

UPDATE OF TREATMENT OPTIONS IN ATOPIC DERMATITIS: A NARRATIVE REVIEW

Neela Patel¹, Jay Modha¹, Bina Modi², Avanita Solanki¹, Jigna Barot¹

¹Department of Dermatology, AMC MET Medical College, Sheth L.G. Hospital, Ahemdabad

²Department of Respiratory Medicine, AMC MET Medical College, Sheth L.G. Hospital, Ahemdabad

Corresponding Author::

Dr Jay Modha

Email: jaymodha78@gmail.com

Abstract

Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by pruritus, inflammatory skin lesions. It causes severe impairment of quality of life along with the impairment of physical well of the patient. The management of AD has been always challenging due to its chronic and recurrent course with periods of remission. As the medical science progresses many modalities of treatment have been introduced, beginning from bathing methodology, topical and systemic. This study tries to give a narrative review of the different management options, which clinical dermatologists can use for the management of atopic dermatitis. These options needs to be evaluated and matched according to the age, sex and severity of atopic dermatitis.

Key Words - Atopic dermatitis, Treatment, Pruritus

Introduction

Atopic dermatitis is a type of endogenous eczema. It is common chronic and pruritic skin condition characterised multiple remission and relapse during its course. Itch or pruritus is the hallmark of atopic dermatitis. It has been estimated that around 10-20% of children and 1-3% of adults suffer from this disease.¹ It may be associated with other disease like food allergy, bronchial asthma and allergic rhinitis.² Genetic and environment factors resulting in, epidermal barrier dysfunction, immune dysregulation and alteration of the cutaneous microflora has been found as the main factors causing atopic dermatitis.³⁻⁵ Atopic dermatitis due to its chronic course it is associated with psychological stress not only in patients but also in the parents, and resulting in impaired Quality of Life (QoL).⁶ Many modalities of treatment are available for the treatment of atopic dermatitis but the treatment of atopic dermatitis is always challenging. This review tries to accumulate the various modalities available for the management of atopic dermatitis.

Management of atopic dermatitis

1. Education and counselling of patients, parents and guardians.
2. Proper bathing.
3. Appropriate use of moisturizers.
4. Use of immunomodulators: phototherapy, topical and systemic medications.
5. Other miscellaneous interventions.
6. Management of coexisting allergies in a patient with atopic diathesis.^{7,8}

Baths

The patient should be advised to have a bath of around five to 10 minutes. It should not be prolonged one as it can remove the skin surface lipids. The water should be just warm not hot.⁹ For the bath, the patient should be asked to use a cleanser that is

fragrance free and the cleanser should be at neutral to low PH. Syndet bars are preferred than soaps or combars. The syndet bars or the synthetic detergent bars contain a synthetic surfactant, which is soap free. The synthetic surfactants may consists of fatty acid isothionates, sulfosuccinic acid esters as their principal ingredient. They have the capacity to preserve the skin surface lipids, which is important for maintaining the barrier function of the skin.¹⁰

Bleach Bath: The bleach bath has the property of prevention of infection and inflammatory cascade, which is an aggravating factor for atopic dermatitis. It is usually advised to have a bleach bath for 2-3 times a week. For the preparation of bleach bath, around 118 ml of household bleach whose active ingredient is NaOCl (Sodium Hypochlorite) is added to 151 litres of water. The patient's body or the affected areas are soaked for around ten minutes and then using a dry towel the body is patted dry. Immediately, the appropriate moisturiser needs to be applied.^{11,12}

Oatmeal Bath: The oatmeal bath can soothe the skin, maintain the barrier function and reduce the inflammation. For an oatmeal bath one cup, which is 236ml, of finely powdered colloidal oatmeal is slowly added to the bathtub slowly so that the colloidal oatmeal dissolves evenly. The water of the bathtub should be just warm. The body should be soaked in the bathtub for 10-15 minutes and then dried by just patting.^{13,14}

Vigorous rubbing after a bath should be avoided as it can irritate the skin. After the bath the soak and smear, technique can be used to apply the anti-inflammatory medications and/or moisturizers. In this technique the moisturizer is applied liberally shortly after the bath, usually within three minutes. The topical anti-inflammatory agents if indicated should be applied before the application of the moisturizer.¹⁵

Moisturizers

The cornerstone and agent of choice for management of atopic dermatitis are moisturizers. Moisturizers are available over the counters as well. Before choosing appropriate moisturizer or

before prescribing one, certain characteristics need to be taken care of. An emollient for a patient of atopic dermatitis should be free of fragrance, preservatives or other additives, which can act as triggering factor for exacerbation of atopic dermatitis. It should have an occlusive property by which it blocks trans-epidermal water loss, humectant property by which it binds water molecules and emollient property by which it maintains skin barrier function. Certain additives in moisturizers contain substances like parabens, fragrances, tocopherol or other biological additives, which can trigger the inflammatory process and aggravate the disease. The emollient can be topped up with certain additives like aloe vera, coconut oil, ceramide, natural moisturizing factor and anti-microbial peptides for their better efficacy. Moisturizing creams are preferred over lotions in atopic dermatitis due to their higher proportion of oil in creams than lotions.¹⁶⁻¹⁹ The moisturizers should be applied using the soak and smear technique for better outcome.¹⁵

IMMUNOMODULATORY THERAPY:

Phototherapy

Natural sunlight is considered useful for atopic patient. However, sunlight and high temperature can induce pruritus start and itch scratch cycle and can be harmful to patient. UV-B, or UV-A or combined UV-AB phototherapy can be beneficial. The UV rays act by inducing apoptosis of the T-Cells, reduction of Th2 cytokines and reduction of the antigen-presenting cell in the skin. It also reduced microbial colonisation in the skin (like *Staphylococcus aureus*).²⁰⁻²³

Topical anti-inflammatory agents

Topical Corticosteroids: Topical corticosteroids is FDA approved for management of atopic eczema and is the first line pharmacologic therapy. The corticosteroids are immunosuppressive, anti-inflammatory, ant proliferative and vasoconstrictive. It also retards the T cell, macrophage and dendritic cell proliferation. Nevertheless, the corticosteroids always remains to be a double-edged sword and proper potency and formulation should be prescribed by the clinician and the adverse effects should be kept in mind. The common side effects consist of skin atrophy, striae, steroid acne, perioral dermatitis, purpura, hypertrichosis, and hypopigmentation. Topical corticosteroids under occlusion can lead to gram-negative folliculitis. Systemic absorption can lead to HPA suppression.^{15,24,25}

Topical calcineurin inhibitors: Topical calcineurin inhibitors are FDA approved for the management of atopic dermatitis. Pimecrolimus 1% cream can be used for the management of mild to moderate disease and tacrolimus 0.03% to 0.1% can be used for moderate to severe disease. They work by suppressing the T cell activation, reducing the secretion of the Th2 profile cytokines and by inhibiting release of other proinflammatory mediators. They reduce the mast cell and dendritic cell activity as well. The topical calcineurin inhibitors are particularly useful for skin of face and intertriginous area, which have higher chances of atrophy after prolonged application of topical corticosteroids. The side of topical calcineurin inhibitors include local stinging and burning sensation.²⁶⁻²⁸

Crisaborole: Crisaborole is a phosphodiesterase 4 inhibitor which is FDA approved for the management of mild to moderate atopic dermatitis. Phosphodiesterase 4 leads to degradation of cyclic AMP and results in increased production of pro-

inflammatory cytokines.²⁹⁻³¹

Topical antimicrobials and antihistamines are other topical agents, which can be used for the management of atopic dermatitis. Topical antibiotics like fusidic acid 2% , or mupirocin 2% might be required where secondary infection has taken place and for the staphylococcal carrier sites, nasal or extra nasal.^{32,33} Topical antihistamines like doxepin can be used for itch relief.^{34,35}

Systemic anti-inflammatory agents

The American Academy of Dermatology (AAD) has laid down certain guidelines for the use of systemic immunomodulatory therapy for a patient of atopic dermatitis. According to AAD, systemic immunomodulatory therapy in a case of atopic dermatitis is given for patients in whom optimised topical regimens do not adequately control signs and symptoms of disease and for the patients whose medical, physical and/or psychological states are greatly affected by their skin disease.³⁶

The systemic anti-inflammatory agents for management of atopic dermatitis include:

Corticosteroids: Corticosteroid has multiple mechanism of action leading to final immunosuppression. It leads to NFkB and AP-1 transcription factor inhibition. It also causes apoptosis of lymphocytes and eosinophils. Corticosteroids act on the arachidonic acid pathway by phospholipase A2 and cyclooxygenase inhibition. The resultant effect is reduced activity of inflammatory cells and inhibition of pro-inflammatory cytokines. The corticosteroids also have effects on the dermal vasculature. They inhibit angiogenesis, causes vasoconstriction and reduced vascular smooth muscle response to histamine and bradykinin.^{37,38}

The dose of corticosteroid in atopic dermatitis is subjective and depends on clinicians' assessment of the patient. The important side effects of systemic corticosteroids include reactivation of tuberculosis and other infection, impaired wound healing, gastritis and gastric ulcer, electrolyte imbalance, fluid retention and hypertension, iatrogenic diabetes, osteoporosis, myopathy, glaucoma, menstrual irregularities, Cushing syndrome, suppression of HPA axis and Addisonian crisis, even psychosis in rare cases. While prescribing a systemic steroid to a child it should be kept in mind that steroid causes growth retardation. While the patient is on systemic corticosteroid therapy proper monitoring needs to be done including weight and growth chart monitoring, blood counts, infection screening, serum electrolyte levels, blood glucose levels, serum triglyceride levels, cardiac monitoring, bone x-rays, routine ophthalmologic examination and others. After a long course of corticosteroid therapy, serum cortisol level should be checked ideally before steroid withdrawal.^{39,40}

Alitretinoin: Alitretinoin or 9-cis retinoic acid is a non-aromatic retinoid. Its special characteristic is that it binds to all the retinoic acid receptors and retinoid X receptors. Upon binding with RAR and RXR it causes reduction in cytokines and chemokines which causes inflammation and mediate apoptotic activity and resulting in antiproliferative effect. Although very less reporting has been done regarding the use of alitretinoin for atopic dermatitis, it can be used in adult with atopic dermatitis at a dose of 30 mg per day. The common side effect include headache, dyslipidaemia, photosensitivity and teratogenicity. It is pregnancy category X drug. If alitretinoin is planned in a case of atopic dermatitis then preliminary investigations must be done

like blood counts, liver function tests, fasting lipid profile, renal function tests and most importantly pregnancy test in a female of reproductive age group.⁴¹⁻⁴³

Azathioprine: Azathioprine is an immunosuppressant and immunomodulatory substance. After administration of azathioprine it is rapidly converted to 6-mercaptopurine. The active metabolites of azathioprine, 6-thioguanine monophosphate and other 6-thioguanine metabolites are structurally similar to the endogenous purines. They get incorporated into the DNA and RNA and inhibit purine metabolism and cell replication. As a result, they also effect the T cell and B cell and antigen presenting cell function. The empirical dose of azathioprine is 2-3 mg/kg daily but the dose may be needed to adjust according to the thiopurine methyltransferase levels. Thiopurine methyltransferase (TPMT) converts 6-mercaptopurine to inactive metabolites. In case of reduced TPMT levels there can be azathioprine toxicity resulting in myelosuppression. Azathioprine is pregnancy category D drug. The important side effects of azathioprine include leucopenia, opportunistic infections, reactivation of latent infections and occasionally lymphoma on long-term usage. Before starting a patient of atopic dermatitis on azathioprine proper risk benefit ratio should be discussed. TPMT levels, pregnancy test, routine blood count, serum biochemistry tests and screening of latent infection should be done.⁴⁴⁻⁵⁰

Cyclosporine: This immunosuppressant and immunomodulatory substance was originally isolated from the fungus *Tolypocladium inflatum*. Cyclosporine causes inhibition of the intracellular enzyme calcineurin. As a result, it leads to reduction in pro-inflammatory factors and reduces the langerhans cell function. It leads to suppression of cellular and humoral immunity, mainly T cell function. Cyclosporine A (CsA) is not cytotoxic, does not suppress bone marrow, and is not teratogenic. Cyclosporine is available as two formulations, the original sandimmune and the neoral form. The neoral formulation is more absorbed and more bioavailable. The dermatologic dosage of cyclosporine is usually 2.5-5 mg per kilograms of body weight per day. It has the propensity to cause renal dysfunction, hypertension and dyslipidaemia. Other side effects of cyclosporine include tremors, headache, GI intolerance, electrolyte abnormalities and even hypertrichosis and hyperplasia of gums. Cyclosporine is contraindicated in extremes of ages, usually in less than 18 years and more than 65 years of age. It is pregnancy category C drug. Before starting a patient on cyclosporine pre-existing renal function, hypertension, malignancy, presence of any active infection should be screened for. A patient on cyclosporine needs to be regularly monitored for alteration in blood pressure and serum creatinine levels. Other relevant investigations like routine blood counts and blood biochemistry tests should always be done at regular intervals and monitored. Intake of grape juice is contraindicated with cyclosporine as it can cause elevation of cyclosporine levels in blood.^{5,50-52]}

Methotrexate: Methotrexate also known as amethopterin causes inhibition of dihydrofolic acid reductase resulting interference with DNA synthesis, repair, and cellular replication. Methotrexate is specific for S phase of cell cycle. It can be administered orally, intramuscularly or intravenously. The dose and route of administration is subjective to the severity of atopic dermatitis and needs evaluation by the treating doctor. Before

administration of methotrexate baseline evaluation for immunosuppressants needs to be done with special emphasis on , blood counts and liver status. Since methotrexate is a pregnancy category X drug, pregnancy must be ruled out before starting a female of reproductive age group on methotrexate. The tests needs to be repeated at regular intervals for proper monitoring. The important adverse effects of methotrexate include hepatotoxicity like liver fibrosis and cirrhosis, pancytopenia, pneumonitis, pulmonary fibrosis a gastrointestinal upset and teratogenicity. At high doses, methotrexate can cause nephrotoxicity and at long-term usage, lymphoma can occur. Methotrexate overdose can cause toxicity which is manifested as mucositis, stomatitis, oesophagitis, acute renal failure, pancytopenia, neurological dysfunction and diarrhoea. Leucovorin glucarpidase and thymidine are the antidotes, which can be used as an antidote for methotrexate toxicity.⁵³⁻⁵⁷

Mycophenolic acid: Mycophenolic acid (MPA) was originally isolated as a fermentation product of *Penicillium stoloniferum* in 1986 is a class of immunosuppressant. MMA inhibits the de novo pathway of purine biosynthesis, the only mechanism of purine biosynthesis that exists in lymphocytes. It also causes reduced recruitment of pro inflammatory cytokines, reduced expression of adhesion molecules and inhibits ant presenting cells and B cells. The adult dose of MPA for atopic dermatitis varies from 100 to 200 mg per day. MPA is notorious to cause hyperglycemia, hypercholesterolemia, electrolyte imbalance, gastrointestinal complaints, haematological abnormalities, pulmonary toxicities and occasionally flu like syndrome. Before starting MPA baseline investigations must be done to avoid the side effects. MPA has been categorised as pregnancy category D drug.⁵⁸⁻⁶⁰

Apremilast: Apremilast is a small molecule, which exerts its mechanism by inhibiting phosphodiesterase-4, and resultant increase of cyclic AMP levels of pro-inflammatory cytokines such as tumour necrosis factor- α , interleukin-23 and Interleukin-12. For adults with atopic dermatitis the dose is 20-30 mg twice daily. Apremilast is comparatively safer drug when compared to other immunosuppressive agents. It is a pregnancy C category drug. The most important side effects include diarrhoea and nausea, which may warrant withdrawal of drug. It is advisable to start with 10 mg once daily dose and gradually increasing the dose to the upper limit.⁶¹⁻⁶³

Dupilumab: Dupilumab is a monoclonal antibody, which got FDA approval for moderate to severe atopic dermatitis in 2017. Dupilumab is fully human-derived monoclonal antibody. Dupilumab binds to the alpha subunit of IL-4 Receptor which is common between IL-4 and IL-13. IL-4 and IL-13 induces differentiation of naïve T cells to Th2 cell line, which is the cornerstone of pathogenesis of atopic dermatitis. Dupilumab is administered subcutaneously. It is available in the market as 200 mg/1.14 ml syringe and 300mg/2ml syringe. The dose of atopic dermatitis is 600mg SC initially followed by 300 mg SC every other week. Dupilumab can cause ocular side effects like conjunctivitis, blepharitis dry eye and keratitis. Injection site reaction and immunosuppression are other side effects. Proper screening should be done before starting Dupilumab as done with every biologics.⁶⁴⁻⁶⁸

Other non-immunomodulatory systemic agents for the management of atopic dermatitis include antimicrobials,

antihistamines and oral Vitamin D3.

Systemic antimicrobials: The use of short course of antibiotics can suppress the Staphylococcal colonization. It is also indicated in a case of a flare of a case of atopic dermatitis.^{69,70}

Systemic antihistamines: Antihistamines control pruritus and hence break the itch scratch cycle. It induces sedation and sleep as well.^{71,72}

Systemic Vitamin D: Vitamin D has immunomodulatory effects both in the innate and adaptive immune systems, and there is increasing data showing its relevance in inflammatory processes such as AD. In combination with standard therapy, vitamin D is sufficient to achieve a reduction in severity of AD.⁷³⁻⁷⁶

OTHER THERAPIES

They include interferon gamma which suppresses and downregulates Th2 and IgE function, immunotherapy with aeroallergen, passing of psoralen treated WBCs through extracorporeal UV-A light system and Chinese herbal medications.⁷⁷⁻⁸¹

MANAGEMENT OF COEXISTING ALLERGIES

Around 20-30% of atopic dermatitis is associated with food hypersensitivity and it forms a component of atopic march. Eggs, milk, peanuts, soy, wheat and fish cause around 85-90% of food allergy. Although they mostly cause immediate hypersensitivity, they have the propensity to cause acute flare of atopic dermatitis and such components might need exclusion from diet. Skin prick test can help in finding the agent of exclusion.⁸²⁻⁸⁴ Dust mites, pollen grains, animal dander can cause aeroallergen allergy resulting in AD exacerbation. Use of vacuum cleaners, avoidance of furry toys and pets can avoid aeroallergen reactivity.⁸⁵⁻⁸⁸ Components of topical medications and skin care products can cause an aggravation of AD.⁸⁹ Proper patch tests can be done to find the offending agent.⁹⁰⁻⁹²

Conclusion

Atopic dermatitis has a chronic course and causes a significant distress to the patients and parents in all aspects. Many modalities of treatment and management are available for controlling the acute phase and prevention of exacerbation of atopic dermatitis. Appropriate methods should be selected alone or in combination assessing the status of the patient and calculating the risk and benefits of each modality of management.

How to cite this article:

Patel N, Modha J, Modi B, Soalnki A, Barot J. Update of Treatment Options in Atopic Dermatitis: A Narrative Review. *JDA Indian Journal of Clinical Dermatology*. 2019;2:61-66.

References

1. Nutten S. Atopic dermatitis: global epidemiology and risk factors. *Annals of Nutrition and Metabolism*. 2015;66(Suppl. 1):8-16.
2. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *Journal of Allergy and Clinical Immunology*. 2003 Dec 1;112(6):S118-27.
3. Leung DY. Pathogenesis of atopic dermatitis. *Journal of Allergy and Clinical Immunology*. 1999 Sep 1;104(3):S99-108.
4. Elias PM, Hatano Y, Williams ML. Basis for the barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. *Journal of Allergy and Clinical Immunology*. 2008 Jun 1;121(6):1337-43.
5. Cooper KD. Atopic dermatitis: recent trends in pathogenesis and therapy. *Journal of investigative dermatology*. 1994 Jan 1;102(1):128-37.
6. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *International journal of clinical practice*. 2006 Aug;60(8):984-92.
7. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, Berger TG, Bergman JN, Cohen DE, Cooper KD, Cordoro KM. 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 Feb 1;70(2):338-51.
8. Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K, Bergman JN, Chamlin SL, Cohen DE, Cooper KD, Cordoro KM. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *Journal of the American Academy of Dermatology*. 2014 Jul 1;71(1):116-32.
9. Hanifin JM. Atopic dermatitis in infants and children. *Pediatric Clinics of North America*. 1991 Aug 1;38(4):763-89.
10. Mukhopadhyay P. Cleansers and their role in various dermatological disorders. *Indian journal of dermatology*. 2011 Jan;56(1):2.
11. Wong SM, Ng TG, Baba R. Efficacy and safety of sodium hypochlorite (bleach) baths in patients with moderate to severe atopic dermatitis in Malaysia. *The Journal of dermatology*. 2013 Nov;40(11):874-80.
12. Gonzalez ME, Schaffer JV, Orlov SJ, Gao Z, Li H, Alekseyenko AV, Blaser MJ. Cutaneous microbiome effects of fluticasone propionate cream and adjunctive bleach baths in childhood atopic dermatitis. *Journal of the American Academy of Dermatology*. 2016 Sep 1;75(3):481-93.
13. Catherine Mack Correa M, Nebus J. Management of patients with atopic dermatitis: the role of emollient therapy. *Dermatology research and practice*. 2012;2012.
14. Gittler JK, Wang JF, Orlov SJ. Bathing and associated treatments in atopic dermatitis. *American journal of clinical dermatology*. 2017 Feb 1;18(1):45-57.
15. Gutman AB, Kligman AM, Sciacca J, James WD. Soak and smear: a standard technique revisited. *Archives of dermatology*. 2005 Dec 1;141(12):1556-9.
16. Hon KL, Kung JS, Ng WG, Leung TF. Emollient treatment of atopic dermatitis: latest evidence and clinical considerations. *Drugs in context*. 2018;7.
17. Giam YC, Hebert AA, Dizon MV, Van Bever H, Tiongco-Recto M, Kim KH, Soebono H, Munasir Z, Diana IA, Luk DC. A review on the role of moisturizers for atopic dermatitis. *Asia Pacific Allergy*. 2016 Apr 1;6(2):120-8.
18. Sethi A, Kaur T, Malhotra SK, Gambhir ML. Moisturizers: the slippery road. *Indian journal of dermatology*. 2016 May;61(3):279.
19. Xu S, Immaneni S, Hazen GB, Silverberg JI, Paller AS, Lio PA. Cost-effectiveness of prophylactic moisturization for atopic dermatitis. *JAMA pediatrics*. 2017 Feb 1;171(2):e163909-.
20. Krutmann J. Phototherapy for atopic dermatitis. *Clinical and experimental dermatology*. 2000 Sep;25(7):552-8.
21. Jekler J, Larkö O. UVB phototherapy of atopic dermatitis. *British Journal of Dermatology*. 1988 Dec;119(6):697-705.
22. Meduri NB, Vandergriff T, Rasmussen H, Jacobe H. Phototherapy in the management of atopic dermatitis: a systematic review. *Photodermatology, photoimmunology & photomedicine*. 2007 Aug;23(4):106-12.
23. Grundmann-Kollmann M, Behrens S, Podda M, Peter RU, Kaufmann R, Kerscher M. Phototherapy for atopic eczema with narrow-band UVB. *Journal of the American Academy of Dermatology*. 1999 Jun 1;40(6):995-7.
24. Simpson EL. Atopic dermatitis: a review of topical treatment options. *Current medical research and opinion*. 2010 Mar 1;26(3):633-40.
25. Fisher DA. Adverse effects of topical corticosteroid use. *Western journal of medicine*. 1995 Feb;162(2):123.
26. Paller A, Eichenfield LF, Leung DY, Stewart D, Appell M, Group TO. A 12-week study of tacrolimus ointment for the treatment of atopic dermatitis in pediatric patients. *Journal of the American Academy of Dermatology*. 2001 Jan 1;44(1):S47-57.

27. Paller AS, Eichenfield LF, Kirsner RS, Shull T, Jaracz E, Simpson EL. Three times weekly tacrolimus ointment reduces relapse in stabilized atopic dermatitis: a new paradigm for use. *Pediatrics*. 2008 Dec 1;122(6):e1210-8.
28. Paller AS, Eichenfield LF, Kirsner RS, Shull T, Jaracz E, Simpson EL. Three times weekly tacrolimus ointment reduces relapse in stabilized atopic dermatitis: a new paradigm for use. *Pediatrics*. 2008 Dec 1;122(6):e1210-8.
29. Paller AS, Tom WL, Lebwohl MG, Blumenthal RL, Boguniewicz M, Call RS, Eichenfield LF, Forsha DW, Rees WC, Simpson EL, Spellman MC. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *Journal of the American Academy of Dermatology*. 2016 Sep 1;75(3):494-503.
30. Zebda R, Paller AS. Phosphodiesterase 4 inhibitors. *Journal of the American Academy of Dermatology*. 2018 Mar 1;78(3):S43-52.
31. Paller A, Tom W, Lebwohl M, Blumenthal R, Boguniewicz M, Eichenfield L, Forsha D, Simpson E, Gold L, Zaenglein A, Call R. Crisaborole topical ointment, 2%: A novel, nonsteroidal, topical anti-inflammatory, phosphodiesterase 4 inhibitor: results from two phase 3 studies treating children and adult patients with mild to moderate atopic dermatitis. *Journal of the American Academy of Dermatology*. 2016 May 1;74(5).
32. Huang JT, Abrams M, Tloughan B, Rademaker A, Paller AS. Treatment of *Staphylococcus aureus* colonization in atopic dermatitis decreases disease severity. *Pediatrics*. 2009 May 1;123(5):e808-14.
33. Hanifin JM, Cooper KD, Ho VC, Kang S, Krafchik BR, Margolis DJ, Schachner LA, Sidbury R, Whitmore SE, Sieck CK, Van Voorhees AS. Guidelines of care for atopic dermatitis. *Journal of the American Academy of Dermatology*. 2004 Mar 1;50(3):391-404.
34. Drake LA, Fallon JD, Sober A, Doxepin Study Group. Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. *Journal of the American Academy of Dermatology*. 1994 Oct 1;31(4):613-6.
35. Williams HC. Atopic dermatitis. *New England Journal of Medicine*. 2005 Jun 2;352(22):2314-24.
36. Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol*. 2014 Aug;71(2):327-49.
37. Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, Gelmetti C, Gieler U, Lipozencic J, Luger T, Oranje AP, Schäfer T. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. *Journal of the European Academy of Dermatology and Venereology*. 2012 Aug;26(8):1045-60.
38. Bußmann C, Bieber T, Novak N. Systemic therapeutic options for severe atopic dermatitis. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*. 2009 Mar;7(3):205-19.
39. Tofte SJ, Hanifin JM. Current management and therapy of atopic dermatitis. *Journal of the American Academy of Dermatology*. 2001 Jan 1;44(1):S13-6.
40. Ricci G, Dondi A, Patrizi A, Masi M. Systemic therapy of atopic dermatitis in children. *Drugs*. 2009 Feb 1;69(3):297-306.
41. Grahovac M, Molin S, Prinz JC, Ruzicka T, Wollenberg A. Treatment of atopic eczema with oral alitretinoin. *British Journal of Dermatology*. 2010 Jan;162(1):217-8.
42. Simon D, Bieber T. Systemic therapy for atopic dermatitis. *Allergy*. 2014 Jan;69(1):46-55.
43. Cheng C, Michaels J, Scheinfeld N. Alitretinoin: a comprehensive review. *Expert opinion on investigational drugs*. 2008 Mar 1;17(3):437-43.
44. Elion GB. The pharmacology of azathioprine. *Annals of the New York Academy of Sciences*. 1993 Jun;685(1):401-7.
45. Oranje AP. Evidence-based pharmacological treatment of atopic dermatitis: an expert opinion and new expectations. *Indian journal of dermatology*. 2014 Mar;59(2):140.
46. Meggitt SJ, Reynolds NJ. Azathioprine for atopic dermatitis. *Clinical and experimental dermatology*. 2001 Jul;26(5):369-75.
47. Younger IR, Harris DW, Colver GB. Azathioprine in dermatology. *Journal of the American Academy of Dermatology*. 1991 Aug 1;25(2):281-6.
48. Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. *The Lancet*. 2006 Mar 11;367(9513):839-46.
49. Anstey AV, Wakelin S, Reynolds NJ. Guidelines for prescribing azathioprine in dermatology. *British Journal of Dermatology*. 2004 Dec;151(6):1123-32.
50. Ho VC, Zloty DM. Immunosuppressive agents in dermatology. *Dermatologic clinics*. 1993 Jan 1;11(1):73-85.
51. Reynolds NJ, Al-Daraji WI. Calcineurin inhibitors and sirolimus: mechanisms of action and applications in dermatology. *Clinical and experimental dermatology*. 2002 Oct;27(7):555-61.
52. Harper JI, Ahmed I, Barclay G, Lacour M, Hoeger P, Cork MJ, Finlay AY, Wilson NJ, Graham-Brown RA, Sowden JM, Beard AL. Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy. *British Journal of Dermatology*. 2000 Jan;142(1):52-8.
53. Weatherhead SC, Wahie S, Reynolds NJ, Meggitt SJ. An open-label, dose-ranging study of methotrexate for moderate-to-severe adult atopic eczema. *British Journal of Dermatology*. 2007 Feb;156(2):346-51.
54. Deo M, Yung A, Hill S, Rademaker M. Methotrexate for treatment of atopic dermatitis in children and adolescents. *International journal of dermatology*. 2014 Aug;53(8):1037-41.
55. Jolivet J, Cowan KH, Curt GA, Clendenin NJ, Chabner BA. The pharmacology and clinical use of methotrexate. *New England Journal of Medicine*. 1983 Nov 3;309(18):1094-104.
56. Olsen EA. The pharmacology of methotrexate. *Journal of the American Academy of Dermatology*. 1991 Aug 1;25(2):306-18.
57. Relling MV, Fairclough D, Ayers D, Crom WR, Rodman JH, Pui CH, Evans WE. Patient characteristics associated with high-risk methotrexate concentrations and toxicity. *Journal of Clinical Oncology*. 1994 Aug;12(8):1667-72.
58. Eugui EM, Mirkovich A, Allison AC. Lymphocyte-selective antiproliferative and immunosuppressive effects of mycophenolic acid in mice. *Scandinavian journal of immunology*. 1991 Feb;33(2):175-83.
59. Grundmann-Kollmann M, Podda M, Ochsendorf F, Boehncke WH, Kaufmann R, Zollner TM. Mycophenolate mofetil is effective in the treatment of atopic dermatitis. *Archives of dermatology*. 2001 Jul 1;137(7):870-3.
60. Strathie Page SJ, Tait CP. Mycophenolic acid in dermatology a century after its discovery. *Australasian Journal of Dermatology*. 2015 Feb;56(1):77-83.
61. Schafer PH, Parton A, Gandhi AK, Capone L, Adams M, Wu L, Bartlett JB, Loveland MA, Gilhar A, Cheung YF, Baillie GS. Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis. *British journal of pharmacology*. 2010 Feb;159(4):842-55.
62. Samrao A, Berry TM, Goreshi R, Simpson EL. A pilot study of an oral phosphodiesterase inhibitor (apremilast) for atopic dermatitis in adults. *Archives of dermatology*. 2012 Aug 1;148(8):890-7.
63. Schett G, Sloan VS, Stevens RM, Schafer P. Apremilast: a novel PDE4 inhibitor in the treatment of autoimmune and inflammatory diseases. *Therapeutic advances in musculoskeletal disease*. 2010 Oct;2(5):271-8.
64. Chipalkatti N, Lee N, Zancanaro P, Dumont N, Kachuk C, Rosmarin D. A retrospective review of dupilumab for atopic dermatitis patients with allergic contact dermatitis. *Journal of the American Academy of Dermatology*. 2019 Apr 1;80(4):1166-7.
65. Boguniewicz M, Alexis A.F., Beck L.A., Block J., Eichenfield L.F., Fonacier L., Guttman-Yassky E., Paller A.S., Pariser D., Silverberg J.I.

- and Lebwohl, M., 2017. Expert perspectives on management of moderate-to-severe atopic dermatitis: a multidisciplinary consensus addressing current and emerging therapies. *The Journal of Allergy and Clinical Immunology: In Practice*, 5(6), pp.1519-1531.
66. Siegfried EC, Igelman S, Jaworski JC, Antaya RJ, Cordoro KM, Eichenfield LF, Levy ML, Paller AS. Use of dupilumab in pediatric atopic dermatitis: Access, dosing, and implications for managing severe atopic dermatitis. *Pediatric dermatology*. 2019 Jan;36(1):172-6.
 67. Hamilton JD, Ungar B, Guttman-Yassky E. Drug evaluation review: dupilumab in atopic dermatitis. *Immunotherapy*. 2015 Oct;7(10):1043-58.
 68. Kraft M, Worm M. Dupilumab in the treatment of moderate-to-severe atopic dermatitis. *Expert review of clinical immunology*. 2017 Apr 3;13(4):301-10.
 69. LEYDEN JJ, MARPLES RR, KLIGMAN AM. Staphylococcus aureus in the lesions of atopic dermatitis. *British Journal of Dermatology*. 1974 May;90(5):525-.
 70. WACHS GN, MAIBACH HI. Co-operative double-blind trial of an antibiotic/corticoid combination in impetiginized atopic dermatitis. *British Journal of Dermatology*. 1976 Sep;95(3):323-8.
 71. Klein PA, Clark RA. An evidence-based review of the efficacy of antihistamines in relieving pruritus in atopic dermatitis. *Archives of dermatology*. 1999 Dec 1;135(12):1522-5.
 72. Wahlgren CF, Hägermark Ö, Bergström R. The antipruritic effect of a sedative and a non-sedative antihistamine in atopic dermatitis. *British Journal of Dermatology*. 1990 Apr;122(4):545-51.
 73. Searing DA, Leung DY. Vitamin D in atopic dermatitis, asthma and allergic diseases. *Immunology and Allergy Clinics*. 2010 Aug 1;30(3):397-409.
 74. Sidbury R, Sullivan AF, Thadhani RI, Camargo Jr CA. Randomized controlled trial of vitamin D supplementation for winter-related atopic dermatitis in Boston: a pilot study. *British Journal of Dermatology*. 2008 Jul;159(1):245-7.
 75. Bäck O, Blomquist HK, Hernell O, Stenberg B. Does vitamin D intake during infancy promote the development of atopic allergy?. *Acta dermato-venereologica*. 2009 Jan 1;89(1):28-32.
 76. Hata TR, Kotol P, Jackson M, Nguyen M, Paik A, Udall D, Kanada K, Yamasaki K, Alexandrescu D, Gallo RL. Administration of oral vitamin D induces cathelicidin production in atopic individuals. *Journal of Allergy and Clinical Immunology*. 2008 Oct 1;122(4):829-31.
 77. Hanifin JM, Schneider LC, Leung DY, Ellis CN, Jaffe HS, Izu AE, Bucalo LR, Hirabayashi SE, Tofte SJ, Cantu-Gonzales G, Milgrom H. Recombinant interferon gamma therapy for atopic dermatitis. *Journal of the American Academy of Dermatology*. 1993 Feb 1;28(2):189-97.
 78. Werfel T, Breuer K, Rueff F, Przybilla B, Worm M, Grewe M, Ruzicka T, Brehler R, Wolf H, Schnitker J, Kapp A. Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multi-centre, randomized, dose-response study. *Allergy*. 2006 Feb;61(2):202-5.
 79. Hjulær KP, Vestergaard C, Deleuran M. A retrospective study of six cases of severe recalcitrant atopic dermatitis treated with long-term extracorporeal photopheresis. *Acta dermato-venereologica*. 2010 Nov 1;90(6):635-6.
 80. Sheehan MP, Rustin MH, Buckley C, Harris DJ, Ostlere L, Dawson A, Atherton DJ, Brostoff J. Efficacy of traditional Chinese herbal therapy in adult atopic dermatitis. *The Lancet*. 1992 Jul 4;340(8810):13-7.
 81. Zhang W, Leonard T, Bath-Hextall FJ, Chambers C, Lee C, Humphreys R, Williams HC. Chinese herbal medicine for atopic eczema. *Cochrane Database of Systematic Reviews*. 2004(4).
 82. Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *The Journal of pediatrics*. 1985 Nov 1;107(5):669-75.
 83. Burks AW, Mallory SB, Williams LW, Shirrell MA. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. *The Journal of pediatrics*. 1988 Sep 1;113(3):447-51.
 84. Burks AW, James JM, Hiegel A, Wilson G, Wheeler JG, Jones SM, Zuerlein N. Atopic dermatitis and food hypersensitivity reactions. *The Journal of pediatrics*. 1998 Jan 1;132(1):132-6.
 85. Platts-Mills TA, Mitchell EB, Rowntree S, Chapman MD, Wilkins SR. The role of dust mite allergens in atopic dermatitis. *Clinical and experimental dermatology*. 1983 May;8(3):233-47.
 86. Ring J, Darsow U, Behrendt H. Role of aeroallergens in atopic eczema: proof of concept with the atopy patch test. *Journal of the American Academy of Dermatology*. 2001 Jul 1;45(1):S49-52.
 87. Tan BB, Weald D, Strickland I, Freidmann PS. Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. *The Lancet*. 1996 Jan 6;347(8993):15-8.
 88. Ricci G, Patrizi A, Specchia F, Menna L, Bottau P, D'angelo V, Masi M. Effect of house dust mite avoidance measures in children with atopic dermatitis. *British journal of dermatology*. 2000 Aug;143(2):379-84.
 89. Meneghini CL, Rantuccio F, Lomuto M. Additives, vehicles and active drugs of topical medicaments as causes of delayed-type allergic dermatitis. *Dermatology*. 1971;143(3):137-47.
 90. Isolauri E, Turjanmaa K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. *Journal of Allergy and Clinical Immunology*. 1996 Jan 1;97(1):9-15.
 91. Niggemann B, Reibel S, Wahn U. The atopy patch test (APT)—a useful tool for the diagnosis of food allergy in children with atopic dermatitis. *Allergy*. 2000 Mar;55(3):281-5.
 92. Roehr CC, Reibel S, Ziegert M, Sommerfeld C, Wahn U, Niggemann B. Atopy patch tests, together with determination of specific IgE levels, reduce the need for oral food challenges in children with atopic dermatitis. *Journal of Allergy and Clinical Immunology*. 2001 Mar 1;107(3):548-53.

