented a series of statements on the management of children and adolescents with moderate-to-severe atopic dermatitis. This section consisted of seven statements.

Table 1 Statements included in the multidisciplinary Delphi Consensus on the management of children and adolescents with moderate-severe atopic dermatitis and relevant answers

Statement	% agreement (scores 4 + 5)	Mean score (SD)
I Definition of the disease and its impact		
1 Atopic dermatitis is a chronic, recurrent inflammatory skin disease characterised by dysregulation of the immune system (innate and adaptive), predominantly Type 2. Atopic dermatitis is currently considered a systemic disease.	95%	4.5 (0.2)
2 Atopic dermatitis, within the atopic diathesis, can precede the onset of other diseases characterised by Type 2 inflammation, such as food allergies, asthma, allergic rhinitis and eosinophilic oesophagitis. This sequence is called the "atopic march".	**84%**	**4.6 (0.3)**
3 The impact of atopic dermatitis on children is mainly determined by skin manifestations that often occur in visible areas of the body, with possible superinfections. The most significant symptoms are mainly itching and related sleep disturbances.	**87%**	**4.5 (0.4)**
4 Atopic dermatitis can negatively affect a child's psycho-emotional and social development (e.g., bullying, isolation, social discrimination, reduced ability to make decisions independently) and consequently affect their learning at school (reduced attention span).	**90%**	**4.8 (0.2)**
5 Particular care should be paid to caregivers of children with atopic dermatitis, especially in terms of the impact on their sleep, work, daily activities and psychological well-being. The economic impact of covering the costs of treatment must also be taken into account.	**95%**	**4.2 (0.3)**
II Diagnosis and staging		
1 There are still no validated biomarkers that can aid in diagnosis. The diagnosis of atopic dermatitis in children (0–11 years), as in all other age groups, is essentially based on medical history, signs and symptoms, which should be assessed by an experienced clinician (dermatologist/paediatrician).	**97%**	**4.4 (0.3)**
2 The diagnostic criteria proposed by Hainikin and Rajka should be used to formulate a diagnosis of atopic dermatitis in children.	**81%**	**4.3 (0.4)**
3 When making a differential diagnosis of atopic dermatitis, a number of conditions must be considered, including seborrhoeic dermatitis, contact dermatitis (irritant or allergic), psoriasis, nummular dermatitis (non-atopic), scabies, ichthyosis, cutaneous T-cell lymphoma, and photosensitivity dermatosis.	**95%**	**4.7 (0.3)**
4 Skin biopsy should only be used in doubtful cases.	**82%**	**4.4 (0.6)**
5 Early onset, high serum levels of total IgE, clinical severity at onset and a family history of allergic diseases are the main risk factors for a possible atopic march.	**81%**	**4.6 (0.1)**
6 When determining the severity of the disease, clinically measured objective parameters (e.g. EASI, SCORAD), the location of lesions in visible and/or sensitive areas, subjective parameters reported by the patient/caregiver (NRS itch and CDLQI) and/or the presence of superinfections must be taken into account.	**97%**	4.7 **(0.2)**
7 Atopic dermatitis in children is defined as severe according to the EASI score: - EASI ≥ 21 - EASI < 21, but at least one of the following conditions 1. NRS itching ≥ 7 2. Localisation in visible areas (face, neck, hands, feet) and/or sensitive areas (genital and perianal areas). 3. CDLQI ≥ 10 if the child is able to complete it.	**94%**	**4.7 (0.1)**
III Management		
1 Atopic dermatitis is a chronic condition that requires long-term management, and therefore is not limited to acute phases (exacerbations of the disease).	**97%**	**4.8 (0.4)**
2 Treatment in children should aim to: a. Reduce itching b. Restore the skin barrier c. Reduce the incidence of skin infections d. Improve the quality of life of both children and caregivers.	**94%**	**4.7 (0.1)**
3 For the proper management of children with severe atopic dermatitis, it is essential to establish a close therapeutic alliance with the caregiver.	**100%**	**4.9 (0.1)**
4 It is essential to consider a multidisciplinary approach in order to assess the presence of comorbidities so that young patients with severe atopic dermatitis can be managed in the best possible way.	**94%**	**4.7 (0.3)**
5 The family pediatrician is the point of reference for families and should always be involved in the management of children with atopic dermatitis, as they play a key role in improving adherence to treatment.	**89%**	**4.4 (0.4)**
6 The use of biological drugs has completely revolutionized the management of severe atopic dermatitis and potentially its natural history, i.e., affecting the natural history, the so-called atopic march.	**98%**	**4.9 (0.1)**
7 Dupilumab has a mechanism of action specifically designed to counteract type 2 pathogenic mechanisms, and the available scientific evidence is based on solid and robust randomized controlled clinical trials starting from 6 months of age	**100%**	**4.8 (0.2)**

Results

A multidisciplinary panel of 36 Italian experts on pediatric AD management attended the face-to-face meeting and voted on all statements. Table 1 summarizes the results obtained.

Definition of the disease and its impact

Statement 1 achieved 95% agreement with a mean score of 4.5. Statement 2 obtained 84% of agreement with a mean score of 4.6. Statement 3 achieved an 87% agreement with a mean score of 4.5. Statement 4 had 90% of agreement with a mean score of 4.8. Statement 5 achieved 95% of agreement with a 4.2 mean score.

Diagnosis and staging

Statement 1 achieved 97% agreement with a mean score of 4.4. Statement 2 obtained 81% of agreement with a mean score of 4.3. Statement 3 achieved 95% of 95% with a mean score of 4.7. Statement 4 had 82% of agreement with a mean score of 4.4. Statement 5 achieved 81% agreement with a mean score of 4.6. Statement 6 reached 97% consensus with a mean score of 4.7. Statement 7 had 94% Consensus and a mean score of 4.7.

Management

Statement 1 achieved 97% agreement with a mean score of 4.8. Statement 2 obtained 94% of agreement with a mean score of 4.7. Statement 3 achieved the complete consensus (100%) with a mean score of 4.9. Statement 4 had 94% of agreement with a mean score of 4.7. Statement 5 achieved 89% agreement with a mean score of 4.4. Statement 6 reached 98% consensus and a mean score of 4.9. Statement 7 had complete consensus (100%) and a mean score of 4.8.

Discussion

Atopic dermatitis represents a common medical condition in children and adolescents. As AD is a chronic inflammatory disorder, it significantly affects the quality of life of young patients and parents. In addition, treatment is usually complex and requires several medications. As a result, the AD burden is relevant. On the other hand, the number of available drugs is conspicuous, and new medicines are constantly appearing on the market. Similarly, several guidelines and research articles are continuously published. So, doctors require a constant update. Based on this background, a steering committee promoted the present multidisciplinary Delphi Consensus to provide shared statements useful in clinical practice.

The findings indicated that all proposed statements achieved good agreement, with more than 80% of participants scoring 4 or 5. As a result, all statements are valuable because they express complete agreement.

The first statement of the first part on the definition of the disease and its impact declared that atopic dermatitis is a chronic, recurrent inflammatory skin disease characterized by dysregulation of the immune system (innate and adaptive), predominantly Type 2. Namely, atopic dermatitis is currently considered a systemic disease. Atopic dermatitis is considered systemic because, although it manifests itself on the skin, its underlying causes are linked to dysfunction of the immune system (polarization 2), genetics, and general inflammation of the body, also affecting other organs and quality of life. It often manifests itself with asthma, allergies, and psychological problems, requiring a therapeutic approach that goes beyond the skin alone. These concepts are well established in the literature and are acknowledged by all guidelines and scientific documents [22].

Statement 2 establishes that atopic dermatitis, within the atopic diathesis, can precede the onset of other diseases characterised by Type 2 inflammation, such as food allergies, asthma, allergic rhinitis, and eosinophilic esophagitis. This sequence is called the "atopic march". This trajectory is well known and widely documented, but it may be mitigated by biologic therapy [23].

Statement 3 establishes that the impact of atopic dermatitis on children is mainly determined by skin manifestations that often occur in visible areas of the body, with the potential for superinfection. The most significant symptoms are mainly itching and related sleep disturbances. Cutaneous complaints are preeminent and lead to impaired quality of life [24]. Consistently, itching control represents a primary goal of management.

Statement 4 highlights that atopic dermatitis can negatively affect a child's psycho-emotional and social development (e.g., bullying, isolation, social discrimination, reduced ability to make decisions independently) and consequently affect their learning at school (reduced attention span). Also, this issue is widely recognized in the literature [25].

Statement 5 reports that particular care should be taken with caregivers of children with atopic dermatitis, especially regarding the impact on their sleep, work, daily activities, and psychological well-being. The economic impact of covering treatment costs must also be considered. However, appropriate therapeutic management of moderate-to-severe atopic dermatitis with targeted topical and/or systemic agents, including biologic therapies such as dupilumab, may significantly reduce this clinical burden [26].

Statement 1 of the second part, concerning diagnosis and staging, stated that no validated biomarkers are currently available to aid diagnosis. The diagnosis of atopic dermatitis in children (0–11 years), as in all other age groups, is essentially based on medical history, signs, and symptoms, which should be assessed by an experienced

clinician (dermatologist/pediatrician). The diagnostic pathway is complex and time-consuming, as many factors should be adequately considered [27].

Statement 2 states that the diagnostic criteria proposed by Hainikin and Rajka should be used to diagnose atopic dermatitis in children. Actually, this statement did not receive unanimous approval because, in reality, these proposed criteria are outdated and other, more comprehensive diagnostic criteria are used in clinical practice [28].

Statement 3 defined that when making a differential diagnosis of atopic dermatitis, several conditions must be considered, including seborrhoic dermatitis, contact dermatitis (irritant or allergic), psoriasis, nummular dermatitis (non-atopic), scabies, ichthyosis, cutaneous T-cell lymphoma, and photosensitivity dermatosis. Namely, differential diagnosis is a compelling task as several conditions should be carefully considered [29].

Statement 4 emphasized that a skin biopsy should be performed only in cases of doubt. In practice, skin biopsy should be reserved for a few carefully selected cases in which the standard diagnostic process has been inconclusive [30].

Statement 5 stated that early onset, high serum total IgE levels, clinical severity at onset, and a family history of allergic diseases are the main risk factors for a possible atopic march. These risk factors facilitate the progression of the atopic march, as immunological involvement is particularly exacerbated [31].

Statement 6 proposed that when determining the severity of the disease, clinically measured objective parameters (e.g., EASI, SCORAD), the location of lesions in visible and/or sensitive areas, subjective parameters reported by the patient/caregiver (NRS itch and CDLQI), and/or the presence of superinfections must be taken into account. These measures represent the gold standard for defining disease severity correctly and identifying eligible candidates for biological therapy [32].

The statement 7 consistently declared that atopic dermatitis in children is defined as severe according to the EASI score ≥ 21 or < 21, but at least with one of the following conditions, such as NRS itching ≥ 7, localisation in visible areas (face, neck, hands, feet) and/or sensitive areas (genital and perianal areas), or CDLQI ≥ 10 if the child can complete it. Namely, these criteria are well documented and define the need for personalized, targeted therapy, including biologics [33].

Statement 1 of the third part, concerning AD management in children and adolescents, proposed that atopic dermatitis is a chronic condition that requires long-term management and is not limited to acute phases (exacerbations). This concept of long-standing disease duration leads to personalized treatment, also based on biological medications targeted to modify the disease course [34].

Statement 2 stated that treatment in children should aim to: (a) reduce itching, (b) restore the skin barrier, (c) reduce the incidence of skin infections, and (d) improve the quality of life of both children and caregivers. The therapeutic objectives are fundamental for achieving clinical remission and for evaluating the effectiveness of prescribed treatments [35].

Statement 3 proposed that for the proper management of children with severe atopic dermatitis, it is essential to establish a close therapeutic alliance with the caregiver. Namely, a valuable liaison between doctors and parents is essential to achieve adherence to and awareness of prescribed treatments [36].

Statement 4 established that a multidisciplinary approach is essential to assess comorbidities, enabling young patients with severe atopic dermatitis to be managed in the best possible way. AD management effectively requires the involvement of various specialists to understand better endotype and phenotype in the field of Precision Medicine [37].

Statement 5 stated that the family pediatrician is the point of reference for families and should always be involved in the management of children with atopic dermatitis, as they play a key role in improving treatment adherence. The role of primary care is fundamental in managing children and adolescents with AD; however, this involvement needs continuous updating and a close relationship between the hospital and the territory [38].

Statement 6 defined that the use of biological drugs has completely revolutionized the management of severe atopic dermatitis and potentially its natural history, i.e., affecting the natural history, the so-called atopic march. There is widespread agreement on the pivotal role of biologics in altering the course of AD [39].

Statement 7 declared that among the biological drugs currently available, Dupilumab is the most interesting, as it has a mechanism of action specifically designed to counteract type 2 pathogenic mechanisms, and the available scientific evidence is based on solid and robust randomized controlled clinical trials. The number of randomised controlled clinical trials on the efficacy and safety of dupilumab in children with AD is truly remarkable and is growing, as recently reviewed [14, 40, 41]. However, it has to be underlined that also other biologics acting on type 2 inflammation are available as recently reviewed [42]. In this regard, tralokinumab and lebrikizumab are two IgG4k monoclonal antibodies that binds IL-13. In particular, tralokinumab obtained the EMA approval for adolescents with severe AD and not responder to topical therapy. In addition, nemolizumab is a humanized monoclonal antibody targeting the receptor A of IL-31 (IL31RA), blocking its pathway. However, this biologic is still under consideration by EMA.

Conclusive remarks

The AD management in children and adolescents is a compelling task and requires updated knowledge. The present multidisciplinary Delphi Consensus provided a series of shared statements based on literature evidence. It has some limitations, including the limited number of participants, and the exclusive focus on a single biological agent. However, this steering committee selected highly qualified participants, and the considered biological drug is currently the most studied among young people.

In conclusion, the present multidisciplinary Delphi Consensus proposes shared and evidence-based statements that may be fruitful in clinical practice.

Abbreviations

AD	Atopic dermatitis
CDLQI	Children's dermatology life quality index
EAACI	European academy of allergy and clinical immunology
EASI	Eczema area and severity index
NRS	Numeric rating scale
SCORAD	SCORing Atopic Dermatitis

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

GLM, AL, MMdM, ABF, MAT, and GC conceptualized and designed the study, GC collected and interpreted data, GC conducted the initial analyses, and drafted and revised the manuscript. AL prepared the platform and analyzed data. GLM, MMdM, ABF, IN, CF, FM, CF, AL, and EG revised and edited the manuscript, and GLM and MMdG commented on it. SM, AL, and MAT revised the literature. All authors participated in the paper discussion, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

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Data availability

All data generated and analyzed during this Delphi Consensus are included in this published article.

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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