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Recent Modalities in Treatment of Atopic Dermatitis: Review Article

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ABSTRACT

Background: Inflammation of the skin marked by itchy, pigmented, dry areas is known as Atopic Dermatitis (AD), also known as Atopic Eczema (AE) or Eczema. Symptoms include red, itchy pimples that leak fluid and crust, scaly or raw skin, or raw or scaly skin. Dermatitis can come in many different forms, such as atopic, contact, or seborrheic. In children, atopic dermatitis is the most prevalent kind of eczema and often occurs in association with other allergic or asthmatic conditions. Eczema is most commonly found on the face, neck, elbows, knees, and toes, among other places. In terms of phototherapy, ultraviolet B phototherapy (280–320 nm) is the "oldest" method that is used in treatment of atopic dermatitis. Platelet rich plasma (PRP) injection utilizes the body's own regenerative mechanisms to help treat disease in the patient. **Objective:** Determination of the updated treatment modalities in Atopic Dermatitis management. **Conclusion:** Clearly there remains a need to find more potent topical agents with fewer side effects. The most gratifying advances in AD therapy have come from better understanding of immune and inflammatory mechanisms.
Keywords: Atopic dermatitis, Ultraviolet B phototherapy, Platelet rich plasma.

INTRODUCTION

Atopic dermatitis is an autoinflammatory skin disease. It has been linked to skin barrier abnormalities in both clinical and molecular studies. Early infancy is usually when it begins although an adult-onset form has been identified [(1)]. AD is the first sign of an allergic illness such as asthma, food allergy, or allergic rhinitis developing in succession. Early or severe AD and skin sensitization to environmental allergens may contribute to later allergy illness at different epithelial barrier surfaces, leading to the "atopic march" notion of an allergic illness developing in succession (e.g. gastrointestinal or respiratory tract). This claim is supported by both cross-sectional and long-term research [(2)].

Epidemiology:

Incidence of AD: Since the 1970s, the prevalence of AD has increased two to three times in developed countries, affecting 15 to 20 percent of children and 1 to 3 percent of adults globally. In the United States, population-based research shows that prevalence is approximately 10.7% in children and 7.2% in adults. The condition usually begins to manifest around the age of five, with the maximum occurrence occurring between the ages of three and six months, but it can strike anyone, regardless of their age [(3)]. In the first year of life, 60 percent of patients get disease, and 90 percent of patients develop disease within the first five years of their existence. The condition will persist in 20% of children who are diagnosed with AD before the age of 2 and will have sporadic symptoms in the remaining 17% by the age of 7. Among individuals with AD, only 16.8% get the disease after adolescence. However, among 10% to 30% of patients will continue to have illness symptoms even after AD has resolved in most cases by the time a kid reaches maturity [(4)]. Prevalence**:** An increasing percentage of children and adults are affected by AD, with AD affecting 15-30% of children and 2-10% of adults. This number is an estimate of the prevalence in industrialized nations. About 2% to 3% of people in China and Iran are affected. In individuals who come from less developed nations and move to the developed world, the incidence is higher [(5)].

Clinical Presentation:

1. Symptoms: As the most common and debilitating symptom of AD, incessant pruritus causes children to scratch themselves excessively and relentlessly [(6)].

2. Physical Examination: A routine skin examination for symptoms of AD is done to rule out acute urticaria and look for dermographism in younger patients who have the disease [(7)]. Eczematous lesions, xerosis, and lichenification are all common AD symptoms. Excoriations and crusting are prevalent, and prurigo nodularis-like lesions can be seen in certain patients. When it comes to finding the eczematous alterations, the patient's age plays a role [(8)]. The following characteristics are crucial (and help with the diagnosis): Early onset of xerosis, atopy, and other related traits can be characterized as follows: hyperlinear palms/ichthyosis/keratosis pilaris changes in the ocular/periorbital region and other regional results including unusual vascular responses [(9)].

Atopic Dermatitis Treatment & Management:

1. General considerations: Most of the treatment for AD is based on keeping your skin healthy by using moisturizer every day, as well as using anti-inflammatory medication as necessary. Topical calcineurin inhibitors (TCIs) and or topical corticosteroids (TCSs) should be used appropriately based on the disease activity when selecting anti-inflammatory therapy [(10)].

2. Contributing factors: When obtaining a medical history, it's crucial to look for anything that could be aggravating. Allergens in the air, foods, climate, stress, hormone levels, cigarettes, irritants, and bacteria are the most common causes of AD. All of the aforementioned

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criteria do not affect every patient with AD. 20–40% of children with AD also have a food allergy, most typically to cow's milk or eggs or fish or almonds or soya beans or wheat (according to statistics) [11]. It is common for patients with food allergy and AD to have one or the other concurrently. Atopic dermatitis patients who have food allergies are more likely to develop skin lesions than adult patients. They're a symptom of the body's susceptibility to specific foods, which might lead to atopic and allergy conditions if consumed [12].

Table (1): Atopic dermatitis: first-line treatment options (AD) [12].

Education	Explain/demonstrate how to apply emollients Various topical medications should be used with intervals In children > 12 months, use shampoos recommended in AD When talking to the patient (guardian), make sure the recommendations are understood and followed Revision of recommendations at least once a year
Prevention	Avoid allergens and irritants: Tobacco smoke Infections Wool clothing Stress
Skin cleansing	Delicate and precise, mechanical cleansing Detergents with/without aseptic substances Suitable galenic forms pH in the range of 6 Fast bath i 5 min, including 2-min bathing in oil at 27-30ºC Adding 1/2 cup of sodium hypochlorite to the bath eliminates itching Bath salts - facilitate the removal of exfoliated skin, skin scales, particularly beneficial in severe impetiginization
Emollient therapy	Application min. 2-3 times a day! Glycerol is better tolerated than urea or sodium chloride Propylene glycol can easily cause irritation in young children < 2 years of age and should not be used in these patients In children < 2 years of age it is recommended to use emollients without protein allergens and haptens Do not use emollients containing peanut extracts which increase the risk of sensitization and allergies! Emollients are poorly tolerated in inflammation sites – use the appropriate doses of emollients (250-500 g/week

3. First-line therapy: emollients: For the most part, treatment for AD focuses on educating patients, preventing more damage, and re-establishing the skin's normal barrier function. Choose emollients according to the degree of dryness, diurnal and nocturnal activities and probable contact allergy on an individual basis [12]. Using so-called "active emollients" (a blend of physiological stratum corneal fats) results in restoration of the compromised epidermal barrier of an AD patient to its normal lipid content. When these substances are present in the cells of the living layers of the epidermis (ceramides, for example), they are carried via specialized receptors and ATP to the cells' cytoplasm for metabolism before joining with the skin's endogenous lipids to form an impermeable lipid barrier [13]. Because ceramides are so low in AD, the best outcomes are obtained with active emollients mostly composed of ceramides. It takes 2 to 4 weeks of consistent therapy to see long-term improvements in the function of the epidermis's physiological differentiation process, with the end-product of the stratum corneum rich in lipid membranes as a result of using emollients to restore the barrier [1]. The use of contemporary emollients containing agonists of peroxisome proliferator-activated receptors is critical in the topical treatment of AD [14]. The treatment's primary goal is to get the skin's top layer back to normal levels of hydration. It is possible to obtain the proper hydration of the stratum corneum by using moisturizing agents, such as emollients, that contain urea, which is a key component of NMF, which is responsible for transporting water and glycerol from the dermis to the epidermis [15].

Cosmeceuticals: Topical treatments known as cosmeceuticals have a high concentration of active substances and therefore have therapeutic qualities or considerably support skin care. They're employed in AD to help rebuild and restore the normal function of the epidermal barrier as well as to calm down local inflammation [16]. Plant extracts (such as arnica, ginkgo biloba), phytoestrogens, b-carotene, active anti-inflammatory chemicals, fruit acids, and cytokines, as well as the recently found antioxidant and ectoin are some of the most important active ingredients used in cosmeceuticals today. With ectoin's help, environmental elements like UV light can have less of an impact on inflammatory processes in the body. It helps to reduce the level of DNA damage, speeds up cellular repair mechanisms, protects Langerhans' cells, enhances the fluidity of the lipid layer, and helps to prevent water loss from the epidermis when applied topically [3].

Wet-wrap treatment: It is a type of treatment for children with severe AD (SCORAD score more than 50) who are six months to ten years old. In this method, a moist dressing saturated with medication (emollients or 0.05 percent fluticasone propionate or mometasone furoate diluted 1: 3 for the body or 1: 9 for the face) is applied directly to skin, and a dry dressing is applied

over it (the moist dressing is applied directly to skin, and the dry dressing is applied over it). The treatment lasts 3–14 days and must be carried out under physician supervision, with morning cortisol levels being monitored. Adrenal suppression is a possible adverse effect of this medication [17].

4. Mild anti-inflammatory medication used as a second line of treatment:

Topical corticosteroids (TCSs):

For more than 50 years, topical corticosteroids have served as the foundation of AD treatment. Especially, when used in conjunction with emollients, they have a very beneficial therapeutic impact. TCSs are recommended in the form of ointments because of the dryness of the skin, unless in the case of oozing skin lesions, in which case lighter formulations must be employed (lotion, spray, cream). The usage of TCSs helps to reduce the amount of staphylococcus aureus colonization on the skin [18]. Exacerbations should be treated with a TCS of medium potency, according to the guidelines. TCSs are frequently overused due to the high efficacy achieved in a short period of time following the commencement of treatment and the low cost of these treatments. Due to the differences in the skin structure of children and adults, these drugs should be taken with caution and under close dermatological supervision in children and adolescents [19].

Steroid phobia (corticophobia):

According to research on steroid fear among AD patients, more than half of those suffering from the disease are terrified of using TCSs. Furthermore, it has been demonstrated that people have minimal understanding of the therapeutic potential of TCSs as well as their side effects, and that doctors and pharmacists are the primary sources of information regarding TCSs for patients [18]. Although steroid phobia is not unique to Poland, it is widespread throughout Europe and contributes to the ineffectiveness of local AD therapy. It appears that adequate patient education and personal engagement, which fosters mutual trust between patients and healthcare workers, could improve the success of AD treatment [20]. It increases the dread and reluctance of patients to use TCS for their AD when TCS prescriptions contain cautious and vague language in their instructions, such as use carefully. The usage of the fingertip unit system has been suggested as a technique of improving communication of instructions between the prescriber and the patient, among other things. In tropical use, a fingertip unit is defined as the amount of topical product that may be administered from the distal skin crease to the tip of the index finger when it is expressed from a tube with a 5 mm diameter nozzle [21].

Topical calcineurin inhibitors (TCIs):

Tacollimus and pimecrolimus, which are topical calcineurin inhibitors, decrease T cell activation as well as the synthesis of pro-inflammatory cytokines in the skin. Pimecrolimus in the form of a 1 percent cream is recommended topically as a first-line therapy for mild AD, and its clinical profile suggests that it may be the treatment of choice for mild to moderate AD in children and adults, particularly in sensitive skin areas [22]. Aside from not inhibiting collagen formation and not promoting epidermal thinning or dilatation, TCIs also do not cause damage to the skin's protective barrier. In addition to itching and irritation of the skin at the site of application, the most common adverse reactions associated with TCIs use are burning and redness of the skin at the site of application that diminish after a couple of days [22].

Proactive (maintenance) therapy:

Active treatment includes application of tacrolimus ointment two time a week for up to 1 year following the removal of skin lesions. Patients suffering from relapsed atopic dermatitis should receive pimecrolimus cream as maintenance therapy to the previously affected skin after the lesions have been completely resolved. The cream should be applied once daily for seven days a week for up to three months, or less frequently, contributed to the case consultant. Patients who receive proactive therapy for AD have reported fewer exacerbations of the disease, higher patient compliance, improved quality of life, and a reduction in the overall cost of their treatment for the disease [23].

Topical anti-microbial:

Each exacerbation of AD can be linked to a bacterial infection; staphylococcal infections are the most prevalent of these infections. In 90 percent of cases, this bacterium has colonized the skin of people with AD disease. However, because of rising drug resistance and the faulty antimicrobial peptide profile in AD, persistent decolonization of the skin is almost impossible. In addition, eradication of staphylococcus aureus has been attempted, but this has not been successful [24]. Octenidine, chlorhexidine, mupirocin, fusidic acid, and retapamulin have all been shown to be effective in clinical trials. Topical antibiotics should not be used on a regular basis due to antibiotic resistance, as previously stated. When there is an exacerbation of AD in conjunction with clinical evidence of bacterial infection, oral antibiotics are used; in other situations, oral antibiotics are not used. We must emphasize that anti-inflammatory medication (TCIs, TCSs, UV) alone has been shown to diminish staphylococcus aureus colonization in AD [25]. Dermatologic illness caused by the herpes simplex virus (HSV) commonly manifests itself in the form of a Kaposi varicelliform eruption, requiring the administration of systemic antiviral medication. For the treatment of superficial infections caused by Malassezia sympodialis, ketoconazole and ciclopiroxolamine have been proposed as effective treatments [26].

Tannins:

Long before the advent of modern dermatology, tannins played a significant role in skin care. In the treatment of inflammatory and exudative skin illnesses

such as atopic dermatitis, they are frequently utilized for their astringent, anti-inflammatory, antipruritic, antibacterial, and desiccant effects. Because tannins are not fully absorbed after application and therefore have no systemic effects, they can be used safely on all age groups, including infants, children, elderly and pregnant women without fear of side effects. Tannins are safe to use on a regular basis and have not been associated with any negative side effects when taken in conjunction with other medications. Lotion, cream, and bath and wrap solutions are all varieties of this product. Creams containing tannins are preferred when exudate, dryness and peeling are limited [(27)].

Tannins and an emollient cream base work together to provide effective treatment for inflammatory skin diseases with skin dryness. This formulation can be used alone in mild cases of AD or in combination with local corticosteroids, antifungals, and antibiotics in more severe cases of AD that are complicated by secondary infection [(25)].

Zinc oxide and talc are added to the lotion form of tannins to provide hygroscopic qualities, making it suitable for use as a monotherapy or supplementary therapy for skin lesions accompanied by exudate and located in close proximity to intertriginous areas. Tannins solutions containing synthetic tannins are available in the form of solutions that may be used for partial and whole-body bathing, washing, and wrapping [(28)].

Dilute bleach bath:

Bleach baths are frequently recommended due to the fact that they are affordable, reasonably safe, and readily available. In contrast to other therapies, bleach baths are multi-step procedures that include many steps: a water bath, exposure to bleach during the bath, and administration of emollients and/or topical anti-inflammatory medications following the bath. Each of these three measures may be beneficial in lowering the severity of AD. Bathing in water alone helps moisturize and soothe the skin, as well as remove scale and serum-crust buildup. Anti-staphylococcal and other disinfection properties of bleach have been hypothesized [(29)]. Bleach and water bath interventions had no discernible effect on S. aureus epidermal colonization or density, according to research. These findings are surprising, given that AD exacerbations are linked to higher levels of epidermal S. aureus density, and bleach baths are thought to reduce AD severity by acting as an antibacterial [(29)].

5. Third-line therapy: systemic treatment:

I. Systemic immunomodulatory agents:

These drugs might be considered for AD patients whose local treatment has not improved their skin condition: treatment options include cyclosporine A, corticosteroids, azathioprine, methotrexate, phototherapy and mycophenolate mofetil [(30)]. In people with severe persistent AD, Cyclosporine A (CsA) is the first-line of treatment. Only in the most severe cases of AD should it be considered for usage in children and adolescents. Individual cohort and randomized controlled trials data are used to make recommendations for use in children [(31)].

There are fewer side effects from cyclosporine A, such as swollen lymph nodes or itching; it also helps with sleep. Start with 2.5–3.5 mg/kg body weight/day in two separate doses; do not exceed 5 mg/kg body weight/day after that. After the skin lesions have improved, it is suggested that the CsA dose be decreased by 0.5–1.0 mg/kg b.w./day every 2 weeks. In as little as 2–6 weeks after starting CsA treatment, patients will notice a reduction in itch and skin inflammation [(1)].

MTX, AZA, and MMF can be used in adult patients with AD off-label if CsA is ineffective or if there are contraindications to its usage. Unfortunately, there aren't nearly enough randomized, double-blind, placebo-controlled clinical trials in children and adolescents with AD to make reliable conclusions on their effectiveness [(32)].

When used off-label, azathioprine has been used to treat a variety of skin disorders, including a severe form of AD that did not respond well to other medications. AZA's precise mechanism of action in AD is still a mystery. AZA has been shown in in vitro tests to have a toxic and suppressive effect on Langerhans cells. Because of its method of action, the therapeutic effect may be delayed with AZA in treating AD, despite its high efficacy [(32)].

For some individuals, it may take up to 12 weeks or longer before they get the full benefits of their treatment. AZA dosages of 1–3 mg/kg b.w./day are advised. An enzyme involved in 6 mercaptopurine metabolism should be tested prior to starting medication because persons with an inherited impairment are at greater risk of myelosuppression. Mutations in the TPMT gene can impact how well AZA works and how safe it is. A better understanding of TPMT levels allows for more precise dosing and less bone marrow injury [(33)].

II. Oral antihistaminics:

Currently, only hydroxyzine is suggested among first-generation antihistamines for people with AD who have sleep disturbances or difficulty falling asleep due to high levels of histamine in the CNS' subcortical areas [(34)].

According to the American Academy of Dermatology's recommendations, antihistaminic action may hasten the restoration of the damaged epidermal barrier. KERATIN 1/10, filaggrin, and loricrin expression decreased significantly when histamine was added to keratinocyte cultures (in vitro), as demonstrated. Patients with AD and conjunctivitis or allergic rhinitis benefit greatly from second-generation antihistamines. Histamine H1 receptor selectivity, half-life and hydrophilic AH2 structure all help these medications work better and be safer [(35)].

Table (2): Guideline grading adapted from AAD guidelines for systemic and topical treatment of atopic dermatitis [(12)].

		Strength of recommendation grading system			
		2006-2014		2015	
Medication type	**Medication**	**Liberal model***	**Conservative Model#**	**Liberal Model***	**Conservative Model#**
Topical	Corticosteroids	A	A	A	A
	Calcineurin inhibitors	A	A	A	A
	Antimicrobials and antiseptics in infected AD (mupirocin only)	B	B	B	B
	Antimicrobials other than recommended	F	**F**	F	F
	Antihistamines	No mention	No mention	B	B
Systemic	Cyclosporine	A	A	B	B
	Azathioprine	B	B	B	B
	Methotrexate	Outside of scope	Outside of scope	B	B
	Mycophenolate mofetil	C	C	C	C
	Interferon γ	A	A	B	B
	Corticosteroids	C	F	B	F
	Antimicrobials	A	F	A	F
	Sedating antihistamines	C	C	C	C
	Nonsedating antihistamines	F	F	F	F
	Antivirals in eczema herpeticum	No mention	No mention	C	C

AAD, American Academy of Dermatology; *AD,* atopic dermatitis.

*Model includes assumption that all systemic corticosteroids were used for acute exacerbations and systemic antimicrobials were used only for objectively confirmed infected AD.

#Model includes assumption that all systemic corticosteroids were not used for acute exacerbations and systemic antimicrobials were not used only for objectively confirmed clinically infected AD.

6. Phototherapy:

UVA (320–400 nm), UVA plus psoralens (5-methoxypsoralen, 8methoxypsoralen – photosensitizing chemicals administered orally 1 or 2 hours before to irradiation), UVA with UVB (UVAB), and UVA1 (340–400 nm) are all useful in the treatment of AD. Due to a scarcity of comparative studies, there is no proof that one strategy is superior to another in terms of effectiveness. All we know is that natural sunlight is less effective than artificial light sources when compared to each other. UVB phototherapy is the most often utilized treatment modality **(35).** Patients with moderate-to-severe illness who have failed to respond to topical medication should be considered for treatment with phototherapy or systemic immunomodulatory drugs. When it comes to phototherapy for AD, narrowband UVB (wavelength = 311 nm) is the most widely used variety (it's normally delivered 2 to 3 times per week). Narrow-band in the case of AD, ultraviolet B radiation is a safe choice that can provide relief from the indications and symptoms **(35).**

7. Specific immunotherapy:

Specific allergen immunotherapy (AIT) is the only approach of treating AD that is proven to be effective. Allergic immunotherapy is appropriate in patients with (AD) when previous treatment has failed and there is established IgE-mediated allergy to allergens in the environment **(31).** For patients who have allergy symptoms to perennial or seasonal aeroallergens, as well as those who are allergic to a single allergen group, we can claim that AIT in AD has a high clinical efficacy in treatment. So far, patients with allergies to dust mites and pollen who utilize AIT have had the best overall clinical outcomes **(32).**

The desensitization of AD patients with other comorbid AD, such as allergic rhinitis or moderate asthma, is not contraindicated. AIT's efficacy is largely determined on how well patients are classified, how well the vaccine's composition is chosen, and how well it is handled. As for vaccine composition, it should be determined by medical history, physical examination, and a complete allergological diagnosis, including skin prick tests and measurements of specific IgE in serum, among other things**.** The efficacy of AIT in patients with polyvalent allergies depends on the right combination of vaccinations and the optimal administration schedule. Patients with AD should not only have skin prick tests when planning AIT, but they should also have their specific IgE levels to allergens assessed as well **(32)**.

Biological treatments:

Due to its unique therapeutic strategy and promise to improve the treatment of AD, dupilumab has received FDA approval for use in adults with moderate-to-severe disease in the EU and US **(33)**.

Dupilumab is prescribed in doses of 600 mg initially (two injections of 300 mg each at distinct sites), followed by 300 mg every two weeks (q2w), with injection sites rotated. It can be used on its own or in conjunction with TCS to get the desired results **(34).** Once the 16-week treatment period has passed with no response, discontinuation of dupilumab should be considered, however for certain individuals who have had an initial partial response, treatment beyond the 16-week mark may be beneficial **(35).** Lyon et al summarize the management of atopic dermatitis by the following **(figure 1)**

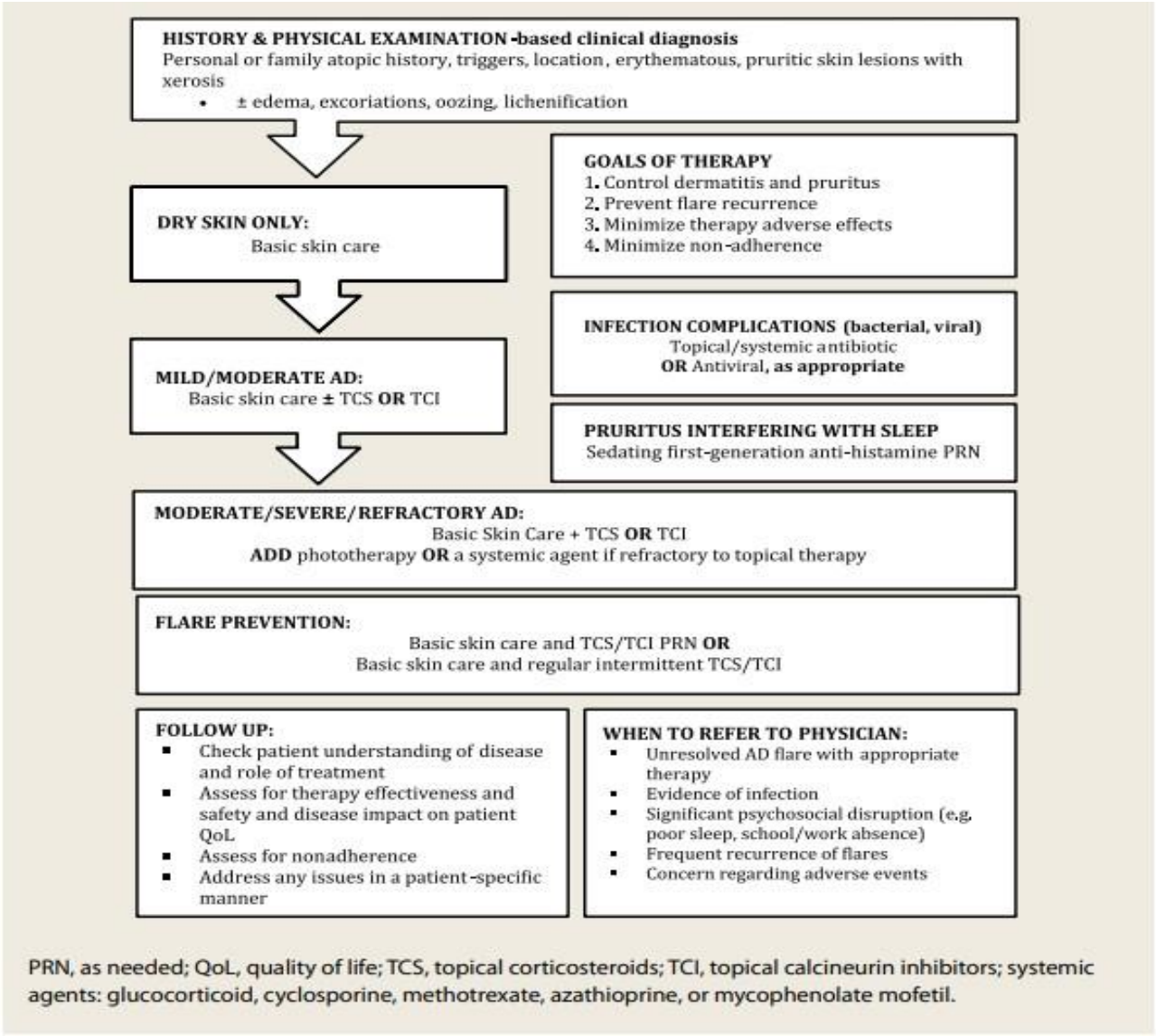

Figure (1): Algorithm summary of atopic dermatitis management [(35)].

CONCLUSION

Clearly there remains a need to find more potent topical agents with fewer side effects. The most gratifying advances in AD therapy have come from better understanding of immune and inflammatory mechanisms.

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