ABOUT THE AUTHOR

Chih-ho Hong, MD, FRCPC

Dr. Hong is a board certified dermatologist working in Surrey BC. He runs a busy clinic with a focus on cosmetic procedures and clinical trials. He is a Clinical Assistant Professor in the Department of Dermatology and Skin Sciences at UBC. His main areas of interest are psoriasis and eczema. He has been an investigator in over 160 trials of treatments in dermatology and has over 50 peer reviewed publications including recent publications in the Lancet and the New England Journal of Medicine. He has lectured locally, nationally and internationally on dermatology treatments

Affiliations:
Clinical Assistant Professor, University of British Columbia

MANAGEMENT AND TREATMENT OF ATOPIC DERMATITIS IN PRIMARY CARE

Atopic dermatitis (AD) is a chronic, relapsing, and remitting, inflammatory skin disease characterized by erythema, edema, xerosis, erosions/excoriations, oozing and crusting.[1] It typically begins in childhood and often in infancy. The disease can wax and wane and for many patients it becomes less severe or even remits over time. Seasonal variation is common, with most patients experiencing a worsening of symptoms in the wintertime, particularly in Canada.

AD is increasingly more common with both the incidence and prevalence increasing over the past several decades, particularly in industrialized countries.[2] The exact reason for the increase is unknown, but thought to be potentially related to environmental factors, and lack of exposure to certain pathogens.[3] AD is often associated with other "atopic" disorders, such as asthma, IgE mediated food allergy, and allergic rhinitis; but may also be associated with chronic rhinosinusitis with or without nasal polyps, eosinophilic esophagitis, and allergic conjunctivitis. The progression of atopic disorders from infancy to childhood to adulthood is known as the "atopic march".[4]

The clinical appearance and location of atopic dermatitis may vary depending on age of the patient, their ethnicity, and baseline disease severity. Infants typically present with AD on the face and extensor surfaces. Children and adolescents typically have flexural involvement, where the neck, antecubital fossae, and popliteal fossae are affected (**Figure 1**). Adults may have flexural disease, but isolated disease on the eyelids, nipples, and hands may also be seen (**Figure 2**).

Pruritus (itch) is a hallmark symptom of the disease. Historically, AD was referred to as the "itch that rashes". Itch is exacerbated by sweating, stress, heat, humidity, and woolen clothing. Sleep disruption is also a common sequelae of itch and in children, the sleep disruption often extends to the family, amplifying the burden of disease.

The pathophysiology of AD is complex and is thought to involve an interplay of genetic factors, cutaneous barrier abnormalities, and dysregulated immune pathways as shown in **Figure 3**.[5]

AD is diagnosed based on clinical features. There are numerous clinical criteria that can be employed, such as the Hanifin and Rajka criteria or several modifications of these criteria proposed subsequently, but these are more appropriately utilized in a research setting. The UK Working Party diagnostic schema or the American Academy of Dermatology (AAD) AD diagnostic guidelines are probably most easily used in clinical practice (**Table 1**).[6] Additional diagnostic tests such as fungal scraping and culture, skin biopsy, and blood tests are only required if there is diagnostic uncertainty or a lack of response to an adequate course of therapy.

While AD and food allergy are often seen in the same patient population, food allergy is rarely implicated in the pathophysiology of AD. Therefore, workup of AD patients for food allergy should not be undertaken as routine clinical practice. A double blind placebo controlled food challenge is the diagnostic test of choice in those rare cases where AD is thought to triggered by a food allergy.

Emollients are the cornerstone of AD treatment and maintenance as they restore and preserve skin barrier integrity. They are often used in conjunction with prescription treatments.[8] In infants, petrolatum can be used as it is inexpensive and not associated with a risk of cutaneous sensitization. Cosmetic acceptability limits its use in older children and adults. Any emollient is better than no emollient. A cream-based emollient is typically preferred over a lotion. Emollients containing ceramides or other barrier enhancing agents may provide additional efficacy over traditional emollient creams and lotions. The use of bland emollients in infants who are highly susceptible to developing AD may reduce the incidence of AD. Further studies in this realm are needed.

Topical treatments are appropriate for the majority of patients, particularly since most patients' AD is limited in extent and severity. Topical corticosteroids are the mainstay of therapy and the usage of topical steroids is supported by numerous clinical studies. Side effects of topical treatments are well known, but fortunately uncommon, particularly when topical agents are utilized appropriately. Topical steroids are grouped into "potency groups". The most commonly used scale has seven groups of topical steroid potencies, ranging from ultrapotent (class I) to low potency (class VII).[9] For most primary

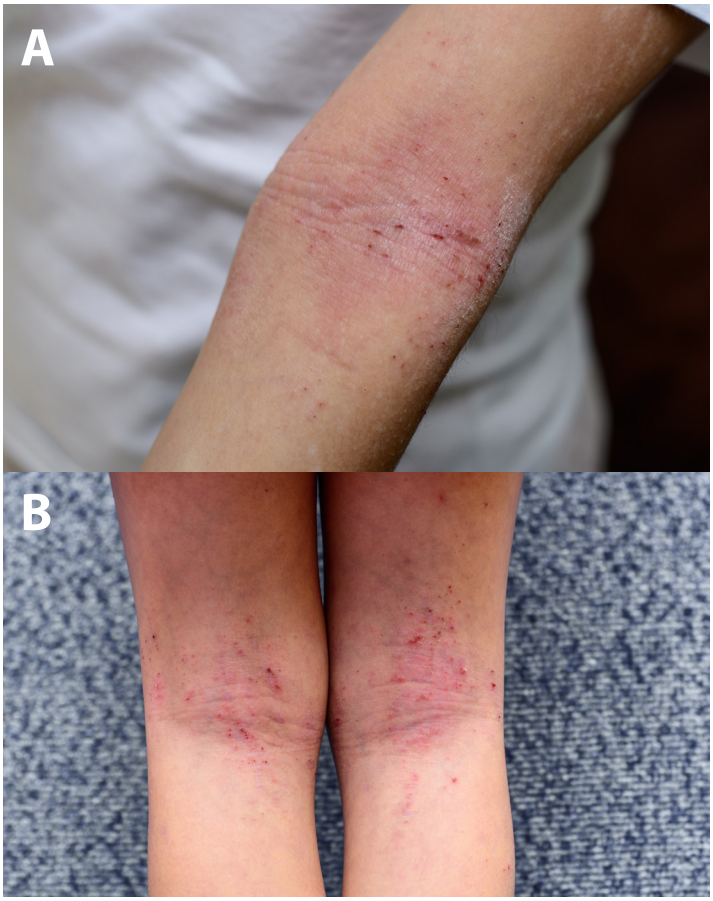

Figure 1. Examples of atopic dermatitis on a child's forearm (A) and the back of the knees (B); from shutterstock.com

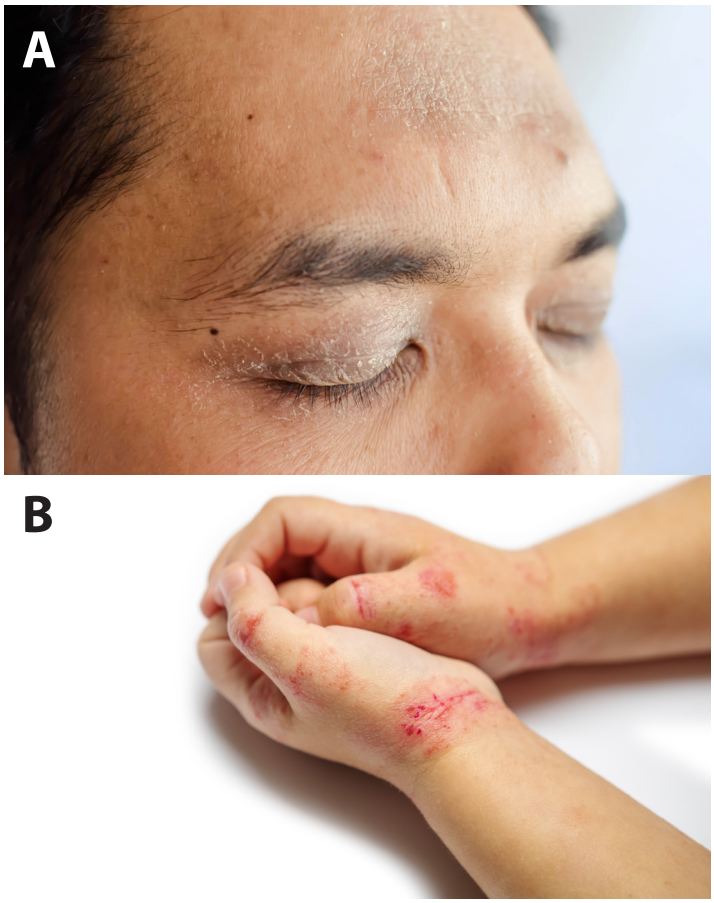

Figure 2. Atopic dermatitis on the eyelid of a male patient (A), and on the hands (B); from shutterstock.com

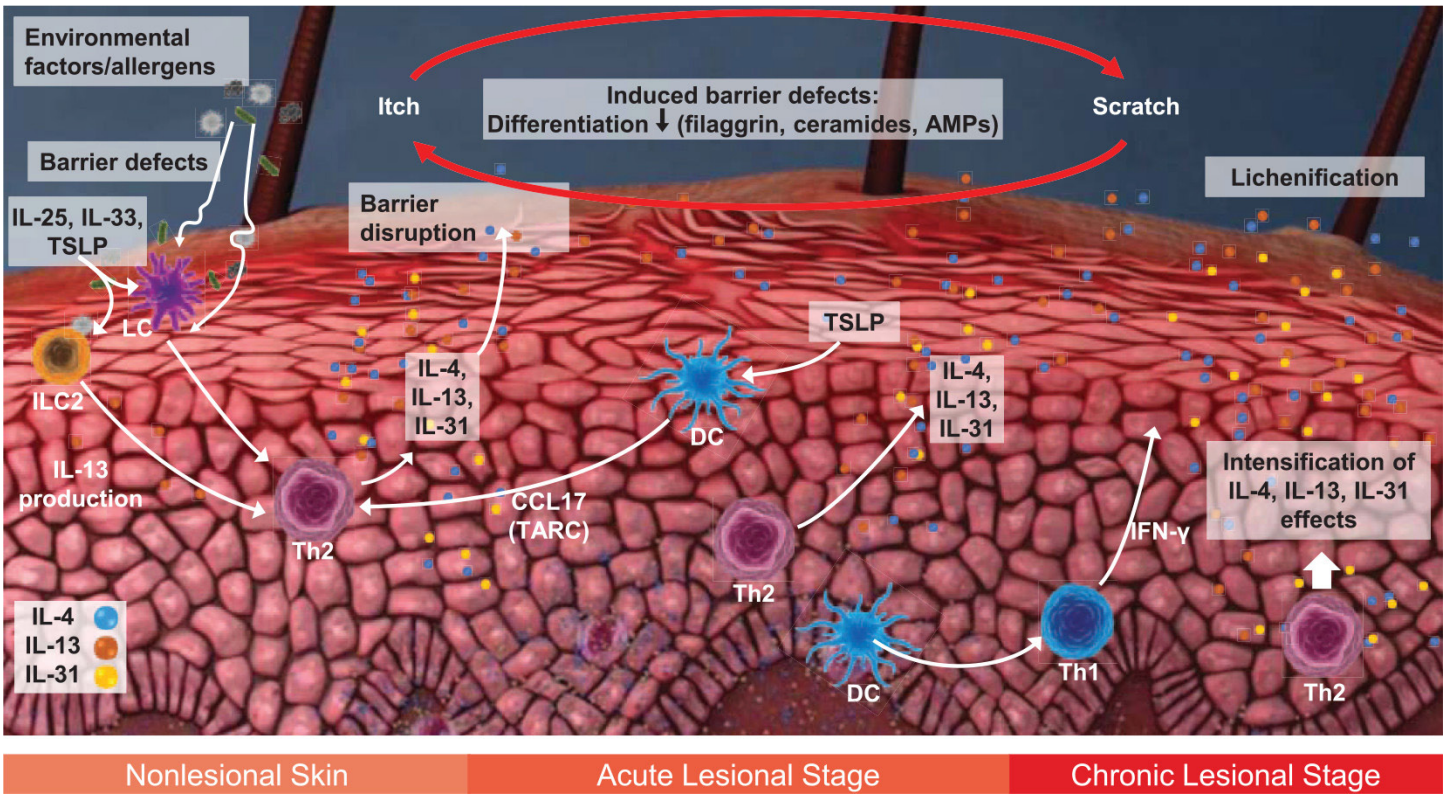

Figure 3. Pathophysiology of atopic dermatitis. (A) Nonlesional skin with underlying barrier defects is susceptible to immune activation in response to environmental factors/allergens. Immune activation by resident innate immune cells leads to type 2 inflammation, led by inflammatory cytokines IL-4, IL-13, and IL-31. (B) Type 2 inflammation mediates barrier disruption, promotes further inflammation, and increases itch, leading to acute skin lesions. (C) Chronic disease is characterized by intensification of the effect of type 2/Th2 cytokines as well as involvement of Th1 inflammation, resulting in lichenification of the skin; used with permission.
AMP, antimicrobial peptide; CCL17, chemokine ligand 17; DC, dendritic cell; IFN, interferon; IL, interleukin; ILC2, type 2 innate lymphoid cell; LC, Langerhans cell; TARC, thymus and activation regulated chemokine; Th, T helper cell; TSLP, thymic stromal lymphopoietin

care practitioners, having familiarity with a low potency steroid, such as hydrocortisone 2.5%, a mid potency steroid, such as betamethasone valeate 0.1%, and a high potency steroid, such as clobetasol propionate 0.05% will suffice. More importantly, is the prescribing of a sufficient enough quantity of medication. To estimate the appropriate quantity of medication to prescribe, it is easiest to do so based on the proportion of body surface area (BSA) affected. The patient's hand (palm and fingers) is approximately equal to 1% of their BSA. Every 1% of BSA that is affected, requires 0.5g to cover once. Therefore, a patient with 2% BSA of AD would need 2g per day if applying b.i.d. Lastly, topical steroids can be prescribed in different vehicles. All the listed topicals are available as a cream, ointment, or lotion. Ointments are typically more effective, but less cosmetically acceptable. Lotions are typically alcohol-based solutions designed for use in hair bearing sites like the scalp and do not have the consistency of emollient lotions.

As with any prescription medication, an appropriate discussion of benefits and risks of therapy is appropriate. Often, the discussion around topical steroids focuses solely on risks which both discourage compliance and adherence to therapy and also perpetuate the feeling that topical steroids are dangerous.

For "steroid phobic" patients or in those whom steroids have not been effective or in those who have had a side effect, there are non-steroidal options that can be considered. Currently there are two classes of non-steroidal medications that are currently approved in Canada and are useful for the treatment of AD. Topical calcineurin inhibitors (TCIs), including tacrolimus and pimecrolimus, are one such class of agent. Studies have shown that when used properly, these agents can be as effective as topical steroids in the treatment of AD. Patients will often experience stinging and burning with initial application, particularly if the skin is acutely inflamed. Another class of agents is the PDE4 inhibitor class. Currently, in Canada, crisaborole is approved for the treatment of mild-to-moderate AD. Again, stinging and burning can be a concern if applied to acutely inflamed skin. The tolerability of both TCIs and crisaborole may be improved if topical steroids are used for a short time to abruptly reduce acute inflammation before either TCIs or crisaborole are used.

ESSENTIAL FEATURES (must be present):
• Pruritus
• Eczema (acute, subacute, chronic)
✓ Typical morphology and age-specific patterns*
✓ Chronic or relapsing history
***Patterns include:**
1. Facial, neck, and extensor involvement in infants and children
2. Current or previous flexural lesions in any age group
3. Sparing of the groin and axillary regions
IMPORTANT FEATURES (seen in most cases; adding support to the diagnosis):
• Early age of onset
• Atopy
✓ Personal and/or family history
✓ Immunoglobulin E reactivity
• Xerosis
ASSOCIATED FEATURES (these clinical associations help to suggest the diagnosis of atopic dermatitis but are too nonspecific to be used for defining or detecting atopic dermatitis for research and epidemiologic studies):
• Atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response)
• Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis
• Ocular/periorbital changes
• Other regional findings (e.g., perioral changes/periauricular lesions)
• Perifollicular accentuation/lichenification/prurigo lesions
EXCLUSIONARY CONDITIONS (it should be noted that a diagnosis of atopic dermatitis depends on excluding conditions, such as):
• Scabies
• Seborrheic dermatitis
• Contact dermatitis (irritant or allergic)
• Ichthyoses
• Cutaneous T-cell lymphoma
• Psoriasis
• Photosensitivity dermatoses
• Immune deficiency diseases
• Erythroderma of other causes

Table 1. Features to be considered in the diagnosis of patients with atopic dermatitis; adapted from Eichenfeld et al, 2003[7]

Data on the use of topical steroids and TCIs suggest that both classes of agents can be used as maintenance therapy in addition to being used for the acute management of AD flares. Twice weekly application of both topical steroid and non-steroidal medications has been shown to be effective as a maintenance strategy to reduce flares. In addition, using topical treatments proactively actually decreases the total amount of topical medication used over the long run.[10,11,12]

Newer topical non-steroidal agents are currently in development. In the US, topical ruxolitinib, a Janus Kinase inhibitor (JAKi), has been approved for treatment of mild-to-moderate AD. As well, two other topical agents have been approved in the US for the treatment of psoriasis. Topical roflumilast has posted positive phase 3 top line data[13] and topical tapinarof was shown to be efficacious in phase 2 studies for AD[14], with the phase 3 AD study currently just reporting positive top line data at the recent American Academy of Dermatology Meeting in 2023.

Equally important to prescribing the right emollient and topical treatment, delivery of clear (preferably written) instructions on how to apply these agents is helpful. An eczema care plan helps to reduce confusion. An easy-to-use eczema care plan can be found at www.eczemahelp.ca. Step 1 typically involves bathing with a gentle cleanser. Step 2 includes the application of prescription medications to the affected areas. If different agents are being used for different anatomic areas, it is clarified here in step 2. The third step incorporates application of the emollient to all areas.

Patients who are not adequately controlled with topicals, or who relapse quickly after acute treatment and cannot be managed with maintenance therapy, should be considered for referral to a dermatologist. Patients with high burden of disease as measured by BSA of involvement can also be considered for referral. Patients with 10% or more BSA should be referred for specialist care.

Patients with moderate-to-severe or extensive AD can be managed with additional treatment options. Phototherapy is a useful adjunct. Narrow band UVB is utilized most commonly in Canada for this purpose. However, access to phototherapy units can be an issue as these are conventionally found in dermatology offices which are most often located in urban or suburban areas in Canada. Convenience is another issue with the use of phototherapy as treatments, although quick, need to be done 2-3 times per week for optimal outcomes.

Systemic immunomodulatory agents, including methotrexate, cyclosporine, azathioprine, or mycophenolate mofetil/mycophenolic acid can be used for the treatment of AD; there are limited studies showing at least short term efficacy for each agent. Side effects may limit the long term use of these treatments.

Since 2017, new systemic agents have been available for the treatment of moderate-to-severe AD. Dupilumab, a biologic agent that blocks interleukin (IL) 4/13 signalling was approved for those ≥ 6 years of age for the treatment of AD and is also approved for the treatment of other atopic conditions including asthma, eosinophilic esophagitis, and chronic rhinosinusitis with nasal polyps. Another biologic agent, tralokinumab, which only blocks IL-13, is also approved for the treatment of adults with AD. One advantage in the use of biologic agents for AD is their relative ease of use as no biochemical laboratory monitoring is required.

New oral agents have also been approved. These extensively studied agents, upadacitinib and abrocitinib, are highly selective inhibitors of the JAK-1 pathway. JAK-1 is an important regulator of cytokine signalling for IL-4, IL-13, as well as other cytokines thought to drive inflammation in AD pathogenesis. Both of these agents have a rapid onset of action, with patients reporting relief from itch in as little as 1-2 days from the initiation of treatment. Appropriate workup and monitoring is required for these agents. Patients need to be screened for latent TB and monitored for potential transient disruptions to hematologic parameters as well as hepatic parameters. Reactivation of zoster is also more common in patients treated with systemic JAKi and appropriate vaccination with zoster vaccine is typically required as part of routine practice.

Systemic steroids should rarely be used in the management of atopic dermatitis, and should only be considered as rescue therapy, while the patient is bridged to a chronic therapy. Chronic oral steroid therapy is inappropriate for long term management of atopic dermatitis.[15]

AD remains a common presenting problem in primary care and in dermatology offices across the country. The treatment landscape has broadened significantly in the past few years and ongoing research into new and novel treatments continues so that patients can achieve superior outcomes and improved quality of life.

Correspondence:
Chih-ho Hong
chihho@mail.ubc.ca

Financial Disclosures:

Advisory Board: Abbvie, Amgen, Arcutis, Bausch Health, Boehringer-Ingelheim, Bristol Meyers Squibb, Celgene, Dermavant, Eli-Lilly, Galderma, GSK, Incyte, Janssen, Leo Pharma, Novartis, Pfizer, Regeneron, Sanofi-Genzyme, Sun Pharma, UCB

Lecturer: Abbvie, Amgen, Arcutis, Bausch Health, Boehringer-Ingelheim, Bristol Myers Squibb, Celgene, Eli-Lilly, Galderma, Janssen, Leo Pharma, Novartis, Pfizer, Sanofi-Genzyme, UCB

Clinical Trials: Abbvie, Amgen, Arcutis, Bausch Health, Boehringer-Ingelheim, Bristol Meyers Squibb, Celgene, Cutanea, Dermira, Dermavant, DS Biopharma, Eli Lilly, Galderma, GSK, Incyte, Janssen, Leo Pharma, Medimmune, Merck, Mirimar, Novartis, Pfizer, Regeneron, Sanofi-Genzyme, Regeneron, Roche, UCB

References:

1. *Gooderham MJ, Bissonnette R, Grewal P, Lansang P, Papp KA, Hong CH. Approach to the assessment and management of adult patients with atopic dermatitis: a consensus document. Section II: tools for assessing the severity of atopic dermatitis. Journal of Cutaneous Medicine and Surgery. 2018 Nov;22(1_suppl):10S-6S.*

2. *Asher MI, Rutter CE, Bissell K, Chiang CY, El Sony A, Ellwood E, Ellwood P, García-Marcos L, Marks GB, Morales E, Mortimer K. Worldwide trends in the burden of asthma symptoms in school-aged children: Global Asthma Network Phase I Cross-sectional study. The Lancet. 2021 Oct 30;398(10311):1569-80.*

3. *Weiss ST. Eat dirt—the hygiene hypothesis and allergic diseases. New England Journal of Medicine. 2002 Sep 19;347(12):930-1.*

4. *Hill DA, Spergel JM. The atopic march: critical evidence and clinical relevance. Annals of Allergy, Asthma & Immunology. 2018 Feb 1;120(2):131-7.*

5. *Kirchhof MG, Landells I, Lynde CW, Gooderham MJ, Hong CH. Approach to the assessment and management of adult patients with atopic dermatitis: a consensus document. Section I: pathophysiology of atopic dermatitis and implications for systemic therapy. Journal of Cutaneous Medicine and Surgery. 2018 Nov;22(1_suppl):6S-9S.*

6. *Eichenfield LF, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. Journal of the American Academy of Dermatology. 2014;70(2):338-51.*

7. *Eichenfield LF, Hanifin JM, Luger TA, Stevens SR, Pride HB. Consensus conference on pediatric atopic dermatitis. Journal of the American Academy of Dermatology. 2003 Dec 1;49(6):1088-95.*

8. *Gooderham M, Lynde CW, Papp K, Bourcier M, Guenther L, Gulliver W, Hong CH, Poulin Y, Sussman G, Vender R. Review of systemic treatment options for adult atopic dermatitis. Journal of Cutaneous Medicine and Surgery. 2017 Jan;21(1):31-9.*

9. *Gabros Sarah, Trevor A. Nessel, and Patrick M. Zito. Topical corticosteroids. (2018).*

10. *Faergemann J, Christensen O, Sjövall P, Johnsson A, Hersle K, Nordin P, Edmar B, Svensson Å. An open study of efficacy and safety of long-term treatment with mometasone furoate fatty cream in the treatment of adult patients with atopic dermatitis. Journal of the European Academy of Dermatology and Venereology. 2000 Sep;14(5):393-6.*

11. *Wollenberg A, Reitamo S, Atzori F, Lahfa M, Ruzicka T, Healy E, Giannetti A, Bieber T, Vyas J, Deleuran M, European Tacrolimus Ointment Study Group. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. Allergy. 2008 Jun;63(6):742-50.*

12. *Weidinger S, Baurecht H, Schmitt J. A 5-year randomized trial on the safety and efficacy of pimecrolimus in atopic dermatitis: a critical appraisal. British Journal of Dermatology. 2017; 177(4):999-1003.*

13. *https://www.arcutis.com/arcutis-announces-positive-topline-results-from-integument-1-pivotal-phase-3-trial-of-roflumilast-cream-in-atopic-dermatitis-in-adults-and-children-aged-six-years-and-older/*

14. *Peppers J, Paller AS, Maeda-Chubachi T, Wu S, Robbins K, Gallagher K, Kraus JE. A phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of atopic dermatitis. Journal of the American Academy of Dermatology. 2019 Jan 1;80(1):89-98.*

15. *Hong C H, Gooderham MJ, Albrecht L, et al. Approach to the assessment and management of adult patients with atopic dermatitis: a consensus document. Section V: consensus statements on the assessment and management of adult patients with moderate-to-severe atopic dermatitis. Journal of Cutaneous Medicine and Surgery. 2018;22(1_suppl): 30S-35S.*