

# Systematic Review of the Topical Steroid Addiction and Topical Steroid Withdrawal Phenomenon in Children Diagnosed With Atopic Dermatitis and Treated With Topical Corticosteroids

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## ABSTRACT

**Background:** A 2015 National Eczema Association study concluded that topical steroid withdrawal is an effect of prolonged, frequent use of topical steroids occurring mostly in adult women. It is unclear whether children develop topical steroid withdrawal.

**Objective:** The aim of this study was to assess current evidence regarding topical steroid withdrawal in children.

**Methods:** This study is a systematic review of medical literature as well as online social media sites and blogs regarding topical steroid withdrawal in children.

**Results:** Literature search yielded zero studies on/or reporting classic topical steroid withdrawal in children; however, periorificial dermatitis, which is generally a

steroid-induced disorder in children, was reported in >320 cases. Of 142 social media blogs on topical steroid withdrawal, 26 were blogs discussing children. Twenty-seven cases were included in this review. Length of topical steroid use ranged from 2 months to 12 years.

**Conclusions:** Topical steroid withdrawal occurs in children and can result from discontinuing topical steroids used for as little as 2 months. Resultant signs/symptoms can last >12 months, even with short duration of use. Clinicians and caregivers should be aware of this possible adverse effect of topical steroids and monitor the effects of topical steroids on infants/children, but more data are needed on this condition.

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For more than 60 years, topical steroids (TSs) have been the mainstay of treatment of atopic dermatitis (AD), with efficacy being established in over 100 different randomized clinical trials (Eichenfield et al., 2014). Adverse reactions to TSs include epidermal thinning, skin discoloration, telangiectasias, and increased bruising in the area(s) of use. Less discussed are the adverse events of TS addiction (TSA) and TS withdrawal (TSW), especially in children (Hengge, Ruzicka, Schwartz, & Cork, 2006).

In 1979, Kligman and Frosch noted an increase in the number and severity of adverse effects of TSs with the emergence of higher-potency preparations. Kligman and Frosch described TSA/TSW as an “insidious type of side reaction,” often unrecognized, and noted that “both the physician and patient may fail to incriminate the steroid.” TSA/TSW—also referred to as “red skin syndrome” and “red burning skin syndrome”—is characterized by continued use of a mid-potency to high-potency TS for weeks to months and may be associated with a constellation of symptoms occurring after cessation of TS application. These symptoms include, but are not limited to erythema, exudation, pruritus, scaling, xerosis, epidermal thinning, telangiectasia, and pustules, which may last for months before resolving, if resolving at all (Kligman & Frosch, 1979; Rapaport & Lebwohl, 2003; Rapaport & Rapaport, 2004; Smith, Nedorost, & Tackett, 2007).

In December 2013, the National Eczema Association (NEA) formed a scientific advisory committee task force in an effort to further study and understand the phenomenon of TSA/TSW (NEA, 2013). They concluded that TSW is an adverse event, “generally occur[ing] with the inappropriate prolonged frequent use of high potency topical corticosteroids.” However, limitations in analysis of TSA/TSW in children were reported; the authors concluded that either children were less likely to develop TSA/TSW or cases of TSA/TSW in children were underreported (Hajar et al., 2015).

TSs are ubiquitously used as first-line treatment of multiple dermatologic conditions including AD, psoriasis, seborrheic dermatitis, as well as allergic contact dermatitis and are often also used as long-term maintenance therapy (Hengge et al., 2006). Although research has shown that TSs are an indicated effective therapeutic option, long-term use is not without adverse effects (Fukaya et al., 2014; Hajar et al., 2015; Rapaport & Lebwohl, 2003).

TSA/TSW is a phenomenon in which a person’s skin becomes “resistant” to TS treatment after prolonged and frequent application to sensitive areas such as the face, genitals, and intertriginous regions. Notably, the skin becomes dependent on the TS and exhibits signs of withdrawal upon cessation. The underlying mechanism of

TSA/TSW is poorly understood; however, epidermal atrophy (due to prolonged TS use) and the subsequent overexpression of tissue proteases and keratinocyte proteins have been suggested. For example, TS increases thymic stromal lymphopoietin activity, a protein produced by keratinocytes. Thymic stromal lymphopoietin acts to shift the T-helper (Th) lymphocyte ratio from a balanced Th1/Th2 population to one of Th2 predominance as is seen in AD (Cork et al., 2006; Komatsu et al., 2007).

Prolonged TS application changes the glucocorticoid receptor (GR) expression pattern on the surface of lymphocytes; patients experiencing resistance to TSs have a low ratio of GR- $\alpha$  to GR- $\beta$  (Hägg, Hurskainen, Palatsi, Ilves, & Oikarinen, 2010). In addition, the erythema characteristic of “red skin syndrome” is due to a release of stored endothelial nitric oxide (NO) and subsequent vasodilation of dermal vessels (Sheary, 2016).

Research has shown women, over the age of 18 years, using mid-potency to high-potency TSs on the face to be most at risk. However, children are an unevaluated population (Fukaya et al., 2014; Hajar et al., 2015; Rapaport & Lebwohl, 2003). Because of the chronic nature of AD, treatment often results in prolonged TS use during childhood and a potentially relatively larger surface area of application, possibly leading to a greater potential to develop TSA/TSW (WHO, 2008). In the absence of formal research and consensus literature of TSA/TSW in adults, an even greater challenge exists in evaluating children. Given the lack of literature on TSA/TSW in the pediatric population, data were obtained through social media network review of blog articles written by parents of children experiencing TSA/TSW as well as international organizations including the NEA and the International Topical Steroid Addiction Network, bringing to light valuable information about TS use in children not currently published (R. C., personal communication). The author (R. C.) reviewed blog sources and presented this information on consumer experience with TSA/TSW in children using TSs for the treatment of presumed irritant dermatitides including contact dermatitis, seborrheic dermatitis, and AD.

## MATERIALS AND METHODS

### Literature Search

PubMed, ClinicalTrials.gov, and Cochrane Library were searched for literature from January 1, 1954, to May 21, 2015. Other modalities for literature search included Google (Mountain View, CA) and Yahoo (Sunnyvale, CA) search engines to find social media blogs from January 1994 to May 2015 concerning TSA/TSW in children as well as any atopic child noted to have a TS use complication. Search terms used were related to TSW in children: “eczema,” “red skin syndrome,” “topical steroid addiction,” “topical steroids,” “red sleeves,” “infants,” “eczema,” “effects

of long-term TS use in children with eczema,” “treatment during TSW,” and “atopic dermatitis in children.” Only literature written in English was considered for inclusion, with the exception of non-English blogs with an in-website language translator. Blogs were reviewed by the author (R. C.) independently for well-delineated time frames, objective measures of signs/symptoms, photos, and treatments.

### Data Extraction and Analysis

Using an information rating (IRat) scale created for use in this study, each blog was rated based on the presence of six basic elements: history, description of signs/symptoms, pictures, temporal relationship between cessation of TS

and TSA/TSW, treatment used for TSW and other meaningful objective measures (including description of TS use as well as other nonsteroidal topical agents, homeopathic treatments, and nonpharmaceutical therapies), detailed procedures, and helpful tips or other organized/systematic quality of information. This allowed for an objective rating scale with a maximum IRat of 6 (Figure 1). Data were combined at an aggregate level and evaluated using descriptive methods.

## RESULTS

### Description of Blogs

The initial search for peer-reviewed cases regarding TSA/TSW in children yielded zero results; however, periorificial

Blog elements	Point value /Points scored
1. History <sup>a</sup>	
A. Age began TS	0.1 _____
B. Indication for TS	0.1 _____
C. Age stopped TS	0.1 _____
D. Reason for stopping TS	0.2 _____
E. Location of initial TS application	0.1 _____
F. Location of final TS application <sup>b</sup>	0.1 _____
G. Frequency of TS use <sup>c</sup>	0.1 _____
H. Duration of TS use <sup>d</sup>	0.1 _____
I. TS features: Types/potencies of TS <sup>e</sup>	0.1 _____
2) Description of signs/symptoms	1 _____
3) Pictures <sup>f</sup>	1 _____
4) Temporal relationship between discontinuation of TS and TSA/TSW signs and symptoms	1 _____
5) Treatments/methods used in TSA/TSW <sup>g</sup>	1 _____
6) Other <sup>h</sup>	1 _____
<b>Sum of blog elements 1-6 is the information rating.</b>	<b>IR =</b> _____

*TS, topical steroid(s); TSA, topical steroid Addiction/TSW, topical steroid withdrawal*

<sup>a</sup> Sum of items A-I, with maximum of 1 point for history  
<sup>b</sup> Prior to TS cessation  
<sup>c</sup> Initial prescription of TS and just prior to TS cessation  
<sup>d</sup> Total length of time TS were used from initial to final application  
<sup>e</sup> First applied and last applied types of TS before TS cessation; other forms of corticosteroids used prior to TSA/TSW (oral, intravenous, inhaled, intramuscular)  
<sup>f</sup> 0.5 points if pictures present; further 0.5 points if pictures show progression or other objective quality  
<sup>g</sup> 0.5 points if mentioned; further 0.5 points if details are provided  
<sup>h</sup> Objective measures, detailed procedures, helpful tips, and/or other organized/systematic quality to the information

**FIGURE 1.** Information rating of blogs used to determine dependability of blog information. Calculating the information rating of various Internet blogs on TSA/TSW using a 6-point scale based on history, description of signs/symptoms, pictures, temporal relationship between discontinuation of TS and TSA/TSW, treatments used for TSA/TSW, and other (objective measures, detailed procedures, helpful tips, or other organized/systematic quality of information).

dermatitis, which is generally a steroid-induced disorder in children, was reported in >320 cases. Identification of blogs through Internet searches found 142 entries, 31 of which described cases of child subjects. Of those 31 blogs, only 26 were considered eligible to be included in this review. Five blogs were excluded based on the subjective criteria that they did not present enough detail regarding TS treatment, did not clearly describe the symptoms of TSA/TSW, or did not present a clear timeline of TSA/TSW development. One subject was known to the primary author. One blog required English translation. The oldest blog started in February 2012. The IRat for the 26 blogs identified above ranged from 2.6 to 6, with the median being 5 of 6. Twenty-seven different cases were reviewed (one blog pertained to two siblings).

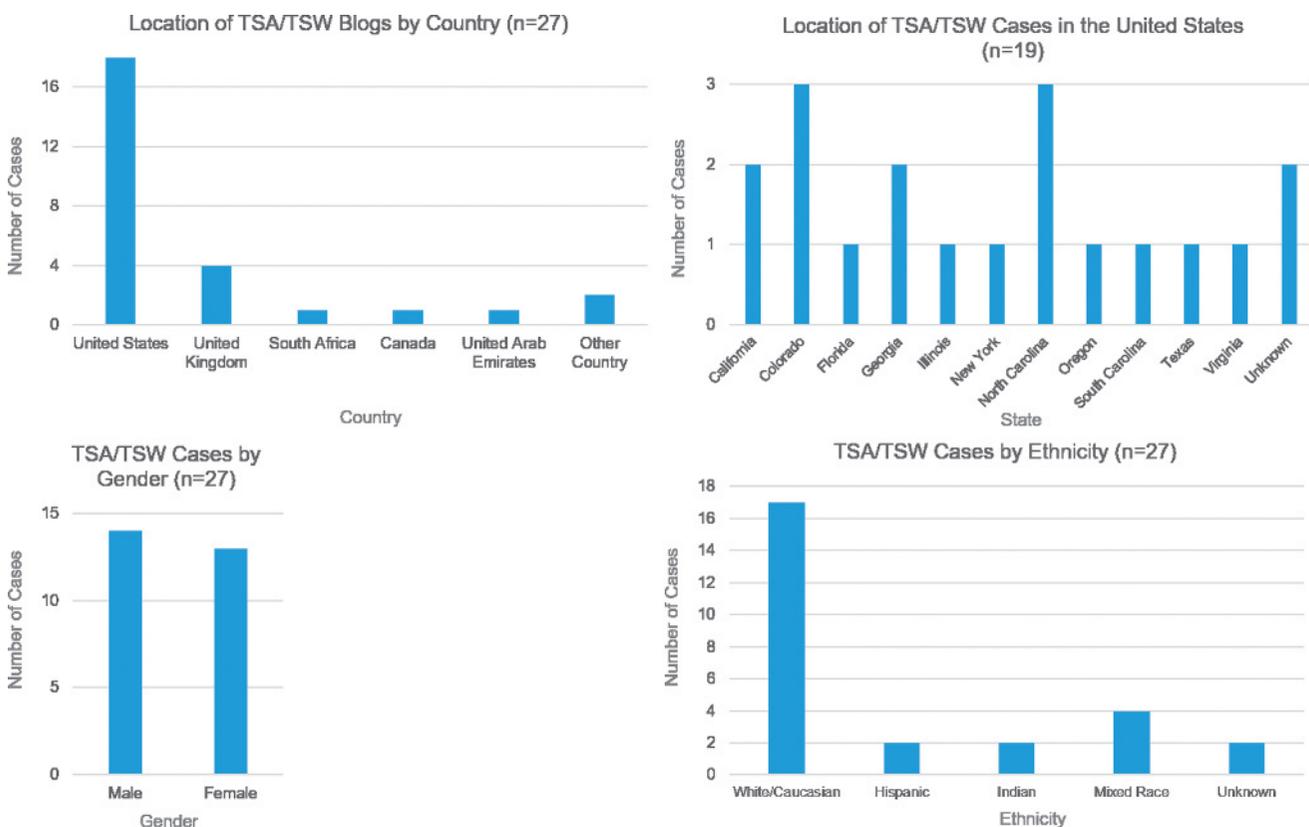
### Demographics

Of the 27 subjects, most were male (51.8%) and of Caucasian descent (62.3%). Subjects originated from the United States, the United Kingdom, South Africa, Canada, and the United Arab Emirates. Most subjects were from the United States and came from at least 11 different states (Figure 2). Allergies were reported in 44% of the subjects, ranging from severe allergies to food products such as eggs, nut, gluten, and dairy as well as

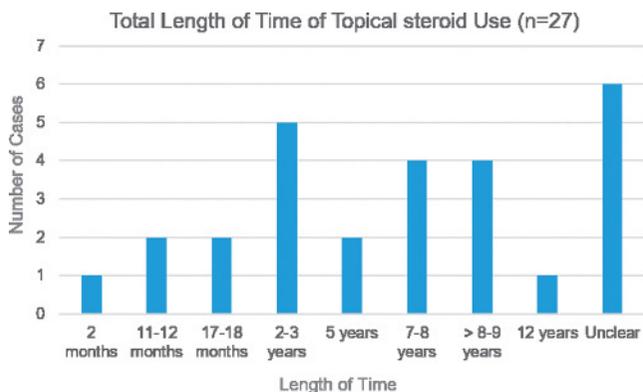
nonspecified allergies to environmental factors such as pets, dust, trees, and grass.

### TS Use

Subjects were prescribed TSs at ages ranging from 2 months to 8 years, with 56% being prescribed TSs at 12 months or younger (Figure 3). In 70% of the cases, caregivers initially had reportedly sought counsel from a medical provider (including primary care, allergy, and dermatology providers [otherwise not specified]) for localized skin eruptions; 30% presented with unknown “skin rash,” bumps, erythema, and pruritus (Table 1). All presentations were initially diagnosed as AD and treated with one or more TSs; those who were also prescribed calcineurin inhibitors used the products briefly before discarding them because of the Black Box Warning for lack of long-term safety data and potential malignancy risk including skin and lymphoma (Ring, Möhrenschrager, & Henkel, 2008; Woitach, 2010). Of the 11 types of TSs initially prescribed, 73% were of the mid-potency to high-potency class (Table 2). TS regimen was reported in 41% of the cases; medical caregiver instructions for topical use varied from “a few times per month” to multiple times per day for 3–30 days or “until [the] skin clears.”



**FIGURE 2.** Demographics. Twenty-six blogs were found; however, there are 27 subjects as one blog described two siblings both affected by TSA/TSW. Most of the blogs found on Internet search were located in the United States. The most common states where TSA/TSW blogs were found included Colorado and North Carolina. Most pediatric subjects described were male and of Caucasian descent.



**FIGURE 3.** Total length of topical steroid use. Of the 27 cases of TSA/TSW found, most subjects used topical steroids for over 2 years. Total time of topical steroid application included breaks in usage.

At least 93 healthcare professionals seen by 21 children recommended continuation of TS therapy despite little to no improvement in skin condition or worsening of skin condition. Caregivers self-discontinued TSs in 70% of the cases because of worsening skin condition and continued AD despite higher potency and increased frequency of TS application.

### Development of TSA/TSW Signs and Symptoms

All of the blogs reviewed included photographs or video documentation of at least one or more signs or symptoms of TSA/TSW including erythema, dryness, flaking, oozing, and pruritus beyond the original treatment site (100%); shedding skin (96%); pain (93%); burning and swelling (85%); and “red sleeves” (63%) (Table 3). Subjective growth delays (e.g. not meeting milestones, decreased weight gain) were reported in 26% of the subjects, which improved after

**TABLE 1.** Indication for TS<sup>a</sup> (n = 27)

n (%)	Signs and Symptoms Before the First Topical Steroid Prescription
19 (70)	AD, cradle cap, facial AD
3 (11)	Fine rash on cheek, “heat rash,” small red patches on the cheeks
2 (7)	Bumps on the left leg like “mosquito bites”; small raised bumps on crook of the elbow and wrists and behind the knees
1 (4)	Contact dermatitis, blister on the cheek
1 (4)	Unbearable itchy and “rashy” patches on the upper thighs and lower abdomen
1 (4)	Skin very red but not flaky or dry, always itchy

AD = atopic dermatitis; TS = topical steroid.

<sup>a</sup>All of these presentations were diagnosed as AD and prescribed with TS.

TS cessation. All school-aged children (n = 13) discussed in these blogs missed multiple consecutive days to weeks and, in one case, even a year of school because of symptoms. Resolution of TSA/TSW symptoms varied after TSW, with 9 subjects reporting full resolution (two reported timing of 9 and 9.5 months; seven required 13 to 24 months). “Of 13 subjects who were 20 months post-TS cessation, seven (54%) continued to exhibit active TSA/TSW symptoms (i.e. shedding, oozing, erythema, pain and itching).”

**TABLE 2.** Topicals Used at Initial Diagnosis of AD and at TS Cessation (n = 27)

n (%) <sup>a</sup>	Initial topical steroids prescribed <sup>b</sup>
9 (33)	Unspecified
8 (30)	Over-the-counter hydrocortisone
5 (19)	Triamcinolone 0.1%
3 (11)	Clobetasol
1 (4)	Hydrocortisone valerate
1 (4)	Desonide
1 (4)	Fluocinonide 0.05%
1 (4)	Fluocinolone body oil
1 (4)	Mometasone
1 (4)	Fluticasone propionate
1 (4)	Alclometasone dipropionate
1 (4)	Betamethasone
5 (19)	Calcineurin inhibitors (tacrolimus/pimecrolimus) <sup>c</sup>
Topical steroids used at the time of topical steroid cessation	
9 (33)	Unspecified
6 (22)	Triamcinolone 0.1% ointment
3 (11)	Fluocinolone scalp/body oil
3 (11)	Over-the-counter hydrocortisone
2 (7)	A regimen of wet wrap therapy with betamethasone dipropionate; triamcinolone on body; desonide on face
2 (7)	Desonide
1 (4)	Clobetasol
1 (4)	Betamethasone
1 (4)	Mometasone
1 (4)	Fluticasone propionate
1 (4)	Dexamethasone
1 (4)	Intravenous steroids

AD = atopic dermatitis; TS = topical steroid.

<sup>a</sup>Indicates number of blogs reporting use of the specific TS. <sup>b</sup>Several subjects were prescribed more than one TS at the initial diagnosis of AD. <sup>c</sup>Some subjects were prescribed both TS and/or tacrolimus/pimecrolimus.

**TABLE 3.** Signs and Symptoms of TS Withdrawal (*n* = 27)

Feature	<i>n</i> (%)
Signs	
Redness	27 (100)
Swelling/edema	23 (85)
Dryness, flaking, cracked skin	27 (100)
Thin skin	18 (67)
Shedding/peeling skin	26 (96)
Oozing/crusting	27 (100)
Swollen lymph nodes	7 (26)
Elephant skin	7 (26)
Caregiver-reported growth delay	7 (26)
Hair loss (scalp, eyebrows, body)	7 (26)
Red sleeves (arms and/or legs)	17 (63)
Symptoms	
Burning/stinging	23 (85)
Increased itching	27 (100)
Pain/"zingers"/"stingers"	25 (93)
Tightness	13 (48)
Hyperesthesia	8 (30)
Decreased tolerance to lubrication	9 (33)
Decreased tolerance to water	11 (41)
Cold or hot all the time	11 (41)
Exacerbation with heat/sun	7 (26)
Sweat stings	7 (26)
Fatigue	11 (41)
Insomnia/altered sleep cycle	20 (74)
Other <sup>a</sup>	
School-aged children ( <i>n</i> = 13)	
Missed school time <sup>b</sup>	13 (100)

TS = topical steroid.

<sup>a</sup>Other reported issues were impetigo, skin infections, increased anxiety, decreased concentration, aching joints, severe dandruff, impaired vision, emotional lability, and infected heel/bone.

<sup>b</sup>Ranged from a few days to an entire year.

### Treatment of TSA/TSW

Despite signs and symptoms, only 6 cases (22%) reported that a medical provider had given them the diagnosis of TSA/TSW. All caregivers provided their children with treatment for TSA/TSW symptoms, which included discontinuation of TS use. Nonpharmaceutical treatments and pharmaceutical treatments offered are summarized in Table 4.

### DISCUSSION

Although locations and living conditions varied, many of the described subjects have underlying similarities in

**TABLE 4.** Treatments Used After Cessation of TS

	<i>n</i> <sup>a</sup>
Nonpharmaceutical treatments	
Cessation of topical steroids	27
Apple cider vinegar baths	11
Ace/gauze wrapping, cotton mitts/gloves	10
Ice packs, cool compresses	9
Psychological support	5
Hot packs/moist or dry heat	4
Narrowband UVB light	3
Pharmaceutical treatments	
Antibiotics (oral)	9
Antibiotics (topical)	4
Antihistamines (oral)	8
Hydroxyzine	4
Analgesics (ibuprofen, acetaminophen)	3
Systemic steroids during hospitalization <sup>b</sup>	1
Tapering topical steroids	0
Moisturizers	
Petroleum jelly	
Coconut and olive oils	
Essential oils (primrose, neem, tea tree, lavender)	
Other: aloe vera, ceramide-containing creams, Sudocrem, organic unrefined shea butter, zinc, Manuka honey, lemongrass balm, Dr. Fukaya's skin repair lotion (Tanaka Science Laboratory, Japan)	
Other interventions	
Apple cider vinegar and salt baths, Epsom salt baths, Topical vitamin D	
Probiotics, cod liver oil, active B vitamins, various vitamins and supplements (prescribed or over the counter)	
Face massage machine, handheld fan, massager, soft tactile stimulation brushes	
Sunlight, exercise and activity as tolerated, deep breathing and relaxation techniques, visualization, acupuncture	
Video games, movies, other distractions and activities requiring two hands	
Changing diets to GAPS, anti-inflammatory, elimination diets, organic/non-GMO, allergan-avoidance	

TS = topical steroid; UVB = ultraviolet B.

<sup>a</sup>Reflects how many blogs mentioned using the intervention; does not imply that other caregivers withheld the intervention.

<sup>b</sup>In-hospital allergist ordered four doses of intravenous steroids, resulting in partial clearance, but subject experienced adverse effect of "fluid (pouring) from every pore in his body" within 48 hours of discharge.

experience with TS therapy. In all cases, the subjects were prescribed a TS, which was initially effective. When the TS became ineffective, caregivers consulted various healthcare providers and were often advised to use a higher-potency TS or increase the frequency of TS application. TSA/TSW was not suspected by caregivers or physicians until Internet research revealed information regarding similar stories and cases in adults and children. In all cases, caregivers ultimately stopped TS application when symptoms did not improve, resulting in the signs and symptoms of TSA/TSW.

TSA/TSW varies in onset and presentation. Most often, patients report burning, stinging, pruritus (at the start of TS application), pain, erythema, and hot flashes in the area of use and adjacent areas, sometimes exacerbated with exposure to infrared or ultraviolet radiation. The “headlight” sign was described in one study and noted a sharp demarcation between erythematous and normal-appearing skin running down the outer cheeks while the nose and ears remained unaffected (Fukaya et al., 2014; Hajar et al., 2015; Kligman & Frosch, 1979; Rapaport & Lebwohl, 2003; Sheary, 2016). The signs and symptoms of TSA/TSW happen to greatly overlap with other dermatologic entities that should be ruled out, including AD, infection, and allergic contact dermatitis. Patch testing is able to delineate whether there is a delayed hypersensitivity reaction to the active steroid agent or to a vehicle excipient in which the TS is delivered.

Symptoms such as burning and confluent erythema lasting days to weeks after discontinuation of TSs and a history of prolonged TS use in sensitive areas make TSA/TSW a more likely diagnosis (Fukaya et al., 2014; Hajar et al., 2015; Rapaport & Lebwohl, 2003; Smith et al., 2007). Recent research has shown that severity of TSA/TSW is associated with the use of TS at a younger age, as well as longer duration and greater quantity of TS exposure. Researchers observed that symptomatology worsened within the first 1.5 years after TS discontinuation, and may be persistent past that time-point in many cases (Berger et al., 2017). The definitive treatment for TSA/TSW is discontinuation of TS use with adjuvant treatment options depending on the subtype of withdrawal clinically seen. Papulopustular eruptions respond to oral antibiotics, and erythematoedematous reactions respond well to antihistamines and cooling compresses (Hajar et al., 2015). The discontinuation of TSs often leads to a robust rebound of the dermatoses being treated. Currently, it is controversial whether a TS taper, topical calcineurin inhibitors, and/or systemic immunosuppression will have added benefit in treatment of this condition (Fukaya et al., 2014; Hajar et al., 2015; Kligman & Frosch, 1979; Rapaport & Lebwohl, 2003; Smith et al., 2007).

In children on TSs, possibility of growth delay due to hypothalamic–pituitary axis suppression and development of avascular necrosis of the developing femoral head must be taken into account. Although it is uncertain in peer-reviewed literature if growth delay occurs with the use

of TS, anecdotal evidence suggests that it may occur. Furthermore, children often are affected by full-body TSA/TSW in contrast to adults in whom the reaction may be confined. The nine children included in this review who have been free of symptoms manifested full-body TSA/TSW symptoms for 8–24 months before reaching resolution; it is not rare that TSA/TSW symptoms may take years to resolve (Fukaya et al., 2014; Kligman & Frosch, 1979; Rapaport & Rapaport, 2004, 2006). Recent research in the field of TS skin penetration/absorption has shown that children with severe AD and <18 months old will absorb high-potency TSs more readily than those with mild to moderate AD and older patients (Halling-Overgaard et al., 2016). Given this new finding, it is no wonder that children with AD are affected by TS adverse events such as TSA/TSW.

It is important for caregivers and clinicians to understand that the underlying disease process, which was initially being treated with TSs, will likely recur upon TS cessation. To determine if a patient is undergoing TSA/TSW, Rapaport and Rapaport recommend checking serum NO levels, which may be elevated in the patient with TSA/TSW. By trending NO levels, healthcare providers may be able to track progression or regression of TSA/TSW (Rapaport & Rapaport, 2004).

## CONCLUSIONS

Despite the possible development of TSA/TSW in the setting of prolonged TS use, it is important to provide the correct treatment of inflammatory dermatoses. It is imperative that healthcare providers be aware of the potential for individuals to develop TSA/TSW, even in children; provide the appropriate TS therapy for the condition they are treating, and counsel caregivers/patients regarding the signs and symptoms of TSA/TSW. The Internet has changed consumers’ approach to medical advice and has included them in the decision tree of their care. Limitations in this review include the lack of peer-reviewed research on TSA/TSW in the pediatric population, small sample size, subjective consumer reports of their child’s health condition, unsubstantiated reports by a healthcare professionals, and reviewer bias. Nevertheless, data obtained through social media reviews of blog articles indicate the need for guidelines pertaining to safe TS dosage in children, time frames for treatment, and advisories on the potential long-term TS effects in susceptible individuals. ■

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