Atopic Dermatitis: Epidemiology and Clinical Phenotypes

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This article is part of a series of reviews dedicated to Atopic Dermatitis, guest edited by Prof Anna Balato.

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ABSTRACT

Atopic dermatitis (AD) is a chronic, lifelong, relapsing condition. The wide spectrum of the possible clinical presentations, depending on patient’s age, age of onset of disease, topography and morphology of dermatitis, limits the epidemiologic information on its prevalence and incidence. A clear definition of the different clinical AD phenotypes and epidemiology is essential for an appropriate patient’s treatment and management, in particular for adults. This review summarizes the most recent epidemiologic data from the 21st century, on AD prevalence and incidence rates either in children or adults, with a special focus on their trends in Europe. Moreover, an effort to categorize diverse AD clinical expressions, has been made, aiming to facilitate differential diagnosis and speed up the start of the correct therapy.
Epidemiology of Atopic Dermatitis: Data From the 21st Century

Updated prevalence and incidence data of AD, across different age groups and countries, increase our understanding of the disease burden. It is well established that in most cases (approximately 80%) AD onset occurs during the first years of life, with frequent remissions in adolescence (approximately 60% of individuals). Recently, some studies have reported an adult-onset AD, even if epidemiological and clinical features of this adult form need to be further clarified [1-4]. AD incidence and prevalence register a stable plateau in Europe and North America, while they are increased in other continents, such as Asia. There are few recent studies on the incidence of AD. Most of them have been conducted in Europe (EU) and USA [5]. Limited information on the prevalence and incidence of AD among adults suggest the wide variability that may be dependent by the population, disease definitions, diagnostic criteria, presence or not of disease register, and lack of a universally accepted index for disease severity. Future studies with more standardized methods need to be conducted to assess epidemiology of AD, especially for adults: they are important to improve healthcare planning and patient management.

AD in Children: Prevalence and Incidence

The point prevalence (the proportion of the population that has the disease at a specific point in time) ranged from 0% (Nigeria) to 18.2% (Turkey) [6,7]. The 1-year period prevalence (the proportion of the population presenting the disease for 1 year) ranged from 4.1% to 22.7%. The 1-year prevalence of doctor diagnosed (the proportion of the population with the disease diagnosed by a doctor in 1 year) ranged from 0.96% to 22.6%, and the lifetime symptom prevalence (the proportion of population that has the disease symptoms at least once in a lifetime) ranged from 4.4% to 17.7% assessed at age 7–15 years [8-12]. The 1-year incidence (the annual incidence, the probability of the disease occurrence in the population) in children ranged from 10.2 per 1,000 person years in Italy (95% Confidence Interval (CI), 9.9–10.6) to 95.6 per 1,000 person years in Scotland (CI 93.4–97.9 %). Many studies reported that the highest incidence of AD occurred during infancy, with a disease onset by the age of 7 years [11,13,14]. The incidence was also high in early childhood during the first 18 months of life [13,15].

AD in Adults: Prevalence and Incidence

In the overall population, the 1-year adult prevalence of AD was 4.9% (95% CI: 4.6% - 5.2%) in the US, 3.5% (95% CI: 3.1%-3.9%) in Canada, and 4.4% (95% CI: 4.2%-4.6%) in Europe (EU) [16,17]. The 1-year prevalence of diagnosed AD ranged from 1.2% (Asia) to 17.1% (EU) [8,9,18]. The lifetime symptom prevalence ranged from 3.0% to 17.7% [8,9,12]. The point prevalence of adult AD was reported to be 2.9% in Japan, with 1-year rate of 3.0% and lifetime prevalence of 3.3% [19]. A significant incidence was also reported during adolescence and adulthood. Studies recorded an incidence rate of AD in adults of 7.41 per 1,000 person years (6.27–8.74) [20], and a proportion of adult onset of 8.0% in Germany at age 28–30 years [16,21,22-25].

Trends of Prevalence by Sex

Both the 1-year prevalence and lifetime prevalence of diagnosed AD were higher in females (range 0.6–24.3%; 1.0–35.5%, respectively) than in males (range 0.8–17.6%; 1.4–37.3%, respectively), except for the UK, where the prevalence was the same (2.5%), and the US, where prevalence was numerically, but not significantly, higher in males (5.1% vs 4.6%) [5,26].

Spotlight on AD Epidemiology in Europe

European trends seem to be in-line with those reported from global studies: AD is more prevalent in children compared to adults, and in overcrowded urban areas [27]. The prevalence in adolescent group is between 1.5% (Lithuania) and 15% (Bulgaria, Denmark, Finland, and Hungary). Epidemiology in adult group remains a challenge. An international, cross sectional, web-based survey was performed in 2018 [26]. It reported 1-year adult prevalence of AD in EU of 4.4% (95% CI: 4.2%-4.6%) with country ranges from 2.2% (95% CI: 1.9%-2.5%) in Germany to 8.1% (95% CI: 7.5%-8.6%) in Italy. Italy and Spain reported a higher point adult prevalence respect to other countries. The prevalence in females was significantly enhanced in Spain (9.3% females vs 5.1% males, P < .05). France, Italy, and Spain had more mild forms of adult AD compared with the ones reported in UK and Germany. Italy had an important regional variability, showing higher adult prevalence rates in Mediterranean regions [28]. The reasons of this variability are many: genetic, behavioral or cultural components, socioeconomic conditions, and climatic factors [29]. In general, mild, or moderate severity were the most common clinical presentations, with low proportions of severe form.

The Thousand Faces of AD: The Wide Spectrum of Clinical Phenotypes

The heterogeneous and intriguing clinical aspects of AD reflects the complex nature of this lifelong disease. Traditionally, clinical lesions are classified as “acute”, characterized by oozing, edema, and erythema, or “chronic”, with prevalent xerosis, lichenification, and dyspigmentation. However, as chronic relapsing condition, both types of lesions can coexist in the same individual, especially during flares. The main hallmark of AD is pruritus, responsible for excoriations and skin lichenification. A clear definition of the different clinical
AD phenotypes (Table 1) is essential to improve its treatment and management, passing from a “one-size-fits-all” to a personalized approach based on differentiation of AD clinical expressions.

### Age-Related Clinical Phenotype

Many clinical pictures of AD have been described based on the age of the patient: infantile AD (3 months/2 years), childhood AD (2-12 years), adolescent/adult AD (12-60 years), and

#### Table 1. Clinical Phenotypes of AD and Related-Differential Diagnosis.

| PHENOTYPE | CLINICAL FEATURES | DIFFERENTIAL DIAGNOSIS |
|-----------|-------------------|------------------------|
| Infantile (0-2 years) | Eczematous lesions typically affect scalp, checks, neck, and extensor parts of the extremities with edematous papulo-vesicles, oozing, and crusting. | Seborrheic dermatitis, psoriasis, scabies, ichthyosis vulgaris, phenylketonuria Genetic syndromes: Di George syndrome, Netherton syndrome, Wiskott-Aldrich syndrome. |
| Childhood (2-12 years) | Eczematous lesions typically affect popliteal and antecubital fossa, hand, and foot, with edematous papulo-vesicles, oozing, crust, and lichenification. | Impetigo, psoriasis, tinea manuum, pedis. |
| Adolescent/adult (12-60 years) | Eczematous lesions prevalently affect head, neck and flexural areas, with xerosis, lichenification, and depigmentation. In females they also involve peri-orbital and nipple areas. | ACD, psoriasis, cutaneous T-cell lymphoma, pityriasis rubra pilaris, pityriasis rosea, asthetotic eczema. |
| Elderly (>60 years) | Extensive eczematous lesions, including flexural areas, up to erythrodermic aspect. | ACD, psoriasis, cutaneous T-cell lymphoma, pityriasis rubra pilaris, pityriasis rosea, asthetotic eczema. |

#### Topography-related clinical phenotypes

**Head and neck**

- Scalp: Erythema, scaling, crusting, lichenification, excoriation, and scarring.
- Face: Erythema, oozing, edema, xerosis, lichenification, dyspigmentation, and excoriation.
- Eyes: Erythema, scaling, crusting, lichenification, depigmentation, and excoriation.
- Lips: Erythema, xerosis, lichenification, fissuration, and dyspigmentation.
- Flexures: Erythema, edema, excoriation, lichenification, oozing, and crusting.
- Nipples: Erythema, scaling, crusting, lichenification, excoriation, and scarring.
- Hand and foot: Erythema, xerosis, lichenification, scaling, crusting, fissuration, and dyspigmentation.

#### Morphology-related clinical phenotypes

- Nummular: Circinate and ovoid plaques with central clearing and peripheral extension of papules and papulo-vesicles.
- Prurigo Nodularis: Excoriated hyperkeratotic and intensely itchy nodules.
- Erythrodermic phenotype: Erythema on >90% of the body surface area.
- Lichenified: Skin is thick with accentuated creases and a leathery appearance.
- Follicular/papular: Papular-lichenoid lesions.

ACD = allergic contact dermatitis; ICD = irritant contact dermatitis.
elderly AD (> 60 years). Pruritus remains the hallmark in all stages, except for very initial disease onset (< 3 months). In the infantile form, eczematous lesions typically affect scalp, cheeks, neck, and extensor parts of the extremities with edematous papulo-vesicles, oozing, and crusting. In the childhood stage both acute and chronic lesions are present. Popliteal, antecubital fossae, wrists, and ankles. It is more prevalent in adolescent and adult Caucasian patients with a chronic persisting course.

**Hand and Foot AD.** This form appears with xerotic, scaly, lichenified, and fissured skin, notably on the dorsal part. This phenotype is more common in adulthood, especially in females. Conditions, such as juvenile palmoplantar dermatitis or dermatitis plantaris sicca, have been described in children, with a possible link to atopic diathesis. The risk of hand dermatitis was greater in children with persistent or severe AD. Dyshidrotic eczema may be a clinical phenotype of hand and foot AD that manifests as vesicles and blisters on the palms and soles.

**Morphology-Related Clinical Phenotypes**

**Nummular phenotype.** The term derives from the coin like appearance of the lesions. Indeed, they are typically circinate and ovoid plaques with central clearing and peripheral extension of papules and papulo-vesicles. Lower extremities are predominantly affected. It is the most common morphologic variant of AD, and it is more prevalent in children and adult-onset forms. However, if nummular eczema is AD in all cases needs to be deeply clarified.

**Prurigo Nodularis phenotype.** In some AD patients the morphology of lesions is characterized by multiple excoriated hyperkeratotic and intensely itchy nodules. A condition defined Prurigo Nodularis secondary to AD. It is more common in adults. Also, for this morphologic variant an accurate differential diagnosis must be considered.

**Erythrodemic phenotype.** It is the presence of erythema on > 90% of the body surface area. This form is frequent in adolescents and adults, especially in those with a life-long disease.

**Lichenified phenotype.** In this variant the skin is thick with accentuated creases and a leathery appearance. It is more common in adolescents and adults from South-East Asia or Africa than in Caucasian patients.

**Follicular/papular phenotype.** It is a morphological subtype more frequent in dark skin, characterized by papular-lichenoid lesions.

**Conclusions and Open Questions**

AD is a heterogeneous disease that can be classified according to many and different criteria, based on morphology, topography, severity, age at onset, or disease course.

The difficulty in identifying AD, for the lack of validated universal diagnostic criteria as well as for the variegated clinical phenotypes, is responsible for the approximation of the epidemiology of this disease. In fact, AD clinical phenotypes and epidemiology clarification are current challenges for dermatologists. It will be useful to realize a practical
guide to distinguish the main features of any clinical phenotypes to perform an earlier diagnosis with more appropriate treatment and management decisions. The variability of AD implicates the need for a personalized therapy. Establishing an association between phenotype and treatment response, sheds light on the different pathogenetic mechanisms that express in distinct clinical presentations and require diverse therapeutic strategies.

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