

# Optimising Treatment of Atopic Dermatitis: The Emollient to Topical Steroid Prescribing Ratio.

## ScientificInsights Report

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Michael J. Cork,<sup>1,2</sup>  
John Timmins,<sup>3</sup> Julie Carr,<sup>2</sup>  
Simon Ward,<sup>1</sup>  
Rachid Tazi-Ahnini,<sup>1</sup>  
Darren Robinson,<sup>1</sup>  
Yiannis Vasilopoulos,<sup>1</sup>  
Catherine Holden,<sup>2</sup>  
Ian Landells<sup>4</sup>, Bonnie L. Kuehl<sup>5</sup>

1. Dermatology – Biomedical Genetics, Division of Genomic Medicine, Royal Hallamshire Hospital, Sheffield, UK S10 2JF  
2. Paediatric Dermatology Clinic, Sheffield; Children's Hospital, Sheffield, S10 2TH  
3. Pharmacy Department, Sheffield; Children's Hospital, Sheffield, S10 2TH  
4. Faculty of Medicine, Memorial University, St. John's, Newfoundland, Canada A1B 3E1  
5. Scientific Insights Consulting Group, Mississauga, Ontario, Canada, L5J 1L3

## Abstract

There is increasing evidence that a genetically determined defective epidermal barrier is a primary event in the development of atopic dermatitis. These genetic changes render the skin barrier more vulnerable to breakdown by environmental agents such as soap, detergents and house dust mites. Emollients result in a partial repair of the skin barrier. The optimal regimen is to replace all soaps and detergents with emollient-based wash products and use large quantities of emollient creams or ointments. With education, 25% of children with mild/moderate atopic dermatitis can be predominantly controlled with emollients.

In this comparative prescribing audit, we have recorded the emollient to topical steroid prescribing ratio in specialist paediatric dermatology clinics in the UK and Canada. In the UK, emollients, topical steroids and topical immunomodulators are prescribed and are reimbursable. In Canada, emollients are not prescribable or reimbursable - reimbursement is restricted to topical corticosteroids and topical immunomodulators.

In the UK paediatric eczema clinic, the emollient to topical steroid prescribing ratio was 14.9 to 1, with the majority of prescriptions being for a moderately potent topical corticosteroid (Eumovate). In contrast, in the paediatric dermatology clinic in Canada, emollients are not prescribed (only recommended), with the majority of prescriptions being for a potent topical corticosteroid (Elocom/Elocon). It appears that dermatologists in Canada use potent, rather than moderately potent topical corticosteroids, because emollients are not reimbursable in Canada. Education, combined with affordable and accessible high-quality products (emollients, topical corticosteroids and topical immunomodulators), are essential to treat atopic dermatitis. Evidence also strongly indicates that the combination of emollients with topical steroids can have a profound steroid sparing effect.

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## Epidemiology of atopic dermatitis

The prevalence of atopic dermatitis (AD) has been rising progressively in developed countries since the 1940's.<sup>1,7</sup> Studies indicate that the prevalence of atopic dermatitis has risen to between 14-24% of the population.<sup>2,3</sup> Epidemiological studies have shown that atopic dermatitis runs in families. If one parent has been affected there is an approximate 20% risk of a child developing the disease and up to a 50% risk if both parents have atopic dermatitis.<sup>7</sup> How can the prevalence of atopic dermatitis have increased so dramatically if it is solely determined genetically? The rise in the prevalence of AD suggests that environmental factors must be crucial in the expression of the disease.<sup>5</sup>

Atopic dermatitis is a multifactorial, heterogenous genetic disease that arises as a result of the interaction of many genes with environmental factors. Different combinations of genetic changes may give rise to the same clinical phenotype of AD. The most likely model for the development of atopic dermatitis is a gene dosage with an environmental

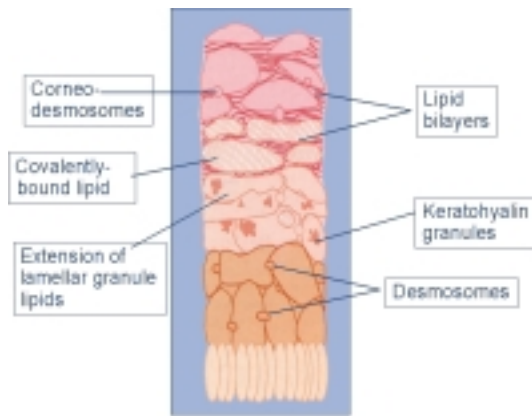
dosage effect. For example, if an individual has a mutation in five major genes for atopic dermatitis, then the environmental factors required to develop the disease may be minimal. If the mutations are only present in two of the genes then a much greater environmental exposure may be required to develop the disease.<sup>8</sup>

Several genes have been associated and/or linked to increased IgE production, with or without atopic dermatitis, including IL-4 and the high affinity IgE receptor.<sup>7</sup> Changes in these genes provide only a partial explanation for the genetic component of atopic dermatitis. Previous studies have found that approximately 30% of index cases with clinically defined atopic dermatitis do not have an elevated IgE.<sup>9</sup> This has also been observed in children, with mild or moderate AD, attending our clinic.<sup>10</sup>

The demonstration that up to 30% of children with clinically defined atopic dermatitis are not immunologically atopic led us to hypothesise that changes in genes which regulate the barrier

function of the skin would be very important in the development of the disease.<sup>11</sup> These genetic changes could render the skin barrier more vulnerable to breakdown by environmental agents such as soap, detergents and house dust mites.

Central to AD is the stratum corneum, which protects the epidermal barrier from water loss and the penetration of irritants and allergens through the skin barrier. This barrier is analogous to a reinforced brick wall, with the corneocytes acting as the bricks, the corneodesmosomes locking the bricks together and the lamellar lipids as a waterproofing cement (Figure 1).



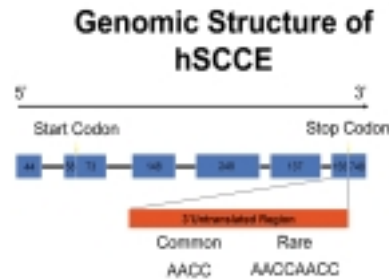
**Figure 1** The skin barrier is located in the lower part of the stratum corneum. The corneodesmosomes lock the corneocytes together and provide the strength of the barrier. The lipid lamellae invaginate in between the corneocytes. The stratum corneum can be visualised rather like a brick wall, with the corneocytes forming the bricks and the lipid lamellae the cement.<sup>9</sup> Using a similar analogy the corneodesmosomes can be thought of as similar to the iron rods that are passed through bricks to give the wall greater strength.

This barrier permits the retention of water within the corneocytes and as a result, they swell up, preventing the formation of cracks between them. This prevents the penetration of irritants and allergens through the skin barrier.<sup>11-13</sup>

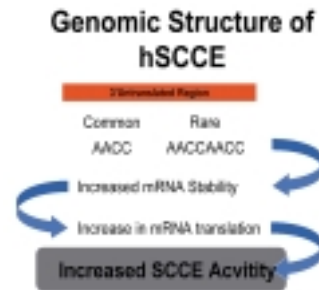
In atopic dermatitis there are several changes in the epidermis which result in the formation of a defective epidermal barrier. One of these changes involves a disturbance in the extruding mechanism of the lamellar lipids and decreased levels of several lipids in eczematous skin.<sup>14</sup> Premature disruption of the corneodesmosomes may also predispose to AD. Corneodesmosomes are broken down by a protease called stratum corneum chymotryptic enzyme (SCCE).<sup>15</sup> This enzyme cleaves the corneodesmosomes and allows the corneocytes to be shed from the surface of the skin. If levels of the SCCE are raised above normal this would lead to an increased proteolysis of corneodesmosomes and premature desquamation of corneocytes. This would result in a thinning of the

stratum corneum which has been observed in non-lesional eczematous skin.<sup>16</sup> High levels of expression of SCCE have also been detected in chronic eczematous lesions.<sup>15</sup>

We have identified a strong association between a genomic AACC insertion in the 3'UTR of the SCCE gene and atopic dermatitis (figure 2).<sup>17</sup> Preliminary function studies of this SCCE genetic variant indicates that it is associated with premature proteolysis of the stratum corneum and a defective skin barrier.<sup>17</sup>



**Figure 2a** There is an insertion (polymorphism) of four bases AACC in the 3' untranslated region of the stratum corneum chymotryptic enzyme gene (SCCE). SCCE is a protease which breaks down corneodesmosomes and reduces the thickness of the stratum corneum. The common form is AACC and the rare form is AACCAACC. The rare form is associated with atopic eczema.

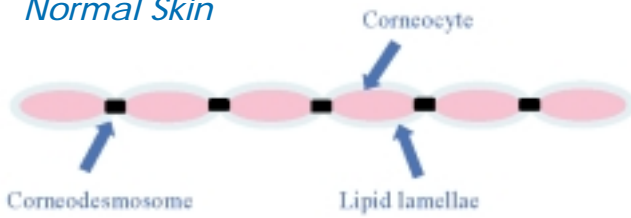


**Figure 2b** Insertions in the 3' untranslated region of genes can alter the stability of mRNA. If the rare form of the SCCE insertion leads to increased SCCE mRNA stability, this will result in higher levels of the SCCE protein. This could then produce excessive breakdown of the skin barrier.

Changes in the epidermal barrier in atopic dermatitis result in a defective barrier with an increased loss of water from the stratum corneum.<sup>18</sup> Treating normal skin with detergents removes some of the epidermal lipids as well as reducing the thickness and number of cell layers in the stratum corneum, resulting in a loss of water from the stratum corneum and a drying of the skin.<sup>19</sup> As a result, the corneocytes shrink and cracks open between them, allowing the penetration of irritants and/or allergens, triggering the development of eczematous lesions<sup>11</sup> (figure 3a-e).

The use of soap on the skin of individuals with AD removes further lipids and thereby exacerbates the defective barrier, promoting the development of eczematous lesions. Atopic individuals therefore react more severely to surfactants<sup>20</sup> and soap products.<sup>16</sup>

## Normal Skin



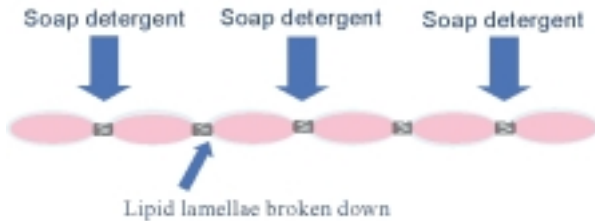
**Figure 3a** The normal skin barrier, lipid lamellae protecting corneocytes and corneodesmosomes. The corneocytes have a high water content and as a result swell up preventing the formation of cracks in between them.

## Genetic Predisposition



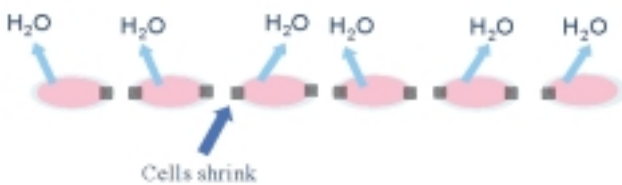
**Figure 3b** In individuals with atopic dermatitis there is a genetic predisposition to premature breakdown of the corneodesmosomes by the skin specific protease stratum corneum chymotryptic enzyme (SCCE).

## Effects of Detergents



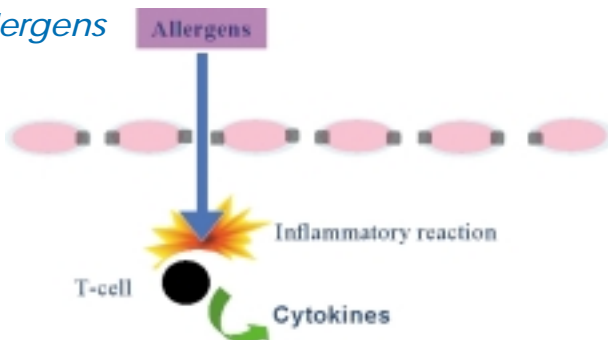
**Figure 3c** Exposure of the genetically predisposed skin to soap and detergents breaks down the lipid lamellae and further weakens the corneodesmosomes. This results in a breakdown of the epidermal barrier.

## Effects of Detergents



**Figure 3d** The corneocytes break apart prematurely and water is lost from the corneocytes. As a result the corneocytes shrink opening cracks between them.

## Allergens



**Figure 3e** Allergens can penetrate through the defective skin barrier, triggering the production of pro-inflammatory cytokines and the development of eczematous lesions.

Using soap also reduces the thickness and number of cell layers in the stratum corneum of normal and atopic individuals, however this effect is more pronounced in those with AD.<sup>16</sup> The non-lesional, unaffected skin of individuals with AD also has a lower threshold for irritation by surfactants and other irritants than normal skin.<sup>21,22</sup>

## Healing The Skin Barrier

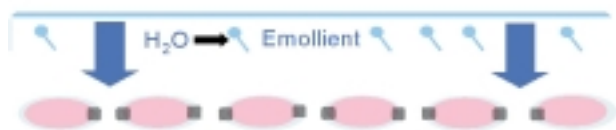
Emollients and moisturizers can help restore the epidermal barrier by providing an oily or occlusive layer over the surface of the stratum corneum, trapping water underneath it that passes back into the horny layer resulting in a reduction in fissuring.<sup>11,22,23</sup> Emollients may also penetrate into the upper layers of the stratum corneum and thereby mimic the barrier effect of the defective lipids (figure 3f-i).<sup>24</sup> The restoration of the epidermal barrier by emollients prevents the penetration of irritants and allergens which could trigger the development of eczematous lesions. To have maximum effect, patients with AD should be treated prophylactically and frequently with complete emollient therapy to produce the maximum rehydration of the stratum corneum, restoring the epidermal barrier and prevention of the penetration of eczema triggering irritants and allergens.<sup>2,25,26</sup> It is essential that no soap-containing products of any kind (including so-called 'moisturising soaps', which contain soap) are used on the skin of children with AD.<sup>18</sup> Figure 3 demonstrates the process of damage caused by detergents and the restoring effects of emollients. Complete emollient therapy<sup>11,25,26</sup> consists of:

- An emollient/moisturizing soap substitute
- An emollient therapeutic bath oil
- An emollient/moisturizing cream/ointment

All of the above clinical, immunological and genetic observations have convinced us that there is a primary defect in the skin barrier which is probably present in all children with AD. In view of the adverse effects of topical corticosteroids (particularly potent and very potent), prescribing large volumes of emollients with proper education regarding their use<sup>17-29</sup> may decrease the quantity and potency of topical steroids that are required to control AD, thereby minimizing the potential for adverse effects.<sup>30</sup> Education is essential as under-utilization of emollients by patients and carers is often observed because they are perceived as "inactive moisturizers." Proper education and demonstration

by a specialist dermatology nurse led to an 89% reduction in the severity of the eczema through an 800% increase in the use of emollients (from 54 to 426g weekly of emollient cream/ointment) and no overall increase in the use of topical steroids (accounting for potency and quantity used).<sup>31,32</sup>

### Effects of Emollients



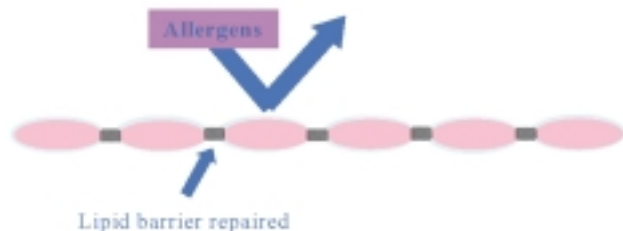
**Figure 3f** A complete emollient therapy regimen avoids the use of all soaps and detergent based products. These are replaced with emollient creams, ointments and emollient wash products. Emollients can produce a partial repair of the defective skin barrier in atopic dermatitis. A layer of oil traps water underneath it.



**Figure 3g** The water trapped under the emollient passes back into the corneocytes and they swell up.



**Figure 3h** The swollen rehydrated corneocytes close the gaps in between themselves. Constituents of emollients may also partially repair the lipid lamellae.



**Figure 3i** The intensive use of complete emollient therapy results in a partial repair of the defective epidermal barrier. As a result it is more difficult for allergens to penetrate through the skin.

There are several clinical trials which demonstrate that the addition of emollients to topical steroids reduce the amount of topical steroid required to control AD.<sup>30</sup> The idea of looking at prescribing ratios as a marker of good prescribing is not new and has been used for inhaled corticosteroids and bronchodilators.<sup>38</sup> In the UK all forms of emollients can be prescribed and are reimbursable (British National

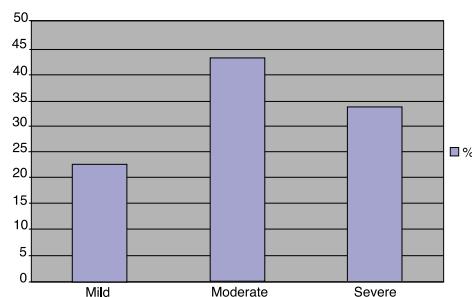
Formulary 2003). In contrast, in Canada, emollient products can only be recommended, not prescribed, by a dermatologist or physician and the patient purchases them without reimbursement. The object of this study was to compare the emollient to topical steroid prescribing ratio in a paediatric dermatology clinic and to track changes each year. This ratio could then be compared with general practitioners in the UK and dermatologists in Canada.

### Methods

#### British arm of study

An audit of the prescribing of emollients and topical corticosteroids was conducted in a paediatric atopic dermatitis clinic at The Sheffield Children's Hospital (SCH) UK. The severity distribution of the children's AD is illustrated in figure 4; 66% of the children had mild to moderate atopic dermatitis. The severity distribution has not altered over the past nine years. The number of patients seen has also not changed significantly (1200 ± 5% in one clinic per week.).

#### Severity Distribution of Atopic Eczema in a Specialist Eczema Clinic



**Figure 4** Illustrates the severity distribution of AD in children at the SCH clinic UK. Approximately 66% of children had mild/moderate AD. The severity distribution has not altered over the past nine years.

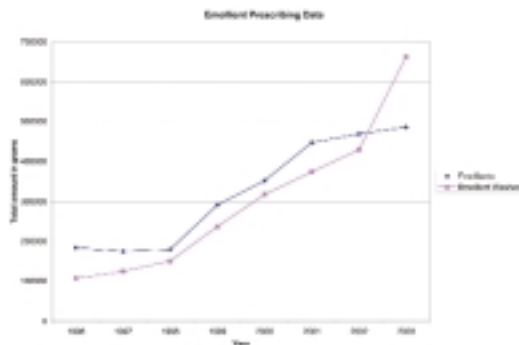
The clinic recorded all of the topical corticosteroids and the total quantity prescribed in grams for each of the past eight years. Data for the topical corticosteroids were subdivided according to potency: mild, moderate, potent, very potent. To determine the amount of emollients prescribed the emollient data was initially gathered into two groups :i) creams and ointments (including Aveeno, Hydromol cream, Hydromol ointment, Ungmentum M, Doublebase, Decubal, Eumobase, Diprobace, Lipobase, Cream E45, Oilatum cream) and; ii) bath, wash and shower emollients (including Oilatum bath oil, Diprobath, Bath E45, Wash E45, Shower E45, Oilatum shower gel, Emulsiderm bath oil, Hydromol bath oil). The data was then pooled. Data was recorded as total number of emollients prescribed in grams/mLs.

## Results

The longitudinal study from the British clinic revealed that over the past five years the prescribing of emollients has risen progressively. This has been accompanied by a fall in the use of potent topical steroids and a rise in the use of moderately potent topical steroids. Figure 5 shows this shift in topical corticosteroid prescribing. Significantly more moderately potent topical corticosteroids were prescribed compared with potent topical corticosteroids. Figure 6 shows the prescribing data for emollients and emollient washes. This data shows the progressive increase in the prescribing of emollients and emollient washes. Prescribing of emollients has increased 4-6 fold over past eight years.



**Figure 5** Demonstrates the shift in topical corticosteroid prescribing over the past five years at the SCH clinic UK. With the increased prescribing of emollients and education around emollient usage more moderately potent topical corticosteroids (predominantly Eumovate) are prescribed than potent topical corticosteroids.



**Figure 6** Shows the prescribing data for emollients (includes creams and ointments) and emollient washes (bath, wash and shower emollients) at the SCH clinic UK. This data shows a progressive increase (4-6-fold) in emollient prescribing over the past eight years.

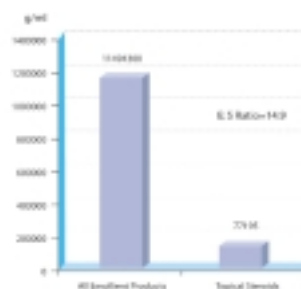
When the emollient to topical corticosteroid data was compared in 2003 the emollient to topical corticosteroid ratio was 14.9 to 1 (1 149 430 g to 77 195 g prescribed). Figure 7a demonstrates the difference between total emollients prescribed and total topical corticosteroids prescribed. Figure 7b breaks the topical steroids down into total amount prescribed by potency. In 1996 we also calculated an emollient to topical steroid prescribing ratio for our clinic and it was 283,080 grams/mls of emollient and 39,470 grams of topical steroid, an emollient to topical steroid ratio of 7 to 1.

## Discussion

There is increasing evidence that a genetically determined defective epidermal barrier is a primary event in the development of AD.<sup>17,34</sup> These genetic changes render the skin barrier more vulnerable to breakdown by environmental agents such as soap, detergents and house dust mites.<sup>34</sup> There has been increasing exposure to these environmental agents over the past 50 years which could explain why there has been such a large increase in the prevalence of AD over this period. Soap and detergents remove lipid from the lipid lamellae and render the defective corneodesmosomes vulnerable to breakdown. As a result water is lost from the corneocytes and they shrink opening up cracks in between them permitting the entry of further irritants and allergens. This triggers the development of eczematous lesions.<sup>11</sup>

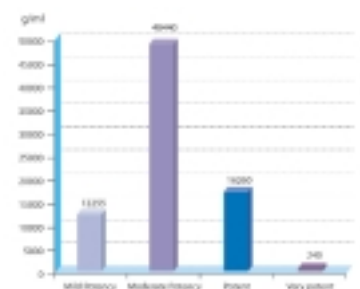
Emollients produce a partial repair of the skin barrier.<sup>11</sup> The optimal regimen is to replace all soaps and detergents with emollient-based wash products and use large quantities of emollient creams or ointments.<sup>11,26,29,35</sup> If large quantities of emollients are used, with intensive education by specialist dermatology nurses, 25% of children with mild/moderate AD can be controlled with emollients most of the time.<sup>32</sup> The combination of emollients with topical steroids can have a profound steroid sparing effect.<sup>30,32</sup> This emollient steroid sparing effect is most marked in children with mild/moderate AD and who do not have a raised IgE.<sup>32,36</sup> In these children only the genetic defects may determine the development of a defective skin barrier.<sup>17</sup>

**Treatment of Atopic Dermatitis: Emollient to Topical Steroid Prescribing Ratio**



**Figure 7a**

**Treatment of Atopic Topical Steroid Potencies**



**Figure 7b**

Compares the emollient to topical corticosteroid prescribing data in total grams prescribed in 2003 at the SCH clinic UK. Figure 7a shows the emollient to topical corticosteroid ratio is 14.9:1. Figure 7b breaks the total topical corticosteroids prescribed in 2003 into potency. This figure demonstrates that significantly more moderately potent topical corticosteroids were prescribed than potent.

The key to the best practice management of AD is a stepped care regimen in order to produce the optimum control with the least adverse effects. The first line management of AD should be the avoidance of irritants and allergens such as soap and detergents and complete emollient therapy regimen.<sup>11,26,31,35</sup> Comparison of treatments between different countries can provide useful information to improve treatment regimens.<sup>37</sup> In this comparative prescribing audit we have recorded the emollient to topical steroid prescribing ratio in specialist paediatric dermatology clinics in the UK and Canada. In the UK, emollients, topical steroids and topical immunomodulators can be prescribed on the National Health system and are reimbursable in the private health system. In Canada, emollients are not prescribable or reimbursable, reimbursement is restricted to topical corticosteroid and topical immunomodulators.

In the UK paediatric eczema clinic the emollient to topical steroid prescribing ratio was 14.9 to 1 (1 149 430 g emollient to 77195 g topical steroids). The majority of the prescriptions were for a moderately potent topical corticosteroid, clobetasone butyrate 0.05% (Eumovate). This was used on the body with 1% hydrocortisone used on the face. In contrast, paediatric dermatology clinics in Canada can recommend emollients but can not prescribe them. Preliminary data from the Canadian dermatology clinics indicate that the predominant topical steroid used on the body was the potent mometasone furoate 0.1% (Elocom/Elocon) rather than the moderately potent (Eumovate) in the UK, with 1% hydrocortisone used on the face. Although emollients are strongly recommended by Canadian dermatologists, utilisation of emollients obtained over the counter appears to be significantly lower than that used in the UK. It appears that dermatologists in Canada have to use potent, rather than moderately potent, topical corticosteroids because emollients are not reimbursable and are underutilized in Canada.

Topical corticosteroids are safe and effective products if they are used according to best practice guidelines.<sup>38</sup> Recent reviews also demonstrate that moderately potent topical corticosteroids, such as Eumovate, can be very safely used on children.<sup>39</sup> The use of large quantities of emollients reduces the quantity and potency of topical steroids required to control AD. The combination of high dose emollients with topical corticosteroids

therefore reduces the chance of adverse effects from the topical steroids. The topical immunomodulators pimecrolimus and tacrolimus are a very important advance in the treatment of AD. Using intensive emollient therapy will also reduce the quantity of pimecrolimus and tacrolimus required to control AD.

In addition to the enhanced safety of a first line intensive emollient treatment of AD, this approach may also produce substantial savings for the National Health services and health insurers. The average price of a high quality emollient cream in Canada and the UK is about 2 cents for one fingertip unit of 0.5g. An amount of 0.5 grams of clobetasone butyrate (Eumovate) costs 43 cents and 0.5 grams of tacrolimus 0.1% (Protopic) costs \$1.70. Reimbursement of the cost of emollients to patients in Canada would, if combined with education provided by dermatologists, improve the control of dermatitis, decrease the adverse effects and produce significant financial savings to the health care providers.

High quality products (emollients, topical corticosteroids, and topical immunomodulators) are essential to treat AD. However, if they are not accompanied by comprehensive education, delivered by dermatologists and specialist dermatology nurses, their effect will be limited. National health services and health insurers must recognise that investment in the time of dermatologists and specialist nurses would improve the quality of care for children with AD and be more cost effective.

## Conclusion:

The use of complete emollient therapy can have a profound steroid sparing effect;

Reimbursement of the cost of emollients would decrease adverse effects, improve control of the eczema and produce cost savings for healthcare providers;

Investment in more education delivered by dermatologists and dermatology nurses is essential to improve the control of atopic dermatitis. This would be a cost effective investment.

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