

# The Care Triangle: Determining the Gaps in the Management of Atopic Dermatitis

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**Background:** Atopic dermatitis (AD) is a chronic, relapsing, intensely pruritic dermatosis that usually affects infants, children, and young adults. The treatment of AD entails an individualized regimen that depends on the age of the patient, the stage and variety of lesions present, the sites and extent of involvement, the presence of infection, and the previous response to treatment.

**Objectives:** To identify the evidence surrounding potential strategies for closing these gaps—ultimately improving the quality of care, the care process itself, and patient outcomes—and to encourage discussions that help develop tools to bridge the gap between suggested therapy and what is done by the patient.

**Methods:** Review of the literature including searches on *PubMed Central* and *Medline* and in seminal dermatology texts.

**Results:** There are several disconnections between the evidence-based guidelines in the management of AD, what the individual dermatologist recommends, and what the patient does.

**Conclusion:** Applying the concept of the care triangle requires a balance of evidence-based medicine, the physician's experiences and the patient's needs and expectations in the decisions surrounding appropriate management of the disease.

**Contexte:** La dermatite atopique (DA) est une dermatose chronique, récidivante, fortement prurigineuse, qui touche les nourrissons, les enfants, et les jeunes adultes. Le traitement de la DA appelle un plan de soins individualisé, établi en fonction de l'âge du patient; du type de lésions, de leur stade, de leur siège, et de leur étendue; de la présence d'infection; et de la réaction à des traitements antérieurs.

**Objectifs:** L'étude visait à trouver des données probantes sur des stratégies qui permettraient de colmater les lacunes—et d'améliorer par le fait même la qualité des soins, le processus de soins lui-même, ainsi que les résultats cliniques—et à susciter des discussions sur l'élaboration d'outils qui combleraient le fossé entre les traitements suggérés et les actions des patients.

**Méthode:** L'étude consistait en un examen de la documentation, notamment en des recherches dans les bases de données *PubMed Central* et *Medline* et dans des textes de fond en dermatologie.

**Résultats:** Il existe plusieurs écarts entre les lignes directrices fondées sur des données probantes en ce qui concerne la prise en charge de la DA, les recommandations des dermatologues pris individuellement, et les actions des patients.

**Conclusion:** L'application du concept du triangle de soins exige un équilibre entre la médecine fondée sur des données probantes, l'expérience des médecins et les besoins, et les espérances des patients dans le processus de décision concernant la prise en charge de la maladie.

ATOPIC DERMATITIS (AD) is a chronic, relapsing, intensely pruritic dermatosis that usually affects infants, children, and young adults and in most cases is

associated with a personal or family history of atopy (seasonal rhinitis, asthma, or eczema). Skin involvement ranges from acute, weeping, and crusted areas of eczema to papular lesions or lichenified plaques. Not only is the epidemiology of AD unclear, the pathogenesis is also complicated and multifactorial. The treatment of AD involves an individualized regimen that depends on the age of the patient, the stage and variety of lesions present (acute, subacute, chronic, lichenified, or a mixture of these), the sites and extent of involvement, the presence of infection, and the previous response to treatment. It also involves a willingness on the part of patients and parents of children with AD to use the recommended therapy. The

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decision making for selecting therapy for the doctor may be influenced by many factors that are not based on evidence. The patient's needs and experience are variable and are influenced by past experiences of treatment and the patient's personality, expectations, cultural context, and risk aversion profile. Our aim is to encourage discussions that help develop tools to bridge the gap between suggested therapy and what is really done by the patient.

### The Care Triangle

The appropriate treatment of disease requires a balance of evidence-based medicine (EBM), the physician's experiences, and the patient's needs and expectations (Figure 1). This concept has been previously coined the *treatment triangle*.<sup>1</sup> This approach is a response to the clinical paradigm modernization to concordant care. As patients are becoming more actively involved in the management of their disease, the profession is obliged to work together with them to optimize outcomes. The objective of this article is to expand on the treatment triangle and fill current gaps in the management of AD. We hope to identify the evidence surrounding potential strategies for closing these gaps—ultimately improving the quality of care and patient outcomes.

#### Evidence-Based Medicine

The concept of EBM was first introduced in 1990<sup>2</sup> and has informed guidelines in the management of many common dermatologic diseases, including AD. EBM forms the cornerstone of our analysis in this section. In the following section, our assessment of the treatment triangle demonstrates gaps in knowledge translation from the evidence to

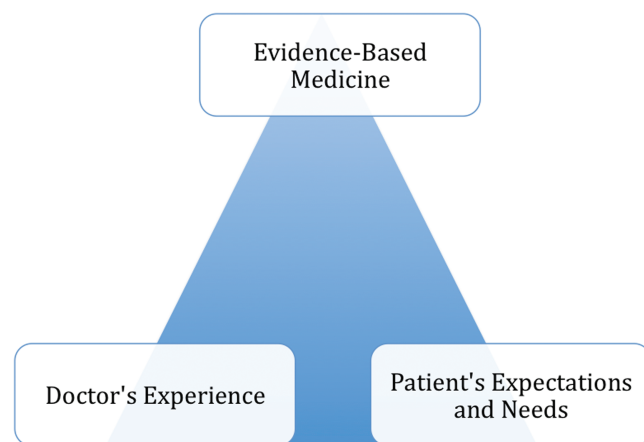


Figure 1. The care triangle.

routine clinical practice. Table 1 shows the level of evidence criteria used in making this classification.<sup>3</sup>

#### Emollients (Level B)

Although there is no current evidence to doubt the belief that regular emollient use is beneficial for the treatment of AD, there is no clear evidence of the benefit of emollients in randomized, controlled trials (RCTs).<sup>4</sup> The paucity of good clinical trial evidence does not reflect the importance of emollient therapy for the treatment of AD, and future trials are warranted to determine the impact of emollient use in the management of AD.

Advances in the understanding of the epidermal barrier and subsequently the role of filaggrin, ceramides, cholesterol, and free fatty acids in the skin barrier have enabled the development of a new generation of barrier repair and maintenance products. Degradation of the lipids results in compromised epidermal barrier function through trans-epidermal water loss.<sup>4</sup> Low filaggrin activity due to genetic mutation has been shown to result in dry, scaly skin and increased clinical severity of AD.<sup>5</sup> Ceramide-based moisturizers in particular have been shown to give equivalent benefit in AD as is achieved by mild- to moderate-potency topical corticosteroids and topical pimecrolimus.<sup>6</sup>

#### Topical Corticosteroids (Level A)

Although topical steroids have been a mainstay of treatment of AD for decades, surprisingly little work has been done to understand how best to use them for the long-term management of AD. Topical corticosteroids are available in creams, ointments, lotions, gels, sprays, shampoos, and foam vehicles. The choice of vehicle used can substantially affect the individual corticosteroid's clinical action, potency, and acceptability to the patient.<sup>7</sup> Although ointments traditionally have been thought to be more potent than creams, other characteristics of the vehicle or the presence of specific excipients can modify absorption.

There is Level C evidence for wet wraps as an adjunctive therapy in the management of severe AD and/or disease that is refractory to standard topical therapies.<sup>3</sup>

Table 1. Levels of Evidence

|         |                                   |
|---------|-----------------------------------|
| Level A | Double-blind study                |
| Level B | Clinical trial $\geq$ 20 subjects |
| Level C | Clinical trial $<$ 20 subjects    |
| Level D | Series $\geq$ 5 subjects          |
| Level E | Anecdotal case reports            |



They may increase skin hydration, which is cornerstone management of AD, as well as serve as a mechanical barrier and an occlusive layer to promote penetration of topical steroids.

There is no clear RCT evidence to support once- versus twice-daily administration.<sup>8</sup> However, research demonstrates that the extent and duration of topical corticosteroid activity in human skin are influenced by the time of day of application.<sup>8,9</sup> The authors concluded that once-a-day dosing regimen in the later afternoon was sufficient for dermatologic therapy.<sup>9</sup> As such, some dermatologists recommend one application in the late afternoon for optimal efficacy.

There is good RCT evidence suggesting that twice-weekly application of potent topical steroids to stabilize AD can decrease the number of flares in children and adults,<sup>10–12</sup> although the long-term safety of this practice has not been studied. Dermatologists must consider the non-RCT evidence from their previous experience before drawing a conclusion on this topic.

#### *Topical Tacrolimus and Pimecrolimus (Level A)*

The evidence is mounting for topical tacrolimus and pimecrolimus in the treatment of AD. Tacrolimus has been shown to be efficacious for moderate to severe AD involving the face and neck as well as the trunk and limbs. Pimecrolimus is indicated for the treatment of mild to moderate AD involving sensitive sites such as the face.<sup>4</sup> New on-label indications exist for twice-weekly topical tacrolimus ointment as preventive or maintenance therapy to prevent flares and to prolong flare-free intervals in patients with moderate to severe AD.<sup>13</sup>

As steroid-sparing agents, these products do not cause thinning of the skin.<sup>4</sup> Patients should be counseled on the common side effect of a transient “burning” sensation at the time of application, as well as the small quantity of medication in each tube and the higher cost of treatment.

The cost-effectiveness of the topical calcineurin inhibitors versus the intermittent use of potent topical steroids has also been studied through case analyses. The results indicate that tacrolimus ointment was more cost-effective than high-potency topical corticosteroids (HPTCs) administered in 2-week treatment cycles and similar in cost-effectiveness to 4-week cycles of HPTCs.<sup>14</sup> Although many RCTs demonstrate the safety of these products in the short term, there is some long term data on associations between calcineurin inhibitors and both local and systemic infection as well as skin and internal cancers (eg, lymphomas) which require physicians to counsel their

patients on risks. We are not aware of human evidence having emerged so far to justify the Food and Drug Administration black box warning for these drugs (European regulators have withdrawn these warnings).

#### *Systemic Immunosuppressants (Level A)*

RCT evidence supports the use of systemic immunosuppressants such as prednisone, methotrexate, cyclosporine, and azathioprine in AD.<sup>4</sup> However, these medications are associated with significant side effects and warrant limited use to short- to medium-term use during major disease flare, returning to conventional treatment once control is maintained.

#### *Phototherapy (Level A)*

A review of seven RCT studies on phototherapy and photochemotherapy demonstrated methodological difficulties that impaired interpretation.<sup>15</sup> Light therapy appears to be very effective in comparison with placebo for AD.<sup>15</sup> In acute eczematous flares, ultraviolet A1 (UVA1) appears to be fast and effective, and there does not seem to be a clear advantage to using a high as opposed to a medium dose. In chronic AD, ultraviolet B (UVB) may be more effective, especially narrowband UVB (NB-UVB). The long-term effects of ultraviolet light to young children with AD in terms of melanoma are unknown,<sup>16</sup> and caution should be used when extrapolating evidence based on adults receiving photochemotherapy. There is a known carcinogenic risk with psoralen plus ultraviolet A (PUVA), and a lack of prospective studies in patients treated with NB-UVB constitutes a barrier to the robust assessment of carcinogenic risk of this phototherapy technique.<sup>16</sup> In North America, NB-UVB is the most commonly used form of phototherapy as there is less concern about the long-term risk of developing cutaneous malignancies with its use.

#### **Dermatologist's Experiences**

In many cases, evidence from RCTs supports traditional management strategies; however, some common practices have little or no evidence behind them. We discuss the gaps between the evidence-based approach to managing AD and the dermatologist's experiences here.

#### *Oral Antihistamines*

The role of oral antihistamines is particularly debated in the treatment triangle. Over 20 RCTs have shown no clear

evidence of benefit, even in the largest and longest-running trial.<sup>4</sup> Even when indices such as quality of life and disease-specific indicators such as disease severity scores or itch assessments were included, the results failed to demonstrate significant benefit. Sleep in particular can be problematic in patients with AD. In addition to the damage caused by excoriations, poor-quality sleep can also diminish the quality of life for patients and their families, as well as have a negative effect on motor and cognitive function.<sup>17</sup> For some patients, sedation delivers a good-night's sleep, which might significantly improve quality of life the next day. It might also mean that parents sleep better, which could translate to better care of the child with AD. This area requires further investigation.

The individuality of effect of an antihistamine on any one person or given situation is variable enough to allow us to ignore pooled studies and go on to recommend antihistamines in those contexts or for those patients for whom a potential benefit is obvious or already noted by the patient, physician, or caretaker.

#### *Antibiotic Therapies*

Although few would dispute the benefit of systemic antibiotics in people with overtly clinically infected eczema, the clinical role of bacteria, *Staphylococcus aureus* in particular, in causing inflammatory flares in clinically uninfected eczema is less clear. Clinical experience sometimes shows that resistant AD may not respond well in an acute flare without oral antibiotics even when clinically obvious infection is absent. A systematic review demonstrated no significant difference in global outcome for clinically infected eczema when oral antibiotics were compared to placebo or when topical steroid antibiotic combinations were compared to steroid alone.<sup>18</sup> Although antistaphylococcal agents reduced *S. aureus* numbers in people with clinically uninfected eczema, none of the studies showed any clinical benefit. Their continued use should be questioned in such situations until longer-term studies show clear evidence of clinical benefit. Bleach baths—the addition of antiseptics to bath water (ie, diluted bleach baths)—have been shown to help reduce the number of local skin infections and the need for systemic antibiotics in AD patients with heavily colonized and/or superinfected skin.<sup>3</sup>

#### *Adjunctive Treatments*

With growing patient interest in nonpharmaceutical approaches to treating disease, adjunctive therapies have

been studied. A physician who is not hostile to patients' inquiries about alternate treatments may build better patient rapport. It is not recommended to support treatments and actions that have no evidence of efficacy but rather to tolerate explorations of nonmedical options by patients, such as the following:

- *House dust mite allergens (level A).* Despite the strong circumstantial evidence to suggest that house dust mite allergens may play a part in AD, it is unfortunate that the seven RCTs that have been conducted have methodological difficulties.<sup>19</sup> Future, large-scale pragmatic trials are needed in this area. In the absence of strong clinical evidence, many dermatologists do recommend allergic-impermeable mattresses, pillow covers, regular vacuuming, and deep freezing pillows as the best ways to reduce house dust mites.
- *Nutritional considerations.* There is little evidence to support the use of diets free of milk or eggs in patients with AD and no evidence to support an elemental or few-foods diet.<sup>20</sup> Studies on the use of probiotics (level A) for AD demonstrate conflicting evidence.<sup>21–23</sup>
- *Complementary and alternative medicine.* Chinese herbal medicines have also long been used in the adjunctive management of AD. Four RCTs have been done that reveal conflicting results and side effects warranting further, large-scale studies.<sup>24</sup>
- *Detergent use.* Evidence from an RCT did not support the belief that washing detergents containing enzymes have a provoking effect on AD in comparison with detergents without enzymes.<sup>25</sup> Likewise, water softening has not demonstrated significant clinical improvement in AD.<sup>26</sup>
- *Skin cleanser type.* Although the type of skin cleanser used does not have any evidence behind it, many dermatologists have favorite recommendations to make. Ideally, the cleanser of choice should be nonsensitizing, nonirritating, hydrating, and well liked by the patient.

#### **Patient's Needs and Expectations**

Despite the accumulating evidence behind various treatment modalities in AD and the dermatologist's personal experience and resultant patient education, it often remains true that the best treatment is the one that the patient will actually use. An acknowledgment of the patient's expectations, needs, and input is paramount to the success of treatment. The quality of the patient-physician relationship is associated with improved patient



compliance.<sup>27</sup> Positive outcomes from incorporating the individual patient's needs and input into the management strategy include increased patient understanding of illness and treatment, adherence, and patient satisfaction.<sup>24</sup> Each encounter requires the dermatologist to use a combination of EBM and personal experience to choose appropriate therapy to suit the patient's needs.

Qualitative studies provide an understanding of what patients with chronic dermatologic conditions desire from their provider. Patients express a desire for hope-giving and open and honest communication from the dermatologist.<sup>27</sup> The subjects also desire an acknowledgment of the social-emotional impact of the disease on themselves and their loved ones.<sup>27</sup>

Patients have also expressed a desire for more disease-specific information to understand the etiology of their disease.<sup>27</sup> Educational strategies useful from the physician's experience include metaphors such as the "barrier function of the skin or 'waterproofing' the skin." Understanding the chronic nature of AD is important, and the need for regular moisturizing when the skin is doing well to try to minimize flare-ups, as well as long-term maintenance therapy, is an important educational component.

Advances in the understanding of atopic dermatitis pathophysiology can help in counselling of affected patients who desire more information about their disease. For instance, the "inside-out" hypothesis, which involves abnormally high numbers of type 2 helper T (Th2) cells, which, on interaction with an allergen produce pro-inflammatory cytokines (interleukins 4, 5, and 13) and antigen specific IgE is one mechanism.<sup>28</sup> Another hypothesis is the "outside-in" view which theorizes that the skin barrier is a dynamic interface with a hostile outside environment and that genetic defects compromise the skin barrier, leading to AD through Th2 cell proliferation and release of Th2 cytokines.<sup>29</sup>

Depending on the patient's level of understanding, providing disease-specific information to enhance understanding of the etiology and management will lead to a higher concordance of care. Most patients can grasp the message of inside-out and outside-in concepts and may use emollients more regularly.

Therapy selection must take into account the patient's needs and input to optimize patient adherence and outcomes.<sup>30</sup> Studies evaluating adherence to topical medications for common dermatologic conditions show low adherence rates in one-third of patients.<sup>30–32</sup> Between 30 and 80% of patients report being nonadherent at some stage of their dermatologic treatment.<sup>33</sup>

### Patient Considerations

The following are a list of patient considerations that the healthcare provider must take into account when selecting the optimal therapy for an individual patient.

- *Economic.* Patients of lower socioeconomic status are more likely to never fill a prescription or not return for follow-up visits.<sup>33</sup> Other indicators of financial constraints include decreasing the frequency or quantity of use to extend the time between refills.<sup>33</sup>
- *Demographics.* Conflicting evidence exists on the association between gender and adherence; some studies show that females have improved adherence to treatment of skin conditions,<sup>34</sup> whereas others reveal mixed findings.<sup>35,36</sup> Patients are less compliant when a treatment interferes with their lifestyle or ability to carry out daily activities.<sup>33,37–39</sup> Geriatric limitations may include poor motivation and understanding of the prescribed treatment, vision problems, the presence of a coincident handicap, and a lack of reliable transportation.<sup>30</sup> Similarly, the pediatric population faces barriers such as requiring additional third-party understanding of the treatment regimen and reliability to carry it out.<sup>30</sup>
- *Vehicle.* Intolerable adverse effects of the medication, such as staining of skin or clothing, smelling, stinging, or burning, are factors that lead to noncompliance with topical treatment.<sup>30</sup> In one study, patients using either a light gel or an ointment demonstrated greater adherence to the gel than the ointment and that the use of ointments or more potent topical steroids as a first choice may be counterproductive.<sup>30</sup>
- *Frequency.* Reduced frequency of application for prescribed medications has been shown to improve patient adherence.<sup>38</sup> Dermatologists should consider single-dose therapy or combination therapy when available.
- *Speed of response to therapy.* It appears that rapid improvement in the condition encourages patients to have faith and continue the recommended therapy. The longer the chronicity of the disease, the worse the patient adherence to therapy.<sup>27</sup>
- *Health literacy.* Ambiguous and subjective instructions such as "apply sparingly" can result in incorrect use of topical medications, especially in vulnerable populations.<sup>39</sup> Adherence is particularly poor in ethnic minorities and the homeless,<sup>39</sup> who face significant barriers to adherence, including poor access to health care, illiteracy, a high prevalence of psychiatric disease and substance abuse, and a lack of a fixed address that would facilitate follow-up appointments.<sup>39</sup>



### Patient Perceptions

Patients must be counseled on the risks of various treatment options. Miscommunication and misinterpretation of instructions or the risk of side effects can ultimately adversely impact treatment adherence.<sup>40</sup> Although information on side effects is included in an effort to increase medical comprehension and as a component of informed disclosure, patients have been shown to vastly overestimate the intended meaning of risk descriptors and be less likely to take the medication.<sup>40</sup> Common examples include “steroid-phobia” or the black box warnings surrounding topical calcineurin inhibitors. An assessment of the patient’s concerns and exploration of their perceptions is important.

### Future Areas of Research

Research supports the value of patient decision-making aids or shared decision-making programs to help patients come to informed decisions. Studies demonstrate that decision aids are better than usual care in improving patients’ knowledge of, comfort with, and participation in decision making without increasing anxiety.<sup>41</sup> More research is needed in this area, and the development of a validated patient decision-making aid specific to AD would be highly valuable.

### Risk Tolerance

A 2010 study on patient decision-making needs in the treatment of psoriasis revealed that patients desired information on how well and how fast the treatment works, side effects, how long the treatment effects last, the benefits and risks of treatments, availability of the treatment, convenience and ease of use of the treatment, cost, route of administration, and the time required for the treatment, among other needs.<sup>27</sup> These are further areas that could be added in the creation of a risk mitigation/treatment discussion tool.

### Conclusion

The optimal treatment of disease requires a balance between EBM, the physician’s experiences, and the patient’s individual expectations. Physician credibility is challenged only if we hide behind EBM. As a profession, we need not only to recognize the individual sufferer’s needs but also to seek an understanding of the patient’s needs and tailor our recommendations according to our assessment of the specific patient. The paradigm shift

toward concordant care has led to a need to further understand the dynamic relationships within the treatment triangle. Future evaluations of a therapy need to take into account all the parameters discussed above to achieve validity in the real world of the patient. We have identified the current disconnection between the application of expert knowledge and patient desires within the triangle in the current management of AD. To address these gaps, the profession as a whole, including primary and clinical researchers and practicing health care providers, need to work together to optimize outcomes and engage patients in their care.

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