

# Contemporary treatments for atopic dermatitis and the dawn of targeted biological therapies

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Atopic dermatitis (AD) is a very common, clinical heterogeneous, chronic systemic disease driven by skin barrier disruption and in large part by immune dysregulation in the form of type 2 inflammation. Typically, the disease will manifest as recurrent flares in childhood with a characteristic distribution pattern, although onset at any age is possible. AD is often associated with other atopic conditions including asthma, allergic rhinitis, allergic conjunctivitis and food allergies. Owing to pruritus (and associated sleep loss) as well as secondary skin infections and the psychosocial burden of visible skin lesions, AD has a major impact on a patient's (and caregiver's) quality of life. The diagnosis of AD is clinical and does not require any routine allergy testing or blood work. Management follows a stepwise approach that builds upon therapeutic patient education of the "general measures" that includes frequent and liberal use of emollients, occlusive dressings, gentle skin cleansing regimens (bath practices) and trigger avoidance *inter alia*. As a basis, pharmacological therapy includes various topical therapies. In individuals where control is not attained (and suitably maintained), stepping-up to broadly acting systemic immunosuppressive therapies or targeted immunomodulating biological therapies should follow without undue delay. Phototherapy (where available) may similarly be trialed. The aim of therapy is to establish long-term disease control; restore the skin barrier function (thereby reducing transepidermal water loss and curtailing antigen entry); achieve relief from symptoms (skin inflammation, visible lesions and pruritus); avoid exacerbations (flares); address comorbidities and improve patient quality of life.

**Keywords:** atopic dermatitis, therapeutic patient education, severity scoring, stepwise management, quality of life

## Introduction

Atopic dermatitis (AD), also known as atopic eczema, is the most common form of eczema and is seen by healthcare professionals (HCPs) almost daily. It is a chronic, systemic condition characterised by immune dysregulation (type 2 inflammation), epidermal barrier dysfunction, intense pruritus, recurrent eczematous lesions, and presents with a relapsing, remitting course.<sup>1,2</sup> The pathophysiology of AD is multifactorial, involving a genetic hypersensitivity predisposition to environmental factors.<sup>1</sup> Although not diagnostic, the disease is often associated with increased IgE levels and commonly occurs alongside other atopic conditions such as allergic rhinoconjunctivitis, asthma and/or food allergies.<sup>2</sup> The morphology and location of AD is considered characteristic for different ages: in infants, lesions tellingly manifest on the cheeks while usually sparing the perioral, perinasal and nappy area. With increasing age, lesions may present on extensor surfaces and classically in flexural folds (commonly the cubital and popliteal fossae), but may readily include the hands, wrists and ankles, head and neck as well as the trunk and shoulders.<sup>1,3</sup> That being said, the clinical features in adults are highly variable.

## Epidemiology

AD is a common condition worldwide, with a prevalence of approximately 15–25% in children<sup>4</sup> and 3–10% in adults.<sup>5</sup>

The majority of patients have mild disease, however, > 20% of patients have moderate-to-severe disease that is difficult to control and may require specialist referral and a step-up in therapy.<sup>6</sup> There is a paucity of prevalence data available for the South African population. The burden of disease has been described as significant in adults.<sup>7</sup> Available data for adolescents (aged 13–14 years old) showed an 8.3% one-year prevalence (increasing to 13.3% on follow-up).<sup>7</sup>

## Diagnosis and natural history

A diagnosis of AD relies on clinical features and cognisance of the patient's (and familial) history. No laboratory testing is prerequisite. Diagnoses in infants who present with a classical distribution pattern of dry pruritic dermatitis is straightforward. Not so for adult-onset AD, where exclusion of several conditions is required.<sup>8</sup> The South African guidelines for diagnosing AD<sup>8,9</sup> are derived from the UK working party,<sup>10</sup> who revised the original criteria set out by Hanifin and Rajka in 1980.

Diagnosis requires the essential feature of pruritus in addition to three (or more) of the following criteria:

- A history of flexural dermatitis (front of elbows or ankles, back of knees, neck or around the eyes).
- Visible flexural dermatitis involving skin creases (or involvement of cheeks and/or extensor surfaces in children aged up to 18 months).

- A history of generally dry skin in the past year.
- A personal history of asthma or hay fever (or a history of atopic disease in a first degree relative in children aged under four years).
- Onset under the age of two years (used only for children aged four years or more at time of diagnosis).

Special investigations (e.g. skin-prick or allergen-specific IgE tests) to identify environmental trigger/s are not diagnostic and rarely necessary, but may be useful in the management of some patients.<sup>9</sup>

Although the disease can manifest at any age, AD onset is typically early in life: roughly 60% before the age of one year old;<sup>11</sup> 85–90% of cases present before the age of five years.<sup>2,4</sup> Different sources inconsistently reference a range between 20–80% of cases that are ‘outgrown’ by puberty.<sup>1</sup> More severe or persistent childhood AD, later onset, or patients with an AD family history are more likely to experience AD persisting into adulthood and are at risk of developing atopic comorbidities, including asthma, allergic rhinitis and food allergies.<sup>12,13</sup> These patients would benefit from early referral and multidisciplinary management.<sup>12</sup>

### The atopic dermatitis burden significantly impacts quality of life

Many factors contribute towards a considerably impaired quality of life (Figure 1). Dependent on disease severity, patients with AD may suffer severe, persistent pruritis that can be debilitating.<sup>1</sup> Itching can also increase at night, leading to disturbed or interrupted sleep (for several days).<sup>14</sup> As a result thereof, parents of children with AD may also experience disrupted sleep as one driver of poor work/school performance and increased absenteeism.<sup>15</sup> Owing to visible flares, there is a huge psychosocial burden and mental health disorders are common.<sup>16</sup> Apart from comorbid atopic diseases,<sup>14</sup> AD patients are at an increased risk of secondary skin infections<sup>17</sup> (staphylococcus, impetigo, eczema herpeticum and molluscum contagiosum are seen and difficult to control, demonstrating an important risk around skin barrier dysfunction and dysbiosis). AD patients are

further prone to other immune-mediated inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease.<sup>1</sup> Treatment of AD should extend to the associated comorbidities. Over and above, there is an economic burden to bear owing to loss of productivity and the costs related to disease treatment.<sup>18</sup>

### Atopic dermatitis treatment in South Africa

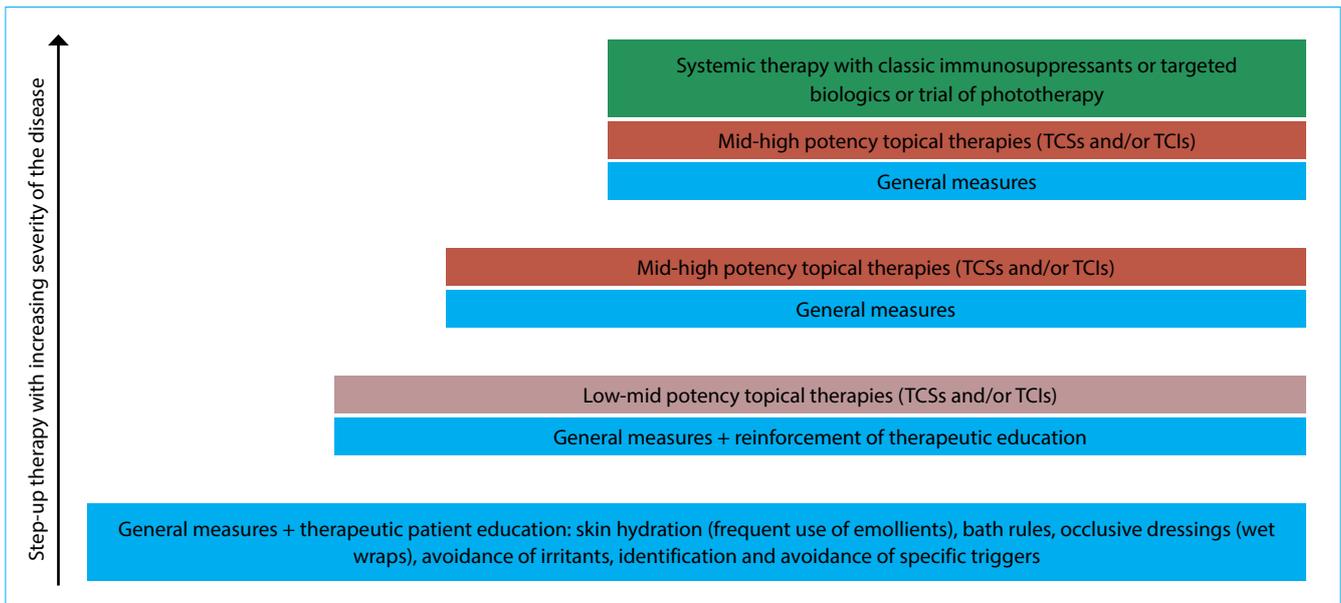
The starting point with the treatment of AD are the ‘general measures’ which include patient education about skincare, frequent use of emollients, bath rules (correct bathing – reduced duration and temperature as well as soap substitution), trigger avoidance and psychological interventions. All these interventions should occur as early as possible.<sup>18</sup> Pharmacological treatment of AD is stepwise and built upon preventative skin care regimens, emollient therapy and occlusive dressings with the aim of breaking the itch-scratch cycle and restoring the skin barrier function. As this can be complex, written care plans are recommended.

Grading of AD as ‘mild’, ‘moderate’ or ‘severe’ should be used to guide treatment. Physician assessed AD severity scales such as SCORing Atopic Dermatitis (SCORAD) and Eczema Area and Severity Index (EASI) in addition to a patient’s reported subjective experience, the Dermatology Life Quality Index (DLQI), has been recommended by a South African expert panel in a recent consensus statement to support a step-up in therapy.<sup>19</sup> Scoring disease severity at baseline and measuring the evolution of the disease over time in response to therapeutic interventions is becoming increasingly important when applying for reimbursement to funders. Several open-source online calculators are available for quick scoring of AD severity. Such measurements are not without limitation, where for instance, in pigmented skin, the evaluation of erythema may be complicated.

Locally available topical treatments consist of two classes: topical corticosteroids (TCSs) formulations of various potencies and topical calcineurin inhibitors (TCIs). Disease severity and the affected areas guide topical treatment selection, with the TCIs being preferred in sensitive body areas. Management of acute exacerbation may necessitate short-term utilisation of a



Figure 1: The disease burden experienced by atopic dermatitis patients



**Figure 2:** Stepwise management of AD patients with the aim of disease control<sup>20</sup>

more potent topical formulation to rapidly control the flare.<sup>18</sup> Maintenance therapy becomes indicated when a patient experiences four or more flares a year. This entails a pro-active approach consisting of ongoing high-frequency emollient use and TCSs or TCIs applied two to three times a week on normal-appearing skin where eczematous lesions usually appear.<sup>18</sup>

AD patients need regular follow-up in the form of therapeutic patient education, reinforcing the value of the 'general measures' of treatment (especially frequent emollient use), as well as the need to use topical therapy (TCSs or TCIs) appropriately (quantity and frequency) with the first sign of eczema to optimise disease control.

Uncontrolled, refractory or more severe disease often requires specialist referral and the step-up of therapy to include narrowband phototherapy (where available) and (non-specific) systemic immunosuppressants (such as short-course cyclosporin and longer-term use of off-label methotrexate, azathioprine and mycophenolate mofetil). The use of systemic corticosteroids is effective in the short-term treatment of flares, but all too often met by rebound disease,<sup>2</sup> confounding well-intentioned tapering strategies. Systemic immunosuppressive therapies are fraught with potential side-effects and necessitate baseline screening and frequent monitoring of clinical chemistries to mitigate risk.

### Atopic dermatitis unmet need and emerging therapies

An unmet need exists with patients for whom the use of conventional systemic medications is contraindicated and who are not controlled on conservative or topical therapies. A greater understanding of the pathogenesis driving AD at a molecular level has allowed the development of targeted, systemic immunotherapies.<sup>2</sup> Numerous small molecules and biologics that target specific cytokines or pathways implicated in AD disease pathogenesis are at various stages of development.

In recent positioning statements, both the Allergy Foundation of South Africa (AFSA) and the Dermatology Society of South Africa have endorsed the consensus-based European guideline for treatment of AD, which recommends biologics for long-term maintenance in adolescents and adults with moderate-to-severe atopic dermatitis, when topical treatment is not sufficient and other systemic treatment is unsuccessful or not advisable.

A recently registered biologic indicated for AD, dupilumab, has proven in a series of clinical trials (Liberty AD program) to address the unmet need of uncontrolled moderate-to-severe AD. Dupilumab is a dual inhibitor of interleukin-4 (IL-4) and IL-13 and unlike traditional AD systemic therapies is not an immunosuppressant. Dupilumab works proximally on the type 2 inflammatory pathway, which relies on innate immune cell (e.g. dermal dendritic cells) producing IL-4 stimulating Th2 helper cells, further eliciting IL-4 and IL-13 expression ultimately propagating type 2 inflammation. This dysregulated immune response results in decreased keratinocyte differentiation (reduced epidermal barrier protein and antimicrobial peptide production leading to skin barrier dysfunction); epidermal hyperplasia; B-cell activation along with IgE class-switching as well as mobilisation of eosinophils.<sup>21</sup>

### Dupilumab and a South African treatment algorithm for moderate-to-severe atopic dermatitis

The availability of a new biologic (dupilumab) indicated for moderate-to-severe AD has necessitated a South African consensus statement for the treatment of adults with difficult-to-treat AD.<sup>19</sup> This publication includes an algorithm for the treatment of moderate-to-severe disease, demonstrating conventional stepwise AD treatment approaches beginning with the general measures and topical therapies in addition to treatment of secondary skin infections. The algorithm recommends that if the skin clears but flares again within a week, topical therapy should be restarted until clear, then twice weekly pro-active therapy is recommended in an attempt to

control flares and extend the period between flares. Persistence with 'basic' treatment or topical therapies alone should ideally not persist beyond two to three months in patients that are not controlled. Patients should be followed-up regularly to promote a step-up in treatment accordingly. Flaring despite pro-active therapy or failure to respond to topical therapy after four to eight weeks (along with meeting moderate-to-severe criteria) should be followed by a step-up in therapy to a trial of systemic therapy (either classical immunosuppressants or a targeted biologic) or a trial of phototherapy (based on availability, practicality and individual patient response). Should the skin fail to improve after a trial of two to three months, an alternative systemic therapeutic approach should be trialed with the aim of attaining disease control and improving quality of life.<sup>19</sup>

## Conclusion

AD is a chronic inflammatory condition which can be easily diagnosed when beginning or continuing from childhood considering characteristic distribution patterns that evolve with increasing age. AD has numerous comorbidities with a severe impact on the quality of life of patients. There are well-established treatment protocols and treatments, but a desperate need exists for better management of recalcitrant patients. Biological drug products that specifically target key drivers of AD pathophysiology, such as dupilumab, can offer a safe, effective and long-term treatment option, vastly improving the quality of life of AD patients.

## Conflict of interest

Dr Visser has received honoraria from Sanofi for participation in advisory boards, speaker engagements and medical education activities. Dr Koot and Dr Terblanche are employees of Sanofi medical affairs department.

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## Ethical approval

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