# Atopic Dermatitis

## Introduction

Atopic dermatitis, commonly known as eczema, is a chronic relapsing inflammatory skin disease. AD affects up to 20% of children (1) and 3% of adults worldwide (2, 3) and is a major public health burden. In the 2010 WHO article into the global burden skin diseases, AD was ranked first by causing the most number of days that people were not at full health (2). The effects of AD are more than skin deep. Children with poorly controlled AD suffer from reduced sleep and increased psychological problems (4). The feature of atopy (raised IgE) relates the disease to other allergic responses such as food allergies, allergic rhinitis and asthma. This so-called 'atopic march' describes the progressive acquisition of atopic diseases in a step-wise manner throughout childhood (5). AD also has a substantial economical impact.

A 2013 study in the United States showed that the direct cost for AD treatment may be as high as $3.8 billion per year (6). One of the most recent Australian studies from 2004 concluded that patients can incur substantial annual out of pocket costs for treatment products and medical consultations (7). Hence effective management of this condition is important both to individuals and our society.

## Diagnosis

The diagnosis of AD is clinical based on historical features, skin lesions morphology and distribution and associated clinical signs. Formal sets of diagnostic criteria have been developed by different groups. The 1980 Hanifin and Rajka criteria (8) is one of the earliest and most recognised sets of diagnostic criteria and requires three of four major criteria and three of twenty-three minor criteria to be met. Although it is comprehensive and often used in clinical trials, the large number of criteria makes it difficult to use in clinical practice. Several international groups have since proposed modifications to improve the above criteria. The United Kingdom (UK) working party, in particular, has simplified the Hanifin and Rajka criteria to a core set (9). In 2003, the American Academy of Dermatology revised Hanifin and Rajka criteria that are deemed more streamlined and applicable to the full range of patient ages (Table 1) (10).

Table 1. Diagnostic features and triggers of atopic dermatitis (AD). Adapted from the American Academy of Dermatology Consensus Conference on Paediatric Atopic Dermatitis (10)

## Diagnostic features and triggers of atopic dermatitis (AD)

**Essential features: must be present and are sufficient for diagnosis**

- Pruritus
- Typical eczematous morphology and age-specific distribution patterns
  - Face, neck and extensor extremities in infants and young children
  - Flexural lesions at any age
  - Sparing of groin and axillae
- Chronic or relapsing course

**Important features: seen in most cases, supportive of diagnosis**

- Early age of onset
- Atopy
- Personal and/or family history
- Immunoglobulin E reactivity
- Xerosis

**Associated features: suggestive of the diagnosis, but less specific**

- Atypical vascular responses e.g. midfacial pallor, white dermographism, delayed blanch
- Keratosis pilaris/pityriasis alba/ hyperlinear palms/ ichthyosis
- Ocular/periorbital changes
- Perifollicular accentuation/lichenification/prurigo lesions

**Exclusionary conditions: diagnosis of atopic dermatitis depends on excluding conditions, such as**

- Scabies
- Seborrhoeic dermatitis
- Contact dermatitis (irritant or allergic)
- Icthyoses
- Cutaneous T-cell lymphoma
- Psoriasis
- Photosensitivity dermatoses
- Immune deficiency diseases
- Erythroderma of other causes

Validated scores to assess the severity of AD include the Eczema Area Scoring Index (EASI), Scoring Atopic Dermatitis (SCORAD) and Patient-Oriented Eczema Measure (POEM).

### Pathogenesis

AD is immunologically characterized by the over-expression of T helper 2 (Th2) cytokines, including interleukin 4 (IL-4), IL-5 and IL-13 and chemokines (C-C motif chemokine ligand 17 (CCL17), CCL18 and CCL22), and IL-22, a Th22 cytokine (11). IL-4 and IL-13 are cytokines central to the pathogenesis of AD and produced mainly by Th2 cells (12, 13). IL-13 is thought to be a primary disease-inducing effector cytokine, whilst IL-4 works as a key amplifier of type 2 immunity by facilitating expansion of the CD4+ Th2-cell population in secondary lymphoid organs (14).

IL-4 and IL-13 can activate and promote Th2 cells survival, induce differentiation and activation of myeloid and atopic dendritic cells, activation of B cells, stimulation of IgE class switching and eosinophil recruitment (15). Type 2 cytokines can cause [1] suppression of terminal differentiation proteins filaggrin, loricrin and involucrin, [2] antimicrobial peptides inhibition, [3] S100As upregulation, [4] epidermal hyperplasia induction, [5] lipid synthesis suppression and [6] spongiosis induction (11). IL-4 and IL-13 levels are found to be correlated with AD disease activity (14).

## Treatment

### General approach

As AD is a chronic relapsing disease, AD management includes patients/parents education, gentle skin care and regular use of emollients, as well as anti-inflammatory therapy. Topical agents represent the mainstay of treatment. Severe disease may require phototherapy or systemic medications in conjunction with continued topical therapy. Factors that may exacerbate AD should be identified and avoided.

### Topical Corticosteroids

Topical corticosteroids (TCS) remain the first line treatment in AD. Their efficacy in AD has been verified in >100 randomized controlled trials (16). TCS have anti-inflammatory, antiproliferative, immunosuppressive and vasoconstrictive actions, and have been demonstrated to decrease the acute and chronic inflammation of AD and the associated pruritus (17).

### Topical Calcineurin Inhibitors

Topical calcineurin inhibitors (TCI) include (1) Tacrolimus 0.03% and 0.1% ointment for moderate to severe AD and (2) pimecrolimus 1% cream for mild to moderate AD. They suppress T-cell activitation and modulate secretion of cytokines and other proinflammatory mediators, and decrease mast cell and dendritic cell activity (18).

TCIs are useful for AD affecting the face and intertriginous areas where corticosteroid-induced skin atrophy may be of concern. TCIs are also useful in managing frequent exacerbation of or persistent AD that would otherwise require continual topical corticosteroids usage.

## Phototherapy

Phototherapy exerts its immunomodulatory effects via T-cell apoptosis induction, dendritic cells reduction and decreased expression of Th2 cytokines including IL-5, IL-13 and IL-31 (19). Phototherapy including narrowband UVB and UVA1 have been demonstrated to improve AD and the associated pruritus. UVB treatment has also been demonstrated to reduce S. aureus colonization of skin in AD. Phototherapy is usually combined with topical corticosteroids. The potential side effects of phototherapy include sunburn reaction and long term treatment may be associated with photoaging and an increased risk of skin cancer. Requirement to travel several times a week to a phototherapy centre may not be practical for some patients and it may be challenging for young children to cooperate with this treatment. However, its side effect profile is still favourable compared to systemic immunosuppressive agents.

## Traditional Systemic Anti-Inflammatory Therapy

Systemic anti-inflammatory medications may be administered for children and adults with moderate-to-severe AD who failed to respond adequately to optimized topical treatment. Combination of systemic treatment and topical corticosteroid therapy is frequently required to maximize therapeutic benefit.

### Cyclosporin

Cyclosporin is a potent inhibitor of T-cell dependent immune responses and IL-2 production. Cyclosporin treatment leads to rapid improvement of AD in adults and children. However, due to potential side effects including nephrotoxicity and hypertension, it is used as a short term treatment for AD, working as a bridge between other therapies.

### Azathioprine

Azathioprine is a purine synthesis inhibitor that reduces leukocyte proliferation. It is a treatment for moderate to severe AD in children and adults. Individuals with genetically determined low activity of the enzyme thiopurine methyltransferase (TPMT) have increased susceptibility to azathioprine-induced myelotoxicity. By determining TPMT activity and/or genotyping for TPMT polymorphisms before starting treatment and adjusting dose accordingly, this can reduce the risk of treatment induced myelotoxicity. Azathioprine has a slow onset of action, with clinical improvement after 1-2 months and full benefit requiring 2-3 months of treatment.

### Methotrexate

Methotrexate reduces allergen-specific T-cell activity. It is used in the treatment of refractory AD in adults and children together with folic acid supplementation. Maximum clinical effect typically is seen after 2-3 months of therapy.

### Mycophenolate mofetil

Mycophenolate mofetil inhibits de novo pathway of purine synthesis, resulting in suppression of lymphocyte function. It is used in recalcitrant AD in adults and children, with maximum therapeutic benefit seen at 2-3 months of treatment.

### Systemic Corticosteroids

A short course of systemic corticosteroids may be considered for severe acute exacerbation of AD while phototherapy or immunomodulatory treatment is initiated.

## Novel Therapies

An increased understanding of the underlying immunopathogenesis of AD has led to development of new biologic therapies and small molecule drugs specifically targeting (inhibiting) immune and inflammatory mediators identified, including the Th2 cytokines IL-4 and IL-13, phosphodiesterase E4 and Janus kinases.

## Dupilumab

Dupilumab is a fully human IgG4 monoclonal antibody administered subcutaneously. It targets the IL-4Rα subunit of the heterodimeric IL-4 and IL-13 receptors, resulting in blockage of the downstream signalling of IL-4 and -13, two important Th2 cytokines implicated in the immunopathogenesis of AD. Dupilumab is the first biologic therapy to have been approved for treating adult patients with moderate to severe AD. Dupilumab treatment has been shown to alter the AD transcriptome in a dose-dependent fashion. Differences in gene expression following administration of dupilumab include (1) downregulation of markers of epidermal proliferation, (2) downregulation of inflammatory mediators, (3) upregulation of structural proteins, (4) upregulation of lipid metabolism proteins, and (5) upregulation of epidermal barrier proteins resulting in normaliization of skin (15). Dupilumab had been reported to significantly reduce serum levels of CCL17 (or thymus and activation-regulated chemokine), a key regulator of Th2-mediated immunity and a specific and objective biomarker of AD disease activity (20).

In Australia, dupilumab was approved by the TGA in January 2018 for the treatment of moderate-to-severe AD in adult patients who are candidates for chronic systemic therapy. At the time of publication, Dupilumab is not PBS listed. In USA, the FDA has also approved Dupilumab for use in adolescent patients with moderate-to-severe AD in March 2019 and there are studies underway investigating the efficacy and safety of dupilumab plus TCS in patients ≥6 years old to <12 years with severe AD, and the safety, pharmacokinetics and efficacy of dupilumab in children ≥6 months to <6 years with severe AD (www.clinicaltrials.gov).

Dupilumab comes as a single-dose 300mg pre-filled syringe for administration as a subcutaneous injection. The recommended dose is an initial dose of 600mg (two 300mg injections in different injection sites) followed by 300mg given every other week. Phase III clinical trials in adults with moderate-to-severe AD have shown that dupilumab as monotherapy (21) or in combination with TCS (or TCIs, if TCS usage was inadvisable) (22, 23) improved multiple measures of disease severity, pruritus, sleep disturbance, anxiety and depression, and quality of life compared with placebo. Improvements in disease severity and itch with dupilumab treatment can be seen within first 2 weeks of treatment.

The most common side effects of dupilumab either as monotherapy or combined with TCS/TCIs include conjunctivitis, injection-site reactions and oral herpes. Other potential side effects include skin infections and exacerbations of AD and nasopharyngitis. The incidence of allergic conjunctivitis was twofold higher in dupilumab plus TCS recipients compared to placebo plus TCS recipients in the CHRONOS study (22). Other ocular treatment-emergent adverse events occurring more frequently with dupilumab plus TCS than with placebo plus TCS in the above trial include eye pruritus, blepharitis and dry eye (22). All cases of conjunctivitis were of mild or moderate severity and resolved with topical eye treatments (22). Patients should be advised to report new onset or worsening eye symptoms to their health care provider. Across all studies, the incidences of serious treatment emergent adverse events for dupilumab (with or without TCS) and treatment emergent adverse events

leading to treatment discontinuation (≤ 2% vs 1-8% in placebo) were low (21-23). Dupilumab was not associated with any clinically significant laboratory abnormalities (21-23). Being a therapeutic protein, immunogenicity may potentially occur. The 52-week CHRONOS study showed 2% of dupilumab plus TCS recipients had anti-drug antibody responses (22), although production of such responses which did not seem to result in loss of efficacy (24). Hypersensitivity reactions (such as serum sickness, serum sickness-like reaction and generalized urticaria) occurred in <1% of dupilumab recipients (25). The use of live vaccines should be avoided in patients receiving dupilumab (25). Inactivated (non-live) vaccines may be administered concurrently with dupilumab (24). Hence it is important to advise patients to discuss travel/vaccination plans prior to commencing dupilumab so that they can be vaccinated appropriately in advance.

## Other New Biologic And Small Molecule Therapies

Crisaborole ointment 2% is a phosphodiesterase 4 (PDE4) inhibitor with FDA approval as topical treatment of mild to moderate atopic dermatitis in patients aged over or equal to 2 years. Cytokine-targeted therapeutic agents for AD in clinical development including the IL-13 inhibitors tralokinumab and lebrikizumab, the IL-31 receptor A inhibitor nemolizumab; the IL-12/IL-23 inhibitor ustekinumab and IL-17 inhibitor secukinumab which are already in clinical use for psoriasis treatment are also being investigated for their roles in AD treatment. Janus kinase (JAK) inhibitors tofacitinib and baricitinib are also in clinical development for AD treatment.

## Summary Points

- AD is an immune-mediated chronic relapsing inflammatory skin disorder characterized by a Th2 immune response and is a major public health burden.
- Historically, there has been a lack of safe and effective long-term treatment options for patients with moderate-to-severe AD which do not respond adequately to first-line topical therapies and second-lint treatment with phototherapy and systemic immunosuppressants.
- Dupilumab is the first biologic agent approved for use in adults with moderate-to-severe AD. It binds to the IL-4R$\alpha$ subunit of the heterodimeric IL-4 and IL-13 receptors, resulting in blockage of the downstream signalling of these two main cytokines implicated in the immunopathogenesis of AD. Dupilumab can be used with or without topical corticosteroids or topical calcineurin inhibitors
- Improvements in disease severity and itch with dupilumab treatment can be seen within first 2 weeks of treatment. Across all studies, the incidences of serious treatment emergent adverse events for dupilumab leading to treatment discontinuation were low. The most common side effects of dupilumab include conjunctivitis, injection-site reactions and oral herpes. Patients should be advised to report new onset or worsening eye symptoms to their health care provider. The use of live vaccines should be avoided in patients receiving dupilumab although inactivated (non-live) vaccines may be administered concurrently with dupilumab. It is therefore important to advise patients to discuss travel/vaccination plans prior to commencing dupilumab so that they can be vaccinated appropriately in advance.

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