



Adult-Onset Atopic Dermatitis: Characteristics and Management

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Abstract

Recent epidemiological studies found the US prevalence of atopic dermatitis in adults to be approximately 7%. In particular, one in four adults with atopic dermatitis report adult onset of their disease. Adult-onset compared to child-onset atopic dermatitis is associated with distinct risk factors, lesional distribution and morphology, associated signs, genetics, and comorbidities. Adult-onset atopic dermatitis is a clinical diagnosis, and must be distinguished from other entities in the differential diagnosis, e.g., allergic contact dermatitis and cutaneous T-cell lymphoma. Further research is necessary to better understand the pathogenesis and optimal treatment approaches in adult-onset/recurrent atopic dermatitis.

Key Points

One in four adults with atopic dermatitis report adult onset of their disease.

Adult-onset atopic dermatitis was found to have different clinical characteristics and lower rates of comorbid atopic disease.

Adult-onset atopic dermatitis is a challenging clinical diagnosis and must be distinguished from a broad differential diagnosis.

1 Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that has been conservatively estimated to have annual medical costs in the USA of US\$5.2 billion [1].

Atopic dermatitis is a heterogeneous disease with a broad spectrum of clinical manifestations. A recent systematic review and meta-analysis of 101 studies identified 78 different clinical signs and characteristics of AD, with considerable variability by global region and patient age [2]. In addition, there is a complex constellation of symptoms in AD, including pruritus, xerosis, pain, and sleep disturbance, which leads to a large impairment in quality of life [3–5].

Atopic dermatitis is thought to occur via a combination of genetic, environmental, and immunologic factors [6–8]. A compromised skin barrier results in increased transepidermal water loss and transcutaneous penetration of microbes and allergens, and ultimately can trigger an inflammatory cascade [9–11]. T-helper cell (Th) type 2 and other T-cell subsets contribute to the pathogenesis of AD. In the acute and chronic phases of AD, a skewed Th2 response is seen, leading to increased activity of interleukin (IL)-4, IL-5, IL-13, and IL-31. Whereas, Th1 responses are upregulated in the chronic phase of AD.

Atopic dermatitis was once thought to be primarily a pediatric disease that remitted with increasing age. However, recent epidemiological studies showed that AD is a heterogeneous disease that can start and persist throughout the life course. This review focuses on adult-onset AD, which has a unique epidemiology, pathophysiology, and clinical presentation.

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2 Epidemiology

2.1 Adult Atopic Dermatitis (AD)

Several studies have examined the epidemiology of adult AD. A 2007 US population-based survey of eczema prevalence found that the peak onset of eczema occurred in young adulthood, and that 54% of adults with active AD reported onset in adulthood [12]. Analysis of 4972 adults from the 2005–6 National Health and Nutrition Examination Survey found the US prevalence of healthcare diagnosed AD in adults to be 7.4% [13]. Similarly, analysis of 27,157 adults from the 2010 National Health Interview Survey found the US prevalence of self-reported AD to fall within 3–10% [14, 15]. A subsequent analysis of 34,613 adults from the 2012 National Health Interview Survey found the US prevalence of self-reported AD in adults to be 7.2%. Notably, this study showed that AD prevalence decreased from 14% in childhood to 8% in adolescence, and then plateaued at approximately 7% throughout the adult years [4]. Similarly, a US population-based survey study (AD in America) found the prevalence of AD to be 7.3% in adults in 2017 [16]. Thus, it appears that the US prevalence of AD is approximately 7% in adults.

The prevalence of adult AD ranged from 2 to 17% in previous international studies [17]. A recent international web-based survey found the prevalence of previously diagnosed and active AD ranged from 2.1 to 4.9% [18]. Similar to the results of the National Health Interview Survey in the USA, AD prevalence was found to decrease from childhood to adolescence, but remained stable into adulthood [17, 19]. Together, it appears that the prevalence of AD in adults is similar to adolescents and is stable throughout adulthood.

2.2 Adult-Onset AD

Previous studies found that 50% of AD starts in the first year of life and 85% starts by age 5 years [20–22]. However, these studies included cohorts of children, but did not assess adolescents or adults. Thus, the proper interpretation of these studies is that most childhood AD starts early in life. However, if a study did not examine adolescents or adults, it would be impossible to make any determinations about how commonly AD starts later in life.

Thus, a recent systematic review and meta-analysis attempted to consolidate the extant data and determine how commonly adult-onset AD occurs [23]. The review included 25 studies that analyzed the age of AD onset beyond 10 years. Seventeen studies were identified that reported the proportion of adult-onset AD. All studies

reported substantial proportions of adults with AD having adult onset of their disease, albeit with a wide range (7.7–59.7%). In a random-effects pooled meta-analysis, 26.1% of adults with AD reported adult onset of their disease. Interestingly, most studies, especially those that assessed older cohorts, found that AD onset commonly occurred across older ages. Further, most of the studies that found very high proportions of childhood-onset AD only studied patients into early adulthood. Together, it appears that AD commonly starts at all ages, and that studies limited to children and/or young adults missed this observation because they simply did not examine older patients.

It could be that patients reporting adult-onset AD may have forgotten they had AD in childhood that remitted. As such, it is possible that some cases of adult-onset AD are actually adult-recurrent AD, rather than adult-onset AD. However, five studies retrospectively examined medical records to confirm that patients with adult-onset AD did not have AD in childhood [24–28]. Further, three studies prospectively followed patients from early in life to verify that the diagnosis of AD was correct and did not change over time [29–31]. Regardless of whether such cases are adult-onset or adult-recurrent AD, clinicians should recognize that adults with AD commonly report adult onset.

A previous study found that foreign-born American children and adults had lower rates of AD and asthma compared with their US-born counterparts, respectively [32, 33]. However, the odds of AD and asthma increased in foreign born children and adults after residing in the USA for more than 10 years, respectively [32, 33]. Similarly, a clinical study found that adult-onset compared with childhood-onset AD was associated with a higher odds of being born outside the USA and with AD developing after migrating to the USA [34].

3 Pathophysiology

Few studies have compared the immune differences of AD in children vs. adults. A recent study of 19 children aged < 5 years with new-onset AD compared the immune phenotype in skin with 15 adults with AD [35]. Children compared to adults with AD showed comparable or greater epidermal hyperplasia and immune infiltration, decreased filaggrin expression on histology and immunohistochemistry, and activation of Th2, Th22, and Th1 axes on quantitative real-time polymerase chain reaction. However, children showed a higher induction of Th17-related cytokines, antimicrobials, Th9, IL-33, and innate markers than adults. A study of 71 adults and 61 children with AD and 31 adult controls found that AD was associated with similarly increased serum levels of thymic stromal lymphopoietin (TSLP),

IL-33, and immunoglobulin E (IgE) in children and adults, IL-31 levels in children, but no elevations of soluble suppression of tumorigenicity 2 (sST2) levels in children or adults [36]. Further, IL-31 and IL-33 levels were higher in children than adults, whereas TSLP, IgE, and sST2 levels were similar in children and adults [36]. These results suggest that the immune mechanisms of AD may differ between children and adults.

Though, the specific mechanisms of adult-onset AD are unknown. It may be that the genetic and/or immune mechanisms of adult- and child-onset AD are similar, but the first exposure to environmental triggers occurs in adulthood. However, the mechanisms of adult-onset AD may be distinct from childhood-onset AD. A study of 241 patients with AD found that the four most common filaggrin loss-of-function mutations were only associated with early childhood-onset AD (age ≤ 8 years), but not late-childhood (age 8–17 years) or adult-onset disease (age ≥ 18 years) [37]. Further research is warranted to determine the mechanism(s) of adult-onset AD.

4 Phenotypical Differences

4.1 Adult AD

A recent US population-based study of 602 adults with AD found that the most common sites of skin lesions were reported to be the popliteal fossae, lower legs, dorsal feet, and antecubital fossae [38]. Other commonly reported sites include the face, scalp, hands, and genitals. Most persons with AD reported symmetry of lesions on the extremities. There were no significant differences of lesional distribution between those who self-report adult-onset vs. child-onset AD.

Few studies examined the phenotypical differences of AD in adults compared to children. Thus, a recent systematic review and meta-analysis attempted to consolidate the extant data and determine phenotypical differences of AD between children and adults [2]. The review included 38 pediatric and 36 adult studies that reported a proportion of at least one AD feature with sufficient data for a meta-analysis. Adults studies reported two-fold or higher rates of erythroderma, Hertoghe's sign (thinning or loss of outer third of eyebrows), hand eczema, papular lichenoid lesions, course influenced by emotions and/or environment, prurigo nodules, lichenification, nail involvement, nipple eczema, and nummular lesions. Thus, it appears that AD manifests differently in adults than children.

4.2 Adult-Onset AD

A few studies examined whether adult-onset AD presents with distinct phenotypes compared to childhood-onset AD.

Wang et al. found that adult-onset AD ($n=407$) vs. pediatric-onset AD ($n=275$) was associated with higher rates of dermatitis affecting the feet (8.8% vs. 4%), with lower rates of dermatitis affecting the conjunctiva/eyelids (7.1% vs. 21.8%), ears (9.6% vs. 18.9%), and face (16.7% vs. 51.3%). The study also found that adult-onset AD was more associated with the presence of vesicles and nodules (19.7% vs. 9.8%; 13.8% vs. 4%, respectively), and less associated with xerosis (55% vs. 60.7%) [39]. Son et al. found that adult-onset AD ($n=48$) vs. pediatric-onset AD ($n=232$) was associated with higher rates of dermatitis affecting the head/neck (22.9% vs. 16.4%), and possibly lower rates of dermatitis of the flexor surfaces of the extremities (29.2% vs. 51.3%). The study also found that adult-onset AD was more associated with white dermatographism (4.2% vs. 2.6%) and the Sign of Hertoghe (thinning or loss of outer third of eyebrows; 8.3% vs. 3.9%), but less associated with xerosis (56.3% vs. 63.8%) and pruritus after sweating (37.5% vs. 51.3%) [40]. A recent study also examined phenotypical differences, and found that adult-onset AD ($n=149$) vs. pediatric-onset AD ($n=207$) was associated with lower rates of dermatitis affecting the conjunctiva (24.2% vs. 53.6%) and face (28.2% vs. 57%), possibly more likely to present morphologically with nummular eczema (14.1% vs. 5.8%), and less associated with pruritus after sweating (60.4% vs. 66.7%) and a Dennie–Morgan fold (extra infra-orbital crease; 10.7% vs. 36.2%) [34].

Adult-onset AD was consistently found to have a less personal history of any allergic disease, particularly conjunctivitis, or a family history of allergic disease [23]. In contrast, adult-onset AD was associated with more personal history of allergic rhinitis, but no differences with asthma [23].

5 Diagnosis

5.1 Diagnostic Criteria

Adult-onset AD is diagnosed clinically based on a combination of a history and physical examination and by ruling out other entities in the differential diagnosis. There are no specific diagnostic criteria specifically for adult-onset AD. The diagnostic criteria of Hanifin and Rajka (H-R) were developed for AD in children and adults in 1980 and arguably remain the gold-standard criteria for AD (Table 1) [41]. Subsequently, different criteria emerged using abridged and/or simplified versions of the H-R criteria, e.g., United Kingdom Working Party (UKWP) or American Academy of Dermatology (AAD). Hanifin and Rajka criteria were the most commonly used criteria in clinical trials of AD, in both children and adults [42].

Hanifin and Rajka and UKWP criteria include flexural lesions as a major criterion. Similarly, the AAD criteria

Table 1 Common atopic dermatitis (AD) diagnostic criteria

Diagnostic criteria	Utility in diagnosing adult-onset AD
Hanifin and Rajka [58]	At least 3 major criteria: - Pruritus - Typical morphology and distribution (<i>flexural lichenification/linearity in adults</i>) - Chronic or chronically relapsing dermatitis - Personal or family history of atopy At least 3 of 23 minor criteria: - Xerosis; ichthyosis, palmar hyperlinearity, or keratosis pilaris; immediate skin-test reactivity; raised serum IgE; early age of onset; tendency towards cutaneous infections; tendency towards non-specific hand or foot dermatitis; nipple eczema; cheilitis; recurrent conjunctivitis; Dennie–Morgan infraorbital fold; keratoconus; anterior subcapsular cataracts; orbital darkening; facial pallor or erythema; pityriasis alba; anterior neck folds; itch when sweating; intolerance to wool and lipid solvents; perifollicular accentuation; food intolerance; course influenced by environmental or emotional factors; white dermatographism Of the major criteria, patients with adult-onset AD are likely to have pruritus and a chronic course; however, these patients often will not have typical flexural distribution. Furthermore, limited evidence suggests patients with adult-onset AD may have less personal and/or family history of other atopic disease. Thus, patients with adult-onset AD may not meet at 3 least major criteria Of the minor criteria, adult-onset AD has had, compared with pediatric-onset, a greater association with non-specific hand/foot dermatitis, nipple eczema, and white dermatographism; and less of an association with xerosis, early age of onset, Dennie–Morgan folds, orbital darkening, pityriasis alba, and pruritus when sweating. Overall, patients with adult-onset AD are likely to meet at least 3 of the 23 minor criteria Hanifin and Rajka may not perform as well for adult-onset AD. [59] However, it is currently the gold standard for AD diagnosis overall and the most comprehensive to ascertain numerous atypical features seen in adult-onset AD
United Kingdom Working Party [60]	Requires presence of pruritus/itchy skin condition plus 3 of 5 criteria - History of xerosis/dry skin - Onset below age of 2 years - Visible flexural dermatitis - Personal history of other atopic disease - History of involvement of skin creases Likely to have a low sensitivity of diagnosing adult-onset AD, as adult-onset AD would not have onset before age 2 years, and has been shown to be less associated with xerosis and flexural dermatitis than pediatric-onset AD. Furthermore, limited evidence suggests patients with adult-onset AD may have less personal history of other atopic disease. Thus, patients with adult-onset AD may not be able to satisfy 3 of the 5 additional criteria required for diagnosis. A previous study found that, of adults diagnosed with adult-onset AD using Hanifin and Rajka criteria, roughly 1 in 4 of these patients did not satisfy United Kingdom Working Party criteria [27]
Japanese Dermatologic Association [61]	Requires presence of three features: - Pruritus - Typical morphology and distribution (<i>for adults: symmetric and more severe on upper half of body</i>) - Chronic or chronically relapsing course (<i>≥ 6 months of disease in adults</i>) Potential to work well for diagnosis of adult-onset AD as this population experiences pruritus and likely experiences ≥ 6 months of disease; importantly, flexural involvement is not required, and there are age-appropriate criteria for distribution. For adults, this consists of distribution on the upper half of the body (i.e., head/neck or trunk lesions)
American Academy of Dermatology [62]	Must have: - Pruritus - Eczema with typical morphology and age-specific patterns (<i>current or prior flexural lesions, sparing of groin/axillary regions; nothing adult specific</i>) and chronic/relapsing history Important features seen in most cases that adds support to diagnosis: - Early age of onset - Atopy (personal and/or family history, IgE reactivity) - Xerosis Associated features that help suggest diagnosis but are too non-specific: - Keratosis pilaris, pityriasis alba, palmar hyperlinearity, ichthyosis, ocular/periorbital changes, perifollicular accentuation, lichenification, prurigo lesions, regional (perioral/periauricular) findings, atypical vascular responses (facial pallor, white dermatographism) Patients with adult-onset AD may not meet must-have “typical pattern” criteria, and are unlikely to have many, if any, important features to support diagnosis. Important to consider these criteria were developed to be more applicable in younger patients

IgE Immunoglobulin E

Table 2 Differential diagnosis of adult-onset atopic dermatitis

Contact dermatitis
Cutaneous T-cell lymphoma
Psoriasis
Nummular dermatitis
Cutaneous lupus
Eczematous drug eruption
Dermatomyositis
Urticarial bullous pemphigoid
Dermatitis herpetiformis
Transient acantholytic dermatosis
Seborrheic dermatitis
Skin infection (i.e., impetigo)
Molluscum dermatitis
Langerhans cell histiocytosis
Scabies
Zinc deficiency
Immunodeficiency (Wiskott–Aldrich syndrome, hyper-IgE syndrome)

IgE Immunoglobulin E

include flexural lesions as an essential feature. Early age of onset is a minor (but not major) criterion in H-R and an important (but not essential) criterion in AAD criteria. In contrast, early age of onset is a major criterion in the UKWP criteria. Thus, a patient can meet the H-R or AAD criteria if they have adult-onset disease without flexural involvement. In contrast, a patient would only meet the UKWP criteria if they have late-onset disease with flexural involvement or early-onset disease without flexural involvement. This has important ramifications because previous studies showed lower rates of flexural lesions in adult-onset AD [23]. Hanifin and Rajka and AAD criteria may perform better than UKWP criteria in adult-onset AD. Further research is warranted to determine the optimal criteria for diagnosing adult-onset or adult-recurrent AD in clinical practice and trials.

While formal diagnostic criteria are used routinely in a clinical trial, they are rarely used in clinical practice. They can be helpful in guiding clinicians towards the diagnosis of AD, particularly in adult-onset AD. However, all criteria for AD are imperfect. Other disorders, e.g., allergic contact dermatitis (ACD) or cutaneous T-cell lymphoma, can occasionally fulfill the clinical criteria for AD. Therefore, it is imperative that clinicians consider the broader differential diagnosis of AD in adults (Table 2, Fig. 1), especially adult-onset AD.

5.2 Biopsy

Diagnostic testing is not required to make the diagnosis of adult-onset AD, but can be useful to support the AD diagnosis and exclude alternate diagnoses. A punch biopsy

with standard hematoxylin and eosin staining can be helpful to exclude other disorders that have distinct histologic patterns, e.g., cutaneous T-cell lymphoma, psoriasis, and cutaneous lupus. Eczematous lesions display several histological characteristics depending on the stage of the lesion. Acute lesions are characterized by epidermal spongiosis and dermal perivascular mononuclear infiltrates with eosinophils and a predominance of T cells and the presence of eosinophils. Chronic lesions are characterized by hyperkeratosis, epidermal hyperplasia, irregular elongation of the rete ridges, and variable amounts of spongiosis and dermal eosinophils. Of note, these patterns are found in other eczematous disorders and cannot distinguish AD from other eczematous disorders, e.g., allergic and irritant contact dermatitis or nummular dermatitis. Direct immunofluorescence may be useful to exclude autoimmune blistering disorders, such as bullous pemphigoid and dermatitis herpetiformis. It is important not to solely rely on biopsies and histopathology to diagnose AD, as they have low reliability to distinguish between inflammatory skin diseases [43] and cannot substitute for a thorough history and physical examination and good clinical judgment.

5.3 Patch Testing

A multidisciplinary consensus guideline recommended that patch testing be performed in all patients with adolescent- or adult-onset AD because ACD can mimic AD and sometimes even present with flexural lesions [44]. Patients with a history of AD that has worsened or become more generalized, including adult-recurrent AD, should also be patch tested, as there may be an allergenic trigger of their underlying AD. Patch testing is also indicated in adults and children with a lesional distribution that is changing or atypical for AD, or one that is localized and suggestive of contact dermatitis. This scenario includes adults with long-standing AD who develop dermatitis of the head and neck, eyelids, hands, and feet later in life. This has been reported to occur in adult AD without any evidence of ACD [34], but may be a sign of an evolving superimposed ACD.

In addition, previous studies have shown high rates of ACD in patients with nummular eczema. Nummular lesions occur with greater frequency in adult-onset AD without evidence of ACD [45], but may be a sign of ACD in a patient with AD [46, 47].

Patients with AD have higher rates of rates of positive patch test reactions to ingredients in their topical medications and personal care products, including lanolin, formaldehyde, sesquiterpine lactone mix, compositae mix, multiple fragrances, neomycin, bacitracin chlorhexidine, and topical corticosteroids [48–50]. An expanded patch-testing screening series is recommended to assess these allergens, such as the American Contact Dermatitis Society Core Allergen

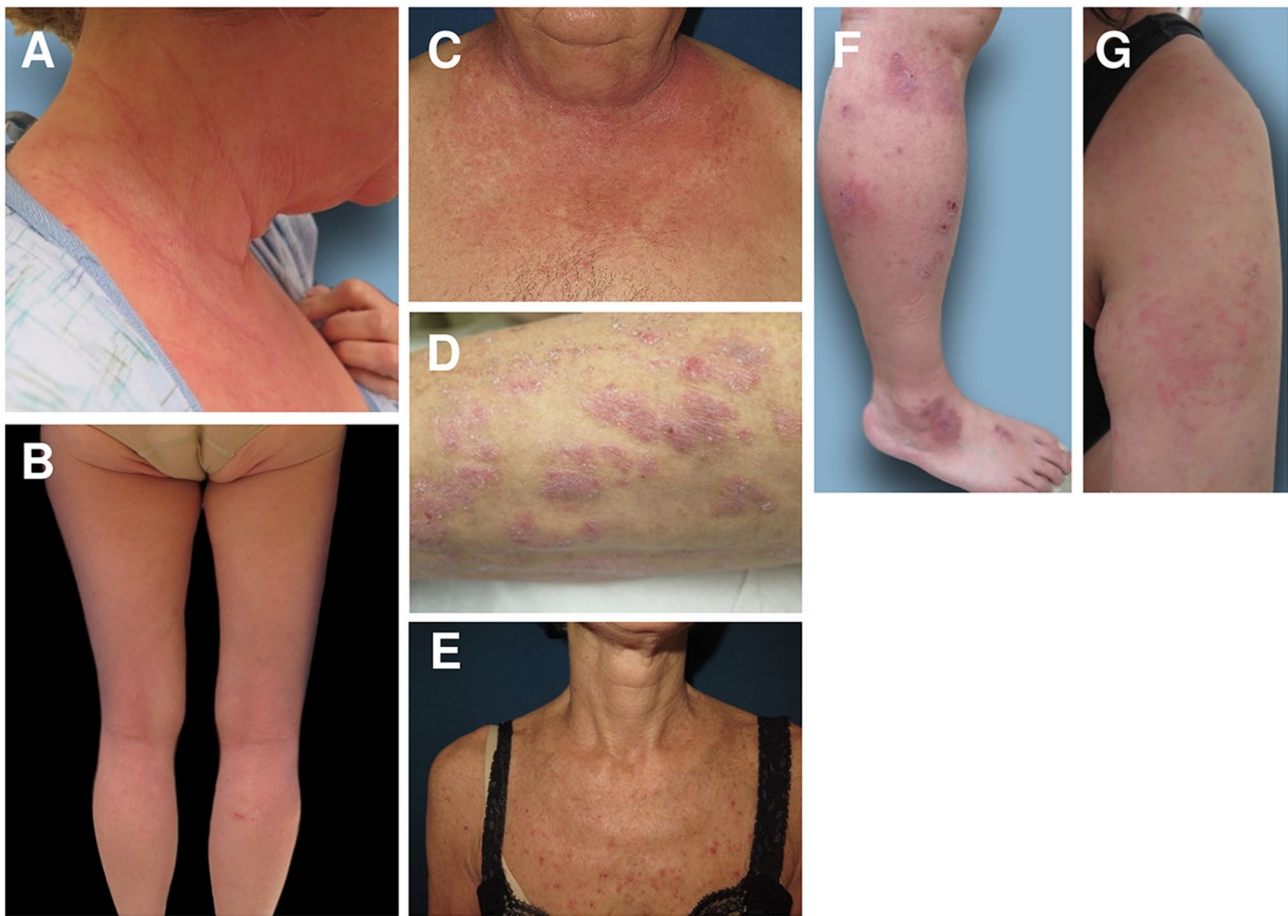


Fig. 1 Examples of different presentations of patients with adult-onset atopic dermatitis (AD) and other disorders in the differential diagnosis of AD. **a, b** Adult-onset AD, **c** photosensitive dermatitis, **d** adult-onset biopsy-confirmed plaque psoriasis, **e** biopsy-confirmed

transient acantholytic dermatosis, **f** generalized nummular dermatitis secondary to allergic contact dermatitis, and **g** cutaneous lupus in adult with adult-onset systemic lupus erythematosus

Series or North American Contact Dermatitis Group Standard allergen series, with supplemental allergen series as indicated [50]. Of note, the Thin-Layer Rapid Use Epicutaneous (TRUE) test lacks many of the allergens previously found to be relevant in patients with AD, including cinnamic aldehyde, propylene glycol, dimethylol dimethyl hydantoin, iodopropynyl butylcarbamate, amidoamine, acrylates, tea tree oil, propolis, benzophenone-3, and sesquiterpene lactone mix [50].

5.4 Other Laboratory Tests

Skin scrapings with in-office microscopic evaluation may be warranted to exclude scabies or fungal infections. Skin prick testing, total serum IgE, allergen-specific IgE, and peripheral eosinophil levels are not required to diagnose AD in children or adults. Moreover, these tests may be even less useful in patients with suspected adult-onset AD, which has been

shown to be associated with lower rates of atopy and atopic disease than child-onset AD. [23].

A white blood cell count may reveal abnormalities secondary to lymphoma. Anti-neutrophil cytoplasmic antibodies may help exclude Churg–Strauss syndrome, which can manifest with a classical presentation of AD [51]. Anti-nuclear antibody, complement levels, erythrocyte sedimentation rate, and other laboratory testing may help exclude systemic lupus erythematosus or other autoimmune disorders. Indirect immunofluorescence may be helpful to exclude autoimmune blistering disease. Genetic testing may help exclude immunodeficiencies that manifest with AD, such as Job syndrome. Testing for human immunodeficiency virus may be indicated to rule out atopic-like dermatitis in human immunodeficiency virus [52]. Testing may be indicated for syphilis, which rarely can present with an eczematous pattern [53].

6 Treatment

There are no specific treatment guidelines for adult-onset AD. In fact, few studies have compared treatment efficacy in AD between adults and children, let alone adult-onset vs. child-onset AD. Thus, current guidelines recommend the same treatment approaches for adult-onset and child-onset AD. All AD treatment guidelines recommend a step-care approach to therapy [54, 55]. Initial patient education should focus on gentle skincare, bathing practices, trigger avoidance, and appropriate use of moisturizers and emollients. Moisturizers and emollients have shown good efficacy in AD and may have adequate efficacy as a monotherapy in the mildest forms of AD. However, they have inadequate efficacy as a monotherapy in many cases of mild AD and virtually all cases of moderate or severe AD. In patients for whom moisturizers and emollients are inadequate, the next step of treatment includes adding anti-inflammatory agents, such as topical corticosteroids, calcineurin inhibitors, and/or phosphodiesterase E4 inhibitors.

In patients for whom optimal use of emollients and topical anti-inflammatory agents are inadequate, the next step of treatment includes adding oral systemic, biological, and/or phototherapy. The AAD guidelines of care for the management of AD recommends phototherapy, cyclosporine, methotrexate, and azathioprine as second-line agents for patients with AD refractory to conventional topical therapy (grade B recommendation) [56]. Interferon gamma (grade B) and mycophenolate mofetil (grade C) were found to be variably effective and can be considered as alternative therapy for refractory AD [56]. Systemic corticosteroids were recommended to be avoided if possible for the treatment of AD. If used at all, systemic corticosteroids should be exclusively reserved for acute severe exacerbations and as a short-term bridge therapy to other non-steroidal systemic therapies [56, 57]. Dupilumab, a monoclonal antibody targeting the IL-4 receptor alpha subunit, is not mentioned in the AAD guidelines, as it was approved by the US Food and Drug Administration after the publication of the guidelines. However, recent consensus statements recommended dupilumab as a second-line agent after failing conventional topical therapy, and can be used instead of phototherapy or oral systemic immunomodulators [54]. However, the optimal choice of therapies, dose, and duration are not well established in adult-onset AD per se. Future studies are needed to determine the efficacy and safety of current and emerging agents in adult-onset AD.

7 Conclusion

Atopic dermatitis is common in adults in the USA and internationally. Atopic dermatitis has different epidemiology, immune phenotypes, and clinical manifestations in

adults than children. In particular, one in four adults with AD report adult onset of their AD. Adult-onset/recurrent AD appears to have distinct genetics, risk factors, and clinical manifestations compared to other subsets of AD. Further research is necessary to better understand the pathogenesis and optimal treatment approaches in adult-onset/recurrent AD.

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Compliance with Ethical Standards

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