Atopic dermatitis

Atopic dermatitis, or eczema, is a chronic relapsing inflammatory skin condition characterized by poorly defined pruritic, erythematous lesions. Acutely, these can be scaly, vesicular or oedematous and can potentially progress to lichenified chronic lesions (*Figures 1–5*) (Treloar, 2005; Williams, 2005; Berke et al, 2012; Thomsen, 2014). Lesions are most commonly found on flexural surfaces, the neck, eyelids and the forehead (Berke et al, 2012). Patients with atopic dermatitis have a higher incidence of other conditions from the atopic triad, including asthma and allergic rhinitis (Berke et al, 2012; Thomsen, 2014).

Atopic dermatitis is present in all age groups, but is more prevalent in children. Worldwide, it affects approximately 10–20% of children, although this varies based on geographical location (Berke et al, 2012; Eichenfield et al, 2014b). In contrast to previously held beliefs, up to 50% of affected children achieve remission in adulthood, with the remainder experiencing a lifelong, chronic condition (Simpson, 2006).

The prevalence of atopic dermatitis is increasing, with levels higher in developed countries, urban environments and smaller families (Eichenfield et al, 2014b; Thomsen, 2014). This is associated with an increasing economic burden; the cost arising from treatment of a patient with atopic dermatitis is similar to one with asthma, and family stress related to caring for a child with atopic dermatitis is similar to that of caring for one with type 1 diabetes mellitus (Berke et al, 2012). In adults, atopic dermatitis can have a profound impact upon career choice and can lead patients to withdraw from the workforce (Thomsen, 2014).

Pathophysiology

The pathophysiology of atopic dermatitis initiation and perpetuation is recognized as a complex interplay between disrupted barrier function and immune dysregulation (Sugarman et al, 2003; Williams, 2005; Novak and Simon, 2011). Genetic analyses have shown that 10–40% of patients with atopic dermatitis possess loss of function mutations in filaggrin, a major structural component in the stratum corneum. Patients with this mutation develop atopic dermatitis at a younger age than their wildtype counterparts (Sugarman et al, 2003; O'Regan et al, 2009). It is purported that the filaggrin loss of function mutation results in impaired barrier function, allowing penetration of foreign antigens, such as dust mite and food allergens, through the skin. This results in the activation of Th-2 cells, cytokine cascades and subsequent B-cell activation (Sugarman et al, 2003; Williams, 2005; Novak and Simon, 2011).

However, this does not explain higher levels of atopic dermatitis in African populations, who typically have low levels

Figure 1. Atopic dermatitis of the foot.

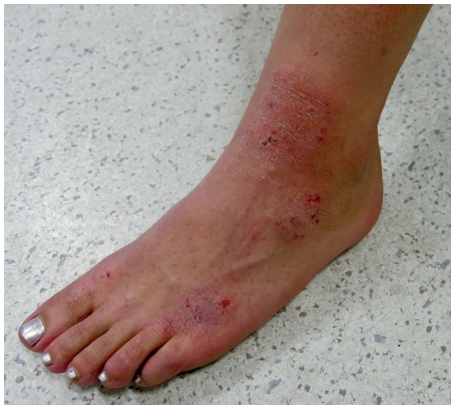

Figure 2. Atopic dermatitis of the hand.

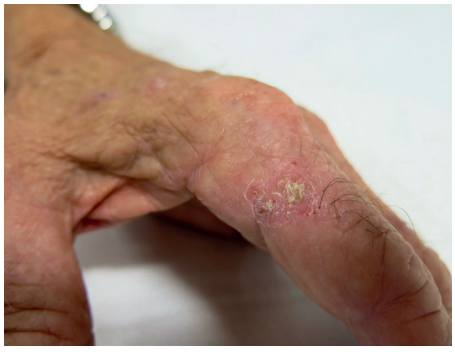

Figure 3. Atopic dermatitis of the posterior knee.

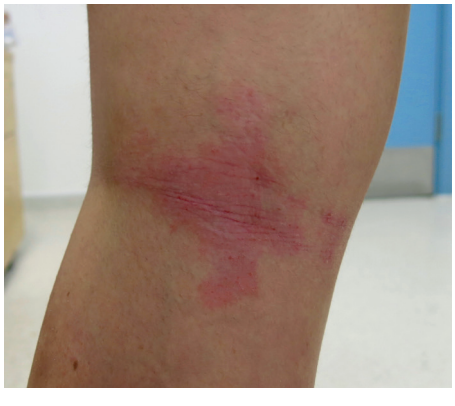

Figure 4. Lichenification.

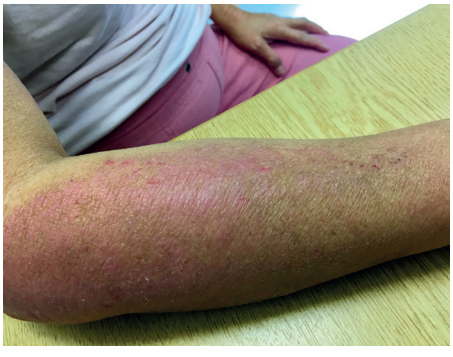

Figure 5. Atopic dermatitis of the hands.

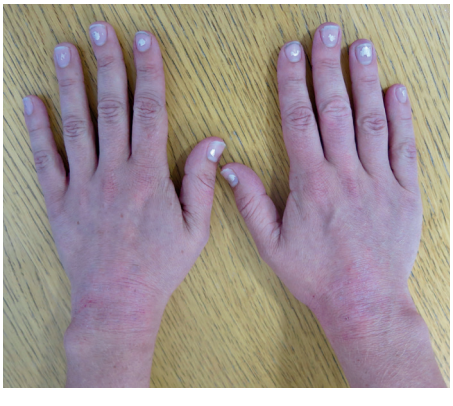

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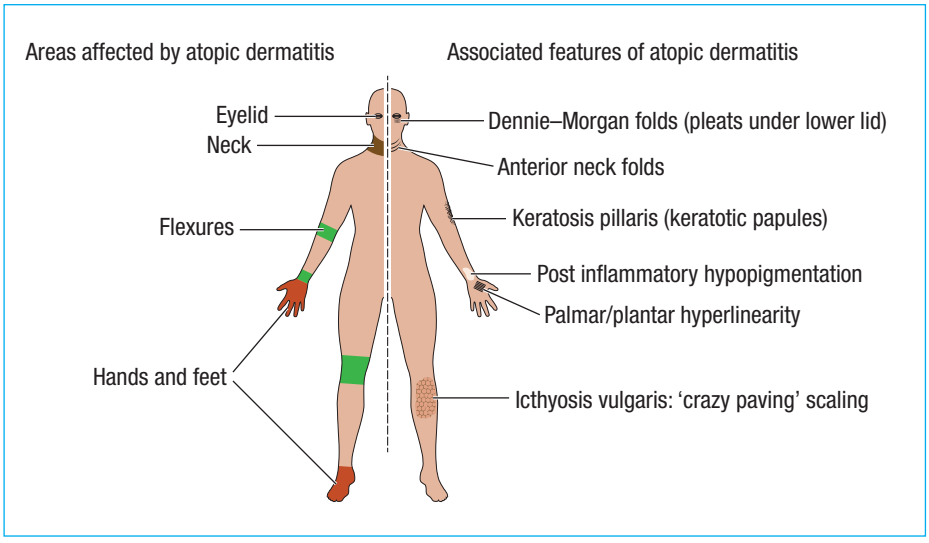
Figure 6. Areas affected by and associated signs of atopic dermatitis.



of filaggrin mutations. Additionally, 40% of people with filaggrin mutations do not experience atopic dermatitis, and the majority of children with mutations who develop atopic dermatitis grow out of their disease (O'Regan et al, 2009). This suggests that further mutations leading to skin barrier defects remain to be identified (Sugarman et al, 2003).

Environmental factors have also been implicated, as genetically similar groups, such as migrants, have higher prevalence of atopic dermatitis in urban areas, higher socio-economic classes and smaller families (Treloar, 2005; Berke et al, 2012).

Diagnosis

Lesions in atopic dermatitis can present in three main phases: acute, subacute and chronic. Acute lesions present as erythematous, oedematous papules and plaques with oozing and crusting. Subacute lesions develop into patches or plaques with scaling before becoming chronic, lichenified scaled plaques. Lesions are particularly pruritic and are often accompanied by excoriations. Lesions have a typical distribution and can be accompanied by a variety of other signs, which may help with the underlying diagnosis (*Figure 6*) (Eichenfield et al, 2014b).

Several criteria have been suggested for the diagnosis of atopic dermatitis, but the UK Working Party's diagnostic criteria for atopic dermatitis is one of the most widely adopted and validated criteria, with 95% sensitivity and 97% specificity (*Table 1*) (Williams et al, 1994).

There are several severity scoring systems available for atopic dermatitis, but the majority are too cumbersome to use in clinical practice and a simplified system has been proposed by the National Institute for Health and Care Excellence (2007) (*Table 2*). Impact upon patients' quality of life is an important contributing factor in deciding appropriate treatment. When reviewing a patient with atopic dermatitis, the impact of the condition upon his/her quality of life should always be taken into account.

Clinically, it is often difficult to differentiate atopic dermatitis from other erythematous, scaly skin disorders (Eichenfield et al, 2014b). Alternative diagnoses, as outlined below, should be sought when patients fail to respond to treatment or when patients present with involvement of non-typical areas (*Figure 6*, *Table 3*).

If the diagnosis remains uncertain, or in other situations outlined in *Table 4*, it is prudent to refer to specialist care.

The lack of objective biomarkers results in the diagnosis of atopic dermatitis being based on clinical history, morphology and distribution of lesions (Berke et al, 2012). Investigations are not usually required, although serum immunoglobulin E levels may be elevated. In the majority of patients, however, immunoglobulin E is not raised (Williams, 2005). Sometimes a skin biopsy may be useful in excluding other pruritic

Table 1. UK Working Party's Diagnostic Criteria (simplified) for diagnosis of atopic dermatitis

Presence of itch with three of:
History of flexural involvement
Visible flexural dermatitis
Personal history of asthma or allergic rhinitis
History of generally dry skin
Onset under the age of 2 years
From Williams et al (1994)

Table 3. Differential diagnoses for atopic dermatitis

	Diagnosis
Inflammatory	Seborrhoeic dermatitis
	Psoriasis
	Contact dermatitis
	Drug eruption
Infectious	Bacterial (impetigo)
	Eczema herpeticum
	Viral exanthem
	Tinea
	Scabies
Malignancy	Cutaneous T cell lymphoma

Table 2. Guide to severity of atopic dermatitis

Severity	Manifestation
Clear	Normal skin, no evidence of active atopic eczema
Mild	Areas of dry skin, infrequent itching (with or without small areas of redness)
Moderate	Areas of dry skin, frequent itching, redness (with or without excoriation and localized skin thickening)
Severe	Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking and alteration of skin pigmentation)
From National Institute for Health and Care Excellence (2007)	

skin conditions that may mimic atopic dermatitis (*Table 3*).

Patients with atopic dermatitis should not be routinely patch tested for allergens. However, patients who present with atypical distribution, who fail to respond to traditional treatments, who have resistant hand eczema, patients who develop atopic dermatitis without a history of paediatric atopic dermatitis or have severe, widespread dermatology before the initiation of oral agents, should be referred for patch testing (Chen et al, 2016). Referral in these situations is encouraged to prevent overlooking contact dermatitis as an important differential diagnosis.

Complications

Owing to defective skin barrier function, patients with atopic dermatitis are at risk of developing secondary infection (Berke et al, 2012). Two main microorganisms are implicated – *Staphylococcus aureus*, which results in impetigination, and herpes simplex virus, which results in eczema herpeticum. Secondary infection should always be suspected and treated in patients who fail to respond to initial therapy or in those who present with fever.

Atopic dermatitis which undergoes impetigination, a highly contagious skin condition, presents with rapidly progressing lesions, changing from small red papules or macules before developing into a vesicle. The vesicular fluid dries, resulting in a golden crust (Liaw et al, 2012). Treatment is with antibiotics and emollients, often requiring hospital admission.

> “Atopic dermatitis is a relapsing and remitting condition and, as such, all patients and families should be educated about skin care and flare avoidance.”

Eczema herpeticum, caused by the superinfection of atopic dermatitis with herpes simplex virus, presents with rapid progression of papulovesicular, crusted, punched-out lesions. Lesions are accompanied by systemic symptoms, including fever and lymphadenopathy. Owing to high mortality, early treatment with systemic antivirals is essential. Should lesions progress to involve the ophthalmic branch of the trigeminal nerve, ophthalmology review should be sought with regards to herpes keratitis which can result in blindness (Liaw et al, 2012).

Table 4. Referral criteria

When to refer:
Suspicion of eczema herpeticum
Uncertain diagnosis
Poor control or lack of response
Psychological or sleep disturbances
Recurrent secondary infections

Treatment

Atopic dermatitis is a relapsing and remitting condition and, as such, all patients and families should be educated about skin care and flare avoidance. Treatment adopts a stepwise approach (*Table 5*), starting with emollients and progressing to topical corticosteroids and calcineurin inhibitors. In recalcitrant cases, phototherapy or oral immunosuppressants are also used (Williams, 2005; Thomsen, 2014).

General measures

Emollients are the cornerstone of treatment and maintenance of atopic dermatitis. All patients with atopic dermatitis should incorporate emollients into their daily skin care regimen, and continue as maintenance. Emollients reduce xerosis, itch and transepidermal water loss, improving overall skin barrier function and lessening signs and symptoms of atopic dermatitis (Berke et al, 2012; Eichenfield et al, 2014a). Use of emollients both reduces the need for and augments corticosteroid treatment (Williams, 2005). Ideally, emollients should be applied at least twice daily and after bathing (Mayba and Gooderham, 2016).

There is no evidence showing preference for any particular emollient, and patient choice should be taken into consideration, offering a variety of different formulations such as creams, ointments, soap substitutes or bath oil (Treloar, 2005; Thomsen, 2014). The difference between formulations lies in the different proportion of lipid and aqueous phase. Ointments have the highest proportion of lipid and lotions possess the lowest. The increased lipid phase affords longer action, but the preparation is greasier and less cosmetically appealing. Creams may also contain preservatives, to which patients are often sensitive. In recalcitrant cases, emollients can be used under wet wraps, which increases penetration (Eichenfield et al, 2014b).

Guidance has been issued as to the amount of emollients which should be prescribed and used (*Table 6*). Emollients should be smoothed into the skin rather than vigorously rubbed.

Patients who experience regular infections, with moderate to severe disease, may benefit from bleach baths (160 ml of household bleach in 80 litres of water; approximately 10 cm deep) and topical

Table 5. Overview of treatments for atopic dermatitis

Mild	Emollients and mild or moderate topical corticosteroids
Moderate	Emollients and moderate topical corticosteroids and/or topical calcineurin inhibitors
Severe	Emollients and potent topical corticosteroids and/or topical calcineurin inhibitors
Recalcitrant	Emollients and phototherapy or oral immunosuppressants with/without topical calcineurin inhibitors

From Eichenfield et al (2014a), Sidbury et al (2014a,b)

Table 6. Amount of emollient to be prescribed for 1 week of twice daily applications

	Creams and ointments (g)	Lotions (ml)
Face	15–30	100
Both hands	35–50	200
Scalp	50–100	200
Both arms or legs	100–200	200
Trunk	400	500
Groin and genitalia	15–25	100

From Joint Formulary Committee (2017)

Table 7. Relative potencies of topical corticosteroids and calcineurin inhibitors

Potency	Corticosteroid	Calcineurin inhibitor
Mild (group I)	Hydrocortisone 0.1–2.5%	Nil
Moderate (group II)	Clobetasone butyrate 0.05% (Eumovate), betamethasone 0.025% (Betnovate RD)	Pimecrolimus 1%
Potent (group III)	Betamethasone valerate 0.1% (Betnovate), fluocinolone acetonide 0.025% (Synlar), mometasone furoate 0.1% (Elocon), hydrocortisone butyrate	Tacrolimus 0.1%
Very potent (group IV)	Clobetasol propionate 0.05% (Dermovate)	

From Joint Formulary Committee (2017)

intranasal mupirocin may be used in those who have positive nasal swabs for meticillin-resistant *S. aureus* (MRSA) (Eichenfield et al, 2014a). Despite elevated abundance of staphylococci in patients with atopic dermatitis, particularly in sites of disease predilection, routine anti-staphylococcal treatment is not beneficial (Kong et al, 2012).

Topical corticosteroids

Topical corticosteroids form the mainstay of treatment for flares of atopic dermatitis, and have done so since their introduction in the 1950s (Mayba and Gooderham, 2016). Their efficacy is well documented, with over 110 published randomized controlled trials to date; they have been shown to be effective in 80% of flares (Williams, 2005; Berke et al, 2012). Corticosteroids suppress inflammatory cells and cytokines, resulting in reduced inflammation and pruritus (Mayba and Gooderham, 2016).

Topical corticosteroids are available in a variety of strengths, which is graded on their ability to induce vasoconstriction (*Table 7*) (Mayba and Gooderham, 2016). Low and medium potency topical corticosteroids are usually sufficient to treat the majority of flares, with potent steroids reserved for short-term treatments, particularly in lichenified areas or recalcitrant cases (Berke et al, 2012; Mayba and Gooderham, 2016). Similarly to emollients, topical corticosteroids are available in a wide variety of formulations, including ointments, creams and gels (Joint Formulary Committee, 2017).

Side effects of topical corticosteroids include skin atrophy, telangiectasia, striae, hypopigmentation and steroid-induced acne, as well as exacerbating coexistent dermatoses such as rosacea, perioral dermatitis or tinea infections (Williams, 2005). To avoid topical corticosteroid-induced atrophy, milder topical corticosteroids should be used in sensitive areas, including the face and neck, axillae and groin (Williams, 2005; Berke et al, 2012). Prolonged courses of high potency topical corticosteroids have the potential for systemic absorption and related systemic side effects, including adrenal suppression. This is more likely in patients using widespread application, recurrent use and those on other sources of steroid (Berke et al, 2012; Mayba and Gooderham, 2016).

Topical calcineurin inhibitors

Topical calcineurin inhibitors, pimecrolimus and tacrolimus, are beneficial as second-line treatment for atopic dermatitis, either as monotherapy or combination therapy with topical corticosteroids (Berke et al, 2012; Thomsen, 2014). Calcineurin inhibitors exert their clinical effect by inhibiting transcription of pro-inflammatory cytokine genes (Mayba and Gooderham, 2016). Although comparative studies are sparse, efficacy at reducing flares appears to be similar to that of topical corticosteroids, equating tacrolimus 0.1% to potent steroids, and pimecrolimus 1% to mild or moderate steroids (Treloar, 2005; Williams, 2005). Unlike steroids, calcineurin inhibitors do not induce skin atrophy, meaning they can be used in areas where steroids are contraindicated or where steroid atrophy has already occurred or is likely to occur. Topical calcineurin inhibitors may result in local dysaesthesia and pruritus, particularly on inflamed skin. This can be reduced by also applying topical corticosteroids during the initial week of application of topical calcineurin inhibitors.

After initial flares have resolved, patients who experience recurrent flares may benefit from a tapering regimen of both topical corticosteroids and topical calcineurin inhibitors. Twice weekly pro-active maintenance applications to previously affected skin may also help prevent future relapses, and is more effective than emollients alone (Berke et al, 2012; Eichenfield et al, 2014a).

Practicalities

Guidance has been issued (National Institute for Health and Care Excellence, 2007; Joint Formulary Committee, 2017) on the amount of topical steroids and calcineurin inhibitors which should be applied, with the 'finger-tip' unit. This provides approximately 0.4–0.5 g of topical agent and treats an area approximately the size of a handprint (*Table 8*).

Phototherapy

In the 1970s Morison et al (1978) observed that patients with refractory atopic dermatitis improved in sunny climates (Meduri et al, 2007). This resulted in the use of light as a treatment for atopic dermatitis. Currently, a range of light forms are used, including natural, narrow and broadband ultraviolet B, and ultraviolet A light (Meduri et al, 2007). These can be used in association with topical or oral psoralen which acts as a photosensitizer. There has been no demonstrable superiority of any particular artificial source of light, but all artificial lights are superior to natural light (Meduri et al, 2007; Sidbury et al, 2014a). Narrow band ultraviolet B is the most commonly

Table 8. Amounts of topical corticosteroids to be used

	Fingertip unit	Amount for 1 week of twice-daily treatment (g)
One hand	1	100
One arm	3	200
One foot	2	200
One leg	6	200
Face and neck	2.5	500
Trunk, front and back	14	100

From Joint Formulary Committee (2017)

used, because of its low risk profile, relative efficacy and availability (Sidbury et al, 2014a). Adverse events, although infrequent, includes local erythema, pruritus, burning and an increased risk of skin cancer (Sidbury et al, 2014a).

Oral agents

For patients in whom topical agents have failed and phototherapy is not suitable or has also failed, oral immunosuppression may be considered. Agents used include ciclosporin, methotrexate and azathioprine. Few studies compare head to head efficacy, and agent choice must depend on individual patient factors (Sidbury et al, 2014a). The long-term use of systemic corticosteroids is cautioned, because of the unfavourable risk–benefit profile (Eichenfield et al, 2014b).

Biologics

Advances in understanding of pathology which underpins atopic dermatitis has led to the emergence of targeted therapies. Dupilumab, a human monoclonal antibody against IL-4 receptor alpha, inhibits signalling of IL-4 and IL-13, thus reducing the immune-mediated inflammatory response. Dupilumab improves signs and symptoms of atopic dermatitis and increases overall quality of life compared to placebo (Simpson et al, 2016). The formal EU regulatory application for dupilumab is currently under review by the European Medicines Agency.

Prevention

Early intervention in infants with atopic dermatitis has been shown to halt the atopic march. Regular application of emollients significantly reduces the rate of development of atopic dermatitis; application of emollients to the whole body from the ages of 3 weeks to 6 months leads to a 50% relative risk reduction in the development of atopic dermatitis (Simpson et al, 2014). There has been no demonstrable effect from dietary allergen avoidance in either pregnancy or lactation and so this is not advised, and the role of vaccinations and/or breastfeeding remains controversial (Kramer and Kakuma, 2014; Oszukowska et al, 2015).

Conclusions

Atopic dermatitis is a common condition which often persists into adulthood, often in conjunction with asthma and hay fever. Treatment adopts a stepwise approach with topical steroids and/or calcineurin inhibitors, and the importance of the use of regular emollients is paramount in maintaining remission. Flares can become complicated with a number of viral or bacterial infections, thus keeping patients in remission is important. In a small number of cases which are not manageable by general physicians or GPs, light therapy or systemic therapies may be used. **BJHM**

Conflict of interest: none.

KEY POINTS

- Atopic dermatitis, or atopic eczema, is a common condition.
- Untreated, it can have a substantial impact upon quality of life.
- Treatment adopts a stepwise approach.
- All patients should use emollients.
- Topical steroids are the mainstay of treatments, but topical calcineurin inhibitors are useful alternatives.
- Recalcitrant cases may need phototherapy or oral immunosuppression.
- Infants at high risk of developing atopic dermatitis would benefit from early application of emollients to prevent development of atopic dermatitis.

Berke R, Singh A, Guralnick M (2012) Atopic dermatitis: an overview. *Am Fam Physician* **86**(1): 35–42.

Chen JK, Jacob SE, Nedorost ST et al (2016) A pragmatic approach to patch testing atopic dermatitis patients. *Dermatitis* **27**(4): 186–192. https://doi.org/10.1097/DER.0000000000000208

Eichenfield LF, Tom WL, Berger TG et al (2014a) Guidelines of care for the management of atopic dermatitis. *J Am Acad Dermatol* **71**(1): 116–132. https://doi.org/10.1016/j.jaad.2014.03.023

Eichenfield LF, Tom WL, Chamlin SL et al (2014b) Guidelines of care for the management of atopic dermatitis. *J Am Acad Dermatol* **70**(2): 338–351. https://doi.org/10.1016/j.jaad.2013.10.010

Joint Formulary Committee (2017) British National Formulary. www.medicinescomplete.com (accessed 11 October 2017)

Kong HH, Oh J, Deming C et al; NISC Comparative Sequence Program (2012) Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res* **22**(5): 850–859. https://doi.org/10.1101/gr.131029.111

Kramer MS, Kakuma R (2014) Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Evid Based Child Health* **9**(2): 447–483. https://doi.org/10.1002/ebch.1972

Liaw FY, Huang CF, Hsueh JT, Chiang CP (2012) Eczema herpeticum: a medical emergency. *Can Fam Physician* **58**(12): 1358–1361.

Mayba JN, Gooderham MJ (2016) Review of atopic dermatitis and topical therapies. *J Cutan Med Surg* **21**(3): 227–236. https://doi.org/10.1177/1203475416685077

Meduri NB, Vandergriff T, Rasmussen H, Jacobe H (2007) Phototherapy in the management of atopic dermatitis: a systematic review. *Photodermatol Photoimmunol Photomed* **23**(4): 106–112. https://doi.org/10.1111/j.1600-0781.2007.00291.x

Morison WL, Parrish J, Fitzpatrick TB (1978) Oral psoralen photo-chemotherapy of atopic eczema. *Br J Dermatol* **98**: 25–30. https://doi.org/10.1111/j.1365-2133.1978.tb07329.x

National Institute for Health and Care Excellence (2007) Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years. National Collaborating Centre for Women's and Children's Health, London

Novak N, Simon D (2011) Atopic dermatitis - from new pathophysiologic insights to individualized therapy. *Allergy* **66**(7): 830–839. https://doi.org/10.1111/j.1398-9995.2011.02571.x

O'Regan GM, Sandilands A, McLean WHI, Irvine AD (2009) Filaggrin in atopic dermatitis. *J Allergy Clin Immunol* **124**(3) Suppl 2: R2–R6. https://doi.org/10.1016/j.jaci.2009.07.013

Oszukowska M, Michalak I, Gutfreund K, Bienias W, Matych M, Szewczyk A, Kaszuba A (2015) Role of primary and secondary prevention in atopic dermatitis. *Postepy Dermatol Alergol* **32**(6): 409–420. https://doi.org/10.5114/pdia.2014.44017

Sidbury R, Davis DM, Cohen DE et al; American Academy of Dermatology (2014a) Guidelines of care for the management of atopic dermatitis. *J Am Acad Dermatol* **71**(2): 327–349. https://doi.org/10.1016/j.jaad.2014.03.030

Sidbury R, Tom WL, Bergman JN et al (2014b) Guidelines of care for the management of atopic dermatitis. *J Am Acad Dermatol* **71**(6): 1218–1233. https://doi.org/10.1016/j.jaad.2014.08.038

Simpson EL (2006) Atopic dermatitis prevention. *Dermatol Ther* **19**(2): 108–117. https://doi.org/10.1111/j.1529-8019.2006.00059.x

Simpson EL, Chalmers JR, Hanifin JM et al (2014) Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol* **134**(4): 818–823. https://doi.org/10.1016/j.jaci.2014.08.005

Simpson EL, Bieber T, Guttman-Yassky E et al; SOLO 1 and SOLO 2 Investigators (2016) Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med* **375**(24): 2335–2348. https://doi.org/10.1056/NEJMoa1610020

Sugarman JL, Fluhr JW, Fowler AJ, Bruckner T, Diepgen TL, Williams ML (2003) The objective severity assessment of atopic dermatitis score: an objective measure using permeability barrier function and stratum corneum hydration with computer-assisted estimates for extent of disease. *Arch Dermatol* **139**(11): 1417–1422. https://doi.org/10.1001/archderm.139.11.1417

Thomsen SF (2014) Atopic dermatitis: natural history, diagnosis, and treatment. *ISRN Allergy* **2014**: 1–7. https://doi.org/10.1155/2014/354250

Treloar V (2005) Atopic dermatitis. *N Engl J Med* **353**(10): 1069–1070, author reply 1069–1070. https://doi.org/10.1056/NEJMc051779

Williams HC (2005) Atopic dermatitis. *N Engl J Med* **352**(22): 2314–2324. https://doi.org/10.1056/NEJMcp042803

Williams HC, Burney PG, Strachan D, Hay RJ (1994) The UK Working Party's Diagnostic Criteria for Atopic Dermatitis II. Observer variation of clinical diagnosis and signs of atopic dermatitis. *Br J Dermatol* **131**(3): 397–405. https://doi.org/10.1111/j.1365-2133.1994.tb08531.x