Skin Barrier Repair in the Management of Atopic Dermatitis

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Background

The term “atopy” was first coined by Cooke and Coca in 1923, derived from the Greek word *atopos*, which means out of place and denotes an immune reaction that is “strange or eccentric”. Atopic dermatitis (AD) is a chronic, waxing and waning, often symmetric inflammatory eruption that is characterized by pruritus and xerosis (dry skin). AD frequently emerges in the first few months of life, but its prevalence decreases with increasing age. It has been reported to affect up to 15% of children worldwide\(^1\) and can persist into adulthood. This pathology is probably caused by the interplay of genetic and environmental factors.

Genetic Factors in Atopic Dermatitis

- A strong genetic involvement in AD has been clearly established.
- Linkage analysis studies and the examination of polymorphisms in a number of candidate genes have identified several chromosomal loci and potential genes as possible susceptibility factors.
- The genetic variants in these loci and genes are postulated to be involved in
  - immunoglobulin E (IgE) antibody production
  - regulation of the immune response in the skin and mucosa
  - epidermal barrier dysfunction, via modulation of epidermal maturation.

Environmental Factors in Atopic Dermatitis

- Genetic factors alone, however, cannot explain the results of epidemiological studies showing the recent significant increase in prevalence of atopic dermatitis, especially in industrialized countries.
- Therefore, a key role for environmental factors in mediating disease expression has been suggested.
- Allergic sensitization to house dust mites and some foods may play an important etiologic role in some patients.
- However, non-allergic factors may also contribute to the pathophysiology of AD by influencing dysregulation, resulting in disruption of the skin barrier. These include:
  - low environmental humidity level
  - *Staphylococcus aureus* (*S. aureus*) colonization
  - exposure (or the absence of it) to certain microbial factors in early infancy
  - exposure to pollutants, detergents, and other irritants
  - excessive heat.
The epidermis of the skin functions not only as a physical and anatomical barrier, but also as a vast immunological organ.

This barrier constantly protects against the entry of different microbes, allergens, and irritants.

In AD, a dysfunctional skin barrier has been shown to provoke increased trans-epidermal water loss (TEWL), resulting in pronounced cutaneous dehydration.

Such a damaged barrier can allow allergens, microbes, and irritants to penetrate the skin and cause a pro-inflammatory reaction that typically characterizes AD.

The extent of barrier dysfunction strongly correlates with the degree of inflammation within AD lesions.

The stratum corneum (SC) of the skin has been compared to a brick wall, consisting of terminally differentiated keratinocytes (bricks) that are surrounded by a matrix of specialized lipids.

- The major lipids in the SC are:
  - ceramides (50% by mass)
  - cholesterol (25% by mass)
  - fatty acids (10-20% by mass).

- These elements create a barrier that helps to keep water within the body and prevent the entrance of pathogens and allergens.

Emollients
- Emollients soften and soothe the skin.
- They are petroleum based gels.

Options for Management

A range of treatments exist for atopic dermatitis, depending on the severity of the disease.

Non-pharmacological Factors
- Flare-ups of AD can be reduced by:
  - wearing soft cotton clothing
  - washing clothes with mild detergents
  - avoiding the use of fabric softeners
  - controlling the ambient temperature and humidity of the home
  - implementing avoidance measures to decrease exposure to dust mites in sensitized individuals
  - more rarely, avoiding specific foods in sensitized patients. If a food trigger is suspected, it may be useful to consult an allergist.

- It is important to emphasize that no good evidence supports highly restrictive diets, which might have a significant psychological impact and can lead to malnutrition.

- Educational programs have demonstrated significant improvement in AD severity and treatment satisfaction in intervention groups compared with control groups.

Emollients
- There is no strong evidence that emollients improve AD directly.
- However, emollients are widely recommended because they improve the appearance and symptoms of dry skin that is commonly present in AD.
- Studies have shown that emollients may reduce the need for topical steroids and enhance the therapeutic response to them.
- In the absence of good studies showing the superiority of one emollient over another, patient preference should guide their usage.

Topical Corticosteroids
- For several decades, topical corticosteroids have been the mainstay of treatment for AD flare-ups.
- A number of agents are available in various vehicles, potencies, and concentrations.
- Low-potency agents should be used in infants and on sensitive skin areas (e.g., face, neck, groin, and axillae) in order to minimize side-effects, such as skin atrophy, acne, and adverse systemic effects.
- Topical corticosteroids should be used for the shortest duration and at the lowest potency possible, while still allowing good control of flare-ups, in order to minimize adverse effects.

The Impairment of the Barrier Function

- It has been shown that AD patients have reduced levels of the SC lipids (e.g., ceramides).
- This barrier defect affects not only the involved, but also the uninvolved skin, which correlates with a decrease in the ceramide fraction of the SC.
- Furthermore, the epidermal dysfunction in AD may also be attributable to several factors including:
  - an altered enzymatic activity
  - an altered pH of the skin
  - an impaired epidermal differentiation and an abnormal expression of structural proteins involved in the cornification process.
- Genetic abnormalities in protease inhibitor expression and reduced levels of cornified envelope proteins, such as filaggrin, fuel the skin damage seen in eczematoid conditions.
- Stress may also aggravate this barrier dysfunction by the production of endogenous glucocorticoids, which suppress epidermal lipid synthesis.
- The skin barrier is further damaged by exposure to proteases from house dust mites and S. aureus.
- Lastly, the intense itching and extensive scratching that is associated with AD can also be an important factor leading to the disruption of the cutaneous barrier.
Because of the better appreciated role of the skin barrier in AD disease pathogenesis, use of agents that can stabilize epidermal defenses may reduce the current exclusive dependence on topical steroids and immunomodulators. These barrier repair creams do not target inflammation directly, but rather act at an earlier stage in the disease process to normalize the barrier function and reduce pro-inflammatory signaling. This approach could potentially lead to better treatment outcomes with lesser side-effects.

**Options for Management (continued)**

- Conversely, misinformed patients and/or parents demonstrating steroid phobia should be informed that withholding appropriate treatment affects their/their children’s wellbeing and unnecessarily prolongs the course of sometimes debilitating disease.

**Topical Calcineurin Inhibitors (TCIs)**

- TCIs are indicated in the management of
  - mild to moderate AD (pimecrolimus)
  - moderate to severe AD (tacrolimus).
- TCIs inhibit T cell activation and release of cytokines involved in the pro-inflammatory cascade of AD.
- Their side-effects include skin irritation and burning at the start of therapy, but usually subside with time.
- Their long-term safety is unknown and amid rare reports of malignancies they should only be used in patients who are unresponsive or show unacceptable side-effects with classic therapy.

**Oral Antihistamines**

- There has been a lack of evidence supporting the use of sedative or non-sedative antihistamines for the treatment of atopic dermatitis.
- The first generation antihistamines (diphenhydramine and hydroxyzine) are sometimes recommended at night for their sedative effects.

**Antimicrobial Agents**

- Secondary superinfection with *S. aureus* is common and is treated with short courses of antibiotics with anti-staphylococcus coverage.
- Antiseptic baths have been advocated by some experts in those chronically colonized.

**Barrier Repair Creams**

- Given the importance of the dysregulated barrier function in AD, the use of topical agents aimed at accelerating its improvement represents a new therapeutic approach.
- As important as emollients are for the alleviation of AD symptoms, these agents may be ineffective at correcting TEWL and the ceramide deficiency resulting from the defective skin barrier of AD patients.
- The efficacy and tolerability of new ceramide-dominant skin repair creams with a more physiologic 3:1:1 ratio of ceramides, free fatty acids, and cholesterol have been studied in two company sponsored trials.
- In one multicenter, investigator-blinded, randomized pediatric study using Epiceram® skin barrier cream, similar efficacy was demonstrated when compared with the mid-potency steroid fluticasone propionate 0.05%. No significant adverse events were observed in either treatment arms. However, 4 of 59 patients in the barrier group experienced an initial flare-up that required short-term fluticasone cream.
- Epiceram®, a steroid-free, lipid-based barrier repair cream was approved by Health Canada in September 2009 and is only available by prescription. Use is indicated for AD patients ≥6 months of age.
- Studies on concomitant use of both topical steroids and skin barrier repair creams are not yet available.

**Conclusion**

Because of the better appreciated role of the skin barrier in AD disease pathogenesis, use of agents that can stabilize epidermal defenses may reduce the current exclusive dependence on topical steroids and immunomodulators. These barrier repair creams do not target inflammation directly, but rather act at an earlier stage in the disease process to normalize the barrier function and reduce pro-inflammatory signaling. This approach could potentially lead to better treatment outcomes with lesser side-effects.

**References**

Head Lice: A Review of Topical Therapies and Rising Pediculicidal Resistance

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Introduction

Head lice infestations (Pediculus capitis) are a worldwide problem with prevalence estimates typically ranging between 1-3% in elementary school aged children.1,2 Although this obligate parasite is a nuisance, infestation does not pose a health risk. Infestations tend to occur more frequently in females,3 and less frequently in black children,4 as it may be more difficult for lice to grasp their oval-shaped hair shafts. It is not associated with poor hygiene. Infestation occurs across all levels of society, but occurs more frequently under conditions of overcrowding. Recent evidence suggests increasing frequency of topical treatment failure may be related to a growing resistance to the neurotoxic pediculicides that have been the first-line treatment for the last 40 years.5 Herein, we will review the current topical treatment options, including newer non-pediculicidal options.

Overview of Facts on Lice

- *Pediculus humanus capitis* (the head louse) is a 2-4 mm blood sucking, wingless insect.
- A louse cannot jump, but rather has 6 legs adapted for crawling along hairs at 23 cm per minute.6
- A louse will feed every 3-6 hours.
- Prior to feeding, the louse injects saliva into the skin.
- The life span is approximately 4 weeks and the female lays 6-8 eggs per day.
- Eggs hatch in 8 days, leaving their shell (“nit”) cemented to the base of the hair.
- Head lice spread by head contact, shared fabrics, shared combs, and other fomites that are commonly in contact with the scalp and hair.
- A louse can survive 2-3 days away from a human host.
- Pets are not vectors.

Diagnosis and Symptoms

Many affected individuals report no symptoms, but the most commonly reported symptom is scalp pruritus.8 The pruritus is thought to be caused by hypersensitivity to the louse saliva that is injected into the scalp during feeding, but the itching often does not begin until 1-4 weeks after infestation. Although any part of the scalp may be colonized, there seems to be a predilection for the nape of the neck and post-auricular areas.

Skin Findings

- Often there are no significant findings on the skin.
- Pruritic, papular lesions may be found at the nape of the neck.
- There may be excoriations on the scalp.
- Secondary staphylococcal infection is possible.
- Possible enlargement of cervical / nuchal lymph nodes.

Hair Findings

- True infestation is confirmed by the presence of live adult lice or nymphs (hatched immature lice) present on the scalp with nits.
- The presence of nits alone does not confirm infestation, as an empty nit can remain cemented to a hair even after the infestation has cleared.
- The distance of the nit from the scalp can be a clue to the duration of the infestation, as it moves with the hair away from the scalp when hair grows.
- A nit within 0.6 mm of the scalp is usually a viable egg. Diagnosis is best made by wet or dry combing the scalp with a fine-toothed nit comb with teeth spaced 0.2 mm apart. One study comparing wet combing with visual inspection found that wet combing accurately diagnosed infestation 90.5% of the time, as compared to 28.6% with visual inspection.2

Directions for Detection by Wet Combing9

- Saturate hair with a conditioner.
- Remove tangles with a regular comb.
- With the nit comb against the scalp, comb to the end of the hair.
- Check the comb for lice after each pull by visual inspection and by cleaning the comb with a tissue and inspecting the contents.
- Dispose of the tissue in a plastic bag.
- Comb the entire scalp at least 5 times.
- Seal the plastic bag and dispose of it.
- If infestation is confirmed, rinse off all conditioner prior to treatment.
Traditionally, topical pediculicides have been the mainstay in the initial treatment of pediculosis. They are widely available without a prescription, which has contributed to the difficulty in gathering data on the true prevalence of infestation. Easy access and improper use has likely contributed to the significant resistance that has developed against topical pediculicides. Knockdown resistance (kdr) is a heritable insensitivity to dichlorodiphenyltrichloroethane (DDT), the pyrethrins, and the pyrethroids. A recent study examining lice collected in Quebec, Ontario, and British Columbia found the allele for resistance present in 97.1% of the 274 lice sampled. These findings suggest that a significant resistance to the traditional first-line treatment options exists within Canada.

### Treatment Options

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<th>Method</th>
<th>Treatment</th>
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| Topical Non-pediculicides | Isopropyl myristate 50% rinse      | • 30-120 mL of solution is applied to dry hair and scalp (especially nape of the neck); leave for 10 minutes  
• Combs wet hair with nit comb and wash with shampoo | • Works by dissolving the outer layer of the exoskeleton of a louse  
• Resistance less likely due to mechanical mechanism  
• 2 applications usually necessary 7-10 days apart  
• Approved for use in patients ≥2 years of age  
• May cause erythema, burning, and dry scalp¹⁰ |
| Herbal remedy (HairClean 1-2-3) |                                    | • Apply product to scalp and hair; leave for 15 minutes before rinsing  
• Applied 3 times with 5-day intervals between applications | • Herbal product containing anise, coconut, ylang ylang oil, and isopropyl alcohol  
• Suggested mechanism is to invoke a “flee response” by creating an undesirable environment for the louse⁹  
• One manufacturer sponsored study in Israel found similar effectiveness (92%) when compared with pediculicide containing permethrin, malathion, and piperonyl butoxide¹¹ |
| Topical Pediculicides | Permethrin cream (1% or 5%)       | • Wash hair with conditioner-free shampoo and towel dry  
• Apply product to scalp and hair for 10 minutes before rinsing (25 mL)  
• Combs wet hair with nit comb  
• Repeat in 7 days | • Synthetic pyrethroid, neurotoxic to lice, but low neurotoxicity in humans  
• 1% preparation is available OTC  
• Not ovicidal, therefore requires retreatment 7-10 days later  
• Approved for use in patients >2 years of age  
• May cause itching or burning of the scalp |
|                         | Pyrethrin 0.33% + Piperonyl butoxide 4% | • Apply product to dry hair for 10 minutes, then add water to form lather  
• Rinse, do not use conditioner  
• Repeat in 7 days | • Made from chrysanthemum extract, neurotoxic to lice but low neurotoxicity in humans  
• Avoid if there is a known chrysanthemum or ragweed allergy  
• Approved for use in patients >2 years of age  
• May cause itching or burning of the scalp |
|                         | Lindane (1% gamma benzene hexachloride) | • Apply product to dry hair that is free of conditioner, gel or hairspray  
• Rub into hair and scalp until wet and leave in place for 4 minutes  
• Rinse, being careful not to spread the product to other body sites | • Organophosphate, neurotoxic to lice and humans  
• Second-line treatment due to the risk of toxicity, which can lead to seizures¹²  
• Contraindicated in patients <2 years of age, pregnancy, breastfeeding, and in patients with a history of seizures |

**Table 1:** Topical treatment options for head lice⁹-¹³

### Management

Traditionally, topical pediculicides have been the mainstay in the initial treatment of pediculosis. They are widely available without a prescription, which has contributed to the difficulty in gathering data on the true prevalence of infestation. Easy access and improper use has likely contributed to the significant resistance that has developed against topical pediculicides. Knockdown resistance (kdr) is a heritable insensitivity to dichlorodiphenyltrichloroethane (DDT), the pyrethrins, and the pyrethroids. A recent study examining lice collected in Quebec, Ontario, and British Columbia found the allele for resistance present in 97.1% of the 274 lice sampled. These findings suggest that a significant resistance to the traditional first-line treatment options exists within Canada.
In recognition of the developing resistance, there has been an increased interest within Canada to explore effective non-pediculicidal options. A recent study found the efficacy of isopropyl myristate 50% to be significantly higher (57%) than the standard treatment with pyrethrin 0.33% + piperonyl butoxide 4%.\textsuperscript{10}

While non-pediculicidal therapy may be efficacious against treatment resistant infestations, re-infestation from close contacts and fomite transmission is a common problem. Along with treatment, it is important to decontaminate the environment.

**Environmental Decontamination\textsuperscript{14}**
- Family members and close contacts should be examined and be treated for any infestation.
- Any clothing, linens, combs, toys, and fabrics used by the individuals in the 3 days preceding treatment should be decontaminated.
- Fabrics can be washed in high heat and put in a hot dryer for 20 minutes.
- Items that cannot be washed can be sealed in a plastic bag for 14 days or placed in the freezer for 24 hours.
- Brushes can be soaked in rubbing alcohol for 1 hour.
- Floors and furniture can be cleaned by vacuuming.
- Spraying the home with a pediculicide is not recommended.
- No nit policies at schools are unnecessary.

**Manual Removal**

Some patients may prefer to attempt mechanical treatments prior to topical therapy. Wet combing, as described earlier, can be both diagnostic and therapeutic. To attempt this method the patient should wet comb the entire scalp until no more lice are found every 3-4 days for 3 weeks, or at least 2 weeks after the last adult louse was found.\textsuperscript{14}
Treatment failure is commonly a result of inadequate or improper treatment, resistance, or reinfestation. If environmental decontamination was performed and the treatment was properly administered, then immediate retreatment with a different agent is advised.

**Conclusion**

Head lice infestation is a common problem for children in Canada. The first-line treatment of using topical pediculicides is unfortunately not as effective as it once was because of a heritable resistance that seems to be rising in prevalence. Topical non-pediculicides may be an effective option in the case of failed treatment due to louse resistance to standard treatment.

**References**

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