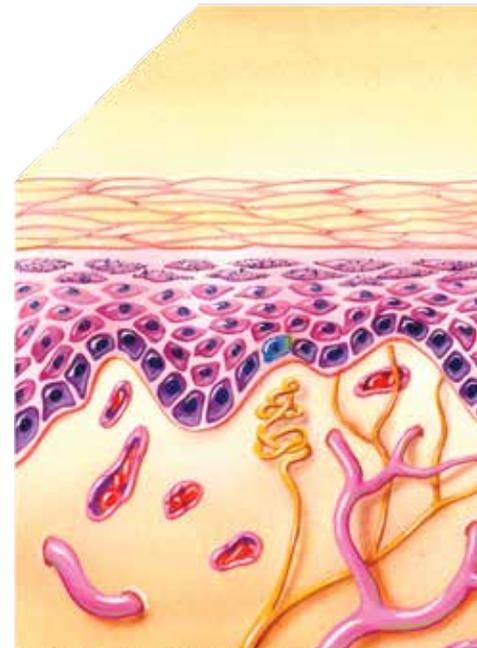




# Adverse effects of topical corticosteroids in paediatric eczema: Australasian consensus statement



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## ABSTRACT

Atopic eczema is a chronic inflammatory disease affecting about 30% of Australian and New Zealand children. Severe eczema costs over AUD 6000/year per child in direct medical, hospital and treatment costs as well as time off work for caregivers and untold distress for the family unit. In addition, it has a negative impact on a child's sleep, education, development and self esteem.

The treatment of atopic eczema is complex and multifaceted but a core component of therapy is to manage the inflammation with topical corticosteroids (TCS). Despite this, TCS are often underutilised by many parents due to corticosteroid phobia and unfounded concerns about their adverse effects. This has led to extended and unnecessary exacerbations of eczema for children.

Contrary to popular perceptions, TCS use in paediatric eczema does not cause atrophy, hypopigmentation, hypertrichosis, osteoporosis, purpura or telangiectasia when used appropriately as per guidelines. In rare cases, prolonged and excessive use of potent TCS has contributed to striae, short-term hypothalamic-pituitary-adrenal axis alteration and ophthalmological disease. TCS use can also exacerbate periorificial rosacea. TCS are very effective treatments for eczema. When they are used to treat active eczema and stopped once the active inflammation has resolved, adverse effects are minimal. TCS should be the cornerstone treatment of atopic eczema in children.

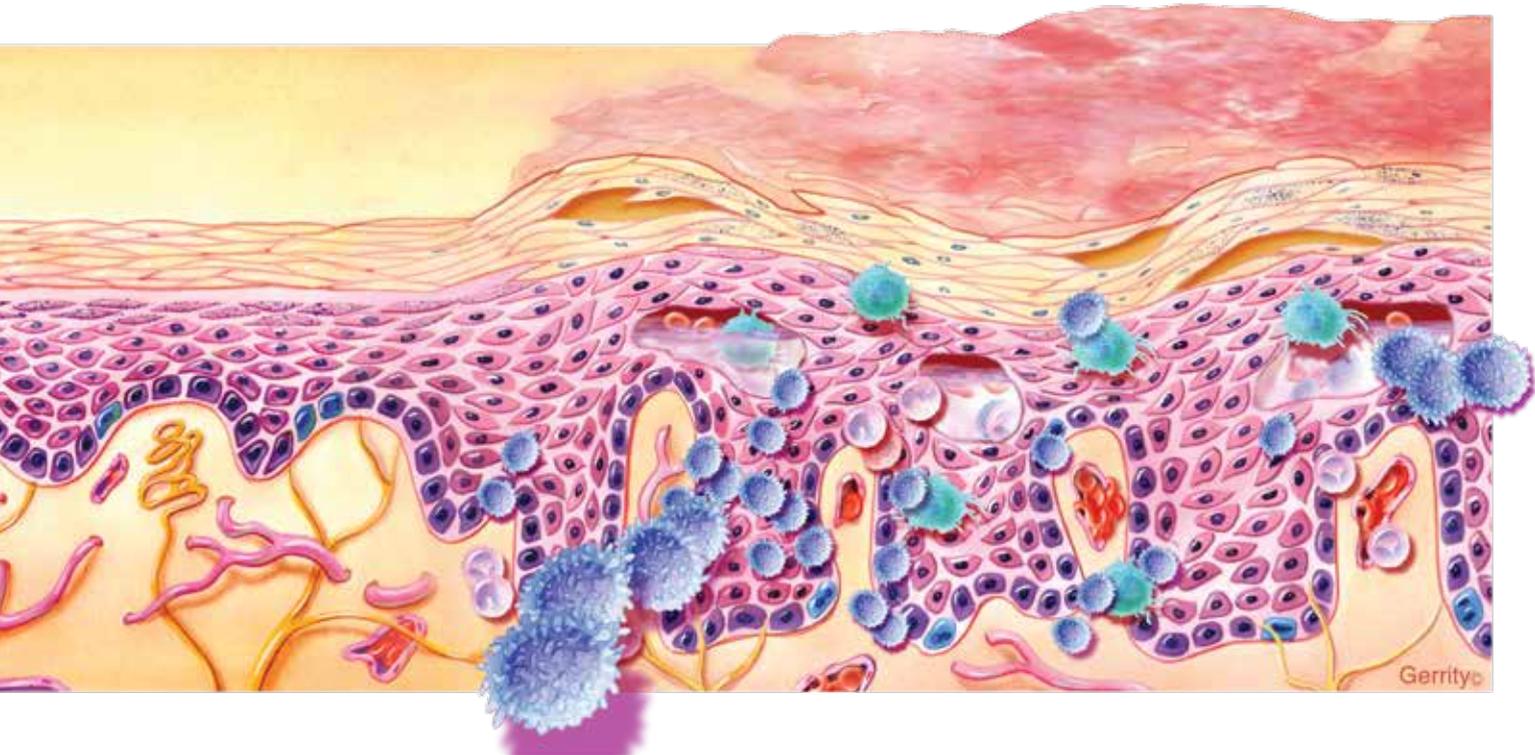
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## Introduction

Atopic dermatitis or eczema is a chronic inflammatory disease of the skin with a relapsing course. It affects 20% of children aged 3–11 years,<sup>1</sup> with a higher incidence in cities in developed countries. The prevalence of eczema in young children in Australia has increased from 10 to 30% over the last 15 years.<sup>2,3</sup>

The financial and social burden of eczema in children is significant. For each child with mild eczema, the direct medical, hospital and treatment costs and the indirect costs such as time off work for caregivers have been estimated to be AUD 1100 per year. For a child with severe eczema, these costs increase to over AUD 6000.<sup>4</sup> The psychological toll on the children and their families is at least as great as that seen in children with diabetes.<sup>5</sup> Therefore, for financial, developmental and emotional reasons, it is of the considerable importance to have an effective and safe treatment.

Fortunately, such a treatment exists. It was developed in the 1950s as compound F, the first topical corticosteroid (TCS) preparation.<sup>6</sup> The potential value and importance of TCS cannot be overstated, but steroid phobia due to misinformation among the general community, pharmacists and prescribing physicians, has led to its underutilisation. We have therefore reviewed the relevant medical literature and have developed a position statement on the safe use of TCS in children with atopic eczema, with a particular focus on adverse effects.

## Methods

An Australian and New Zealand panel of physicians with an interest in managing paediatric eczema was constituted to review the use of TCS in children with atopic eczema. The aim of the consensus meeting was to identify and address misconceptions on corticosteroid treatment of eczema, using published evidence combined with over 430 person

years of clinical practice in paediatric dermatology. The panel included practicing paediatric dermatologists from Australia and New Zealand, paediatricians, dermatology nurses and advanced dermatology trainees. Each reported TCS side effect was reviewed in the context of a paediatric eczema population and key practice points agreed upon. These are listed at the end of this review.

## Results

There was universal agreement that the underutilisation of TCS due to the widespread fear of side effects leads to worse outcomes for children with eczema in both the short and long term.

### Corticosteroid efficacy and potency

Glucocorticosteroids have anti-inflammatory, immunosuppressive, anti-proliferative and vasoconstrictive effects.<sup>7</sup> In the target cell, glucocorticoids bind to receptors in the cytoplasm before traversing the nuclear envelope and binding, either directly or indirectly, to DNA. Gene regulation and transcription of various mRNA follows, resulting in both the beneficial and potentially deleterious effects of steroids.<sup>7</sup> TCS reduce protein synthesis and cellular mitosis as well as inhibiting the proliferation, migration and chemotaxis of fibroblasts. The secretion of certain interleukins is inhibited and the vasoconstrictive effects of adrenaline promoted. TCS also reduce the inflammatory action of histamine and bradykinin.

The potency of TCS depends on the inherent characteristics of the particular steroid molecule and the amount of the molecule that reaches the target cell. Only 1% of hydrocortisone cream is absorbed in the forearm skin of a normal individual.<sup>8</sup> In a single application study using radiolabelled hydrocortisone, absorption

**TABLE 1. POTENCY RANKING OF SELECTED TOPICAL CORTICOSTEROID PREPARATIONS**

Topical corticosteroid	Concentration (%)
<b>Class I: mild</b>	
Hydrocortisone	0.5–1.0
Hydrocortisone acetate	0.5–1.0
<b>Class II: moderate</b>	
Clobetasone butyrate	0.05
Hydrocortisone butyrate	0.1
Betamethasone valerate	0.02
Betamethasone valerate	0.05
Triamcinolone acetonide	0.02
Methylprednisolone aceponate	0.1
Triamcinolone acetonide	0.05
<b>Class III: potent</b>	
Betamethasone dipropionate	0.05
Betamethasone valerate	0.05–0.1
Mometasone furoate	0.1
<b>Class IV: very potent</b>	
Betamethasone dipropionate in optimised vehicle	0.05
Clobetasol propionate	0.05

varied from 0.25 to 3%.<sup>8</sup> Factors that influence absorption of TCSs through the skin include:

#### **Penetration**

How the TCS is formulated will influence its penetration through the skin. In a comparison of a cream, ointment, gel and foam formulation of betamethasone, the foam produced the highest vasoconstrictor activity (a measure of potency) and the cream the least.<sup>9</sup> In a similar comparison of cream, gel and ointment preparations of fluocinolone acetonide, the cream formulation was more potent than the ointment preparation, with the gel having an intermediate activity.<sup>10</sup> Occlusion has been reported to cause increased absorption in 96-h studies, but not in 24-h.

#### **Concentration**

A number of experimental (animal and human) studies from the 1970s and 1980s show little or no correlation between the vasoconstrictor test results and the concentration of topical steroid applied.

#### **Saturation**

Within three applications a steroid reservoir develops in the dermis (once it has been absorbed through the epidermis), which influences the rate of subsequent absorption. Doubling the number of hydrocortisone molecules on the skin from a 1–2% hydrocortisone cream increases absorption in a linear fashion with the first application, but absorption falls once dermal saturation occurs, thereby negating the concentration effect.<sup>11</sup>

#### **Elimination**

The elimination of steroids from the dermis affects subsequent absorption. This occurs either by transport into the circulation or via its metabolism.

The most important factor, however, in determining the potency of a TCS is how well the active agent binds to corticosteroid receptors (i.e. the inherent potency of the steroid molecule) (Table 1). TCS potency is measured by the cutaneous vasoconstrictor assay.<sup>9,12–14</sup> This measures the degree of pallor of the skin caused by both an augmentation of the vasoconstrictive response to adrenaline/noradrenaline and via occupancy of classical glucocorticoid receptors.<sup>7,15</sup>

#### **Steroid concentration**

There is very little clinical difference in the potency of 0.5%, 1% and 2% hydrocortisone. Diluting a strong steroid by mixing it in a moisturiser base will not make it significantly less potent. If you wish to reduce potency, use a less potent steroid molecule.

#### **Frequency of application**

Putting a steroid on thrice daily adds very little to a once daily application, particularly after several days of use. Apply steroids once or twice daily as directed.

#### **Use liberally**

The recommendation ‘use sparingly’ is nonsensical and has no value. Moreover, it unfortunately promotes inadequate use of the drug. In focus groups of parents, significant concern was generated by the instruction to use sparingly. Parents felt this created the impression that cortisone should be used only when eczema was severe and that this contributed to the underutilisation of TCS.<sup>16</sup> It is better to recommend that the steroid is applied liberally and then carefully rubbed or massaged into inflamed skin. A very thick application is, however, wasteful. Use the fingertip unit as a guide to the quantities that should be used (Appendix 1).<sup>17,18</sup>

## Atrophy

The most frequent fear and misunderstanding about TCS use is clinically relevant skin thinning. In a survey of 276 pharmacists (Dr S. Smith, pers. comm., 2014), 46% stated that atrophy of the skin is the most common side effect of TCS use. Two-thirds (67%) reported telling patients not to use TCS for a period longer than 2 weeks at a time.

This fear is not well founded. Much of the early literature on the side effects resulting from TCS use comes from 1960–1980s.<sup>19–22</sup> In these articles, cutaneous atrophy is highlighted as a potential side effect of TCS use. However, these studies were generally of low quality, with small numbers of patients, and methods that are not consistent with the manner or nature of steroid use today (i.e. prolonged continuous application under occlusion in flexural areas).<sup>20,21</sup>

At the biological level, atrophy refers to a decrease in dermal connective tissue and is characterised by the loss of elasticity and thinning. Histologically, there is a reduction in size of the corneocyte in the epidermis as well as thinning of the dermis.<sup>23</sup> The initial reduction in size of the keratinocytes reflects a reduction in metabolic activity. With prolonged exposure to high-potency steroids the number of cell layers is reduced, with the disappearance of the stratum granulosum and the thinning of the stratum corneum.<sup>22,24,25</sup> In a study of three cases, there was significant resorption of mucopolysaccharide ground substance after 6 weeks of very potent steroid application (clobetasol propionate under occlusion in Duhring chambers).<sup>22</sup> This rapidly reversed on discontinuation.<sup>22,25,26</sup>

However, these observations have little clinical relevance. A recent Australian cross-sectional study<sup>27</sup> stressed that routine, long-term use of TCS in children with eczema does not cause skin atrophy. In total, 70 children were initially treated with a potent to moderately potent TCS (betamethasone dipropionate ointment 0.05% or methylprednisolone aceponate) before changing to a less potent TCS

(betamethasone valerate). The mean amount of potent topical steroid per month used was 79 g, medium potency TCS was 128 g and weak potency TCS was 34 g. A validated dermoscopic technique was used to determine skin atrophy at 210 TCS sites and 70 control sites.<sup>28,29</sup> None of the treatment or control sites demonstrated atrophy (all scored 0). Seven sites did show grade 1 telangiectasia, all in the cubital fossa; however, the same degree of telangiectasia was observed in the control group (3.2% vs 3.1%), suggesting that having some telangiectasia in the cubital fossa is a normal variation in the paediatric population.

A randomised controlled trial in adults with active eczema treated with 2 weeks of daily potent TCS (fluticasone 0.0005% ointment) followed by 16 weeks of twice weekly application showed no evidence of atrophy in the serial skin biopsies compared to placebo.<sup>30</sup> In a study of 174 children with atopic eczema those treated with a 3-day burst of a potent TCS (0.1% betamethasone valerate) showed no difference in skin thinning compared with those treated with a mild TCS for 7 days.<sup>31</sup> Using ultrasonography the baseline thickness was measured at 0.91 mm thick. At the end of the 18-week study there was only 0.01 mm difference compared with baseline.

In the combined experience of the panel members no cases of steroid atrophy has been observed if TCS were used for the treatment of atopic eczema and if it were discontinued once the acute inflammation had settled. The cases of steroid atrophy seen in children by the panel members were in the setting of 'off label use' to areas of hyperpigmentation or hypopigmentation for prolonged periods of time (months), particularly in higher absorption sites such as the axillae, flexures and groin. Occlusion, particularly with plastic wraps, has also been observed to increase the risk in these sites. It is, however, very important to recognise that parents and nondermatologists often incorrectly ascribe the changes of active atopic eczema to be evidence of 'skin thinning'.



**Figure 1.** Atopic eczema in the cubital fossae. COURTESY OF ASSOCIATE PROFESSOR GAYLE FISCHER, SYDNEY.

## Summary

What is commonly referred to as skin thinning by parents and nondermatologists is usually a misrepresentation of active eczema; irreversible skin thinning does not occur when TCS, used for eczema in children, is stopped on resolution of the dermatosis.

## Striae/rubra distensae

Striae are visible, linear scars forming in areas of dermal damage produced by the stretching of the skin. Initially there may be inflammation and oedema of the dermis, followed by the deposition of dermal collagen along the lines of mechanical stress. Histologically, striae are characterised by the thinning of the overlying epidermis, with fine dermal collagen bundles arranged in straight lines parallel to the surface.<sup>32</sup> Striae represent scar tissue and therefore, once they have developed, are permanent. They occur most commonly in association with rapid vertical growth (i.e. the back of young teenagers, excessive weight gain or loss and in association with pregnancy [striae gravidarum]).

The evidence that TCS lead to striae is mostly low level, and includes five case reports, two small case series, one randomised controlled trial and three review articles. In total, striae were observed in 15 of 312 patients. In a head to head



**Figure 2.** Atopic eczema in the popliteal fossae. COURTESY OF ASSOCIATE PROFESSOR GAYLE FISCHER, SYDNEY.

comparison of pimecrolimus and TCS (0.1% triamcinolone acetonide to the trunk or limbs and 1% hydrocortisone to the face, neck or intertriginous areas) for 1 year in 658 adults, only three patients developed striae.<sup>33</sup> However, in a specific study of TCS (moderate and potent) used in children over a mean of 10.8 months, in 210 test sites and 70 controls no striae were observed.<sup>27</sup>

In over 430 person-years of paediatric dermatology practice, the panel recalls only one case of striae in a child using TCS for eczema. In contrast most of the panel members had seen striae, albeit very rarely, when used for noneczematous conditions, particularly in overdose and under occlusion for extended periods of time.

Although concern is occasionally expressed over the possibility of delayed striae formation due to childhood use of TCS, there is no evidence to support this, even when TCS have been used inappropriately. Striae do occur commonly in children and teenagers during rapid growth phases with an estimated incidence of 25–35%,<sup>34</sup> but TCS do not produce striae in children using standard TCS treatment for eczema.

### Summary

TCS do not induce striae when used to treat atopic eczema in children unless used inappropriately or in overdose and only then at certain sites (i.e. the axillae and groin).

### HPA axis suppression

HPA axis suppression can occur following use of any exogenous steroid. Physiological adrenal suppression has been defined as a 'cortisol level below the normal range but with the capacity for prompt recovery' while pathological adrenal suppression is described as 'a state of adrenal insufficiency, adrenal crisis or persistent laboratory evidence of adrenal suppression without prompt recovery'.<sup>35</sup> Following exposure to exogenous corticosteroid, the body adjusts the HPA axis through the physiological suppression of endogenous cortisol. Following weeks to months of persistent exogenous corticosteroid exposure, the adrenal glands may become atrophic and are temporarily unable to produce adequate glucocorticoids to meet the body's requirements. In this situation, the adrenal suppression becomes pathological and an adrenal crisis may occur.

Following TCS use, temporary physiological adrenal suppression may be apparent within 2–4 weeks but is quickly reversible and the patient recovers fully.<sup>35–38</sup> We are unaware of any reports of pathological adrenal suppression during the use of TCS that is discontinued on resolution of the active eczema.

In a review of 16 TCS trials that recorded HPA suppression, only one reported pathological adrenal suppression: five adult psoriasis patients who used more than 100 g clobetasol propionate a week for between 10 weeks to 18 months developed features of Cushing's syndrome. On withdrawal they suffered symptoms of adrenocortical insufficiency; and in addition they developed pustular psoriasis.<sup>35</sup>

There are 25 paediatric case reports in the literature of HPA axis suppression. These children had mostly used super-potent topical steroids (clobetasol propionate) for 1–17 months for diaper eczema.<sup>39–47</sup>

There have been two reports of death due to sepsis in association with marked overuse of TCS in very young infants.<sup>48,49</sup>

It is clear that physiological HPA axis suppression can occur for the duration of treatment with potent TCS. When used for routine eczema management in children, pathological HPA suppression has not been reported.

### Summary

Physiological HPA axis suppression can occur with widespread and prolonged, or occlusive use, of potent/superpotent TCS. Clinically significant or pathological adrenal suppression is very rare in the treatment of paediatric eczema with topical agents.

### Infected or excoriated skin

Most children with eczema are colonised with *Staphylococcus aureus*<sup>50,51</sup> and many will develop secondary bacterial or viral infections, such as herpes simplex or molluscum. Conversely, children's eczema will often flare following primary skin infection.<sup>52</sup> There is, however, little evidence that treatment with TCS worsens any outcomes associated with infection. Indeed, adequate treatment of the eczematous skin with TCS generally restores the barrier function of the skin and greatly aids control of any associated infection, without the need for antibiotic or antiviral treatment.<sup>53,54</sup> In children with significant secondarily infected eczema, TCS use should be combined with oral antibiotics or antivirals as clinically indicated. Topical antibiotics should generally be avoided to minimise the development of antibiotic resistance.

Children with atopic eczema often have areas of excoriated or weeping skin, or both. Corticosteroids have the potential to slow the healing of ulcerated skin, through reduced epidermal DNA synthesis and morphological changes in fibroblasts.<sup>19</sup> When applied daily to incised pigskin, triamcinolone acetonide was found to reduce the rate of wound healing in the pigs by 62% by day 7.<sup>19</sup> However, the control of inflammation of atopic eczema by using

TCS far outweighs the slight reduction in the rate of wound healing. There is little evidence to contraindicate the use of TCS on excoriated atopic eczema.

The members of the panel recommend moderate to potent strength TCS for children with atopic eczema with superimposed bacterial or viral infection, provided they are also receiving appropriate antiseptic, antibacterial or antiviral treatment if clinically indicated.

### Summary

TCS should be the first-line treatment for excoriated or infected eczematous skin. Concurrent infection (e.g. *S. aureus*, herpes simplex, molluscum) should be treated if clinically significant. There is no evidence that putting TCS on excoriated or infected eczema is deleterious.

### Allergic contact dermatitis to TCS

TCS allergy is a delayed hypersensitivity reaction whose reported prevalence is increasing.<sup>55,56</sup> The low molecular weight of corticosteroid molecules should prevent it from becoming immunogenic but the degradation of the C17 side chain allows it to bind to amino acids to generate a hapten-protein complex, which can act as an allergen.<sup>57</sup>

There is significant geographical variability in the reported prevalence of TCS allergy in both adults and children. This is due, in part, to regional differences in patch test methodology and the prescribing habits of different countries.<sup>58-60</sup> A meta-analysis by Dooms-Goossens and colleagues showed that approximately 1% of children patch tested demonstrate allergy to TCS, although the relevance was not always clear.<sup>61</sup> In children who do not respond to, or are made worse by topical steroid use, the incidence of steroid allergy was found to be 25%, although the overall incidence was not reported;<sup>62</sup> 85% of those with positive patch test had multiple allergies.<sup>63</sup>

### Summary

Allergy to TCS is uncommon in children with atopic eczema but should be considered

in those children who demonstrate a poor response to appropriate-strength TCS.

### Osteopenia/osteoporosis

Osteopenia or osteoporosis with resulting bone fractures is a well-known side effect following the chronic use of oral corticosteroids in adults and children alike.<sup>64-66</sup> The quality of evidence that TCS has any effect on bone mineral density (BMD) manifesting as osteopenia or osteoporosis, is relatively low. In one case-control study of 43 children with eczema using TCS, only children also on oral cyclosporin were found to have lower BMD and bone mineral apparent density in the lumbar spine.<sup>67</sup> However, when the six patients with cyclosporin were excluded there was no significant difference found between those treated with TCS and the controls. There was no correlation between corticosteroid variables (eczema severity scoring system, dose of TCS, years of TCS usage, affected body surface area) and bone density at any site. The body location of eczema, vitamin D intake and the use of occlusion with TCS were not examined as potential confounders. Cyclosporin itself is thought to activate osteoclasts and suppress osteoblasts and bone formation,<sup>68</sup> and is known to be associated with an increase in osteocalcin levels, pointing to a secondary process of bone loss.<sup>69</sup>

The limited research available to date suggests the risk of bone thinning in children with moderate to severe atopic eczema does not appear to differ from the expected prevalence of low BMD in the general population.<sup>70</sup>

### Summary

Reduced BMD is unlikely to occur in children with eczema treated with TCS. The panel has not identified any children with atopic eczema using only TCS who have developed osteopenia or osteoporosis.

### Ocular effects

Potential adverse effects of systemic corticosteroids on the eyes include changes to intraocular pressure (glaucoma), cataract

formation and infection. There is medium quality evidence that the prolonged application of corticosteroid eyedrops for ophthalmological conditions can result in ocular complications such as cataracts, glaucoma and ocular infections.<sup>71</sup> There is, however, only level 4 and 5 evidence on the ocular side effects of corticosteroid used topically near the eye.

Intraocular side effects are rare when TCS is used appropriately in the periocular region (i.e. one week of moderate or potent TCS use, followed by mild potency TCS or calcineurin inhibitors for maintenance). A recent study assessed 88 patients with atopic eczema who utilised topical steroids to the eyelids and periocular region, with no increased risk of glaucoma observed.<sup>72</sup> However, there are a few case reports of adverse effects, which are primarily based around medication errors.<sup>73-75</sup> In most of these cases there has been prolonged use of potent or very potent TCS for months to years. In many instances the TCS was originally prescribed for use in nonfacial areas or for another patient altogether.

In the setting of atopic eczema, cataracts can develop through one of two distinct pathways. The more common is related to the disease itself; persistent itching and rubbing of the eyelids may induce traumatic cataracts. Systemic steroids (>15 mg prednisone/day for over 12 months) can also induce posterior subcapsular cataracts.<sup>76</sup> Lower doses of systemic corticosteroids in combination with TCS used in the periocular and subconjunctival region as well as nasal TCS sprays have also been associated with posterior subcapsular cataracts, with seven cases reported in a 5-year period to 2001.<sup>77</sup>

In a study of 37 atopic eczema patients who used moderate potency TCS periorbitally for an average of 6 months/year over 5 years, seven were found to have cataracts.<sup>72</sup> Two of these patients were also using oral steroids, four of the seven were found to have age-related cataracts and one patient was found to have cataracts secondary to rubbing, in the setting of atopic eczema. None was directly related to TCS use.

It is currently unclear as to whether there is a threshold of TCS use which can induce cataract or glaucoma. It is possible that susceptible individuals, such as those with a personal or family history of cataracts, glaucoma, diabetes, myopia or previous eye problems have a lower threshold.

### Summary

In predisposed individuals, the prolonged use of potent TCS in the periorbital area has been rarely associated with cataract and glaucoma. However, there is little evidence that less potent TCS used on the eyelids and periorbital area, even if used for a long duration, cause ocular sequelae. TCS use elsewhere on the face or body has not been shown to cause ocular sequelae. If potent TCS are to be used for prolonged periods in high-risk patients it may be advisable to obtain a baseline ophthalmology review and consider using a topical calcineurin inhibitor instead.

### Hypertrichosis

Hypertrichosis may be generalised or localised, congenital or acquired. It must be differentiated from hirsutism. There is no high-quality evidence to support an association between TCS use and hypertrichosis. While various texts report an association between the two, each references a statement in a previous article or textbook, with no actual cases clearly documented. However, nine members of the consensus group report having seen localised hypertrichosis in children with a discoid pattern of atopic eczema (with or without prurigo nodularis), in the skin immediately surrounding the discoid patches or nodules. The localised hypertrichosis resolved on discontinuation of the potent TCS (and the eczema). It is unknown whether this reported localised hypertrichosis is an epiphenomenon due to lichenification, traumatic rubbing or itching, the underlying discoid pattern of atopic eczema or an adverse effect of TCS use.

### Summary

TCS do not cause permanent hypertrichosis. Transient hypertrichosis has been seen in discoid eczema and prurigo nodularis treated with potent TCS.

### Periorificial dermatitis/rosacea

The pathogenesis of perioral dermatitis or rosacea is not completely understood. Fluorinated TCS, tacrolimus, inhaled steroids, *Demodex* mites, tartar control toothpastes, cosmetics, hormonal influences, occlusive moisturisers, cosmetics and amalgam fillings have all been implicated at one time or another.<sup>78-82</sup> TCS are commonly prescribed in children for mild perinasal, periocular or perioral erythema, which initially are often effective. However, continued use or discontinuation, or both, can induce perioral dermatitis. In a study of 79 children with periorificial rashes, two-thirds (66%) were reported to be using TCS at the time of the initial evaluation.<sup>79</sup> However, it was not clear whether the periorificial rash had occurred prior to use of the TCS or following treatment. All cleared with the cessation of the topical steroid and use of topical metronidazole.

A number of studies have reported a rosacea-like eruption occurring in patients using tacrolimus.<sup>80-82</sup> One study of 16 children with periorificial dermatitis compared those using topical tacrolimus with those using TCS.<sup>80</sup> The clinical presentation was similar, with a significant colonisation of *Demodex* mites occurring in both groups. All patients cleared on stopping the topical agents and treatment with topical metronidazole. There have been reports of inhaled steroids inducing perioral rosacea.<sup>83</sup>

The consensus group believes that perioral dermatitis or rosacea can be induced in predisposed children, even by simple emollients or mild over-the-counter TCS (e.g. 1% hydrocortisone). The presence of a perioral, perinasal or periocular rash should raise suspicion of possible perioral dermatitis or rosacea. TCS should not be used to treat rosacea, as they typically lead to a cycle of dependence with flare on treatment withdrawal.

Perioral dermatitis or rosacea is generally easy to manage by avoiding all topical preparations (TCS, thick emollients, sunscreens, cosmetics, etc.). If treatment is required, consider 6 weeks of systemic antibiotics (e.g. erythromycin or tetracycline if the patient is over 12 years of age). If systemic treatment is inappropriate, consider topical metronidazole or azelaic acid. Patients should be warned to expect a flare following the cessation of treatment, and counselled about the importance of avoiding topical preparations, including TCS on the central portion of the face.

### Summary

TCS may aggravate a tendency for perioral dermatitis/rosacea in predisposed individuals. Physicians who prescribe TCS for facial eczema should be aware of this complication.

### Red face

The presentation of patients with a red face, often with the headlight sign (large areas of facial erythema with sparing of the nose and upper lip), has been described in adults using potent TCS, mostly for seborrhoeic dermatitis.<sup>84</sup> Nitric oxide is suggested to be a mediator of the rebound vasodilation reported in these cases. These patients are often described as being steroid dependent or addicts. Treating this involves cessation of all topical steroids and other skin-care products but it may take many months of discomfort to achieve this. Systemic therapy with anti-inflammatory antibiotics is often necessary (e.g. tetracyclines). The red face has not been reported as occurring in children, but should be kept in mind in teenagers whose inflammatory dermatosis deteriorates despite increasing steroid potency use.

### Summary

The red face has not been described in children with eczema but should be kept in mind in teenagers who continue to deteriorate despite increasing steroid potency.

### Tachyphylaxis

Tachyphylaxis refers to a progressive reduction in efficacy of an agent with its continued use and is often reported by patients and their families following TCS usage. The evidence for tachyphylaxis is, however, weak and is confounded by issues of non-compliance, and other reasons for failure to respond to treatment (e.g. acute flare due to secondary infection or exposure to irritants). In a mouse model TCS cause the inhibition of DNA synthesis and mitosis in the epidermis. With ongoing treatment DNA synthesis and mitosis recover and the tissue becomes insensitive to further stimulation.<sup>85</sup>

A study of adolescents and adults<sup>86</sup> used either fluticasone 0.05% cream or ointment, or the equivalent base. Following clearance, patients entered a 16-week follow-up study. All patients applied an emollient once daily; half the patients then applied a TCS twice weekly, while the control group applied the base twice weekly. Those patients using twice weekly TCS had a median time to relapse of more than 16 weeks as opposed to 6 weeks for the base only. Most patients who applied a potent TCS twice weekly had not relapsed at 4 months.

In a 12-week study, none of the 32 patients being treated for psoriasis with TCS exhibited detectable signs of tachyphylaxis.<sup>87</sup> In another review there was no evidence that the clinical efficacy of glucocorticoids had diminished significantly in long-term continuous use in inflammatory skin diseases.<sup>88</sup> However, in 10 volunteers with normal skin, a histamine-induced wheal was suppressed following 14 days of daily fluocinolone acetonide 0.01% applied under occlusion to the flexor aspect of the forearm. Maximal wheal suppression occurred on day 8, but by day 14 the study reported almost total tolerance to the TCS.<sup>89</sup>

Noncompliance with treatment or the inadequate use of TCS is often a more common explanation for loss of response to TCS. Lack of adherence results from many factors: the chronic nature of eczema, the need for the ongoing

application of creams, the prohibitive costs of topical agents and complexities in coordinating school, work and family plans. A study of adherence to topical treatment of eczema revealed only a 32% adherence in 8 weeks of treatment.<sup>90</sup> Non-compliance is particularly affected by steroid phobia. In one study 73% of dermatology outpatients reported being worried about using TCS and 33% confessed to noncompliance.<sup>91</sup>

### Summary

There is no evidence to show that tachyphylaxis occurs in children with eczema treated with TCS. While there are some animal studies showing tachyphylaxis with TCS use, clinical studies have generally failed to confirm this.

### Purpura

Purpura is not uncommon in individuals with significant sun damage, particular if they have also received prolonged courses of systemic or topical steroids. Purpura develops secondary to the loss of the supporting architecture of the local vasculature and is precipitated by shearing stress. It is usually asymptomatic.<sup>92,93</sup> Although it is commonly listed as an adverse effect, the evidence for TCS-induced purpura without significant phototrophy, is poor.

A small study of six patients reported atrophy, telangiectasia and purpura related to TCS use.<sup>94</sup> One patient had used flurandrenolide 0.05% under occlusion for 5 years and experienced easy bruising. A second patient had used the same agent four times daily for 10 months. Two other patients used very potent TCS up to four times a day for 18 months and 5 years, respectively. All had continued to use the potent TCS long after the initial dermatosis had settled, i.e. they were being applied to nondiseased skin.

Purpura is a theoretical risk with TCS use but the literature does not support its presence in children nor in any individual using TCS to treat active eczema and ceasing on the resolution of disease

activity. In addition, none of the consensus group had experience of TCS-related purpura in children.

### Summary

Purpura does not occur in children with eczema being treated with TCS when they are stopped on the resolution of the active dermatosis.

### Hypopigmentation

TCS produce vasoconstriction, which can be confused with hypopigmentation. It is mediated via occupancy of classical glucocorticoid receptors.<sup>15</sup> The time profile of vasoconstriction is dependent on the agent used, with carbon-11-chlorosteroid being the quickest.<sup>95</sup> The vehicle used also seems to contribute to the blanching profile, with betamethasone dipropionate ointment having a different profile to the same chemical in a cream base.<sup>95</sup>

Although there are very few reports in the literature of TCS causing hypopigmentation, this side effect continues to be widely reported. The literature includes two case reports<sup>96</sup> of hypopigmentation following the use of intralesional steroids, and one case of hypopigmentation localised to sites of use of flurandrenolide impregnated tape.<sup>97</sup> Fortunately, the hypopigmentation resolved within 7 days on cessation of use.

Hypopigmentation in the context of treating eczema in children is very common. This is largely due to the underlying disease (e.g. pityriasis alba).<sup>98-99</sup> In the experience of the review group, only two children have been observed to develop localised hypopigmentation; both occurred in Fitzpatrick skin types IV-V and both had been using potent or very potent TCS. Fortunately, the hypopigmentation occurred only at the treated site, and in each case the pigmentary change was transient and resolved completely over a period of a few weeks to months following cessation of the TCS.

## KEY POINTS

- There is little difference in the clinical effect between 0.5, 1 and 2% hydrocortisone.
- Diluting a strong steroid with moisturiser does not reduce its clinical effect. Potency reduction is achieved by using a less potent steroid molecule.
- Most topical steroids can be applied once daily, preferably in the evening or at night.
- The recommendation 'use sparingly' is nonsensical and has no value. Use the fingertip unit as a guide.
- What is commonly referred to as skin thinning by parents and nondermatologists is usually a misinterpretation of active eczema.
- When TCS used for eczema in children are stopped on resolution of the dermatosis, irreversible skin thinning does not occur.
- TCS do not induce striae when used to treat atopic eczema in children, unless used inappropriately, or in overdose and only then at certain sites (i.e., axillae and groin).
- Physiological HPA suppression can occur with very widespread and prolonged, or occlusive use of potent/superpotent TCS. This recovers quickly.
- Clinically significant/pathological adrenal suppression is very rare in the treatment of paediatric eczema with TCS.
- There is no evidence that applying TCS on excoriated or infected eczema is deleterious.
- TCS should be the first-line treatment for atopic eczema, regardless of whether the skin is excoriated or infected.
- Clinically significant concurrent infection (e.g. *Staphylococcus aureus*, herpes simplex, molluscum) should be treated.
- Allergy to TCS is rare in children with atopic eczema, but should be considered in those children who demonstrate a poor response to appropriate strength TCS.
- Reduced bone mineral density is very unlikely to occur in children with eczema treated with TCS.
- Prolonged use of potent TCS in the periorbital area has rarely been associated with cataract and glaucoma.
- TCS use away from the eyes has not been shown to cause ocular sequelae.
- Transient hypertrichosis has been seen in discoid eczema and prurigo nodularis treated with potent TCS.
- TCS may aggravate a tendency for periorificial/perioral dermatitis, in predisposed individuals.
- The red face has not been described in children with eczema, but should be kept in mind in teenagers who continue to deteriorate despite increasing steroid potency.
- There is no evidence to show that tachyphylaxis occurs in children with eczema treated with TCS.
- TCS do not induce purpura in children with atopic eczema.
- The hypopigmentation seen in patients treated with TCS, as their eczema clears, is caused by the eczema (as in pityriasis alba), not the treatment.
- TCS do cause short-term vasoconstriction, which can be mistaken as hypopigmentation.
- Routine use of TCS in children with eczema should not cause telangiectasia.

## Summary

The hypopigmentation seen in patients with eczema is usually secondary to the eczema (e.g. pityriasis alba). It resolves with appropriate treatment of the eczema, particularly after exposure to UV light. TCS do cause short-term vasoconstriction, which may be mistaken as hypopigmentation. Very potent TCS have been used inappropriately as a skin lightening agent.

## Telangiectasia

There is some evidence from animal studies that triamcinolone acetonide and fluocinolone acetonide can induce telangiectasia in rats.<sup>100</sup> It is notable that the studies used excessive quantities of TCS. While telangiectasia have been reported with prolonged, excessive and occlusive

use of TCS,<sup>100–105</sup> there is little evidence that telangiectasia occur when used to treat active childhood eczema when treatment is stopped on resolution of the dermatosis.

In a recent study, 92 Australian children treated using mild to potent TCS or emollients as per their eczema severity were followed over a mean of 10.6 months.<sup>27</sup> Mild grade 1 telangiectasia was seen in 3% of the cases, all of which involved the antecubital fossa. However, this was similar to the control group (3%).

In another study investigators undertook a right-left comparison in the same individual using between hydrocortisone 1% cream and pimecrolimus 1% cream. This was an 8-week single centre study of the uninvolved forehead skin of 20 patients with atopic eczema.<sup>33</sup> Following a

twice-daily application for 2 months, no dermal thinning or telangiectasia was demonstrated, as measured by ultrasound or dermoscopic photography.

Alclometasone dipropionate 0.05% was compared with hydrocortisone 1% in a randomised double blind manner in 32 children with eczema, looking for evidence of atrophy or telangiectasia following its twice-daily application for 3 weeks. There was no evidence of telangiectasia or sign of cutaneous atrophy in any child.<sup>102</sup>

It is the panels' opinion that telangiectasia can develop after the prolonged use of very potent TCS, but is very unlikely in children when TCS are used appropriately for active eczema. Care should be taken with prolonged and excessive use of very potent topical steroids,

particularly when used in combination with inhaled, intranasal and systemic steroids.

**Summary**

Routine use of TCS in children with eczema should not cause telangiectasia.

**Conclusion**

TCS remain the mainstay of the management of active atopic eczema in combination with the regular use of emollients, the management of triggers and the treatment of concurrent infection. The safety profile of TCS remains robust when it is used appropriately. Appropriate use is defined as 1–2 generous applications per day to all the inflamed skin until the active eczema is controlled as per guidelines (Appendix 1). The advice given by dermatologists to parents of children with eczema regarding the use of TCS is unfortunately frequently undermined by other health professionals. There is a pressing need for the re-education of these health professionals on the excellent safety record of these medications. MT

**References**

A list of references is included in the website version of this article ([www.medicinetoday.com.au](http://www.medicinetoday.com.au)).

**APPENDIX I. GUIDELINES FOR THE PRACTICAL USE OF TCS**

**When to apply**

Apply 1–2 applications per day as per the product information, to all the inflamed skin until eczema is cleared. There is no requirement for intervals without therapy.

**How much to apply**

There is no requirement to use sparingly. Please refer to the following table of application volume recommendation.

**TABLE A1. FINGERTIP UNIT<sup>17,18</sup>**

Patient's age	Face and neck	Arm and hand	Leg and foot	Anterior chest and abdomen	Back and buttocks
3–12 months	1	1	1½	1	1½
1–3 years	1½	1½	2	2	3
3–6 years	1½	2	3	3	3½
6–10 years	2	2½	4½	3½	5
>10 years	2½	4	8	7	7

# Adverse effects of topical corticosteroids in paediatric eczema: Australasian consensus statement

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